Research Report
2012/2013

Max Planck Institute for Human Cognitive and Brain Sciences

Leipzig

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Research Report 2012/2013

Preface

Throughout 2012/13, the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig continued to pursue its successes in research and development, as this research report shows in detail. The institute currently houses four full departments, seven research groups, and three methods and development units. Up to 350 members of staff use and enjoy the various spaces of the institute—including scanner buildings and laboratories, researchers' offices and the library, meeting rooms, lecture venues and even social areas like the cafeteria—on a daily basis, giving the institute its fascinating spirit of buzzing science, work, and communication.

The newest of our departments, the Department of Social Neuroscience (Tania Singer), is now fully established and—among many other projects—is half way through an unparalleled longitudinal study on Eastern and Western methods on mental training. Another unique longitudinal study is being conducted in the Department of Neuropsychology (Angela D. Friederici) on the neural basis of the development of syntax processing as a crucial capacity of the human species. The Department of Neurology is involved in a large-scale health study on the cause and development of widespread common diseases at the University of Leipzig, LIFE.

Despite the settlement of our newest department, there is still a notion of movement at the institute: In February 2014, Professor Robert Turner, director of the Department of Neurohysics, is retiring. In addition, two new independent research groups have started work: the Otto Hahn Group "Neural Bases of Intonation in Speech" (Daniela Sammler) and the Max Planck Fellow Group "Cognitive and Affective Control of Behavioural Adaptation" (Florian Schlagenhauf). Several of our research group leaders and senior researchers have received prestigious professorial positions at universities in Denmark, Germany, UK, and USA: Tobias Grossmann, Stefan Kiebel, Sonja Kotz, Jutta Mueller, Jonas Obleser, Hellmuth Obrig, Burkhard Pleger, Matthias Schroeter, Jonathan Smallwood, and Katharina von Kriegstein.

The International Max Planck Research School on Neuroscience of Communication (NeuroCom) has been very productive over the last two years, successfullly undergoing its first evaluation and recruiting a second cohort of doctoral students while at the same time seeing the students of the "old" cohort to their completions and holding regular annual summer schools in London and Leipzig. Following its first evaluation, the IMPRS was recommended by the international MPG IMPRS commission to be renewed and funded for another six years (2015–2021).

The aforementioned are, of course, only tasters to whet your appetite for the full content of this book, which we hope you will enjoy reading as you discover more about our institute and its research.

Angela D. Friederici
Tania Singer
Robert Turner
Arno Villringer

Preface

Introductory Remarks 5
Table of Contents 6

Scientific Members and Boards

Scientific Members 8
Scientific Advisory Board & Board of Trustees 9

The Institute

The Max Planck Institute for Human Cognitive and Brain Sciences 10
Organizational Structure 11

Department of Neurology:
Plasticity
Arno Villringer

Research Report 12
Appendix: Scientific and Professional Activities 41

Department of Neuropsychology:
Neurocognition of Language
Angela D. Friederici

Research Report 50
Appendix: Scientific and Professional Activities 80

Department of Social Neuroscience:
Foundations of Human Sociality
Tania Singer

Research Report 86
Appendix: Scientific and Professional Activities 119

Department of Neurophysics:
Mapping Brain Structures Using MRI Techniques
Robert Turner

Research Report 124
Appendix: Scientific and Professional Activities 153

Research Groups

Max Planck Research Group "Neural Mechanisms of Human Communication" (Katharina von Kriegstein)
Research Report 165
Appendix: Scientific and Professional Activities 172

Max Planck Research Group "Auditory Cognition" (Jonas Obleser)
Research Report 174
Appendix: Scientific and Professional Activities 182

Minerva Research Group "Brain Modes" (Petra Ritter)
Research Report 185
Appendix: Scientific and Professional Activities 192

Max Planck Research Group "Neuroanatomy & Connectivity" (Daniel S. Margulies)
Research Report 193
Appendix: Scientific and Professional Activities 200

Max Planck Fellow Group "Cognitive and Affective Control of Behavioural Adaptation" (Florian Schlagenhauf)
Research Report 202
Appendix: Scientific and Professional Activities 208

Max Planck Research Group "Early Social Development" (Tobias Grossmann)
Research Report 210
Appendix: Scientific and Professional Activities 217

Otto Hahn Group "Neural Bases of Intonation in Speech" (Daniela Sammler)
Research Report 219
Appendix: Scientific and Professional Activities 223

Nuclear Magnetic Resonance (Harald E. Möller)
Research Report 228
Appendix: Scientific and Professional Activities 236

MEG and EEG – Cortical Networks and Cognitive Functions (Thomas R. Knösche, Burkhard Maess)
Research Report 240
Appendix: Scientific and Professional Activities 248

Department of Psychology and Research Group "Infant Cognition and Action" (Wolfgang Prinz / Moritz M. Daum)
Research Report 256
Appendix: Scientific and Professional Activities 261

Max Planck Research Group "Music Cognition and Action" (Peter E. Keller)
Research Report 265
Appendix: Scientific and Professional Activities 269

Max Planck Research Group "Body and Self" (Simone Schütz-Bosbach)
Research Report 271
Appendix: Scientific and Professional Activities 277

Minerva Research Group "Neurocognition of Rhythm in Communication" (Sonja A. Kotz)
Research Report 279
Appendix: Scientific and Professional Activities 284

International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity
PhD Students and Projects 288
Faculty 292
IMPRS NeuroCom 296

297

301

Methods & Development Units

Former Departments and Groups

IMPRS NeuroCom

Administrative, Scientific, & Other Services

Index of Names

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The Max Planck Institute for Human Cognitive and Brain Sciences

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 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 this centre in Leipzig also established exceptional conditions for interdisciplinary behavioural and neurobiological research into human cognition.

The institute currently consists of four departments: Neurology, Neurophysics, Neuropsychology, and Social Neuroscience. The institute also hosts several research groups, including four Max Planck Research Groups: "Auditory Cognition" (Jonas Obleser), "Early Social Development" (Tobias Grossmann), "Neural Mechanisms of Human Communication" (Katharina von Kriegstein), and "Neuroanatomy & Connectivity" (Daniel Margulies), as well as a Minerva research group on "Brain Modes" (Petra Ritter) and an Otto Hahn Group on the "Neural Bases of Intonation in Speech" (Daniel Sammler). With the renewal of Professor Heinze as a Max Planck Research Fellow at our Institute, the Max Planck Fellow Group "Cognitive and Affective Control of Behavioural Adaptation" (Florian Schlagenhauf) has been initiated. Three methods and development units facilitate scientists' access to the Institute's state-of-the-art technical equipment, while at the same time conducting research into the methodology of high-resolution imaging and digital data processing.

Research foci

Research at the Max Planck Institute for Human Cognitive and Brain Sciences revolves around human cognitive abilities and cerebral processes, with a focus on the neural basis of brain functions like language, emotions and human social behaviour, and music and action. Our many studies investigate the perception, planning, and generation of these brain functions, to reveal the interaction between, and common functional bases of, their production and perception. Other research focuses on plastic changes in the human brain and the influence this has on various cognitive abilities, and also the neuronal and hormonal basis of 'modern diseases' such as high blood pressure and obesity. In addition, the further development of imaging methods for the neurosciences is an important focal point of research at the Institute.

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, which are increasingly being used in traditional psychological approaches, are utilized and, most importantly, improved at the Institute. Hosting the entire bandwidth of techniques and approaches that are established within human cognitive 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 the University of Leipzig. The first cooperation agreement between the Max Planck Society and Leipzig University, involving the (then) Max Planck Institute of Cognitive NeuroScience and the University of Leipzig, goes back to September 1994. In December 2006/January 2007, the Max Planck Society signed a cooperation agreement with the University of Leipzig 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 cooperation 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

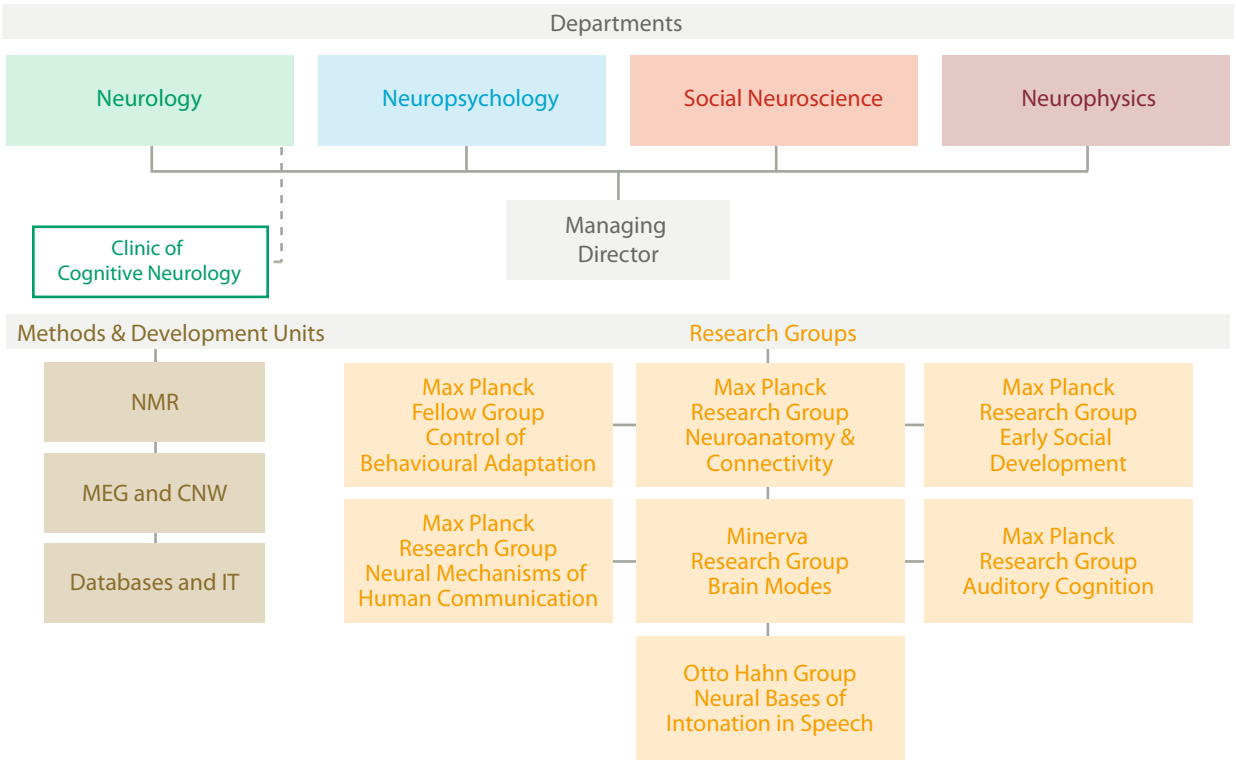
the University; 2) the exchange of scientific information and experience; 3) the undertaking of joint research projects and cooperation in individual research ventures; 4) the teaching and fostering of junior scientists; and 5) the mutual use of facilities. A new cooperation agreement between all Leipzig Max Planck Institutes and the University of Leipzig, further extending and strengthening existing collaborations, has been drafted and is currently being reviewed and finalised.

In 2010, a collaboration agreement with the Institute of Cognitive Neuroscience (ICN) at University College London, 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 organization 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, which is based at the institute and the University of Leipzig, and also involves the Max Planck Institute for Evolutionary Anthropology, Leipzig and the Institute of Cognitive Neuroscience at University College London, UK. We are currently looking into the integration of new international partners for the IMPRS.

A further cooperation agreement exists between the Max Planck Society and the Otto von Guericke University Magdeburg involving the Max Planck Institute for Human Cognitive and Brain Sciences, dating from October 2005. According to this arrangement, the Max Planck Society and the University of Magdeburg agree for the directors of the Max Planck Institute and Professor Dr Hans-Jochen Heinze to cooperate in the domain of methodological developments in the ultra-high-field area as well as in cognition research. In order to further extend the existing cooperation, in October 2010 Professor Heinze was renewed as Max Planck Research Fellow at the Institute for a further five years.

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 or Fraunhofer. 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 and the Excellence Cluster "Languages of emotion" at the Free University Berlin.

Organizational structure



Professor Dr Arno Villringer
Director

1 Plasticity

Department of Neurology

The research focus of the Department of Neurology at the Max Planck Institute together with the Department of Cognitive Neurology at the University Hospital Leipzig is on human neuroplasticity. We pursue this topic with twinned foci on stroke (clinical) and the sensorimotor system (model system for behavioural studies). We aim to

(i) develop and test models of human brain plasticity in healthy subjects,
(ii) identify patterns and modulating factors of plasticity in pathological conditions,
(iii) understand the underlying neural mechanisms of plasticity, and
(iv) develop and evaluate new tools for intervention to induce plasticity.

(i) Towards models of human brain plasticity

We assess *short-term*, *mid-term,* and the *transition to long-term neuroplasticity* in studies using a complex motor learning task (balancing) (Taubert et al., 2010, J Neurosci, 30, 11670–11677; Taubert et al., 2012). We observe that functional and structural changes of the brain do not follow a simple monophasic time course, but dynamically evolve in several temporal phases involving different sets of brain areas: after only an hour of learning there is increased cortical thickness in the primary motor areas, which, however, is transient (1.1) and no longer detectable after two weeks. In the following weeks, pre-motor areas show changes in grey matter density which are also transient (Taubert et al., 2010). The longest-lasting changes affect prefrontal grey matter, the underlying fibre tracts, and modulate functional and structural connectivity between prefrontal and motor areas (Taubert et al., 2011, NeuroImage, 57(4), 1492–1498). From these findings, we conceptualize a novel "multiphase" model of brain plasticity during learning that is depicted in Figure 1.

In follow-up studies on the same subjects we note preservation of the behavioural gains for at least 15 months—indicating long-lasting plasticity. In addition, we have also performed a number of cross-sectional studies on *long-term neuroplasticity*. We try to go beyond simple "group differences" approaches to associate behavioural and/or functional correlates with structural and functional changes in the brain. For example, we study the effects of musical training-induced plasticity by relating structural features of the corpus callosum (in musicians and non-musicians), as indexed by fractional anisotropy, to transcallosal inhibition (IHI), as measured by transcranial magnetic stimulation (1.3). In a study on groups of athletes who undergo different training regimes, we show differences in movement velocity to be related to structural features of the cerebellum (data not shown).

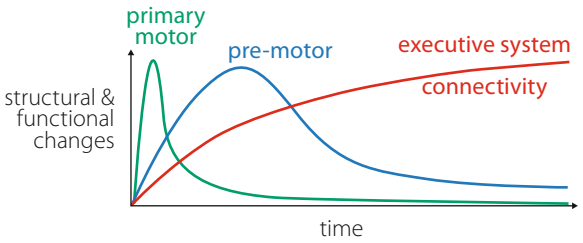


Figure 1 Multiphase model of structural and functional changes during learning a complex motor task

(ii) Human brain plasticity in pathological conditions

We show that elderly subjects and patients with Parkinson's disease recruit different brain regions when learning the same task as young healthy volunteers: Hippocampal changes are more pronounced in elderly healthy subjects, while cerebellar changes dominate in subjects with Parkinson's disease (Sehm et al., 2013b). Hence, the brain areas/networks involved can differ depending on the baseline characteristics of a certain "brain state".

Obviously, stroke patients also start from a different "baseline" when (re)- learning certain abilities or tasks. Firstly, they typically suffer from vascular risk factors many years before the stroke and, secondly, the stroke lesion itself alters the brain. Both of these aspects are addressed in our research:

As *risk factors for stroke*, we focus on obesity and hypertension. In subjects with obesity we find alterations in subcortical and cortical grey matter (Horstmann et al., 2011, Front Hum Neurosci, 5:58; Müller et al., 2012; Raschpichler et al., 2013) as well as diffuse changes in white matter (Müller et al., 2011, PLoS One, 6(4)). Our intervention study with exercise in overweight subjects gives first hints for a potential reversibility of some obesity-related cerebral changes (1.15). Studies on morphological features in hypertension are underway in the large LIFE cohort study in which, to date, 1600 subjects have been recruited and received MRI scans. Furthermore, we study cognitive and behavioural features in subjects with these risk factors (1.13, 1.14) along with possible interventions (1.16).

In *acute stroke* and thereafter, the lesion will affect the brain locally (at the site of the lesion) but also leads to changes in distant brain areas. The former is typically assessed with diffusion and perfusion MRI and T2-weighted MRI. Perfusion MRI relies on contrast agent administration since, so far, non-contrast based approaches such as arterial spin labelling (ASL) have not been sensitive enough. Based on a new time-shift analysis of resting-state MRI, we propose and provisionally validate a novel non-invasive alternative (1.18, Lv et al., 2013). This approach has recently been confirmed by another group (Amemiya et al., 2013, Radiology).

The pronounced spatial heterogeneity of lesions is a major problem for longitudinal studies on (chronic) stroke-induced brain plasticity. While the usual approach is to search for patients with very similar lesion locations which are then grouped into one study (e.g. our earlier study on thalamic stroke by Taskin et al., 2006, Cereb Cortex, 16,1431–1439), we now propose a new approach which classifies patients according to affected network(s) rather than according to lesion sites (1.19, Ovadia-Caro et al., 2013). This approach allows the inclusion of lesions at different locations and sizes into one generalized "model" of (affected/non-affected) brain networks.

In addition to these prospective studies on the network effects of focal lesions, we continue to take advantage of "classical" lesion studies for identifying structure-function relationships in patients with chronic stroke (Henseler et al., in press) and dementia (Schroeter et al., 2012).

(iii) Underlying mechanisms of neuroplasticity

The "multiphase plasticity model" given in Figure 1 is consistent with findings from experimental studies in animals showing phases of synapse gain and subsequent selective stabilization and elimination during motor learning (which would result in "transient" changes in grey matter density), along with the formation of specific new memory traces associated with changes in brain connectivity (Caroni et al., 2012, Nat Rev Neurosci, 13, 478–490).

Beyond this general conceptual framework, we specifically address the following questions on the mechanisms underlying plasticity: (i) Which of the observed brain areas are really essential and which are an "epiphenomenon"? We assess interference during transcranial stimulation to establish a causal role(s) for different brain regions. We show that interference with the PFC (right) attenuates learning efficacy of a balancing task, but this was not the case for interference with the SMA (Kaminski et al., 2013). In another example we show that perceptual learning of severely degraded speech can be induced by facilitatory stimulation of the inferior frontal cortex with transcranial direct current stimulation (1.7, Sehm et al., 2013). (ii) Which cortical layers undergo learning-related plasticity? We have preliminary data (Taubert et al., work in progress) indicating that the most superficial layers (layers 1/2) undergo the most pronounced changes during learning. Detailed studies with ultra-high spatial resolution at 7 Tesla are currently underway (Steele et al., work in progress). (iii) Can the *memory trace* really be identified as a modulation of functional and structural network connectivity? While the tight correlation between fronto-parietal network connectivity and behavioural change that we have found supports this notion (Taubert et al., 2011, NeuroImage, 57, 1492–1498; Taubert et. al., 2012), we are prospectively testing this in additional learning models and in lesion models. Related to this, (iv) what is the potential role of brain rhythms as identified in EEG? In a recent study, alpha rhythm strength explained up to 64% of learning variability (Freyer et al., 2013, J Neurosci, 33, 2900–2907). This links to our work on alpha rhythm as modulators of activity in sensory cortical areas and its relationship to inhibitory interneuron activity both in the somatosensory (1.10) and the visual system (1.12). The recent proposal that certain inhibitory interneurons may play a fundamental role in motor learning (Donato et al., in press, Nature) represents an exciting hypothesis which we are currently trying to translate into human studies. Alpha rhythms have also been ascribed a role in cortico-subcortical interactions that are thought to subserve top-down regulation of sensory input and cognitive and emotion control. Therefore, (v) what role do cortico-subcortical interactions play in plasticity and can their influence be modified (for example by TACS)? We study cortico-subcortical interactions in models of obesity (1.13) and of blood pressure control during emotions such as anger (model given in 1.16). In obese subjects, we provide evidence that functional alterations in the fronto-striatal system are related to modulation of dopamine neurotransmission (1.13).

(iv) Development and validation of new interventions

The main clinical aims for which we develop new interventions are (i) to restore function after stroke, and (ii) to reverse maladaptive plasticity associated with vascular risk factors leading to stroke. One focus is on understanding and further developing transcranial stimulation methods (e.g. 1.2, 1.4, 1.7). We assess the effects of transcranial direct current stimulation (TDCS) with fMRI (1.2), and (related to our work on alpha rhythms) we show that transcranial alternating current stimulation (TACS) tuned to the individual alpha frequency can modulate brain function in a phase-dependent manner (1.9). Also related to alpha rhythm, we apply a brain computer interface (BCI) approach and show that after only 30 minutes of biofeedback to one's alpha rhythm in the sensorimotor cortex, brain connectivity patterns are altered (1.8). We postulate that interventions based on the modulation of alpha rhythm (TACS, BCI) may also be useful in other situations. Specifically, we hypothesize that prefrontal-subcortical interactions during emotion control could be mediated by alpha rhythm and may also modulate emotion- or stress-induced blood pressure changes (1.16) and/or eating behaviour.

Of relevance for physical therapy in stroke patients, we have found that the subjective effort during motor performance appears reduced when the task is perceived as musical agency (1.17, Fritz et al., 2013). Finally, we have shown that a single dose of escitalopram (a serotonin reuptake inhibitor, which is a class of drugs that has been suggested to influence brain plasticity) can profoundly alter brain connectivity (1.17).

In 2012/2013, we published a total of 157 papers in international journals, among them the *New England Journal of Medicine* (x1), *Proceedings of the National Academy of Sciences* (x3), *Annals of Neurology* (x1), *Brain* (x3), *Diabetes Care* (x1), *The Journal of Neuroscience* (x2), *Journal of Cerebral Blood Flow and Metabolism* (x3), *NeuroImage* (x19), *Human Brain Mapping* (x3), *Cortex* (x2), and *PLoS Comput Biology* (x2) (see reference list).

In the years ahead we are expecting to gain further insights into basic mechanisms of plasticity from studies with recently implemented new technologies such as simultaneous PET/fMRI, TDCS/fMRI, and real-time fMRI. The ongoing large cohort studies also allow us to examine plasticity related to vascular risk factors in more detail, and to investigate possible genetic links. Furthermore, we are expecting results of several prospective follow-up studies in stroke patients on delayed development of (maladaptive) plasticity-related symptoms such as

thalamic post-stroke pain, post-stroke depression, and post-traumatic stress disorder (PTSD). Finally, several intervention trials with a focus on (i) combining aerobic exercise (to increase BDNF) with cognitive and behavioural training, (ii) combining sports with dieting, (iii) working memory training, and (iv) mirror-based motor training in stroke patients are on the way.

We are convinced that combining investigations into basic mechanisms of human plasticity with clinical patient studies performed within a coherent conceptual framework, and in cooperation with our partners at universities and university hospitals, is optimal for achieving our mission of preventing stroke and improving recovery from stroke (please visit also: http://www.cbs.mpg.de/depts/n-3).

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1.1

Immediate increase in motor cortical thickness through physical training or imagery-induced reactivation of an acquired motor memory trace

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It has been shown that the adult human brain adapts to new experiences and structural brain plasticity can be observed after motor and cognitive training interventions. In our previous study, we were able to show dynamic structural grey and white matter changes in frontal brain regions during six weeks of balance training (Taubert et al., 2010, J Neurosci, 30, 11670–11677). Motivated by recent animal studies showing structural plasticity after minutes to hours of motor training (Rüdiger et al., 2012, Nature, 473, 514–518; Xu et al., 2009, Nature, 462, 915–919), the aim of the present study was to investigate immediate changes in brain structure following single training sessions. Furthermore, a large body of evidence suggests reconsolidation-related structural plasticity in neuronal circuits encoding the original memory trace (Nader & Hardt, 2009, Nat Rev Neurosci; 10, 224–234). We therefore hypothesized that motor skill training as well as imagery-induced motor skill reactivation both induce structural changes in similar circuits in the adult human brain. First, 45 minutes of balance training resulted in a rapid and training-specific increase in motor cortical thickness. These changes were prominent in the leg representation of the left primary motor cortex. Second, motor imagery of balance performance for 45 minutes increased cortical thickness in the same region in experienced (1–2 prior balance training sessions) but not in naive subjects (no prior balance training). Third, reanalysis of our previous data set (Taubert et al., 2010, J Neurosci, 30, 11670–11677) suggests that motor cortical thickness increases are transient and are no longer observable after two weeks of balance training. These results demonstrate rapid motor cortical thickening through physical training and imagery-induced reactivation of an acquired motor memory trace. Collectively, this supports the view of a cascade of transient structural changes from posterior to anterior frontal regions during the time course of complex motor skill learning.

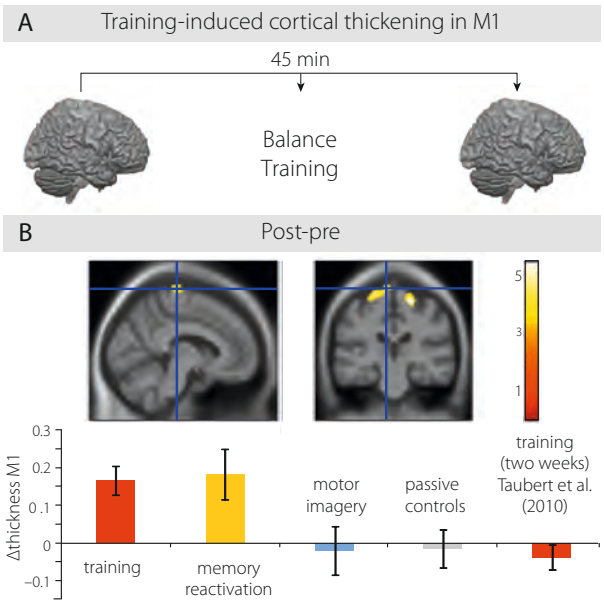

Figure 1.1 Training-induced changes in cortical thickness. (A) Time-course of MRI measurements (20 minutes for each session) and intervention (45 minutes). Post-MRI was performed approx. 5–10 minutes after the end of the intervention. (B) Increase in motor cortical thickness (post-pre MRI) in the balance training group (bar indicates t value). Bar graph shows cortical thickness changes (crosshair in slice) in each of the four groups as well as in our previous data set.

1.2

Transcranial direct current stimulation modulates intra- and interhemispheric functional connectivity of the human motor cortex

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Transcranial direct current stimulation (tDCS) applied over the primary motor cortex (M1) has been shown to induce changes in motor performance and learning in both healthy human volunteers and patients with motor deficits after stroke. Recent evidence suggests that bilateral tDCS over M1 yields more prominent effects in both healthy subjects and chronic stroke patients than unilateral tDCS, potentially via an increased modula-

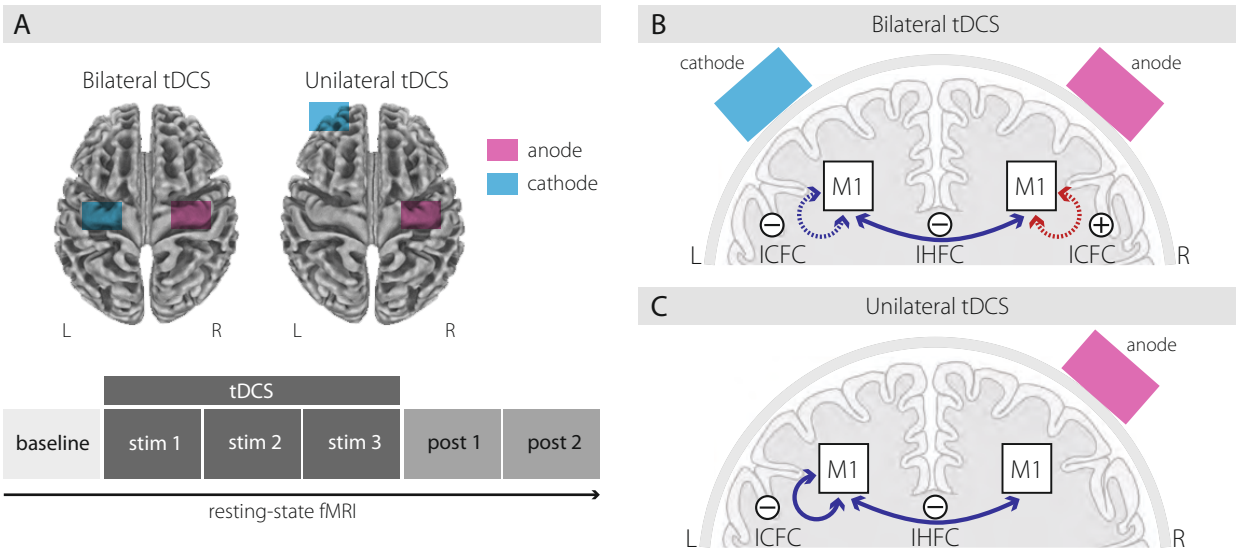

Figure 1.2 (A) Experimental setup and design. All subjects underwent rsfMRI during and after bilateral (cathode over left, anode over right M1), unilateral (anode over right, cathode over left supraorbital region), or sham tDCS (not displayed) in three separated sessions (upper row). Resting-state fMRI measurements were conducted in six blocks before, during, and after tDCS application (lower row). (B) and (C): Schematic summary of intracortical and interhemispheric functional connectivity changes induced by bilateral (B) and unilateral (C) tDCS. Solid lines indicate online-, dotted lines after-effects; blue lines indicate decreases, red lines increases in functional connectivity induced by the respective tDCS setup as compared to sham. ICFC, intracortical functional connectivity; IHFC, interhemispheric functional connectivity; M1, primary motor cortex; L, left; R, right.

tion of interhemispheric inhibitory processes. However, the underlying mechanisms have not been studied so far. We here investigated the temporal evolution of online- and after- effects of tDCS on functional connectivity within and across the stimulated M1. Two different tDCS setups were investigated: (i) unilateral tDCS (anode over right M1, cathode over the contralateral supraorbital region) and (ii) bilateral tDCS (anode over right M1, cathode over left M1). In a randomized single-blinded crossover design, 12 healthy subjects underwent resting-state functional magnetic resonance imaging at rest (rs-fMRI) before, during, and after 20 min of either bi-, unilateral, or sham tDCS. Seed-based functional connectivity analysis (FC) was used to investigate tDCS-induced changes across and within M1. We found that bilateral tDCS induced (a) a decrease in interhemispheric FC during stimulation and (b) an increase in intracortical FC within right M1 after termination of the intervention. While unilateral tDCS also resulted in similar effects during stimulation, no such changes were observed after termination of tDCS. Our results provide evidence that depending on the electrode montage, tDCS acts upon a modulation of either intracortical and/or interhemispheric processing of M1.

1.3 The relationship between interhemispheric inhibition and the corpus callosum: A comparison between musicians and non-musicians

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Musical training is associated with a number of functional and structural brain changes, making it an attractive paradigm for investigating long-term motor plasticity in humans. Physiological interhemispheric inhibition (IHI) as examined by transcranial magnetic stimulation has been shown to be related to anatomical properties

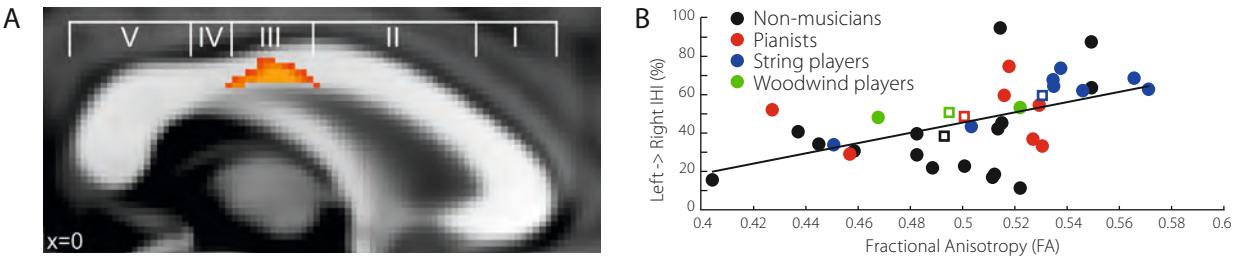

Figure 1.3 (A) Fractional anisotropy in the posterior midbody of the corpus callosum was positively correlated with baseline IHI across all participants. A is overlayed with the classification scheme of Hofer and Frahm (2006). (B) Mean FA extracted from the significant region plotted against IHI. Non-musician controls are depicted in black, pianists in red, string players in blue, woodwind players in green, and group centroids are denoted with squares. The solid line depicts the linear regression through the plotted points. Group-wise correlations performed on the extracted FA values revealed that the positive correlation is also present within non-musicians ($r = .44$, $p < .05$), musicians ($r = .52$, $p < .05$), and string players ($r = .97$, $p < .005$).

of the corpus callosum as indexed by fractional anisotropy (FA). However, whether or not this relationship can be modified by extensive musical training remains unknown. We investigated this question in non-musicians and musicians educated in instrumental playing with strong (piano players, N = 7; woodwind players, N = 2) or little (string players, N = 8) requirement for independence of bilateral finger movements. IHI values were generally higher in musicians, but differed from non-musicians only in string players. IHI was correlated with FA in the posterior midbody of the corpus callosum across all participants. Crucially, subsequent analyses revealed that this relationship may be modulated by different training regimes. String musicians showed a strong positive structure-function relationship and had greater IHI than non-musicians. Conversely, there was no significant structure-function relationship in pianists and the amount of IHI was comparable to that of non-musicians. Our findings indicate that both functional and structural interhemispheric connectivity can be enhanced by long-term musical training, and that the degree of interhemispheric connectivity may be modulated by the requirements of the training task.

Anodal transcranial direct current stimulation (tDCS) over supplementary motor area (SMA) but not pre-SMA promotes short-term visuomotor learning

1.4

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Non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) has been shown to modulate cortical excitability and thereby influencing motor behaviour and learning. While there is increasing knowledge about the importance of the primary motor cortex (M1) in short- and long-term motor skill learning, little is known about the role of secondary motor areas such as the supplementary and pre-supplementary motor area (SMA/pre-SMA) especially in short-term motor performance. Since SMA but not pre-SMA is directly connected to M1, we hypothesized that anodal tDCS over SMA but not pre-SMA will facilitate visuomotor learning. We applied anodal tDCS ($tDCS_{anodal}$) over left SMA, pre-SMA, or M1 (n = 12 in each group) while subjects performed a visuomotor pinch force task (VPFT) with their right hand and compared VPFT performance relative to sham ($tDCS_{sham}$). In a previous study (Gryga et al., 2012, Front Syst Neurosci., 6, 37) we demonstrated that performing the SPFT on five consecutive days resulted in structural brain alterations in motor-related brain regions. In the present study, we show that apart from tDCSanodal over left M1 also SMA but not pre-SMA stimulation promotes short-term improvements in visuomotor learning relative to $tDCS_{(sham)}$. Our findings provide novel evidence about the role of SMA in short-term visuomotor performance. This knowledge might be beneficial in developing hypothesis-driven clinical studies in neurorehabilitation.

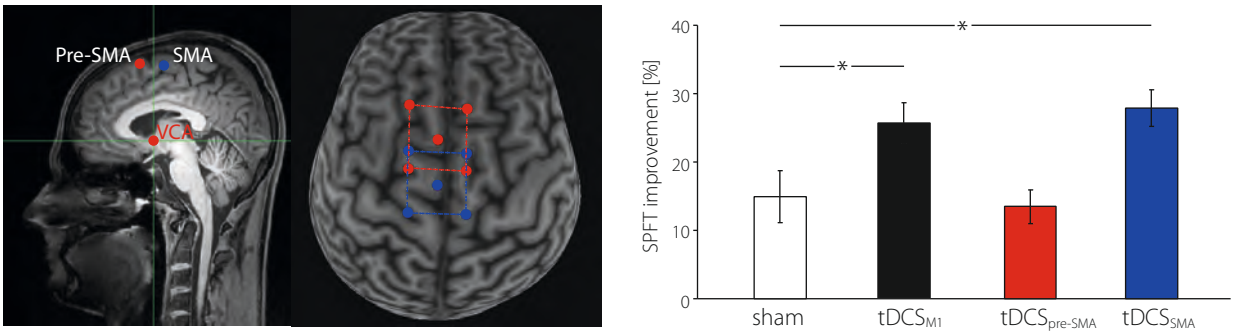

Figure 1.4 Upper figure: Target coordinates for left pre-SMA (MNI: –3, 18, 57) and SMA proper (–3, –2, 57) in the sagittal view of a representative subject's T1-weighted MRI scan. Please note that both target coordinates show the same distance to the vertical commisure anterior line (VCA). Target regions for SMA/pre-SMA projected on a 3D reconstruction for one representative subject. The rectangles represent the electrode placement of the active anode tDCS electrode around the target coordinate, blue for the SMA and red for the pre-SMA condition. In all conditions, the cathode was positioned over the forehead. Lower figure: Sequence-specific learning of the right hand (expressed as sequence learning minus random learning in percent of baseline performance) in the SPFT. Subjects receiving anodal tDCS over SMA or M1 showed an enhanced visuomotor learning as compared to subjects receiving anodal tDCS over pre-SMA or sham.

1.5 Overlapping and parallel cerebello–cerebral networks contributing to sensorimotor control

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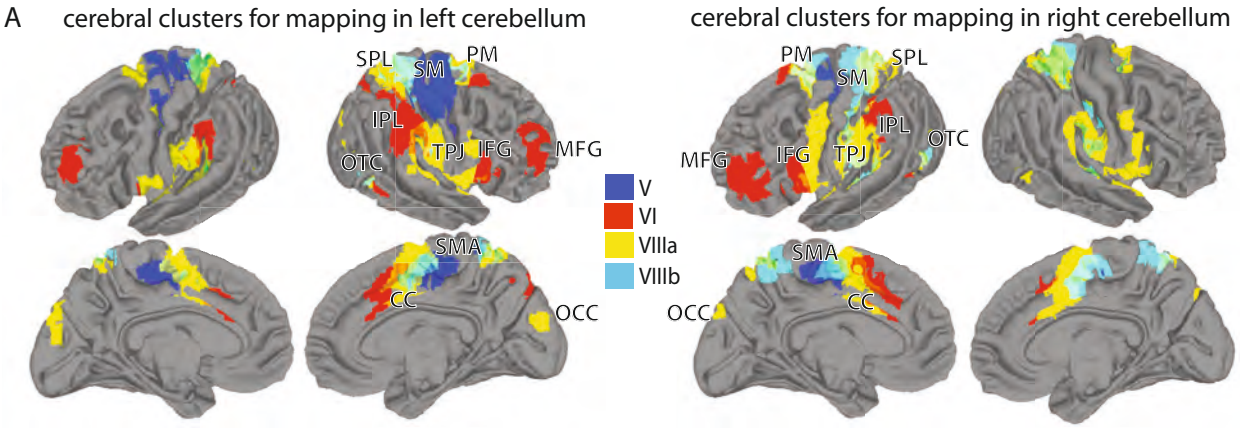
In concert with sensorimotor control areas of the cerebrum, the cerebellum shows differential activation patterns during a variety of sensorimotor-related tasks. However, the spatial details and extent of the complex and heterogeneous cerebello–cerebral systems involved in action control remain uncertain. We used intrinsic functional connectivity (iFC) to examine cerebello–cerebral networks of five cerebellar lobules (I–IV, V, VI, and VIIIa/b) that have been empirically identified to form the functional basis of sensorimotor processes. In a first analysis, a refined cerebellar seed-region selection allowed us to identify a network of primary sensorimotor and supplementary motor areas (I–V), a network of prefrontal, premotor, occipito-temporal and inferior-parietal regions (VI), and two largely overlapping networks involving premotor and superior parietal regions, the temporo-parietal junction as well as occipito-temporal regions (VIIIa/b) (Fig. 1.5A). All networks involved the medial prefrontal/cingulate cortex. In a second analysis, the time series of cerebral clusters were then used in a partial correlation analysis to systematically map cerebral connectivity throughout the entire cerebellum (Fig.



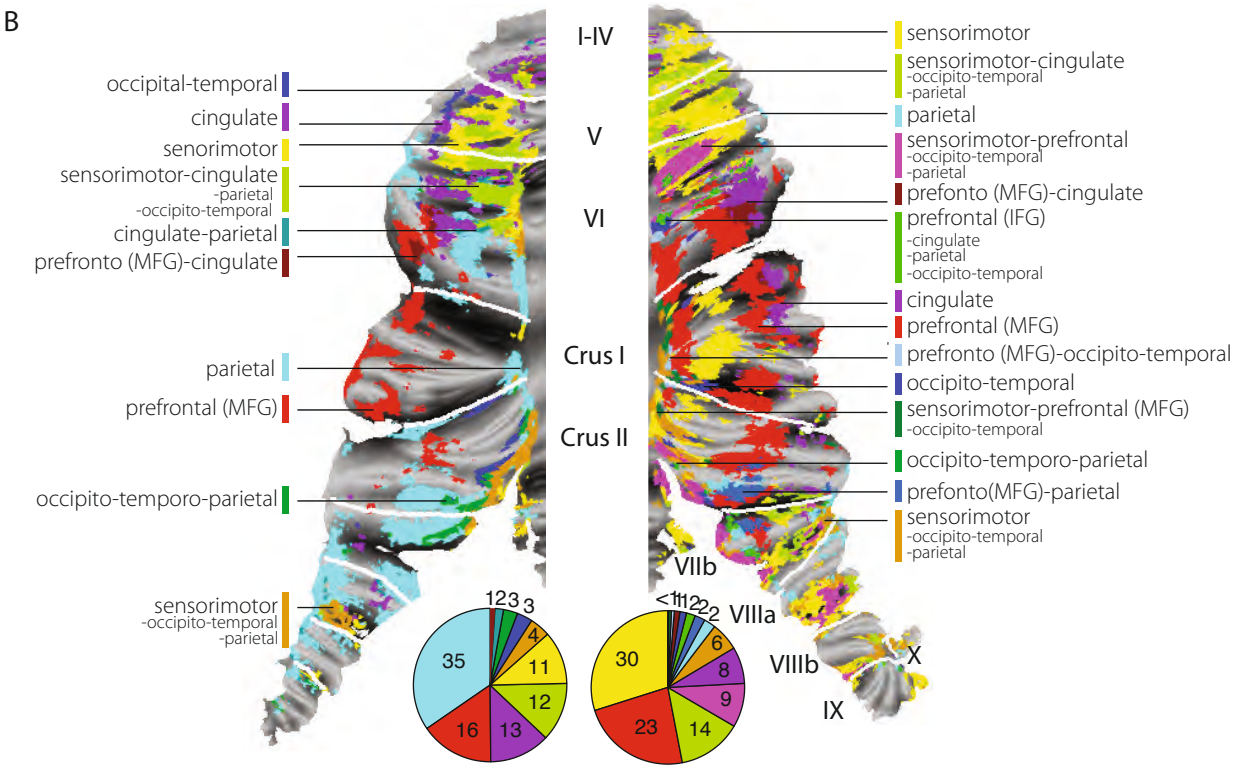


Figure 1.5 Cerebellar sublobular and cerebral functional zones contributing to sensorimotor control. (A) Thresholded, eroded, dilated, and colour-coded 18 cerebral clusters of voxelwise cerebello–cerebral iFC analysis overlaid on partially inflated cerebral surface maps. Cerebral overlaps are displayed by means of translucent colours. (B) Thresholded and colour-coded cerebral connectivity across the entire cerebellum along with a description of the connected cerebral regions. The colour-coded pie charts at the bottom represent the cerebral connectivity distribution for each cerebellar hemisphere (in percentage).

1.5B). The distinct sublobular functional topography of prefrontal, parietal, sensorimotor, cingulate and occipito-temporal regions support a cerebellar role in affective and cognitive control, sensorimotor, multisensory, and executive/language systems. However, all areas showed overlapping connectivity to various degrees in both hemispheres. The results of both analyses demonstrate how sublobular functional divisions of the cerebellar lobules may dominate in different aspects of primary or higher-order sensorimotor processing. This systems-level cerebellar organization provides a more detailed structure for cerebello–cerebral interaction which contributes to our understanding of complex motor behaviour.

Musical agency reduces perceived exertion during strenuous physical performance

1.6

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Music is known to be capable of reducing perceived exertion during strenuous physical activity. The current interpretation of this modulating effect of music is that music may be perceived as a diversion from unpleasant sensory sensations that go along with exhaustion. Here we investigated the effects of music on perceived exer-

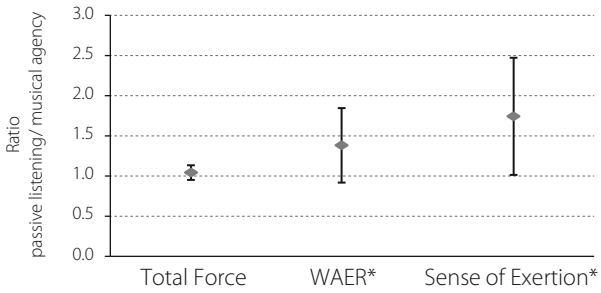

Figure 1.6 Data from those participants who were connected to the spirometer and force meter while working out on a tower fitness machine. The figure shows average ratios of total force (1.043, $p = 0.054$)), W_{AER} (1.382, $p = 0.002$) and sense of exertion (1.743, $p < 0.001$) between the passive listening condition and the musical agency condition along with the respective standard deviations (ratios that are significantly different from 1 are marked with *).

tion during a physically strenuous task, varying musical agency, a task that relies on the sensory experience, rather than simply diverting from it.

For this we measured psychologically indicated exertion during physical workout with and without musical agency, while simultaneously acquiring metabolic values with spirometry. The physical workout was conducted with three different fitness machines, and the movement of the machines was mapped to a composition software so that the deflection corresponded to musical parameters of an acoustic feedback signal. The feedback was designed so that the three fitness machines created sounds that could be interactively combined into a holistic musical piece.

Results showed that musical agency significantly decreased perceived exertion during workout, indicating that musical agency may actually facilitate physically strenuous activities. In addition to the data displayed in Figure 1.6, this could also be shown when comparing the musical agency condition to another control condition where subjects were asked to perform only isometric movements during passive music listening. Although in this control condition less oxygen was used and less work was done, it was perceived as more exhausting.

The findings indicate that the positive effect of music on perceived exertion cannot always be explained by an effect of diversion from sensory feedback. Furthermore, this finding suggests that the down-modulating effect of musical agency on perceived exertion may be a previously unacknowledged driving force for the development of music in humans: Making music makes strenuous physical activities less exhausting.

1.7 Facilitation of inferior frontal cortex by transcranial direct current stimulation induces perceptual learning of severely degraded speech

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Speech comprehension requires the rapid mapping of complex and often highly variable sounds to meaning. While the healthy human brain affords this task almost without effort, this function might be lost or hindered in neurological conditions such as stroke. One of the underlying processes to reinstate this ability is perceptual learning that requires the generalization of categorical perceptual sensitivity from trained to untrained items. For degraded speech, perceptual learning modulates activation in a left-lateralized network, including inferior frontal gyrus (IFG) and inferior parietal cortex (IPC). In this study we demonstrate that facilitatory anodal transcranial direct current stimulation ($tDCS_{anodal}$) can induce perceptual learning. In a sham-controlled, parallel design, 36 volunteers were allocated to three intervention groups: $tDCS_{anodal}$ over left IFG, IPC, or sham. Participants decided on the match between an acoustically degraded and an undegraded written word by forced same-different choice. Acoustic degradation varied in 4 noise-vocoding levels (2, 3, 4, and 6 bands). Participants were trained to discriminate between minimal (/Tisch/-FISCH) and identical word pairs (/Tisch/-TISCH) over a period of three days, and $tDCS_{anodal}$ was applied during the first 20 minutes of training. Perceptual sensitivity (*d'*) for trained word pairs, and an equal number of untrained word pairs, was tested before and after training. Increases in *d'* indicate perceptual learning for untrained, and a combination of item-specific and perceptual learning for trained word pairs. Most notably for the lowest intelligibility level, perceptual learning occurred only when $tDCS_{anodal}$ was ap-

plied over left IFG. For trained pairs, improved *d'* was seen on all intelligibility levels irrespective of tDCS intervention. Over left IPC, $tDCS_{anodal}$ did not modulate learning but instead introduced a response bias during training. Volunteers were more liberal to respond "same", potentially indicating enhanced perceptual fusion of degraded auditory with undegraded written input. Our results supply first evidence that neural facilitation of higher-order language areas can induce perceptual learning of severely degraded speech.

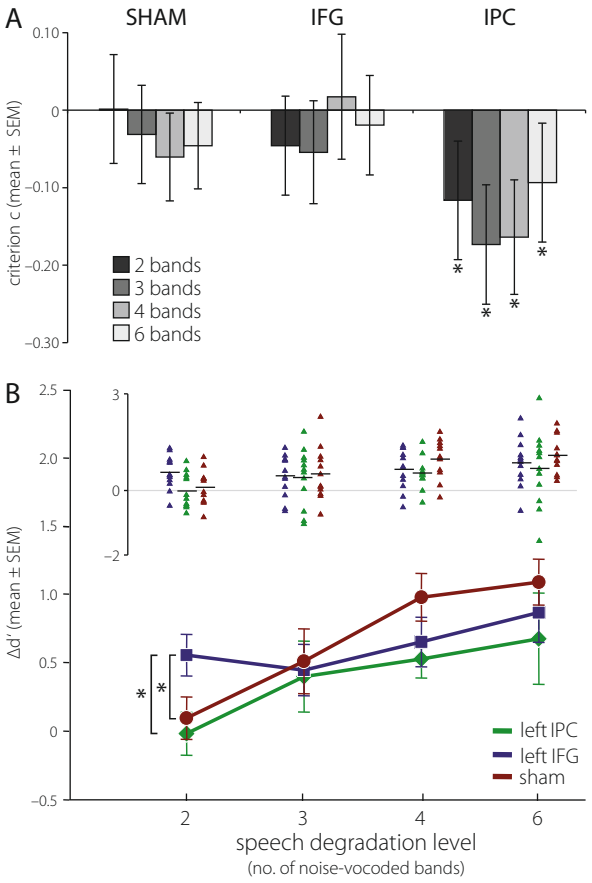

Figure 1.7 Differential effects of facilitatory tDCS on task performance as a function of the stimulation location: (A) tDCS over left IPC during training led to a modulation of the decision criterion towards a more liberal response tendency but did not affect perceptual learning. (B) tDCS over left IFG induced perceptual learning (i.e. an improvement in *d'* from pretest to post-test in untrained items) in the condition with the most severely degraded items (2 bands) while here, no perceptual learning was observed for IPC or SHAM (n = 12 each). No significant group differences were observed in the other degradation levels (3, 4, and 6 bands). Error bars indicate ± SE. Asterisks indicate significant differences ($p = 0.05$).

Brain-computer interface based on alpha desynchronization induces brain plasticity

1.8

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A Brain-Computer Interface (BCI) is a system that enables people to operate a computer by means of brain signals, usually EEG. In sensorimotor rhythm-based (SMR) BCI, during a motor imagery task people learn to modulate sensory alpha desynchronization and thus increase BCI performance over time. Here, we investigate if learning to use an adaptive SMR-BCI system induces brain plasticity. Adaptive BCI systems are known to accelerate the learning of the users as measured by performance. Functional connectivity MRI (fcMRI) was employed in a group of completely non-experienced BCI users before and after just one hour of SMR-BCI training. The modula-

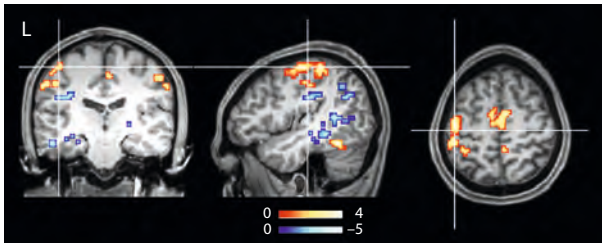

Figure 1.8 Changes in functional connectivity of SI during subliminal stimulation revealed by ECM. Results of a paired t-test are shown for contrasting SMR versus Control group after subtracting EC-maps before and after BCI training. Warm colours indicate an increase, cold colours a decrease in centrality (slice coordinates x = 44, y = 114, z = 50; L indicates left hemisphere).

tion of the sensory alpha rhythm was achieved by motor imagination of the left hand, right hand, or feet. As control, we investigated a second group but with a visual evoked potential-based (VEP) BCI instead.
Eigenvector centrality mapping (ECM) was used to identify changes in whole-brain functional connectivity. The comparison of ECM results before and after BCI training of the SMR group revealed increased functional connectivity in primary sensorimotor areas. The comparison with the control group showed these changes to be significant for the SMR-BCI group (Fig. 1.8). The pronounced lateralization of the effect to the left hemisphere might be due to subjects' right-handedness.
In summary, our findings demonstrate that a relatively short (one-hour) training of SMR-BCI induces brain plasticity as measured with fcMRI. The significance for SMR-BCI versus the control group suggests an important role for the alpha rhythm to induce brain plastic changes. This could also have a great impact on all fields where the goal is to learn new or lost functions (e.g. neuro-rehabilitation).

1.9 Modulating somatosensory detection thresholds with transcranial alternating current stimulation

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Ongoing oscillations are associated with brain functions such as somatosensory perception. The perception of near-threshold stimuli was linked to different parameters of these oscillations, like amplitude (Linkenkaer-Hansen et. al., 2004, Humans J Neurosci, 24(45), 10186–10190) and phase (Busch et. al., 2009, J Neurosci, 29(24), 7869–7876). Transcranial alternating current stimulation (tACS) may offer the possibility to modulate oscillatory activity (Herrmann et. al., 2013, Front Hum Neurosci., 7:279).
We examined the effect of tACS applied at each participant's individual Mu frequency on threshold levels of somatosensory perception. We hypothesized that (a) tACS modulates somatosensory perception thresholds and (b) perception thresholds vary as a function of the phase of tACS. In a randomized, single-blinded, crossover design, 18 participants (mean age: 27.2; female: 10) underwent a combined EEG/tACS experiment in two separate sessions (real or sham tACS). After identifying a subject's individual Mu frequency, somatosensory detection thresholds were determined in a block of 16 min using an adaptive staircase procedure of weak electric stimuli presented at the right index finger. In between, 5 min of tACS was applied at the individual Mu frequency in a bilateral montage over both primary somatosensory cortices (S1). For sham, 30 s of 1 mA random noise stimulation was applied. We observed no differences in the average

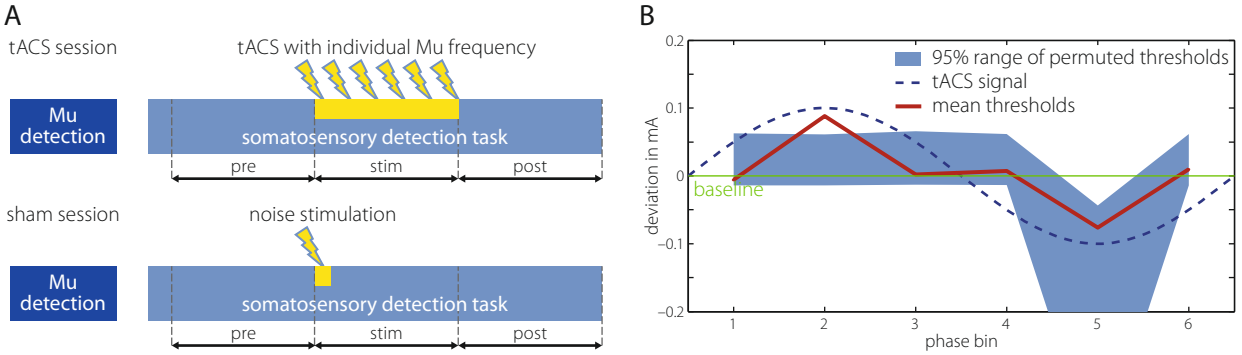

Figure 1.9 (A) Schematic illustration of the experimental design for the two separate sessions. For both sessions each participant's Mu-alpha frequency was determined, which was then followed by a somatosensory detection task during which either real or sham stimulation was applied. (B) Perception thresholds for each phase bin of the tACS signal curve averaged across 13 subjects in red. Blue area indicates range of 95% of synthetic thresholds resulting from 10,000 permutations. Note: Mean perception threshold at phase bin 5 is larger than 95% of synthetic thresholds derived from permutation tests. Blue line: illustration of tACS signal curve in an arbitrary scale.

somatosensory perception thresholds between real and sham stimulation. However, during tACS, somatosensory detection thresholds changed as a function of the phase of tACS with thresholds differing maximally for stimuli presented at opposite phases (at minima and maxima) of the tACS signal curve. Our findings suggest that functionally relevant intrinsic oscillations may be modulated using non-invasive brain stimulation.

Attention modulates cerebral responses to subliminal somatosensory stimuli

1.10

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Although not perceived consciously, somatosensory stimulation below perception threshold influences cerebral processes. In the human EEG, an event-related potential (P60) and an increase of sensorimotor alpha (or Mu) were identified as corresponding markers (Nierhaus et al., submitted). In the current study, we examined whether selective tactile attention, as a form of executive control, has a modulatory impact on unconscious stimulus processing. Subjects received 960 imperceptible electrical pulses over 16 two-minute blocks to the left hand, separated by 2 s each, with a jitter of +/- 300 ms. Additionally, in each block, up to four perceptible stimuli were randomly presented to the left or right hand. Subjects responded to perceived stimuli at the cued side and ignored stimuli at the other side. Accordingly, we derived two conditions where the unconsciously stimulated hand was either attended or ignored. When subjects directed attention to the left hand, unconscious stimulation evoked the P60. However, the P60 was not observed when attention was directed to the right hand. Furthermore, unconscious stimulation induced an activity enhancement of sensorimotor alpha starting after 300 ms when the left hand was attended, and after 100 ms when the right hand was attended. In line with the attentional sensitization model for unconscious cognition (Kiefer, 2012, Front Hum Neurosci, 6, 61), an absence of the P60 might be related to directing a subject's attention away from the unconsciously stimulated hand, thereby attenuating the sensitivity of task-irrelevant pathways and, in turn, enhancing the processing of task-relevant pathways. According to the proposed functional role of alpha as being a mediator of inhibitory gating

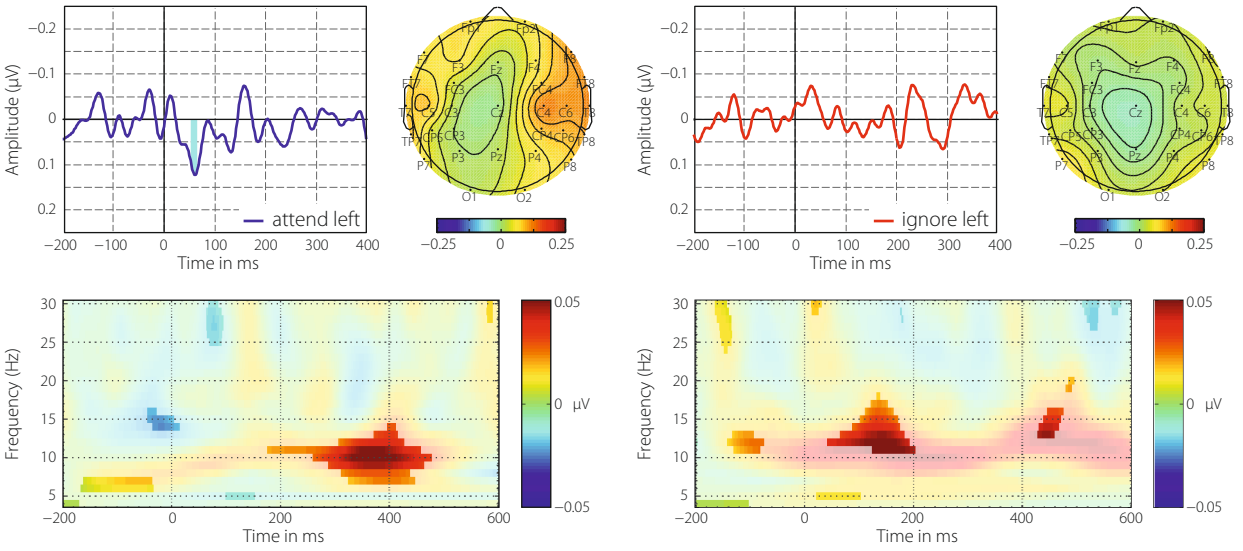

Figure 1.10 Upper: ERPs with topography for attend left (left side) and attend right (right side) condition show a P60 only for attend left. Lower: iTFR for attend left on the left and iTFR compared to baseline [-300 -100] for attend right on right panel. Areas with bright colours in TFR plots or cyan colour in ERP plot resemble significant variations from the chosen baseline, respectively (paired t-test, $p<0.05$).

(Jensen et al., 2012, Trends Cogn Sci, 16, 200–206), the time shifted Mu increases complement the ERP pattern. In conclusion, we argue that attention interacts differentially with unconscious cerebral stimulus processes, the P60 and sensorimotor alpha, and therefore these processes might have different functional implications.

1.11 Imperceptible somatosensory stimulation reshapes the functional architecture of primary somatosensory cortex

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Previously, we have shown that subliminal (imperceptible) somatosensory stimulation is associated with (behavioral) inhibition of the somatosensory system, an evoked potential (P60), and an increase in Mu rhythm strength (see also Forschack et al in this report). Here, we evaluated the effect of subliminal somatosensory stimulation on a network level employing functional connectivity MRI (fcMRI). Two sets of fcMRI experiments were conducted with healthy subjects, both involved electrical stimulation of the left index finger (every 4 ± 0.5 s) while measurement blocks of 180 volumes (6 min) were acquired. The first fMRI session consisted of two blocks, one resting-baseline block followed by a second block during which subliminal stimuli (intensity 15% below perception threshold) were applied. In the second fMRI session, in addition to resting-baseline and subliminal

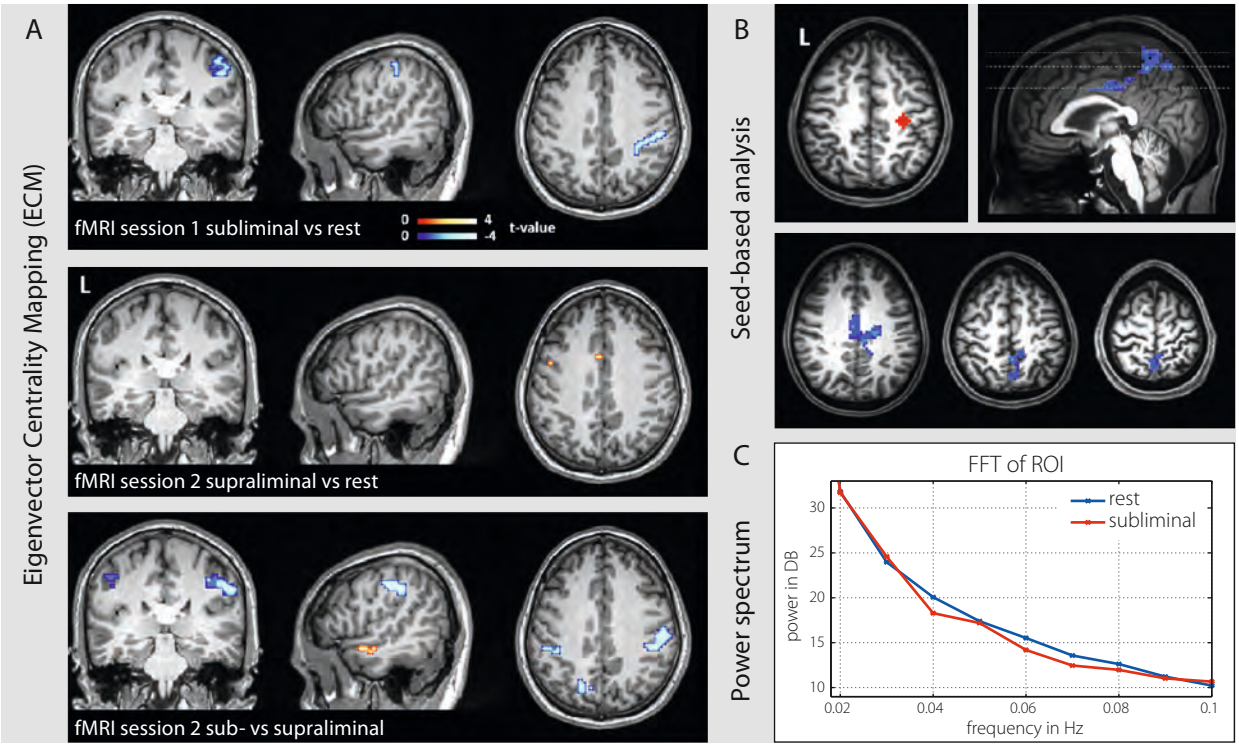

Figure 1.11 (A) Reduced functional connectivity of SI during subliminal stimulation revealed by ECM. Results of a paired t-test are shown for contrasting subliminal vs rest (upper plots), supraliminal vs rest (middle plots), and sub- vs supraliminal (lower plots). Warm colours indicate an increase, cold colours a decrease in centrality (slice coordinates x = 144, y = 121, z = 66). (B) Reduced connectivity of SI to medial parietal and midcingulate cortex revealed by seed-based functional connectivity. The seed location in area 3b of right SI is indicated in red in the upper left axial slice. Horizontal dashed lines in the sagittal slice indicate locations of the lower axial slices. Blue areas indicate decreased correlation to the seed region, resulting from a paired t-test contrasting functional connectivity maps of the subliminal stimulation block vs rest block (fMRI session 1). Light blue to dark blue means -min to -max. (C) Power-Spectrum of the time course of the area defined by the ECM results (decreased centrality in SI, fMRI session 1) for both, resting-state baseline (blue) and the subliminal stimulation (red). A reduction of the low frequency BOLD fluctuations in SI during subliminal stimulation can be observed (paired t-test $0.01 < f < 0.1$Hz, $p = 0.0489$).

stimulation, we acquired an additional block with supraliminal stimulation (intensity 50% above perception threshold). The order of sub- and supraliminal stimulation blocks was counterbalanced across subjects.

Eigenvector centrality mapping (ECM) revealed reduced whole-brain functional connectivity of SI during subliminal stimulation which—based on a seed-based analysis—seems mainly due to reduced connectivity to precuneus and midcingulate areas. In contrast, supraliminal stimulation did not affect functional connectivity of somatosensory areas. Furthermore, a decreased low-frequency intrinsic brain activity in SI during subliminal stimulation points towards a focal suppression of neuronal activity.

Together with our previous reports showing that subliminal stimulation increases the rolandic background rhythm (Nierhaus et al., submitted; Forschack et al. in this report), our findings collectively suggest a general mechanism by which subliminal sensory input reshapes a sensory system which may help to suppress irrelevant information and sharpen the sensory perception in space and time.

Subliminal visual stimuli elicit increases in alpha-band power

1.12

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It has been shown previously that undetectably weak somatosensory stimuli cause a functional inhibition in somatosensory cortex (Blankenburg et al., 2003, Science, 299, 5614–1864) which is associated with an increase in Mu rhythm strength. We tested whether invisible visual stimuli result in an equivalent neuronal inhibition indicated by an increase in alpha-band power. We investigated electrophysiological responses to subliminal and supraliminal visual stimuli after estimating each participant's detection threshold. Stimuli consisted of peripherally presented small circular patches displayed on a background consisting of a random white noise pattern (see Fig. 1.12.1).

We demonstrate that subliminal and supraliminal stimuli each elicit specific neuronal response patterns. Supraliminal stimuli evoked an early response representing the evoked potential and induced a decrease in alpha-band power from 400 ms onwards. By contrast, subliminal visual stimuli induced an increase of alpha-band power around 300 ms (see Fig. 1.12.2). This increased alpha-band response for stimuli that are invisible due to their low contrast points to an inhibitory mechanism for reducing spurious visual activation that is unlikely to result from external stimuli.

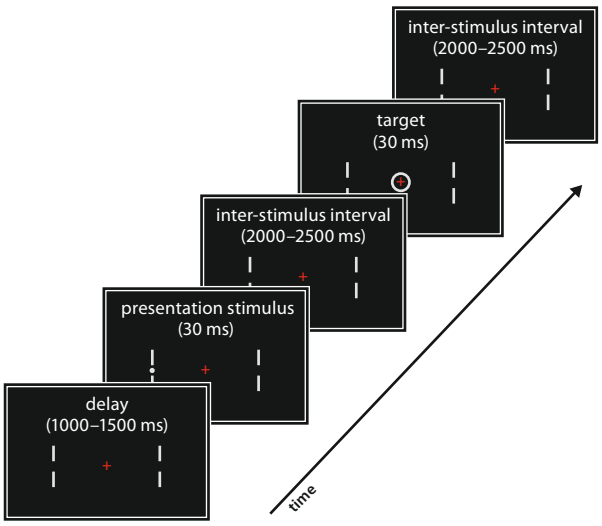

Figure 1.12.1 Illustration of the paradigm during electrophysiological recording. Trials started with the presentation of a fixation cross and peripheral markers. After a variable delay, supraliminal or subliminal stimuli were presented on two-thirds of the trials. The remaining were stimulus-absent blank trials. Participants were asked to count targets —non-filled circles—that were randomly interspersed at fixation between peripheral presentations.

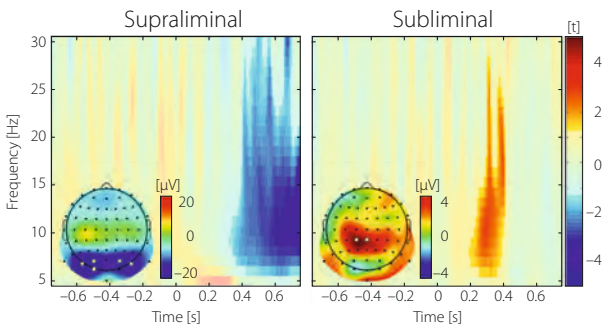

Figure 1.12.2 Analysis of oscillatory power. Electrodes with strongest alpha-power (8–12 Hz; 0–800 ms) are highlighted in the topographies for supraliminal and blank trials (left), as well as subliminal and blank trials (right). Time–frequency representation of event-related power changes were averaged across channels with strongest alpha-power, showing oscillatory responses to supraliminal stimuli (left), as well as subliminal stimuli (right) as compared to blank trials. Non-significant regions are dimmed to improve visibility of the significant time–frequency clusters.

1.13 Obesity is associated with general functional alterations in the fronto-striatal dopaminergic system

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Evidence has accumulated indicating that obesity is related to functional changes in the fronto-striatal dopaminergic system. To date, these alterations have been revealed in tasks that mainly focused on food-specific stimuli. Here we investigated whether obesity-related changes in the fronto-striatal system extend beyond the food context and relate to general alterations in dopaminergic signalling. Fifty-eight healthy lean and obese subjects matched for age and educational background performed 200 trials of the weather prediction task (WPT) (Knowlton et al., 1994, Learn Mem, 1, 106–120) in an event-related fMRI design. The WPT is a probabilistic classification learning task that has been widely used to assess the integrity of the fronto-striatal dopaminergic pathway (Shohamy et al., 2004, Behav Neurosci, 118, 676–686; Jahanshahi et al., 2010, Neuropsychologia, 48, 1096–1103). To relate functional alterations to a possible underlying dopaminergic pathology, task performance

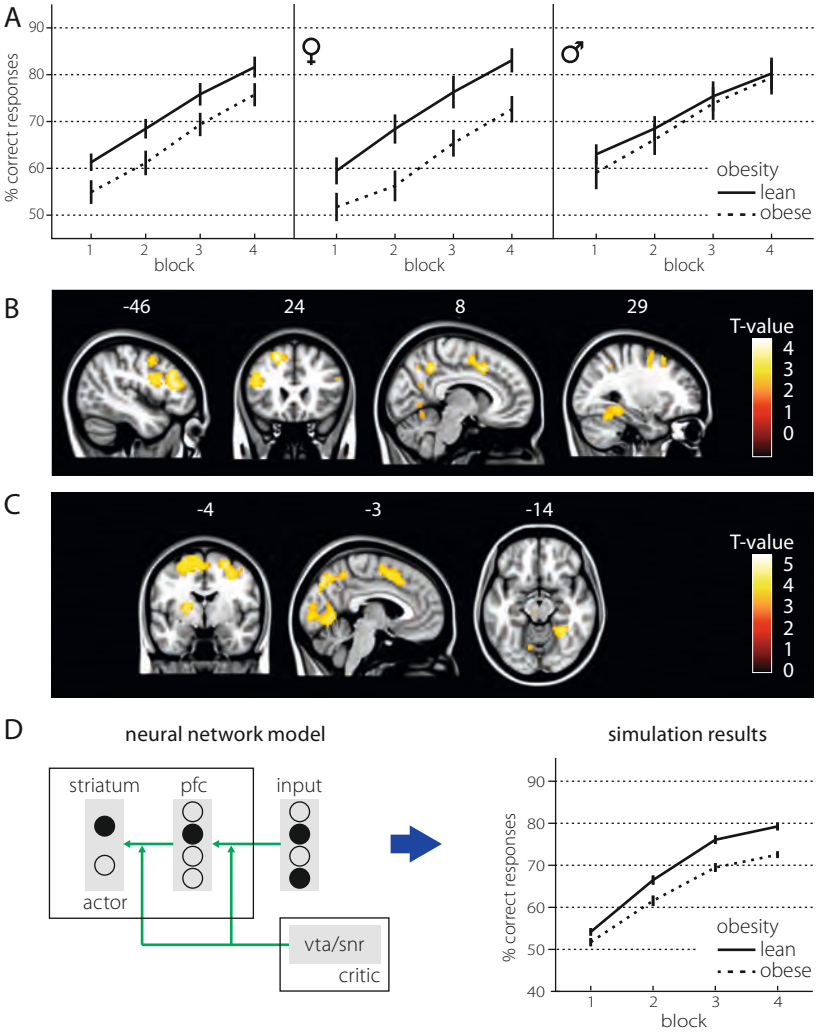

Figure 1.13 (A) Task performance (percentage of correct responses) of lean and obese participants over the four task blocks and separated for women and men. (B) Lean women revealed greater learning-related BOLD activation than obese women in lateral PFC and dACC among other regions. (C) Lean subjects recruited dorsal striatum, dACC, and parahippocampus more strongly with increasing stimulus complexity than obese subjects. (D) Simulating the impact of alterations in tonic and phasic dopamine signalling in striatum and PFC with a neural network model yielded learning curves that matched task performance of lean and obese women.

of obese and lean subjects was modelled using a modular neural network model (Moustafa et. al., 2010, J Cog Neuroscience, 23, 151–167) that simulates the impact of phasic and tonic dopamine signalling in prefrontal cortex and striatum during learning. Gender and impulsivity were included into our analyses to investigate possible modulatory effects.

Behavioural results show that obesity is associated with a decreased classification learning performance throughout the task (Fig. 1.13A). This was related to a lower information exploitation from complex stimulus patterns and a more random-like response behaviour in obese compared with lean subjects. High trait impulsivity aggravated this effect. Neuroimaging results link behavioural alterations to a lower BOLD activation for lean compared with obese subjects within the fronto-striatal system (Fig. 1.13B,C), including lateral prefrontal cortex, dorsal anterior cingulate, and dorsal striatum. Obesity-related differences in BOLD activation and behaviour were more pronounced in female subjects. Simulating learning performance of obese and lean women (Fig. 1.13D) by means of a neural network model points at an imbalance between tonic and phasic dopamine transmission in obese women as a possible underlying pathology. Our findings show for the first time that obesity is associated with general functional alterations in the fronto-striatal system and that these changes may translate to alterations in dopamine transmission.

Feedback processing and reinforcement learning in obesity

1.14

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Positive and negative action consequences are a powerful source of information to successfully adapt to changing environments. Previous studies have reported that obesity is associated with altered neural responses during the anticipation and receipt of positive and negative feedback. In this study we investigated whether obesity-related differences in reinforcement processing affect learning from positive and negative feedback.

Learning performance and evoked heart rate (HR) as an indicator of feedback processing were measured while obese (BMI ≥30 kg/m^2) and lean (BMI 18.5–24.9 kg/m^2) adults performed a probabilistic learning task. Subjects learned to choose between a high and low feedback probability option based on monetary feedback in separate gain, loss, and neutral conditions. Feedback-related evoked HR was analyzed using three inter-beat-intervals (IBI) around the time of feedback presentation (IBI –1, IBI 0, IBI +1).

The analysis of an initial sample of 17 obese and 18 lean subjects revealed that obese individuals exhibited a decreased learning performance in both monetary gain and loss trials (Fig. 1.14A). Monetary loss was associated with a HR deceleration that was strongest in the early phase of the task and significantly more pronounced in lean than in obese subjects. Importantly, group differences were found in particular after choosing the dis-

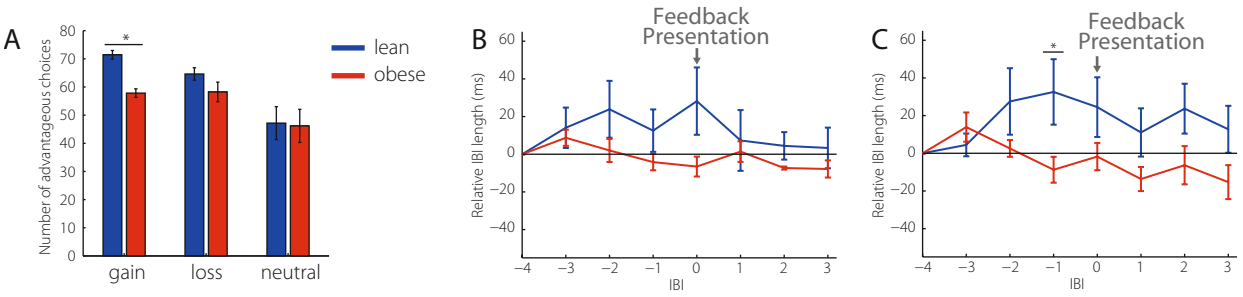

Figure 1.14 Learning performance and evoked heart rate responses to monetary feedback in lean and obese individuals. (A) Number of advantageous choices in the monetary gain, loss, and neutral condition. (B) Evoked heart rate when receiving a monetary gain after choosing the disadvantageous gain option. (C) Evoked heart rate when receiving monetary loss after choosing the disadvantageous loss option.

advantageous gain and loss option, which provided a high informative value. Lean subjects showed a stronger HR deceleration than individuals with obesity when receiving an unexpected gain after choosing the low gain probability option (Fig. 1.14B) as well as before monetary losses when they had chosen the high loss probability option (Fig. 1.14C). Our results suggest that obesity is associated with an altered feedback monitoring system leading to impairments in the utilization of learning-relevant positive and negative feedback and decreased associative learning.

1.15 Exercise impacts brain structure: A longitudinal VBM and TBSS study in overweight and obese subjects

Mueller, K.[1], Möller, H. E.[1], Anwander, A.[1], Busse, F.[1], Horstmann, A.[1,2], Lepsien, J.[1], Schroeter, M. L.[1,3], Blüher, M.[2], Villringer, A.[1,2,3], & Pleger, B.[1,3]

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A growing number of studies combining structural magnetic resonance (MR) brain imaging with voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) suggest that obesity is associated with altered grey and white matter structure. What remains less clear is whether these structural alterations are the cause or consequence of the elevated body weight. To address this question we conducted a longitudinal brain imaging study on 16 overweight and obese subjects who participated in an intense physical training over a period of three months.

Comparing structural images before and after intense training, we showed grey matter density (GMD) increase in the left hippocampus, insula, and cerebellum, which provides evidence for an impact of physical exercise on brain structure (Fig. 1.15). In addition, we detected white matter differences with an increase of fractional anisotropy (FA) in the vicinity of the observed GMD increase. Various studies observed a decreased FA in obese subjects particularly in the corpus callosum while an elevated radial diffusivity was found in women. Interestingly, we also detected a decrease of radial diffusivity with physical exercise in wide brain regions including the whole corpus callosum. The way in which physical exercise affected grey and white matter structures suggests an impact of physical exercise on overweight-related changes in brain structure, even within a relatively short time period of three months.

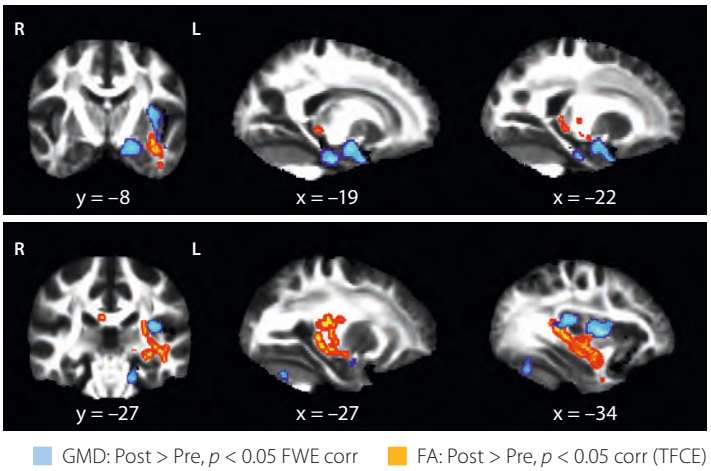

Figure 1.15 Significant increase of grey matter density (GMD, colour-coded in blue) and fractional anisotropy (FA, colour-coded in red/yellow) in overweight and obese subjects comparing images of two scanning sessions before and after a period of three months of physical exercise. Analysis was performed with a group of 16 young overweight and obese volunteers (9 female, age 27.2±6.7 years, BMI 33.6±5.9 kg/m^2, mean±standard deviation).

Don't look back in anger: Emotion regulation in the context of vascular health

1.16

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Our goal is to understand the relation between anger and its modulation by emotion regulation strategies on vascular reactivity, particularly on blood pressure and heart rate. So far, despite extensive previous work on anger regulation on the experiential level with regard to social functioning and well-being (e.g. Denson et. al., 2012, Behav Ther, 43, 355–356), this information has been missing. We investigated the impact of four emotion regulation strategies, namely cognitive reappraisal, distraction, suppression, and angry rumination, which are hypothesized to be anticlimactically adaptive on anger experience and vascular reactivity. In this between-subject two-session study, anger was induced in 79 young men (M = 24.74, SD = 3.11) with a standardized real-life provocation method developed by Stemmler et al. (2001, Psychophysiology, 38, 275–291). On the following day, participants recalled the anger-inducing experience and were given standardized regulation instructions in one of the four possible emotion regulation strategies. The measurement of relevant personality traits controlled for sub-sample heterogeneity. Emotion self-reports and continuous blood pressure responses were assessed in the two sessions. Cognitive reappraisal decreased, whereas suppression and angry rumination increased anger experience (F (3, 58) = 6.99, p = .000). While results of the distraction emotion regulation strategy and blood pressure analyses revealed solely non-significant trends, the *a priori* contrast of angry rumination versus the remaining conditions was confirmed for self-reported anger (t (63) = –2.67, p = .01) (t (63) = –2.67, p = .01) and diastolic blood pressure level (t (63) = –2.32, p = .024), revealing the maladaptive nature of angry rumination. With the achievement of establishing a highly standardized experimental design, which provides a promising basis for future studies on the impact of different anger regulation strategies on psychological and physiological parameters, this study might be the first step towards new prevention- and intervention approaches implementing emotion-regulation training (Suls, 2013, Prog Cardiovasc Dis, 55, 538–547; DiGuiseppe & Tafrate, 2003, Clin Psychol Sci Practice, 10, 70–84).

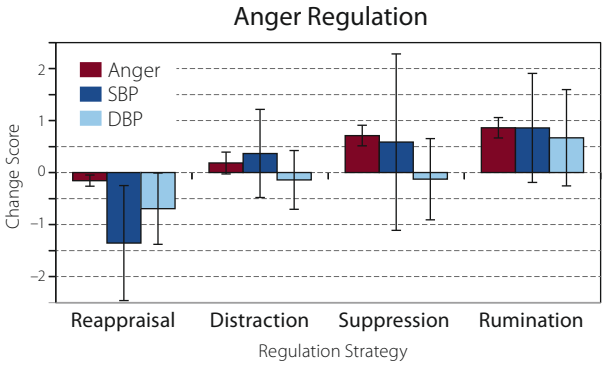

Figure 1.16 Changes from baseline in anger experience and systolic (SBP) and diastolic blood pressure (DBP) as a function of emotion regulation condition. Error bars display standard errors.

Degree centrality mapping reveals widespread change in functional brain connectivity following a single dose of selective serotonin reuptake inhibitor

1.17

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The serotonin transporter (5-HTT) is essential to maintaining adequate brain serotonin homeostasis, and alteration of its function has been linked to heightened susceptibility for depression and anxiety (Holmes et al., 2003, Biol Psychiatry, 54, 953-959). Differences in the 5-HTT genotype have also been recently related to variation in intrinsic functional brain organization (Li et al., 2012, PLoS One, 7, e36513). Preliminary evidence sug-

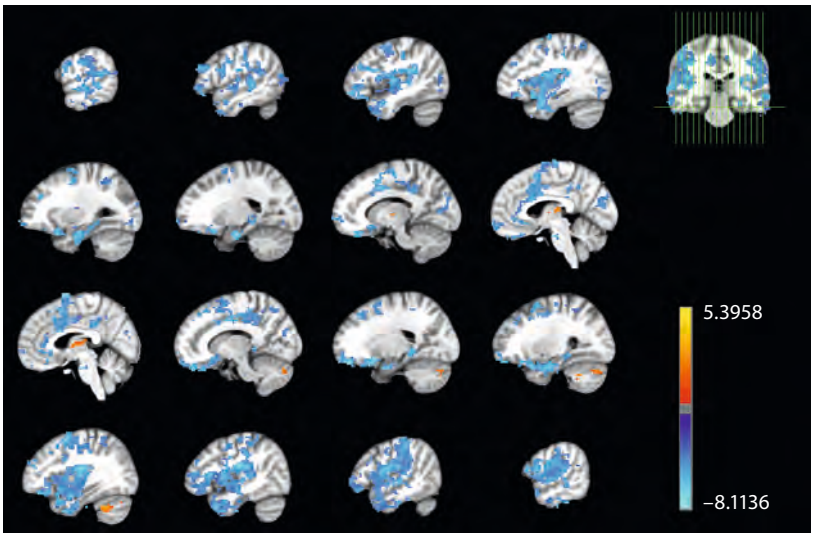

Figure 1.17 The effect of a single dose of a serotonin reuptake inhibitor (SSRI) onto intrinsic brain connectivity compared to a placebo. Sagittal slices show widespread reductions (blue) of connectivity in the cerebrum, and increases of connectivity (orange) in thalamic and cerebral areas. Green lines in the coronal view (top right) indicate the position of the sagittal slices. Effects are significant at p = 0.01, whole-brain cluster corrected.

gests a link between the serotonergic system and intrinsic brain activity. However, the extent to which the brain's functional organization is modulated by serotonin is not known. Here we demonstrate that a single dose of a selective serotonin reuptake inhibitor (SSRI) dramatically alters intrinsic functional connectivity throughout the human brain. Degree centrality (DC) mapping of resting-state functional magnetic resonance imaging (rsfMRI) data was applied to 21 individual data-sets of healthy, anti-depressant naive participants following a single oral dose of the selective serotonin reuptake inhibitor (SSRI) escitalopram in a randomized placebo-controlled design. DC-analysis revealed a widespread decrease in connectivity in most cortical and subcortical areas, with the exception of localized increases in cerebellar and thalamic regions (p = 0.01, cluster corrected), following the oral intake of a single dose of 20 mg escitalopram. The increase in connectivity found in the thalamus and cerebellum may be of particular relevance for the excitability of the many serotonergic projection neurons that terminate in the thalamus. By cerebellar modulation these neurons can turn from burst into tonic mode, a mechanism hypothesized to alert cortical networks. Our findings are the first to directly link a single dose of an SSRI to a global change of intrinsic functional connectivity in the human brain. The evidence we present for this acute and global change in functional connectivity following a single dose of escitalopram suggests there is much to be learned about the neurochemical systems underlying large-scale network coordination, and also provides a first step towards identifying noninvasive neural biomarkers for individual responsivity of the human brain to serotonergic modulation.

1.18 Identifying the perfusion deficit in acute stroke with resting-state functional magnetic resonance imaging

Lv, Y.[1,2], Margulies, D. S.[1,2], Craddock, C.[5], Long, X.[1], Winter, B.[3,4], Gierhake, D.[3,4], Endres, M.[2,3,4,6], Villringer, K.[3,4], Fiebach, J.[3,4], & Villringer, A.[1,2,3,4]

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Perfusion and diffusion magnetic resonance imaging (MRI; perfusion-weighted imaging: PWI; diffusion-weighted imaging: DWI) are employed in clinical practice and in research to identify pathophysiological patterns in patients with acute stroke (Dani et al., 2011, Ann Neurol, 70, 384–401; Merino et al., 2010, Nat Rev Neurol, 6, 560–571; Sorensen et al., 1996, Radiology, 199, 391–401; Wardlaw et al., J Int Med, 267, 172–190). DWI

is thought to roughly reflect the severely damaged infarct core, whereas PWI reflects the area of hypoperfusion. Their volumetric difference is also termed the PWI/DWI mismatch, and has been suggested as an MRI surrogate of the ischemic penumbra (Karonen et al., 1999, Stroke, 30, 1583–1590; Schlaug et al., 1999, Neurology, 53, 1528–1537). However, the major drawback of PWI is that it requires the application of contrast agent (Rosen et al., 1990, Magn Reson Med, 14, 249–265; Villringer et al., 1988, Magn Reson Med, 6, 164–174), which has potentially severe side effects, and also precludes repetitive examinations for monitoring purposes. In this study we use rsfMRI as a new approach to give similar pathophysiological information to that given by PWI in the acute phase of stroke.

Data were acquired from 17 patients with acute ischemic stroke at 1 day after stroke onset, and 1 healthy participant. Data acquisition included: (1) DWI, (2) PWI, and (3) resting-state fMRI.

Time-shift analysis (TSA): For each voxel in the brain, we shifted the time course from –3*TR to 3*TR and correlated it with the average model time course at each TR. Each voxel was then assigned a value based on the time shift required for the maximal correlation coefficient (Fig. 1.18.1).

In all 11 patients, TSA showed areas with a pronounced time delay relative to the respective mean time course (Fig. 1.18.2). Overall, these areas corresponded to the areas of hypoperfusion as identified by MTT maps and not to the infarct cores (DWI). In the healthy brain, the areas showing a clear time delay to the global mean were symmetrically distributed and located within the ventricles and white matter.

We successfully used rsfMRI to identify hypoperfused areas in acute stroke. We suggest that an assessment of time delays of the spontaneous low frequency fluctuations of the BOLD signal may provide information comparable to that provided by parameters of contrast-based perfusion MRI, and thus serve as a useful diagnostic tool for stroke MRI.

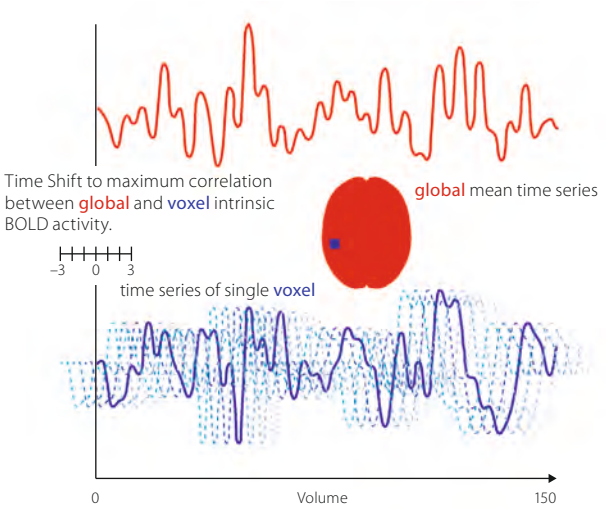

Figure 1.18.1 Illustration of the basic methodology for the time-shift analysis (TSA).

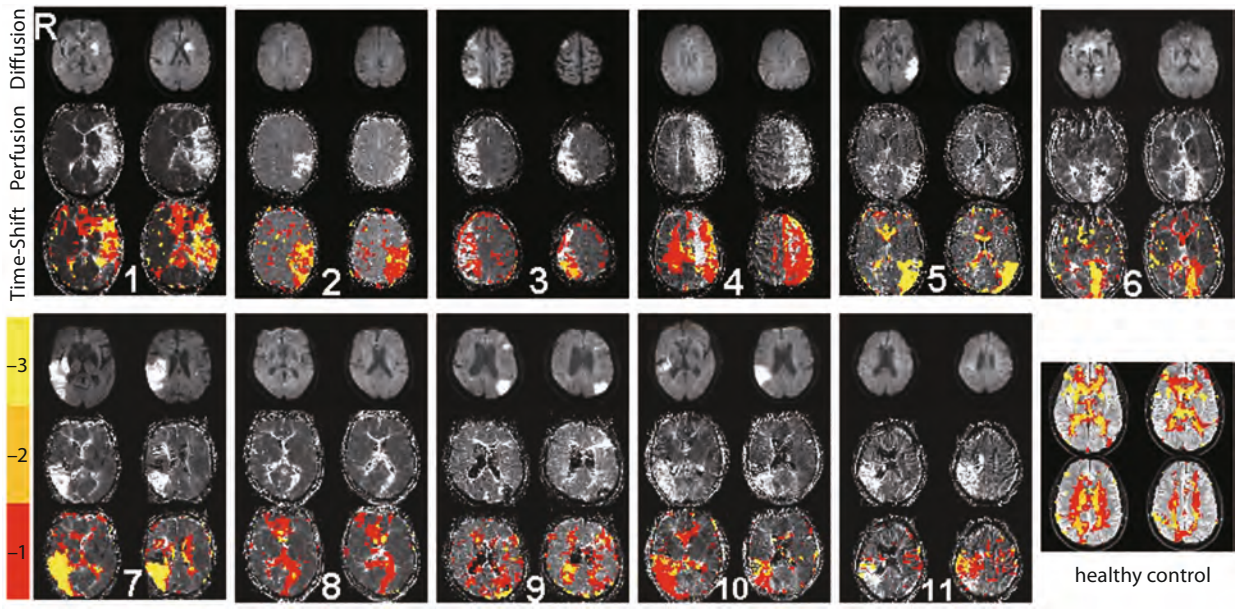

Figure 1.18.2 Time-shift analysis (TSA) results of 11 stroke patients and 1 healthy control with time-shift range from –3 TR to +3 TR. In 11 patients, areas affected by the ischemic stroke (hypoperfused) show a pronounced time delay to the global mean time course. In 1 healthy control, the time-lagged areas were approximately symmetrically distributed within ventricular areas. –1, –2, –3 in colour bar indicate –1 TR, –2 TR, –3 TR time shift.

1.19 Longitudinal effects of lesions on functional networks after stroke

Ovadia-Caro, S.[1,2,3], Villringer, K.[4,5], Fiebach, J.[4,5], Jungehulsing, J. G.[4,5], van der Meer, E.[2,3], Margulies, D. S.[1,2], & Villringer, A.[1,2,4]

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This work was carried out in collaboration with the group "Neuroanatomy & Connectivity".

While ischemic stroke reflects focal damage determined by the affected vascular territory, clinical symptoms are often more complex and may be better explained by additional, indirect effects of the focal lesion. Assumed to be structurally underpinned by anatomical connections, supporting evidence has been found using alterations in functional connectivity of resting-state fMRI data in both sensorimotor and attention networks. In order to assess the generalizability of this phenomenon in a stroke population with heterogeneous lesions, we investigated the distal effects of lesions on a global level. Longitudinal resting-state fMRI scans were acquired at three consecutive time points, beginning during the acute phase (days 1, 7, and 90 post-stroke) in 12 patients following ischemic stroke. Individual lesions were mapped into affected/unaffected networks based on overlap of lesion masks and a template of eight previously published independent networks (Beckmann et al., 2005, Philos Trans R Soc Lond B Biol Sci, 360, 1001–1013). In order to assess the stability of the functional networks over time for each individual, we used dual regression analysis based on the templates. Correlation concordance coefficient of the resulting network maps was used to quantify the functional change over the time points. We found a preferential functional change in affected networks (i.e. networks containing lesions changed more during recovery when compared with unaffected networks). This change in connectivity was further significantly correlated with clinical changes assessed with the NIHSS. Our results provide evidence that the functional architecture of large-scale networks is critical to understanding the clinical effect and trajectory of post-stroke recovery.

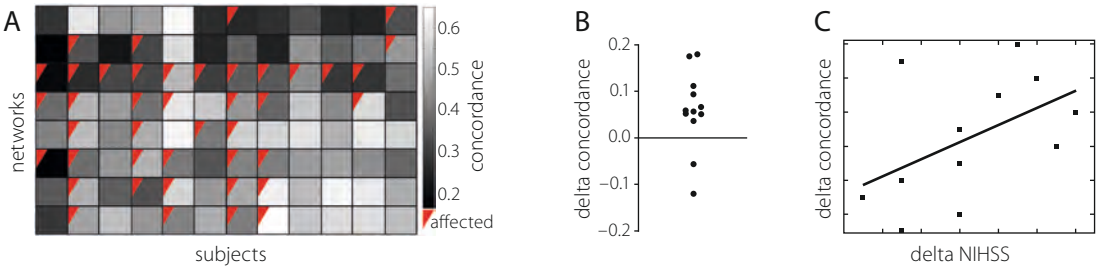

Figure 1.19 Changes in functional connectivity are enhanced in affected versus unaffected networks. (A) Spatial concordance as computed over time for each patient (x-axis) and for each network (y-axis). High values reflect a small change in the functional connectivity pattern. Red triangles depict affected networks. (B) Delta concordance (μ(unaffected)-μ(affected)) was computed for each patient demonstrating a significant positive distribution as tested by one-sample t-test. (C) Relationship between delta concordance and clinical change. Positive correlation between changes in clinical scores over time as measured by delta NIHSS (x-axis) and changes in functional connectivity as measured by delta concordance (y-axis). Both axes depict the ranked values (as Spearman's correlation was applied to statistically test the relationship). Black line depicts the fitted regression line.

Conceptualizing neuropsychiatric diseases with multimodal data-driven meta-analyses: The case of behavioural variant frontotemporal dementia

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[6] Integrated Research and Treatment Center (IFB) Adiposity Diseases, Leipzig, Germany

Uniform coordinate systems in neuroimaging research have enabled comprehensive systematic and quantitative meta-analyses. Such approaches are particularly relevant for neuropsychiatric diseases, the understanding of their symptoms, prediction, and treatment. Behavioural variant frontotemporal dementia (bvFTD), a common neurodegenerative syndrome, is characterized by deep alterations in behaviour and personality. Investigating this disease elucidates the healthy social and emotional brain. Here, we combine three multimodal meta-analyses approaches—anatomical and activation likelihood estimates and behavioural domain profiles—to identify neural correlates of bvFTD in 417 patients and 406 control subjects and to extract mental functions associated with this disease by meta-analyzing functional activation studies mainly from the comprehensive probabilistic functional brain atlas of the BrainMap database in approximately 42,000 healthy subjects. The analyses identify the frontomedian cortex, basal ganglia, anterior insulae, and thalamus as most relevant hubs, with a regional dissociation between atrophy and glucose hypometabolism (Fig. 1.20.1). Neural networks affected by bvFTD were associated with emotion and reward processing, empathy, and executive functions (mainly inhibition), suggesting these functions as core domains affected by the disease and finally leading to its clinical symptoms (Fig. 1.20.2). In contrast, changes in theory of mind or mentalizing abilities seem to be secondary phenomena

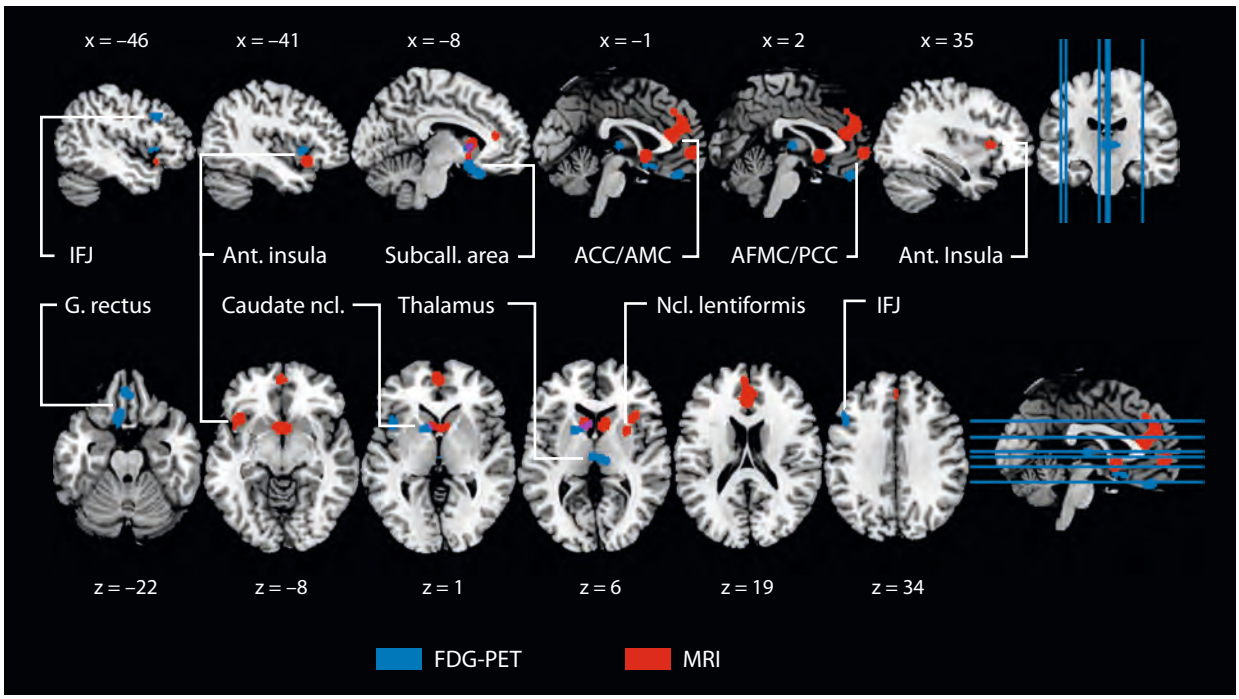

Figure 1.20.1 Impaired brain regions in bvFTD in comparison with healthy control subjects—anatomical likelihood estimates. Atrophy as measured by MRI red, hypometabolism as measured by FDG-PET blue, overlap pink. Nine MRI and 11 FDG-PET studies. Left is left. MNI coordinates. Acc. accumbens, ACC/AMC anterior cingulate and midcingulate cortex, AFMC/PCC anterior frontomedian/paracingulate cortex, Ant. anterior, FDG-PET 18F-fluorodeoxyglucose positron emission tomography, G. gyrus, IFJ inferior frontal junction, MNI Montreal Neurological Institute, MRI magnetic resonance imaging, Ncl. nucleus, Subcall. subcallosal.

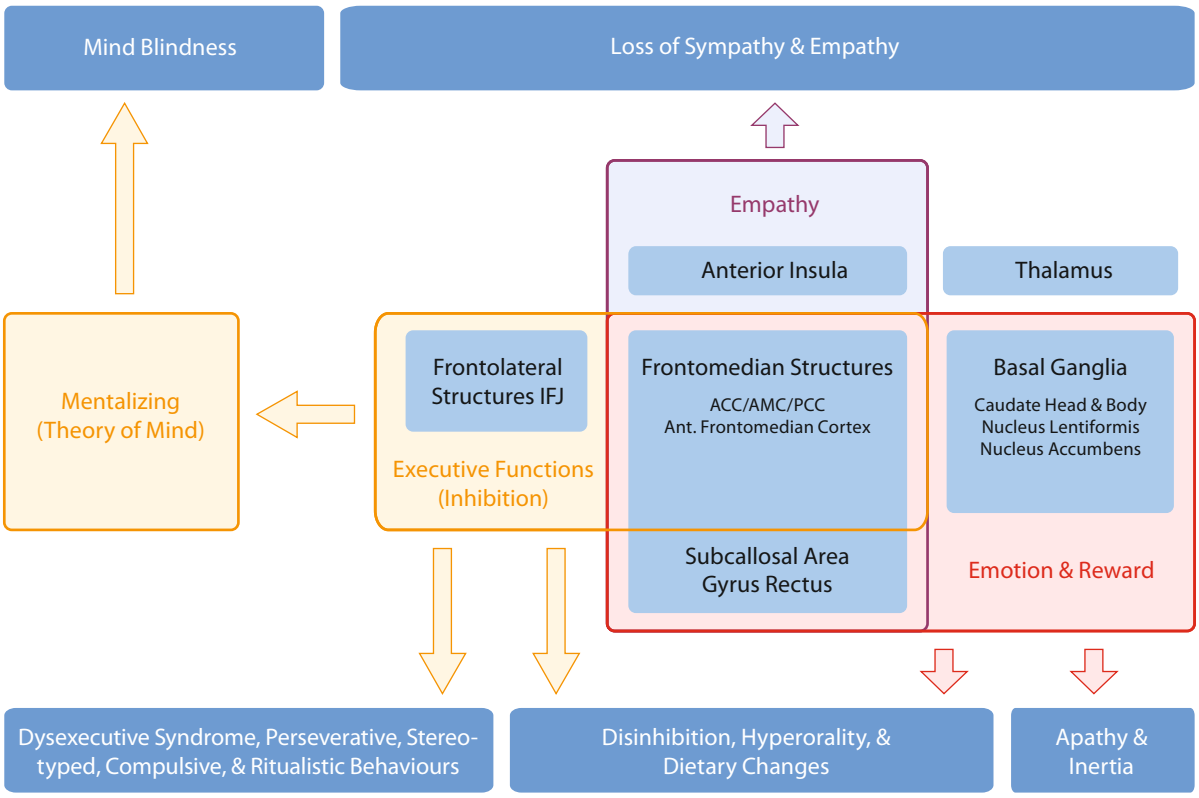

Figure 1.20.2 Conceptualizing bvFTD with combined meta-analyses. The figure illustrates brain regions involved in the disease (light blue), their related cognitive and behavioural correlates (orange, purple, and red), and clinical symptoms (dark blue). ACC/AMC anterior cingulate and midcingulate cortex, Ant. anterior, IFJ inferior frontal junction, PCC paracingulate cortex.

of executive dysfunctions. The study creates a novel conceptual framework to understand neuropsychiatric diseases by powerful data-driven meta-analytic approaches that will be extended to the whole neuropsychiatric spectrum in the future.

1.21 Validating MRI imaging data with serum biomarkers and the whole genome gene expression database of the Allen Human Brain Atlas

Schroeter, M. L.[1,2], Mueller, K.[1], Streitbürger, D. P.[1], Arelin, K.[1], Sacher, J.[1], Holiga, S.[1], Kratzsch, J.[3], & Villringer, A.[1,2]

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Former studies have investigated the potential of serum biomarkers for diseases affecting the human brain. In particular the glial protein S100B, a neuro- and gliotrophin inducing plasticity, seems to be involved in the pathogenesis and treatment of psychiatric diseases such as major depression and schizophrenia. Neuron-specific enolase (NSE) is a (presumably) specific serum marker for neuronal damage. However, the specificity of these biomarkers for cell type and brain region has not been investigated *in vivo* until now. We acquired magnetic resonance imaging parameters sensitive to changes in grey and white matter (T1-weighted/diffusion tensor imaging) and obtained serum S100B and NSE levels. Additionally, we analyzed whole brain gene expressions of S100B and NSE in another cohort using the Allen Human Brain Atlas. The glial serum marker S100B was specifically related to white matter structures, namely the corpus callosum, anterior forceps, and superior longitudinal fasciculus (Fig. 1.21.1). This effect was observed in fractional anisotropy and radial diffusivity—an indicator of myelin changes. Histological data confirmed a co-localization of S100B with oligodendrocyte markers in

the human corpus callosum. The neuronal marker NSE was related to grey matter density in the amygdalae in healthy subjects, and cerebellar grey matter density in young obese subjects (Fig. 1.21.2). S100B was most abundantly expressed in the corpus callosum and NSE in the cerebellum according to the whole genome Allen Human Brain Atlas. Combining MRI imaging data with cell specific serum biomarkers and the whole genome gene expression database of the Allen Human Brain Atlas opens new perspectives to validate the specificity of imaging markers and serum biomarkers *in vivo*, particularly in major neuropsychiatric disorders.

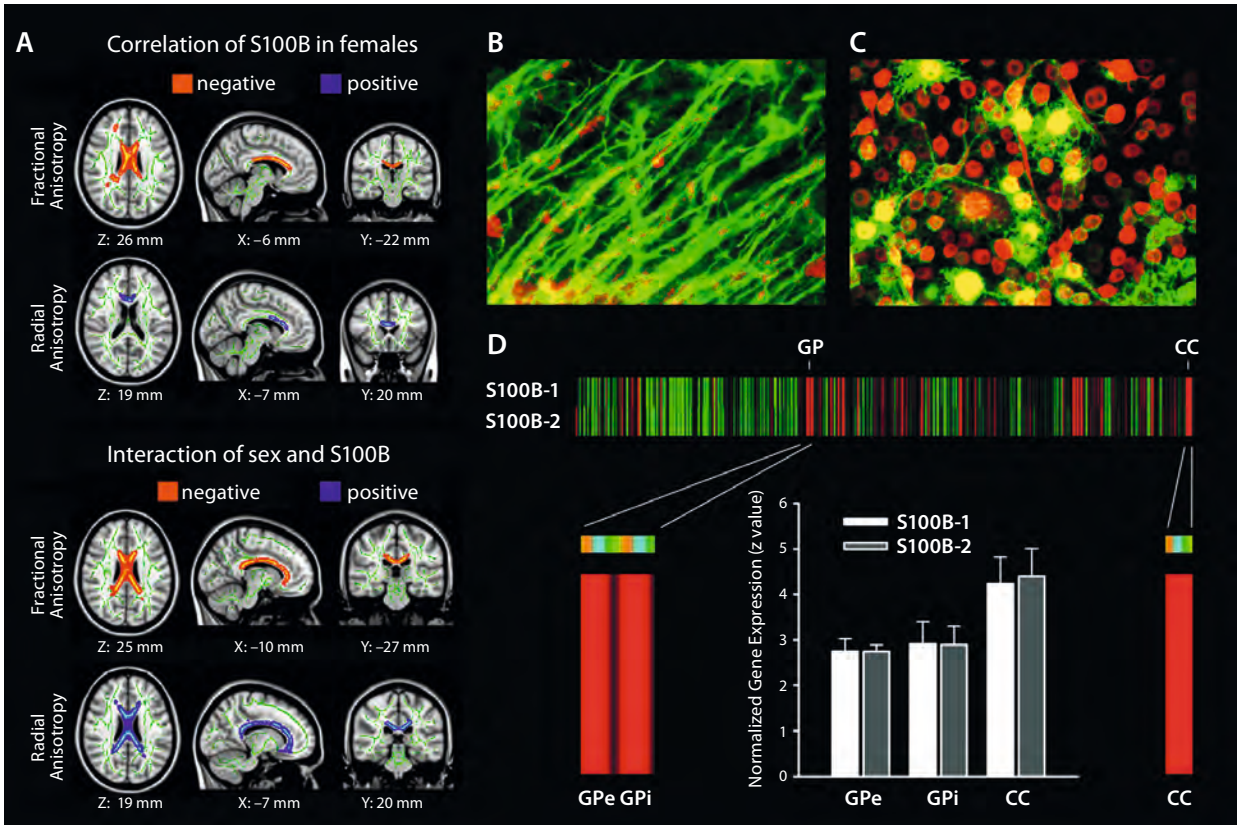

Figure 1.21.1 Associations between S100B and the brain. (A) Diffusion tensor imaging parameters correlate with serum S100B in white matter structures of the female brain (upper row) and in comparison with male brains (lower row). (B-D) Expression and localization of S100B in the human brain and in cultured oligodendrocytes. Co-localization (yellow) of S100B (red) and oligodendrocyte specific markers (green) in (B) the human corpus callosum and in (C) the oligodendrocyte cell line OLN-93. (D) Individual normalized gene expression of S100B in heat map in z scores normalized to whole human brain expression. Highest expression (red) was detected in the corpus callosum (CC), followed by globus pallidus (GP). Bar chart shows quantitative values in CC and external/internal (e/i) GP (mean±SD).

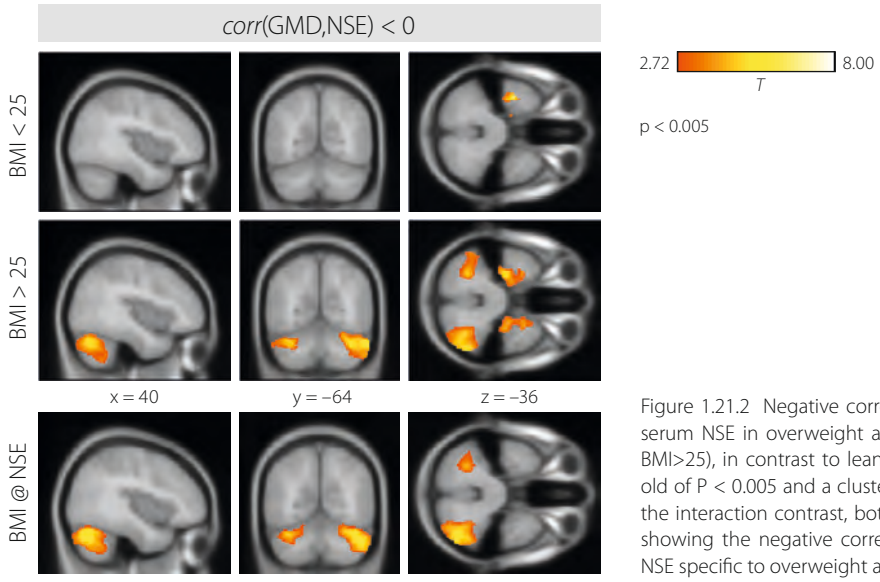

Figure 1.21.2 Negative correlation between grey matter density and serum NSE in overweight and obese participants (body mass index, BMI>25), in contrast to lean subjects (BMI<25), using a voxel threshold of P < 0.005 and a cluster threshold of P < 0.05, FDR-corrected. In the interaction contrast, both cerebellar clusters remained significant showing the negative correlation between grey matter density and NSE specific to overweight and obese subjects.

1.22 Perceptual decision making: Equivalence of drift-diffusion and Bayesian models

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When subjects perform the experimental task to categorize noisy stimuli as quickly as possible, they tend to make errors and their reaction times (RT) vary greatly. A simple mechanism can account for the observed accuracy and RT distributions: So-called drift-diffusion models accumulate noisy pieces of evidence towards a decision bound (Smith & Ratcliff, 2004, Trends Neurosci, 27, 161–168). Single neuron evidence for this mechanism has been found in the lateral intraparietal cortex of non-human primates (Gold & Shadlen, 2007, Ann Rev Neurosci, 30, 535–574).

Recently, Bayesian models have been proposed to explain how information is extracted from noisy input as typically presented in perceptual decision making tasks (e.g. Drugowitsch et al., 2013, J Neuroscience, 32, 3612–3628). It has long been known that drift-diffusion and Bayesian models of perceptual decision making are tightly linked, but the precise relationship between the two mechanisms remains unclear. Elucidating this link may be useful for deepening our understanding of how the brain makes perceptual decisions and also for developing advanced quantitative models of decision making. Using a novel Bayesian model, we derived equations which relate parameter values between models exactly and showed that this equivalence also holds in practice when fitting data.

Our results show that the Bayesian model is an adequate description of the hypothesized accumulation mechanism. In contrast to the drift-diffusion model, the Bayesian model lends itself to a large variety of extensions from which new experiments for testing novel hypotheses will be derived. For example, the Bayesian model considers the particular stimuli given to subjects and can, in principle, predict single-trial responses. This would be highly useful for developing new analysis methods that fit the behavioural data with unprecedented accuracy.

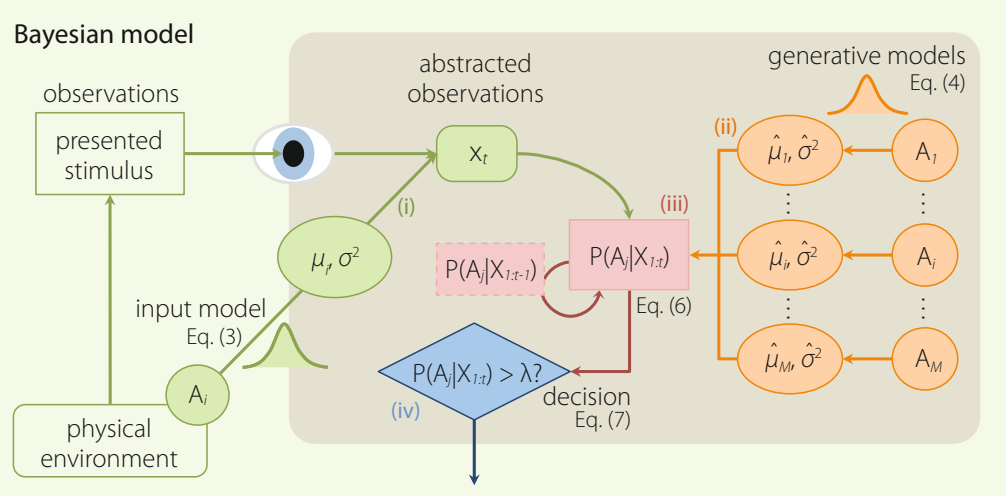

Figure 1.22 Schematic of Bayesian model of perceptual decision making. The stimulus at time *t* is modelled by a Gaussian distributed feature value x_t with mean μ and standard deviation σ. Decision makers observe the noisy feature values (green) over time and use Bayesian inference to compute posterior beliefs (red) about the stimulus from their prior beliefs and their internal, generative models (orange) of the different stimuli. When decision makers reach a certain value of posterior belief (λ), which indicates sufficient confidence, they commit to a decision (blue).

Congresses, Workshops, and Symposia

2012

Neumann, J. (October). *Cognitive Science Center Amsterdam MSC Research Visit*. Workshop. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Villringer, A. (January). *Competence Network Stroke:* White Matter Lesions – die kognitiven Folgen unerkannter Schlaganfälle *[White matter lesions – cognitive implications of undetected stroke]*. Symposium. Meeting of Neuro Intensive Medicine (ANIM). Symposium. Deutsche Gesellschaft für NeuroIntensivMedizin and Notfallmedizin [German Society for Neuro Intensive Medicine and Emergency Medicine] (DGNI), Deutsche Schlaganfall-Gesellschaft [German Stroke Society] (DSG), Berlin, Germany.

Villringer, A. (November). *3. Prophylaxe-Seminar des Kompetenznetzes Schlagfanfall [3rd Prophylaxis Seminar of the Competence Network Stroke]*. Symposium. Competence Network Stroke, Leipzig, Germany.

2013

Babayan, A.. (March). *Mind-Brain Symposium*. Brain Awareness Week. Berlin, Germany.

Horstmann, A., & Pleger, B. (March). *Obesity and associated changes in brain and behaviour*. Workshop. 57. Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und funktionelle Bildgebung [57th Annual Meeting for the German Society of Clinical Neurophysiology] (DGKN), Leipzig, Germany.

Villringer, A. (March). *5. Internationales Schlaganfallsymposium, Kompetenznetz Schlaganfall (KNS) & Centrum für Schlaganfallforschung Berlin (CSB) [5th International Stroke Symposium, Competence Network Stroke & Centre for Stroke Research Berlin]*. Symposium. Competence Network Stroke, Leipzig, Germany.

Okon-Singer, H. (August). *Control of Emotional Reactions*. Symposium. 18th Annual Meeting of the European Society for Cognitive Psychology (ESCoP), Budapest, Hungary.

Pleger, B. (August). *The human somatosensory system – from perception to decision making*. Workshop. FENS-IBRO Imaging Training Center (ITC), Lausanne, Switzerland.

Aue, T. & Okon-Singer, H. (September). *Neural mechanisms underlying positive and negative cognitive biases in emotion*. Symposium. 53rd Annual Meeting of the Society for Psychophysiological Research (SPR). Florence, Italy.

Luck, T., & Schroeter, M. L. (September). *Epidemiologie neurologischer & psychischer Erkrankungen – Kognition [Epidemiology of Neurological & Psychiatric Disorders – Cognition]*. Symposium. 8th Annual Meeting of the German Society for Epidemiology, Leipzig, Germany.

Horstmann, A., & Preissl, H. (October). *Basic Science Session*. Workshop. 29. Jahrestagung der Deutschen Adipositas-Gesellschaft [29th Annual Meeting of the German Obesity Society] (DAG), Hannover, Germany.

Schroeter, M. L., & Walter, H. (November). *Kritische Philosophie der Neurowissenschaften [Critical Philosophy of Neuroscience]*. Symposium. Annual Meeting of the German Association for Psychiatry and Psychotherapy (DGPPN), Berlin, Germany.

Villringer, A. (January). *Competence Network Stroke: Innovative Bildgebung beim Schlaganfall [Innovative imaging in stroke]*. Symposium. Meeting of Neuro Intensive Medicine (ANIM). Symposium. Deutsche Gesellschaft für NeuroIntensivMedizin and Notfallmedizin [German Society for Neuro Intensive Medicine and Emergency Medicine] (DGNI), Deutsche Schlaganfall-Gesellschaft [German Stroke Society] (DSG), Mannheim, Germany.

Villringer, A. (November). *4. Prophylaxe-Seminar des Kompetenznetzes Schlagfanfall [4th Prophylaxis Seminar of the Competence Network Stroke]*. Symposium. Competence Network Stroke, Leipzig, Germany.

Appointments

2013 Horstmann, A. *Group leader.* Integrated Research and Treatment Center (IFB), Federal Ministry of Research and Research (BMBF), Germany.

Pleger, B. *W2 Professorship*. University of Leipzig, Germany.

Sacher, J. *Group leader.* Branco Weiss Fellowship Society in Science. ETH Zürich, Switzerland.

2012 Kiebel, S. J. *W3 Professorship*. Friedrich Schiller University Jena, Germany.

Schroeter, M. L. *APL Professorship*. University of Leipzig, Germany.

Obrig, H. *APL Professorship*. University of Leipzig, Germany.

Awards

2013 Okon-Singer, H. *Fellowship Award*. Marie Curie Foundation, EU.

2012 Frisch, S., Quinque, E. M., Arelin, K., Dukart, J., Roggenhofer, E., Streitbürger, D. P., Villringer, A., Mueller, K., Schroeter, M. L. *Poster Award*. Society for Neuropsychology (GNP).

Sacher, J. *Fellowship Award*. European College of Neuropsychopharmacology (ECNP).

Taubert, M. *Otto Hahn Medal*. Max Planck Society.

Publications

Books and Book Chapters

Exner, C., & Lincoln, T. (2012). *Neuropsychologie schizophrener Störungen*. Göttingen: Hogrefe.

Fritz, T., & Koelsch, S. (2013). Acoustically mediated emotional contagion as an across-species homology underlying music processing. In E. Altenmüller (Ed.), *Evolution of emotional communication: From sounds in nonhuman mammals to speech and music in man* (pp. 300–312). Oxford: Oxford University Press.

Nierhaus, T., Margulies, D., Long, X., & Villringer, A. (2012). fMRI for the assessment of functional connectivity. In P. Bright (Ed.), *Neuroimaging: Methods* (pp. 29–46). Rijeka: InTech. doi:10.5772/23864.

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Articles

Adamaszek, M., D'Agata, F., Kirkby, K. C., Trenner, M. U., Shem, B., Steele, C. J., Berneiser, J., Strecker, K. (in press). Impairment of emotional facial expression and prosody discrimination due to ischemic cerebellar lesions. *Cerebellum.*

Aue, T., Guex, R., & Okon-Singer, H. (in press). Relating attention and expectancy biases in spider phobia. *Frontiers in Neuroscience.*

Battistella, G., Niederhauser, J., Fornari, E., Hippolyte, L., Perrin, A. G., Lesca, G., Forzano, F., Hagmann, P., Vingerhoets, F. J. G., Draganski, B., Maeder, P., & Jacquemont, S. (2013). Brain structure in asymptomatic FMR1 premutation carriers at risk for fragile X-associated tremor/ataxia syndrome. *Neurobiology of Aging, 34*(6), 1700–1707.

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2 Neurocognition of Language

Department of Neuropsychology

Language has long been identified as a specific human trait. Since other animals are able to learn words and to process simple sequences, syntax has been claimed to be the core of the human language capacity. In the context of this claim a number of questions arise: First, is there a special brain system for syntax; second, if so, what are the structural and functional connectivity patterns underlying this system; and last but not least, how does this syntax system work together with other systems such as phonology, semantics, or gesture to ensure language comprehension?

Over the past few years, the Department of Neuropsychology has approached these questions using different perspectives looking at the mature and the developing brain. The Neurocognition of Language Processing Group focused on the mature brain with the goal to further specify the brain system supporting syntactic processes and its interaction with other cognitive systems, both functionally and structurally. The Neurocognition of Language Development Group's work is viewed as an alternative window to the neurobiological basis of language, possibly allowing novel insights into the system, as it has not yet fully matured. This work is reflected in ongoing research in the group and is additionally funded by an ERC advanced grant for the project Neural Basis of Syntax in the Developing Brain. A second larger project funded by the Fraunhofer Society and Max Planck Society focuses on the biological basis of dyslexia both with respect to its neuroscientific and genetic foundations.

Besides these empirical research activities, a couple of theoretical advancements were achieved. In 2012 Angela D. Friederici formulated a neural network model describing the information flow between different brain regions within The Cortical Language Circuit published in *Trends in Cognitive Sciences* (Friederici, 2012a). In the same year Angela D. Friederici, together

with Tecumseh Fitch (University of Vienna) and Peter Hagoort (MPI for Psycholinguistics, Nijmegen), edited a Special Issue in the *Philosophical Transactions of the Royal Society* (Fitch, Friederici, & Hagoort, 2012) on Pattern Perception and Computational Complexity which covers recent research on perception and rule learning grounded in formal language theory. Finally, together with Robert Berwick (MIT, Cambridge), Noam Chomsky (MIT, Cambridge), and Johan Bolhuis (University of Utrecht), Angela Friederici formulated a highly recognized theoretical paper on Evolution, Brain, and the Nature of Language, published in *Trends of Cognitive Science* (Berwick, Friederici, Chomsky, & Bolhuis, 2013).

The current model

The cortical language circuit

The model presented in the last Research Report (Fig. 2.1, p. 51 therein) has laid down the brain basis of language processing, specifying the relevant brain regions and the structural connections between them. In the following, I have formulated an advanced model (Friederici, 2012a) describing the auditory cortical language circuit specifying the information flow between the different brain regions and their functional significance (Fig. 2). The process described starts from auditory input in the primary auditory cortex and proceeds to the recognition of words and phrases in the temporal cortex, before the information is transferred to the inferior frontal gyrus (IFG) where further processing takes place. In the IFG, lexical-semantic processes are supported by BA 45/47, while processes of syntactic hierarchy building involve BA 44.

Back-projections from BA 45/47 to the middle temporal gyrus via a ventral pathway are assumed for further lexical-semantic processes, whereas further syntactic processes engaged in the comprehension of complex sentences are supported by back-projections from BA 44 via a dorsal pathway to the posterior superior temporal cortex. In addition, the model also discusses forward-projections from the posterior temporal cortex via the parietal cortex to the BA 44 possibly involved in aspects of phonological working memory based processes supporting sentence comprehension (for more details see Friederici, 2012a, and Figure 2).

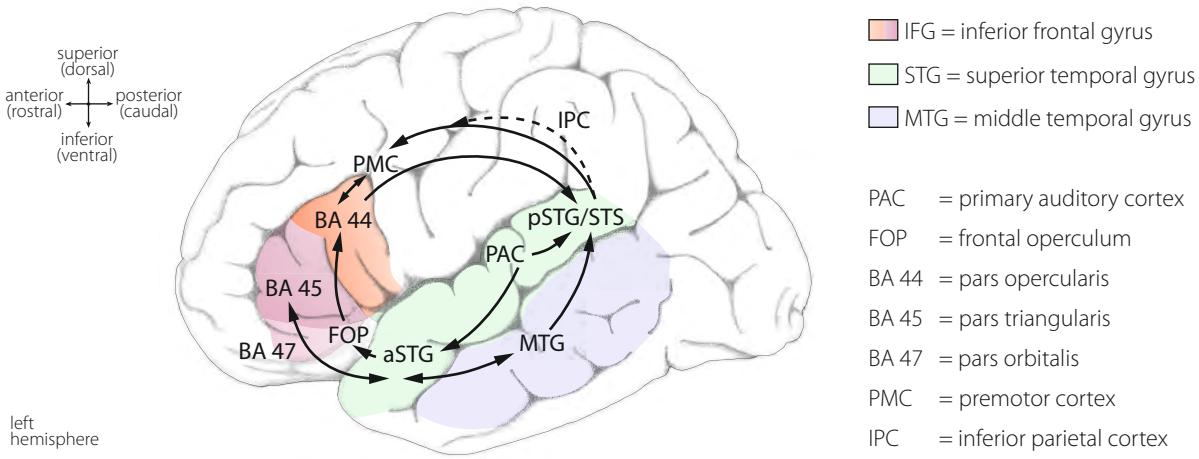

Figure 2 The cortical language circuit (schematic view of the left hemisphere). The major gyri involved in language processing are colour-coded. In the frontal cortex, four language-related regions are labelled: three cytoarchitectonically defined Brodmann [39] areas (BA 47, 45, 44), the premotor cortex (PMC), and the ventrally located frontal operculum (FOP). In the temporal and parietal cortex the following regions are labelled: the primary auditory cortex (PAC), the anterior (a) and posterior (p) portions of the superior temporal gyrus (STG) and sulcus (STS), the middle temporal gyrus (MTG), and the inferior parietal cortex (IPC). The solid black lines schematically indicate the direct pathways between these regions. The broken black line indicates an indirect connection between the pSTG/STS and the PMC mediated by the IPC. The arrows indicate the assumed major direction of the information flow between these regions. During auditory sentence comprehension, information flow starts from PAC and proceeds from there to the anterior STG and via ventral connections to the frontal cortex. Back-projections from BA 45 to anterior STG and MTG via ventral connections are assumed to support top-down processes in the semantic domain, and the dorsal back-projection from BA 44 to posterior STG/STS to subserve top-down processes relevant for the assignment of grammatical relations. The dorsal pathway from PAC via pSTG/STS to the PMC is assumed to support auditory-to-motor mapping. Furthermore, within the temporal cortex, anterior and posterior regions are connected via the inferior and middle longitudinal fasciculi, branches of which may allow information flow to and from the mid-MTG.

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(16) Graduate School of Mind and Brain, Humboldt University Berlin, Germany/funded by German Research Foundation (DFG)
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(34) Programm Beatriu de Pinos, Generalitat de Catalunya, Spain
(35) European Union, ERC Advanced Grant, funded by European Research Council
(43) German National Academic Foundation
(46) Project 'Legascreen', funded by Max Planck Society/Fraunhofer Gesellschaft

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2.1 Neurocognition of Language Processing

The language network has been defined to include inferior frontal, temporal, and parietal regions in the left hemisphere. Here we describe the function and the structural connectivity of the language network (2.1.1), and, moreover, specify the functional connectivity between the prefrontal, parietal, and temporal regions of the language network for syntactic processes (2.1.2). Additionally, we demonstrate the particular role of the parietal cortex (2.1.3) and of the hippocampus (2.1.4) in the interplay of syntax and working memory. Further studies focus on the internal functional structure of Broca's area. First, we show that BA 45 is responsible for the processing of semantics and derivational morphology, whereas BA 44 is responsible for syntax and inflectional morphology (2.1.5). Second, we demonstrate that BA 44 can be specified to represent the most basic syntactic computation, i.e. merge (2.1.6). Third, we discribe how ERP data from patients with lesions in the left inferior frontal gyrus provide causal evidence that this brain region indeed supports fine-grained syntactic processes (2.1.7).

We investigate the role of the prefrontal cortex in cognitive control and syntax processing in the first and second language domain as well as in the non-language domain and find that the prefrontal cortex is organized according to two principles, the hierarchy of a cognitive task and the automaticity of a cognitive function (2.1.8). Moreover, we investigate the role of the prefrontal cortex during language learning in the adult brain by down-regulating its function while learning a novel grammar (2.1.9). Finally, in a further study we identify the neural correlates of the impact of gesture information on syntactic processes within the language network (2.1.10).

2.1.1 Functional roles and anatomy of the language fibre tracts

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Which fibre tracts support specific language functions and the nature of their explicit anatomy is widely debated. We combined functional magnetic resonance and diffusion tensor imaging using a within-subjects design to track the fibre bundles involved in speech repetition and in syntactic and semantic processes. First, we identified two separable dorsal fibre tracts and their functional roles: One tract (D1) corresponding in its fronto-parietal part to the superior longitudinal fascicle, which connects the left dorsal premotor cortex with the posterior middle temporal gyrus branching to the parietal lobe, is involved in speech repetition. Another tract (D2) corresponding to the arcuate fascicle, which connects the posterior Broca's area with the posterior superior temporal gyrus, is involved in the processing of complex syntax. Second, processing simple syntactic structures and word-level semantics appears to be supported by ventral fibre tracts (see Fig. 2.1.1.1, 2.1.1.2, 2.1.1.3). With these data we provide a neurocognitive model of the fibre tracts involved in language processing that solves hitherto conflicting results.

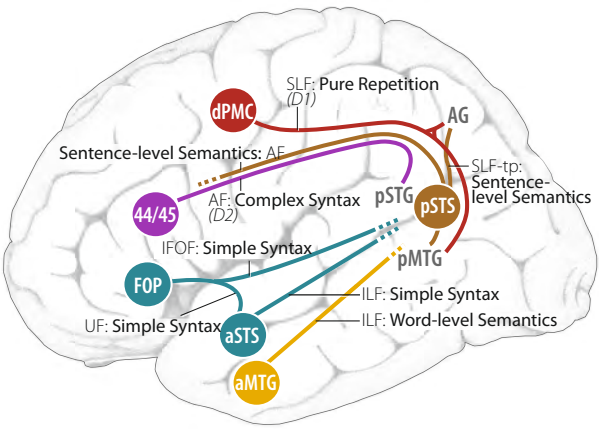

Figure 2.1.1.1 Simplified schematic outline of the model proposed by the tractography data of the present study. Lines represent the core long-distance fibre tracts starting at the following seed regions: The dorsal premotor cortex (red), BA 44/45 (purple), the frontal operculum (turquois), the anterior MTG (yellow), and the posterior STS (ocher) are laid on a rendered standard. Filled circles represent seed regions used in the present study. Terminating regions are outlined, however individual continuations of the tracts are probable. Dotted lines are drawn if the continuations of the tracts are fanned out. AF = arcuate fascicle; AG = angular gyrus; D1, D2 = dorsal tracts as explained in the main text; IFOF = inferior fronto-occipital fascicle; ILF = inferior longitudinal fascicle; MTG = middle temporal gyrus; p = posterior; SLF(-tp) = (temporo-parietal part of) superior longitudinal fascicle; STG = superior temporal gyrus; STS = superior temporal sulcus; UF = uncinate fascicle.

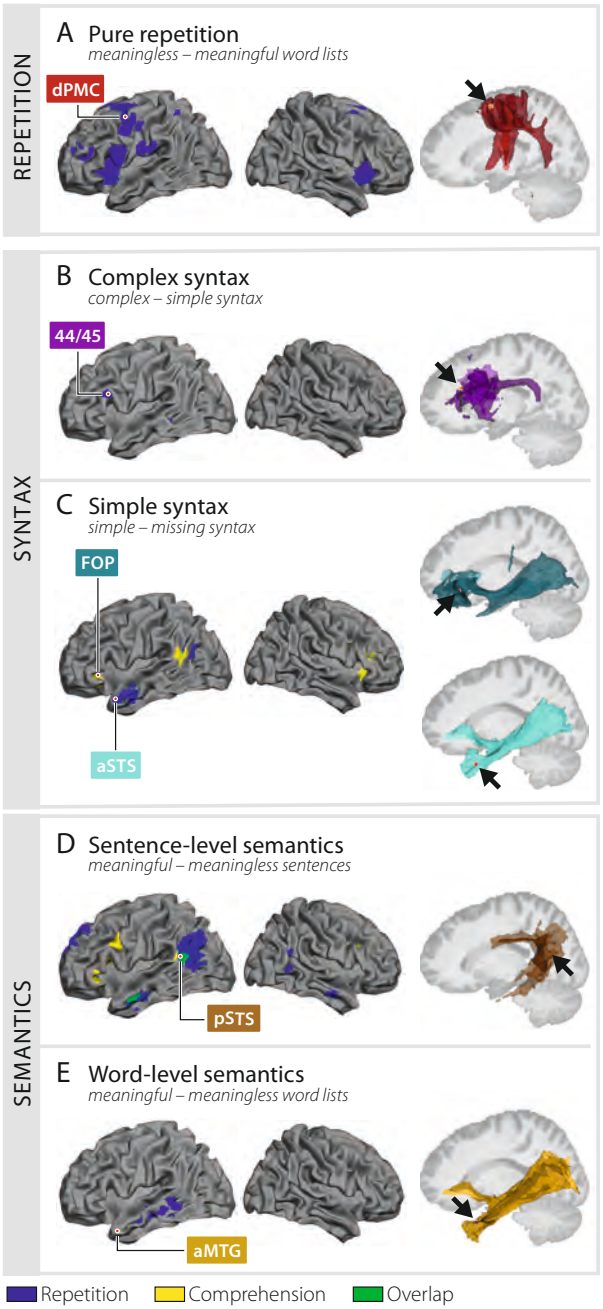

Figure 2.1.1.2 (First column) FMRI results of the contrasts of interests overlaid on a rendered standard brain. Repetition activations appear in blue, comprehension activations in yellow, overlap is shown in green. The regions used as seed points for fibre tractography are indicated and outlined as red dots. (Second column) Statistically significant group-level results of the probabilistic fibre tracking. Arrows point at the seed regions used for fibre tracking which are outlined as red dots. 44/45 = Brodmann areas 44 and 45; aMTG = anterior middle temporal gyrus; aSTS = anterior superior temporal sulcus; dPMC = dorsal premotor cortex; FOP = frontal operculum; pSTS = posterior superior temporal sulcus.

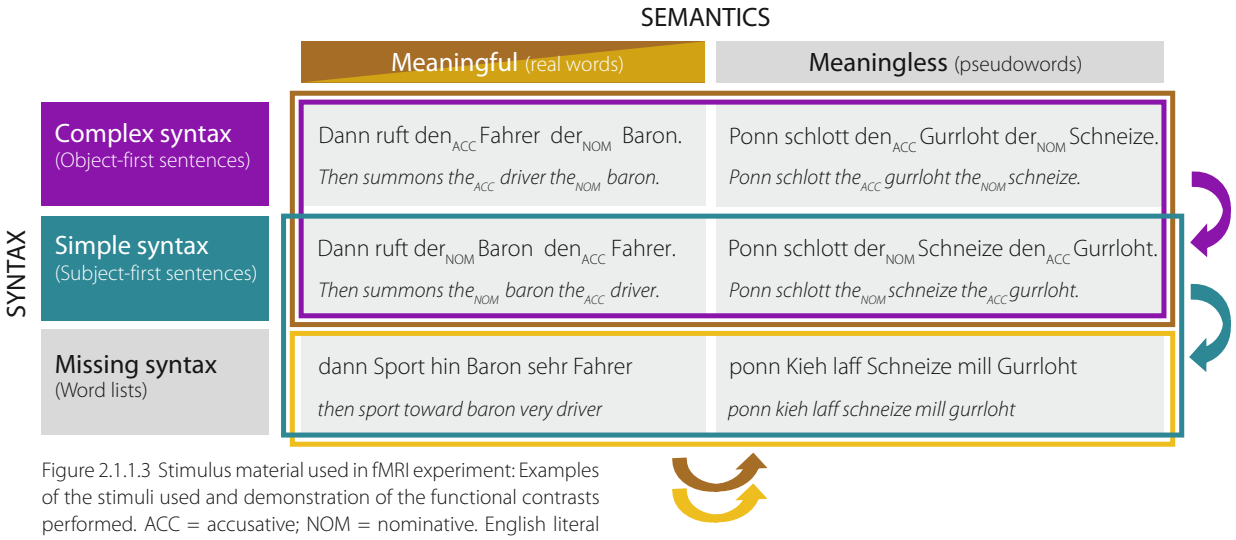

Figure 2.1.1.3 Stimulus material used in fMRI experiment: Examples of the stimuli used and demonstration of the functional contrasts performed. ACC = accusative; NOM = nominative. English literal translations are given in italic.

Hierarchical functional connectivity between the core language system and the working memory system

2.1.2

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Language processing inevitably involves working memory operations, especially for sentences with complex syntactic structures (displayed in Fig. 2.1.2.1). Evidence has been provided for a neuroanatomical segregation between core syntactic processes and syntax-related working memory processes in a previous study (Makuuchi, Bahlmann, Anwander, & Friederici, 2009, Proc Natl Acad Sci USA, 106, 8362–8367). Here, we explored the dynamic relation between these systems. In the present functional magnetic resonance imaging (fMRI) study, we investigated the network dynamics of regions involved in syntax-related working memory operations which support sentence processing during reading, comparing a set of dynamic causal models (DCM) with different assumptions about the underlying connectional architecture. The DCMs incorporated the core language processing regions, namely the pars opercularis (PO) and

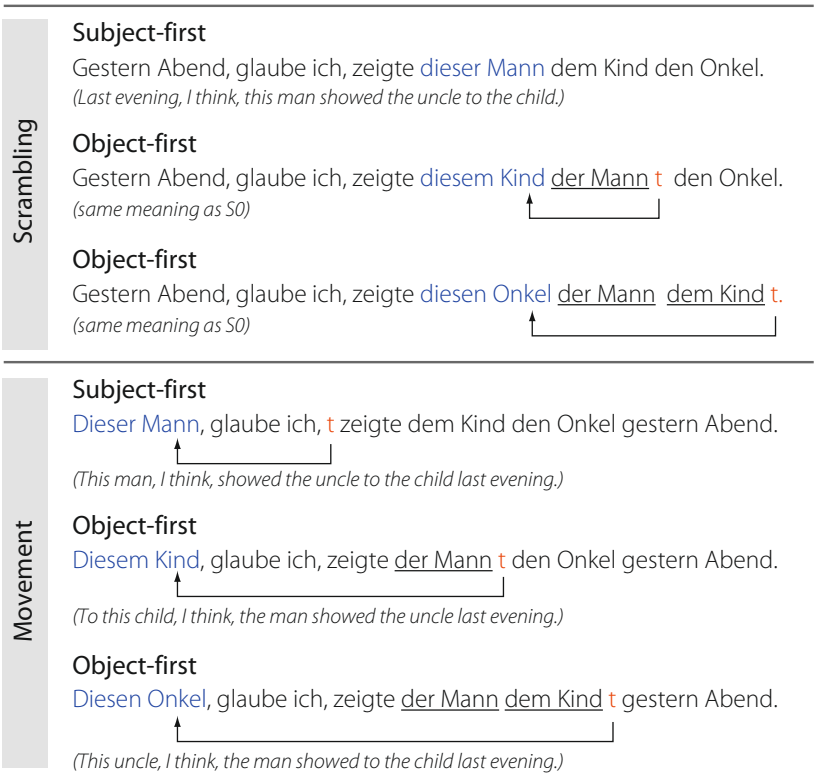

Figure 2.1.2.1 Schematic representation stimulus materials. Two types of object displacements, Movement and Scrambling, are investigated. Noncanonical object-first sentences are derived by a displacement of one of the NPs (either direct or indirect) out of the canonical word order position from the subject-first sentence. The traces (t) indicate the original position of the dislocated NP. The distance of the dislocation of the NPs is indicated by arrows (blue text).

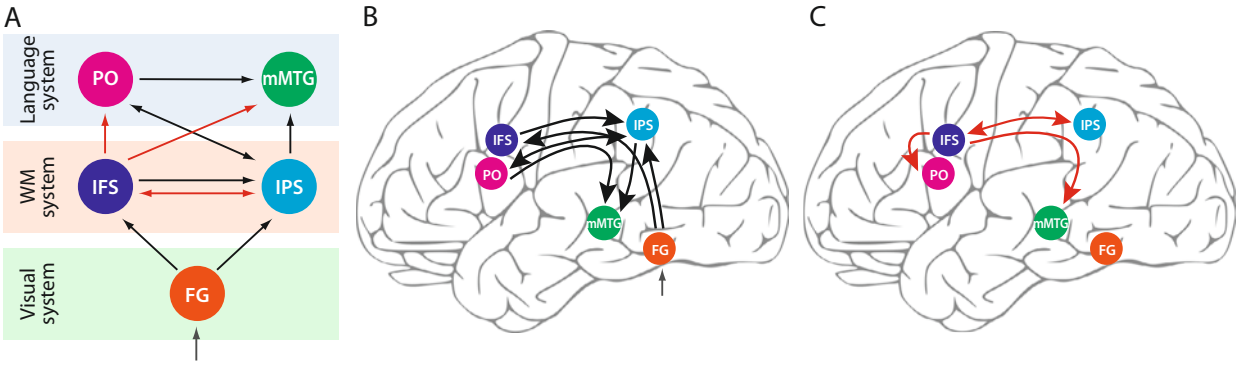

Figure 2.1.2.2 Significant endogenous connections and significant modulatory effects on connections by the increased WM load. (A) Hierarchical diagram for the functionally segregated regions (WM, core language, and visual systems) and their connections. Statistically significant endogenous connections (FDR correction q < .05) and significant modulation of connections are shown by arrows. The factor Type (Scrambling vs Movement) showed a significant modulatory effect on the self-connection of the IFS only. Black arrows indicate endogenous connections. All self-connections (e.g. FG/FG) were significant and are not indicated on the figure. Red arrows indicate significantly increased connection strengths by the factor Distance of object-NP dislocation. The modulation of all self-connections was significant (not indicated on the figure), except in the FG. The vertical grey arrow below the FG represents the input to the visual system. (B) Significant endogenous connections plotted on a schematic brain. (C) Significantly modulated connections by the factor Distance plotted on a schematic brain.

the middle temporal gyrus (MTG), working memory related regions, i.e. the inferior frontal sulcus (IFS) and the intraparietal sulcus (IPS), and the visual word form area (fusiform gyrus, FG). The results indicate a processing hierarchy from the visual system (FG) to working memory related systems (IFS and IPS) to core language systems (PO and MTG), and, moreover, a clear increase of connectivity between WM regions and language regions as the processing load increases for syntactically complex sentences (see Fig. 2.1.2.2).

2.1.3 Alpha oscillations during verbal working memory-intensive sentence processing: Insights from spatiotemporal EEG

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Verbal working memory plays a crucial role during sentence processing, subserving the storage of subjects and objects until these can be integrated with their verb. There is recent evidence that alpha oscillations (7–13 Hz) play a critical role in verbal working memory outside of the sentence processing domain. Our work links this proposal to the sentence processing domain. Time-frequency analyses and source localization were performed on electroencephalography data recorded during the processing of auditorily presented sentences involving either a short or a long dependency between either a subject or object and their respective verb. Oscillatory alpha-band power was hypothesized to increase during long-dependency sentences, since increasing temporal proximity between either subject or object and their verb should result in increased verbal working memory demands. The results met this hypothesis, showing sustained oscillatory enhancement at 10 Hz during argument storage prior to the sentence-final verb, turning into a transient power increase in the beta band (13–20 Hz) at the sentence-final verb (see Fig. 2.1.3A). The sources of the alpha effect were localized to occipital and left-parietal cortices (see Fig. 2.1.3B); source activity in left-parietal cortex was negatively correlated with verbal working memory abilities (see Fig. 2.1.3C). These findings indicate that the domain-general role of alpha oscillations in verbal working memory extends to the language domain, and, more specifically, sentence processing. We suggest that the function of the left parietal cortex underlying verbal working memory storage during sentence processing is to inhibit the premature release of verbal information that will subsequently be integrated.

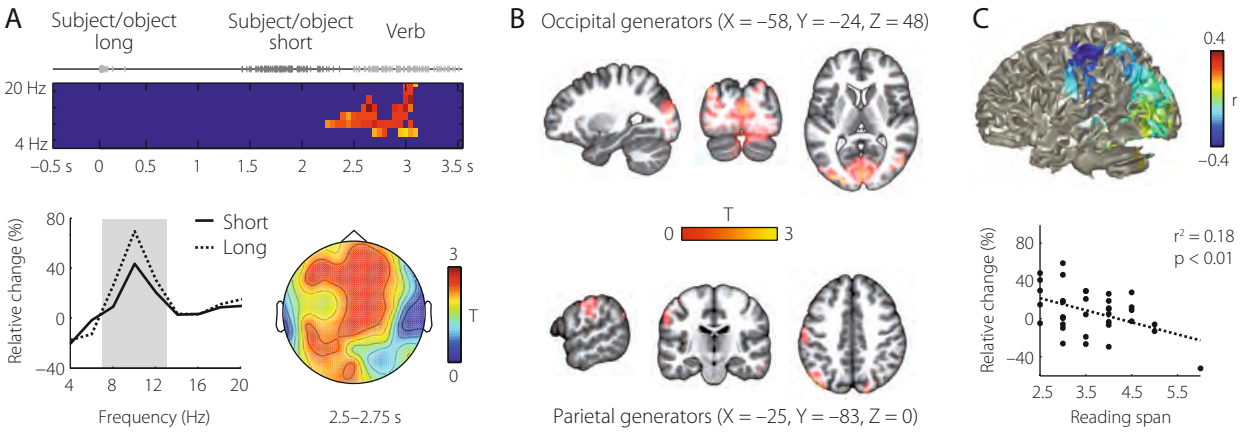

Figure 2.1.3 Spatiotemporal electroencephalography results during verbal working memory intensive sentence processing; (A) time-frequency result indicating an oscillatory-power increase in the alpha band during the storage of a subject or object prior to their verb; (B) source-localization result suggesting occipital and parietal alpha-power generators; (C) correlation analysis stating a correlation between parietal alpha-power changes and verbal working memory span.

How sentence structure supports working memory

2.1.4

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Sentences are easier to memorize than ungrammatical word strings—a phenomenon known as the sentence superiority effect (Brener, 1940, J Exp Psychol, 26, 467–482). Recently, Jefferies and colleagues suggested that this alleviation effect might be due to better chunking (Jefferies, Lambon Ralph, & Baddeley, 2004, J Mem Lang, 51, 623–643). However, to date, it remains unclear how exactly higher-order linguistic information facilitates verbal working memory and how this is implemented in the neural system. The goal of this fMRI study was to specify the brain mechanisms underlying the sentence superiority effect during encoding and during maintenance in working memory by manipulating syntactic structure and working memory load. As depicted in Figure 2.1.4 below, the encoding of sentence material, compared to the encoding of ungrammatical word strings, recruited not only inferior frontal (BA 47) and anterior temporal language-related areas, but also the medial temporal lobe, a region that is not classically reported for language tasks, presumably indicating relational binding or long-term memory enrichment processes during encoding. In the subsequent maintenance phase, it was sentence structure rather than ungrammatical word strings which led to activation decrease in regions that have been previously associated with attention, cognitive control and rehearsal such as Broca's area, SMA, and parietal regions. Furthermore, in Broca's area an interaction effect revealed a load effect for ungrammatical word strings but not for sentences. The sentence superiority effect is thus neurally reflected in a twofold pattern, consisting of increased activation in classical language as well as memory areas during the encoding phase and decreased maintenance-related activation. This pattern reflects how chunking, based on sentential syntactic and semantic information, alleviates rehearsal demands and leads to improved working memory performance.

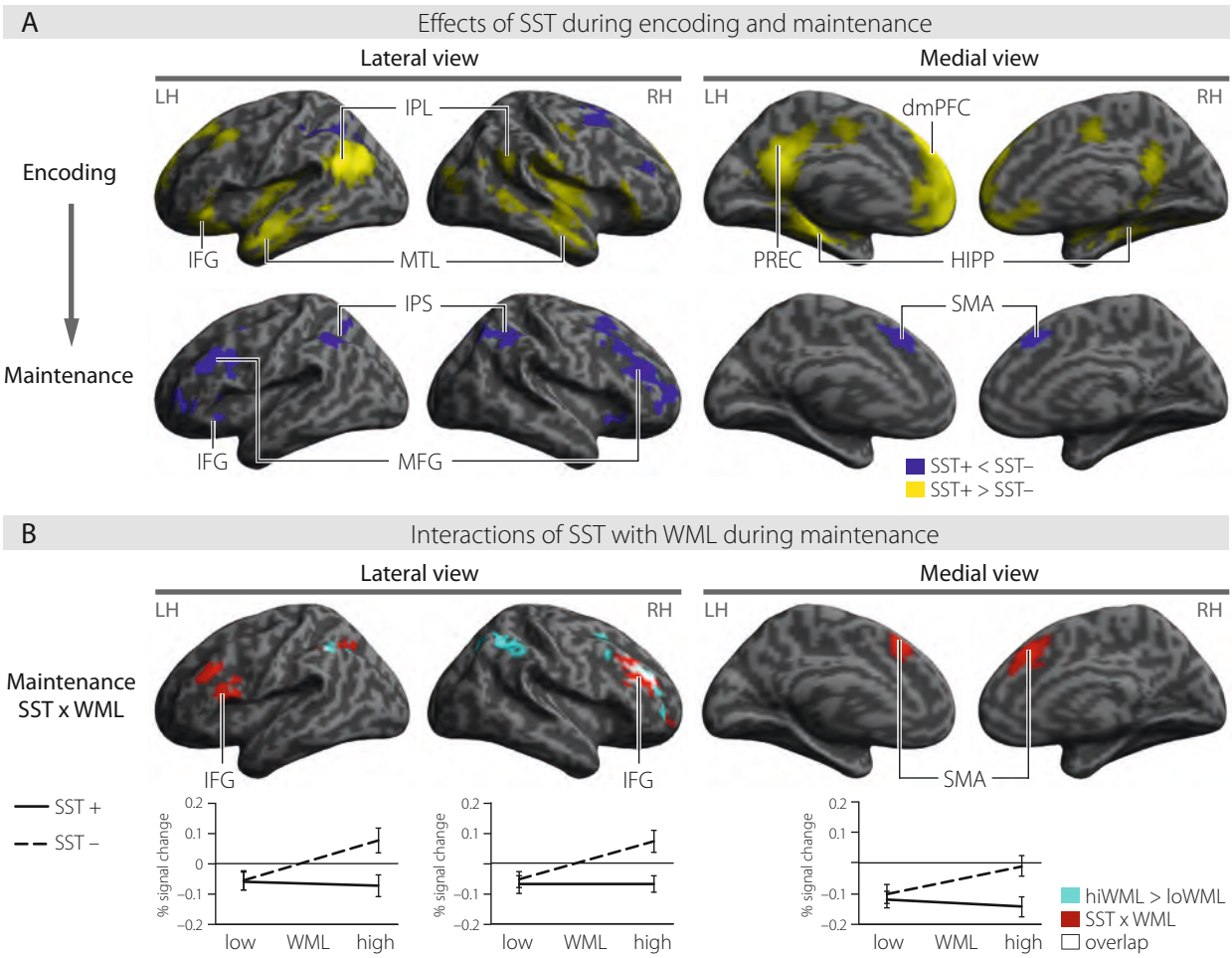

Figure 2.1.4 FMRI activation maps. (A) Main effect of sentence structure during encoding (top row) shows significantly increased activations for structured compared to unstructured memoranda in yellow marked regions, and unstructured compared to structured memoranda in blue marked regions. During the maintenance period, structured memoranda produce less activity (blue) than unstructured memoranda (bottom row). (B) Significant activations for the main effect of working memory load (WML+ > WML-, cyan), the interaction of working memory load and sentence structure (red), and the overlap between effects (white) during maintenance. Diagrams below the activation maps display the results of ROI analyses (see Methods section) for the interaction clusters. All activations are rendered onto an inflated representation of the brain template provided by SPM8, with a threshold of $p < 0.001$ (corrected for cluster size, $p < 0.001$). Error bars represent the standard error of the mean (SST, sentence structure; WML, working memory load).

2.1.5 Stripping off semantics from the syntax skeleton: The functional role of BA 45 and BA 44 in Broca's area

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There is an ongoing debate whether only the posterior region of Broca's area— Brodmann area (BA) 44—is responsible for syntax processing. While German studies show activation in BA 44 proper as a function of syntactic complexity (e.g. Makuuchi, Bahlmann, Anwander, & Friederici, 2009, Proc Natl Acad Sci USA, 106, 8362-8367), English studies show additional anterior activation in BA 45 (e.g. Tyler, Shafto, Randall, Wright, Marslen-Wilson & Stamatakis, 2010, Cereb Cortex, 20, 352–364). According to our framework this activation should be due to parallel semantic processing. We therefore varied semantic information across conditions with and without sentence structure in two fMRI experiments. Subjects performed an auditory Word-Monitoring Task (Marslen-Wilson & Tyler, 1980, Cognition, 8, 1–71) where a target word was presented at trial onset and had to be detected within a sentence.

In Experiment 1, we first compared complex sentences with word sequences and found activation in BA 44, BA 45, the left anterior temporal lobe, and the posterior superior temporal sulcus (pSTS) (Fig. 2.1.5A). We tested analogous conditions, where content words (carrying meaning) were replaced by pseudowords (non-existing words carrying no meaning), keeping derivational (e.g. *-ness* in *happiness*) and grammatical (e.g. *-ed* in *opened*) affixes intact. The syntactic contrast yielded activation in BA 44, BA 45, and the pSTS (Fig. 2.1.5B). We interpreted the unexpected activation in BA 45 as a consequence of semantic information in derivational affixes. We thus also deleted the derivational affixes of pseudowords in Experiment 2, maintaining grammatical affixes. Now, in their absence, only BA 44 was active (Fig. 2.1.5C).

The experiments show that Broca's area (BA 44/BA 45) is activated as a whole during sentence processing, as long as semantic information is available. However, once all semantic information is deleted and only pure syntactic information is left, only BA 44 is activated. Therefore, these data indicate that BA 44 is the core area in syntax processing.

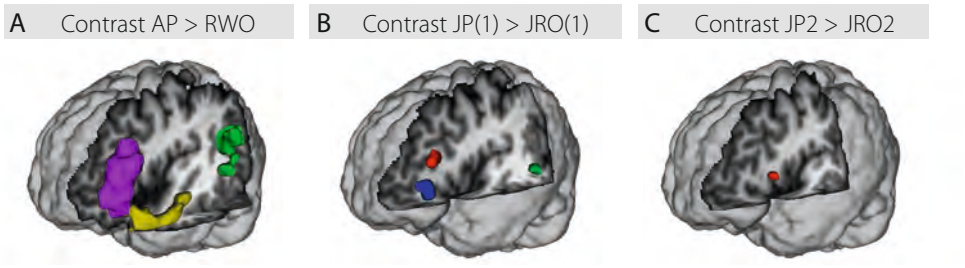

Figure 2.1.5 Brain activation corresponding to the syntactic contrasts with (A) real words (from Experiment 1), (B) pseudowords with derivational affixes (from Experiment 1 and replicated in Experiment 2), and (C) pseudowords without derivational affixes (from Experiment 2). AP = Anomalous Prose; RWO = Random Word Order; JP = Jabberwocky Prose; JRO = Jabberwocky Random Word Order; JP2 and JRO2 without derivational morphology.

The internal functional organization of BA 44: Evidence from phrasal merge

2.1.6

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Brodmann Area (BA) 44 comprises the posterior part of Broca's region in the left inferior frontal gyrus. Dissimilarities between competing neurolinguistic models (Friederici, 2012a; Rogalsky & Hickok, 2011, J Cogn Neurosci, 23, 1664–1680) exist with respect to the exact linguistic functions—i.e. syntax, verbal working memory, and phonology—thought to selectively involve BA 44.

One way to reconcile observed experimental divergences is to evaluate the possibility of BA 44 being a rather macro-region with internal cluster-to-function organization. Anatomically, Amunts et al. (Amunts, Lenzen, Friederici, Schleicher, Morosan et al., 2010, PLoS Biol, 8:e100489) showed that BA 44 can be split into a more anterior dorsal part and a more posterior ventral part, according to the receptor density of the area. Functionally, Clos et al. (Clos, Amunts, Laird, Fox, & Eikhoff, 2013, NeuroImage, 83, 174–188) used a meta-analytic connectivity-based parcellation (CBP) to further decompose BA 44 into five separate clusters, employing co-activation data from a large amount of studies with high domain variability—i.e. language, music, and action planning. While these first findings suggest that regional subdivision within BA 44 could serve an important role in explaining functional heterogeneity, direct evidence showing one-to-one mapping between regional clustering and sub-domain function is still missing.

In this fMRI experiment, we offer first direct evidence in favour of a functional subdivision of BA 44 with respect to language. Specifically, we found out that: (1) Simple syntactic phrasal merge of two-word length yielded a significant activation mass in the most anterior-ventral portion of BA 44, compared to lists (Fig. 2.1.6A-I); (2) This mass of activity fell exclusively within one cluster (C3) of the CBP study above (Fig. 2.1.6A-II); (3) Signal change differences between phrases and lists were limited to the same C3 cluster only, rather than being spread across BA 44 (Fig. 2.1.6B); (4) Cluster-sensitivity was subject-consistent (Fig. 2.1.6C). We conclude that BA 44 comprises distinct functional subregions.

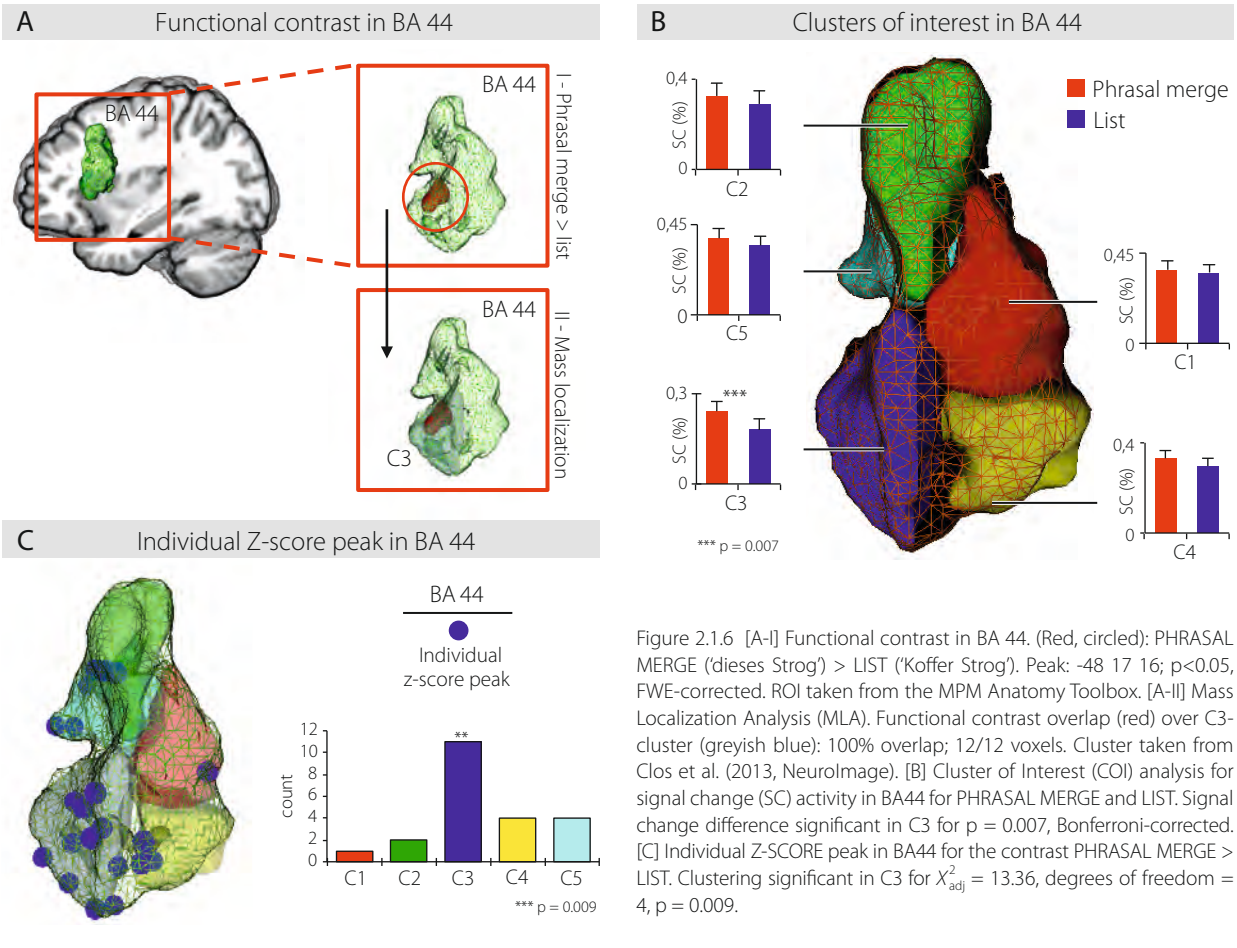

Figure 2.1.6 [A-I] Functional contrast in BA 44. (Red, circled): PHRASAL MERGE ('dieses Strog') > LIST ('Koffer Strog'). Peak: -48 17 16; p<0.05, FWE-corrected. ROI taken from the MPM Anatomy Toolbox. [A-II] Mass Localization Analysis (MLA). Functional contrast overlap (red) over C3-cluster (greyish blue): 100% overlap; 12/12 voxels. Cluster taken from Clos et al. (2013, NeuroImage). [B] Cluster of Interest (COI) analysis for signal change (SC) activity in BA44 for PHRASAL MERGE and LIST. Signal change difference significant in C3 for p = 0.007, Bonferroni-corrected. [C] Individual Z-SCORE peak in BA44 for the contrast PHRASAL MERGE > LIST. Clustering significant in C3 for X^2_{adj} = 13.36, degrees of freedom = 4, p = 0.009.

2.1.7 On the function of the left inferior frontal gyrus in morphosyntactic processing: ERP evidence from left hemisphere damaged patients

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Neurocognitive models of language comprehension have proposed different processing mechanisms underlying the processing of inflected words with different neural substrates engaged in human language comprehension (e.g. Marslen-Wilson & Tyler, 2007, Phil Trans R Soc B, 362, 823–836; McClelland & Patterson, 2002, Trends Cogn Sci, 6, 465-472; Ullman, 2001, Nat Rev Neurosci, 2, 717–726). In particular, the role of the left inferior frontal gyrus (IFG) is controversially debated with respect to the processing of (morpho)syntactic information. The present study addresses this issue by examining the role of the left IFG in morpho-phonological analysis and syntactic reanalysis of German irregular verb inflection, e.g. singen (sing) > gesungen (sung) > sang (sang) by using event-related brain potentials (ERPs). Investigating the processing of morphosyntactic subregularities in neurological patients with lesions merely in the left IFG involving Broca's area, i.e. Brodmann area 44/45, in comparison to age-matched healthy controls reveals whether this brain region is engaged in grammatical operations. In response to the morphosyntactic violations, different ERP patterns were observed in the patients and the controls. While in the patients an N400 component was seen for ungrammatical, i.e. compatible and incompatible, verb inflection relative to the grammatical equivalent, a negativity-P600 pattern emerged in the controls (see Fig. 2.1.7). The present findings provide strong causal evidence for the involvement of the left IFG in grammatical operations.

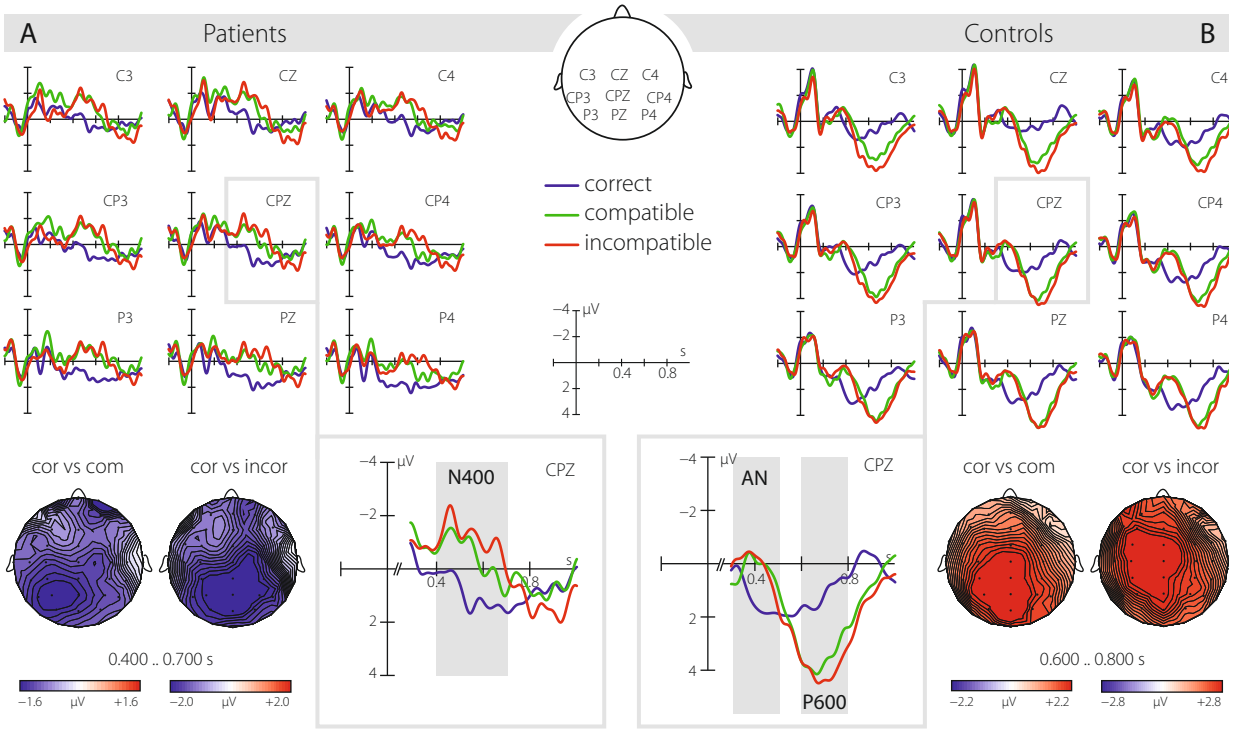

Figure 2.1.7 Grand average ERPs at the onset of the past tense utterances that were either grammatically correct (blue line), or ungrammatical, i.e. compatible (green line) and incompatible (red line). The zoom of the CPZ electrode below illustrates the different ERP patterns seen in (A) the patients and (B) the controls.

Syntax and cognitive hierarchy in the prefrontal cortex: Hierarchy and automaticity as two principles of organization

2.1.8

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The lateral prefrontal cortex (PFC) is known to be organized by cognitive hierarchies following a posterior-to-anterior gradient; contextual level (CONT) for the lowest hierarchy, branching level (BRAN) for the highest hierarchy, and episodic level (EPIS) for the middle (Koechlin & Summerfield, 2007, Trends Cogn Sci, 11, 229–235). Here, we test whether this model applies across different cognitive domains by varying levels of cognitive hierarchy in three domains: first language (L1), second language (L2), and non-language (NL). These domains vary in their degree of automaticity with L1 being the most automatic. Our findings can be summarized as follows. First, we found that both L2 and NL activated the left PFC in a hierarchical manner, moving from posterior-to-anterior regions as the level of hierarchy increases (Fig. 2.1.8.1). Second, the automaticity of L1 processes did not map onto the gradient pattern observed for NL and L2. For L1 the highest level of hierarchy, i.e. the processing of centre embedded sentences, activated the most posterior portion of the left PFC, the pars opercularis (BA 44). Third, to verify that the degree of automaticity elicited a regional difference between posterior and anterior activation within the left PFC, we conducted a correlation analysis between the individual coefficient of variation in response times (CVRT) and the percent blood oxygen level-dependent (BOLD) signal change from the activated foci of L2/NL and L1. While positive correlation was found in BA 47 and BA 10, negative correlation was found in BA 44. This strongly suggests that the regional difference in anterior and posterior areas was determined by the degree of automaticity (Fig. 2.1.8.2). Fourth, this regional difference was also reflected in structural connectivity patterns to the temporal cortex: the ventral pathway for L2/NL and the dorsal pathway for L1. The current data strongly suggest that functional segregation of the PFC is determined by two principles: the cognitive hierarchy and the degree of automaticity.

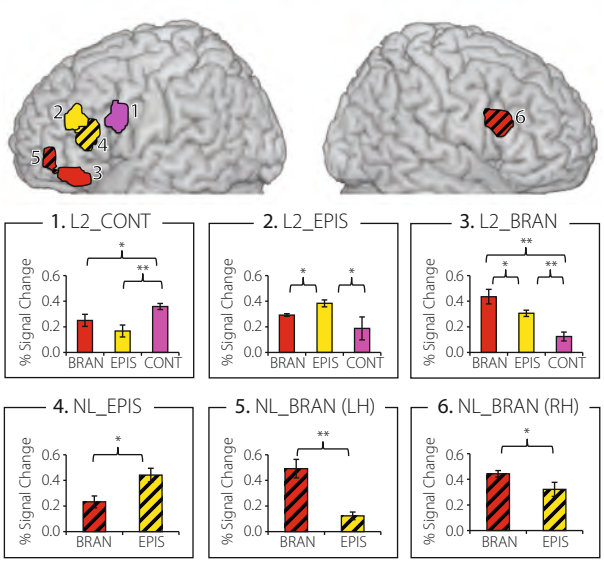

Figure 2.1.8.1 A gradient pattern of activations depending on the levels of cognitive hierarchy across L2 and NL. As the level of hierarchy increases, the activation moves from posterior to anterior part of the left PFC in both the L2 and NL domains. The activation of each condition was numbered with 1 for CONT (context level), 2 for EPIS (episodic level), and 3 for BRAN (branching level), with solid colours for L2, and with 4, 5, and 6, with diagonal colours for NL (no significant activation was found for L2 CONT). Plots of the percent BOLD signal change in each condition within the local maxima are provided at the bottom; error bars denote s.e.m. (*P < 0.05, **P < 0.01, n = 20, two-tailed paired t-test. LH, left hemisphere; RH, right hemisphere).

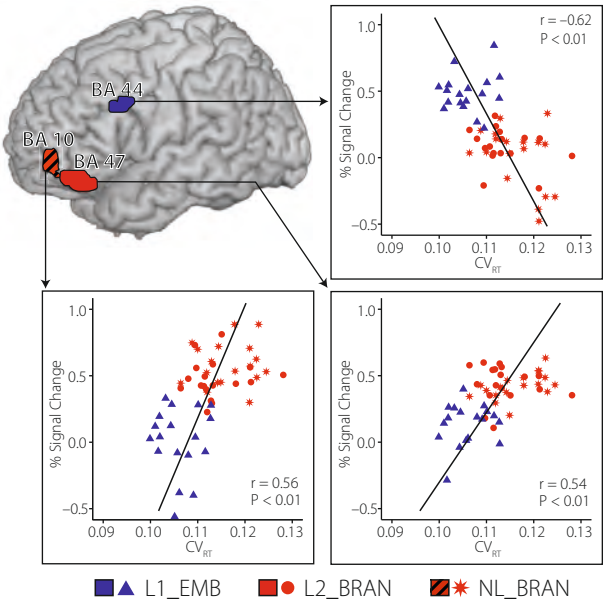

Figure 2.1.8.2 Influence of the degree of automaticity on the activation areas of the left PFC. Activations for the highest level of hierarchy in L2 (BA 47), NL (BA 10), and L1 (BA 44) were rendered on the top left. All the peak activations were provided with a scatter plot of each individual's level of automaticity (CV_{RT}) as a function of the percent BOLD signal changes from the regions. L1_EMB, centre-embedded sentences in the first language; L2_BRAN, branching control in the second language; NL_BRAN, branching control in the non-language.

2.1.9 Language learning without control: The role of the prefrontal cortex

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Learning takes place throughout lifetime but differs in infants and adults because of the development of the PFC, a brain region responsible for cognitive control. To test this hypothesis for language learning, adults were investigated in a language-learning paradigm under inhibitory, cathodal transcranial direct current stimulation (tDCS) over PFC. The experiment included a learning session, interspersed with test phases, and a test-on-

A	Correct structure		sta … *x*-ando is … *x*-ing			puo … *x*-are can … *x*-∅	
B	Correct sentences	La sorella The sister	sta is	cantando singing	Il fratello The brother	puo can	cantare sing
C	Incorrect structure		sta … *x*-are is … *x*-∅			puo … *x*-ando can … *x*-ing	
D	Incorrect sentences	*Il fratello *The brother	sta is	cantare sing	*La sorella *The sister	puo can	cantando singing

Figure 2.1.9.1 Structure and examples of Italian stimulus sentences. The figure displays the grammatical dependency between the auxiliaries (*sta/is* and *puo/can*) and the respective Italian verb inflections (*-ando* and *-are*). (A) Correct grammatical relation between *sta* and *-ando* as well as *puo* and *-are* with x as a place holder for the verb stem. (B) Correct example sentences for the structure represented in (A). (C) Incorrect grammatical relation between *sta* and *-are* as well as *puo* and *-ando* with x as a place holder for the verb stem. (D) Incorrect example sentences for the structure represented in (C). Relation between crucial non-adjacent elements is indicated by arrows. An asterisk indicates an incorrect sentence.

ly session. The stimulus material required the learning of grammatical dependencies between two elements in a novel language. In a parallel design, cathodal transcranial direct current stimulation over the left PFC, right PFC, or sham stimulation was applied during the learning session but not during the test-only session. Event-related brain potentials (ERPs) were recorded during both sessions. Whereas no ERP learning effects were observed during the learning session, different ERP learning effects as a function of prior stimulation type were found during the test-only session, although behavioural learning success was equal across conditions. With sham stimulation, the ERP learning effect was reflected in a centro-parietal N400-like negativity indicating lexical processes. Inhibitory stimulation over the left PFC, but not over the right PFC, led to a late positivity similar to that previously observed in prelinguistic infants indicating associative learning. The present data demonstrate that adults can learn with and without cognitive control using different learning mechanisms. In the presence of cognitive control, adult language learning is lexically guided, whereas it appears to be associative in nature when PFC control is downregulated.

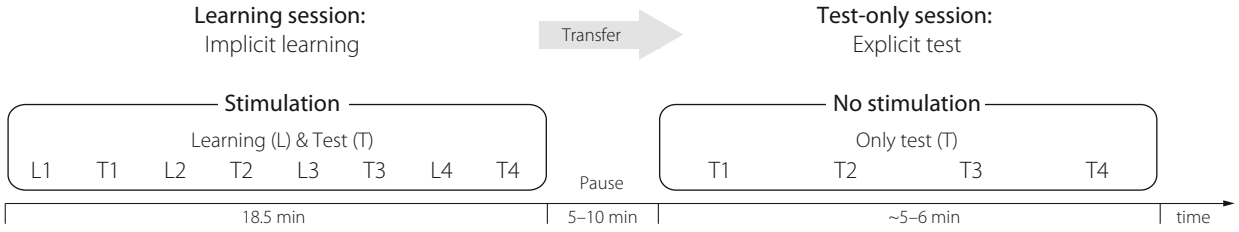

Figure 2.1.9.2 Experimental procedure. The experimental procedure consisted of two sessions. The learning session and a test-only session: a learning session contained four learning phases of approximately 3.3 min (64 correct sentences) and four short test phases of approximately 1.3 min (eight correct and eight incorrect sentences) during which stimulation (left PFC, right PFC, and sham) was applied. The test-only session contained four test sessions of 1.3 min during which no stimulation was applied.

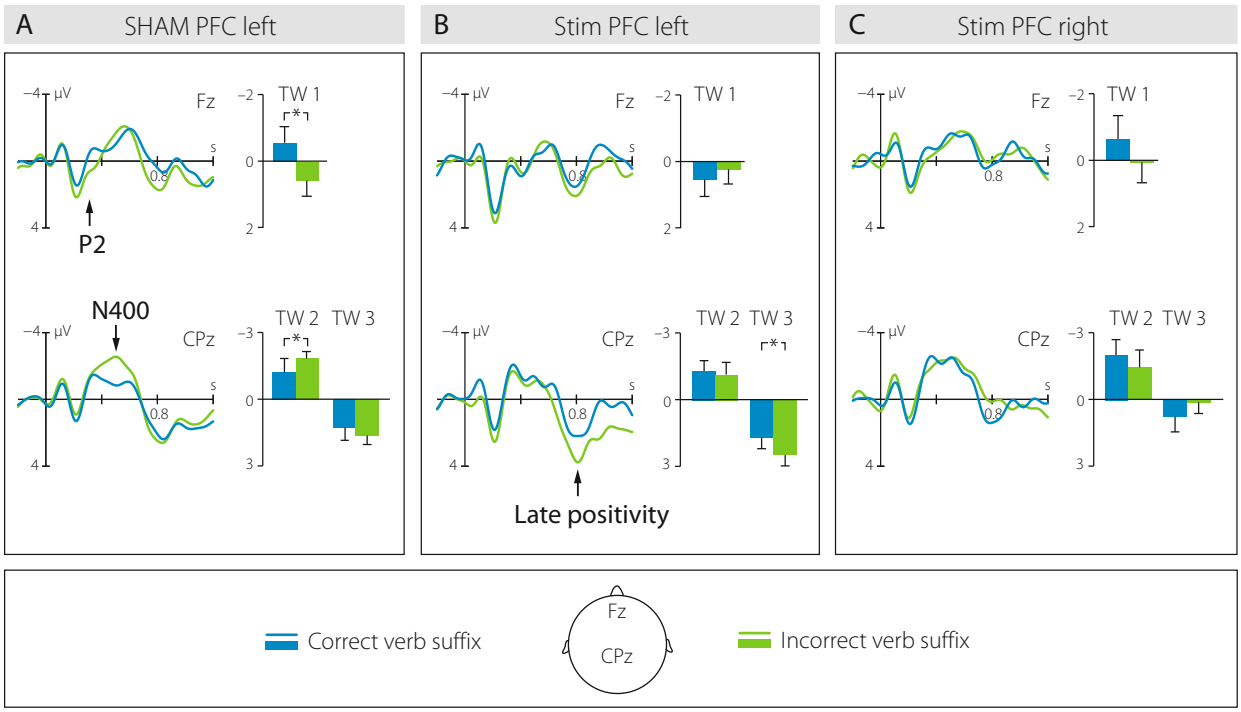

Figure 2.1.9.3 ERP results from the test-only session. Grand-averaged ERPs for the three types of stimulation: sham (A), left PFC (B), and right PFC (C) for the frontal electrode Fz and the centro-parietal electrode CPz. ERPs (left) and mean amplitudes (right) for different TW bars are displayed for correct (blue) and incorrect (green) sentences for each stimulation type. In the ERP plots, the vertical line marks the onset of the verb suffix, and negativity is plotted upwards. In the amplitude plots, bars are displayed for the different TWs: TW 1, 280–380 ms (P2); TW 2, 350–500 ms (N400); and TW 3, 650–900 ms (late positivity). Significant effects are indicated by *, that is, $p < .005$.

2.1.10 Neural correlates of gesture-syntax interaction within the language network

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In a communicative situation, gestures are an important source of information which also impact speech processing. Gesture can help, for instance, when speech perception is troubled by noise (Obermeier, Dolk, & Gunter, 2012), or when speech is ambiguous (Holle & Gunter, 2007, J Cogn Neurosci, 19, 1175–1192). Recently, we have shown that not only meaning, but also structural information (syntax) used during language comprehension is influenced by gestures (Holle, Obermeier, Schmidt-Kassow, Friederici, Ward, & Gunter, 2012). Beat gestures, which highlight particular words in a sentence, seem to be able to disambiguate sentences that are temporarily ambiguous with respect to their syntactic structure. Here we explored the underlying neural substrates of the gesture-syntax interaction with fMRI using similar ambiguous sentence material to Holle et al. (2012). Participants were presented with two types of sentence structures which were either easy subject-first (Subject-Object-Verb, SOV) or more difficult object-first (Object-Subject-Verb, OSV) in their syntactic complexity. A beat gesture was shown either at the first or the second noun phrase (NP). Activations related to syntactic complexity were primarily lateralized to the left (IFG, pre-SMA, pre-central gyrus, and MTG) and bilateral for the Insula (Fig. 2.1.10.1). An ROI-based analysis showed interactions of syntax and gesture in the left MTG, left pre-SMA, and in the bilateral Insula activations (Fig. 2.1.10.2). The pattern of the interaction reflects that a beat on NP1 facilitates the easy SOV structure and inhibits the more difficult OSV structure and vice versa for a beat on NP2. Interestingly, no interaction was found in the IFG—it appears that this region plays an independent role in syntax processing.

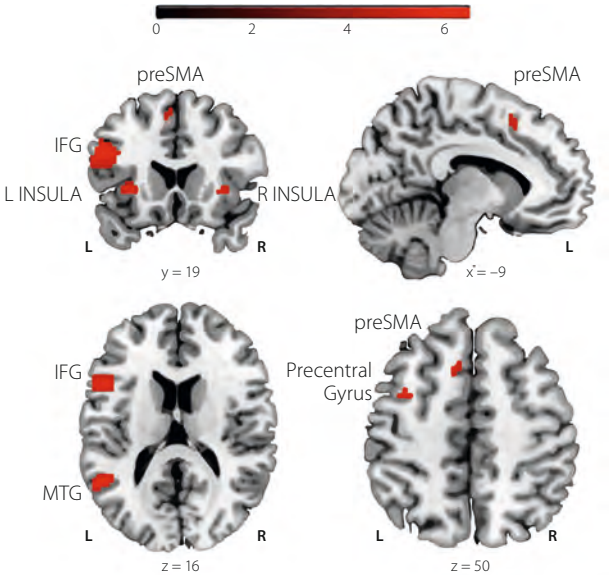

Figure 2.1.10.1 Visualization of significant clusters for the object-first (OSV) vs subject-first (SOV) contrast. The colour bar represents z-values.

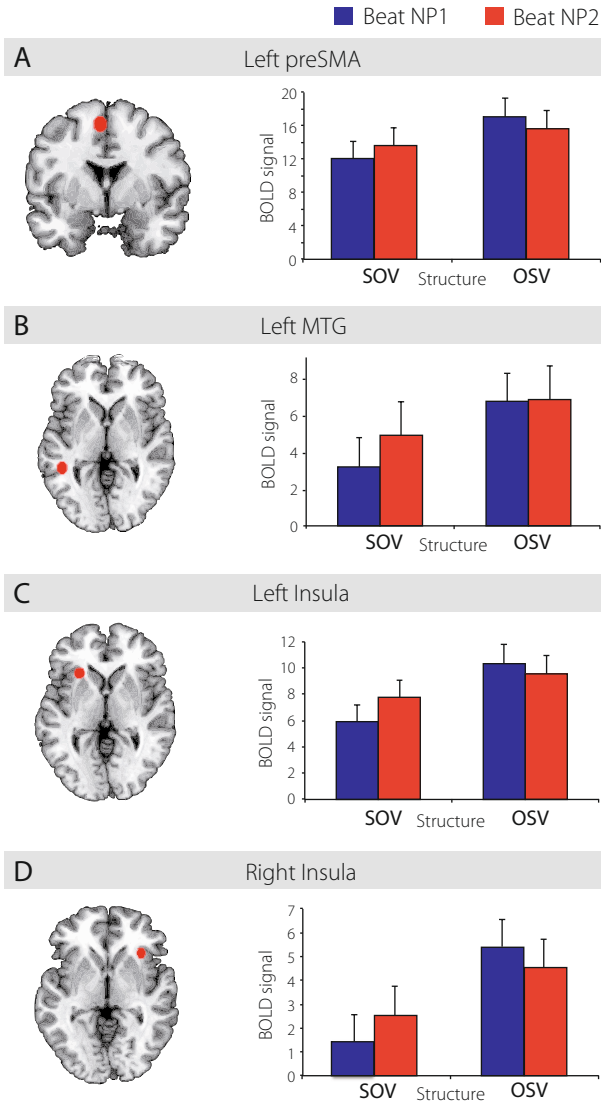

Figure 2.1.10.2 Significant interaction effects in the ROI analysis. Left panel: The images illustrate the location of the ROIs. Please note that the images are only shown for illustrative purposes and do not depict the actual size of the ROIs. Right panel: Mean BOLD response for the conditions SOV and OSV sentences with beat on NP1 (blue bars) and on NP2 (red bars) displayed for four ROIs (A) left pre-SMA, (B) left MTG and (C) left and (D) right Insula. The error bars represent the standard error. SOV = subject-first sentences; OSV = object-first sentences.

2.2 Neurocognition of Language Development

Our knowledge concerning the neural underpinning of language development is still sparse. In the last Research Report we presented initial electrophysiological and imaging data on young children. In 2012 we not only started a major longitudinal project on the neural basis of syntax in the developing brain, but were able to generate a couple of cross-sectional data sets on the development and coevolution of brain function, brain structure, and language behaviour in children between 3 and 10 years of age (2.2.2–2.2.5). A most recent data set allows us to present a first model of the neural basis of language processing during development. The data indicate a correlation between brain function and behaviour, on the one hand, and the correlation between brain structure and behaviour, on the other hand, as well as a correlation between the language regions relevant for syntactic processing. Moreover, the maturation of the fibre tracts connecting these language regions is also specified in the model (2.2.1 and Fig. 2.2.1).

A second line of research concerns the neural and genetic correlates of dyslexia. Here, specific risk genes and their impact on white matter brain structure and on phonological awareness could be identified (2.2.6). Moreover, we find a significant correlation between dyslexia phenotype, genotype and grey matter probability in two brain regions known to support auditory-sensory processes and working memory processes, respectively (2.2.7).

2.2.1 Syntax in the developing brain: Function, structure, and behaviour

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Basic language skills are normally acquired by the age of 3 years, however, full language skills are not present until much later. Even by the age of 7 years, children make errors when processing grammatically complex sentences. We hypothesized that children's language performance depends on the maturation of a particular fibre bundle that connects two language-relevant brain regions, the posterior portion of Broca's area (pars opercularis, PO) and the posterior superior temporal gyrus (pSTG). To test this hypothesis we investigated four age groups: children

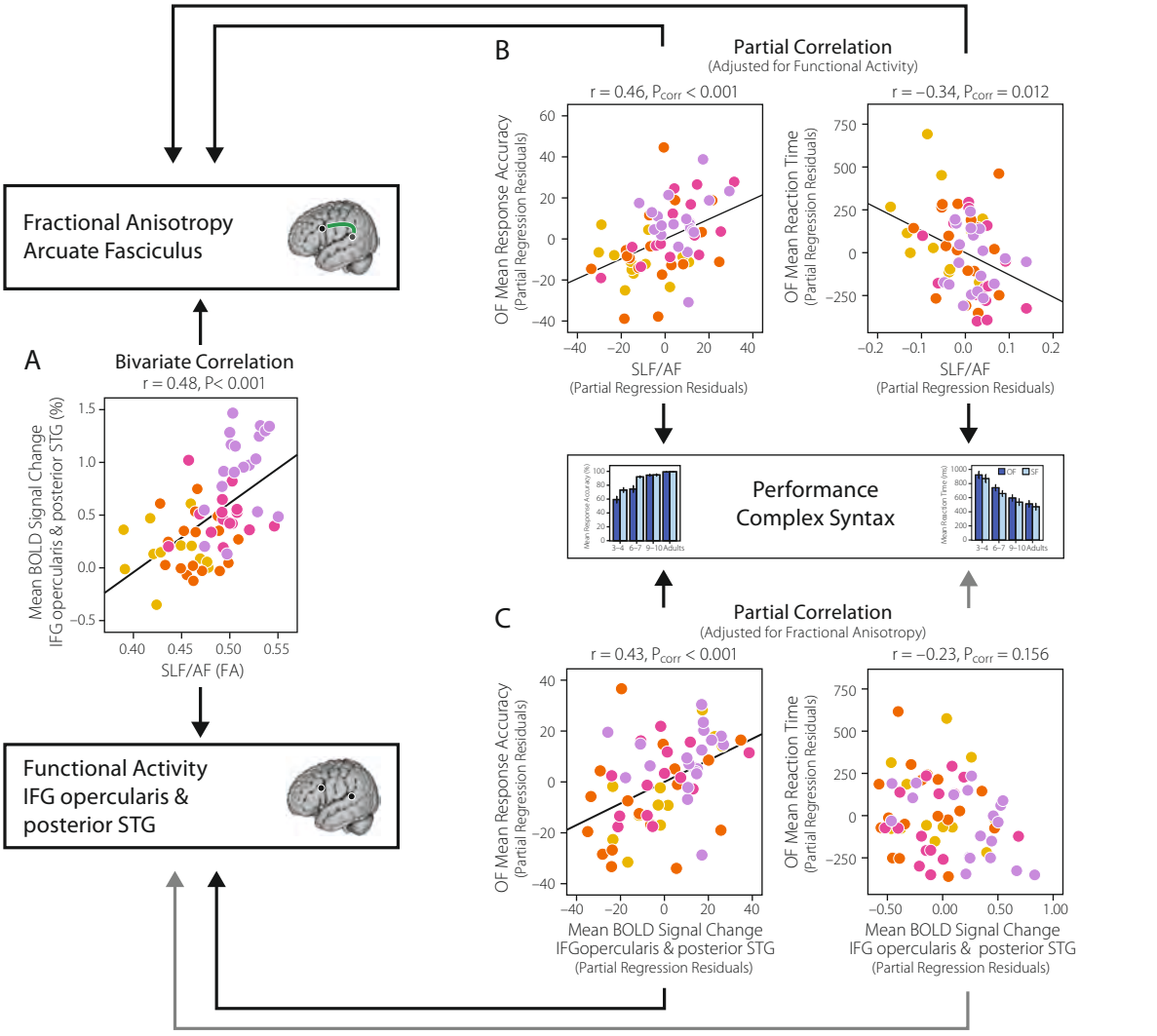
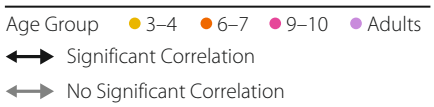


Figure 2.2.1 Relations between brain structure, brain function, and behavioural performance. (A) Bivariate structure-function correlation of the FA values of the SLF/AF and the percental BOLD signal change of the IFG opercularis and posterior STG. (B) Partial structure-behaviour correlations of the FA values within the SLF/AF and syntax performance (accuracy and RT). The individual fractional anisotropy (FA) values were significantly related to the individual syntax performance (both accuracy and RT) when adjusting for the effect of the BOLD signal changes. (C) Partial function-behaviour correlations of the percental BOLD signal change within the IFG opercularis / posterior STG and syntax performance (accuracy and RT). The individual BOLD signal changes were significantly related to the individual accuracy but not the RTs for syntactically complex sentences when adjusting for the effect of the fractional anisotropy (FA) values. Thus, brain structure turned out to be a better predictor for syntax performance than brain function.



at 3–4 years, 6–7 years, 9–10 years, and adults; taking three measures each: a behavioural measure to test the comprehension of syntactically complex object-first sentences, functional magnetic resonance imaging (fMRI) to identify the relevant language regions, and structural diffusion weighted imaging (dMRI) to investigate the strength of the fibre bundles connecting the language regions. Each measure was analyzed and correlations between them were calculated. First, in order to see whether the dorsal pathway is, as hypothesized, crucial for the processing of complex syntax, we performed a correlational analysis between the behavioural performance and the connection strength as measured by fractional anisotropy (FA). The result indicated that the connection strength of SLF/AF is a better predictor for the performance in processing syntactically complex sentences (Fig. 2.2.1). Second, the brain structure-brain function correlation indicated that the higher the connection strength of the SLF/AF, the stronger the functional recruitment of the PO and the pSTG (Fig. 2.2.1). Finally, a correlation of the brain function-behaviour relationship revealed a significant correlation between reaction time for sentence comprehension and the activation in PO and pSTG. The current findings allow us for the first time to specify the tripartite relation between brain structure, brain function, and language behaviour across development. The data suggest that as long as the functional activation of the PO and the pSTG as well as the structural and the functional connectivity between these regions is low, the behavioural performance in complex syntax is poor.

How the language network attunes to sentence processing

2.2.2

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The confinement of language acquisition to a critical phase suggests a fundamental time window of neural plasticity in the language network. However, the link between brain-structural changes inside the language network and its brain-functional attunement is yet to be established. To elucidate this missing link, the current study

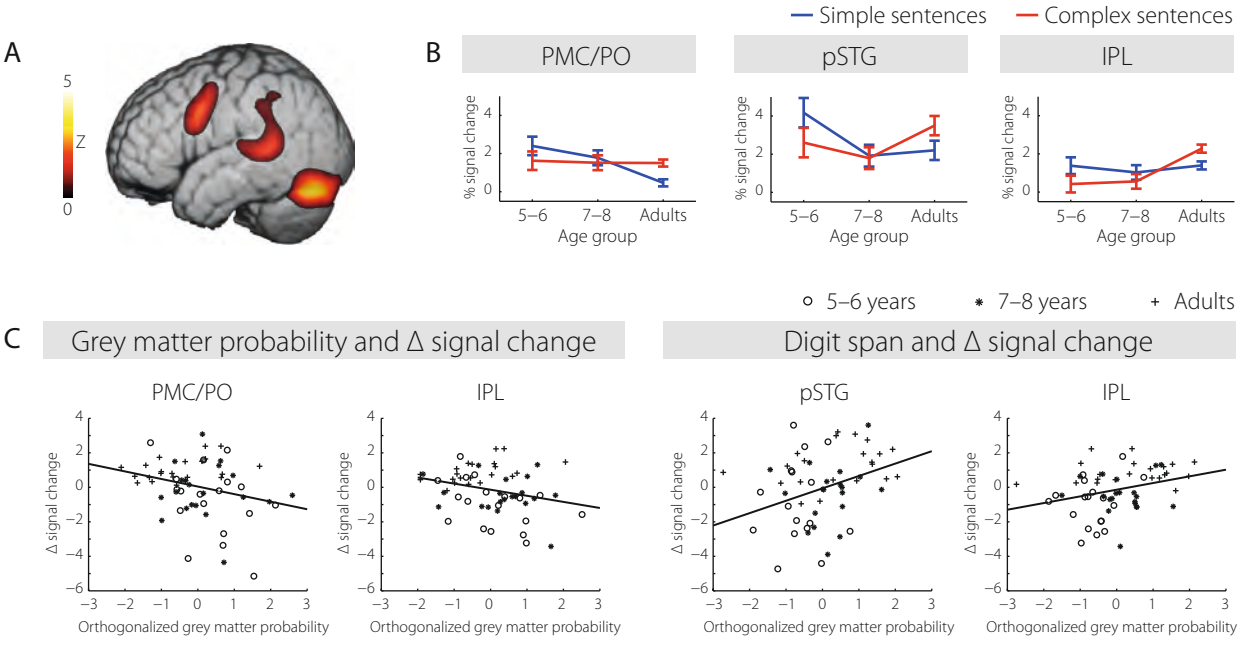

Figure 2.2.2 (A) Results of the whole-brain analysis reveal an interaction between age and sentence structure in left pars opercularis extending to the premotor cortex (PMC/PO), left posterior superior temporal gyrus (pSTG), left inferior parietal lobe (IPL), and bilateral cerebellum ($p < 0.001$, corrected); (B) post-hoc analyses in each region of interest on percentage signal change for each condition (blue = simple sentences, red = complex sentences) yield a decrease of activation with age for simple sentences in the PMC/PO and in the left pSTG, as well as an increase of activation with age for complex sentences in the left IPL; (C) multiple regression analyses show that while the activation pattern in the PMC/PO is predicted by grey matter probability and the activation pattern in the pSTG by digit span, the activation pattern in the IPL is predicted by both factors (all $p < 0.05$; circles = 5–6 years; asterisks = 7–8 years; pluses = adults).

first assessed the functional brain activity for increasingly complex sentences in children of different age groups (5–6 years and 7–8 years) and adults. We then correlated the functional brain activity with brain-structural data and behavioural performance measures from the language and verbal working memory domains. In adults the brain activity increased with syntactic complexity in left pars opercularis (BA 44) extending to the premotor cortex (BA 6), hereafter (PMC/PO), the left posterior superior temporal gyrus (pSTG), and the left inferior parietal lobe (IPL); in children this network appeared complexity-insensitive. Subsequent region-of-interest analyses indicate differential patterns of attunement to sentence processing across the age trajectory, with an activation decrease in PMC/PO and the pSTG for simple sentences, and a simultaneous increase in IPL for complex sentences. Voxel-based morphometry and subsequent multiple regression analyses revealed a relationship between grey matter probability (GMP) and the functional activity in the PMC/PO, but not in the pSTG, where the observed functional effect is rather predicted by verbal working memory performance. In the left IPL, we observed the influence of both factors. These results indicate a complex interplay between structural brain maturation and functional brain attunement to sentence processing. We conclude that grey matter changes in the PMC/PO and the IPL contribute to the functional attunement to sentence processing, and we suggest that the decrease of activation together with the decrease of GMP in the PMC/PO may be related to the closure of the critical phase for language acquisition.

2.2.3 White matter network supporting the processing of object-first sentences in 3-year-old children

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The language network is assumed to be mainly composed of two pathways, one ventral—involved in lexical-semantic processes and local phrase structure building— that matures early during development, and one dorsal—responsible for complex syntactic processes—that matures later (Friederici, 2012a).

In order to test the developmental trajectory of these pathways, diffusion-weighted images were acquired from a sample of children (N = 16, F = 10, Age = 3 years 6 months, SD = ±2.7 months) and the fractional anisotropy (FA) maps were estimated. Outside the scanner children performed a picture selection task in which object-first and subject-first sentences were presented auditorily and children had to choose a picture accordingly. The response accuracy for each sentence type was then fed to voxelwise statistical analysis on the FA data using TBSS. If the dorsal pathway is already mature, it should support the processing of complex object-first sentences processing, while the ventral pathway should support only subject-first sentences.

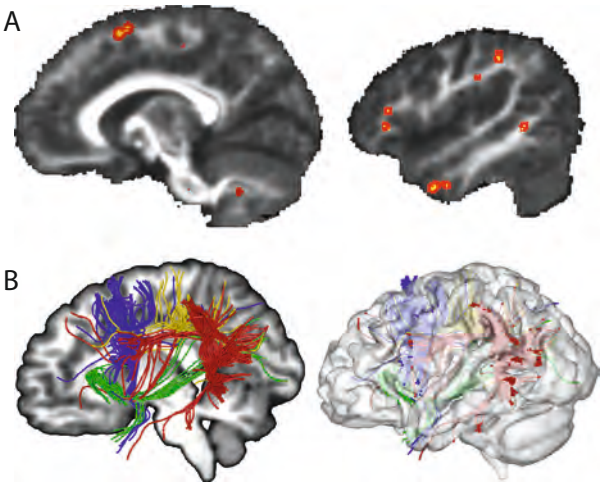

Figure 2.2.3 (A) Significant clusters ($p < .005$, uncorrected) for the contrast Object-First > Subject-First Sentences. (B) Deterministic fibre tracking for a representative subject, estimated using the clusters depicted in Figure 2.2.3A as seeds.

The difference between the performance for object- and subject-first sentences showed clusters in the white matter of the left hemisphere in the proximity of the inferior frontal gyrus (pars triangularis, BA 45), the superior frontal gyrus (SFG), the supramarginal gyrus (SMG), and the anterior and posterior middle temporal gyri (aMTG and pMTG) ($p < .005$, uncorrected). Using these areas as seeds, deterministic tractography revealed that the IFG and the aMTG clusters involved the external capsule fibre system and the uncinate fascicle, respectively. The SFG cluster projected mainly to the inferior frontal gyrus (pars opercularis, BA 44) and the premotor cortex, while pMTG showed connections to the SMG and to the premotor cortex.

This suggests that for sentence comprehension, children at 3 years of age may still be relying more on the lexical-semantic system than on the syntactic system, which might be due to the immaturity of the system for complex syntax.

Sentence processing in 2- and 5-year-old children: Syntactic and semantic categories in competition

2.2.4

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One of the challenges for preschool children is the interpretation of different linguistic cues in a sentence in order to understand the relationships between its main participants. Previous studies on the acquisition of German syntax have shown that the use of syntactic cues, such as case-marking, increases as a function of age (Schipke, Knoll, Friederici, & Oberecker, 2012). The present study aims to track the role of semantic and syntactic cues during sentence processing. Event-related potentials (ERP) were collected in adults, 5-year-old children, and 2-year-old children who were exposed to sentence material in which two factors are manipulated, namely as a semantic factor the animacy status of the noun phrase (animate vs inanimate) and as a syntactic factor the canonicity of syntactic structure (subject-initial vs object-initial). The brain response of adults reveals a negative-going component at the initial accusative noun phrase (NP) both for animate and inanimate nouns (Fig. 2.2.4.1C and 2.2.4.1F). The 5-year-olds show a similar negativity between 200–400 ms only for accusative-marked sentence initial animate nouns (Fig. 2.2.4.1B). In 2-year-old children, an early negativity is followed by a negative deflection between 800–1000 ms in both animacy conditions (Fig. 2.2.4.1A and 2.2.4.1D). Thus, the adults process case-marking at the initial NP irrespective of the semantic features of the noun. The absence of an adult-like ERP pattern for inanimates in the 5-year-olds implies that semantic information still influences syntax processing at this age. For the youngest group, however, animacy does not elicit any significant behavioural effect on sentence processing. Since they do not even perform above chance for the subject-first sentences, the brain responses of the 2-year-olds probably reflect perceptual differences between the articles, with *der* marking the subject and *den* marking the object. Taken together, these results show the importance of the semantic information at the intermediate stages of language development.

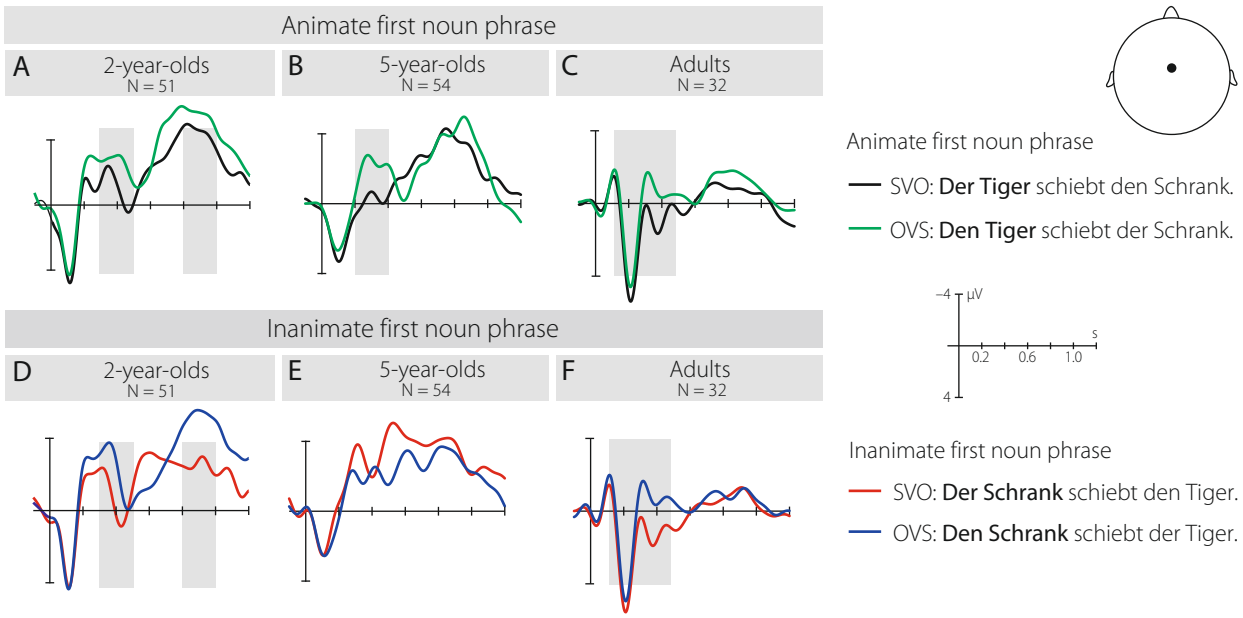

Figure 2.2.4.1 Grand average ERPs of 2-year-old children, 5-year-old children, and adults for object-initial versus subject-initial sentences for the animate (A-C) and inanimate (D-F) noun phrase. SVO = subject-first sentences; OVS = object-first sentences. Translation of vocabulary: Tiger/tiger, schiebt/pushes, Schrank/wardrobe.

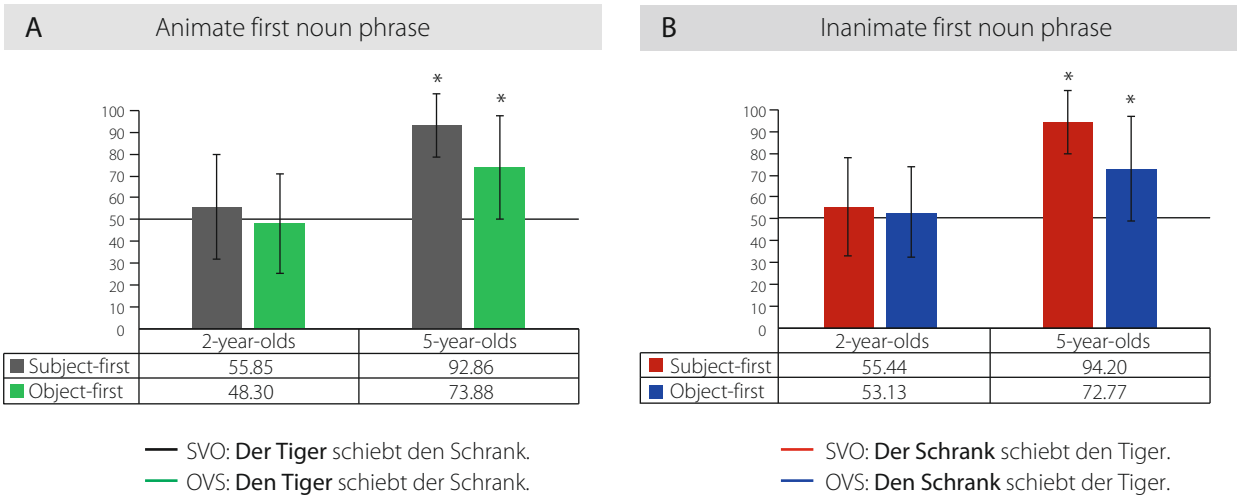

Figure 2.2.4.2 Mean accuracy in percent for picture-matching task in 2-year-old (N = 57) and 5-year-old (N = 56) children ± SD for sentences with (A) animate first noun phrases and (B) inanimate first noun phrases. Solid line represents the chance level 50%. Asterisk indicates the accuracy is significantly different from the chance level. Translation of vocabulary: Tiger/tiger, schiebt/pushes, Schrank/ wardrobe.

2.2.5 Dorsal and ventral pathways in language development

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The dorsal and the ventral information streams between the inferior frontal and temporal language regions in the human brain are implemented by two fibre pathways that consist of separable tracts. We compared the maturation of the two pathways including their subcomponents in three different age groups: newborn infants, 7-year-old children, and adults. Our results reveal a maturational primacy of the ventral pathway in the language

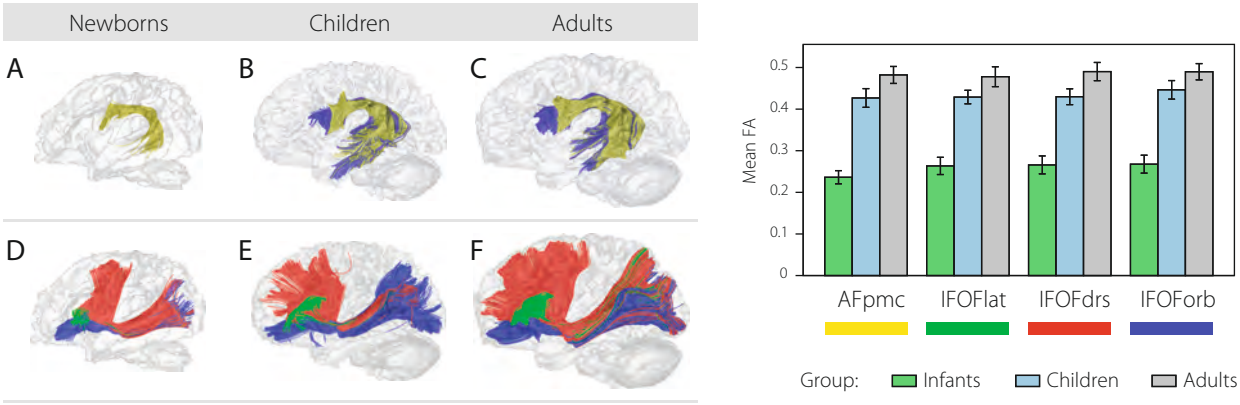

Figure 2.2.5 Left: The dorsal and ventral pathways of the language network in newborn infants, 7-year-old children, and adults. For newborns (A), no connection between the IFG and temporal regions is observed. Rather, they only show a connection terminating in the premotor cortex. In addition to this dorsal pathway D1 (in yellow), children (B) also show a connection to the dorsal portion of BA 44 in the IFG, thus the dorsal pathway D2 (in blue) is present from at least childhood onwards. In newborns (D), the ventral pathway directed to BA 45 in the IFG (IFOFlat, in green) is already in place, though much weaker than in children (E) who show only small differences in this connectivity pattern compared to adults (F). Thus, this superficial tract is the only fronto-temporal connection from the posterior temporal lobe to the IFG in the language network of infants. For all three groups, the deep tract of the ventral pathway can be separated into at least two subcomponents (D–F): an anterior component connecting to the orbito-frontal cortex and frontal pole (IFOForb, in blue), and a posterior component (IFOFdors, in red). Figures A and C after Perani et al. (2011). Right: Mean FA values for the dorsal pathway D1 (AFpmc) and the three components of the ventral pathway (the lateral portion of the IFOF: IFOFlat, the dorsal portion of the IFOF: IFOFdors, and the orbital portion of the IFOF: IFOForb in infants, children, and adults. Infants show lowest FA values for all tracts, while adults show highest.

network connecting the temporal areas to the inferior frontal gyrus during early development, being already established at birth. Likewise, a dorsal connection from temporal cortex to the premotor cortex is observable at this early age. This is in contrast to the dorsal connection to the inferior frontal gyrus which matures at later stages in development and probably plays a role in more complex language functions.

Dyslexia risk gene SLC2A3 alters neural connectivity profiles and affects phonological awareness in children

2.2.6

Skeide, M. A.[1], Kirsten, H.[2,3], Kraft, I.[1], Schaadt, G.[1,4], Müller, B.[2], Brauer, J.[1], Wilcke, A.[2,3], Boltze, J.[2,3,5], Emmrich, F.[2], & Friederici, A. D.[1]

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Developmental dyslexia (DD) depends on genetic, brain structural, brain-functional, and behavioural factors. So far, however, no study has successfully integrated all explanatory levels within a single coherent analysis in order to provide a comprehensive account of DD.

In the present study, 34 children aged 9 to 12 years were genotyped in 3 haplotypes (8 SNPs) acting on the genes KIAA0319, DCDC2, and SLC2A3, scanned with anatomical and functional MR imaging sequences and underwent phonological awareness and spelling assessment. For the first time we demonstrate that SLC2A3, but neither KIAA0319 nor DCDC2, affects the anisotropy of the arcuate fasciculus (AF), which in turn proves to be specifically related to phonological awareness (Fig. 2.2.6.1). Furthermore, we provide first evidence that a genetic risk for DD alters the functional connectivity of the dorsal language network already at resting-state in the absence of any linguistic stimulation (Fig. 2.2.6.2).

Our results indicate a specific link between an SLC2A3 genotype and a phonological awareness phenotype which is mediated by the anisotropy of the arcuate fasciculus and reflected in the resting-state functional connectivity of fronto-temporal cortices.

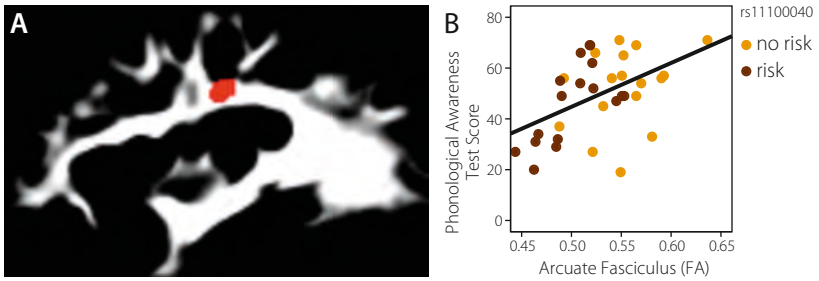

Figure 2.2.6.1 (A) Fractional anisotropy (FA) differences between children either with or without risk alleles affecting the gene SLC2A3. Children who do not carry any risk allele have significantly higher FA values in a cluster located in the left arcuate fasciculus (AF) (k = 40; MNI coordinates: –34 –16 34; p < .003, cluster size corrected to p < .001, Bonferroni corrected). (B) FA in the left arcuate fasciculus (AF) is correlated with phonological processing performance. Individual FA values in the sub-portion of the left AF predict the individual phonological awareness scores when adjusting for age, gender, and IQ, for the functional connectivity correlation coefficients as well as for speech therapy, instrument instruction, and attention deficits (partial r = 0.51, p < .025, Bonferroni corrected).

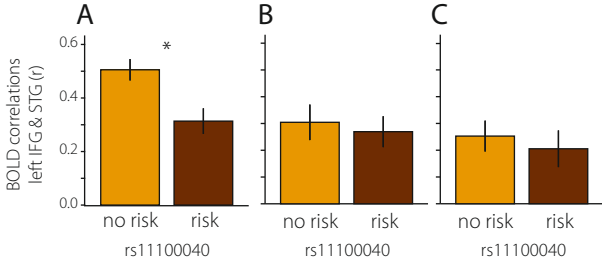

Figure 2.2.6.2 Group differences between pair-wise temporal correlations of low frequency BOLD signals at resting-state in 3 seed regions (left IFG: –51, 10, 10; left STG: –53, –31, 9, and left TPJ: –59, –45, 15) known to support phonological processing. Children without any risk allele in SLC2A3 show significantly higher correlations between the left IFG and the left STG compared to children with a genetic risk (A) [F(1, 33) = 3.58, p < .003, Bonferroni corrected]. No significant group differences were found for the two other seed pairs (B, C).

2.2.7 Working memory endophenotype relates to dyslexia phenotype and *TNFRSF1B* genotype

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*These authors contributed equally to the work.

Developmental dyslexia, the severe impairment of reading and writing, has a neurological basis and a strong genetic background. While effects of individual genetic variations on dyslexia-associated behavioural deficits are only moderate, genotypes have a comparably stronger impact on mediating neuronal endophenotypes. Applying the imaging genetics approach, we used voxel-based morphometry in dyslexic and unaffected participants to investigate grey matter changes associated with impaired language-processing performance as a conjunctive indicator of particular dyslexia-associated genetic variations and dyslexia diagnosis. We obtained two grey matter clusters in the left posterior temporal cortex related to verbal working memory capacity (Fig. 2.2.7A): First, a cluster in auditory-sensory regions (HG/pSTG) positively correlated with verbal working memory, and second, a cluster in auditory-association regions (pSTS) negatively correlated with verbal working memory. These two clusters were differently related to dyslexia diagnosis and genetic risk variants in *TNFRSF1B*. Regional cluster differences revealed that dyslexics and high genetic risk participants exhibit a structural asymmetry towards auditory-association areas (pSTS), which may partly compensate for deficient early auditory-sen-

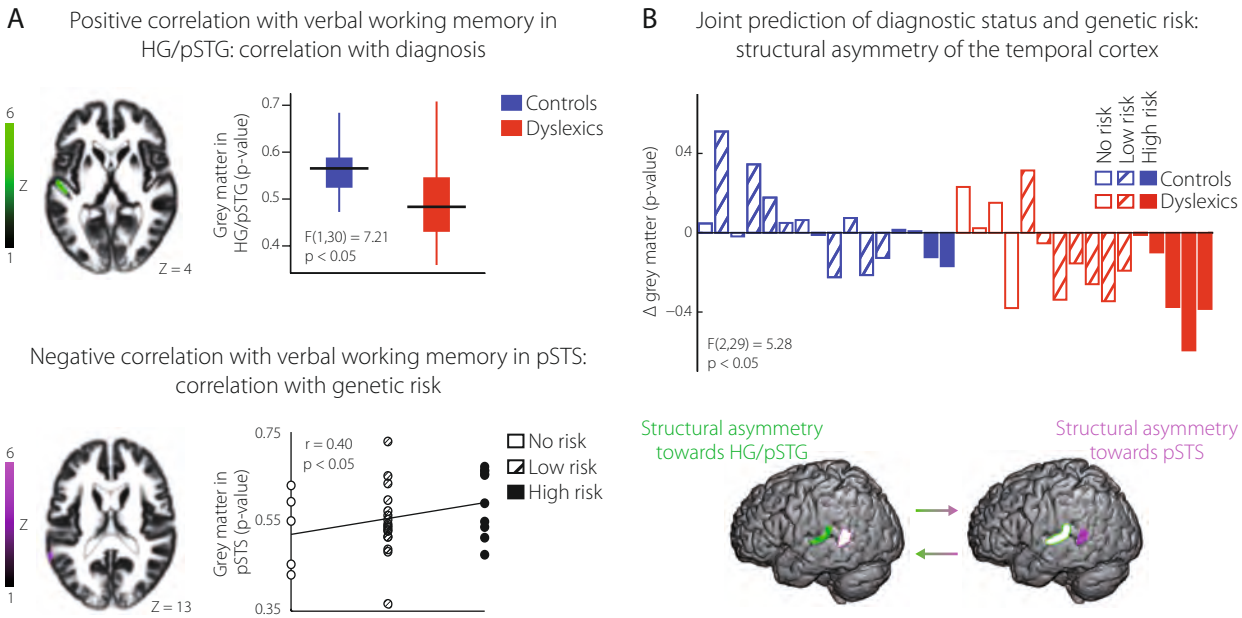

Figure 2.2.7 (A) Whole-brain results of verbal working memory related grey matter regions ($p < 0.001$, corrected): Grey matter probability in left Heschl's gyrus/posterior superior temporal gyrus (HG/pSTG) is positively correlated with verbal working memory capacity (upper panel); grey matter probability in the left posterior superior temporal sulcus (pSTS) is negatively correlated with verbal working memory capacity (upper panel); (B) Joint predictability of individual participant grey matter differences between HG/pSTG and pSTS by diagnostic status and genetic risk: It is visible that most low genetic risk controls show a structural asymmetry towards HG/pSTG, while most dyslexics, especially those with high genetic risk, show a structural asymmetry towards pSTS relative to HG/pSTG.

sory processing stages of verbal working memory (Fig. 2.2.7B). The reverse asymmetry towards auditory-sensory areas (HG, pSTG) observed in healthy and low genetic risk participants may instead reflect reliance on these auditory-sensory processing stages. Both of these regions related to verbal working memory have been shown to be involved in reading. Our findings suggest that endophenotypical changes in the left posterior temporal cortex may comprise novel pathomechanisms for verbal working memory related processes translating *TNFRSF1B* genotype into dyslexia-associated phenotypical deficits.

Congresses, Workshops, and Symposia

2012

Boesch, C., Friederici, A. D., Hoppe-Graff, S., Keller, H., Schröger, E., Schücking, B., et al. (November–December 2012). *Experimental and anthropological perspectives on early childhood*. Symposium. University of Leipzig, Germany.

Démonet, F., Friederici, A. D., Naito, E., Mattingley, J., Papagno, C., & Vallar, G. (June 2012). *International Neuropsychological Symposium 2012. Topic 1. Neuroplasticity*. Bonifacio – Corsica, France.

Haspelmath, M., Heck, F., Regel, S. (September 2012). *Decomposition and natural classes in argument coding. Workshop*. University of Leipzig, Germany.

Friederici, A. D. (October–March). *Language Series – Winter Semester 2011/2012*. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Friederici, A. D. (April–September). *Language Series – Summer Semester 2012*. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Friederici, A. D. (October–March). *Language Series – Winter Semester 2012/2013*. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

2013

Friederici, A. D. (April–September). *Language Series – Summer Semester 2013*. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Friederici, A. D. (October–March). *Language Series – Winter Semester 2013/2014*. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Degrees

PhD Theses

2012

Gierhan, S. *Brain networks for language. Anatomy and functional roles of neural pathways supporting language comprehension and repetition*. University of Leipzig, Germany.

Schipke, C. *Processing mechanisms of argument structure and case-marking in child development: Neural correlates and behavioral evidence*. University of Potsdam, Germany.

Skeide, M. *Syntax and semantics networks in the developing brain*. University of Leipzig, Germany.

2013

Bacha-Trams, M. *Neurotransmitter receptor distribution in Broca's area and the posterior superior temporal gyrus*. University of Leipzig, Germany.

Knoll, L. J. *When the hedgehog kisses the frog. A functional and structural investigation of syntactic processing in the developing brain*. University of Potsdam, Germany.

Merrill, J. *Song and speech perception – Evidence from fMRI, lesion studies and musical disorders*. University of Potsdam, Germany.

Meyer, L. *The working memory of argument-verb dependencies*. University of Potsdam, Germany.

Appointments

Kotz, S. A. *Professorship.* University of Manchester, United Kingdom. **2012**

Mueller, J. L. *Assistant Professorship.* Osnabrück University, Germany. **2013**

Awards

Vavatzanidis, N. *1st Place Poster Award*: *Basic auditory detection abilities as prerequisites for language acquisition*. 9th Congress of Spanish-German Society of Otorhinolaryngology, Head and Neck Surgery, Dresden, Germany. **2012**

Vavatzanidis, N. *Rehder-Poster Award*: *Zur Diskriminationsfähigkeit sprachrelevanter Merkmale bei jungen Cochlear-Implant-Kindern*: *Eine EEG-Studie*. 15th Annual Meeting of The German Society of Phoniatrics and Pediatric Audiology (DGPP), Germany.

Heidemann, R. M., & Anwander, A. *Winners of the Max Planck Award "Hidden Treasures"*. Max Planck Society, Germany. **2013**

Vavatzanidis, N. *Annelie-Frohn-Award*. The foundation's prize was awarded at the 16th Annual Meeting of the The German Society of Phoniatrics and Pediatric Audiology (DGPP), Germany.

Publications

Note: For publications by Kotz, S. A. and colleagues, please see publication list in chapter 7.4 (Former) Minerva Research Group "Neurocognition of Rhythm in Communication".

Books and Book Chapters

Friederici, A. D. (in press). Is there a brain basis of recursion? In F. Lowenthal, & L. Levebvre (Eds.), *Language and Recursion*. New York, USA: Springer.

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Knoll, L. J. (2013). When the hedgehog kisses the frog: A functional and structural investigation of syntactic processing in the developing brain (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 150*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

Männel, C. (2012). Die Schnittstelle Prosodie-Syntax im Spracherwerb. In C. Kauschke, S. Ott, & V. Maihack (Eds.), *Prosodie und Kindersprache: die Bedeutung der Prosodie und ihrer Schnittstellen für Spracherwerb und Sprachtherapie; Tagungsbericht zum 13. Wissenschaftlichen Symposium des dbs e.V. am 27. und 28. Januar 2012 in Marburg* (pp. 95–116). Köln: ProLog.

Merrill, J. (2013). Song and speech perception: Evidence from fMRI, lesion studies and musical disorder (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 148*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

Meyer, L. (2013). The working memory of argument-verb dependencies: Spatiotemporal brain dynamics during sentence processing (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 145*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

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Index of Published Figures

Figure 2
Friederici, A. D. (2012). The cortical language circuit: From auditory perception to sentence comprehension. *Trends in Cognitive Sciences, 16*(5), 262–268.

Figure 2.1.2.1
Figure adapted from Makuuchi, M., Grodzinsky, Y., Amunts, K., Santi, A., & Friederici, A. D. (2013). Processing non-canonical sentences in Broca's region: Reflections of movement distance and type. *Cerebral Cortex, 23*(3), 694–702.

Figure 2.1.2.2
Makuuchi, M. & Friederici, A. D. (2013). Hierarchical functional connectivity between the core language system and the working memory system. *Cortex, 49*(9), 2416–2423.

Figure 2.1.3.1
Figure adapted from Meyer, L., Obleser, J., & Friederici, A. D. (2013). Left parietal alpha enhancement during working memory-intensive sentence processing. *Cortex, 49*(3), 711–721.

Figure 2.1.8.1, Figure 2.1.8.2
Jeon, H.-A. & Friederici, A. D. (2013). Two principles of organization in the prefrontal cortex are cognitive hierarchy and degree of automaticity. *Nature Communications*, *4*:2041. doi:10.1038/ncomms3041

Figure 2.1.9.1
Friederici, A. D., Mueller, J., Oberecker, R. (2011). Precursors to natural grammar learning: Preliminary evidence from 4-month-old infants. *PLoS ONE, 6*(3): e17920.

Figure 2.1.9.2, Figure 2.1.9.3
Friederici, A. D., Mueller, J. L., Sehm, B., & Ragert, P. (2013). Language learning without control: The role of the PFC. *Journal of Cognitive Neuroscience, 25*(5), 814–821.

Figure 2.2.5
Figure adapted from Brauer, J., Anwander, A., Perani, D., & Friederici, A. D. (2013). Dorsal and ventral pathways in language development. *Brain and Language*. Advance online publication. doi:10.1016/j.bandl.2013.03.001.

Professor Dr Tania Singer
Director

3 Foundations of Human Sociality

Department of Social Neuroscience

The scientific focus of the Department of Social Neuroscience is on understanding the foundations of human social cognition and social behaviour. Through an interdisciplinary and multi-method approach, we study the neuronal, hormonal, developmental, and evolutionary foundations of human social cognition and social emotions such as empathy, compassion, revenge, and *Schadenfreude*, as well as our sense of fairness and envy, in children, adults, and clinical populations. Furthermore, we are interested in how social motivation and cognition influence social and economic decision making and how they can be regulated and trained to achieve better cooperation, well-being, and health. One major focus is on investigating the plasticity of the social brain. This focus is reflected in a large-scale longitudinal mental training study, the *ReSource Project*, in which we investigate the effects of socio-affective and cognitive mental training on structural and functional brain plasticity as well as on changes in subjective well-being, prosociality and economic decision making, emotion-regulation capacities, attentional and executive cognitive functions, and stress- and other health-related parameters in 160 subjects over a period of more than nine months.

The four major interconnected research foci of the department are:

1. Foundations of Human Sociality and Neuroeconomics
2. Developmental Social Neuroscience
3. Plasticity of the Social Brain
4. Psychopathology of the Social Brain

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3.1 Foundations of Human Sociality and Neuroeconomics

One important part of our research programme is to identify the various routes underlying social cognition and emotions, that is, our ability to understand others. Here, we are working towards a unifying model of social cognition. Previous research in social neuroscience has identified at least three major networks for social cognition that are essential to our ability to understand others: (a) motor actions—the so-called mirror neuron system, (b) beliefs and desires—the so-called mentalizing or Theory of Mind (ToM) system, and (c) affective states—our ability to empathize. On the one hand, these different routes of social cognition seem to rely on different brain networks, but on the other hand, there are common mechanisms in our brain which enable an experience of intersubjectivity. For example, so-called "shared networks" or "simulation mechanisms" rely on the activation of representations underlying our own motor actions, thoughts, and feelings to understand these states in others. In the last few years, we have expanded these "shared network" models of social cognition to also explain how such simple projection mechanisms can sometimes lead to non-adaptive "empathic distress" when exposed to the strong suffering of another. Alternatively, it can lead to emotional egocentricity bias (EEB) if one fails to engage in clear self-other distinction, especially in situations where states of oneself are incongruent to another person's states (see also paragraph 3.2). Furthermore, we have developed new paradigms to study the interaction between different routes of social cognition (e.g. the EmpaToM) as well as to understand the commonalities and differences between social emotions such as emotion contagion (e.g. stress contagion), empathy, and compassion (see also paragraph 3.3).
Another focus was to study the role of another unique feature of social human beings, our ability to engage in self-generated thoughts (SGTs), i.e. to ponder events which are unrelated to the events in the here and now. The aim here is again to obtain a better understanding of mechanisms underlying social cognition. We achieve this by exploring different contents of SGTs, or more specifically whether these are future- or past-, self- or other-related, or negatively- or positively valenced. Additionally, it is crucial to investigate how engagement in different thought content is dependent on the context and how SGTs can be understood in terms of the brain's attempt to make predictions in order to navigate the complex social world in which we live.

Finally, the department has once again begun to focus on neuroeconomics, a topic which was at the heart of Tania Singer's research programme throughout her years in Zurich. In line with the overall research programme of the Department of Social Neuroscience, the main question here focuses on how social cognition and emotions can explain human social interaction and human economic decision making. The new research programme, funded by the Institute for New Economic Thinking (INET) in cooperation with Professor Dennis Snower, president of the Kiel Institute of World Economy, explores new avenues of how psychological and neuroscientific knowledge about human motivation, emotion, and social cognition can inform models of economic decision making in addressing global economic problems. In particular, the programme seeks to create a new generation of economic models that allow for more cooperative, pro-social, and sustainable economic behaviours. In sum, this research aims to provide a new vision of a "caring economics".

3.1.1 The EmpaToM: A novel task separating cognitive and affective routes to social cognition

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Social neuroscience has differentiated at least two neural networks underlying the understanding of others: one allowing for affect sharing (empathizing) and another underlying the inference of thoughts and beliefs (mentalizing or Theory of Mind (ToM)). A task that reliably and efficiently distinguishes between them within an individual, therefore also enabling the investigation of their interaction, is still lacking. We therefore developed a novel paradigm, the EmpaToM, which presents participants with naturalistic video stimuli in which people talk about emotionally negative or neutral episodes of their lives. Each video is followed by affect ratings probing empathic responses and specific questions probing ToM. The results show that answering ToM-questions activates the well-described mentalizing network including the temporoparietal junction, the temporal poles, and the medial prefrontal cortex (Fig. 3.1.1). These clusters largely overlapped with a classical false-belief ToM-task assessed in the same participants (Dodell-Feder et al., 2011, NeuroImage, 55, 705–712). Witnessing emotional compared to neutral videos, in contrast, activated a distinct network including the anterior insula and the anterior midcingulate cortex. This network overlapped with a previously developed empathy task, tested in the same participants (Klimecki et al., 2013a).

The data confirm that the EmpaToM allows us to separate the ability to empathize and mentalize within a single paradigm of only 30 minutes duration within individuals. This means that the task is highly likely to be of tremendous use for the comprehensive characterization of specific deficits in socio-affective as well as socio-cognitive functioning in different psychopathologies and for the measurement of differential mental training effects based on affective or cognitive interventions, both on the level of behaviour and brain functioning.

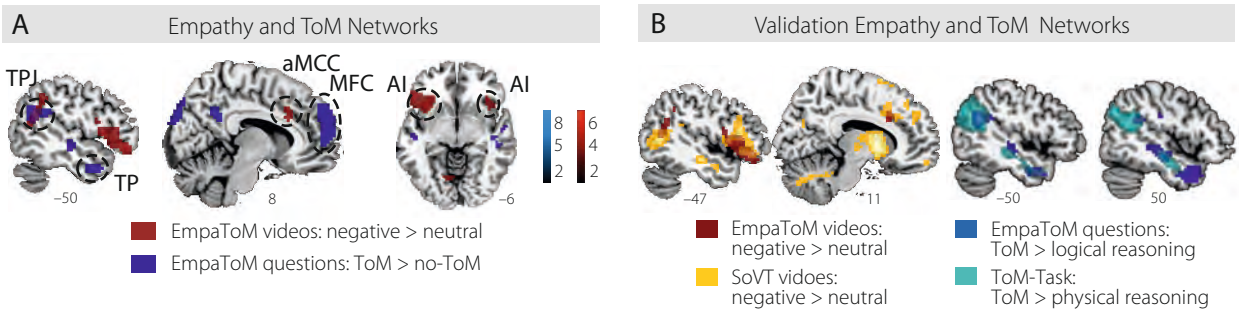

Figure 3.1.1 (A) Activation for Theory of Mind (ToM) in the temporoparietal junction (TPJ), the temporal poles (TP), and the medial frontal cortex (MFC) and for empathy in the anterior insula (AI), and the anterior midcingulate cortex (aMCC). (B) Overlap of the activations shown in A with those in the Socio-affective Video Task (SoVT) and an established ToM task.

3.1.2 Structural covariance networks of dorsal anterior insula predict individual differences in empathy

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Previous fMRI studies have shown key roles of dorsal anterior insula (dAI) in empathy for others' suffering. Brain connectivity research has suggested that empathic inferences rely on the integration of affective information with socio-cognitive processes such as action observation and perspective taking. Whether such network interactions are reflected in inter-regional structural brain networks, and whether these relate to individual differences in empathy, remains unexplored. Here, we mapped structural covariance networks centred on dAI and studied how

these networks are modulated by individual differences in empathic responding. In 94 women, individual differences in empathic responses were quantified through empathy state ratings during a Socio-affective Video Task (SoVT) that depicts people in distress, and an empathy trait questionnaire. Based on T1*-weighted MRI, we measured cortical thickness using FreeSurfer. Covariance networks were mapped by correlating dAI thickness with thickness across the cortical mantle. We studied the parametric interaction between seed covariance and inter-individual differences in empathic state ratings and trait scores. We observed widespread dAI covariance patterns to prefrontal, temporo-limbic, and midline regions (Fig. 3.1.2A). Participants with high empathy state ratings during high relative to low emotion videos (Fig. 3.1.2B) showed increased covariance of left and right dAI to prefrontal and limbic regions (Fig. 3.1.2C). Right dAI covariance to prefrontal cortices was also positively modulated by trait empathy scores. Covariance analysis indicated a hub-like connectivity profile of the dAI. Importantly, dAI networks consistently related to individual differences in empathic responding. Our work provides novel evidence for a contribution of fronto-limbic structural networks to individual differences in social emotions.

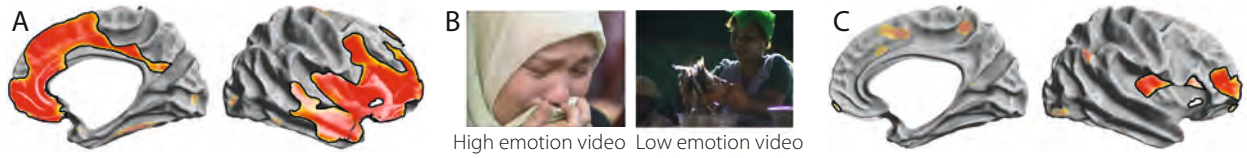

Figure 3.1.2 (A) Structural covariance networks of the right dorsal anterior insula (dAI) in 94 healthy women. Significant correlations between cortical thickness in dAI and thickness of cortical target regions were interpreted as structural networks. (B) The Socio-affective Video Task employed to measure individual differences in empathic responding. Participants watched a series of high and low emotion videos and provided state ratings of positive affect, negative affect, and empathy. (C) Positive interactions between the degree of structural covariance of dAI and empathy ratings during the Socio-affective Video Task, indicating higher structural coupling of dAI in subjects with higher empathy ratings relative to those with lower ratings. Findings in A and C are thresholded at *FEW* < 0.05.

Cortisol increase in empathic stress is modulated by social closeness and observation modality

3.1.3

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The incidence of stress-related disorders is steadily on the rise. In this context, the question arises whether the stress inevitably unfolding around us has the potential to "contaminate" and compromise us. We here investigated a) the existence of such empathic stress, b) whether it permeates to the core of the stress system, the hypo-

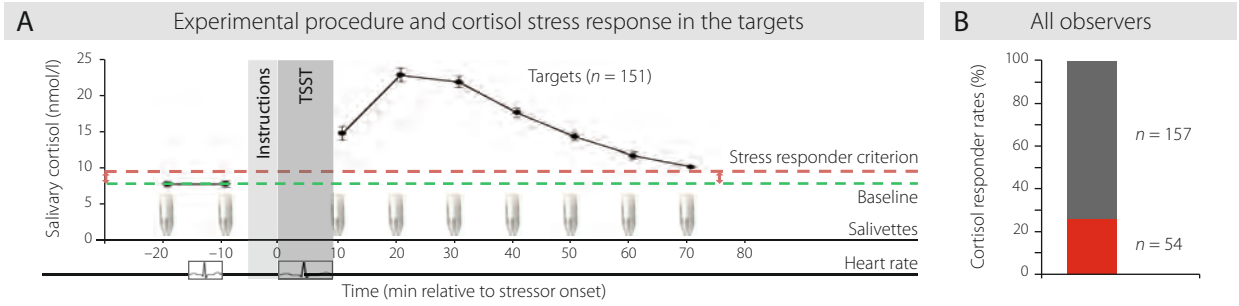

Figure 3.1.3.1 (A) Participants attended one 130-min session at the laboratory. All participants rested for a period of 30 min. At 45 min after arrival, the targets were provided with the test instructions. Stress induction started at 50 min after arrival. Subsequent to the stress phase, participants were asked to rest for 60 min. Saliva samples (for cortisol and alpha-amylase assessments) were taken at 20 and 10 min before stressor onset, immediately after stressor cessation, and at 10-min intervals thereafter. Heart rate was measured for a 5-min baseline between 15 and 10 min prior to stressor onset and during the 10-min stress phase. The target's raw cortisol values are projected onto the experimental timeline showing a significant first-hand stress response to the Trier Social Stress Test. The dashed red line marks what has been defined as a significant physiological cortisol stress response of at least 1.5 nmol/l over the baseline. (B) Rates of observers (the entire observer sample; $N = 211$) responding with physiologically significant cortisol increases after passively watching a target undergo the Trier Social Stress Test. In the entire observer sample ($N = 211$).

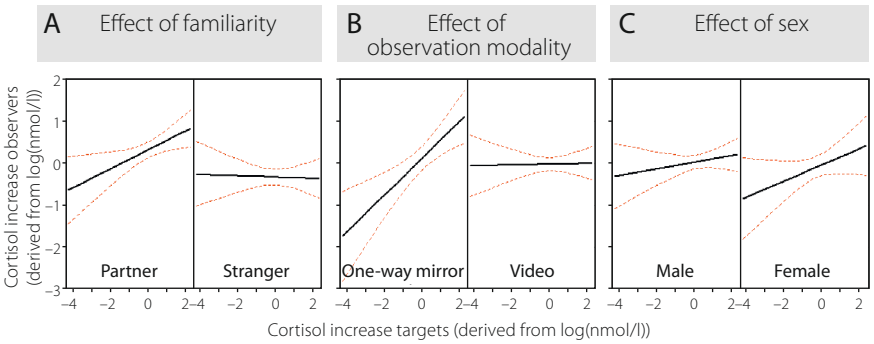

Figure 3.1.3.2 Modulatory factors of cortisol stress resonance. (A) The calculated linear mixed-effects model showed higher stress resonance in emotionally close observer-target dyads ($p = 0.05$) such that observers' and targets' ($N = 111$ for both) cortisol responses were positively correlated in the partner condition. There was no association between observers' and targets' ($N = 100$ for both) cortisol responses in the stranger condition. (B) Indicating higher stress resonance given the real-life representation of the stressful situation ($p < 0.001$), observers' and targets' ($N = 50$ for both) cortisol responses were positively correlated in the direct observation condition. There was no association between observers' and targets' ($N = 161$ for both) cortisol responses in the indirect observation condition. (C) Observer sex had no significant influence on stress resonance ($p > 0.10$).

thalamic-pituitary-adrenal (HPA) axis, and c) by which factors empathic stress responses may be modulated. Participants were tested in dyads, paired with a loved one or a stranger of the opposite sex. While the target of the dyad was exposed to a psychosocial stressor (Trier Social Stress Test; Kirschbaum et al., 1993, Neuropsychobiology, 28, 76–81), the observer watched through a one-way mirror or via live video transmission. Overall, 26% of the observers displayed physiologically significant cortisol increases. This empathic stress was more pronounced in intimate observer-target dyads (40%) and during the real-life representation of the stressor (30%). Empathic stress was further modulated by interindividual differences in empathy measures. Despite the higher prevalence of empathic stress in the partner and direct observation conditions, significant cortisol responses also emerged in strangers (10%) and the indirect observation modality (24%). The occurrence of empathic stress down to the level of HPA-axis activation, even in total strangers and when witnessing another's distress on TV, may have important implications for public health policy.

3.1.4 Mind your thoughts when stressed: Switching from negative to future-focused social thoughts accelerates stress recovery

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Stress is a major health burden in today's society. Research shows that negative cognitive styles are associated with increased stress reactivity, low mood, and accelerated cellular aging. We examined how the induction of psychosocial stress (Trier Social Stress Test; Kirschbaum et al., 1993, Neuropsychobiology, 28, 76–81)

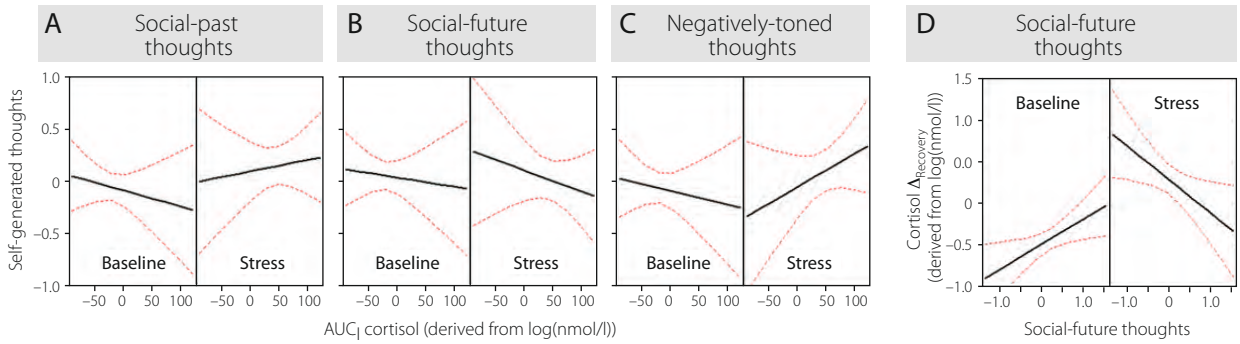

Figure 3.1.4 (A) Results of the linear mixed effects model testing the influence of cortisol levels on self-generated thoughts (SGTs). Cortisol levels had no significant influence on (A) Past-oriented SGTs and (B) Future-oriented SGTs. (C) There was a significant interaction of session and the area under the curve with respect to increase (AUCI) on the emotional component of SGTs in the hypothesized direction ($t = 2.010$*), i.e. thoughts be-

came more negative with higher stress-induced cortisol increases, while thoughts and AUCI were unrelated in the baseline condition. (D) Results of the linear mixed effects model testing the influence of baseline and stress-induced cognitions on cortisol recovery (diurnal decline). An interaction of session and future-oriented thoughts ($t = -3.167^{**}$) showed that more future thoughts came with a less steep decline in diurnal cortisol levels in the baseline condition. Inversely, in the stress condition, more engagement in future-oriented thinking was associated with a steeper decline and thus a faster return of cortisol levels to baseline.

influenced thought processes and how, in turn, post-stress thoughts influenced stress recovery measured in terms of hypothalamic-pituitary-adrenal axis and sympathetic activity. Features of self-generated thoughts were assessed using thought sampling while participants performed cognitive tasks in a baseline condition or following stress induction. Higher cortisol stress responses predicted more negative post-stress thinking. However, individuals focusing on future-oriented social content recovered faster from stress. Our results, therefore, illustrate the reciprocal relationship between psychosocial stress and self-generated thoughts. Critically, we identified the importance of the temporal focus of thoughts in adaptively coping with acute stress—a finding that may have important implications for understanding and counteracting the high incidence of stress-related disorders in today's society.

Classifying the wandering mind: Revealing the affective content of thought during task-free rest periods

3.1.5

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Many powerful human emotional thoughts are generated in the absence of a precipitating event in the environment (Killingsworth, & Gilbert, 2010, Science, 330, 932–932). Here, we tested whether we can decode the valence of internally driven, self-generated thoughts in a task-free session based on neural similarities with task-related affective mental states. To address this issue, we acquired functional magnetic resonance imaging (fMRI) data while participants generated positive and negative thoughts as part of an attribution task (Session A) and while they reported the occurrence of comparable mental states during task-free rest periods (Session B).

With the use of advanced multivariate pattern analyses (MVPA) (Kriegeskorte et al., 2006, PNAS, 103, 3863–3868), we identified response patterns in the medial orbitofrontal cortex (mOFC) that encode the affective content of thoughts that are generated in response to an external experimental cue. Importantly, these neural signatures of task-driven emotional thought reliably predicted the occurrence of affective thoughts that were generated during unconstrained rest periods recorded one week apart (Fig. 3.1.5). This demonstrates that at least certain elements of task-cued and task-independent affective experiences rely on a common neural code. Furthermore, our findings reveal the role that the mOFC plays in determining the affective tone of internally driven, unconstrained thoughts, which have been linked to low levels of mood in daily life and are dysfunctional in individuals with depression. More generally, our results suggest that MVPA is an important methodological tool for attempts to understand unguided subject-driven mental states such as mind-wandering and daydreaming based on neural similarities with task-based experiences.

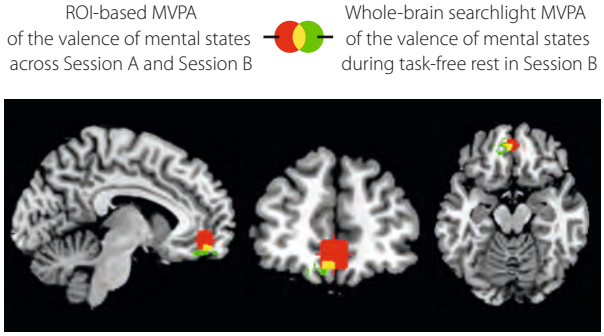

Figure 3.1.5 Cross-session multivariate pattern analyses (MVPA) revealed that response patterns in the medial orbitofrontal cortex (mOFC, illustrated in red) obtained during task-based attributions in Session A predicted the valence of unconstrained thoughts during task-free rest in Session B (average of 57% decoding accuracy across participants, ± 2.94 S.E.M, $p = 0.03$). Supplemental whole-brain MVPA (searchlight decoding) confirms the role of the mOFC (illustrated in green) in decoding the valence of unconstrained self-generated mental states during rest periods in Session B ($p < 0.05$, FWE corrected for multiple comparisons at the cluster level). Yellow indicates the overlap of predictive clusters in the mOFC.

3.2 Developmental Social Neuroscience

Social processes and behaviour as well as affective experience are subject to considerable changes from childhood to adulthood. In line with our general theoretical framework of the Department of Social Neuroscience, our efforts have focused largely on identifying the developmental mechanism underlying different routes of social cognition and social emotions as well as social interaction and decision making. For instance, studies on social and economic decision making in children using game-theoretical paradigms have pinpointed the importance of executive functions and particularly impulse control for the generation of behaviours typically described as mature, such as being fair or patient. Using a range of methods, including functional and structural imaging and an extensive battery of behavioural tests, it has been possible to isolate the functional development of the left dorsolateral prefrontal cortex (lDLPFC) as a key structure in implementing behavioural control at the time of making social or economic decisions. Furthermore, we could show that this brain region continues to play a role in decision making into adulthood independently of any developmental changes. Other studies have focused on the emergence and change of social emotions such as envy and *Schadenfreude*, as well as the ability to make empathic judgments when in an incongruent affective state to the target, i.e. to overcome emotional egocentricity bias (EEB). On the basis of a few newly developed paradigms to optimally assess social emotions and EEB during development, we could show that envy and *Schadenfreude* decrease with age during childhood presumably as a function of improved emotion regulation abilities, a decrease predictive also of age-related changes in spiteful decisions. Additionally, we report in several independent studies that overcoming EEB improves with age. While this was not related to age-related changes in overcoming cognitive egocentricity in the context of Theory of Mind tasks, it could be explained in terms of structural development and therefore also by a functional recruitment of the right supramarginal gyrus (rSMG). This latter is a region we had previously identified to be crucial in distinguishing between one's own and another's affective experience in adults (see also paragraph 3.2.1). Further connectivity analyses suggested that it was the late maturation of both rSMG and DLPFC, the latter being necessary to implement those social judgements, that caused the observed developmental differences in EEB. In sum, our work has made considerable progress in exploring the developmental time course of social emotions and cognition from the age of 6 onwards, and it identifies some of the relevant neurocognitive mechanisms that allow children to increasingly make socially adequate sound decisions and resolve conflicts in their own and another's emotional experience.

Future studies will focus on extending these findings to include both even younger children and adolescents. Studies on younger children will focus on the critical periods at which certain key social faculties such as empathy, compassion, or Theory of Mind emerge and which brain structures give rise to these. Exploring the period of adolescence, on the other hand, will allow us to bridge studies on children and adults and to see if changes in this period follow a linear trajectory or are in fact subject to the kind of non-linear changes that are typically observed in brain development during this phase. In particular, this last question offers exciting avenues for potential intervention, given that such a presumed reorganization indicates heightened plasticity.

3.2.1 Overcoming emotional egocentricity bias with age results from functional development of right supramarginal gyrus

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Humans typically judge others egocentrically, assuming that they feel or think similarly to themselves. Such an emotional egocentricity bias (EEB) occurs especially in situations when others feel differently to oneself. Cognitive development through childhood is marked by difficulties in cognitive perspective taking, a capacity which improves with age and into adulthood. What remains unknown, however, is whether the development of overcoming affective egocentricity undergoes a similar and comparable ontogenetic trajectory and which kind of brain regions support its development.

Thus, we studied the neurocognitive mechanisms underlying the developmental capacity to overcome such EEB in 30 children aged from 6 to 13 years and compared them with 20 adults aged from 21 to 30 years. We show that children display a stronger EEB than adults (Fig. 3.2.1A) and that this results from reduced activation in the right supramarginal gyrus (rSMG; Fig. 3.2.1B). Crucially, rSMG activation correlated with age-related differences in cortical thickness of this region. The region of rSMG identified in the present study shows a considerable overlap with the rSMG identified in previous studies looking at the EEB by means of a paradigm using visuo-tactile stimulation in adults (Silani et al., 2013; Fig. 3.2.1C). These findings show that children's difficulties in overcoming EEB may be due to late maturation of regions distinguishing between conflicting socio-affective information.

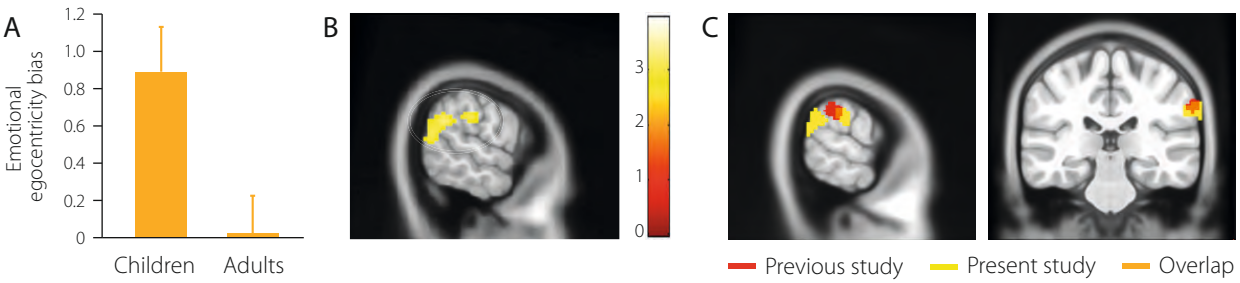

Figure 3.2.1 (A) Children showed considerably stronger EEB than adults. (B) This could be explained by significantly reduced activation of the rSMG for children compared to adults. (C) Activation of the rSMG observed in the present study overlapped with the rSMG activation of a previous study using visuo-tactile stimulation to induce an EEB.

3.2.2 Children's increased emotional egocentricity bias (EEB) compared to adults is mediated by their ability to resolve emotional conflict

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Previous developmental research found that children as compared to adults (see 3.2.1) show an increased EEB, which relies on late maturation of brain structures required to overcome EEB such as the right supramarginal gyrus (rSMG) and its connectivity to DLPFC. As the exact mechanisms subserved by rSMG are yet unclear, we aimed to explore underlying cognitive functions possibly subserved by rSMG such as attentional, inhibitory-, or emotion regulation functions. To elucidate the underlying cognitive mechanisms explaining age-related decreases in emotional egocentricity, we developed a new taste-paradigm that can be used equally well in children and adults to reliably assess EEB. In addition we assessed children's (N = 30, 7–12 years) and adults' (N = 30, 20–30 years) abilities in inhibitory control, emotional conflict processing (Flanker task), emotion regulation, attentional reorienting, perceptual fluency, and visual perspective taking. In the taste-paradigm, two participants tasted either pleasant (juices) or unpleasant (e.g. salt solutions) liquids. They then had to judge either their own or the

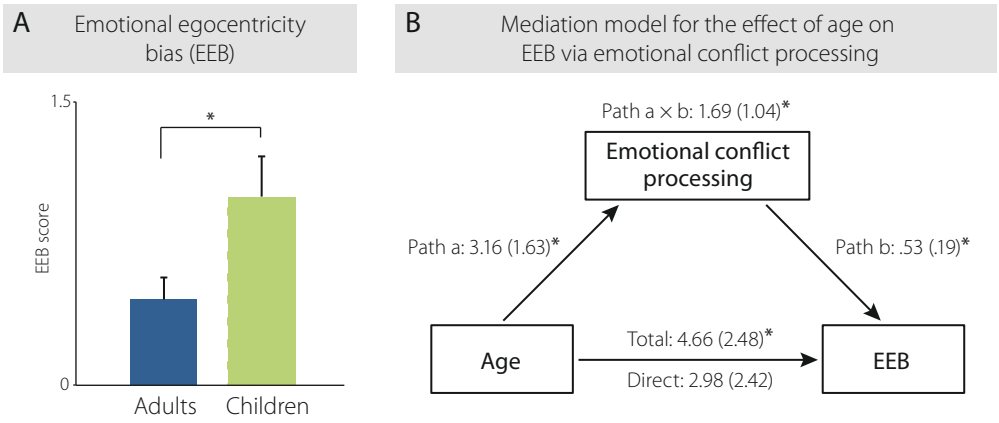

Figure 3.2.2 (A) The EEB was defined as the difference between ratings in incongruent and congruent trials when judging the other, as compared to the difference when judging one's own feelings (Silani et al., 2013). Whereas both adults and children show an EEB, children's EEB is significantly larger and more than double the size of the adults' EEB. (B) Display of the mediation model with emotional egocentricity bias as outcome variable, age as independent variable, and emotional conflict processing as mediator variable. Values are unstandardized regression coefficients, and asterisks indicate significant coefficients (*$p < 0.05$). There was a significant mediation effect of emotional conflict processing with respect to the relationship between age and the EEB.

other participant's emotion. The emotional experiences of both participants could be either congruent or incongruent. Results showed a highly significant EEB for both children and adults, but for children this EEB was significantly larger (Fig. 3.2.2A). A mediation analysis revealed that age-related decrease in EEB was fully mediated by age-related improvements in resolving emotional conflict, whereas all other functions did not seem to play a significant role in overcoming EEB (Fig. 3.2.2B). Our findings therefore suggest that the increased EEB in children compared to adults is mediated by children's ability to resolve emotional conflict, and not by other cognitive abilities that have also been largely associated to functions of the right temporal parietal junction including rSMG such as attentional reorienting, visual perspective taking, or inhibitory control.

Age-related changes in envy and *Schadenfreude* predict spiteful decisions during childhood

3.2.3

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Social comparison, which can encompass physical attributes as well as income, occurs pervasively amongst humans. Depending on whether one emerges favourably or not, this can lead to particular kinds of social emotions, such as *Schadenfreude* and envy. These social emotions can act as motivational forces to alter social interaction and decision making. However, little is known about how this occurs and if such a link already exists during child development. We hypothesize that the extent to which *Schadenfreude* and envy are differentially experi-

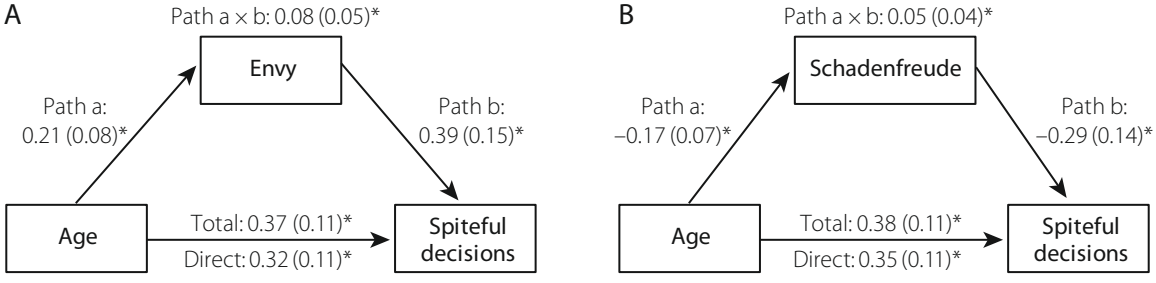

Figure 3.2.3 Age-related changes in spiteful decisions are partially mediated by developmental changes in (A) envy and (B) *Schadenfreude*.

enced during development is predictive of spiteful monetary decisions (i.e. decisions which aim to maximize the economic difference between oneself and another in favour of oneself). Given that previous studies have shown a decrease in spiteful behaviour during childhood, we hypothesized that this decrease might be a result of age-related decreases in the experience of envy and *Schadenfreude*. Using a speeded reaction time paradigm in which children were rewarded or punished by means of winning or losing monetary units (MUs), we created a competitive situation in which 210 children aged 7 to 13 years could win as much as, or as little as, or more, or less than a competitor. After seeing their own and their competitor's wins and losses, children were asked to indicate how they felt. In a second paradigm, children could allocate resources between themselves and another anonymous child in a series of three games. We show a significant decrease in envy and *Schadenfreude* with age as well as a significant decrease in spiteful decisions made in the allocation games. Importantly, we show that this decrease in spite was mediated by the decrease in the experience of both envy (Fig. 3.2.3A) and *Schadenfreude* (Fig. 3.2.3B). These data suggest that developmental differences in the experience and presumably also in the regulation of social emotions are linked to age-related changes in prosocial behaviour.

3.2.4 Development of functional coupling between vmPFC and lDLPFC predicts age-related changes in intertemporal choice during childhood

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Human decision making is faced with a myriad of challenges of what to choose when multiple options are available. When these options vary in their temporal availability, humans, like most other species, will opt for what is more immediately available, something also known as temporal discounting. Whereas it has been shown that discounting the future decreases with age, little is known about the neurocognitive mechanisms underlying this developmental change.

We tested 20 children ranging from 6 to 12 years and let them choose between rewards differing in size and availability. Specifically, we offered one small reward available immediately (SS) and a larger reward available at a later point (LL) in the future. We show that with age, children chose the LL option more often, showing improvements in delaying gratification. At the neural level, we observed that individuals who chose the delayed reward more frequently also showed more connectivity between the ventromedial prefrontal cortex (vmPFC) and the left dorsolateral prefrontal cortex (lDLPFC; Fig. 3.2.4). This functional coupling was also modulated by age and the ability to inhibit prepotent impulses as indicated by performance on a motor inhibition task. These data suggest that developmental improvements in resisting temptation of immediately available rewards occur as a function of an age-related increase in connectivity between brain regions dedicated to valuation (i.e. vmPFC) and behavioural control (i.e. DLPFC).

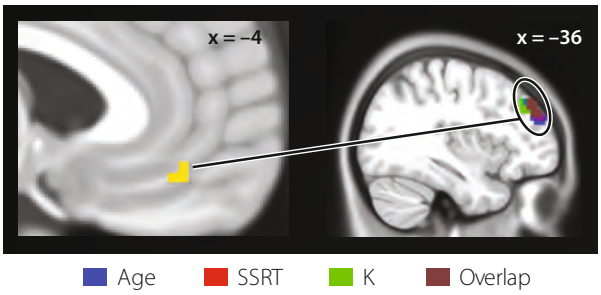

Figure 3.2.4 During intertemporal choice functional connectivity between the vmPFC and the DLPFC was significantly modulated by individual differences in temporal discounting, as well as age and an independent measure of impulse control.

Age-corrected cortical thickness of left DLPFC in children is associated with impulsive behaviour and in turn predicts strategic decision making

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Human social exchange is often subject to conflicts of interest which require resolution. Little is known about the cortical substrates that allow such conflicts to be resolved in the context of social interactions and how the development of these gives rise to typically observed age-related changes in social behaviour. We studied 28 children ranging in age from 6 to 13 years and looked at their decisions made in the context of two economic games differing in their demand on strategic behaviour: the Dictator and the Ultimatum Game (DG and UG, respectively). In both games, Player A is given a sum of money to divide with Player B. Whereas in the DG, Player A can decide however much to allocate without Player B being able to take an active part in the process, in the UG Player B can decide to accept or reject the offer made by Player A. In the case of acceptance, the money is divided between the players as proposed. In the case of a rejection, neither player obtains anything. Thus, Player A needs to take this sanctioning threat into consideration when making the offer in the UG and the difference in offer size between the two games thus provides a good measure of strategic social behaviour. We measured cortical thickness of a region of interest in the left dorsolateral prefrontal cortex (lDLPFC) and correlated this with age, our measure of strategic social behaviour, and an additional measure of impulse control. We found that whereas there was no change in cortical thickness of lDLPFC with age in our children sample (Fig. 3.2.5A), when correcting for age, thickness in lDLPFC was positively related to strategic behaviour (Fig. 3.2.5B) as well as impulse control abilities (Fig. 3.2.5C). These findings are among the first to demonstrate a link between brain structure and a high-level socio-cognitive function such as strategic social behaviour and could either reflect an effect of genetic predisposition on brain structure and subsequent behaviour, or an expertise effect of behaviour shaping brain structure.

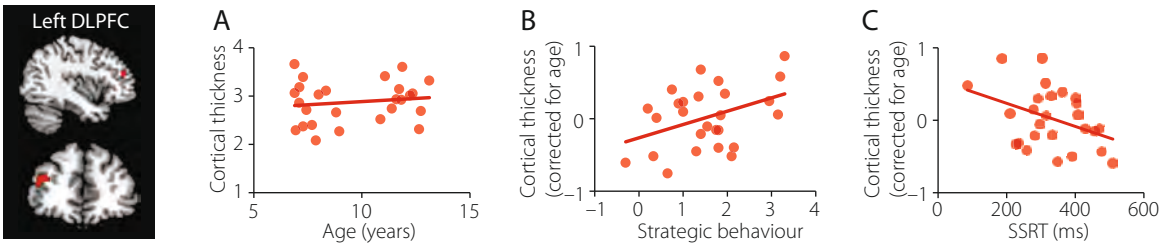

Figure 3.2.5 (A) There were no age-related changes in cortical thickness in the left DLPFC between the ages of 6 and 13. (B) Age-corrected cortical thickness of the left DLPFC correlated positively with strategic social behaviour as well as (C) with an independent measure of impulse control.

3.3 Plasticity of the Social Brain

Modern society is characterized by economic and environmental crises, increasing levels of stress- and depression-related diseases, marked individualism, and increasing egoism. The development of scientifically validated mental training programmes focusing on the cultivation of compassion and altruism has thus the potential to help increase mental and physical health on individual levels but also the development of prosocial motivation, increased levels of cooperation, and ultimately more sustainable and caring economic, social, and political systems. This research focus aims to investigate the subjective, behavioural, neuronal, and hormonal changes associated with mental training of socio-affective as well as cognitive capacities ranging from attention and mindfulness, empathy, prosocial motivation, and compassion to emotion-regulation and perspective taking on self and others.

Even though plasticity research has a long tradition in fields such as psychology and neurosciences, especially in the latter the focus of investigation has largely been on the malleability of cognitive or motor functions and systems. In contrast, little is known about the neural substrates underlying socio-affective plasticity and the training of positive social affect, prosocial motivation, or compassion. In order to reliably study neural, physiological, and behavioural changes induced by such mental training programmes, we started to develop a range of new tasks optimized for repeated measurements of socio-affective functions in longitudinal intervention designs as well as new short- and long-term intervention programmes. All the programmes used are secular in nature and mostly based on practices derived from contemplative traditions in the East as well as different approaches from the West. The latter includes dyadic exercises, web-based training, and group exercises. They all aim to achieve better mental and physical health.

One major study of the department was the realization of a European funded (ERC) 1-year longitudinal mental training study, the *ReSource Project*. This unusual and large-scale mental training study involves nearly the entire department, a group of 17 teachers, and more than 200 participants. The latter are tested repeatedly with a battery of many paradigms and questionnaires while they are undergoing mental training every day over a period of nine months (see paragraph 3.3.1). We also explore whether cultivating compassion via mental training in healthy adult populations is based on genetic differences or induces epigenetic modifications, and whether these are then associated with changes in stress physiology, social behaviour, and brain plasticity.

Finally, we investigate the plasticity of the social and compassionate brain using expert models. More specifically, we compare structural and functional neuroimaging and behavioural data from meditation experts (i.e. people who participated at least once in a full-time 3-year meditation retreat and practise meditation regularly) with naive control subjects. We are interested, for example, in the effect of compassion training expertise on pain analgesia, emotion-regulation capacities, and economic decision making. This will also allow us to reconfirm results we have found and will find with naive non-trained participants before and after short- and long-term compassion training. As a multi-method approach is characteristic for the department, we investigate brain plasticity by complementing our analyses with data from computer tasks, autonomic measurements, game-theoretical paradigms, questionnaires, observer reports, subjective measures, virtual reality scenarios, immune and stress-physiological analyses, as well as analyses of gene variants and epigenetic markers.

3.3.1 The *ReSource Project:* Investigating the effect of mental training on structural and functional brain plasticity, behavioural and health changes as well as subjective experience and well-being

Bernhardt, B. C.[1], Bornemann, B.[1], Böckler, A.[1], Engen, H.[1], Engert, V.[1], Grant, J. A.[1], Hildebrandt, L.[1], Kanske, P.[1], Kok, B. E.[1], Lumma, A.-L.[1], McCall, C.[1], Skottnik, L.[1], Tusche, A.[1], Valk, S. L.[1], Trautwein, M.[1], & Singer, T.[1]

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Recently, studies in the emerging field of contemplative sciences have given first evidence that mental training focusing on increasing both cognitive as well as socio-affective and motivational capacities can alter stress responses, physical health, resilience, attention, perception, emotional experience, social behaviour, and subjective well-being. Evidence for these first results is mostly based on single studies extending mostly over a period of 1–8 weeks of intervention using either subjective reports of participants only, or observed endocrinological and behavioural alterations or changes in brain function and structure.

The present study, called the *ReSource Project,* represents a multi-disciplinary and multi-method large-scale 1-year longitudinal mental training study teaching more than 200 subjects with 17 teachers in different types of mental training techniques. We assess their progress with a battery of more than 31 tasks (at the computer, in virtual world scenarios, or in the scanner), structural brain analyses, more than 50 questionnaires, subjective measures (e.g. experience sampling with smartphones), stress- and health-related measures, and (epi-)genetic analyses (Fig. 3.3.1.2). For the purpose of this study we developed a *ReSource* Model of Compassion (Fig. 3.3.1.1), which is based on a cognitive-affective neuroscience perspective of compassion. More specifically, the cultivation of "compassion" is centred around the training of many subprocesses in a meaningful sequence of three 3-month training modules called: presence, affective, and perspective (Fig. 3.3.1.1). These different domains rely on different neurocognitive systems, making the distinction not only conceptually but also biologically plausible. The presence module first aims to stabilize the mind to cultivate basic skills such as attentional faculties and learning in order to turn the focus from external events to internal mental and bodily events (interoception). The affective domain comprises skills and dispositions of handling difficult emotions, of generating feelings of love, warmth, and benevolence, as well as prosocial motivations. The cognitive domain in the model is termed "perspective"

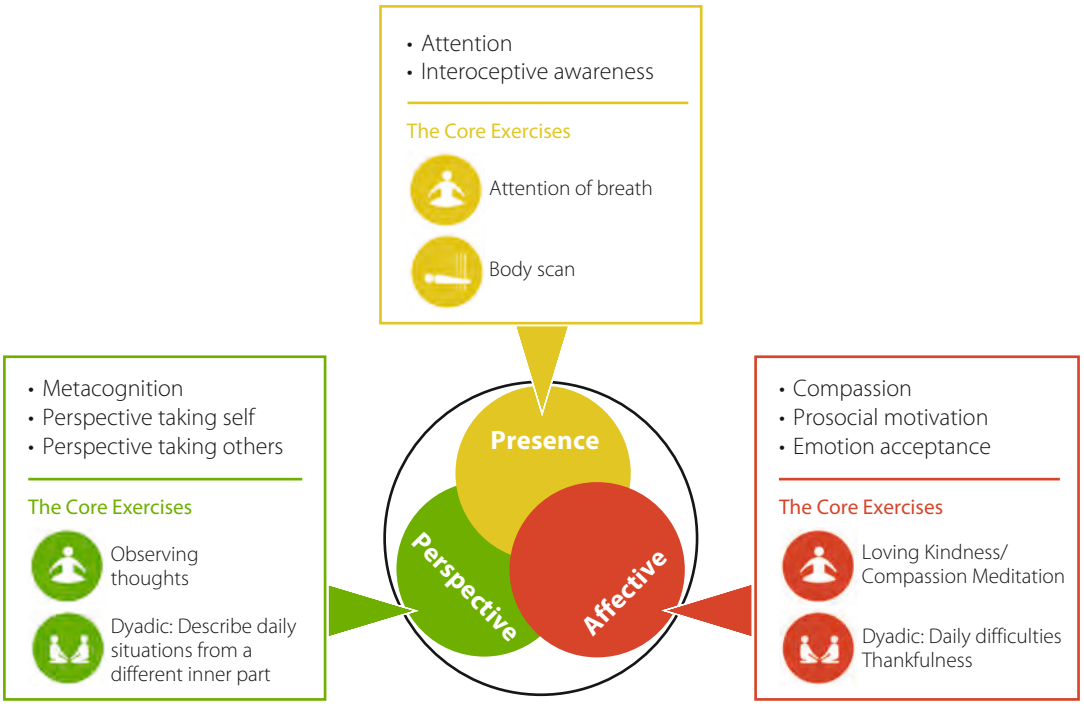

Figure 3.3.1.1 The compassion training model of the *ReSource Project*. This figure depicts the two core exercises of each training module.

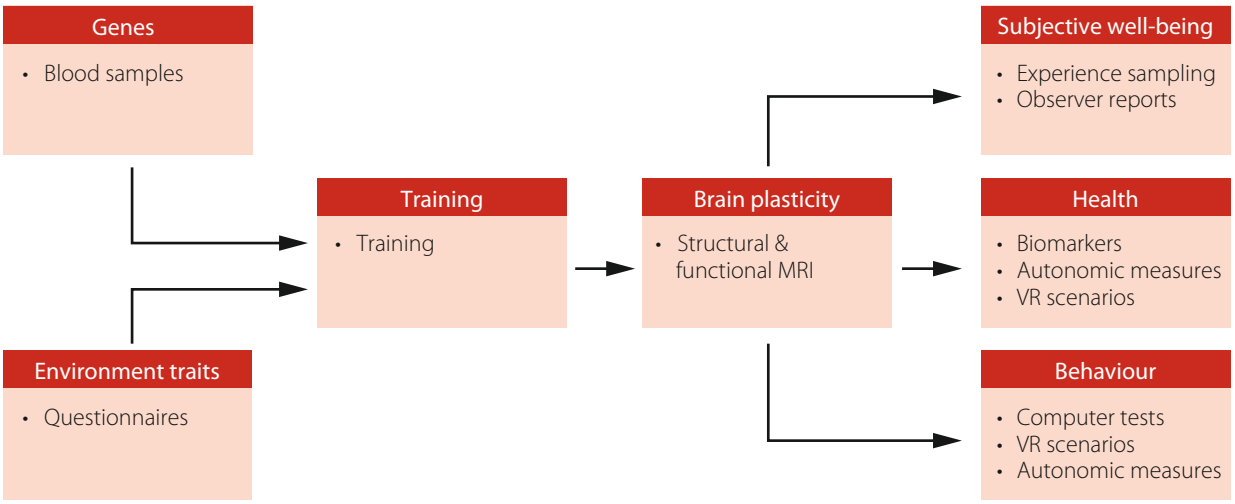

Figure 3.3.1.2 Overview of the dependent measures of the *ReSource Project* in order to test brain plasticity, subjective well-being, health, and behavioural changes after a 9-month compassion training programme.

because it refers to the abilities to assume a certain observational perspective on thoughts (metacognition), to be aware of the different aspects of "self", shift between these aspects at will, and to take the cognitive perspectives of other people. The division in an affective and perspective part is also inspired by our previous work identifying cognitive and affective routes of social cognition with different underlying brain circuitries: Whereas metacognitive and cognitive perspective taking processes on the self and others are associated with late-developing frontal and parietal brain regions (e.g. medial prefrontal cortex, temporo-parietal junction, precuneus), the socio-affective processes associated with prosocial motivation, positive affect, affiliation, benevolence, and emotional awareness are rather rooted in old motivational systems associated with functions of the somatosensory, interoceptive, limbic, and paralimbic cortices that develop early in life.

The protocol for the *ReSource Project* is a secular programme developed by a team of experienced meditation teachers, scientists, and psychotherapists. It is conducted in Leipzig and Berlin with 160 subjects undergoing the training. Eighty subjects undergo the training in the order presence-affective-perspective, while the other 80 subjects train in the order presence-perspective-affective, thus functioning as active control group for each other respectively. Several control groups (2 retest control groups totalling 90 subjects and one active control group that only trains the affective domain over three months from T0 to T1; $N = 80$) are also included (Fig. 3.3.1.3). The overall design is composed of three 3-month modules and thus the training focus changes every 13 weeks. All modules begin with a 3-day retreat. After this, participants meet with a team of teachers (usually two) and their group for a weekly 2-hour session. The *ReSource* Internet platform, specially developed for the study, helps the subjects to incorporate the training into their daily routine at home. Each module features two core exercises that the participants are recommended to engage in for a minimum of 30 minutes per day. They are designed to train the core processes of the module. Additional exercises help to deepen and widen the targeted skills and dispositions and foster their application in everyday life (Fig. 3.3.1.1).

- Presence Core Exercise 1: Awareness of the Breath
- Presence Core Exercise 2: Body Scan
- Affective Core Exercise 1: Heart Meditation
- Affective Core Exercise 2: Dyad "Difficult Emotions and Gratefulness"
- Perspective Core Exercise 1: Observing Thoughts
- Perspective Core Exercise 2: Dyad "Perspective on Self and Other"

The above-mentioned measures should give a fuller picture of the mechanisms behind mental training and compassion, its trainability, and its effect on brain, well-being, health, and behaviour (Fig. 3.3.1.2). The outcomes of the study could have implications far beyond the laboratory. If this training programme is shown to be effective in increasing pro-social behaviour and creating healthier individuals, it could serve as a scientifically tested model for other training programmes in businesses, organizations, and educational settings. It is also hoped that such mental training programmes could one day promote a more caring and peaceful society and ease the effects of the stresses of modern life on individuals.

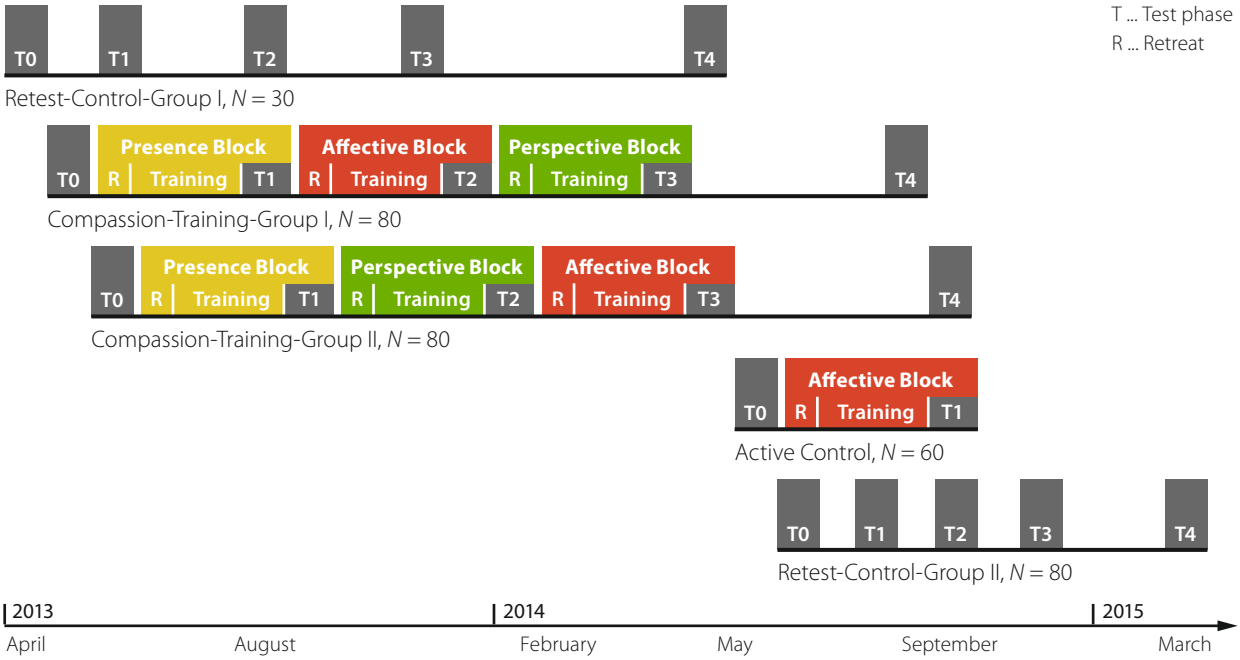

Figure 3.3.1.3 A rough overview of the study design of the *ReSource Project*. Two training groups are tested before training and after each module (T0–T4). Please note that the order of the affective and perspective modules is interchanged in both groups. Moreover, we have two retest control groups and one smaller active control group that only undergoes the affect training programme.

3.3.2 Differential pattern of functional brain plasticity after compassion and empathy training

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Empathy, which is usually defined as the capacity to share others' emotions, is crucial for successful social interactions. However, excessive empathic sharing of others' suffering can be maladaptive when it causes empathic distress. A potential remedy for the excessive sharing of negative affect may be compassion, i.e. a feeling of concern for the suffering of others that is associated with the motivation to help. To investigate functional neural plasticity underlying the augmentation of empathy and to test the counteracting potential of compassion, we conducted a short-term training study with an active control group. One group of 25 female volunteers was first trained in empathic resonance and subsequently in compassion, while another group of 28 female volunteers received two memory training sessions. Participants' affective and functional neural brain responses to videos depicting others' suffering were tested before the training (Pre), after the empathy training or first memory training (Post1), and after compassion training or the second memory training (Post2) using the Socio-affective Video Task (SoVT; Klimecki et al., 2013a). As shown in Figure 3.3.2A, empathy training, but not memory training (control group), increased self-reported negative affect and empathy, while compassion training decreased negative affect to baseline and augmented positive affect. On the neural level, empathy training led to stronger activation in the insula and the anterior mid cingulate cortex (Fig 3.3.2B). Cross-sectional meta-analyses concur that these regions are crucially implicated in empathy for pain (e.g. Lamm et al., 2011, NeuroImage, 54, 2492–2502). Subsequent compassion training increased activations in a non-overlapping brain network spanning the ventral striatum, the pregenual anterior cingulate cortex, and the medial orbitofrontal cortex (Fig. 3.3.2B). This is consistent with previous cross-sectional and longitudinal studies on compassion (e.g. Klimecki et al.,

2013a). Together, these data show that training two similar social emotions can lead to very different patterns of functional brain plasticity associated with opposing affective experiences and suggest that compassion training may reflect a new coping strategy to overcome empathic distress and strengthen resilience.

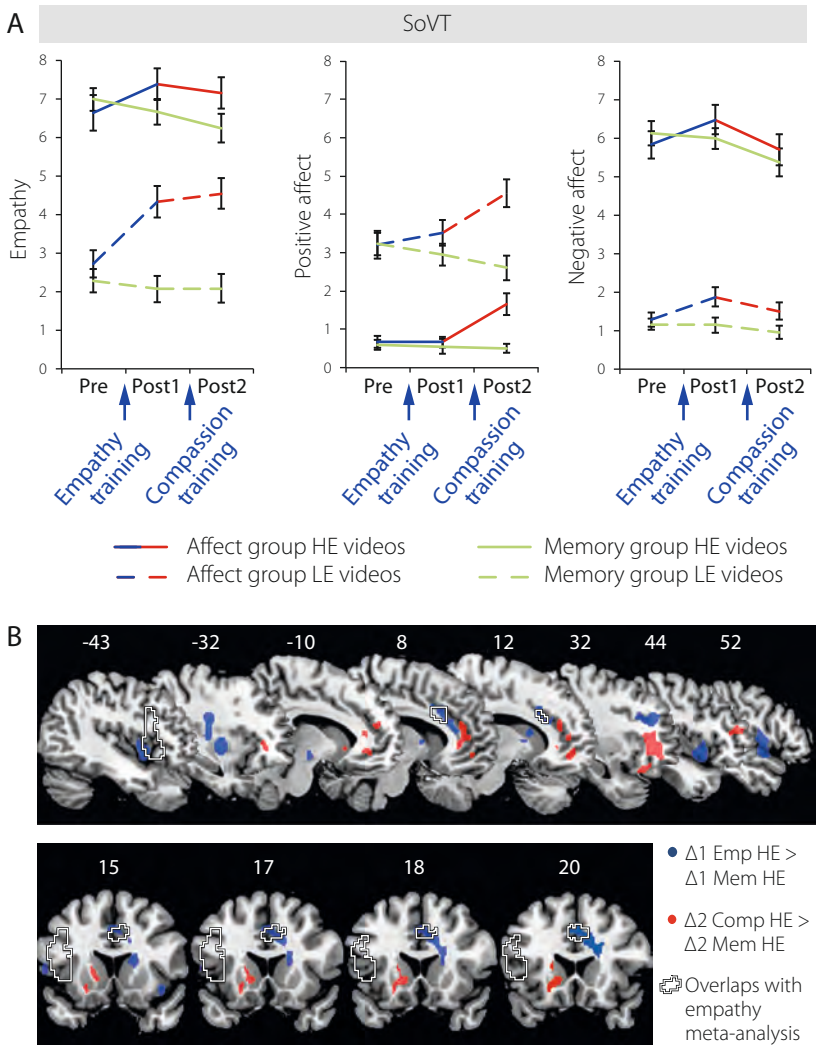

Figure 3.3.2 (A) Self-reported empathy and negative affect significantly increased after empathy training (both $p < 0.01$). Conversely, compassion training decreased negative affect ($p < 0.01$) and augmented positive affect ($p < 0.001$). Error bars indicate standard error of mean. (B) Functional neural changes related to empathy (blue) and compassion training (red) in comparison with the memory control group ($p < 0.05$, FWE corrected). Regions in which changes related to empathy training overlap with a recent empathy for pain meta-analysis (Lamm et al., 2011, NeuroImage, 54, 3, 2492–2502) are indicated by dashed lines. Δ1 Emp HE > Δ1 Mem HE, Affect Group (High Emotion Videos at Post1-Training – High Emotion Videos at Pre-Training) > Memory Group (High Emotion Videos at Post1-Training – High Emotion Videos at Pre-Training); Δ2 Emp HE > Δ2 Mem HE, Affect Group (High Emotion Videos at Post2-Training - High Emotion Videos at Post1-Training) > Memory Group (High Emotion Videos at Post2-Training – High Emotion Videos at Post1-Training); LE, Low emotion; HE, High emotion videos.

Comparing compassion meditation with cognitive reappraisal as emotion-regulation strategies

3.3.3

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Compassion-based mental training and meditation have been shown to improve positive affect, reduce stress, and activate brain networks associated with positive feelings and affiliation. While these findings suggest a role of compassion in coping with and strengthening resilience, it has not yet been compared to established emotion regulation (ER) strategies. It is likely that the mechanisms underlying the effect of compassion meditation on emotional responses differ markedly from more commonly employed ER strategies, as these typically rely on cognitive, rather than affective, means of modulation. We used fMRI to investigate the behavioural and neural consequences of compassion meditation when employed as an ER strategy and compared this to cognitive ER via reappraisal. Fifteen expert compassion meditators were scanned while using compassion meditation or reappraisal to regulate their emotional reactions to short film clips of people in distress (Fig. 3.3.3A). Subjective ratings

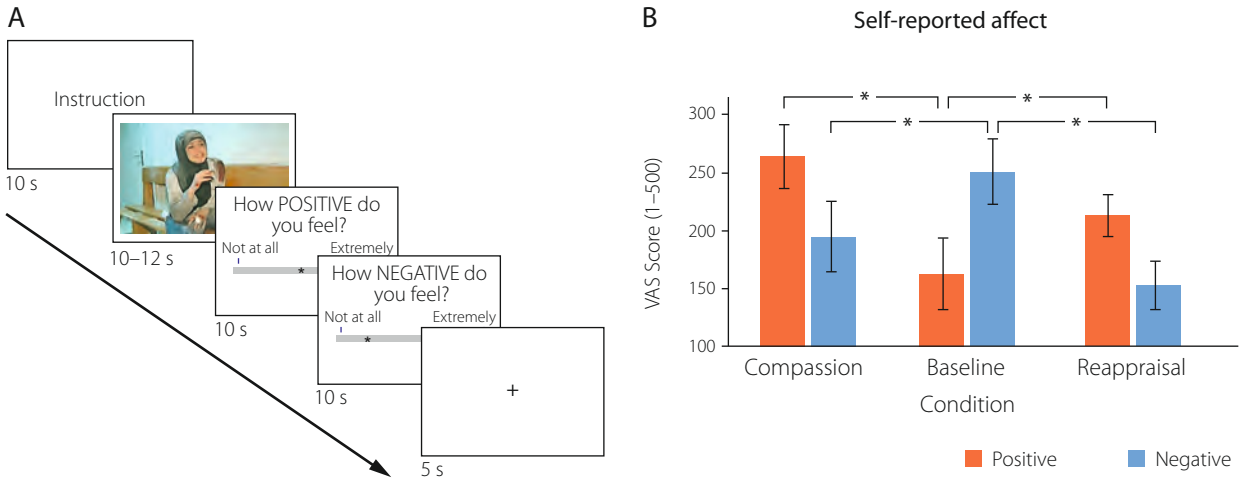

Figure 3.3.3 (A) Schematic of the paradigm employed. At the beginning of each trial, subjects were instructed to either employ reappraisal or compassion, or view the following film clip as they would normally (passive viewing). Subjects were then presented with a short film clip depicting individuals in either neutral or socially distressing situations. Subjects were then asked to rate how positive and negative they felt after the film clip. (B) Modulations of subjective affect as a function of technique employed when watching distressing clips. Compassion selectively increased positive affect, while reappraisal selectively decreased negative affect. Error bars denote SEM.

showed that compassion meditation primarily *increased* positive affect while reappraisal primarily *decreased* negative affect (Fig. 3.3.3B). Mirroring behavioural results, compassion contrasted with reappraisal revealed higher activation in amygdala, insula, ventral striatum, medial orbito-frontal cortex, and subgenual anterior cingulate cortex. Relatively lower activation was observed in the frontoparietal network and inferior frontal gyrus. Our findings demonstrate the efficacy of compassion meditation as an ER strategy, and that the regulatory mechanism of compassion is primarily the up-regulation of neural systems involved in positive affect, rather than the cognitive down-regulation of the neural correlates of negative affect. Since most other ER and coping strategies are focused on the effortful control of negative affect, the focus of compassion on the self-generation of positive affect suggests it could be a powerful strategy for fostering resilience in daily life.

3.3.4 Effects of compassion and empathy induction on pain analgesia in advanced meditation practitioners

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Prior work has established that meditative practice can positively influence the experience of pain. Studies have so far, however, focused primarily on practices targeting attention and/or mindfulness. Compassion has been proposed to be an opioid-mediated state, which, due to the pain-relieving properties of opioids, may therefore confer heightened pain tolerance. Importantly, compassion (involving positive feelings and a motivation to help) is distinguished from empathy, which, in the case of pain, is viewed as resonance with the suffering of the other and hence associated to negative affect (see paragraph 3.3.2).

To test this hypothesis, 16 advanced practitioners with specific focus on compassion meditation were compared to 15 newly trained, matched controls. Short noxious and innocuous electrical stimuli were applied intermittently to the forearm. In separate conditions participants were asked to enter four different mental/emotional states: positive other-focused (compassion), negative other-focused (empathy), positive self-focused (imagery of loved-food), and negative self-focused (imagery of disgusting-food). It was hypothesized that compassion, specifically in meditators, would have the strongest analgesic effects on pain, that is, reducing the affect dimen-

sion of pain in comparison to empathy (a negative other-related emotion) and loved-food (hypothesized to be a positive, self-focused, non-opioidergic state).
Post-hoc *t*-tests following a significant MANOVA interaction (Condition x Group) show that compassion reduced pain unpleasantness in meditators compared to empathy and loved-food as well as compassion in controls (Fig. 3.3.4). The sensory dimension of pain was also reduced for meditators during compassion in relation to loved-food. This suggests that compassion may indeed be a powerful state to induce opioidergic processes and that the accompanying analgesic effects on pain cannot simply be attributed to the induction of a positive self-related state.

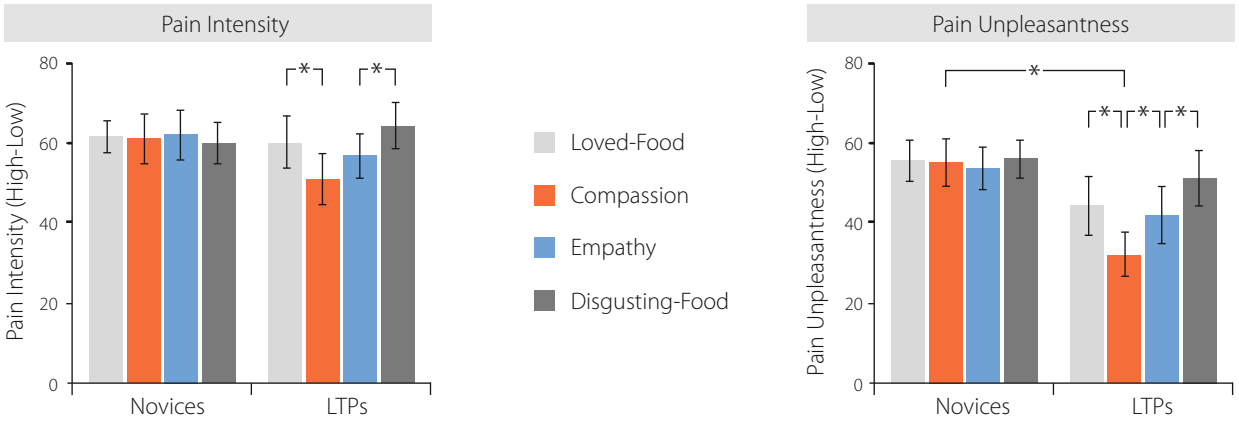

Figure 3.3.4 Pain intensity (sensory) and unpleasantness (affective) ratings in meditators and controls during compassion, empathy, loved-food, and disgusting-food. MANOVA revealed an interaction between Condition and Group ($F = 2.95$, $p = 0.03$) with post-hoc *t*-tests showing that pain unpleasantness is selectively reduced in meditators during a compassionate state in comparison to empathy ($t = -2.87$, $p = 0.01$) and loved-food ($t = -2.24$, $p = 0.04$) as well as compassion in controls ($t = -2.82$, $p = 0.01$). Pain intensity was also reduced for meditators in compassion compared to the loved-food condition ($t = -2.12$, $p = 0.05$). Error bars reflect within-group SEM.

3.4 Psychopathology of the Social Brain

One of the four major areas of research of the Department of Social Neuroscience is studying the psychopathology of the social brain. In order to understand the underlying mechanisms that produce inadequacies in social behaviour, we study populations with affective and social deficits such as people with mild autistic spectrum disorder (ASD) (e.g. Asperger's syndrome), alexithymia, narcissistic personality disorder, borderline disorder, and depression. The main goal of this research focus is to gain a more differentiated understanding of the specific subcomponents, which might explain the observed social and affective deficits. We hereby focus on testing the functioning of the different routes of social cognition and emotions identified in our previous research in healthy adults to provide a more complete picture of social deficits observed in different disorders. For instance, we investigate whether people with Asperger's syndrome are equally deficient in empathic and cognitive perspective taking routes, or merely in the latter. Our previous studies have shown that whereas people with ASD are deficient in Theory of Mind, they may only be deficient in empathy if they also have high traits of alexithymia. In a similar vein, we investigate if by consequence people with ASD may display a heightened egocentricity bias in the cognitive domain—subserved by functions of the right temporoparietal junction (rTPJ)—but not necessarily in the emotional domain. Thus, as outlined in chapters 3.1 and 3.2, overcoming emotional egocentricity bias (EEB) has been associated with functions of the right supramarginal gyrus (rSMG) rather than rTPJ. Furthermore, rSMG seems to be connected to paralimbic structures such as the anterior cingulate cortex (ACC) and insula cortices, which are not necessarily impaired in ASD populations, whereas rTPJ connects to brain regions associated with mentalizing abilities such as the medial prefrontal cortex (mPFC) and precuneus: a network which has been shown to be deficient in autism. To contrast such an impairment profile of social cognition with other patient populations, we are extending this work to people with strong narcissistic traits, depressed people, and patients with borderline personality disorder to see whether these populations differ in their profiles when focusing on preserved or impaired empathy, cognitive perspective taking, self-other distinction, emotional egocentricity bias, and emotion-regulation capacities. For example, we are interested in studying which of these social deficits come with an enhanced egocentric bias, whether this is related to the inability to disengage from one's own current emotional experience in order to accurately infer that of someone else, and whether this emotional egocentricity is biased towards a specific affective valence (e.g. negative in depressed, positive in narcissists). In all our investigations, the use of game-theoretical paradigms helps to quantify the degree of deficient social behaviour in these different patient populations in a well-controlled laboratory setting. They also allow us to empirically validate claims such as heightened aggressive or lower cooperative behaviour. Overall, we hope to develop a comprehensive socio-affective battery for the differential assessment of social cognitive, affective, and behavioural deficits often observed in psychopathology, to go beyond a simple diagnosis of "impaired social cognition" or "social behaviour", and to move towards a neuroscientifically informed model of complex underlying patterns of specific neurocognitive and affective deficits.

3.4.1 Disruption of socio-cognitive networks in autism and alexithymia: An MRI covariance analysis

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Autism spectrum condition (ASC) is a neurodevelopmental disorder characterized by abnormal social cognition. A core feature of ASC is disrupted Theory of Mind (ToM), our ability to infer the mental states of others. Moreover, ASC is commonly associated with alexithymia, a trait characterized by altered interoception and empathy. Here, we applied cortical thickness covariance analysis to assess whether ASC diagnosis and alexithymia differentially relate to inter-regional structural network alterations. To map networks involved in ToM, we seeded from the temporoparietal junction (TPJ) and the dorsomedial prefrontal cortex (dmPFC); networks involved in alexithymia and empathy were mapped by seeding from the fronto-insular cortex (FI). Based on previous fMRI findings (Bird et al., 2010, Brain 133, 1515–1525), we expected to find that ASC relates to disruptions in ToM networks while alexithymia specifically affects networks centred on FI. Compared to controls, ASC indeed showed decreased structural covariance networks of dmPFC and TPJ, but not FI (Fig. 3.4.1A). Covariance reductions in ASC were observed from left dmPFC to lateral and medial fronto-central regions and from left TPJ to lateral parietal and posterior temporal cortices. Conversely, while degrees of alexithymia modulated covariance networks centred on FI, they did not modulate those centred on dmPFC and TPJ (Fig. 3.4.1B). In particular, high alexithymia was related to low covariance from left FI to supramarginal, posterior insula, and occipital regions. Our results in individu-

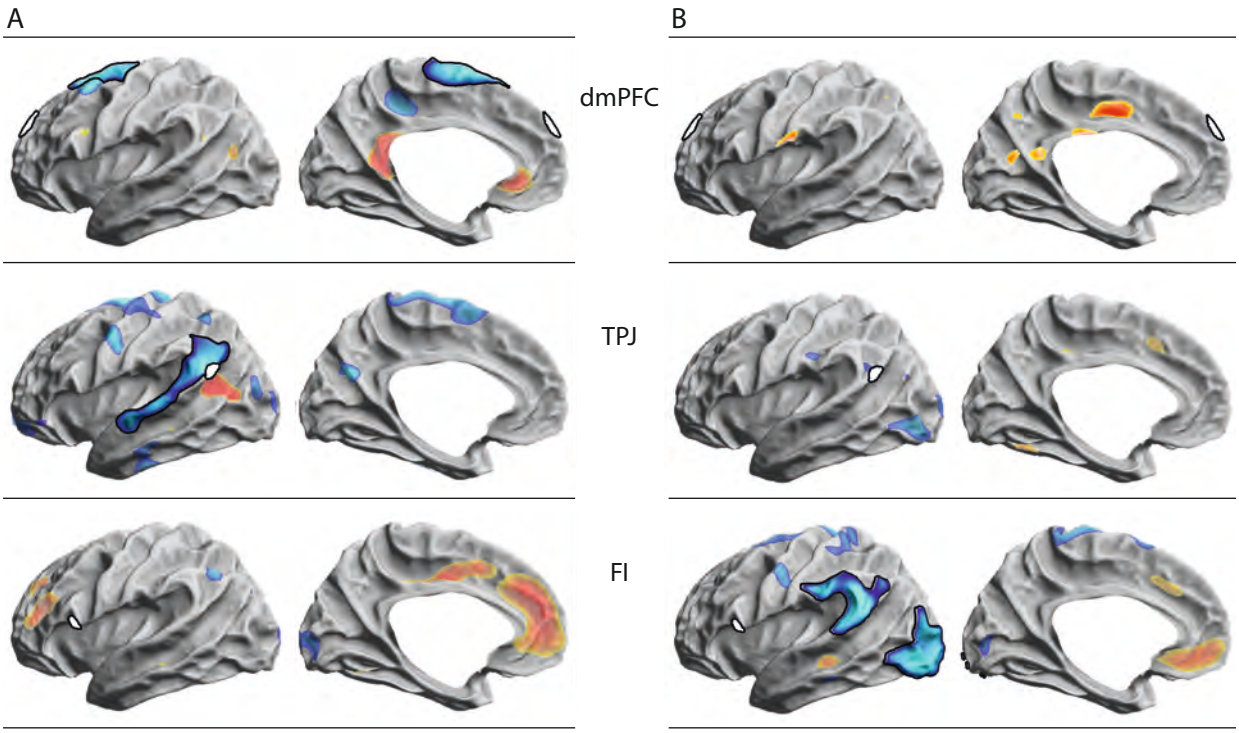

Figure 3.4.1 (A) Covariance alterations in autism spectrum conditions (ASC). Relative to controls, individuals with ASC showed decreases in covariance networks when seeding from the dorsomedial prefrontal cortex (dmPFC) and the temporo-parietal junction (TPJ), but not from the fronto-insular regions (FI). (B) The opposite pattern was seen when assessing modulations of covariance by alexithymia, with high degrees of alexithymia relating to low FI covariance but not to dmPFC and TPJ covariance. Findings are thresholded at *FWE* < 0.05.

als with ASC and alexithymia thus support previous fMRI findings of dissociated cognitive and affective functions in social processing. We could show divergent effects of ASC and alexithymia on structural covariance patterns in social cognition networks associated to ToM on the one hand and to interoception and empathy on the other.

Multi-centre mapping of reproducible structural network alterations in autism

3.4.2

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Autism spectrum conditions (ASC) are neurodevelopmental disorders characterized by atypical social cognition. While abundant functional studies have shown aberrant activity in socio-cognitive networks encompassing the medial prefrontal cortex (mPFC) and medial parietal regions such as the posterior cingulate cortex and the precuneus (PCC/PCU), general patterns of structural abnormalities have been reported less consistently. A reason for this divergence may possibly stem from small sample sizes employed by previous research. The current work assessed reproducible structural network changes in ASC, taking advantage of the recently released multi-centric Autism Brain Imaging Data Exchange database (ABIDE). We studied 220 individuals (107 ASC; 113 controls, 6–50 years) from three different sites that had T_1*-weighted MRI available from adults and children in both groups. *FreeSurfer* was used to measure cortical thickness and to map structural covariance networks. Compared to controls, individuals with ASC showed increases in cortical thickness in the bilateral mPFC and the lateral prefrontal cortex (Fig. 3.4.2). Findings were consistent across all three sites and seen in both children and adults. Seeding from dorsal mPFC clusters of cortical thickening, we furthermore observed a consistent decrease in covariance to fronto-central and medial parietal regions encompassing PCC/PCU. Our findings provide novel multi-centric evidence for structural network alterations in primarily medial prefrontal regions in ASC. Cortical thickening in children and adults with ASC relative to controls in medial and lateral prefrontal cortex may reflect a combination of infant brain overgrowth and incomplete pruning during neurodevelopment. Conversely, decreased covariance between mPFC and PCC/PCU may indicate impaired structural connectivity between anterior and posterior midline networks subserving Theory of Mind function. These findings may provide a robust structural explanatory basis for socio-cognitive deficits in ASC.

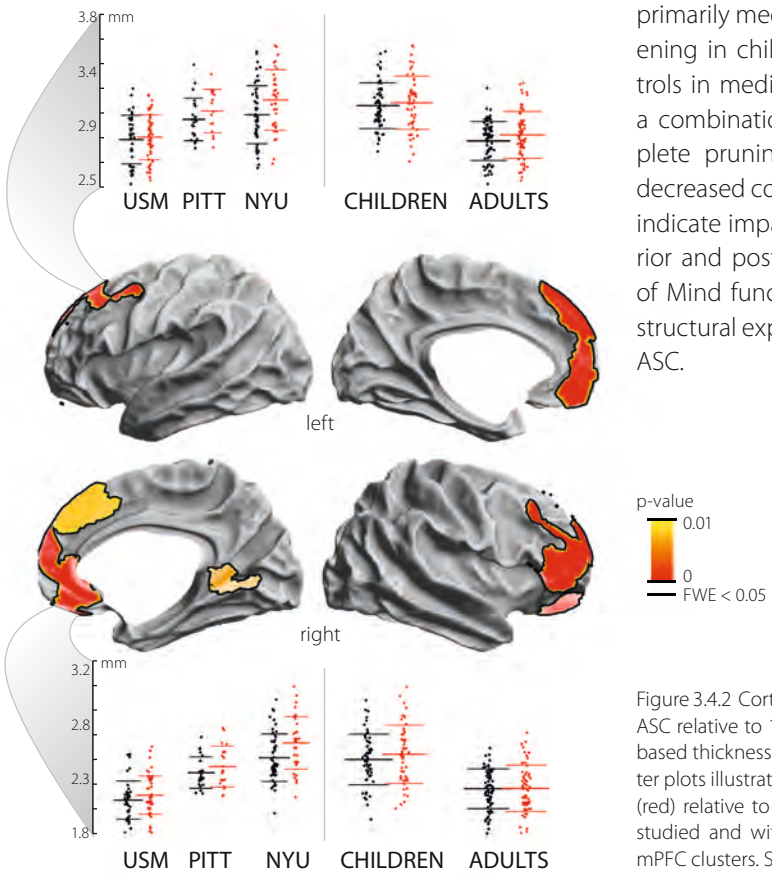

Figure 3.4.2 Cortical thickness increases in a multi-centric sample of 107 ASC relative to 113 healthy controls (6–50 years, males only). Surface-based thickness findings were corrected for age and centre. Inset scatter plots illustrate the consistency of cortical thickness increases in ASC (red) relative to controls (black) within each centre (USM, PITT, NYU) studied and within adults and children separately for two selected mPFC clusters. Surface-based findings are thresholded at *FWE* < 0.05.

3.4.3 Differences in cognitive but not affective perspective taking between individuals with autism spectrum disorder and healthy controls

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Individuals suffering from Autism Spectrum Disorders (ASD) display deficits in Theory of Mind (ToM) and associated underlying brain circuitries such as tight temporoparietal junction (rTPJ) and the medial prefrontal cortex (mPFC). The rTPJ has been associated with self-other distinction in the domain of cognitive (ToM) and motor functions (action imitation). Recent work focusing on emotional egocentricity bias (EEB; Silani et al., 2013) suggests that self-other distinction in the affective domain relies on the function of right supramarginal gyrus (rSMG), a brain region adjacent to rTPJ. In this study we therefore investigated whether individuals with ASD show deficits in both cognitive and affective perspective taking or only in the former. Cognitive perspective taking was assessed with the Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006, J Autism Dev Disord, 36, 623–636) and the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001, J Child Psychol Psyc, 42, 241–251). Self-other distinction in the motor domain was assessed with the imitation-inhibition task (Spengler et al., 2010, Biol Psychiat, 68, 1148–1155), and the ability to overcome EEB was studied with the "affective touch" paradigm (Silani et al., 2013) in which two participants were touched simultaneously with either pleasant or unpleasant stimuli on their hands and had to either judge their own or the other participant's emotion. The emotional experiences of both participants could be either congruent or incongruent. The EEB was defined as the difference between ratings in incongruent and congruent trials when judging the other, as compared to the difference when judging one's own feelings. As expected, individuals with ASD showed significant deficits in ToM (Fig. 3.4.3A) and imitation inhibition (Fig. 3.4.3B) compared to controls. However, there was no significant difference in EEB between the groups (Fig. 3.4.3C). These results suggest that while the ASD group showed deficits in ToM and imitation inhibition, these deficits do not extend to comparable tasks in the affective domain, indicating spared socio-affective abilities in ASD and bringing further behavioural evidence for a possible functional segregation of rTPJ and rSMG in social cognition with the former subserving self-other distinction in the motor and cognitive domain and the latter in the affective domain.

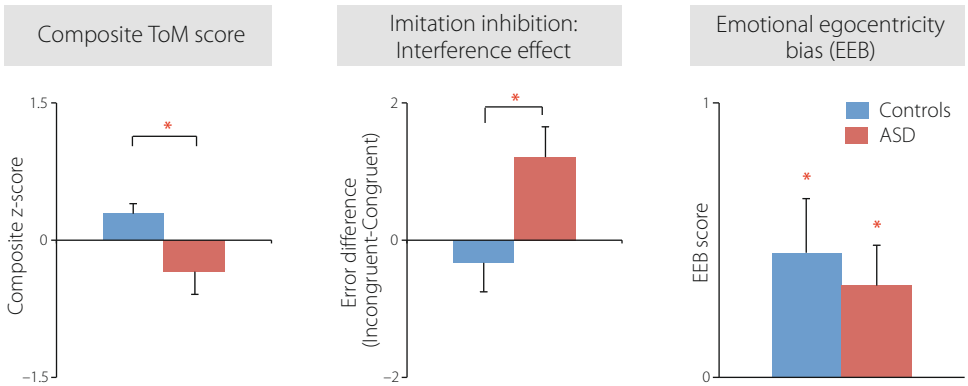

Figure 3.4.3 (A) Composite Score of the two z-scored accuracy scores of the Movie for the Assessment of Social Cognition and the Reading the Mind in the Eyes Test. As expected, the control group showed a significantly greater ToM score than the ASD group. (B) Difference in errors made between incongruent and congruent conditions during imitation inhibition. The ASD group made significantly more errors in inhibiting imitation compared to the control group. (C) Display of the emotional egocentricity bias (EEB). Both groups displayed a significant EEB but the size of the EEB was similar for ASD and controls.

3.4.4

Neural correlates of emotional distractibility in bipolar disorder, unaffected relatives, and individuals with hypomanic personality

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Neuropsychological deficits and emotion dysregulation are present in symptomatic and euthymic patients with bipolar disorder. However, there is little evidence on how cognitive functioning is influenced by emotion, what the neural correlates of emotional distraction effects are, and whether such deficits are a consequence or a precursor of the disorder (Strakowski et al., 2005, Mol Psychiat, 10, 105–116).

We used a two-step fMRI procedure to first localize the neural network specific to a certain cognitive task (mental arithmetic) and then to test the effect of emotional distractors on this network. Euthymic patients with bipolar-I disorder ($N = 22$), two populations at high risk for developing the disorder (unaffected first-degree relatives of bipolar patients ($N = 17$), and healthy participants with hypomanic personality traits ($N = 22$)) were tested, as well as three age-, gender-, and education-matched healthy comparison groups ($N = 22$, $N = 17$, $N = 24$, respectively).

There were no differences in performance or activation in the task network for mental arithmetic. However, while all participants showed slower responses when emotional distractors were present, this response slowing was greatly enlarged in bipolar patients (Fig. 3.4.4A). Similarly, task-related activation was generally increased under emotional distraction; however, bipolar patients exhibited a further increase in right parietal activation that correlated positively with the response slowing effect (Fig. 3.4.4B-D).

The present study suggests that emotional dysregulation leads to exacerbated neuropsychological deficits in bipolar patients as evidenced by behavioural slowing and task-related hyperactivation. The lack of such a deficit in high-risk populations suggests that it occurs only after disease onset, rather that representing a vulnerability marker.

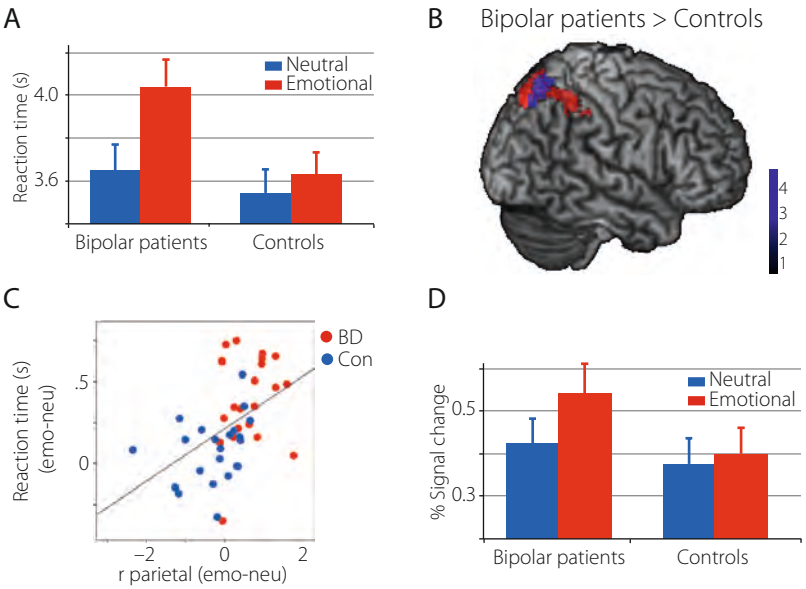

Figure 3.4.4 (A) Reaction times showing enlarged distraction effects through emotional background pictures in bipolar patients. (B) Activation differences between bipolar patients and their controls (in blue) are shown on the main effect of distraction (in red) together with (D) the respective percent signal change. (C) Correlation of the reaction time distraction effect and the parietal hyperactivation for mental arithmetic on emotional background pictures.

3.5 Other Activities

3.5.1

Using immersive virtual environments to study cognition, affect, and behaviour: The *Wunderkammer*

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We live in complex environments with a wide array of stimuli and opportunities for action. Immersive virtual environments (IVEs) mimic this complexity by placing participants inside richly detailed 3D digital worlds. With the *Wunderkammer*, we present a new set of IVEs to measure several facets of cognition, affect, and behaviour. "The Changing Room" (Fig. 3.5.1A) measures the ability to perceive subtle visual changes in the environment, such as gradual shifts in the colour or shape of objects. Our data demonstrate that these observational skills are determined by both executive control and sensory thresholding. "The State Room" (Fig. 3.5.1B) places participants in a virtual museum filled with images that vary in their valenced and arousing nature. Through analyses of movement and gaze, we determine affective preferences, identifying both common biases (i.e. for positively valenced images) as well as individual differences (i.e. excitement-seeking people gravitate toward arousing images). In "The Crowded Room" (Fig. 3.5.1C) we measure responses to others' emotions. Participants encounter several human-like agents and our analyses of their non-verbal behaviour reveal implicit responses to those agents' emotional displays, with participants avoiding angry agents and attending closely to emotionally wrought faces. Finally, "Room 101" (Fig 3.5.1D) elicits and measures anxiety by exposing participants to a series of startling events (e.g. explosions or being surrounded by snakes). Increases in galvanic skin response and chang-

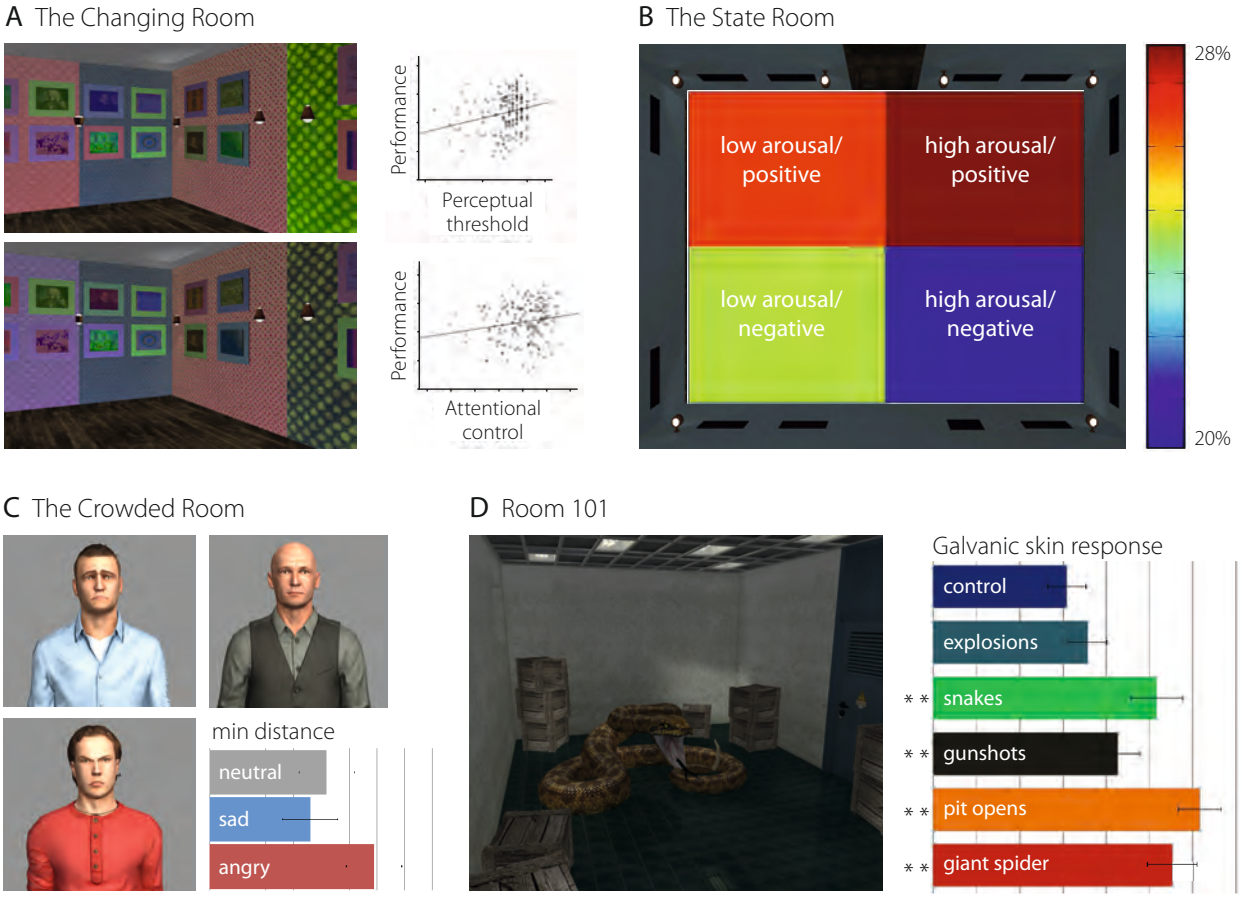

Figure 3.5.1 Screenshots and sample data from the four chambers of the *Wunderkammer*. (A) The ability to observe changes in "The Changing Room" is predicted by executive control ($t(171) = -3.079$, $p < 0.01$) and sensory thresholding ($t(171) = 2.010$, $p < 0.05$) as measured in two separate tasks. (B) Participants ($N = 177$) show clear biases in their preferences for different corners of "The State Room". (C) Participants ($N = 177$) keep a greater distance from the angry agent than other agents in "The Crowded Room". (D) Different episodes of "Room 101" elicit different levels of arousal as measured by galvanic skin response ($N = 54$).

es in heart rate variability, as well as post-hoc subjective reports demonstrate significant increases in arousal and anxiety. Together these four IVEs produce an affective, cognitive, psychophysiological, and behavioural profile of an individual in under an hour, helping us better understand how that person functions in the real world.

3.5.2 Investigating the phylogenetic origins of *Schadenfreude*

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Deriving pleasure from the misfortune of others, also referred to as *Schadenfreude*, is a motivation that is opposed to empathy. The latter refers to suffering with the other's suffering, whereas in *Schadenfreude* the misfortune of another leads to a positive emotion in oneself (Ortony et al., 1988, Cambridge University Press, Cambridge). The current study aimed to investigate the phylogenetic origins of *Schadenfreude* by examining whether, and to what extent, chimpanzees (*Pan troglodytes*) derive pleasure from the misfortune of others. Chimpanzees watched an experimenter punishing another experimenter (i.e. beating him/her with a stick). This latter experimenter could have previously been acting in a generous or in a non-generous manner in a food-exchange task. After the initial punishment period the punished experimenter either 1) remained in his/her initial position (area A in Fig. 3.5.2.1) while the punishment continued (stay condition) or 2) moved into the other part of the room (area B in Fig. 3.5.2.1) where he/she continued to be punished (leave condition). In this last case, the chimpanzees had to open a sliding door (previously learned) in order to continue witnessing the experimenter being punished. We hypothesized that if chimpanzees can experience something like *Schadenfreude*, they should invest effort in witnessing a disliked person undergoing a misfortune, and thus open a sliding door to witness a previously non-generous experimenter being punished. Preliminary results seem to show that chimpanzees preferred to open the sliding door to continue witnessing the punishment of the non-generous experimenter as compared to the punishment of the generous one (Fig. 3.5.2.2). Moreover, chimpanzees seem to produce longer display and distress calls while watching the punishment of the generous experimenter as compared to the punishment of the non-generous one. Together, these results seem to suggest that *Schadenfreude* is a social emotion that is also present in one of our closest living relatives.

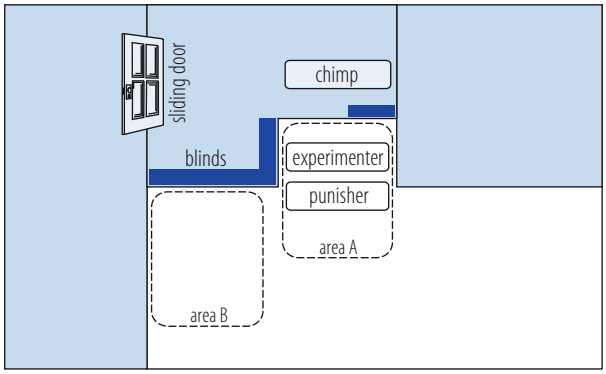

Figure 3.5.2.1 Schematic illustration of the setup. The generous or non-generous experimenter entered the testing room and sat in front of a window in the chimpanzees' room (area A). Afterwards, a second experimenter, the punisher, entered the room. The punisher approached the experimenter from behind and started beating him/her with a foam stick. After this initial punishment period the experimenter 1) remained in her initial position for the duration of the punishment (area A), so-called *stay* condition, or 2) left his/her initial position and went into area B of the room where the punishment continued, the so-called *leave* condition. Now the chimpanzees no longer had visual access to the punishment due to the blinds on the windows in the middle area. Thus, if the chimpanzees wanted to continue witnessing the punishment they had to open the sliding door and move in front of the area B window.

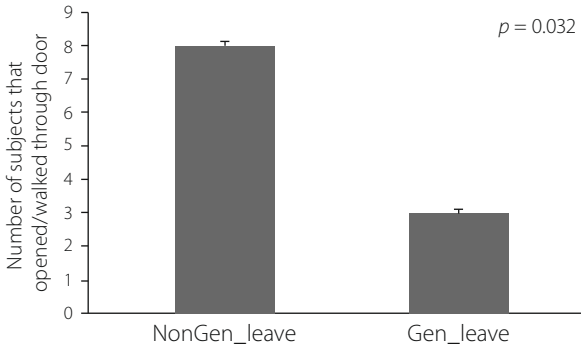

Figure 3.5.2.2 Significantly more chimpanzees opened/walked through the sliding door after the non-generous experimenter (NonGen_leave) moved into the other part of the room compared to when the generous experimenter (Gen_leave) did so (exact Wilcoxon test: $Z = 15$, $N = 5$, $p = 0.032$, 1-tailed).

Congresses, Workshops, and Symposia

Singer, T. (April). *International Symposia for Contemplative Studies.* Denver, Colorado, USA. **2012**

Singer, T. (October). *Mind and Life Europe Symposium for Contemplative Studies*, Berlin, Germany. **2013**

Appointments

Smallwood, J. *Reader position (Psychology).* University of York, United Kingdom. **2013**

Degrees

PhD Theses

Klimecki, Olga Maria. *Training the Compassionate and the Empathic Brain.* University of Zurich, Switzerland. **2012**

Przyrembel, Marisa. *Der empathische Egoist – Die Perspektive der Zweiten Person und soziale Interaktion.* [The empathic egoist–*The perspective of the second person and social interaction.*] Humboldt University, Berlin, Germany.

Awards

Bornemann, B. *Best Psychological Diploma Thesis of 2011.* Humboldt University Berlin, Germany. **2012**

Grant, J. A. *Post Doctoral Fellowship.* Natural Sciences and Engineering Research Council (NSERC), Canada.

Kanske, P. *Young Investigator Award.* German Society for Psychophysiology and its Application, Gießen, Germany.

Przyrembel, M. *Award for the conception and evaluation of a training on delivering death messages.* German Police University, Münster, Germany.

Bernhardt, B. C. *Jeanne Timmins Costello Award.* Montreal Neurological Institute, Canada. **2013**

Kanske, P. *Lilly Young Investigator Fellowship in Bipolar Disorder.* International Society for Bipolar Disorder, Pittsburgh, PA, USA.

Kanske, P. *Young Investigator Award of the European Brain and Behaviour Society.* The European Brain and Behaviour Society, Amsterdam, the Netherlands.

Trautwein, F.-M. *Forschungspreis (2. Preis) für die Studie "Der Einfluss von Metta-Meditation auf selbstreferentielle neuronale Prozesse".* Society for Meditation and Meditation Research, Cologne, Germany.

Publications

Note: This list also includes publications of members of the research team of the Department of Social Neuroscience that were published prior to their arrival. These articles are included as they are highly relevant to our research topics and speak to the unique qualifications of the team members.

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Professor Dr Robert Turner
Director

4 Mapping Brain Structures Using MPI Techniques

Department of Neurophysics

Physics in Neuroscience

In the seven years of its existence, the Department of Neurophysics in the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig has become a major world centre in the rapid advance of imaging techniques for cognitive neuroscience. In the last two years we have published approximately 60 research papers and generated about 70 conference abstracts, most of which describe new neuroscientific findings using data originating from our 7T MRI scanner.

The main cumulative achievements of this department comprise the following:

a) Measurement of structure, function, and connectivity using MRI in the same living human brain at a microscopy scale well below 1 mm. For the first time in human imaging neuroscience, this enables reliable association of brain function with its cytoarchitectural substrate in individual brains and with accurately defined axonal connections as they innervate the cerebral cortex.

b) Network analysis using Eigenvector Centrality Mapping, a highly efficient data-driven method for assessing the hubness of network nodes, related to the Google search algorithm, which has substantially ad-

vanced the understanding of functional connectivity in human brain. Furthermore, we have provided a powerful critique of a currently popular strategy, Dynamic Causal Modelling, showing that it is too simplistic to adequately capture the complexity of normal brain operation.

c) In MRI hardware development, we are leaders in modelling radiofrequency fields, such that advice is often sought by other laboratories regarding simulation, testing and validation and in drafting international guidelines for RF safety standards. We have invented and successfully simulated a novel and simple method for attaining the valuable goal of uniform RF transmit magnetic field strength across the brain, but which does not require laborious preparatory measurements and tuning for each human subject.

d) We have demonstrated the feasibility of parcellating human cerebral cortex, *in vivo* and in cadaver brain samples, into distinct myeloarchitecturally defined regions, corresponding to Brodmann areas.

e) We have perfected a set of novel software tools optimized for *in vivo* neuroanatomy of human brain, including level-set based methods for cortical segmentation and delineation of subcortical nuclei. These tools are more powerful, more accurate, and computationally faster than other packages currently available.

f) We have discovered and implemented a method for predicting the locations of cortical cyto- and myeloarchitectonic layers in histological and MR structural brain images, the depth of which varies naturalistically with local cortical curvature. Use of this technique has enabled surface registration of maps reflecting myeloarchitecture across subjects, a vital first step in establishing like-with-like group comparisons in brain activity.

g) Using state-of-the-art techniques of proton beam microscopy, we have established that values of the MRI quantities T_1, T_2* and magnetic susceptibility in tissue can be almost entirely explained by the concentrations of iron and myelin. This implies that the longitudinal relaxation rate $1/T_1$, as measured using MRI, can be used as an index of cortical myelination.

The work of this department currently falls into three closely interconnected areas: MRI Techniques at 7T, led by Dr Robert Trampel; Neuroanatomy and Image Analysis, led by PD Dr Stefan Geyer and Dr Pierre-Louis Bazin; and High Field RF Technology, led by Dr Mikhail Kozlov. (Dr Gabriele Lohmann, who formerly led the Image Analysis Group, took a position at the University of Tübingen in June 2013). These subgroups work together in order to jointly optimize 7T scanner performance, image contrast and spatial resolution, image analysis, and neuroanatomical interpretation.

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4.1 MRI Techniques at 7T

In this report we include four important neuroscientific studies: direct visualization of the subthalamic nucleus by means of quantitative susceptibility weighted imaging, probing intra-cortical connectivity using diffusion weighted imaging (DWI), investigating the neurovascular coupling in regions of negative BOLD (Blood Oxygenation Level Dependent), and studying the fundamentals of water diffusion in human white matter.

The development of new MR techniques and the optimization of common approaches for anatomical and functional imaging have remained core activities for the Neurophysics MRI team. In order to tap the full potential of high field MRI, spatial resolution must be improved still further without sacrificing image quality, while keeping scan time reasonably short. We were the first to show that sub-millimeter resolution in Echo-Planar Imaging (EPI) is possible by combining outer-volume suppression and parallel imaging. Using this approach, combined with 'multiband' acquisition (simultaneous excitation of multiple slices) enables whole-brain DWI with high angular resolution and 1-mm isotropic voxels. In addition, we have developed an exceptionally fast and accurate MR method for mapping temperature, which can evaluate brain temperature *in vivo* to an accuracy of 0.2 °C.

Finally, we have addressed fundamental questions in functional neuroimaging. The first of these relates to the importance of motion artifact in functional MRI (fMRI). Using a radical definition of false-positive attribution of activation, we have investigated the beneficial effects of prospective motion correction. Secondly, we have explored the interpretation of changes in cerebral blood volume during brain functional activity, using finite-element modelling and physical simulation.

4.1.1 Quantitative susceptibility mapping (QSM) at 7T for visualization of the subthalamic nucleus

Schäfer, A.[1], Forstmann, B. U.[2], Mietke, A.[1], & Turner, R.[1]

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Recent attention in MRI research has shifted to quantitative parameter mapping, rather than qualitative imaging. Distributions of the longitudinal relaxation time T_1 and the transverse relaxation times T_2 and T_2* are typically calculated from appropriate input image data. In brain tissue, T_1 depends mainly on myelin concentration, whereas T_2* is strongly decreased both by brain iron and myelin. Phase image data can now be used to calculate magnetic susceptibility distributions, independent of magnetic field strength, which enable discrimination of diamagnetic myelin and paramagnetic iron. The subthalamic nucleus (STN), a small structure rich in iron among the basal ganglia, is an important target for deep brain stimulation, which greatly benefits from reliable 3D mapping. To calculate the T_1 maps, the MP2RAGE sequence with an isotropic resolution of 0.7 mm was used. A 3D multi-gradient-echo sequence with a resolution of 0.5 x 0.5 x 0.6 mm^3 was used to calculate the T_2* map. The first echo of the phase image of the FLASH data was unwrapped, high-pass filtered, and then used to calculate the QSM. Figure 4.1.1 displays the T_1-, T_2*- and quantitative susceptibility maps for one subject. The basal ganglia are best visible in the T_2* map and the QSM, due to the high iron content. The susceptibility map clearly distinguishes the STN quantitatively from the adjacent substantia nigra (SN). The subthalamic nucleus (STN) can thus be precisely delineated by combining the increased SNR in high-resolution phase images at 7T with quantitative susceptibility mapping.

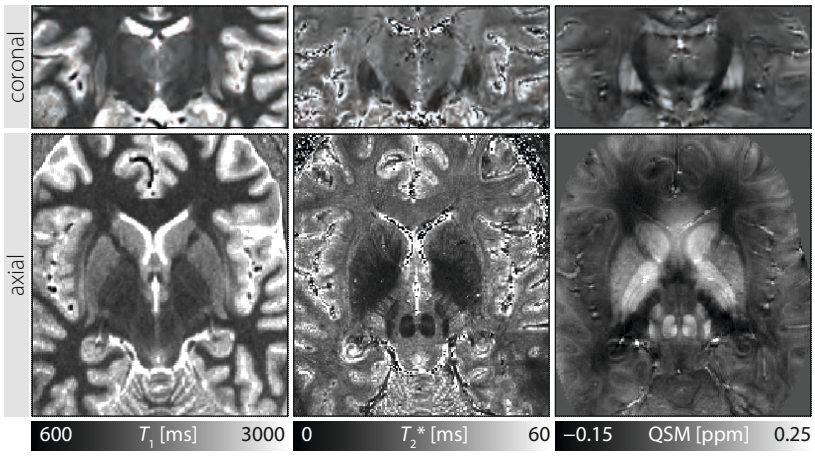

Figure 4.1.1 The T_1-, T_2*- and susceptibility map (QSM) for one subject shown in the coronal view (top row) and the axial view (bottom row).

4.1.2 Layer-specific intracortical connectivity revealed with diffusion MRI

Leuze, C.[1], Anwander, A.[1], Bazin, P.-L.[1], Dhital, B.[1], Stüber, C.[1], Reimann, K.[1], Geyer, S.[1], & Turner, R.[1]

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Diffusion weighted magnetic resonance imaging (dMRI) enables measurement of anisotropic structures such as nerve fibre bundle pathways by measuring the diffusivity of protons in various directions and applying models that relate these measures to the underlying tissue structure. While dMRI has already been extensively applied to white matter, within the cortex the lower diffusion anisotropy makes it difficult to obtain useful dMRI data. MRI 3D examination of the detailed cortical tissue structure would help more than histology's 2D insights in understanding how the fibre pathways are organized within the human brain. We used dMRI for the first time to show layer-wise differences in the direction-dependent diffusion properties in the visual cortex of a fixed brain sample (see Fig. 4.1.2) and measurement of the organization of fibre pathways within different cortical layers.

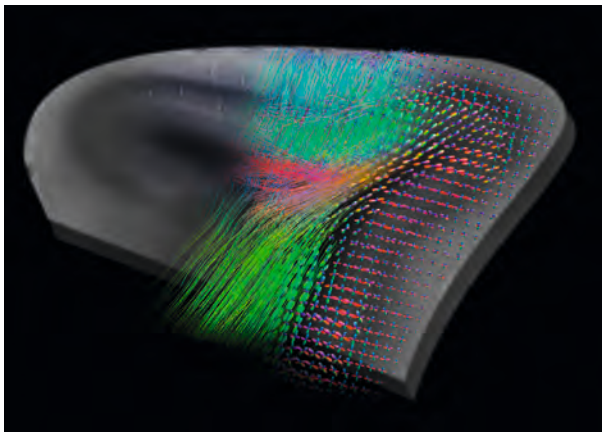

Figure 4.1.2 Composite image of primary visual cortex, cadaver human brain. From left to right: Spin-echo MR image showing the stria of Gennari; Myelin stain showing the same feature; Tractogram showing mainly radial fibres arriving from the white matter but also tangential bundles within the stria of Gennari and on the cortical surface; Fibre orientation distribution function (fODF) showing the corresponding fibre crossings.

Neurovascular coupling in regions of negative BOLD

4.1.3

Huber, L.[1], Goense, J.[2], Kennerley, A.[3], Ivanov, D.[4], Krieger, S. N.[1,5], Lepsien, J.[1], Trampel, R.[1], Turner, R.[1], & Möller, H. E.[1]

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Stimulus-dependent decreases in blood oxygenation level dependent (BOLD) signal and their underlying neurovascular origins have recently gained considerable interest. We have used a multi-echo, BOLD-corrected vascular space occupancy (VASO) functional magnetic resonance imaging (fMRI) technique to investigate neurovascular responses during excitatory and inhibitory visual tasks in human brain at 7T. Changes over time in stimulus-induced BOLD, cerebral blood volume (CBV), and cerebral blood flow (CBF) were mapped with respect to neural excitation and inhibition, and the effects of larger blood vessels found at the cortical surface. Because arterial and venous blood differ in T_2*, blood volume compartments could be isolated and compared.

Although mean CBV, CBF, and BOLD signal changes are tightly correlated with neural excitation and inhibition, there are significant differences in neurovascular coupling between excitatory and inhibitory tasks such as

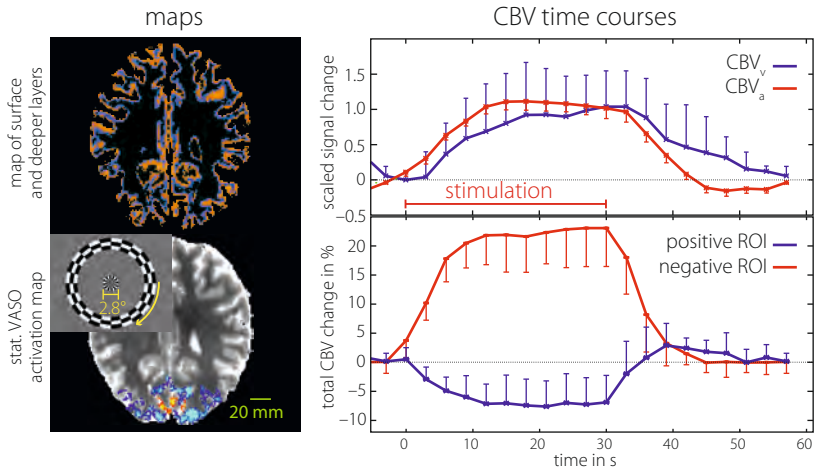

Figure 4.1.3 Observation of the interaction of arterial and venous blood volume, blood flow, and BOLD signal with respect to three neurovascular features. First, with respect to sensitivity to cortical surface vs deeper layers, second with respect to temporal evolution, e.g. post-stimulus-undershoot, and third with respect to neural excitation and inhibition.

the temporal response and cortical depth dependence. Positive BOLD response is associated with vessel dilation in all vascular compartments, while negative BOLD response appears to be accompanied with vasoconstriction only in larger superficial arterial vessels, which react faster than downstream vascular compartments. The high SNR method developed here enables investigation of neurovascular features that have previously been seen only in anaesthetized animals.

4.1.4 Modelling diffusion in white matter *in vivo* at ultra-long diffusion times

Dhital, B.[1], & Turner, R.[1]

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The self-diffusion of water in human brain white matter (WM) varies according to its orientation, location, maturity, and pathology. A popular biexponential model with two components in slow exchange unfortunately yields volume fractions that are directionally dependent, and the ADC obtained depends on the highest b-factors employed. Our new model assumes that: (i) the water pool associated with membranes, filament proteins, and microtubules has a very low ADC and long residence times (ii) water in the extra-axonal and the intra-axonal spaces has similar ADC values parallel to the WM fibre orientation and cannot be distinguished (iii) in the intra-axonal space, water diffusion perpendicular to the fibre orientation is greatly reduced and cannot be separated from the slow water pool. Thus intra-axonal diffusion can be modelled as a tensor that behaves like a fast or a slow component depending on the direction measured.

Diffusion measurements in a transverse direction were performed in volunteer subjects for five diffusion times up to 1500 ms. The maximum b-value used was 20,000 s/mm^2. We fitted the data both to a two-component exchange model and our proposed model. The proposed model estimates a homogeneous slow diffusion fraction with realistic estimates (Fig. 4.1.4). For most of the WM, adding a volume fraction for the third component reveals more information. The exchange time is found to be on the order of a second. Our model requires one additional parameter, the volume fraction of the slow water pool, but it allows parameters that have stable physical meaning to be obtained.

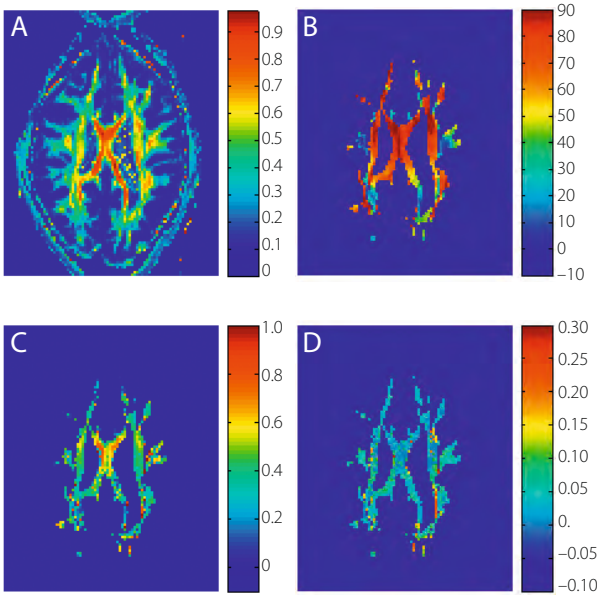

Figure 4.1.4 Top Row: (A) FA map, Only voxels with FA > 0.45 were used. (B) Angle made by the fibre direction with the diffusion measurement direction. Bottom Row: Volume fraction of the slow component (C) two-component exchange model, (D) our proposed model. While the exchange model is dependent on the fibre orientation direction, our model is not.

Isotropic submillimeter fMRI in the human brain at 7 T: Combining reduced field-of-view imaging and partially parallel acquisitions

4.1.5

Heidemann, R. M.[1,2], Ivanov, D.[1], Trampel, R.[1], Fasano, F.[3], Meyer, M.[2], Pfeuffer, J.[2], & Turner, R.[1]

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Echo-planar imaging (EPI) is the most widely used imaging sequence for fMRI due to its fast acquisition, but has well-known image artifacts. Since these effects scale with echo train length (ETL) and field strength, they must be addressed to achieve high resolution EPI at ultra-high field. Partially parallel acquisition (PPA) methods can be used to improve the image quality of EPI. However, PPA can be affected by aliasing artifacts and noise enhancement. The ETL can also be shortened by reducing the field-of-view (FOV) while maintaining the same spatial resolution. However, to achieve significant acceleration the resulting FOV becomes very small. We have perfected a novel approach, combining reduced FOV imaging with PPA. This approach enables high quality single-shot EPI acquisition, with sub-millimeter isotropic resolution and good signal to noise ratio, for fMRI at ultra-high field strength. This is demonstrated in fMRI of human brain at 7T with an isotropic resolution of 650 µm.

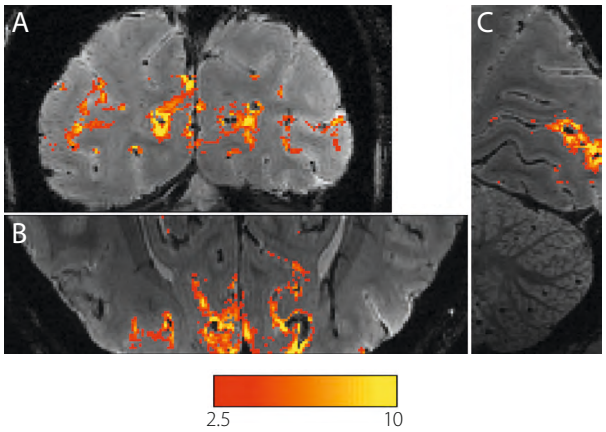

Figure 4.1.5 Results from a visual fMRI experiment with ZOOPPA. The activation pattern, t-score map with a threshold at a significance level of $p < 0.05$ (FDR), derived from the ZOOPPA acquisition with 0.65-mm isotropic resolution is registered and overlaid onto the 0.6-mm isotropic resolution anatomical acquisition. Coronal (Fig. 4.1.5A), axial (Fig. 4.1.5B) and sagittal (Fig. 4.1.5C) views are shown.

Slice accelerated diffusion-weighted imaging at ultra-high field strength

4.1.6

Eichner, C.[1,2], Setsompop, K.[2,3], Koopmans, P. J.[4], Lützkendorf, R.[5], Norris, D. G.[6], Turner, R.[1], Wald, L. L.[2,3], & Heidemann, R. M.[1,3]

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Diffusion magnetic resonance imaging (dMRI) data with very high isotropic resolution can be obtained *in vivo* at 7T. However, extensive brain coverage requires many slices, which can result in very long acquisition times (TA), given the need for multiple averaging. However, to accelerate acquisition, multiple slices can be acquired simultaneously (SMS), if receiver coil information is used to unfold overlapping slice in a later step. We combined zoomed and parallel imaging to achieve high isotropic resolution dMRI data with a low level of distortions at 7T. The blipped-CAIPI (controlled aliasing in parallel imaging) SMS approach was used to acquire several slic-

es simultaneously. To address the high specific absorption rate (SAR) of conventional multiband RF pulses, we used a novel low-SAR multislice Power Independent of Number of Slices (PINS) RF pulse. Combining zoomed and slice-accelerated diffusion acquisition allows 1-mm isotropic resolution dMRI data to be obtained in most of a human brain in about 20 minutes with 60 diffusion directions and four averages. Without slice acceleration a similar acquisition would take approximately one hour. Without averaging, 1.4-mm isotropic resolution dMRI data of the entire brain can also be obtained with good SNR and 60 diffusion directions in a total scan time of 6 minutes (see Fig. 4.1.6).

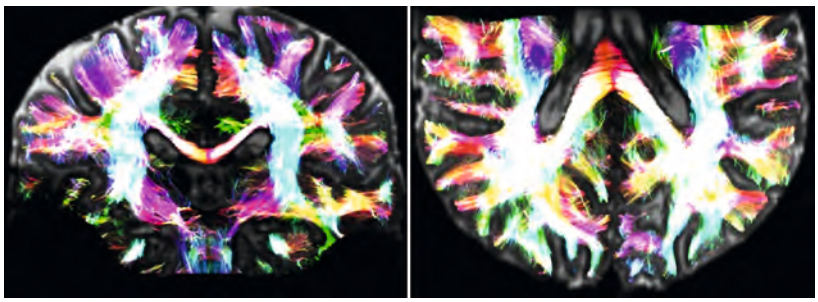

Figure 4.1.6 Streamline fibre tracking of 100,000 fibres (5 mm-slab) of coronal and axial brain slices overlaid on b = 0 image: Four times averaged 7T DW data with 1-mm isotropic resolution, 60 diffusion directions with b = 1000 s/mm^2.

4.1.7 Fast accurate MR thermometry using phase referenced asymmetric spin-echo EPI at high field

Streicher, M. N.[1], Schäfer, A.[1], Ivanov, D.[1], Müller, D.[1], Reimer, E.[1], Huber, L.[1], Dhital, B.[1], Rivera, D.[1], Kögler, C.[1], Trampel, R.[1], Pampel, A.[1], & Turner, R.[1]

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MR thermometry based on phase imaging is inherently very sensitive to any additional causes of local frequency change, such as magnetic field drift, tissue movement, or susceptibility changes. To avoid such errors we have developed an asymmetric spin-echo (ASE) EPI sequence which is made frequency-selective to water or a temperature-stable reference substance by controlling the slice-select gradient polarity or duration of the excitation and refocusing radiofrequency pulses. In a phantom RF heating experiment, dissolved dimethyl sulfoxide (DMSO) was used as a reference substance. Images were acquired pairwise (50 ms apart), and the temperature-sensitive water images were corrected for field fluctuations using the reference images. The temperature within the phantom was also monitored at two different locations with fluoroptic temperature sensors. Figure 4.1.7.1 shows

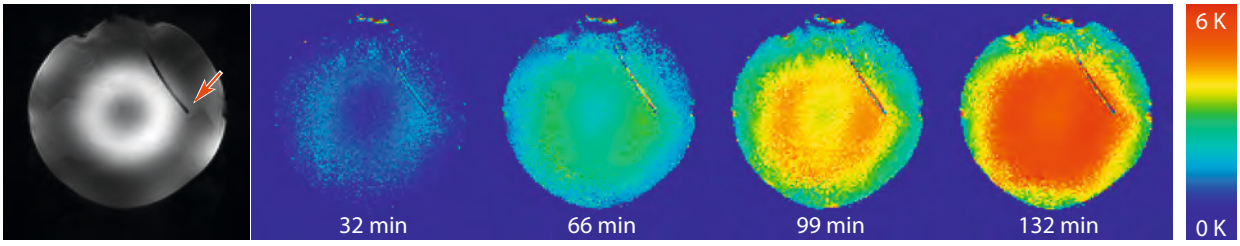

Figure 4.1.7.1 An axial phantom water magnitude image and successive temperature maps (acquisition times below each figure). The red arrow indicates the tip of temperature sensor 2.

an axial water magnitude image of the phantom and four MR temperature maps during heating at the position of sensor 2. The 2 h high SAR sequence increased the temperature of the water/DMSO phantom by approximately 6 K in the centre and 3 K at the edge. Figure 4.1.7.2A shows a time-series for the axial slice through sensor 1. The uncorrected time course shows an artifactual temperature drift compared with the temperature measurement of sensor 1, which is absent after correction using the reference substance. Figure 4.1.7.2B shows the corrected temperature time courses for ROIs around both sensors. The corrected MR measured temperature-increase at the sites of the sensors was 5.7 ± 0.2 K (sensor 1) and 4.6 ± 0.2 K (sensor 2) compared to the temperature sensor reading of 5.7 ± 0.1 (sensor 1) and 4.5 ± 0.1 K (sensor 2).

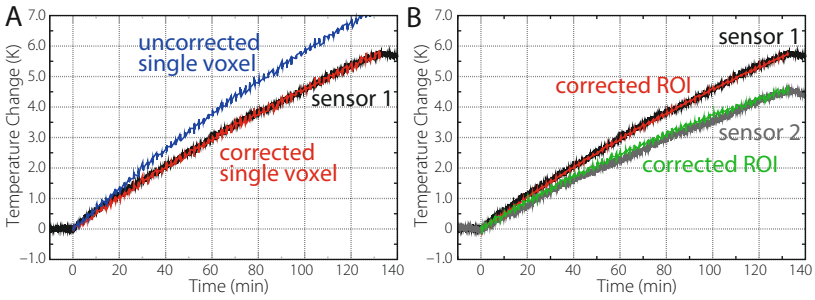

Figure 4.1.7.2 Phantom heating experiment. (A) Sensor 1 unsmoothed temperature time course (black) with a temporal resolution of 1 s. On top, a single voxel uncorrected time course (blue) and the corrected time course (red) in a voxel close to sensor 1. (B) The corrected MR thermometry time courses of ROIs around sensor 1 (black) and sensor 2 (grey) are shown as red and green graphs, respectively.

4.1.8

Prospective slice-by-slice motion correction reduces false positive activations in fMRI with task-correlated motion

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[2] Department of Radiology, Stanford University, CA, USA
[3] Department of Radiology, Medical Physics, University Medical Center Freiburg, Germany

We have developed an optical embedded tracking system that measures the head position of a volunteer to enable prospective motion correction (PMC) during an MRI scan, and integrated the position data from our tracking system into several MR sequences.
Motion artifacts are an issue not only in long-duration high-resolution anatomical scans but also in functional experiments. Motion correlated with the task may lead to false positive apparent brain activation. To investigate the influence of PMC on the rate of false positive activations compared to standard data processing using retrospective motion correction (RMC), we designed a paradigm involving strong task-correlated head motion (a left-right motion of the lifted right leg) and acquired functional data in 15 volunteers with and without slice-by-slice PMC at 7T. A standard group analysis was performed involving smoothing. We found that PMC

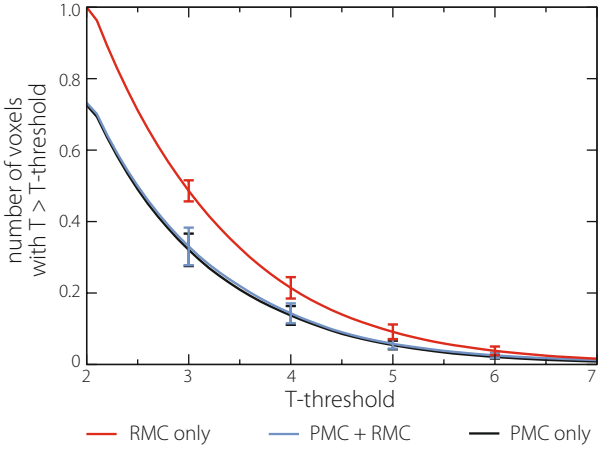

Figure 4.1.8 Normalized number of false positive activations (i.e. activations outside the grey matter masks) with T-values higher than T-threshold plotted against different thresholds. The error bars indicate the standard error on the mean.

increases both the spatial extent and the peak T-value. To evaluate the number of false positive activations, we performed a subject-by-subject analysis without spatial smoothing. All active voxels outside of a grey matter mask derived from high resolution anatomical data were counted as false activations. The numbers of false positives for RMC only, PMC only, and PMC+RMC were normalized to the number of RMC only with $T > 2$ and averaged over all volunteers (see Fig. 4.1.8). PMC significantly reduces the number of artifactual activations.

Since September 2013, this project has been funded by the Max Planck Society's EXIST Forschungstransfer Phase I, as a commercial start-up company.

4.1.9 Cerebral blood volume changes during brain activation

Krieger, S. N.[1], Streicher, M. N.[1], Trampel, R.[1], & Turner, R.[1]

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Going beyond BOLD, fMRI studies have begun to utilize changes in cerebral blood volume (CBV) which may better localize neural activity. The finding that capillaries expand during increases of CBF is still poorly recognized, and the concept of CBV itself has received little analysis. According to the Monro-Kellie doctrine, the sum of CBV, CSF volume and brain tissue volume must remain constant over time to minimize changes of intracranial pressure (ICP), due to the inextensibility of the skull. An increase of one compartment can only occur at the expense of another. The question becomes: how can cerebral capillaries expand inside the rigid cranium, keeping brain tissue and CSF volume constant, without dangerously increasing the ICP? We have proposed that changes in CBV are largely facilitated by exchange of water between capillaries and surrounding tissue via the plentiful aquaporin channels. To explore this idea, we developed a novel hemodynamic boundary value model and found approximate solutions using a numerical algorithm. We constructed a macroscopic experimental model of a single capillary to provide biophysical insight (Fig. 4.1.9). The experimental and theoretical approaches respect the Monro-Kellie doctrine as well as the elastic and permeable properties of capillaries. When a permeable 'capillary' was used, for a realistic change of input pressure, relative pipe volume changes of 17–21% were observed, matching recent measurements of capillary volume changes during various stimuli. We observed no significant pressure changes within the modelled 'cranium'. In contrast, impermeable model capillaries gave high intracavity pressure changes, demonstrating the importance of capillary permeability in preventing intolerable ICP changes during vasodilation. Blood-brain barrier permeability to water may need to be taken into account for quantitative modelling of the fMRI BOLD signal.

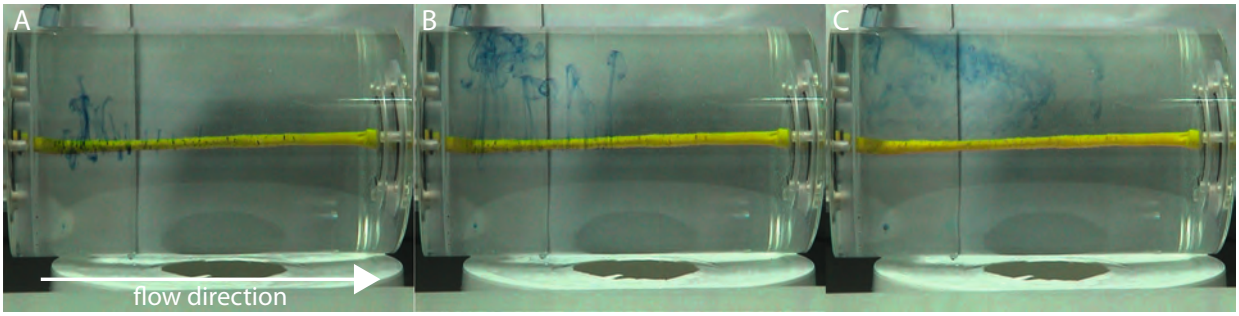

Figure 4.1.9 Experimental model of a single capillary using ink as a tracer at (A) t = 0.5 s, (B) t = 3 s and (C) t = 10 s.

4.2 Neuroanatomy & Image Analysis

At best, current human functional imaging studies correlate activations only with brain macroanatomy. Invasive electrophysiological studies in nonhuman primates show dramatic differences in functional activity across cytoarchitectonic borders. These borders vary topographically across human brains, throwing into question structure-function correlations based solely on macroanatomy. Worse, currently widespread methods that use spatial normalization to a standard template brain, with extensive spatial smoothing to align homologous functional areas, have resulted in regrettably imprecise spatial localization, and throw away experimental power that might be gained using anatomically appropriate regions of interest based on native maps of individual brains.

Image analysis and computational modelling

Functional areas of the human cerebral cortex have been studied either anatomically at the microscopic scale in cadaver brains or functionally at much coarser scales *in vivo* with fMRI, EEG, or MEG. With 7Tesla MRI, data can now be acquired at a scale well below 1 mm, allowing anatomy and function to be studied in the same living individuals. However, powerful image processing techniques are needed to segment the cortex at a mesoscopic scale. In addition, careful anatomical modelling of the effects of cortical folding on the organization of cortical layers is essential to extract as much information as possible from cortical profiles. We have developed the first computational model of cortical lamination that follows closely across sulci and gyri the cortical layers observable in ultra-high resolution cadaver brain scans. One classical hypothesis is that cytoarchitecture predicts myeloarchitecture. We have extended this to infer contrast in high-resolution T_1 maps of *in vivo* human cerebral cortex. Finally, we have built a novel strategy for the accurate coregistration of cortical surfaces, making it possible to average data consistently across subjects within individual cortical areas. Taken together, these may enable precise anatomical definition of functional areas in individual living subjects, allowing assignment of cortical function to its specific neuronal substrate.

4.2.1 Microstructural parcellation of the human cerebral cortex: From Brodmann's post-mortem map to *in vivo* mapping with high-field magnetic resonance imaging

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

This book was published in 2013 by Springer Verlag.

- The book explains why cortical areas and their boundaries are "classically" defined by their cyto- and myeloarchitectonic pattern *ex vivo*, i.e. in post-mortem brains
- The book illustrates how state-of-the-art high-field magnetic resonance imaging (MRI) technologies can generate in living brains individual-specific maps of cortical microstructure that are based on differential grey matter myelination between areas
- The book shows that the ultimate research goal is direct structure-function correlation in the same subjects, which can now be achieved by matching MRI-based microstructural and functional maps in the same living brains

Unravelling the functional properties of structural elements in the brain is one of the fundamental goals of neuroscientific research. In the cerebral cortex this is not trivial, since cortical areas are defined microstructurally in post-mortem brains but functionally in living brains with electrophysiological or neuroimaging techniques—and cortical areas vary in their topographical properties across individual brains. Being able to map both microstructure and function in the same brains noninvasively *in vivo* would represent a huge leap forward. In recent years, high-field MRI technologies with spatial resolution below 0.5 mm have set the stage for this by detecting structural differences within the human cerebral cortex, beyond the Stria of Gennari. This provides the basis for an *in vivo* microanatomical brain map, with the enormous potential to make direct correlations between microstructure and function in living human brains.

The book starts with Brodmann's post-mortem map published in the early 20th century, moves on to the almost forgotten microstructural maps of von Economo and Koskinas and the Vogt-Vogt school, sheds some light on more recent approaches that aim at mapping cortical areas noninvasively in living human brains, and culminates with the concept of "*in vivo* Brodmann mapping" using high-field MRI, which was introduced in the early 21st century.

4.2.2 A computational framework for ultra-high resolution cortical segmentation at 7 Tesla

Bazin, P.-L.[1], Weiss, M.[1], Dinse, J.[1,2], Schäfer, A.[1], Trampel, R.[1], & Turner, R.[1]

[1] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2] Simulation and Graphics Department, Faculty of Computer Science, Otto von Guericke University, Magdeburg, Germany

State-of-the-art imaging techniques at 7T can provide whole-brain *in vivo* quantitative MRI measurements at 0.4-mm isotropic resolution. Such high-resolution images require efficient computational methods that scale well with the increase in data size, handle quantitative contrasts, and identify the fine structural details now visible. We have developed a fully automated computational framework for brain segmentation and cortical reconstruction at the ultra-high resolution of 0.4 mm, based on quantitative T_1 images acquired at 7T with the MP2RAGE sequence. The method includes skull stripping, whole brain segmentation, and cortical extraction, all within a computation time below 6 h. Our approach integrates a classical intensity and statistical atlas-based classification model into a topology-preserving multi-object geometric deformable model, ensuring both smoothness and topological correctness of all structural boundaries. The computation time scales sub-linearly with image size and structure number, and can easily integrate new image contrasts, making further increases in data complexity manageable. The corresponding software package, "CBS High-res Brain Processing Tools", has been publicly released after extensive validation experiments on simulated phantoms and human subject data.

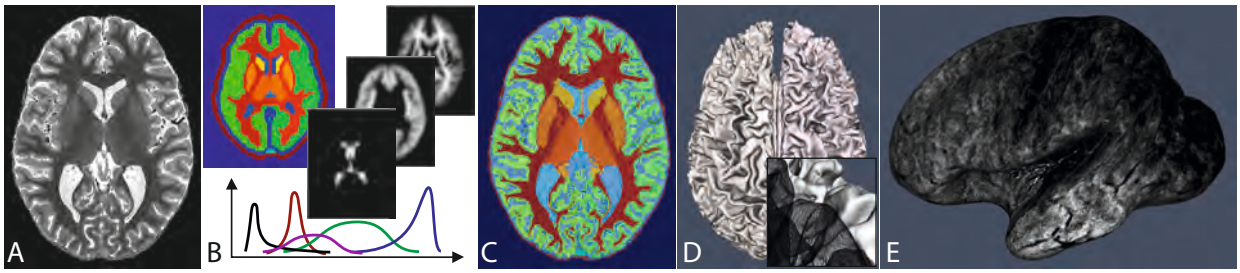

Figure 4.2.2 Brain segmentation pipeline: First the quantitative T_1 are skull-stripped and aligned to MNI space at 0.4 mm (A), then priors of shape, intensity, and topology are used (B) to segment the brain (C). The cortical surface is further refined and extracted into a high-resolution mesh (D) ready to be inflated for cortical analysis (E).

Anatomically motivated modelling of cortical laminae

4.2.3

Wähnert, M. D.[1], Dinse, J.[1,2], Weiss, M.[1], Streicher, M. N.[1], Wähnert, P.[3], Geyer, S.[1], Turner, R.[1], & Bazin, P.-L.[1]

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[3] Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany

Recent improvements in the spatial resolution of structural and functional MRI enable the analysis of intracortical structures such as heavily myelinated cortical layers in 3D, a prerequisite for *in vivo* parcellation of individual human brains. This parcellation can be performed precisely only if the profiles used in cortical analysis are anatomically meaningful. Profiles are generally constructed as traverses that are perpendicular to a computed layering of the cortex into laminae. Methods to model the laminae used so far either keep a constant distance to the cortical boundaries ("Equidistant model") or follow equipotentials of the Laplace equation ("Laplace model").
To evaluate the laminae models we compared them with post-mortem MR images of the stria of Gennari in primary visual cortex. Contours from Equidistant and Laplace models both fail to follow the stria. Similar results have been observed in other post-mortem samples. Indeed, Bok (1929) argued that layer thickness changes with local cortical curvature, so that cortical segments preserve their volume. Following his insight, we have derived a novel Equi-volume model which adapts layer thickness to curvature, to generate a three-dimensional well-adapted undistorted coordinate system for the cortex. When defined by this coordinate system, cortical depth is anatomically meaningful and the corresponding cortical profiles are not distorted by local curvature. The method has been validated quantitatively on *ex vivo* MRI and integrated in the freely-available CBS Tools software package.

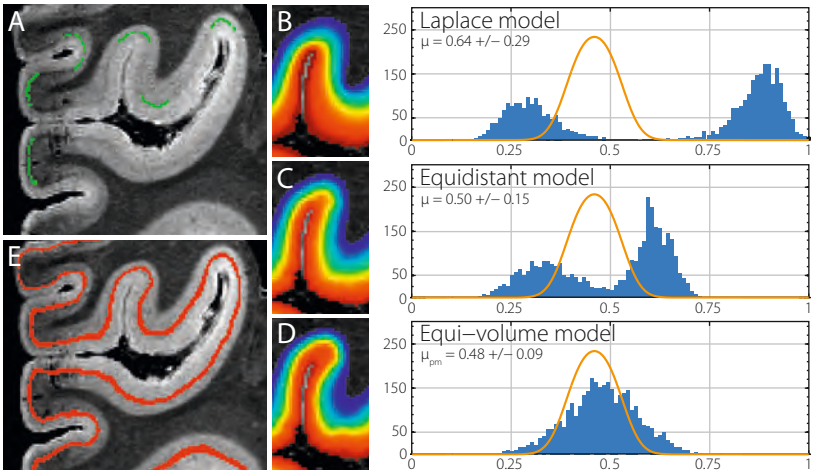

Figure 4.2.3 Modelling the three-dimensional laminae of the stria of Gennari: manual labels on the stria of Gennari have been sampled in highly curved regions (A) , and histograms of the corresponding cortical depth values computed with the Laplace (B), equidistant (C), and Equi-volume model (D) have been compared. The previous models result in bimodal histograms separating sulci and gyri (B, C) and only the Equi-volume model (D) has a unimodal histogram (ochre lines: literature values of the cortical depth and width of the stria of Gennari; μ are the mean and standard deviations of the histograms). The isocontour of μ_{pm} values from the Equi-volume layering follows closely the stria (E).

4.2.4 A histology-based model of quantitative T_1 contrast for *in vivo* cortical parcellation of high-resolution 7 Tesla brain MR images

Dinse, J.[1,2], Wähnert, M. D.[1], Tardif, C.[1], Schäfer, A.[1], Geyer, S.[1], Turner, R.[1], & Bazin, P.-L.[1]

[1] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2] Simulation and Graphics Department, Faculty of Computer Science, Otto von Guericke University, Magdeburg, Germany

A concordance atlas comparing cortical myeloarchitecture and cytoarchitecture does not yet exist. Following Hellwig, 1993, we developed a novel generative model which predicts, on the basis of known cytoarchitecture, myelin patterns in different cortical areas and, in turn, the corresponding patterns that might be observable in quantitative maps of T_1 measured *in vivo* using MRI. Given accurately defined cortical profiles, we compared the predicted patterns to intracortical variations of T_1, in order to differentiate even closely related cortical functional areas such as Brodmann areas 4, 3b, 1, and 2 using quantitative MR contrast alone.

We tested our model using a similarity distance metric, which can distinguish cortical areas at the single-subject and group level. The model can be readily extended to many of the cortical areas quantified by von Economo and Koskinas, and may also be used in reverse to predict the cytoarchitecture of missing areas. Additional information (such as spatial priors, regularization, topological constraints, etc) may also be needed to parcellate robustly and automatically a larger set of cortical areas. From a conceptual point of view, our approach provides new perspectives for both imaging and modelling the relationship between myelo- and cytoarchitecture, leading the way towards *in vivo* histology using MRI.

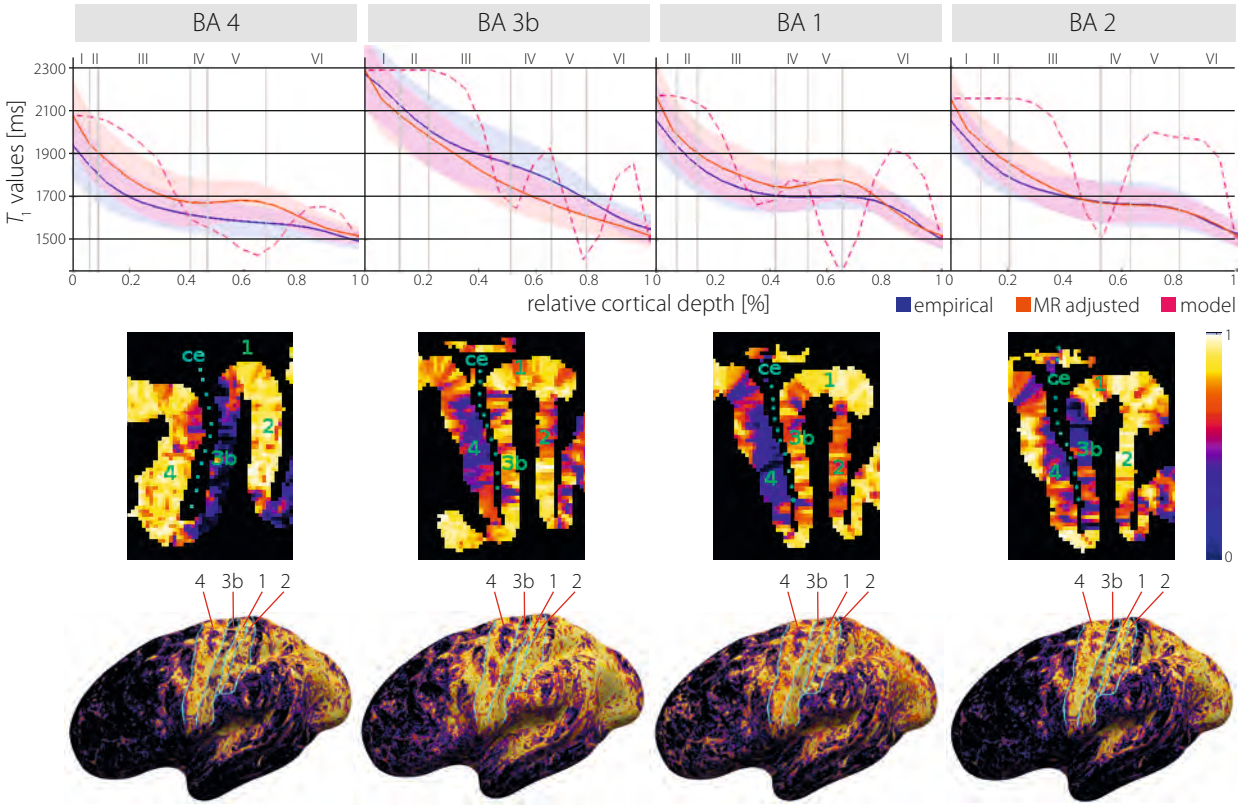

Figure 4.2.4 Predictive model of T_1 contrast for Brodmann areas 4, 3b, 1, and 2: comparison between modelled and observed cortical profiles (top), corresponding similarity value volumetrically across the M1/S1 region (middle) and on the inflated surface of the whole cortex (bottom). Although there are matching areas of similar cyto- and myelo-architecture outside the region, the contrast between similarity functions is enough to delineate area boundaries.

4.2.5

Multi-contrast cortical surface registration using magnetic resonance imaging T_1 maps for improved alignment of myeloarchitectonic areas

Tardif, C.[1], Dinse, J.[1,2], Schäfer, A.[1], Turner, R.[1], & Bazin, P.-L.[1]

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Image registration is crucial for brain mapping studies, such as comparative morphometry and group analysis of functional data, in order to compensate for differences in position, size, and shape of brain structures across individuals. The cerebral cortex is highly convoluted and variable, so that functionally distinct cortical areas may be close in volume space but very distant along the cortical surface. Non-linear volume-based registration algorithms perform well for deep brain structures, but they fail to accurately align the cortex. To align cortical areas across subjects or with an atlas, it is thus preferable to use surface-based registration, aligning 2D manifolds using cortical geometry. Cortical folding patterns can predict the location only of primary cortical areas with reasonable accuracy. Recently, *in vivo* MRI has enabled intra-cortical myelin-based contrast to be mapped onto the cortical surface. These "myelin maps" reflect the location of functionally specialized areas of the cortex using task and resting-state fMRI and compare well with Brodmann's cortical parcellation.

To improve the alignment of cortical areas we have introduced surface-based registration of T_1 maps, which quantitatively index myelin content. Our novel multi-contrast surface-based registration technique offers accurate surface registration, with key improvements over

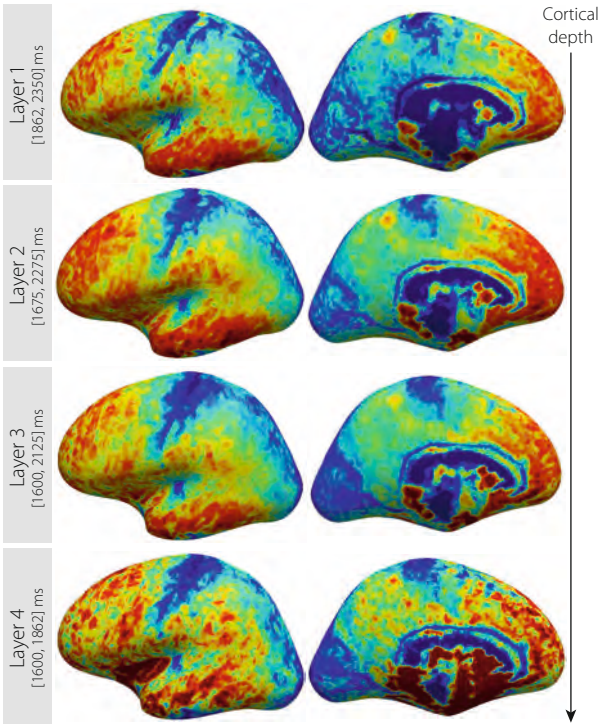

Figure 4.2.5.1 Average T_1 map of six subjects using surface-based registration of T_1 maps at four cortical depths. The intra-cortical T_1 contrast varies with cortical depth, and matches the myeloarchitectonic descriptions of the cortex.

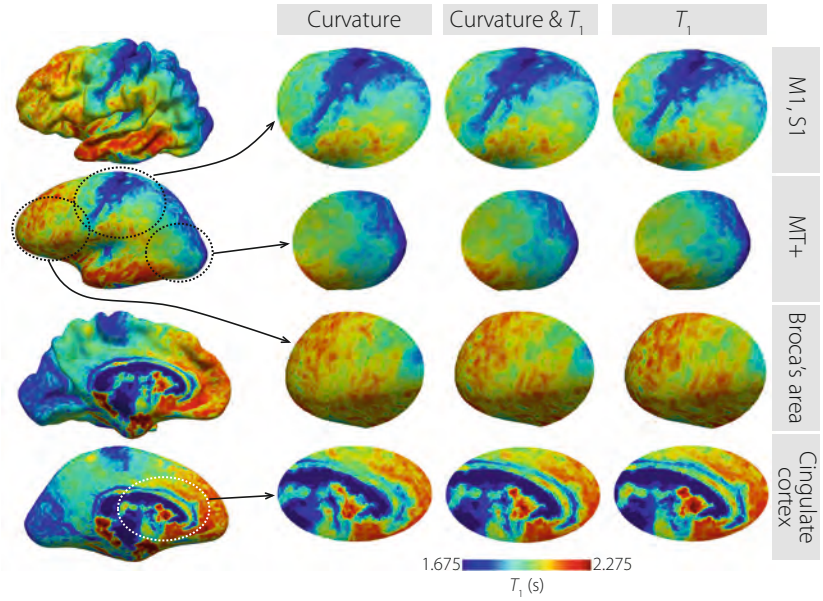

Figure 4.2.5.2 Average T_1 map of six subjects using multi-contrast surface-based registration with three different contrast combination: curvature, curvature and T_1, T_1 only. The cortical areas labelled to the right are better aligned using T_1 than curvature.

current methods, using a non-linear volume-based registration algorithm for surface information represented in volume space, rather than computing a deformation restricted to a spherical manifold. Our multi-scale approach is applied to partially inflated surfaces, and outputs a direct symmetric diffeomorphic transformation between the original surfaces. We include four contrasts: the level-set representation of the cortical surfaces, two curvature metrics (curvedness and shape index), and intra-cortical T_1 contrast. The method can be extended to include other contrasts, such as functional data. In qualitative and quantitative comparisons, the inclusion of T_1 contrast results in improved alignment in group averages. With this method, we have produced a group-averaged 0.5-mm isotropic T_1 map on the cortical surface at different cortical depths with unprecedented structural detail that clearly reflects myeloarchitecture.

4.2.6 Development and evaluation of an algorithm for the computer-assisted interactive segmentation of the human hypothalamus on 7-Tesla magnetic resonance images

Schönknecht, P.[1], Schindler, S.[1], Schmidt, L.[1], Anwander, A.[2], Strauß, M.[1], Trampel, R.[2], Bazin, P.-L.[2], Möller, H. E.[2], Hegerl, U.[1], Turner, R.[2], & Geyer, S.[2]

[1] Department of Psychiatry and Psychotherapy, University Hospital Leipzig, Germany
[2] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

The hypothalamus is a small grey matter brain region of the diencephalon that surrounds the anterior portion of the third ventricle. As a part of the limbic system it connects the cerebral cortex with the visceral system and hence is deemed a 'mediator between mind and body'—which are both affected in psychiatric diseases. Structural correlates have been described with mood disorders, schizophrenia, anxiety, borderline personality disorder, narcolepsy, and frontotemporal dementia. Since the hypothalamic region is less than 4 cm^3 in size, and hard to distinguish from its surroundings, sub-millimeter magnetic resonance imaging (MRI) is essential for its *in vivo* structural investigation. Interactive segmentation guided by anatomical landmarks is still state of the art for defining the human hypothalamus on MR images. The traditional anatomical landmarks of the hypothalamus were refined using 7T T_1-weighted magnetic resonance images (voxel size 0.7 mm isotropic). A detailed segmentation algorithm (unilateral hypothalamus) was developed for colour-coded, histogram-matched images, and evaluated in a sample of ten subjects. Test-retest and inter-rater reliabilities were estimated in terms of intraclass-correlation coefficients (ICC) and Dice's coefficient (DC). The computer-assisted segmentation algorithm ensured test-retest reliabilities of ICC ≥ .97 (DC ≥ 96.8) and inter-rater reliabilities of ICC ≥ .94 (DC = 95.2).
We present a computer-assisted algorithm for the manual segmentation of the human hypothalamus using high-resolution T_1-weighted images acquired at 7T. The estimated volumes lie within the range of previous measurements *ex vivo* (i.e. histology) and *in vivo* (i.e. neuroimaging). Once applied in larger samples of neuropsychiatric patients, high-resolution volumetry of the hypothalamus will improve our understanding of the pathogenesis of psychiatric disorders.

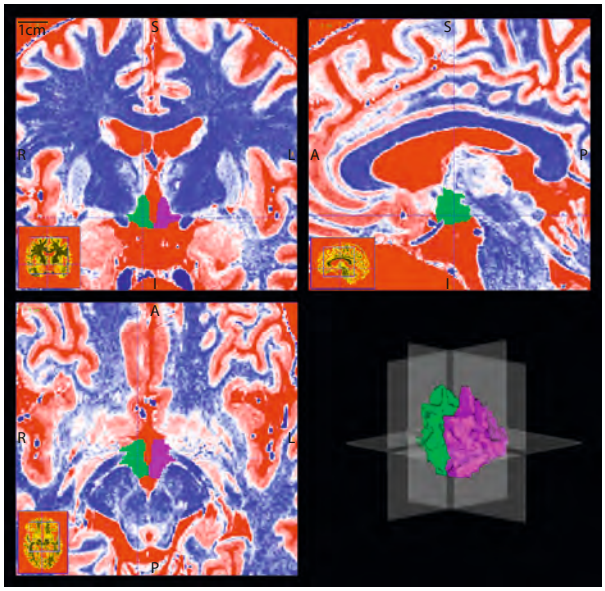

Figure 4.2.6 Triplanar view of the segmented left (purple) and right (green) hypothalamus in colour-coded images. Coronal plane (top left), sagittal plane (top right), and transverse plane (bottom left) (cf. dotted lines in other planes). Left side of the images (coronal and transverse planes) corresponds to right side of the brain. A 3D reconstruction of the hypothalamus mask (left anterolateral view) is shown in the lower right image.

4.2.7

Habenula volume increases with disease severity in un-medicated major depressive disorder as revealed by 7-Tesla magnetic resonance imaging

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[1] Department of Psychiatry and Psychotherapy, University Hospital Leipzig, Germany
[2] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

The habenula is a paired epithalamic structure which is involved in the pathogenesis of Major Depressive Disorder (MDD). Evidence comes from its impact on the regulation of serotonergic and dopaminergic neurons, its role in emotional processing, studies on animal models of depression, successful deep brain stimulation in depressed patients, and reduced post-mortem habenula volumes in depressed patients' brains. Investigations with positron emission tomography in un-medicated depressed patients showed a relationship between the response to antidepressant treatment and the pretreatment ratio of serotonin transporter availability.

In the present study, for the first time *in vivo* habenula volumes were investigated in 20 un-medicated and 20 medicated MDD patients and 20 healthy controls with a 3D segmentation algorithm on 7T magnetic resonance (MR) whole-brain T_1 maps. Analyses of variance did not show significant differences in bilateral or unilateral habenula volumes between the three groups. However, we found (i) in un-medicated MDD patients a significant positive correlation between MDD severity scores and absolute right, absolute left, relative left, and absolute bilateral habenula volumes and (ii) higher habenula volumes in severely compared to mildly depressed patients. These findings point towards a severity-dependency of habenula volumes at the onset of the disease. Further tractographic and functional investigations with high-resolution *in vivo* MR imaging are warranted to confirm these interesting findings.

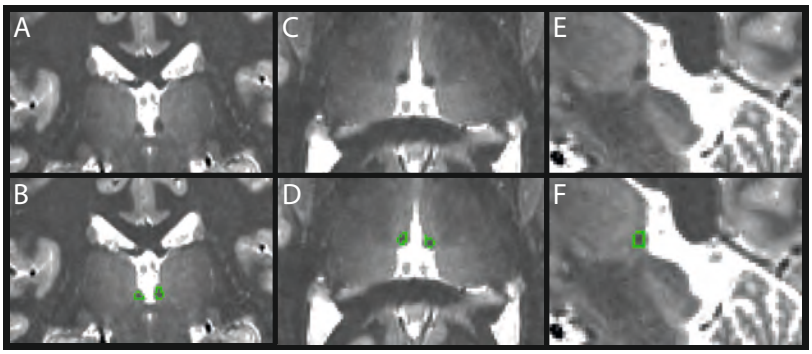

Figure 4.2.7 Habenula nuclei in the coronal (A, B), transverse (C, D), and sagittal (E, F) planes. Native T_1 maps (A, C, E) and T_1 maps with segmented habenula voxels overlaid in green (B, D, F).

4.3 High Field RF Technology

Research in radiofrequency (RF) technology for MRI at 7T has two main objectives: to optimize transmit and receive coil performance, and to ensure subject safety. For both purposes, given the electromagnetic field regime at 300 MHz between near-field and far-field, high quality field and circuit simulations are vital for progress. We have developed dramatically improved methods for such simulations, based on techniques published by Kozlov in 2009 based on 3D electromagnetic and RF circuit co-simulation. Furthermore, we have set up an RF coil construction facility, we have built efficient RF coils that are already in use for cadaver brain imaging at 7T, and we are building prototype RF coils based on Kozlov designs that show great promise to simplify the problem of generating spatially uniform transmit RF fields.

4.3.1 Novel fabrication technique for RF transmit coil arrays using printed circuit board technology

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

We have developed a novel fabrication method for building three-dimensional circuits that incorporates standard printed circuit board batch processes (Fig. 4.3.1). The method allows high precision in fabrication and thus enables accurate computer simulations for optimizing safety and transmit performance of transmit arrays. Inaccuracies in transmit array fabrication present a potential safety risk, as emphasized by Kozlov, as well as deviations from the optimized transmitted magnetic field. The method incorporates multiple printed circuit board pieces (and supporting mechanical pieces), each with a connector such as a slot or tab, assembling with self-alignment to form transmit array coils with sub-millimeter precision. Design of the printed circuit board components is fully automated. Array parameters (e.g. overall diameter, number of elements, element dimensions, trace widths, number of components) are entered into a custom-built script, which in turn generates code that is read into a commercial circuit board layout package.

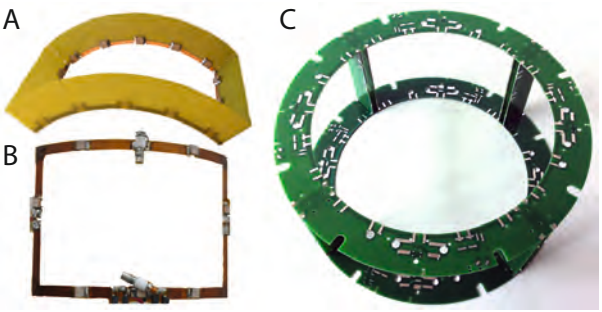

Figure 4.3.1 (A) Single element of an RF transmit coil fabricated with novel printed-circuit board technique. (B) Similar element fabricated by hand. (C) Photograph of a 4-element printed-circuit array.

4.3.2 Simulation-driven design and optimization of RF coil arrays for MRI

Kozlov, M.[1], & Turner, R.[1]

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Due to the complexity of magnetic resonance imaging (MRI) arrays at the high radiofrequency of 300 or 400 MHz, experimental coil optimization alone is extremely time consuming and costly. Numerical simulation is thus desirable, especially of the specific absorption ratio (SAR), because experimental SAR measurement is almost impossible for human subjects *in vivo*.

In our investigations of MRI array safety and performance optimization we include in the simulation domain the entire scanner RF system—power source, feed sub-circuit, radiative elements, and their decoupling. This results in reliable simulation of the interactions between the radiative elements, between the radiative elements and the array load, and correct calculation of the array

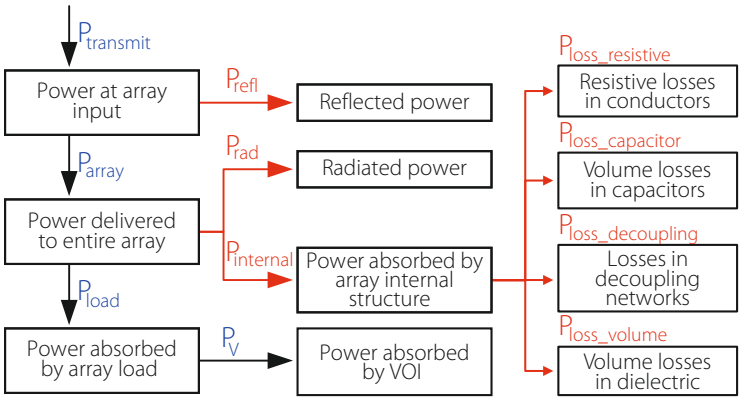

Figure 4.3.2.1 Array power budget.

power budget, as presented in Figure 4.3.2.1 as required by draft regulations (IEEE/IEC 62704-1).

RF circuit and 3D EM co-simulation offers a reliable and fast workflow for array analysis. A developer may not only simulate the feed, decoupling networks and the MRI coil as a single system, but can also obtain near-field data and SAR for different tuning, feeding, and decoupling conditions without rerunning the time consuming 3D simulation.

The most important goals of high-field array design are presented in Figure 4.3.2.2. A solution has not yet been found for global optimization of all these goals. There are solutions regarding trade-off performance for robustness and safety, and some other trade-offs.

The required values of maximum B_1+ and homogeneity within a given VOI are mostly defined by MRI examination considerations. At high radio frequencies, a multipurpose array targeted to excite a large VOI is likely to provide a lower integral performance measure, as compared with an application-specific array optimized with regard to the issues presented in Figure 4.3.2.3. A developer can use several degrees of freedom to improve array design. Figure 4.3.2.4 presents the relevant issues.

If dominance of non-conservative electrical fields is ensured for a VOI whose dimensions are comparable to the RF wavelength, we have shown that the local excitation efficiency varies little over a large range of MRI array designs, for a given excitation mode.

Because transmitted, reflected, radiated, and absorbed RF power are all closely interrelated, an efficiency increase requires simultaneous minimization of all energy wasting terms and maximization of the transmitted power. For every array geometry and fabrication design, this can be increased by near-field optimization, resulting in a set of appropriate excitation conditions. In addition, by means of circuit optimization, reflected power can also be minimized for this set of excitation conditions.

Because circuit optimization changes the array tuning, which influences the starting values for near-field optimization, near-field and circuit optimizations need to be iteratively repeated until the results converge. A sensitivity analysis for the array design and details of fabrication characterizes the influence of the available degrees of freedom on reflected and transmitted power.

To allow a reduced safety margin and thus increased scan rate, the RF magnetic field within an array must be insensitive to variation of tuning condition, geometry and electrical properties of all RF coil parts, human size, and human position (Fig. 4.3.2.4).

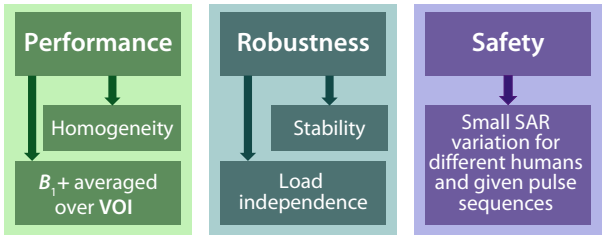

Figure 4.3.2.2 Goals of high-field array design.

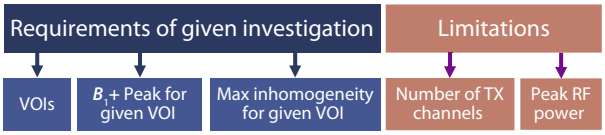

Figure 4.3.2.3 Application-specific performance optimization.

Figure 4.3.2.4 MRI array parameter space.

Engineering of 7T transmit multi-row arrays

4.3.3

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To obtain values of the variable array components—the decoupling inductors, tune, and match capacitors—we used three circuit-level array optimization strategies, with different cost functions. As with any other optimization procedure, MRI array tuning is guided by minimization of an error or cost function (EF), which is a measure of the difference between the actual and desired transmitter conditions.

4.3.4 Effects of tuning condition, head size, and position on the SAR of a MRI dual-row transmit array at 400 MHz

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In most reported studies, the decoupling of array elements is assumed to be ideal. However, even when experimental and numerical B_1+ fields agree, SAR estimation may be unreliable, because E and B fields can be independently constructive and destructive at the same point in space. Typically, only the amplitudes of actual and simulated element matching, and the adjacent-element coupling, are compared. The influence of coupling phase on SAR has generally been neglected, despite the well-known existence of under-coupled and over-coupled cases. Variation of tuning conditions can result in a different pattern of constructive E-field interference for different excitation conditions.

The RF coil design parameter space is huge. Answering the question "What happens if …?" requires data for MRI arrays with many parameter variations, because most parameter dependencies are non-linear. In other words, sensitivity analysis cannot be done without a huge number of 3D EM simulations followed by a huge number of RF circuit simulations for each tuning condition and 3D EM post-processing steps for each excitation condition. Therefore a simulation work-flow was developed and optimized for 24/7 high level outcome.

We numerically investigated the effects of tuning condition, head size, and position on the specific absorption ratio (SAR) of a 9.4T dual row 16-channel transmit array, which was fabricated at MPI Tübingen.

The array was loaded by typical human head models with three scaling factors. We analyzed geometries where the head was placed symmetrically in the transverse plane, and where the head was positioned 22 mm

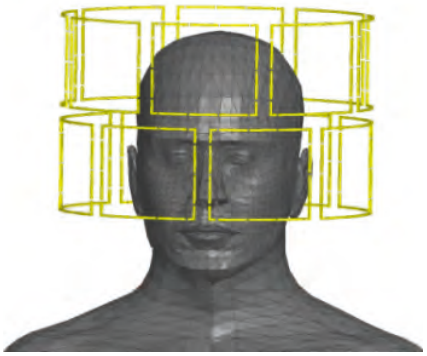

Figure 4.3.4.1 9.4T array geometry setup. Only radiative elements and human model are shown.

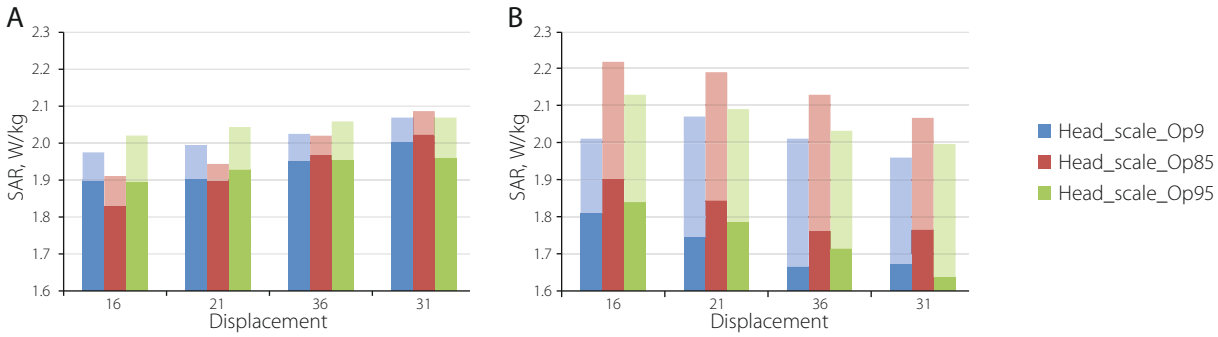

Figure 4.3.4.2 SAR_{10g} variations for different head displacements and head scales. (A) CP mode, (B) "+90" mode.

lower, to allow space for the mirror of a visual stimulus system. In both geometries each human body model was located at four axial positions so that the distance between crown of the head and array top was 16, 21, 26, and 31 mm. We use the following abbreviations for head displacement from end of coil: "16 mm", "21 mm", "26 mm", and "31 mm".

The circuit-level array performance was fine-tuned for each head location using S parameter based and "mode" optimizations. Then the SAR was evaluated for different array excitation conditions and all variants of the array tuning condition.

The tuning condition had a significant impact on the spatial-average 10-gramm SAR of the dual row array investigated, especially if excitation was not CP mode (Fig. 4.3.4.2, 3, and 4).

A precise match of dual row array conditions in numerical and actual domains is essential for reliable SAR assessment. When the array diameter is relatively large, and variations of head position result in insignificant variations of array circuit level measures, SAR_{10g} differences are expected to be relatively small (less than 20%) and can be easily covered by the typical array safety margin. However it is impossible to provide a general conclusion that a variation of an array property provides negligible influence on SAR_{10g} for any dual row array. A dual-row array of interest needs to be comprehensively and reliably investigated (including a sensitivity analysis) in order to define scanner SAR assessment parameters. If the precise match of conditions or a sensitivity analysis cannot be obtained, the coil safety margin should be increased considerably.

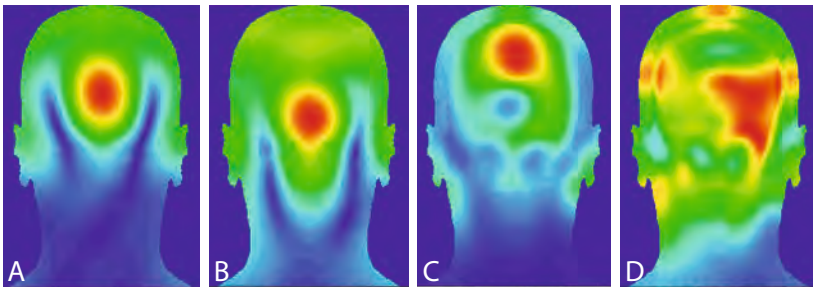

Figure 4.3.4.3 Simulation data for the array with head displacement "16 mm" and Tuning condition for displacement "16 mm". (A) and (B) $\boldsymbol{B}_1$+ slices rescaled to individual maximum, (C) and (D) SAR_{10g} slices rescaled to individual maximum; (A) and (C) CP mode, (B) and (D) "+90" mode.

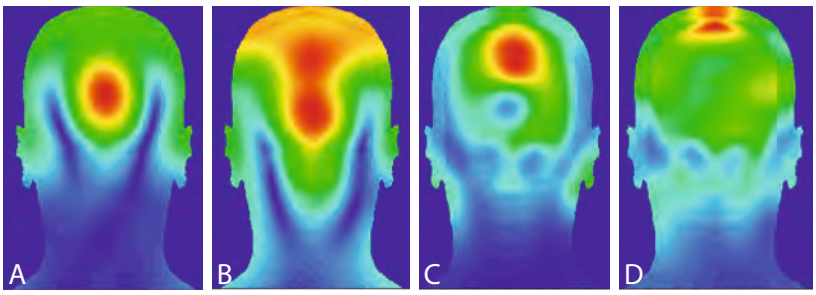

Figure 4.3.4.4 Tuning condition for displacement "26 mm". (A) and (B) $\boldsymbol{B}_1$+ slices rescaled to individual maximum, (C) and (D) SAR_{10g} slices rescaled to individual maximum; (A) and (C) CP mode, (B) and (D) "+90" mode.

4.3.5 RF transmit performance comparison for several 7T MRI head array geometries

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We numerically investigated several magnetic resonance imaging radiofrequency transmit coil arrays with different array diameters (Fig. 4.3.5.1) and tuning conditions. Compared with a dual-row array of 250 mm in diameter, it is difficult to achieve high transmit performance when the diameter is increased to 280 mm, while maintaining high load independence and a predictable distribution of current through each element. Despite very similar values of inhomogeneity over the entire brain, the B_1+ distributions are not the same. As shown in Figures 4.3.5 2–3, the simulated B_1+ differed in the forehead and at the back of the head, in sagittal (A), coronal (B) and central transverse (C) sections.

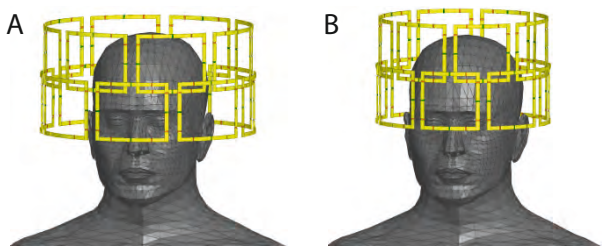

Figure 4.3.5.1 Array geometry setup: (A) Ø280 mm and the head displacement 12 mm, (B) Ø230 mm and the head displacement 27 mm. Only radiative elements and human model are shown.

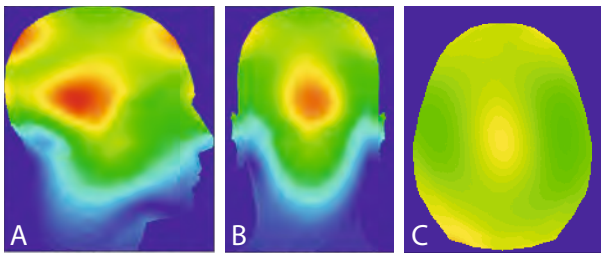

Figure 4.3.5.2 Array 280. B_1+ slices rescaled to max = 1.76 uT.

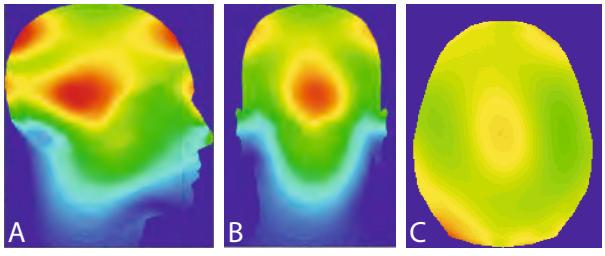

Figure 4.3.5.3 Array 250. B_1+ slices rescaled to max = 1.88 uT.

Manual tuning of a fabricated multi-coil array is extremely laborious. Analysis of near-field transmit properties, obtained for about a dozen numerical tuning conditions similar to that of a constructed array, is important in order to conclude that an array is robust. If near-field transmit properties vary considerably in the numerical domain, the corresponding constructed array will not provide good robustness, and margin required for maintaining safety in operation should be significantly increased.

Similarity between the experimental and numerical B_1+ cannot guarantee the similarity of SAR_{10g}, especially when the "noisiness" of experimental B_1+ is taken into account. For reliable SAR_{10g} assessment, it is essential for the E-field or power loss density distributions for several excitation conditions to be properly validated. However, some questions remain open: How many different human models, how many positions, and how many non-ideal tuning conditions should be investigated, and how many different excitation conditions should be validated to demonstrate array robustness and safety in operation?

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Turner, R. & Geyer, S. (April). *International workshop on in vivo Brodmann mapping*. Workshop. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Geyer, S. & Turner, R. (June). *Microstructure meets function in the same brain in vivo – high-field MRI sets the stage*. Workshop. 19th Annual Meeting of the Organization for Human Brain Mapping, Seattle, USA. **2013**

Degrees

PhD Theses

Ivanov, D. *Functional mapping of hemodynamic parameters and oxygen utilization in human brain using magnetic resonance imaging techniques at 7 Tesla*. University of Leipzig, Germany. **2012**

Stahl, B. *Treatment of non-fluent aphasia through melody, rhythm and formulaic language*. University of Leipzig, Germany. **2013**

Leuze, C. *Probing intracortical microstructure with diffusion-weighted magnetic resonance imaging (dMRI) – How 3D dMRI can complement 2D histology*. University of Leipzig, Germany.

Stüber, C. *MR tissue contrast as a function of iron and myelin concentration*. University of Leipzig, Germany.

Awards

Leuze, C. *Certificate of Merit*. 2012 European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) Congress. Lisbon, Portugal. **2012**

Rivera, D. *Visiting Scientist Award*, the Netherlands Organisation for Scientific Research (NWO), the Netherlands.

Streicher, M. *Summa Cum Laude Merit Award for the abstract "Fast MR thermometry using phase referenced asymmetric spin-echo EPI for high field"*. 20th Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Melbourne, Australia.

Turner, R., & Trampel, R. *3rd place poster prize category "Muscle-skeletal system"*. 93rd German X-Ray Congress, Hamburg, Germany.

2013

- Dinse, J. *Young Scientist Award (1st Place)* 16th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), Nagoya, Japan.
- Eichner, C. *ISMRM Summa Cum Laude Award for the abstract "Slice accelerated diffusion-weighted imaging at ultra-high field strength"*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.
- Gauthier, C. *Governor General's Academic Gold Medal*. Governor General of Canada, Canada.
- Gauthier, C. *Poster award*. 4th Annual Ultrahigh Magnetic Field Symposium, Berlin Ultrahigh Field Facility, Germany.
- Heidemann, R. M., & Anwander, A. *Max Planck Award – Hidden Treasures?*. Max Planck Society, Germany.
- Huber, L. *ISMRM Magna Cum Laude Merit Award for the talk "Cerebral blood volume changes in negative BOLD regions during visual stimulation in humans at 7T"*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.
- Ivanov, D. *ISMRM Merit Award Magna Cum Laude for abstract "In vivo estimation of the transverse relaxation time dependence of blood on oxygenation at 7T"*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.
- Krieger, S. *ISMRM Summa Cum Laude Merit Award for the abstract "Simultaneous acquisition of cerebral blood volume, blood flow and blood oxygenation weighted MRI signals at 7T"*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.
- Stüber, C. *Best Technical Poster*. 2nd Workshop on MRI Phase Contrast and QSM, Ithaca, NY, USA.
- Tardif, C. L., *ISMRM Summa Cum Laude Merit Award for the abstract "High-resolution quantitative T1 maps of the human Stria of Gennari at 7 Tesla"*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.
- Tardif, C. L., *ISMRM Magna Cum Laude Merit Award for the abstract "High-resolution quantitative T1-based cortical thickness estimates at 7 Tesla*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.
- Tardif, C. L., *ISMRM Poster Prize "High-resolution quantitative T1-based cortical thickness estimates at 7 Tesla"*. 21st Scientific Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, USA.

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5 Research Groups

5.1 Max Planck Research Group "Neural Mechanisms of Human Communication"

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5.3 Minerva Research Group "Brain Modes"

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Dunja Kunke (66)

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(Commenced January 2012)

5.5 Max Planck Fellow Group "Cognitive and Affective Control of Behavioural Adaptation"

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5.6 Max Planck Research Group "Early Social Development"

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Dr Merle Fairhurst-Menuhin Guest researcher

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5.7 Otto Hahn Group "Neural Bases of Intonation in Speech"

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5.1 Max Planck Research Group "Neural Mechanisms of Human Communication"

The aim of our research programme is to identify the sensory processes that enable us to communicate successfully with each other.

Research on patients with brain lesions and neuroimaging of healthy people has provided considerable insights into the mechanisms for communication. Specialized sensory cortices have been identified that are involved in processing distinct aspects of communicative signals like auditory speech or facial expression. These findings have led to the text-book view that the communicating brain is separated into mostly non-interacting, specialized cortices processing specific parts of the sensory input with integration occurring only at a later stage by higher level brain regions.

Our two main hypotheses are that (i) the specialized regions in the human brain interact much more and at earlier stages than previously thought and (ii) subcortical structures are already optimized for processing human communication stimuli. Findings of such cortical interactions and specialization at early subcortical levels are important because they may explain how the brain, in communication, can achieve its speed, accuracy, and robustness to adverse conditions. To test our hypotheses and develop novel communication models, we acquire behavioural and neuroimaging data and employ neurostimulation techniques. We also test the predictions of our models on populations with selective hereditary communication difficulties. For example, roughly 2% of the population cannot recognize others by face (prosopagnosia) and 5–10% have difficulties understanding speech in noise (e.g. dyslexics).

Our research programme will provide an integrated view on the communication abilities of our brain and we assume that our findings will prompt a revision of conventional models. Examples for such findings and potential revisions are given in four of the following abstracts. The fifth abstract represents a study on auditory perception and memory—the basis for more complex communication abilities. In the long term we expect that our research will lead to two useful applications: (i) The identification of the underlying causes of hereditary communication deficits and the development of tailored treatment regimes, e.g. for autism spectrum disorders and dyslexia and (ii) neurobiologically plausible computational models which implement novel approaches in automatic speech recognition.

5.1.1 A neural mechanism for recognizing speech spoken by different speakers

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Understanding speech from different speakers is a sophisticated process, particularly because the same acoustic parameters convey important information about both the speech message and the person speaking. How the human brain accomplishes speech recognition under such conditions is unknown.

One view is that speaker information is discarded at early processing stages and not used for understanding the speech message. An alternative view is that speaker information is exploited to improve speech recognition. Consistent with the latter view, there are functional interactions between left- and right-hemispheric superior temporal areas that process speech- and speaker-specific vocal tract parameters, respectively (von Kriegstein et al., 2010, J Neurosci, 30, 629–638).

Here, using functional magnetic resonance imaging (fMRI), we investigated whether a similar interaction exists for glottal fold parameters—the other main acoustic feature that determines speaker identity and part of the speech message (i.e. linguistic prosody). Participants recognized linguistic prosody (prosody task), determined by variations in glottal pulse rate (GPR), from speakers who differ in mean GPR (GPR change). As control conditions, the experiment included speakers who differ in

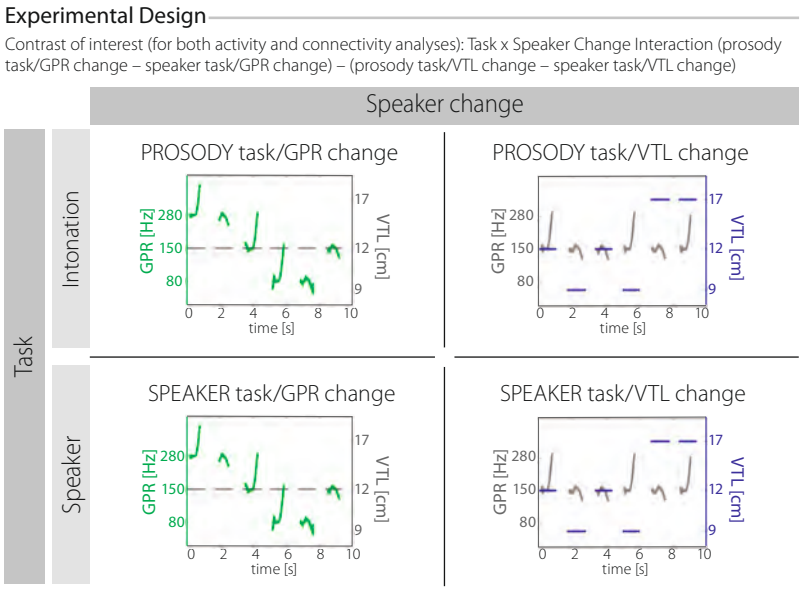

Figure 5.1.1.1 Experimental design: The study was a 2 × 2 factorial design with the factors task [prosody task (top) vs speaker task (bottom)] and speaker change [GPR change (left) vs VTL change (right)]. Each of the four cells of the panel shows an example syllable block within the respective condition. The same syllable blocks are presented during the prosody and the speaker task. For the activity analyses, the contrast of interest was the task × speaker change interaction: (prosody task/GPR change – speaker task/GPR change) – (prosody task/VTL change – speaker task/VTL change). This interaction was also used for the psychological variable in the connectivity analyses.

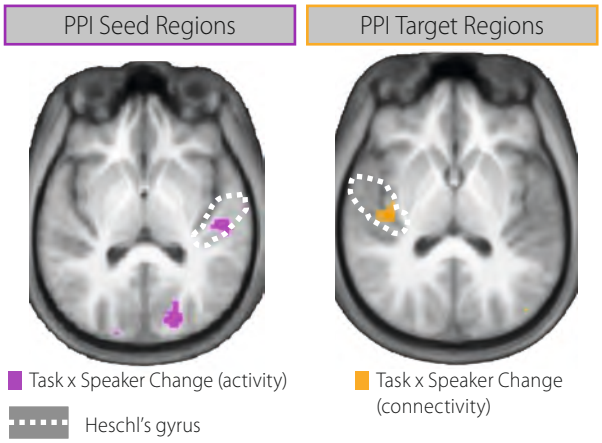

Figure 5.1.1.2 FMRI results. BOLD response associated with recognition of linguistic prosody from speakers who differ in GPR, as revealed by the task × speaker change interaction: (prosody task/GPR change – speaker task/GPR change) – (prosody task/VTL change – speaker task/VTL change) (magenta). Right Heschl's gyrus was used as a seed region for a functional connectivity analysis (PPI). The target region identified by the PPI analysis (task x speaker change, connectivity) is shown in green [MNI coordinates: x = -39, y = -22, z = 7; Z = 3.05]. For display purposes only, the activation and connectivity patterns are shown at $p < 0.005$ uncorrected. Apart from Heschl's gyri, no other area showed connectivity or activity responses that conformed to the significance criteria.

vocal tract length (VTL change) and a control task which required speaker recognition (speaker recognition) (Fig. 5.1.1.1).
The results show that right Heschl's gyrus is involved in recognition of linguistic prosody from speakers who differ in glottal fold parameters (Fig. 5.1.1.2; magenta). Furthermore, this region in right Heschl's gyrus was functionally connected to left Heschl's gyrus when dealing with GPR-induced speaker changes during recognition of linguistic prosody (Fig. 5.1.1.2; green). The findings suggest that interactions between left- and right-hemispheric areas are specific to the processing of different acoustic features, and that they represent a general neural mechanism when understanding speech from different speakers.

Early auditory sensory processing of voices is facilitated by visual mechanisms

5.1.2

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How do we recognize people who are familiar to us? There is overwhelming evidence that our brains process voice and face in a combined fashion to optimally recognize both who is speaking and what is said. Surprisingly, this combined processing of voice and face seems to occur even if one stream of information is missing. For example, if subjects only hear someone familiar talking, without seeing the face, visual face-processing areas are active. One reason for this crossmodal activation might be that it is instrumental for early sensory processing of voices—a hypothesis that is contrary to current models of unisensory perception. Here we test this hypothesis by harnessing a temporally highly resolved method, i.e. magnetoencephalography (MEG), to identify the temporal response profile of the fusiform face area in response to auditory-only voice recognition. Participants briefly learned a set of voices audio-visually, i.e. together with a talking face (face-learned voices) or in visual control stimulus (occupation-learned voices). After learning, we measured subjects' MEG signals in response to the auditory-only, now familiar voices. The results revealed three key mechanisms that characterize the sensory processing of facially familiar speakers' voices: (i) activation in the face-sensitive fusiform gyrus at very early auditory processing stages, i.e. only 100 ms after auditory onset (Fig. 5.1.2.1) (ii) a temporal facilitation of auditory processing (M200) (Fig. 5.1.2.2A) and (iii) a correlation of this temporal facilitation with recognition performance (Fig. 5.1.2.2B and 5.1.2.2C). These findings suggest that a neural representation of face information is evoked even before recognizing the identity of the voice and that the brain uses this visual representation to optimize early sensory processing of auditory-only voices.

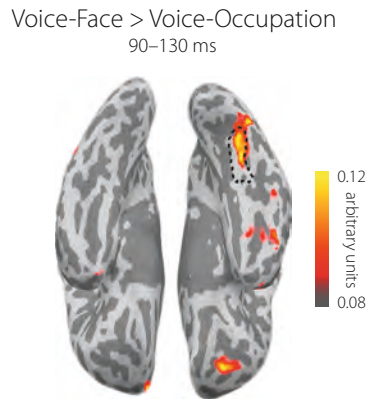

Figure 5.1.2.1 Fusiform gyrus activity. The difference (voice-face learned > voice-occupation learned voices) of estimated source activity is averaged over the 90–130-ms time window and shown for the ventral cortical surface of both hemispheres. The dashed contour delineates the independently and anatomically identified ROI (right posterior fusiform gyrus). Within the ROI, source activity to face-learned voices is significantly stronger than to occupation-learned voices ($p < 0.01$).

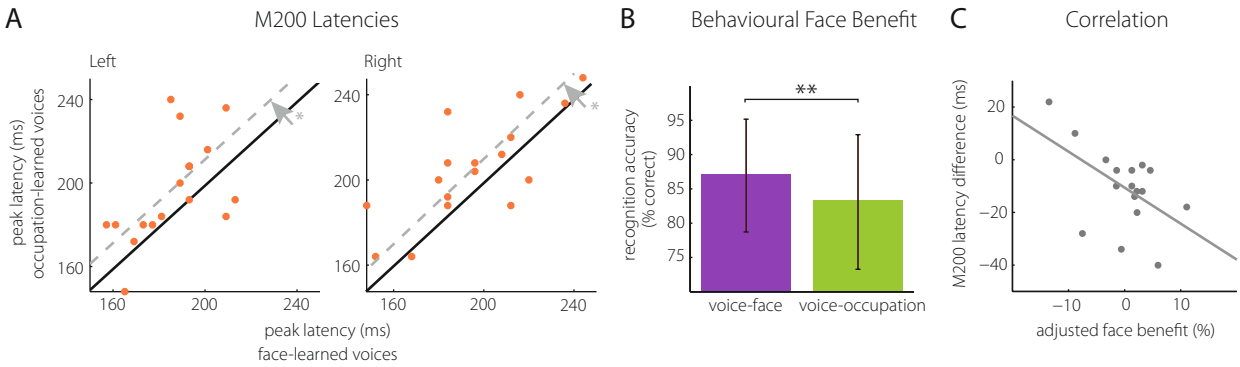

Figure 5.1.2.2 (A) M200 peak latencies. For each participant, the peak latency (ms) to face-learned voices (x-axis) is plotted against the peak latency to occupation-learned voices (y-axis). Data points are systematically shifted above the main diagonal (black line), i.e. peak latencies are on average shorter for face-learned than for occupation-learned voices. The mean shift in latency is illustrated by the dashed line and significant for both left ($p < 0.02$) and right hemisphere ($p < 0.02$). (B) Behavioural Performance. Recognition accuracy is shown as percentage correct for voice-face (purple) and voice-occupation (green) learned voices. Error bars represent standard deviations. Stars indicate statistical significance ($p < 0.01$). On average, there is a face benefit (% of correctly recognized voices after voice-face learning – % of correctly recognized voices after voice-occupation learning) of 3.81%. (C) Correlation of behavioural face benefit with M200 latency difference. Face benefit scores (x-axis) of individual participants are plotted against M200 latency differences (voice-face learned – voice-occupation-learned) (y-axis, upper panel) together with the fitted regression line. Note that this analysis is part of a multiple regression controlling for participant-specific M200 peak latencies. The face-benefit is adjusted accordingly. The multiple regression is significant for M200 latency differences ($p < 0.02$).

5.1.3 How the human brain exchanges information across sensory modalities to recognize other people

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Recognizing the identity of other individuals across different sensory modalities is critical for successful social interaction of many species. For example, monkeys, horses, crows, and human infants can indicate the correct face identity when they hear the voice of a familiar conspecific. How is this so-called cross-modal individual recognition implemented in the brain? In the human brain, face and voice recognition areas are separate, but structurally connected. For faces, specific visual areas are sensitive to identity and to physical properties like the shape of eyes. It is an open question whether only identity-based or also physical property information is shared across sensory modalities. This would mean that visual areas receive information about physical properties of the face when just the voice is heard. To test this, we used functional magnetic resonance imaging in humans and a voice-face priming design in which familiar voices were followed by morphed faces that matched or mismatched with respect to identity or physical properties. Strikingly, we found that both identity and physical property information was provided by the voice to face areas (Fig. 5.1.3). The activity and connectivity profiles differed between face-sensitive areas: (i) The occipital face area received information about both physical properties and identity (Fig. 5.1.3B), (ii) the fusiform face area received predominantly identity (Fig. 5.1.3.C), and (iii) the anterior temporal lobe received exclusively identity information from the voice (Fig. 5.1.3D). These results are in line with a predictive coding scheme where both identity and physical property information is used across sensory modalities to recognize individuals.

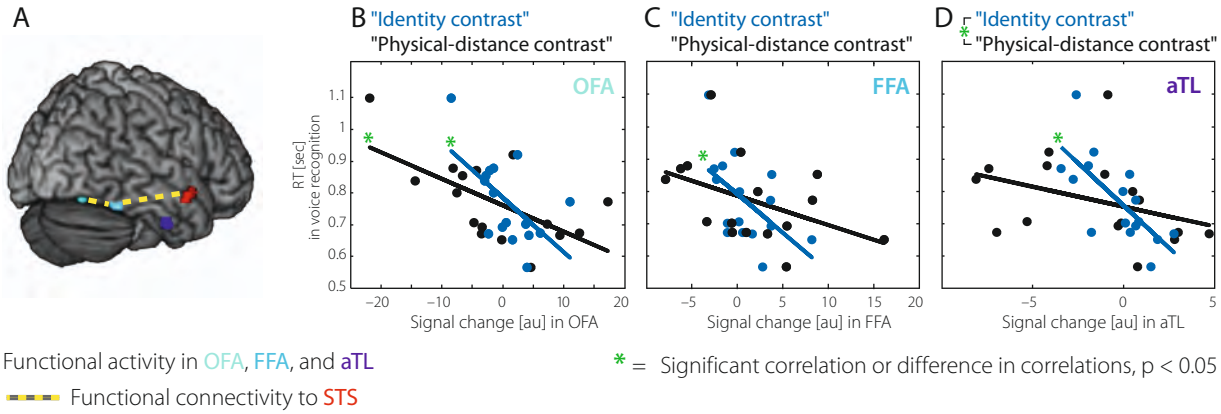

Figure 5.1.3 Effects of voice primes on activity in face-sensitive regions and on functional connectivity between and within face- and voice-sensitive regions. (A) Effects masked with regions of interest displayed on rendered Colin brain image. The occipital face area (OFA, cyan) and fusiform face area (FFA, blue) were defined by activity in an independent functional localizer. The anterior temporal lobe (aTL, dark blue) and superior temporal sulcus (STS, red) were defined by published coordinates. Functional connectivity (yellow) between FFA and voice-sensitive STS and between FFA and OFA was enhanced during mismatch with identity and physical properties between voice prime and face. (B) In right OFA, there were significant effects for both mismatch between voice prime and face with identity and physical properties. (C) In right FFA (light blue), there was a significant effect for mismatch between voice prime and face with identity, but not for mismatch with physical properties. (D) In right aTL (dark blue), there was a significant effect for mismatch between voice prime and face with identity, but not for mismatch with physical properties. In this region, the effect for mismatch in relation to identity was significantly stronger than the one concerning physical properties.

Differential activation patterns in visual and motor areas support foreign language vocabulary knowledge

5.1.4

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Learning foreign language vocabulary can be improved by enriching verbal materials (e.g. texts) with visual and motor information. For example, pictures that illustrate the meaning of a word lead to higher vocabulary learning rates than text annotations. Also, performing gestures during learning improves performance. The brain mechanisms that underlie the beneficial enrichment effects are unknown. At present, there are two general memory frameworks that could explain why enrichment improves learning outcome. The deeper semantic encoding theory proposes that frontal and temporal semantic areas are crucial for the beneficial effect of enrichment (Nyberg, 2002, Memory, 10, 345–348). Alternatively, the multimodal representations theory proposes that areas processing enrichment are critical (Shams & Seitz, 2008, Trends Cogn Sci, 12, 411–417). Here we used functional magnetic resonance imaging (fMRI) to adjudicate between the two theories. We taught adults vocabulary in the artificial language Vimmi. Participants learned Vimmi words in three conditions: self-performing gestures symbolic to the word meaning, copying pictures illustrating the word meaning with the right index finger in the air, and without enrichment. After learning, participants performed a vocabulary test during fMRI. Multivariate pattern analysis allowed us to decode from specific visual and motor areas under which enrichment condition a word was learned. Vimmi words learned with self-performed gestures led to specific neuronal patterns in premotor cortex (BA6) and in the left superior temporal sulcus, an area involved in processing body motion (Fig. 5.1.4 A and B). In contrast, Vimmi words learned with pictures led to specific neuronal patterns in anterior lateral occipital complex, an area involved in processing pictures (Fig. 5.1.4 C). Importantly, for visual and motor areas we found correlations between decoding accuracy and behavioural performance, indicating a relationship between the neuronal activation pattern and the learning outcome (Fig. 5.4.1, column 3). We did not find evidence for activation in semantic areas during the translation task. Our findings highlight the importance of multimodal representations for learning outcome.

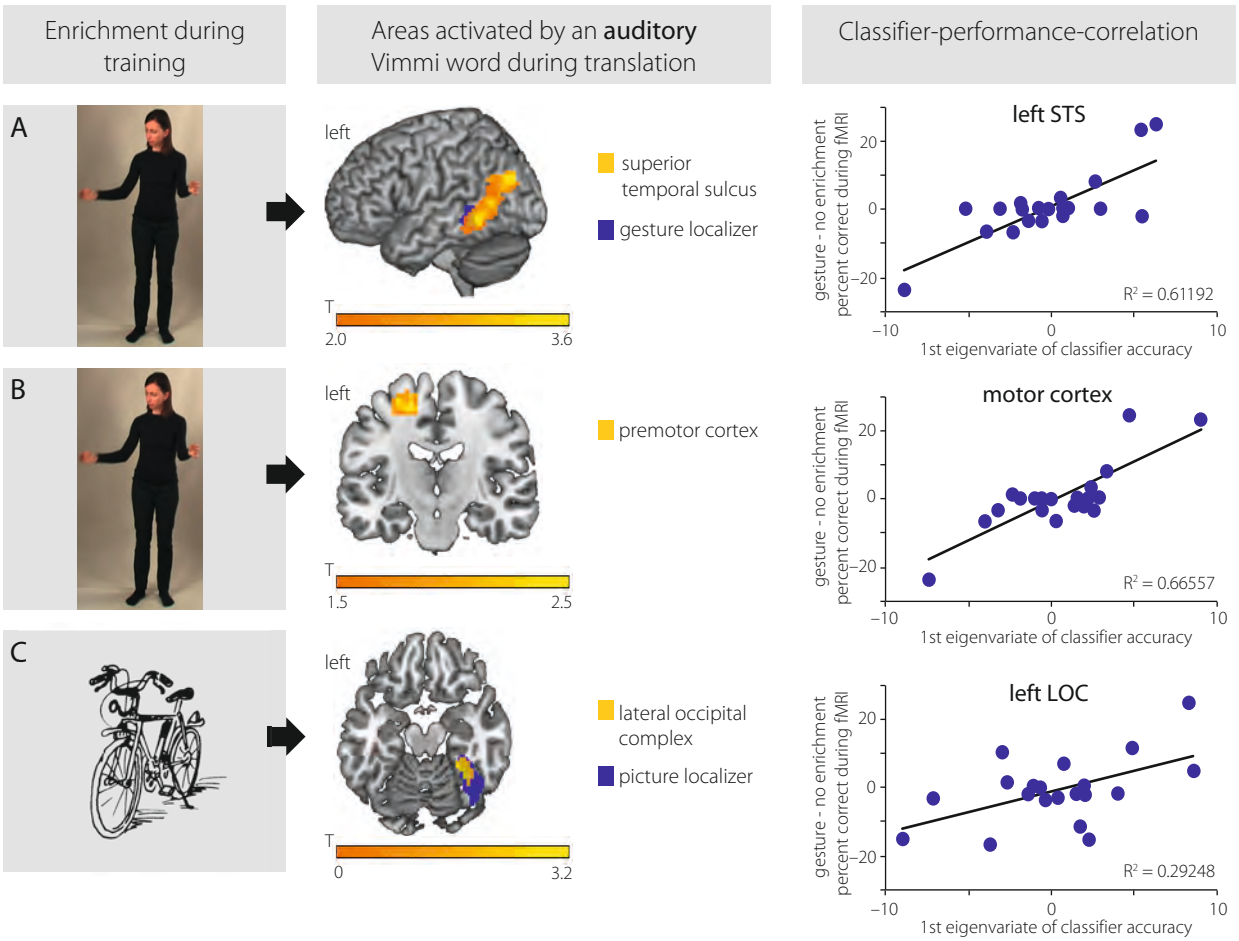

Figure 5.1.4 (A) Gesture enrichment/visual areas. (B) Gesture enrichment/premotor areas. (C) Picture enrichment/visual areas. First column: enrichment provided during training. Second column: fMRI results for the vocabulary test. Third column: correlation between the accuracy of the classifiers and behavioural accuracy. Note that LOC only showed a trend towards significance, $p_{FWE} < 0.10$. Gesture localizer: localizer for the biological motion sensitive parts of the superior temporal sulcus (STS). Picture localizer: localizer for lateral occipital complex (LOC).

5.1.5 Percepts, not acoustic properties, are the units of auditory short-term memory

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For decades, researchers have sought to understand the organizing principles of auditory and visual short-term memory. Previous work in audition suggests that there are independent memory stores for different sound features, but the nature of the representations retained within these stores is currently unclear. Do they retain perceptual features, or do they instead retain representations of the sound's specific acoustic properties? The present study addressed this question by measuring listeners' abilities to keep one of three acoustic properties (interaural time difference, ITD, interaural level difference, ILD, or frequency) in memory when the target sound was followed by interfering sounds that varied randomly in one of the same properties (Fig. 5.1.5A). Critically, ITD and ILD evoked the same percept (spatial location), despite being acoustically different and having different physiological correlates, whilst frequency evoked a different percept (pitch) (Fig. 5.1.5B). The results showed that lis-

teners found it difficult to remember the percept of spatial location when the interfering tones varied either in ITD or ILD, but not when they varied in frequency. The study demonstrates that percepts are the units of auditory short-term memory, and it provides testable predictions for future neuroscientific work on both auditory and visual short-term memory.

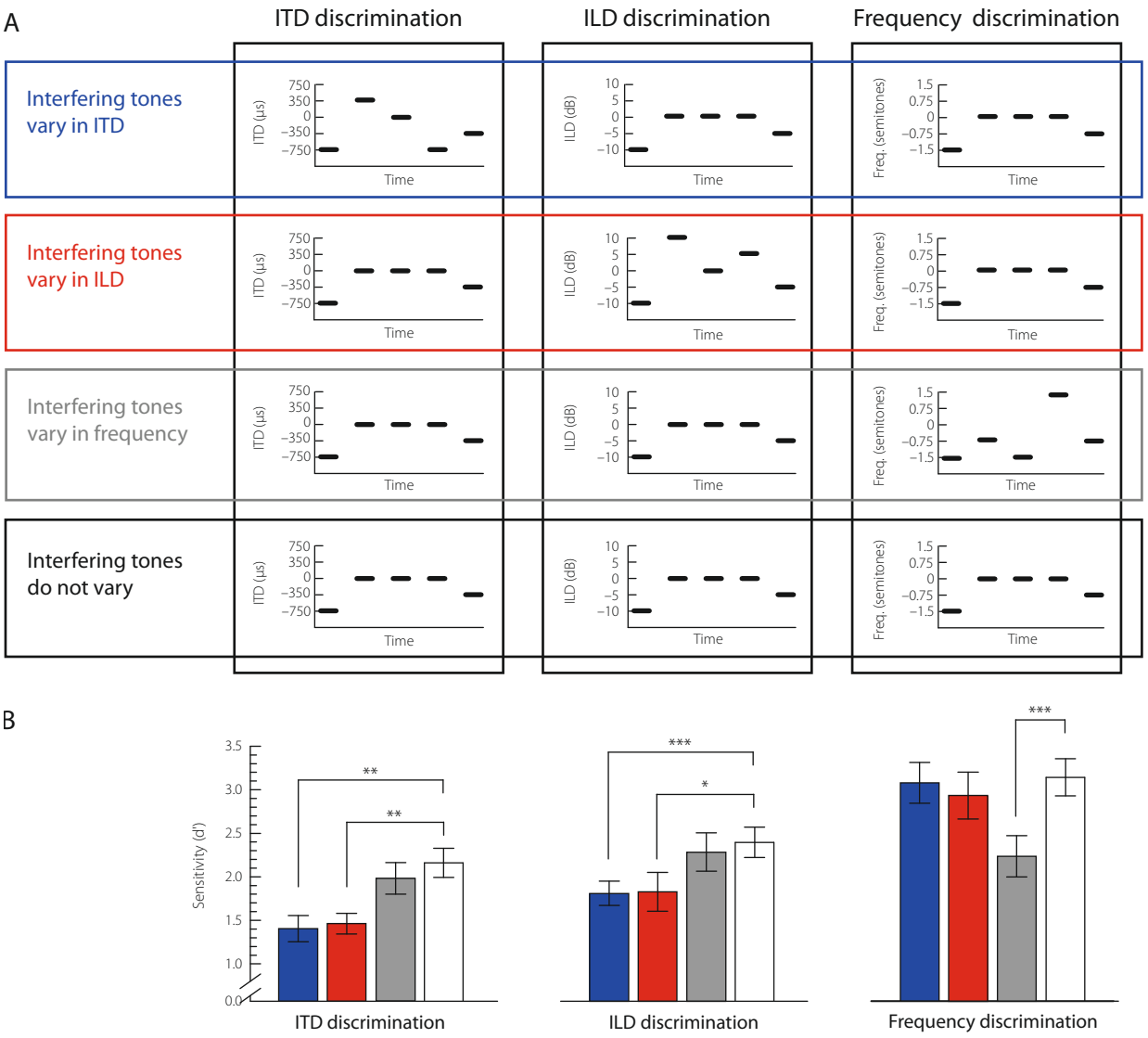

Figure 5.1.5 (A) Overview of the 12 conditions in the experiment. Each diagram illustrates an example trial (one per condition); in each case, the correct response would be "different". The diagrams are organized into columns depending on which acoustic property listeners discriminated in the condition, and rows depending on which property varied in the intervening tones in the condition. (B) Group mean *d'* scores. Bars are grouped depending on which property listeners discriminated, and bar shades represent which property varied in the intervening tones. Error bars are +/- 1 standard error of the mean. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Degrees

PhD Theses

2013 Blank, H. *Processing of faces and voices during human communication.* University of Leipzig, Germany.

Appointments

2013 von Kriegstein, K. *W2 Professorship (Cognitive and Clinical Neurosciences).* Humboldt University Berlin, Germany.

Awards

2012 Diaz Menendez, B. *Marie Curie Intra-European Fellowship for Career Development.*

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5.2
Max Planck Research Group "Auditory Cognition"

Humans adapt well to acoustic challenges. Upon entering a crowded restaurant, the ambient noise makes conversation difficult—but rarely impossible. An intricate orchestration of brain functions must be enabling this impressive human feat, but individuals vary considerably in their ability to adapt to, and successfully communicate in, such adverse listening situations.

In addition, hearing acuity declines markedly with age. In middle to late adult life, listening under adverse conditions becomes progressively difficult, often growing from a nuisance to a serious handicap. Here again, individuals differ vastly in the difficulties they experience.

Accordingly, this Max Planck Research Group has been devoted to studying the neural bases of "Auditory Cognition" since 2011 and we focus on two key questions: What are the psychological and neurophysiological factors that support perception and comprehension under challenging listening conditions? How do domain-specific, auditory processes interface with domain-general, cognitive processes?

Specifically, we aim to delineate the fine balance between beneficial, highly automatized processes (e.g. regularity detection, prediction formation, neural entrainment), and costly, effortful strategies (e.g. deployment of selective attention, increased memory load). Building on this hypothesized trade-off (Fig. 5.2), we work towards a better understanding of the neurocognitive determinants that allow individual listeners to adapt more or less successfully to changes and challenges in their listening environments and abilities.

The 2012–2013 period saw the group pursuing a wide array of psychophysical, structural and functional neuroimaging, and neural oscillatory studies in young and older listeners. The projects presented here exemplify our vertical approach: At its most basic level, we compared neural response specificity in older and younger listeners (5.2.1) and explored optimal neural-phase–to–stimulus alignment in auditory target detection (5.2.2). Precise neural phase configurations were also explored for more cognitive functions such as illusory percepts of time (5.2.3) and lexical decision in noise (5.2.4). The role of domain-general, executive functions when coping with acoustic degradation was scrutinized in projects 5.2.5 (cognitive load reduction through facilitatory cues), 5.2.6 (simultaneous EEG–fMRI in rapid cue switching), and 5.1.7 (on-line hemodynamics of adaption to degraded speech).

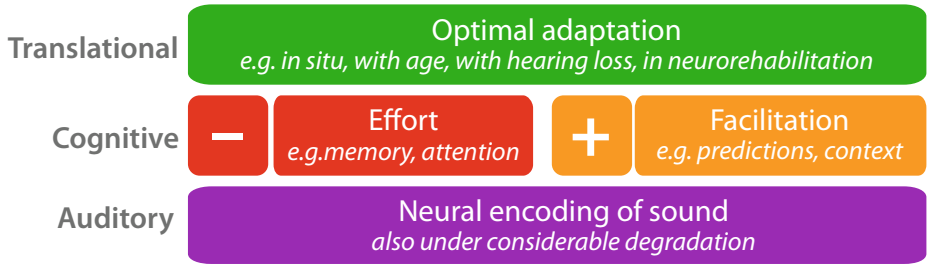

Figure 5.2 The framework guiding our current research. Note the (hypothesized) trade-off of separable cognitive factors that a listener's brain needs to balance in order to attain optimal adaptation to hearing and listening challenges.

Auditory filter width affects response magnitude but not frequency specificity in auditory cortex

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Spectral analysis of acoustic stimuli occurs in the auditory periphery (termed frequency selectivity) as well as at the level of auditory cortex (termed frequency specificity). However, the effects of aging on frequency-specific neural adaptation and the link between peripheral frequency selectivity and neural frequency specificity have not received much attention.

Two groups of normal-hearing participants, younger (aged 20–31 years, N = 15) and older (49–63 years, N = 16), underwent two experiments. First, in a psychophysical notched noise experiment the threshold of detecting a sine tone in white noise stimuli with different spectral notch widths was determined and, in turn, used to estimate individual auditory filters (frequency selectivity; Fig. 5.2.1A). Second, electroencephalograms were recorded while participants listened to sine tones which randomly varied in tone frequency. The degree of frequency-specific neural adaptation was estimated using quadratic fits to N1 amplitudes of the event-related potentials (Fig. 5.2.1B, Fig. 5.2.1C).

The shape of auditory filters was comparable between age groups and thus shows intact frequency selectivity in normal aging. In auditory cortex, both groups showed N1 frequency-specific neural adaptation effects (quadratic coefficients, Fig. 5.2.1C), while N1 responses were overall larger for older than younger participants (intercept, Fig. 5.2.1C). Importantly, the overall N1 amplitude, but not frequency-specific neural adaptation was correlated with the pass-band of the auditory filter (Fig. 5.2.1D). Thus, the current findings show a dissociation of peripheral frequency selectivity and neural frequency specificity but suggest that widened auditory filters are compensated for by a response gain in frequency-specific areas of auditory cortex.

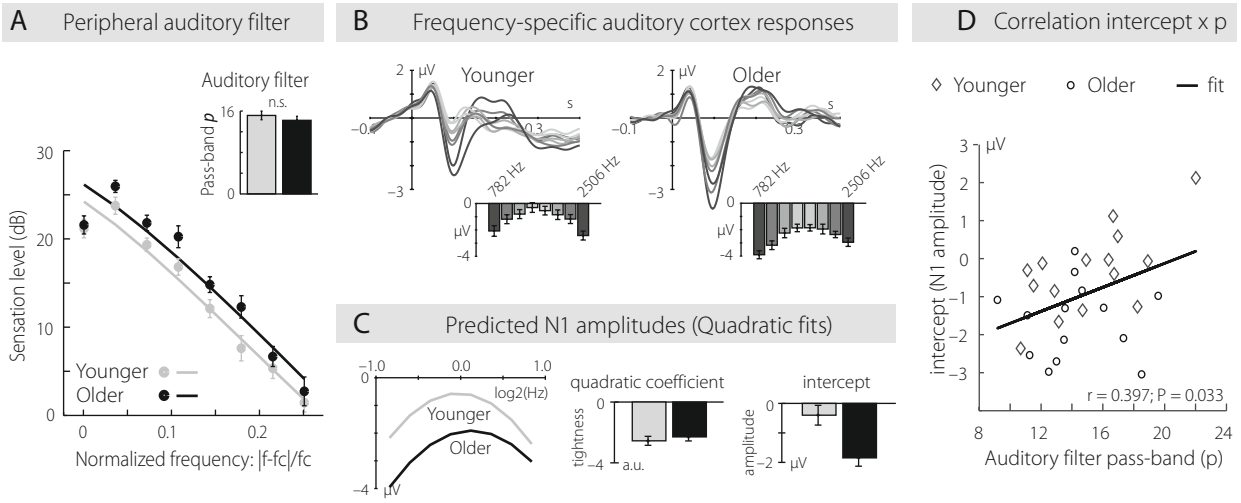

Figure 5.2.1 Peripheral frequency selectivity and neural frequency specificity. (A) Tone thresholds from notched noise experiment and auditory filter fits. (B) Event-related potentials to tones varying randomly in frequency, and mean N1 amplitudes (80–120 ms, bar graphs). (C) Quadratic fits to N1 amplitudes and mean estimated coefficients. (D) Correlation between N1 amplitude (intercept from quadratic fit) and the auditory filter pass-band.

5.2.2 Frequency modulation entrains slow neural oscillations and optimizes human listening behaviour

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The human ability to continuously track dynamic environmental stimuli, in particular speech, is proposed to profit from entrainment of endogenous neural oscillations, which involves phase reorganization such that optimal phase comes into line with temporally expected critical events, resulting in improved processing. In a human electroencephalography (EEG) study, we asked whether auditory perception performance is modulated by the phase of neural oscillations entrained by ongoing rhythmic stimuli without abrupt onsets. Listeners detected near-threshold gaps that were embedded in 10-s frequency-modulated complex tones (Fig. 5.2.2A). Critically, gaps were placed uniformly with respect to the phase of the 3-Hz frequency modulation. Under the assumption that neural oscillations would be entrained by the rhythmic stimulation, this meant that we sampled auditory target detection uniformly with respect to neural oscillatory phase. Spectral analysis of the EEG signal confirmed that neural oscillations in the 3-Hz frequency band were phase locked to the frequency modulation in our stimuli (Fig. 5.2.2B). Gap-detection hit rates were modulated by both stimulus phase and the entrained neural phase at the time of gap onset (Fig. 5.2.2C). Estimates of "optimal" phase were inconsistent across listeners as a function of stimulus phase but were significantly concentrated in one-half of the neural oscillation. Finally, pre-target 3-Hz neural phase determined the form of single-trial evoked responses to gaps (Fig. 5.2.2D). The results strongly suggest that frequency fluctuations in natural environmental input provide a pacing signal for endogenous neural oscillations, thereby influencing perceptual processing.

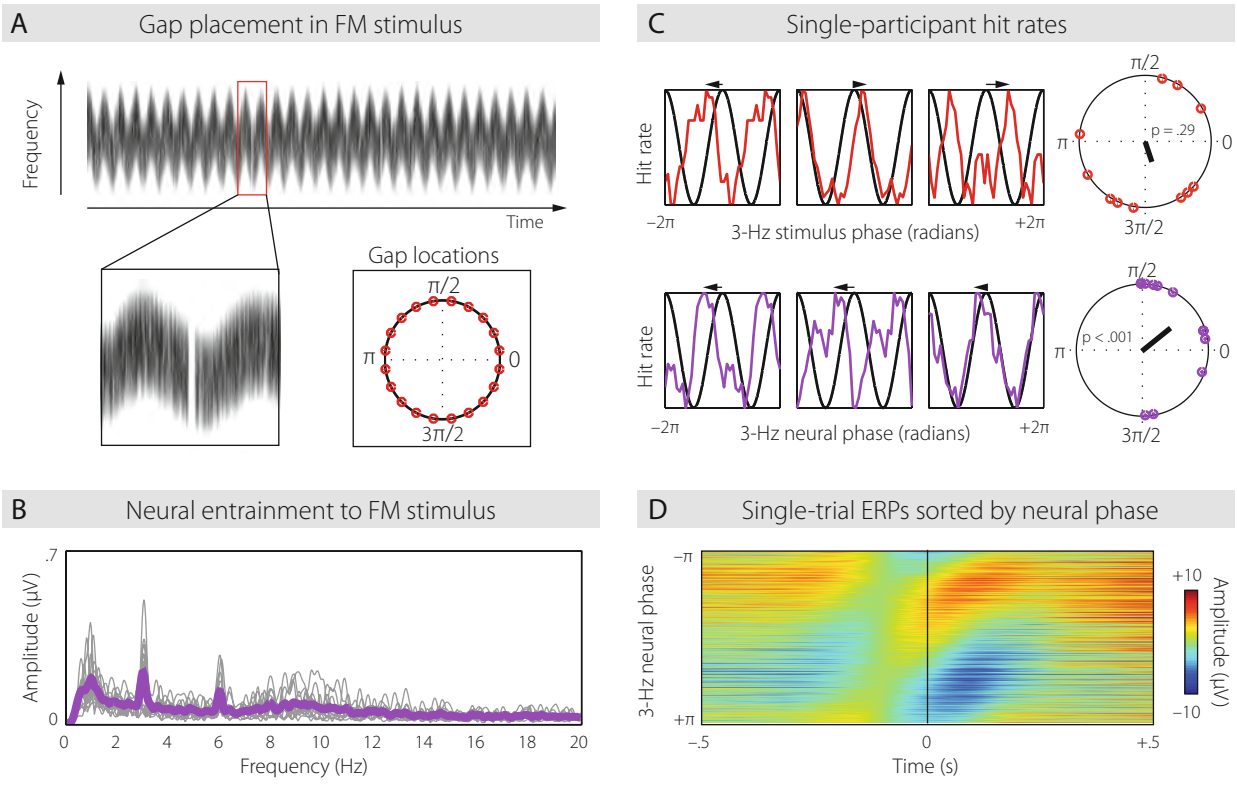

Figure 5.2.2 (A) Gaps were placed uniformly with respect to the phase of 10-s complex tones, frequency modulated at 3 Hz. (B) Neural oscillations were entrained by the 3-Hz rhythm. (C) Hit rates for target detection were modulated by 3-Hz stimulus phase (top) and pre-target neural phase (bottom) in the entrained 3-Hz frequency band. However, optimal phase for performance was only consistent with respect to neural phase (circle plots, right). (D) The form of single-trial evoked responses to gaps was also determined by pre-gap phase in the 3-Hz frequency band.

5.2.3

Oscillatory phase dynamics in neural entrainment underpin illusory percepts of time

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Neural oscillations are a candidate mechanism to steer perception of temporal rate change, but it has thus far remained unaddressed how context-induced illusory percepts of temporal rate change are coded for in neural oscillatory dynamics.

Magnetoencephalography was recorded while human participants (N = 18) judged the direction of rate change of frequency-modulated (FM) sounds in a 3 × 3 design, varying modulation rate (decrease; no change; increase) and pitch (decrease; no change; increase) over the duration of the sound. Neural oscillatory dynamics were investigated using inter-trial phase coherence (ITPC; from time-frequency wavelet analysis). Neural best frequency (where ITPC was largest) at sound offset and epoch-final ITPC strength were extracted from linear fits to ITPC values. Behavioural data showed that with increasing rate and increasing pitch, participants reported that the modulation rate of the sounds increased (speeding up). Thus, participants perceived rate changes, but at the same time were strongly biased in their modulation rate judgments by changes in pitch (illusory rate change).

Inter-trial phase coherence indicated robust neural entrainment in auditory cortex by FM sounds, and the modulation rate changes directly affected the exact neural frequency of the neural oscillation. However, pitch-induced illusory rate changes were unrelated to the exact

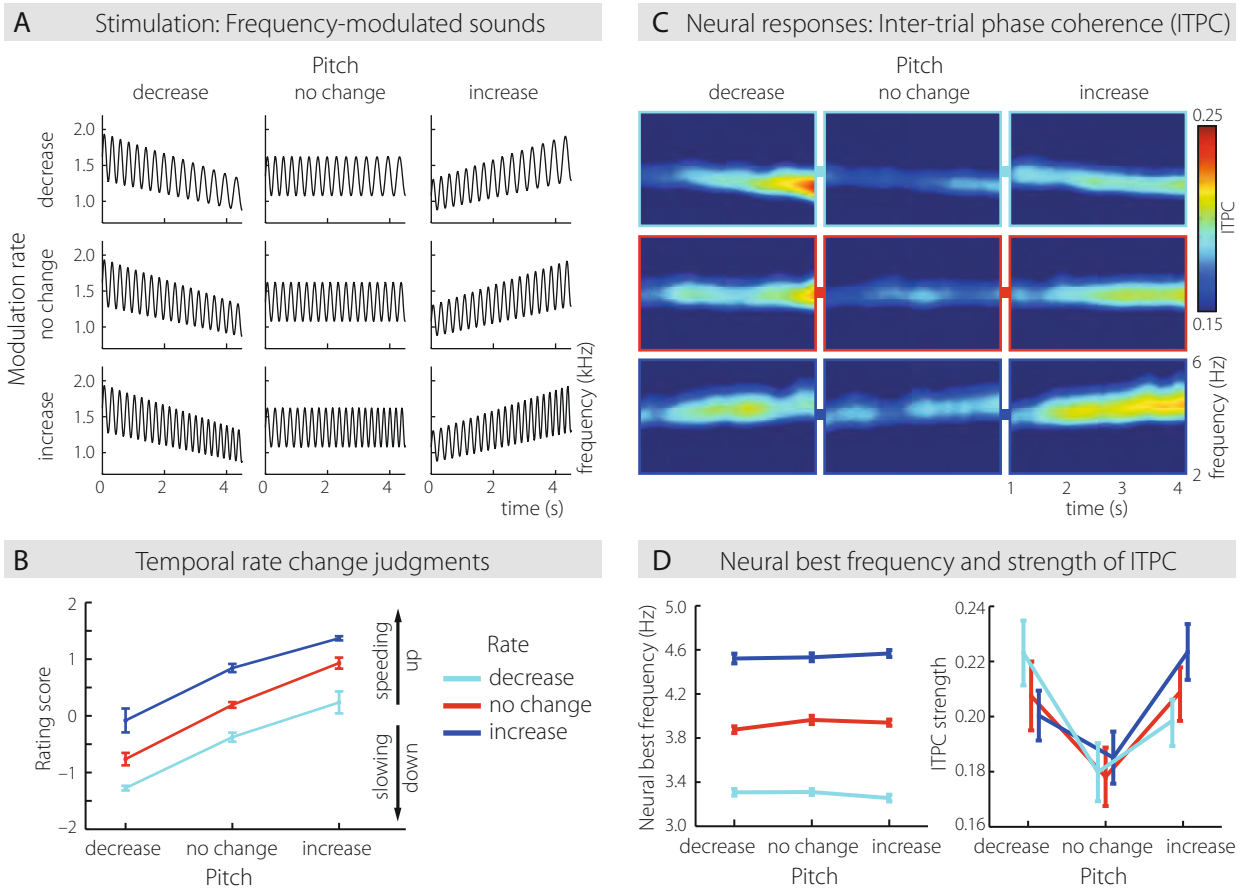

Figure 5.2.3 Rate × Pitch stimulus design and corresponding neural responses. (A) Depicts the frequency modulation of example sounds. (B) Shows mean behavioural ratings (positive = "speeding up", negative = "slowing down"). (C) Inter-trial phase coherence for gradiometer channels over auditory cortices. (D) Neural best frequency (in Hz) at sound offset (4.5 s) and epoch-final ITPC strength (3.8–4 s time interval).

frequency of the neural responses. The rate change illusion was instead linked to changes in ITPC. That is, illusory under- or overestimations of perceived rate change were tightly coupled to increased inter-trial phase coherence.

To summarise, the current findings provide insight into how illusory percepts of time are coded for by neural oscillatory dynamics, and thus bears relevance for oscillator models of time perception.

5.2.4 Pre-stimulus alpha phase determines successful lexical decisions in noise

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The detection of near-threshold targets in the visual as well as the auditory domain (Henry & Obleser, 2012) has been shown to depend on slow oscillatory brain phase. But how far up, from low-level detection to more complex perceptual judgments, will such brain-state dependence permeate? By using a lexical decision task in noise in an EEG study, we tested whether slow oscillatory brain phase might also be predictive of accuracy in linguistic processes. Pseudowords differed from the original real words in one vowel only. For 11 healthy participants, individual noise-thresholds were determined so that they detected this difference in 70% of the cases. The phase bifurcation index, a measure to compare phase angles of two experimental conditions, revealed that pre-stimulus alpha (8–12 Hz) oscillations were 180° anti-phase for correctly versus incorrectly judged trials (~ -75 ms; right-anterior topography). Thus, stimuli arriving in a putatively inhibitory phase of the alpha oscillation were more likely to be judged incorrectly. Notably, pre-stimulus oscillatory power measures did not correlate with later lexical decision accuracy, thereby underlining the non-redundant information provided in neural phase. Furthermore, alpha phase might index mechanisms that have hitherto not been subject to closer electrophysiological examination in speech and language studies. To this end, our study constitutes a first step towards characterizing oscillatory neural signatures of processes that enable spoken word recognition in noise.

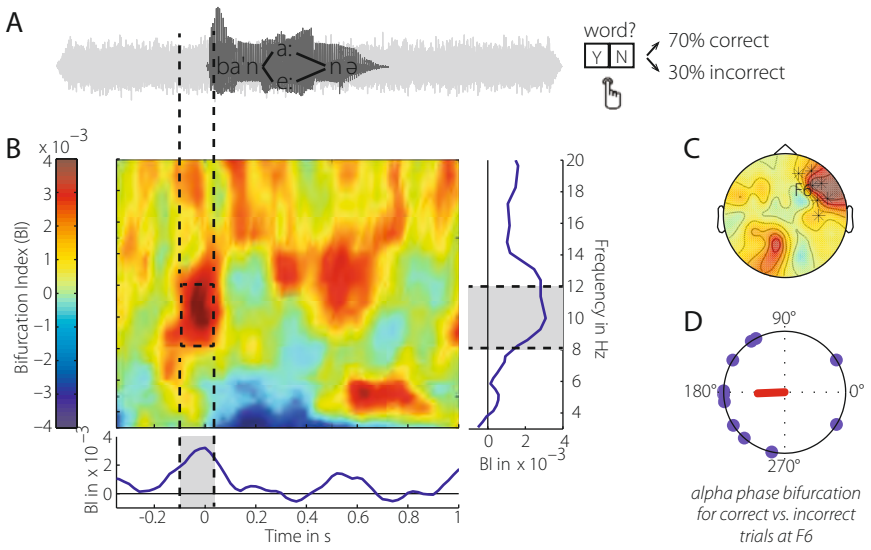

Figure 5.2.4 (A) Trial design. After 1s of white noise the stimulus was played. A delayed prompt asked for lexical decision resulting in an overall accuracy of ~70%. (B) Time-frequency representation of the phase bifurcation index (BI). Line graphs show the BI mean over time (8–12 Hz) and frequency (–0.12–0.04 ms), respectively. (C) Pre-stimulus alpha bifurcation cluster; cluster-member electrodes are highlighted. (D) Mean phase distances per subject between correct and incorrect trials are exemplified for electrode F6.

Alpha oscillatory dynamics index temporal expectation benefits in working memory

5.2.5

Wilsch, A.[1], Henry, M. J.[1], Herrmann, B.[1], Maess, B.[1], & Obleser, J.[1]

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

Enhanced alpha power reflects attentional demand when listening to and memorizing speech in noise. However, can facilitatory knowledge about *when* to listen (temporal expectations) potentially counteract this demand and concomitantly reduce alpha? The current magnetoencephalography (MEG) experiment induced attentional demand using an auditory delayed-matching-to-sample task with two syllables S1 and S2 presented in speech-shaped noise. Temporal expectation about the occurrence of S1 was manipulated in three different cue conditions: "Neutral" (unknown foreperiod), "early" (short), and "late" (long). Alpha power was highest when the cue was uninformative about the onset time of S1 (neutral) and lowest for the late-cued condition. This alpha-reducing effect of specific compared to neutral cues was evident during memory retention in noise and originated in the right insula. Overall, the results indicate that temporal expectations can facilitate the encoding of speech in noise, and concomitantly reduce neural markers of attentional demand.

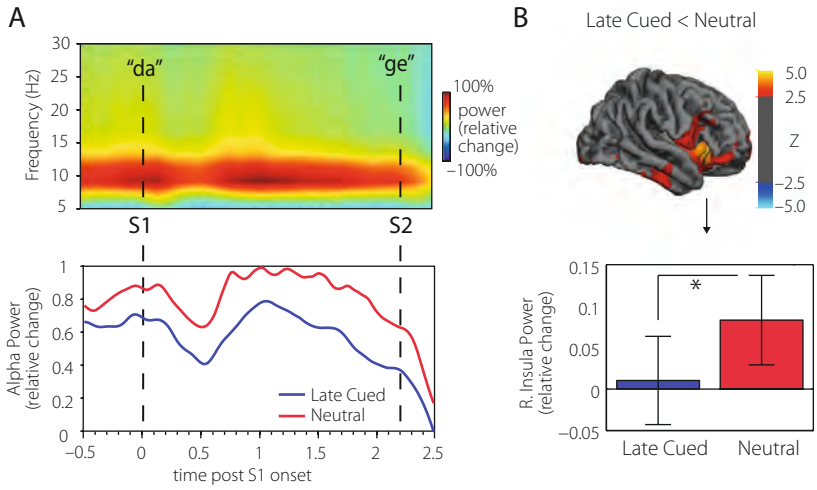

Figure 5.2.5 Temporal cues reduce alpha power during verbal memory retention. (A) Overall frequency fluctuations (5–30 Hz) throughout syllable retention (upper panel) and differences in alpha power fluctuations (8–13 Hz) between cueing conditions (lower panel). (B) Alpha-power source projections (right hemisphere). Z-values index the neutral > cued alpha power difference.

Multi-modal assessment of cue utilization in auditory categorization

5.2.6

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Auditory categorization involves selectively attending to the most informative stimulus cues. These cues might change depending on the listening situation. We modelled such a change by first presenting participants with stimuli from two categories (Fig. 5.2.6A) that could best be discriminated by spectral peak. Later, spectral degradation rendered stimulus duration the more informative cue. Participants (N = 36) performed the categorization task in the MRT scanner. In 15 participants, we simultaneously recorded EEG. Behaviourally, degradation decreased perceptual sensitivity and was also accompanied by smaller N1 amplitudes (Fig. 5.2.6B), with differences in the single-trial correlation between N1 amplitude and BOLD response to be located in posterior parts of the right superior temporal gyrus. Importantly, participants utilized the duration cue more under degradation, and

the individual degree of doing so was predicted by grey matter probability in (right) inferior parietal lobule. There we also found a stronger correlation between duration cue utilization and BOLD response in the degraded compared to the nondegraded condition (Fig. 5.2.6C). These data provide converging evidence from multiple methodologies (brain structure, hemodynamics, electrophysiology) that the parietal attention network supports optimal cue utilization in auditory categorization, and that the superior temporal gyrus is sensitive to stimulus degradation.

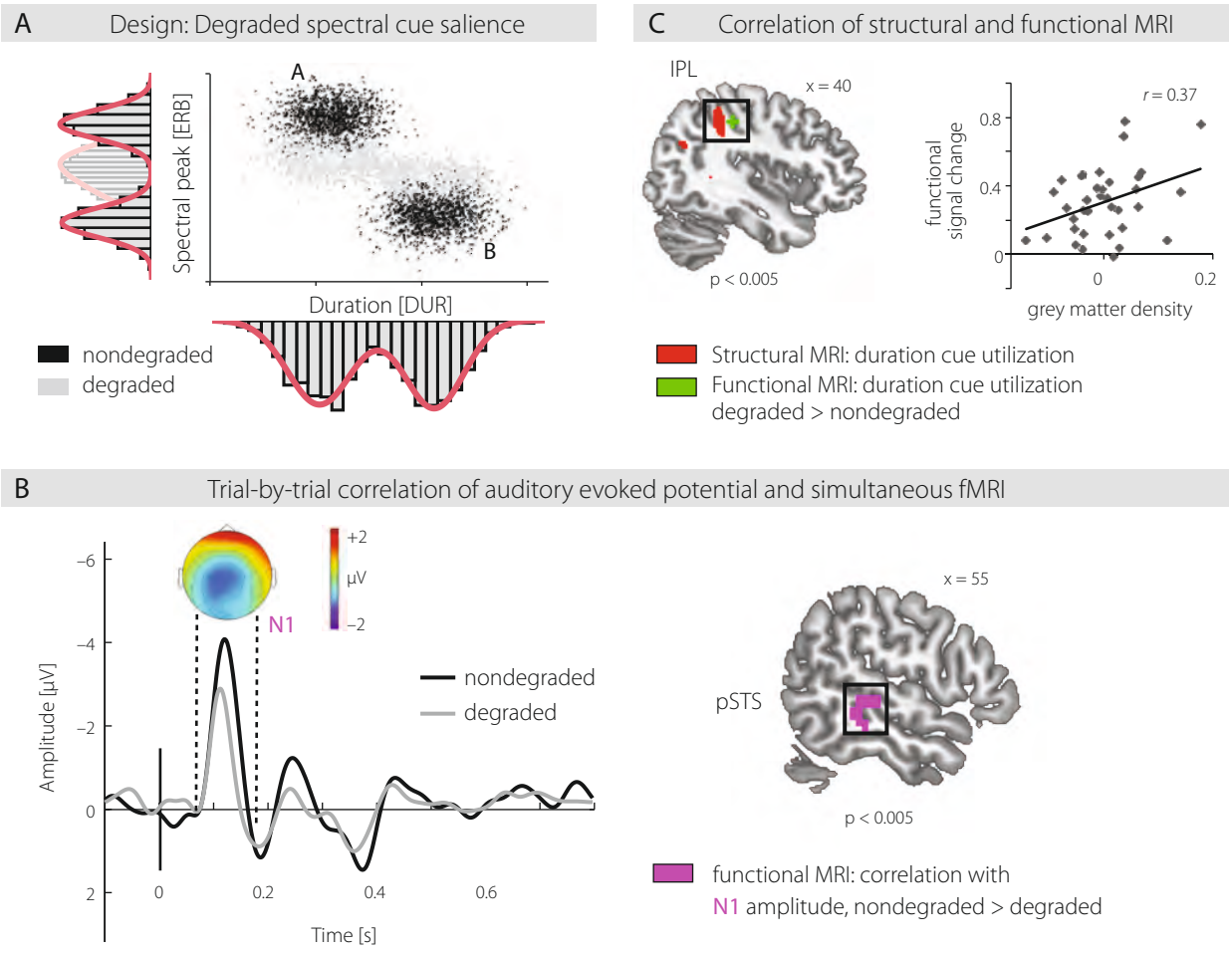

Figure 5.2.6 A summary of the design (A), the correlation of electrophysiological and functional brain measures (B), and the correlation of structural and functional brain measures (C) during auditory categorization.

5.2.7 The brain dynamics of rapid perceptual adaptation to adverse listening conditions

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Humans have the capability to rapidly adapt to degraded or altered speech. This challenge is particularly relevant to cochlear implant (CI) patients adapting to an extremely distorted auditory input delivered by their device. Therefore, we addressed the question as to which neural processes support this adaptation to degraded speech.

In a sparse-sampling, cardiac-gated functional magnetic resonance imaging (fMRI) study, we investigated short-term neural adaptation to 4-band vocoded sentences. Vocoding degrades the spectral information of the acoustic signal while the temporal envelope is preserved, thus simulating CI-transduced speech (Fig. 5.2.7A). An additional fMRI experiment on amplitude modulation rate discrimination quantified the convergence of neural mechanisms that subserve coping with challenging listening conditions for speech and non-speech.

The study elucidates the central neural mechanisms of rapid adaptation to acoustic speech degradation with respect to three points. First, the degraded speech task revealed an "executive" network (comprising the anterior insula and anterior cingulate cortex), parts of which were also activated in the non-speech discrimination task (Fig. 5.2.7B). Second, not only acoustic speech clarity but also trial-by-trial fluctuations in successful speech comprehension drove hemodynamic signal change in classic "language" areas (bilateral temporal cortices, Fig. 5.2.7C). Third, as listeners perceptually adapted to degraded speech, down-regulation in a cortico-thalamic-striatal circuit was observable (Fig. 5.2.7D). The data highlight differential up- and down-regulation in auditory-language and executive networks, respectively, and provide first evidence of subcortical contributions (see also Erb, Henry, Eisner, & Obleser, 2012) when successfully adapting to a challenging listening situation.

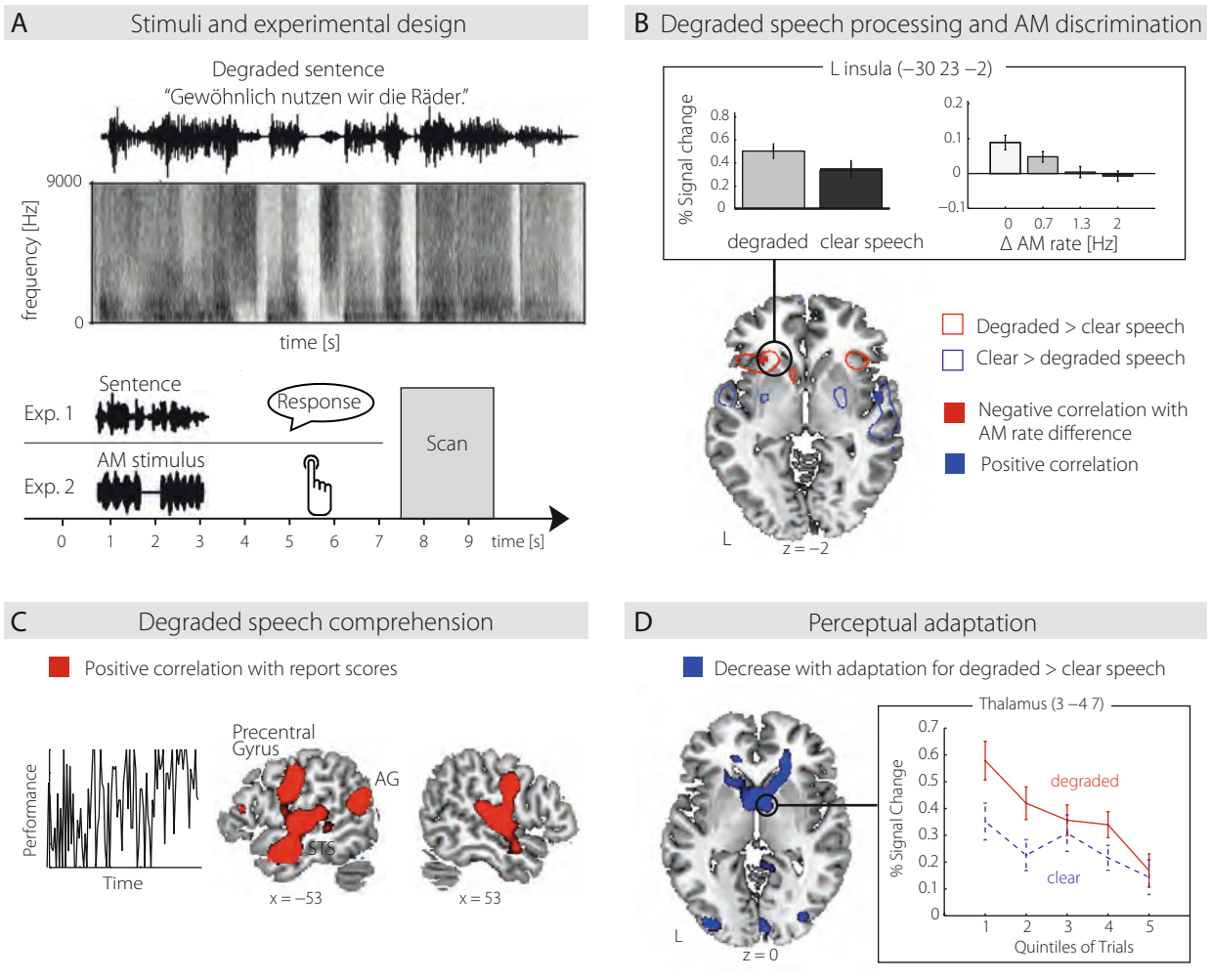

Figure 5.2.7 (A) Top panel shows the oscillogram and spectrogram of a vocoded sentence. Lower panel illustrates listening tasks: In Experiment 1, listeners hear and repeat back 4-band-vocoded or clear speech (baseline) sentences; Experiment 2 is an AM rate discrimination task. (B) When both listening tasks become increasingly difficult, listeners rely on a common executive network, involving the anterior insula (for degraded more than clear speech and for discrimination of more similar AM stimuli). (C) Successful degraded speech comprehension (report scores) correlates with activity in temporal cortices, precentral and angular gyrus. (D) Short-term neural adaptation is reflected in a stronger hemodynamic down-regulation for degraded relative to clear speech in the anteroventral thalamic nucleus.

Congresses, Workshops, and Symposia

2013 Obleser, J. (December). *Signal and Noise along the Auditory Pathway (SNAP)*. Workshop. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Obleser, J., & Herrmann, C. (June). *Alpha re-visited: Neural oscillations in human perception and cognition.* The 39th Annual Meeting "Psychologie und Gehirn", Würzburg, Germany.

Appointments

2013 Obleser, J. *Associate Professor in Auditory Neuroscience / Assistive Hearing Devices*. Department of Electrical Engineering. Technical University of Denmark, Copenhagen, Denmark. (Declined)

Awards

2012 Obleser, J. *Fellowship in the Mentoring programme for outstanding young scientists*. Biopsychology Section of the German Society for Psychology (DGPs).

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Index of Published Figures

Figure 5.2.1
Figure adapted from Herrmann, B., Henry, M. J., Scharinger, M., & Obleser, J. (2013). Auditory filter width affects response magnitude but not frequency specificity in auditory cortex. *Hearing Research, 304*, 128–136.

Figure 5.2.2
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Figure 5.2.3
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Figure adapted from Erb, J., Henry, M. J., Eisner, F., & Obleser, J. (2013). The brain dynamics of rapid perceptual adaptation to adverse listening conditions. *The Journal of Neuroscience, 33*(26), 10688–10697.

5.3 Minerva Research Group "Brain Modes"

The brain is a highly adaptive, self-organizing complex system, which has evolved such that neuronal responses and related behaviour are continuously optimized with respect to the external and internal context. This capability is achieved by the modulation of neuronal interactions depending on the history of previously processed information. Such meaningful connectivity changes, together with stochastic processes, influence ongoing neuronal dynamics. The resulting state-dependent fluctuations may be one of the fundamental computational properties of the brain, being pervasively present in human behaviour and leaving a distinctive fingerprint in neuroscience data. By combining advanced multimodal neuroimaging and computational modelling, we aim to identify generative mechanisms of ongoing neuronal dynamics and to elucidate principles of interaction between ongoing dynamics and incoming events or tasks.

Together with an international consortium—the Brain Network Recovery Group (BrainNRG)—we develop The Virtual Brain (TVB) platform. This neuroinformatics platform allows the simulation of neuronal large-scale activity of a whole primate brain up to imaging resolution. By incorporating the DTI/DSI derived anatomical skeleton of individual subjects, TVB allows the building of personalized brain models (5.3.1). Employing EEG measurements, we have investigated how ongoing brain states influence the ability to learn. We found that the alpha band (8–12 Hz) power before and during learning explains up to 64% of the behavioural outcome variability, i.e. it predicts how well the subjects learn (5.3.2). We demonstrated that learning changes resting-state functional connectivity, and, more specifically, tactile perceptual learning increases resting-state alpha band coherence between the pre- and post-central gyrus. This finding is in line with previous evidence of increased sensorimotor integration abilities after tactile perceptual learning and supports application of similar paradigms in stroke patients for rehabilitation purposes (5.3.3). In order to reveal the underlying precise biophysical mechanisms of brain function, we build computational large-scale models. For parameter estimation the models are fitted to empirical functional brain data such as EEG and fMRI. We developed an algebraic form of the model to allow for model inversion, i.e. model fitting to empirical EEG and fMRI data (5.3.4). We also implemented brain state dependent plasticity rules in large-scale models of the brain to account for learning, disease, or age-related changes of brain function (5.3.5).

5.3.1 The virtual brain integrates computational modelling and multimodal neuroimaging

Ritter, P.[1,2,3,4], Schirner, M.[2,3], McIntosh, A. R.[5], & Jirsa, V. K.[6]

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[3] Department of Neurology, Charité University Medicine Berlin, Germany
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Brain function is thought to emerge from the interactions among neuronal populations. Apart from traditional efforts to reproduce brain dynamics from the micro- to macroscopic scales, complementary approaches develop phenomenological models of lower complexity. Such macroscopic models typically generate only a few selected—ideally functionally relevant—aspects of the brain dynamics. Importantly, they often allow an under-

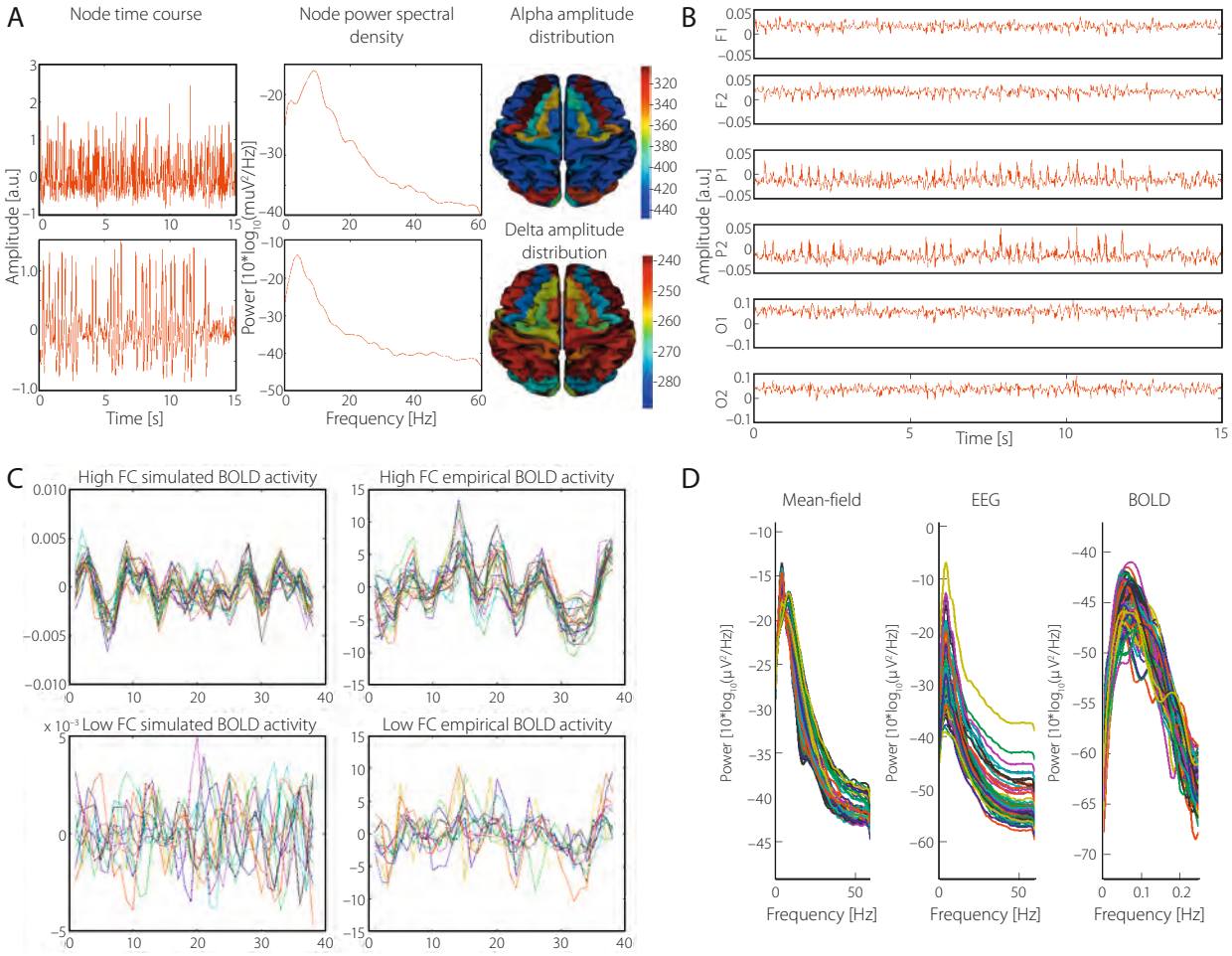

Fig. 5.3.1 Simulations of EEG and fMRI data using The Virtual Brain platform. (A) Exemplary local field source activity of two different nodes. Left: 15 seconds of local mean field activity. Middle: Power spectra. While in the upper panel we see dominant alpha oscillations, the source in the lower panel exhibits dominant delta activity. Right: Topography of the alpha and delta rhythms. (B) Simulated EEG. Displayed are 15 seconds of approximated EEG activity for six selected channels referenced to channel FCz. (C) BOLD time series of ROIs exhibiting high FC (top row) and low FC (bottom row). Left: Simulated BOLD signal. Right: Empirical BOLD signal. Time courses of identical ROIs are shown for empirical and simulated data. (D) Frequency spectra of mean field source activity, EEG and BOLD signals of exemplary nodes/channels. Note peaks in the delta/alpha range for the electrophysiological simulations and in the < 0.1 Hz range for BOLD.

standing of the underlying mechanisms beyond computational reproduction. Adding detail to these models will widen their ability to reproduce a broader range of dynamic features of the brain. For instance, such models allow for the exploration of consequences of focal and distributed pathological changes in the system, enabling us to identify and develop approaches to counteract unfavourable processes. To this end, 'The Virtual Brain' (www.thevirtualbrain.org), a neuroinformatics platform with a brain simulator that incorporates a range of neuronal models and dynamics at its core, has been developed. This integrated framework allows the model-based simulation, analysis, and inference of neurophysiological mechanisms over several brain scales that underlie the generation of macroscopic neuroimaging signals. Our study describes how The Virtual Brain works, and we present a first proof of concept (Ritter, P., Schirner, M., McIntosh, A. R., & Jirsa, V. K., 2013).

State-dependent perceptual learning

5.3.2

Freyer, F.[1,2,3], Becker, R.[1,2], Dinse, H. R.[3]*, & Ritter, P.[1,2,4,5]*

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* Shared senior authorship

Learning constitutes a fundamental property of the human brain—yet an unresolved puzzle is the profound variability of the learning success between individuals. Here we highlight the relevance of individual ongoing brain states as sources of the learning variability in exposure-based somatosensory perceptual learning. Electroencephalogram recordings of ongoing rhythmic brain activity before and during learning revealed that pre-learning parietal alpha oscillations as well as during-learning stimulus-induced contralateral central alpha changes are predictive for the learning outcome. These two distinct alpha rhythm sources predicted up to 64 % of the observed learning variability, one source representing an idling state with postero-parietal focus and a potential link to the default mode network, the other representing the sensorimotor Mu rhythm, whose desynchronization is indicative for the degree of engagement of sensorimotor neuronal populations during application of the learning stimuli. Unspecific effects due to global shifts of attention or vigilance do not explain our observations. Our study thus suggests a brain state-dependency of perceptual learning success in humans opening new avenues for supportive learning tools in the clinical and educational realms (Freyer, F., Becker, R., Dinse, H., & Ritter, P., 2013).

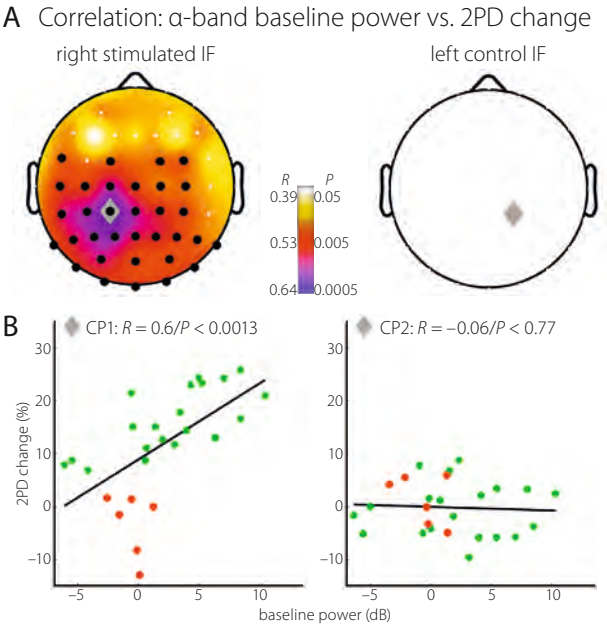

Figure 5.3.2 Correlation between 2PD change (left column: stimulated right IF; right column: control left IF), and alpha band resting-state EEG power before perceptual learning. (A) Top row: scalp distribution of Pearson's correlation coefficients R and corresponding P-values. Black dots: channels within significant cluster ($p_{clust} < 0.002$). Grey diamond: channel CP1 with maximum correlation to learning rate (for right IF)/ corresponding contralateral channel CP2 (for left IF) (B) scatterplot of single subject values at channels CP1/CP2, successful learners in green (n = 20), other subjects in red for illustration purposes—no categorization/collapsing was done for correlation analysis.

5.3.3 Repetitive tactile stimulation changes resting-state functional connectivity: Implications for treatment of sensorimotor decline

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Neurological disorders and physiological aging can lead to a decline of perceptual abilities. In contrast to the conventional therapeutic approach that comprises intensive training and practice, passive repetitive sensory stimulation (RSS) has recently gained increasing attention as an alternative to countervail the sensory decline by improving perceptual abilities without the need for active participation. A particularly effective type of high-frequency RSS, utilizing Hebbian learning principles, improves perceptual acuity as well as sensorimotor functions and has been successfully applied to treat chronic stroke patients and elderly subjects. High-frequency RSS has been shown to induce plastic changes of somatosensory cortex such as representational map reorganization, but its impact on the brain's ongoing network activity and resting-state functional connectivity has not been investigated so far. Here, we applied high-frequency RSS in healthy human subjects and analyzed resting-state electroencephalography (EEG) functional connectivity patterns before and after RSS by means of imaginary coherency (ImCoh), a frequency-specific connectivity measure which is known to reduce overestimation biases due to volume conduction and common reference. Thirty minutes of passive high-frequency RSS lead to significant ImCoh-changes of the resting-state Mu rhythm in the individual upper alpha frequency band within distributed sensory and motor cortical areas. These stimulation induced distributed functional connectivity changes likely underlie the previously observed improvement in sensorimotor integration (Freyer, F., Reinacher, M., Nolte, G., Dinse, H. R., & Ritter, P., 2012).

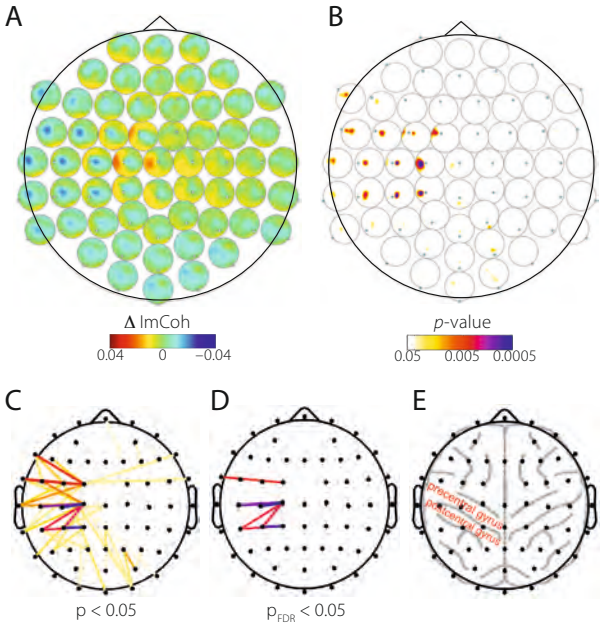

Figure 5.3.3 Change of resting-state functional connectivity after high-frequency RSS (A) ImCoh difference between pre- and post-session (before and after RSS). Dots: Channel relative to which ImCoh is shown. (B) Corresponding p-values indicating statistically significant changes of ImCoh. A cluster of significant connectivity changes is located over contralateral central areas. (C) Different visualization of data shown in panel B. dots indicate channel locations, lines indicate channel pairs with statistically significant ImCoh changes (colour coding as in panel B). (D) Same as panel C, but only significant ImCoh changes after FDR-correction for multiple comparisons. (E) Outline of typical locations of cortex gyri and sulci, indicating that the main change of ImCoh is located over pre- and post-central cortical areas.

A canonical model of multistability and scale-invariance in biological systems

5.3.4

Freyer, F.[1,2], Roberts, J. A.[3], Ritter, P.[1,2,4,5], & Breakspear, M.[3,6,7]

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Multistability and scale-invariant fluctuations occur in a wide variety of biological organisms from bacteria to humans as well as financial, chemical, and complex physical systems. Multistability refers to noise driven switches between multiple weakly stable states. Scale-invariant fluctuations arise when there is an approximately constant ratio between the mean and standard deviation of a system's fluctuations. Both are an important property of human perception, movement, decision making, and computation and they occur together in the human alpha rhythm, imparting it with complex dynamical behaviour. Here, we elucidate their fundamental dynamical mechanisms in a canonical model of nonlinear bifurcations under stochastic fluctuations. We find that the co-occurrence of multistability and scale-invariant fluctuations mandates two important dynamical properties: Multistability arises in the presence of a subcritical Hopf bifurcation, which generates co-existing attractors, whilst the introduction of multiplicative (state-dependent) noise ensures that, as the system jumps between these attractors, fluctuations remain in constant proportion to their mean and their temporal statistics become long-tailed. The simple algebraic construction of this model affords a systematic analysis of the contribution of stochastic and nonlinear processes to cortical rhythms, complementing a recently proposed biophysical model. Similar dynamics also occur in a kinetic model of gene regulation, suggesting universality across a broad class of biological phenomena (Freyer, F., Roberts, J. A., Ritter, P., & Breakspear, M., 2012).

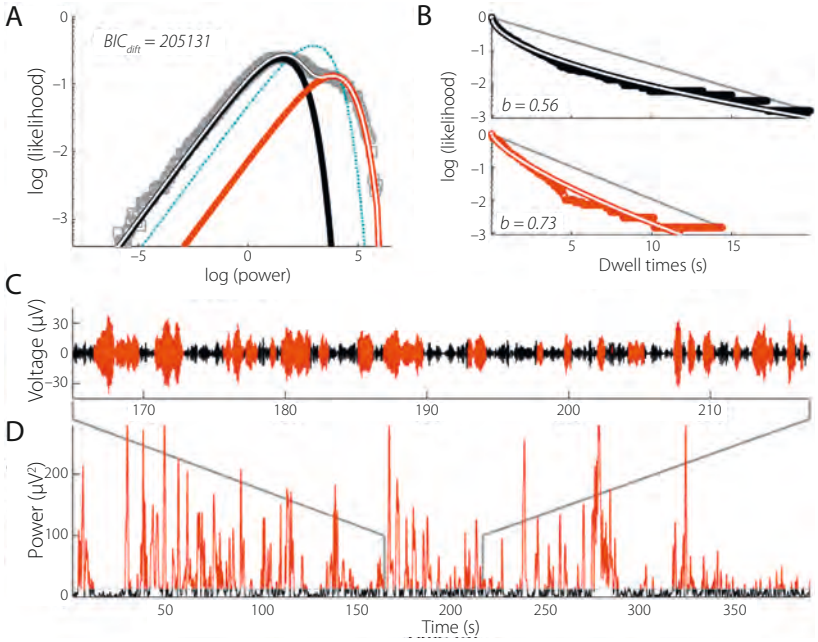

Figure 5.3.4 Multistability in human EEG data. (A) PDFs derived from long recordings of EEG time series exhibit a low (black) and a high (red) amplitude mode. The overall PDF is well described by their bimodal sum (white). (B) The corresponding dwell times of each mode are well described by stretched exponentials (white). The grey line indicates a simple exponential form. (C) Time series of filtered (8–12 Hz) EEG. (D) Corresponding power fluctuations of 10 Hz oscillations (colour coded according to the crossing of the distributions in panel A.

5.3.5

Revealing how local and global plasticity shapes the brain's dynamical landscape using The Virtual Brain

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It is well established that spontaneous large-scale brain activity, i.e. activity in the absence of controlled stimulus input or an active task, is topologically organized in multiple functional networks maintaining a high degree of coherence that are referred to as resting-state networks (RSNs). Resting-state networks are not only constrained by the underlying anatomical connectivity between the salient brain areas, but are also influenced by the history of previous task-related activation in those areas. However, the precise rules that link plastic changes and ongoing dynamics of resting-state functional connectivity remain unclear. We identify potential computational mechanisms that alter the dynamical landscape leading to reconfigurations of functional networks and to modi-

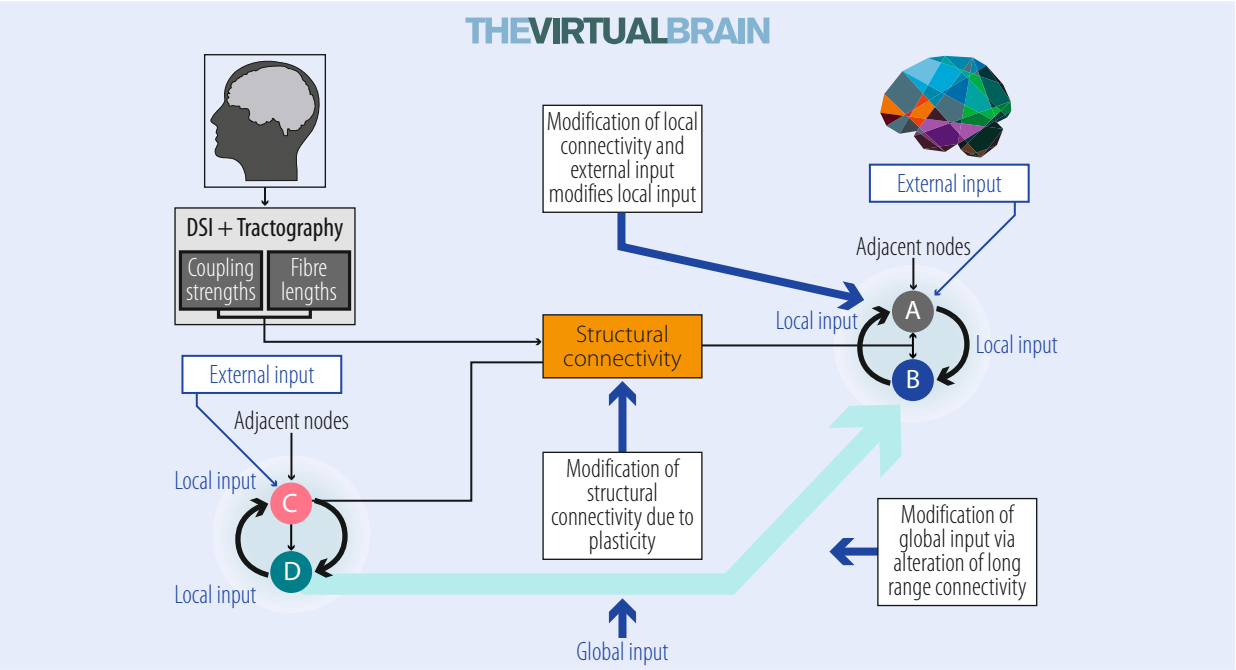

Figure 5.3.5 Local and global interactions, perturbations of input—an integrated view using The Virtual Brain: Using model-based simulation within TVB framework one can use informed structural connectivity (shown in a purple box) data sets combined with implementation of local brain area model described in the above figure as nodes A, B, C, and D respectively. TVB implements specific node dynamics using spiking attractor dynamics, firing rate dynamics, oscillator models. These models receive local input (shown with bold black arrow) from adjacent neural population models; external time varying input (e.g. noisy input, AC/DC current input) and a global input between distant populations as shown here with a transparent arrow. There are various ways to modulate the input received by the node models, i.e. the neuronal context: modifying structural connectivity, local network connectivity, long distance connectivity, and external input.

fications of behavioural performance. More specifically, we propose ways of incorporating plasticity mechanisms in existing computational models that are capable of generating ongoing spontaneous activity as a function of transmission delays, noise, and connectivity. We demonstrate how, in principle, plasticity in local populations can change dynamical stability of the global functional network distributed across multiple brain areas. To this end, we first simulate three types of cortical node models: a spiking attractor model, a rate model (neural mass model), and a canonical normal form model. In all three forms noise drives explorations of a multistable attractor space. We demonstrate that network activity in the absence of plasticity is characterized by irregular oscillations between a low-amplitude asynchronous and a high amplitude synchronous state. Next, we incorporate state-dependent plasticity in the locally balanced spiking network model. Specifically, we implement phase-dependent STDP to understand how the asynchronous spontaneous dynamics change. We demonstrate the capability of intrinsic alpha (8–10 Hz) oscillations to efficiently influence STDP. Additionally, we show how state dependent STDP alters underlying dynamical landscape from an irregular to a highly periodic alpha-like state. Finally, we demonstrate how changes in large-scale SC between brain areas can alter distinct features of global network FC. Disentangling these effects of local and global network changes in a systematic fashion is enabled by the open source neuroinformatics platform "The Virtual Brain".

Congresses, Workshops, and Symposia

2012 Ritter, P. (June). *Brain Connectivity Workshop 2012*. Workshop Chengdu, China (Advisory Board).

2013 Ritter, P. (September). *Bernstein Focus State Dependencies of Learning*. Workshop. Berlin, Germany.

Ritter, P. (June). *Brain Connectivity Workshop 2013*. Workshop. Vancouver, Canada (Advisory Board).

Degrees

PhD Theses

2013 Reinacher, M. *Relationships of ongoing activity, stimulus response variability, and behavioral performance in the human brain*. Charité, Universitätsmedizin Berlin.

Publications

Articles

Freyer, F., Becker, R., Dinse, H., & Ritter, P. (2013). State-dependent perceptual learning. *The Journal of Neuroscience, 33*(7), 2900–2907.

Freyer, F., Reinacher, M., Nolte, G., Dinse, H. R., & Ritter, P. (2012). Repetitive tactile stimulation changes resting-state functional connectivity: Implications for treatment of sensorimotor decline. *Frontiers in Human Neuroscience, 6*: 144. doi:10.3389/fnhum.2012.00144.

Freyer, F., Roberts, J. A., Ritter, P., & Breakspear, M. (2012). A canonical model of multistability and scale-invariance in biological systems. *PLoS Computational Biology, 8*(8): e1002634. doi:10.1371/journal.pcbi.1002634.

Ritter, P., Schirner, M., McIntosh, A. R., & Jirsa, V. K. (2013). The virtual brain integrates computational modeling and multimodal neuroimaging. *Brain Connectivity, 3*(2), 121–145.

Patents

McIntosh, A. R., Mersmann, J., Jirsa, V. K., & Ritter, P. (2013) Method and Computing System for Modelling a Primate Brain. Patent application 137PCT1754.

5.4
Max Planck Research Group "Neuroanatomy & Connectivity"

The prefrontal cortex is a densely interconnected and functionally complex region that has evaded a coherent, generally accepted model of function. Our research agenda aims to characterize its connectivity and organization, and does so by branching into three interwoven topics: (1) cortical organization, primary as described by intrinsic functional connectivity; (2) its relationship to self-generated thought; and, (3) the modulation of functional brain organization by changes in higher-order internal frameworks that constitute an individual's identity. Our initial period of research has focused on the first two topics, including methodological developments (Fig. 5.4). *Connexels*, which describe a connection between two voxels, provides the conceptual unit for addressing analytic and visualization challenges (Worsley et al. 1998, Hum Brain Mapp, 6, 364–367). Knowledge of prefrontal organization from macaque monkey tract-tracing and cytoarchitectonic studies provides the anatomical basis for delineation of corresponding areas in humans (5.4.1). Investigating these patterns of connectivity on the individual level is made possible using two novel visualization techniques addressing the challenges of high-dimensional connexel space, which we apply to the manual delineation of prefrontal areas (5.4.2). On-going work aims at integrating findings from these approaches into automated pipelines for prefrontal parcellation of large-scale datasets (5.4.4), and incorporating knowledge from the literature to map function (5.4.3). The convergence of interest in spontaneous fluctuations in brain activity with prefrontal organization has coalesced into research on the networks underlying self-generated thought (5.4.5). This rapidly evolving research terrain requires a versatile tracking of its changing terminologies and conceptual frameworks. Here we employ methodologies from the humanities and social sciences to conduct historical and bibliometric analyses (5.4.6) to understand this changing field, and to generate new research questions.

Human prefrontal cortical mapping		
Methodology	Structure/function	Cognition/behaviour
Connexels visualization (5.4.2) analytics (5.4.3/4)	Parcellation inter-species (5.4.1) individual-level (5.4.1)	Self-generated thought phenotypic variability (5.4.5) conceptual framework (5.4.6)

Figure 5.4 Research overview: Research structure of the initial phase of the Neuroanatomy & Connectivity Research Group with references to the project descriptions.

5.4.1 Parcellation of prefrontal cortex in macaques and humans

Goulas, A.[1], Hutchison, R. M.[3], Stiers, P.[2], Petrides, M.[4], & Margulies, D. S.[1]

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Delineating the distinct cortical fields within the human prefrontal cortex (PFC), and their connectivity patterns, offers substantial challenges. Histological analysis of the macaque monkey PFC provides the gold standard for the cytoarchitectonic and connectional architecture of the primate brain; however, extrapolation of such findings, especially for this higher-order region, may mask features unique to humans. To address potential divergence, a rigorous comparative analysis of the PFC architecture of the two species is needed.

Resting-state fMRI (rsfMRI) has emerged as a powerful tool for delineating cortical fields of the human PFC *in vivo* (Goulas et al. 2012, J Neurosci, 32, 10238–10252), as well as on the individual level (Fig. 5.4.1.1, Margulies & Petrides, 2013, J Neurosci, 33, 16846-16852), and for examining and comparing the connectivity of distinct cortical areas in macaques and humans (Margulies et al., 2009, PNAS, 106, 20069–20074). As the same modality can be acquired in both species, it serves as an ideal data type for independent parcellation of PFC, thus allowing for subsequent quantitative connectivity-based homology assignment of cortical fields.

Using recently developed module detection algorithms from network science, we parcellated the macaque PFC using rsfMRI data (N = 11). The distinct subregions delineated from the algorithm are topographically consistent with known cortical fields, and their connectivity corresponds to findings from the macaque tract-tracing literature (Fig. 5.4.1.2). A rigorous quantitative framework for assigning homologies is currently in development in order to exploit classic homology criteria, such as connectivity similarity (Campbell & Hodos, 1970, Brain Behav Evol, 3, 353–367).

The current project translates between macaque and human research on PFC. Additionally, it offers the potential to map unique connectional features of cortical fields in the human brain, with implications for understanding the inter-species divergence in cognitive abilities.

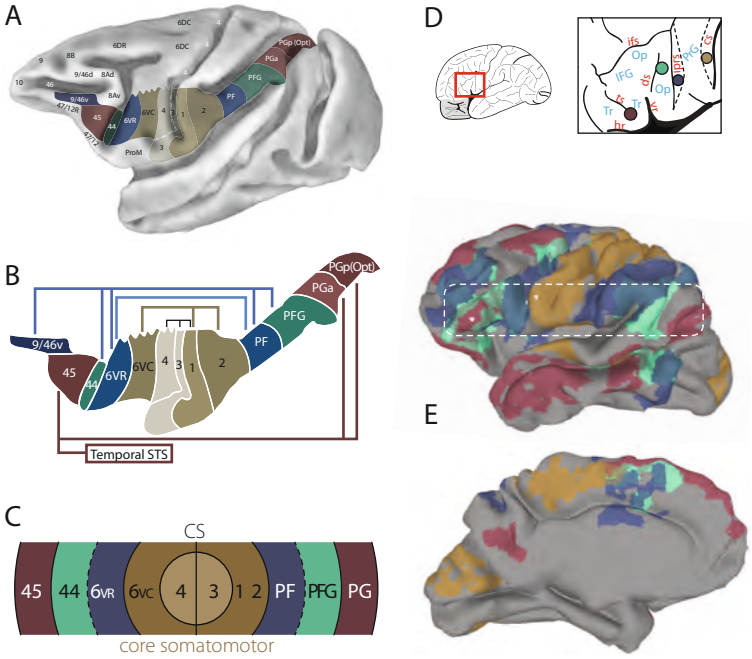

Figure 5.4.1.1 Individual-level parcellation of ventrolateral prefrontal cortex: (A,B) Areas of the ventrolateral prefrontal cortex in the macaque monkey, and their respective connectivity patterns to areas of the parietal and temporal cortex. (C) Schematic illustration of the distinguishing patterns of connectivity as a hypothesis for delineating areas in the human brain. (D) Seed regions based on morphology of ventrolateral prefrontal cortex in the human. (E) Results of functional connectivity from an individual brain.

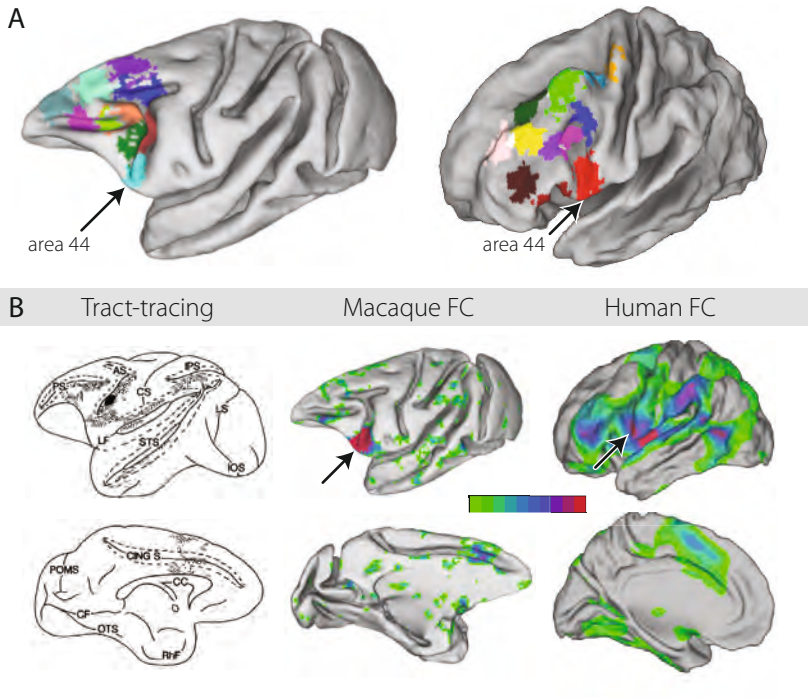

Figure 5.4.1.2 *In vivo* parcellation of the lateral prefrontal cortex in macaques and humans: (A) Parcellation and functional connectivity map in humans adopted from Goulas et al., 2012, Cereb Cortex (B) Prefrontal cortical parcellation in the macaque reveals neuroanatomically plausible subregions. Whole-brain functional connectivity maps of putative region 44 in both species suggest a similar connectional fingerprint. Functional connectivity maps are thresholded at an FDR corrected level ($q < 0.05$). Correspondence to gold standard tract-tracing is demonstrated by comparing the functional connectivity pattern of putative area 44 to case 6 in Pandya & Yeterian, 1996, Phil Trans R Soc Lond B, 351, 1423–1432.

Visualization of cortical connectivity

5.4.2

Böttger, J.[1], Schurade, R.[1], Jakobsen, E.[1], & Margulies, D. S.[1]

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Methodological advances in structural, diffusion-based, and functional MRI have increased the resolution of data describing the degree of connectedness between cortical areas. The visualization of whole-brain connexel data poses a challenge, owing to its high dimensionality (Margulies et al., 2013, Neuroimage, 80, 445-461). Drawing a graph of the connections in 3D anatomical space leads to undecipherable images, since the connections obfuscate each other. The exploration of connectivity data in relation to anatomy can therefore profit from application of visualization techniques and interactive software.

We have developed two approaches towards that end: edge-bundling and connectivity glyphs. Mean-shift edge-bundling (Böttger et al., 2013, IEEE Trans Vis Comput Graph) groups geometrically similar connec-

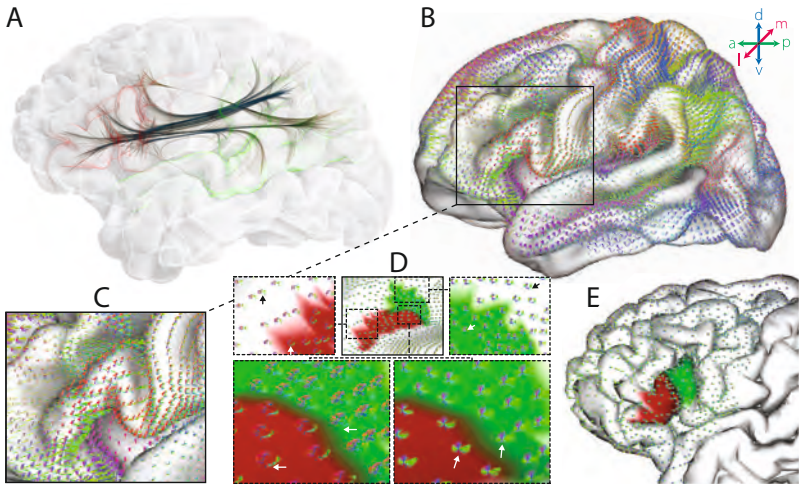

Figure 5.4.2 Novel connexel visualization techniques and application to cortical parcellation: (A) Edge-bundled connectivity graph for a single healthy participant, containing connections between two regions of interest (ROIs). (B) Vector-based connectivity glyphs with detail image of the left ventrolateral prefrontal cortex. (C) The colours denote orientation of the connections emanating from the single nodes as displayed in the legend in the upper-right corner. (D) Criteria for manual segmentation of areas 44 and 45 on an individual brain using glyph information, (E) and the resulting labels.

tions together, thus clarifying the structure of complex, high-resolution connectivity graphs. While edge-bundling yields an overview of network structure, the anatomical placement of the connections' termination points remains difficult to discern (Fig. 5.4.2A).
Connectivity glyphs provide a solution by integrating connectivity information into the contours of the cortical surface (Böttger et al., 2013, Visualization in Medicine and Life Sciences, Leipzig, Germany). Local connectivity profiles are represented as small iconic renderings, ranging from little brains to pie charts. The different glyphs emphasize various aspects of connexel structure, allowing the user to integrate differences across neighbouring nodes on the cortical surface. Our initial application of the method is the manual segmentation of Brodmann areas 44 and 45 (Fig. 5.4.2D, E), an approach which we are pursuing throughout the prefrontal cortex.
Both novel methods are made available through the in-house open-source software brainGL.

5.4.3 Bridging the gap between exploratory and hypothesis-driven brain analyses by collecting and incorporating prior knowledge

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The vast majority of studies in human cognitive neuroscience are built upon assumptions supported by previous research. In MRI-based studies, these are often used to improve the power of statistical brain mapping methods by restricting the search space to a specific region of interest (ROI), in voxel and connexel space. Such masks are binary—drawing an arbitrary border in the continuum of uncertainty.
We have developed a novel inference method that can improve power by using a prior probability map (Gorgolewski et al. 2013, PRNI, Philadelphia, USA). Using a probabilistic ROI, the approach applies a hierarchical Gamma-Gaussian model to classify each data point to a signal or noise class (Fig. 5.4.3). Because each class is modelled explicitly, false discovery or false non-discovery rates can be used to set a desirable threshold. The modular nature of a Bayesian framework lends itself to easy extensions.
Prior probability maps can be obtained from different sources such as tissue probability maps or functional localizers. However, the most powerful usage is based on previous studies. Unfortunately, databases such as Neurosynth and BrainMap are limited by the peak-based input data they received. To improve this situation we are introducing a new database for sharing unthresholded statistical maps: NeuroVault.org (Gorgolewski et al. 2013, OHBM, Seattle, USA). The website is designed to streamline the uploading experience, and provides the user with interactive data visualization.
In contrast to statistical maps, full data sets require substantial effort to be properly described and annotated. To boost data-sharing of complex data sets, we propose the concept of a "data paper" (Gorgolewski et al., 2013, Front Neurosci, 7, 9), a publication fully devoted to a description of a data set. Data papers establish recognizable credit for those involved in data acquisition by making a data set citable.
Together these three mechanisms are significant steps towards better, more reusable and reproducible science.

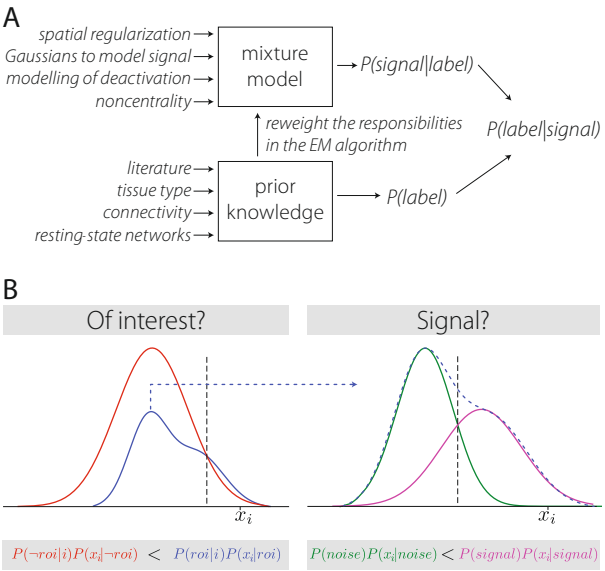

Figure 5.4.3 Probabilistic ROIs: (A) Overview of the probabilistic ROI concept. Label ("active" or "not active") is inferred by combining the information from data with prior knowledge. (B) Two levels of probabilistic ROI inference. P(roi), reflecting the prior probability, is combined with evidence from the data P(x) to classify data points. Inference is performed in two steps: comparison of ROI and non-ROI probability distributions is followed by comparison of noise and signal probability distributions. All parameters are estimated from data using the prior probability map.

5.4.4

Incorporating XNAT into the data management and processing infrastructure

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In the context of neuroimaging studies, large sample sizes of diverse multi-modal participant data correlated with MR data sets offer the possibility to explore novel relationships. By conducting lightweight, effective studies on large data sets, it is possible to gain further insights into the relationship between brain and cognitive function, disease traits, anatomical traits, and genetic data.
In order to harvest fruitful results from such studies, a secure, scalable, and computationally adequate infrastructure needs to be in place to support data management and analysis due to the large amounts of memory and data throughput required when archiving, viewing, post-processing, and sharing imaging (and their associated) data sets. With this in mind, in 2012 we deployed the extensible Neuroimaging Archiving Toolkit (XNAT) to manage and store project data at the institute. XNAT offers a robust, internally decoupled architecture, and extensive support for common data types used in MR informatics. Moreover, XNAT allows users to securely perform a number of standard MR pre-processing tasks and share data with collaborators. To allow for multi-centre collaboration, a sync-manager developed in-house synchronizes data between the XNAT instance in Leipzig and XNAT servers at collaborating sites. After an initial test phase,

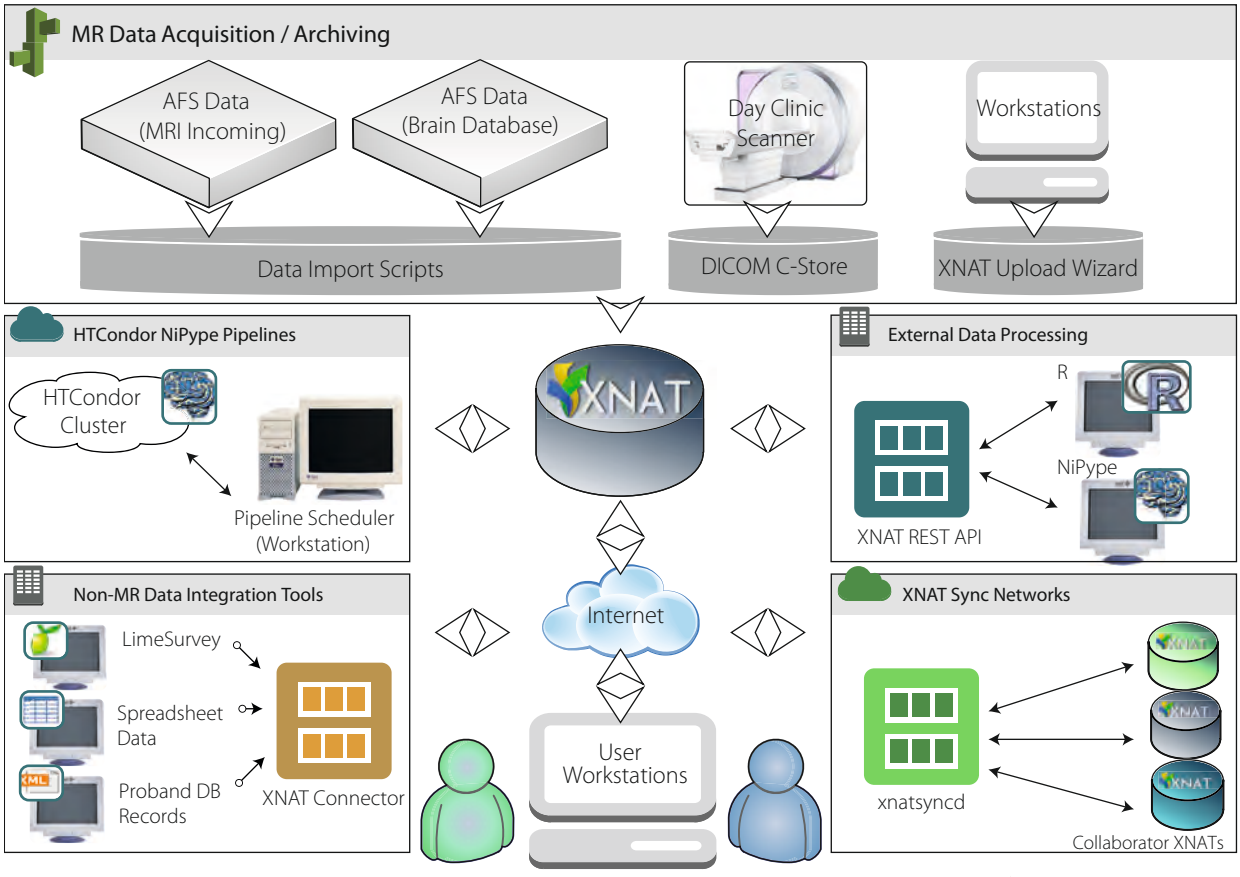

Figure 5.4.4 XNAT integration with diverse data acquisition, processing, and sharing infrastructures: *Non-MR Data Integration Tools*: XNAT's native functionality has been enhanced to facilitate data import. A data uploader imports and quality-checks different data types; a data connector facilitates the import of demographic and questionnaire data from other sources. *HTCondor Nipype Pipelines:* Pre-processing tasks (i.e. DICOM to NIFTI conversion, defacing, FreeSurfer cortical reconstruction and VBM-SPM analyses) in XNAT can be done with parallel processing via the integration of XNAT to the HTCondor Cluster. *XNAT Sync Network*: Data sharing with collaborating centres is supported via *xnatsyncd,* a distributed data synchronization tool developed at the institute. *External Data Processing:* Via XNAT's REST API, it is possible to prepare/expose XNAT data for complex analysis using common tools such as R, Python, SPSS, Matlab, etc. Results and reconstructed data are then uploaded to XNAT.

XNAT is now being used by three research groups at the institute to manage their multi-modal (structural MRI/activation fMRI, EEG, demographic psychological, and derived genetics) project data (Fig. 5.4.4). It is hoped that other research groups at the institute will soon benefit from XNAT and that this resource will consolidate as an important addition to the data processing and managing infrastructure.

5.4.5 Connectomic correlates of self-generated thought

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In a complex environment, adaptive cognition emerges through an appropriate balance of information from immediate sensory input and information representative of long-term goals. Although distinct aspects of how memory and perception are processed are reasonably well understood, we lack a detailed understanding of how they are integrated in a holistic manner in normal healthy functioning. One way to understand this process of integration is to explore the role of highly connected cortical 'hub' regions in integrating information across domains to afford adaptive cognition. One cortical hub is the frontopolar cortex, or Brodmann area 10, which is thought to be important in the capacity to reflect upon the effectiveness of on-going behaviour, known as metacognition. In a comparison of intra-individual variability in metacognitive capacity for perceptual decisions and memorial judgments using resting-state functional connectivity (rs-fcMRI) (Baird et al., 2013, J Neurosci,33, 16657-16665), we found evidence that the frontopolar cortex was important in these two behaviourally distinct forms of metacognition (Fig. 5.4.5). Using a similar approach, we explored the role of another hub region, posterior cingulate cortex (PCC), in coordinating narrative comprehension. Successful reading depends on information from the text on the page as well as more general representations of the context within which the narrative unfolds, and so is likely to depend on integrative processing (Smallwood et al., 2013, Front Hum Neurosci, 7, 734). We found that the PCC showed distinct connectivity patterns that were predictive of both better (right anterior insula) and worse comprehension (ventral striatum). Furthermore, we found that the same region

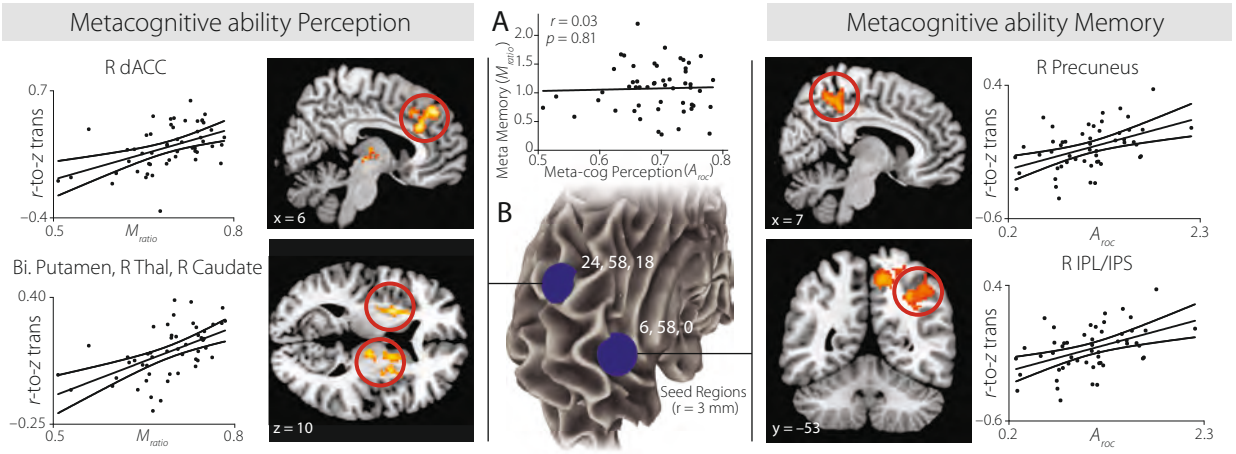

Figure 5.4.5 Double dissociation of metacognitive ability for memory and perception: We directly compared intra-individual variability in metacognitive capacity for perceptual decisions and memorial judgments and used resting-state functional connectivity (rs-fcMRI) to relate this variability to the connectivity of the medial and lateral regions of aPFC (B). (A) We found a behavioural dissociation in metacognitive ability for perceptual and memorial judgments. Furthermore, functional connectivity analysis revealed distinct patterns of connectivity that correlated with individual differences in each domain. Metacognitive ability for perceptual decisions (left) was associated with greater connectivity between lateral regions of aPFC and right dorsal anterior cingulate cortex, bilateral putamen, right caudate, and thalamus, whereas metacognitive ability for memory retrieval (right) predicted greater connectivity between medial aPFC and the right central precuneus and intraparietal sulcus/inferior parietal lobule.

of frontopolar cortex that facilitated metacognition for memory showed a similar pattern of enhanced connectivity with the PCC for individuals who managed to maintain focus on what they were reading. Together, these results suggest that one mechanism through which the brain integrates information across long and short time scales is through hub regions that influence the transmission and dissemination of neural information across distinct regions of cortex.

Tracking the fields of resting-state and mind-wandering

5.4.6

Callard, F.[1], Golchert, J.[2], Smallwood, J.[3], & Margulies, D. S.[2]

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[3] Department of Psychology, University of York, United Kingdom

The research approaches of the humanities and social sciences offer a unique vantage to investigate the emergence, characteristics, and challenges facing the nascent field of resting-state fMRI. What is notable about this field is that it was initially constituted through the coming together of what had been, in the mid- to late 1990s, two conceptually distinct lines of research that were addressing, respectively, neurophysiological and neuropsychological questions. We use various methods (including traditional historical methods of close readings of scientific and lay literature that addresses 'resting-state' and 'default mode', as well as bibliometric analyses), to trace how these research fields came together, as well as to identify some of the confusions and conflations that have resulted from this consolidation (Callard & Margulies, 2011, Subjectivity, 4, 227–257). Of particular interest is how certain formulations of the default mode network have been closely tied to models of mind-wandering (Callard et al., 2012, Front Psychol, 3, 321), and how this is driving certain lines of scientific investigation rather than others (Callard et al., 2013, Front Psychol, 4, 891). We are now exploring this literature in more finely-grained detail using bibliometric methods (Fig. 5.4.6) to investigate how certain assumptions have become (perhaps prematurely) embedded; how certain terms and concepts (e.g. mind-wandering) have gained prominence in part through the growth of resting-state research; and how a variety of normative claims (explicit or implicit) frequently accompany scientific data regarding the phenomena under investigation. This helps further to refine the terms and assumptions that we are using elsewhere in bringing spontaneous thought and connectomics together.

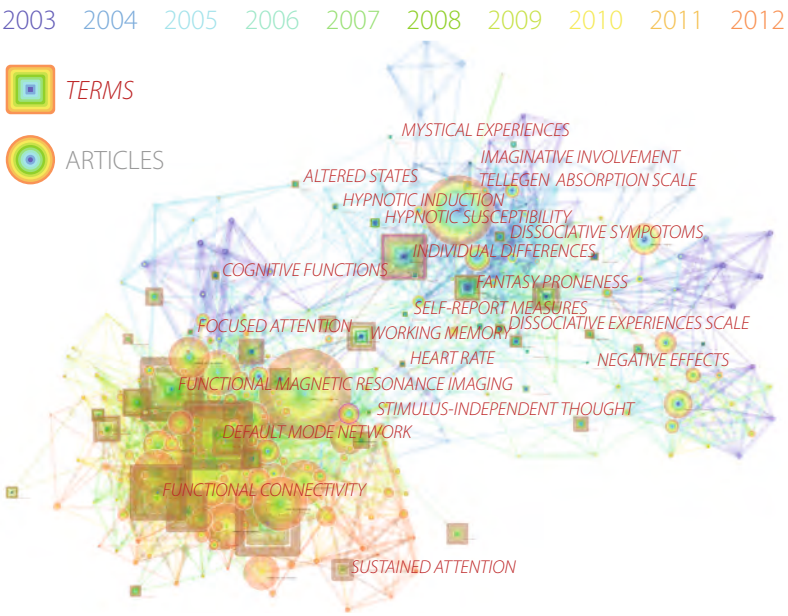

Figure 5.4.6 Bibliometric graph visualization of the mind-wandering literature from 2003–2012: CiteSpace was used to visualize the mind-wandering literature from 2003–2012. The colours represent years, the squares are highly used terms (labelled), and the circular nodes are cited articles (not labelled here for visual clarity). Each coloured circle represents the number of citations/uses during that year. Edge links between nodes represent co-occurrence (in the case of terms) and co-citation (in the case of articles), with the colour representing the first year in which the connection was found.

Congresses, Workshops, and Symposia

2012 Gorgolewski, C. (September). *Nipype Connectivity Workshop*. Otto von Guericke University Magdeburg, Germany.

Margulies, D. S. (September). *Brainhack 2012*. Workshop. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

2013 Gorgolewski, C. (May). *Nipype Workshop*. University of Trento, Italy.

Gorgolewski, C., Margulies, D. S., Smallwood, J. (October). *Resting State*. Workshop. University of York, UK.

Margulies, D. S. (May). *Neuroscience and Art in Dialogue: A reflection on the work of Tino Sehgal*. Symposium. Neuroesthetics Symposium, Peggy Guggenheim Collection in conjunction with the opening of the Venice Biennale. Association of Neuroesthetics, Venice, Italy.

Margulies, D. S. (October). *Brainhack 2013*. Workshop. The Neuro Bureau, Paris, France.

Gorgolewski, C., Ghosh, S. (December). *Nipype workshop*. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Awards

2012 Moreno-Dominguez, D. *PhD stipend*. FAZIT Foundation, Germany.

Publications

Book and Book Chapters

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5.5 Max Planck Fellow Group "Cognitive and Affective Control of Behavioural Adaptation"

Various neuropsychiatric diseases are characterized by a loss of the subject's ability to stop certain maladaptive behaviours although aware of their negative long-term consequences. In alcohol and drug addiction, subjects display compulsive drug intake; in obesity, binge eating may occur; and in obsessive-compulsive disorder, patients suffer from repetitive behaviours. Reward processing and basal learning mechanisms contribute to the development and maintenance of such habitual and compulsive behaviours by altered neuronal value and learning signals. A gradual shift in behaviour guided by outcomes and their consequences (so-called "goal-directed") to automatic, habitual behaviour may be one prominent factor underlying the maintenance of such maladaptive behaviours. Furthermore, disease specific, e.g. drug or food related, cues may prompt disadvantageous habits by acquiring excessive salience and exerting a strong influence on choice selection, while poor response inhibition leads to a failure to suppress stimulus-evoked behaviour and is related to impulsivity and addictive states.

In our group we study the neuronal representation of value and other learning signals relevant for behavioural adaptation. A multimodal imaging approach combined with computational reinforcement learning modelling allows us to investigate the underlying fronto-striatal circuitries. In healthy controls, we study trait and state factors contributing to a loss of behavioural control like impulsivity or stress. Furthermore, adopting a transdiagnostic approach, we investigate various psychiatric patient populations with the common characteristic of a dysfunctional control over certain behaviours. One project focussed on the balance between goal-directed and habitual behavioural control and its relation to dopaminergic neurotransmission and alterations in disease states. Another project investigated the influence of trait impulsivity in a group of high compared to a group of low impulsive individuals on response inhibition. Current, ongoing projects investigate reward learning in addicted patients as well as patients with obsessive-compulsive disorder in cooperation with clinical facilities in Leipzig and Berlin. Furthermore, a task assessing extinction learning has been developed to investigate pharmacological influences.

Emerging technologies like deep brain stimulation emphasize the need to better describe and understand the neuro-circuitries mediating these maladaptive behaviours. Therefore, a better understanding of the behavioural and neuronal mechanisms underlying a failure of behavioural adaptation in various disease states is highly relevant for therapeutic interventions.

Model-free and model-based learning: Relation to impulsivity and alcohol dependence and modulation by presynaptic dopamine

5.5.1

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Decision making was theoretically proposed to be mediated by two different controllers, a model-free and a model-based system. Model-free control is closely associated with habits where an action associated with a reward is likely to be repeated. In contrast, model-based control refers to the individual's ability to map action-outcome consequences and to use this information to guide goal-directed behaviour. Addictive behaviours and their trait risk factors such as impulsivity—both closely linked to dopamine neurotransmission—were hypothesized to be associated with predominantly model-free control over choice behaviour. Further, measures of presynaptic dopamine were proposed to modulate the dominance of one of the two controllers (Wunderlich et al., 2012, Neuron, 75, 418–424).

Here, we quantified the arbitration of model-free and model-based choice behaviour on a trial-by-trial level using a sequential decision making task in combination with computational modelling (Daw et al., 2011, Neuron, 69, 1204–1215). First, we show that the relative degree of model-free versus model-based learning is best predicted by cognitive speed and that this interacts with trait impulsivity. We replicate this finding in a cohort of preselected high-impulsive individuals and additionally demonstrate that their choices depend more strongly on reward-prediction errors. Second, we show that alcohol-dependent patients are shifted to a predominantly model-free decision pattern. Third, using multimodal imaging, we demonstrate that presynaptic dopamine is negatively associated with ventral striatal model-free signals but positively predicts the relative degree of model-based learning signals in lateral prefrontal cortex. This work provides evidence that presynaptic dopamine is involved in modulating the relative influence of model-free or model-based control on decisions, which provides a potential mechanism for the predominance of model-free choice behaviour in alcohol dependence and associated risk factors.

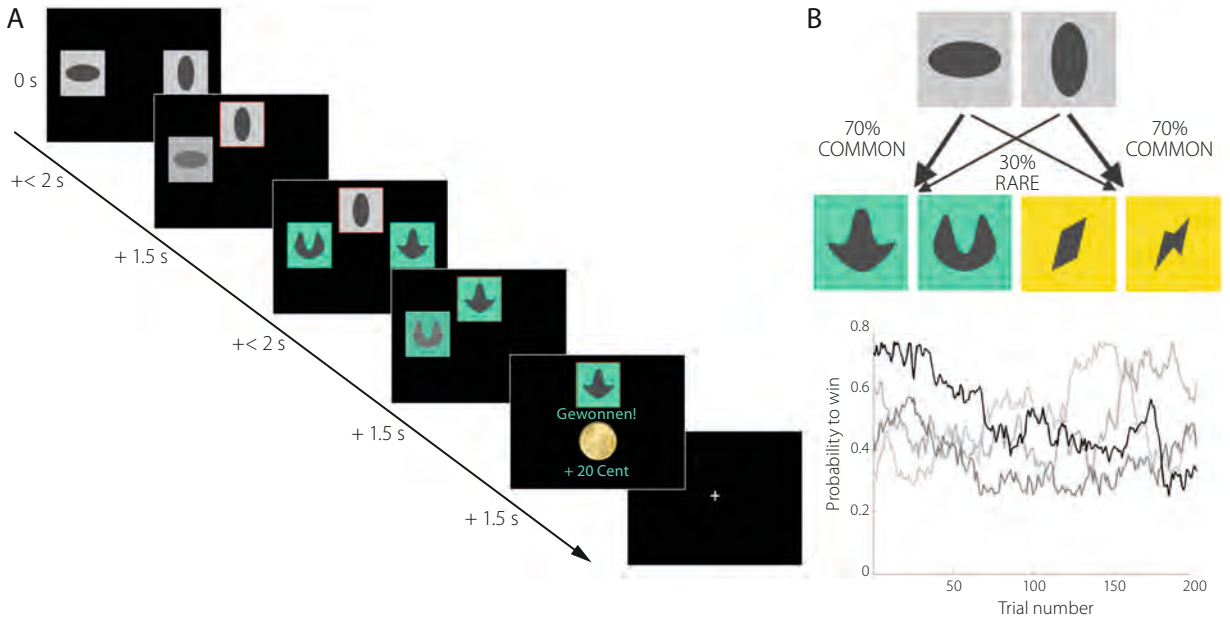

Figure 5.5.1 (A) In the first stage of each trial, participants chose between two options; the chosen option was highlighted by a red frame and moved to the top of the screen. In the second stage, one of two pairs of coloured stimuli was presented and participants were again required to choose one. Subsequently, a monetary outcome (gain or no gain of 20 cent) was delivered. (B) One pair of coloured stimuli occurred commonly (on 70% of trials; "common state") after choice of one first-stage stimulus, while the other pair was associated equally strongly with the other first-stage stimulus. On the remaining 30% of trials, first-stage actions resulted in a transition to the other, rare second-stage stimulus pair. (C) Reward probabilities for each second-stage stimulus changed slowly and independently according to Gaussian random walks with reflecting boundaries at .25 and .75 and are displayed as a function of trial number.

5.5.2 Learning signals during reversal learning: Modulation by presynaptic dopamine and alterations in alcohol dependence and schizophrenia

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[2] Department of Psychiatry and Psychotherapy, Charité University Medicine Berlin, Germany

Behavioural adaption to a changing environment is fundamentally involved in reward-optimizing decision making. Reward prediction errors (PEs) are crucially involved in learning decision values of alternative actions. Inflexible decision making is observed in two major psychiatric diseases: alcohol dependence and schizophrenia. Neurobiological hypotheses propose a close link to dopamine-driven error learning but putatively different involvements in both illnesses. Therefore, dopamine-dependent regulation of neural learning signals is of great importance to provide a better understanding of flexible behavioural adaption and its impairments.

A reversal learning task was applied during functional magnetic resonance imaging, and we assessed PE-related ventral striatal activation based on trial-by-trial PEs derived from computational reinforcement learning modelling in a series of three studies. First, we investigated healthy volunteers that also underwent positron emission tomography with ^{18}F-DOPA to assess dopamine synthesis capacity. This revealed a negative relationship between ventral striatal dopamine synthesis capacity and ventral striatal reward PEs (Schlagenhauf et al., 2013). Second, we applied the same experimental setup in recently detoxified alcohol-dependent patients. While ventral striatal PEs were negatively correlated with craving for alcohol, the negative relationship between ventral striatal dopamine synthesis capacity and ventral striatal reward PEs observed in healthy controls was disrupted in alcohol-dependent patients. This disruption was associated with chronic alcohol intake (Deserno et al., under review). Third, we studied un-medicated schizophrenia patients and observed a blunted ventral striatal coding of reward PEs (Schlagenhauf et al., in press).

These results point towards crucial but different contributions of dopamine-regulated learning signals to inflexible decision making in major psychiatric diseases like alcohol dependence and schizophrenia.

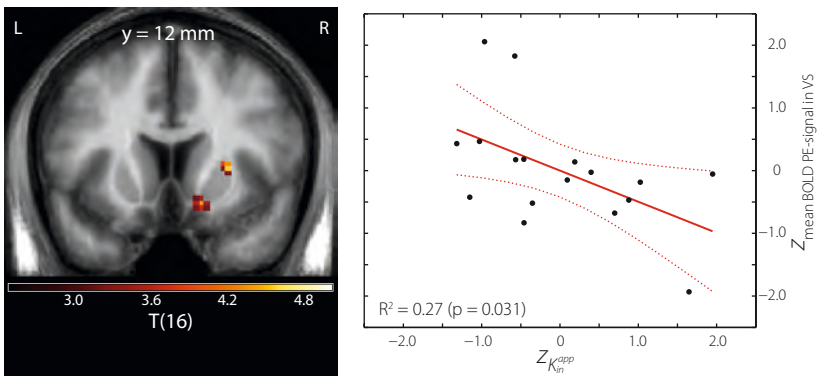

Figure 5.5.2 Negative correlation between dopamine synthesis capacity as assessed *in vivo* with FDOPA PET and the BOLD prediction error signal in the ventral striatum. *Left panel:* Voxel-by-voxel association between FDOPA K_{in}^{app} and BOLD prediction error signal from the Biological Parametric Mapping analysis. Coronal slice at MNI coordinate y = 12, statistical threshold t > 3.0, minimum cluster size = 20 voxels). *Right panel:* Plot of z-standardized mean K_{in}^{app} value derived from the right VS VOI and mean BOLD prediction error signal derived from the right ventral striatal VOI.

Transdiagnostic investigation of neuronal value representations of universal and disease-specific reinforcers

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In current addiction theory, drug-related cues are claimed to play a pivotal role in the maintenance of and relapse into addictive behaviour. It has been proposed that addiction-related stimuli acquire an extensive value compared to natural reinforcers which might lead to a so-called *Hijacking* of the neural reward system. Consequently, drug-specific stimuli elicit conditioned physiological responses and might contribute to a loss of behavioural control—patients relapse despite an actually firm will not to.

During Appetitive Pavlovian Conditioning a stimulus-reward association is learned and there is evidence in healthy controls that brain activation patterns coding the value of predicted rewards (e.g. orbitofrontal cortex, dorsolateral prefrontal cortex, dorsal striatum) become similar to the patterns coding the value of actual received rewards (Kahnt et al., 2011, J Neurosci, 31, 14624–14630). This might involve overlapping and segregated networks for different types of reinforcers (Metereau & Dreher, 2013, Cereb Cortex, 23, 477–487).

Here, we investigate the neuronal value representation and learning signals of disease-specific vs conventional reinforcers in psychiatric diseases. Adopting a transdiagnostic approach, we use functional magnetic resonance imaging to investigate participants suffering from alcohol dependence vs binge eating disorder—both psychiatric conditions that share the breakdown of control over certain actions (drinking and eating, respectively) as a common ground. A Pavlovian learning paradigm with multiple disease-specific (alcoholic beverages, high-calorie food) vs conventional reinforcers (e.g. money) as unconditioned stimuli (UCS) allows us to track the neuronal value representation of multiple reinforcer categories over the course of learning (Fig. 5.5.3).

This paradigm will enable us to explore the differences between our experimental groups concerning the neuronal value representation and learning signals. We expect a heightened signal for the respective disease-specific cues in areas responsible for value representation like the striatum, ventromedial PFC, OFC, and insula. This allows us to specifically test the proposed *hijacking* of the neural reward system across different types of rewards.

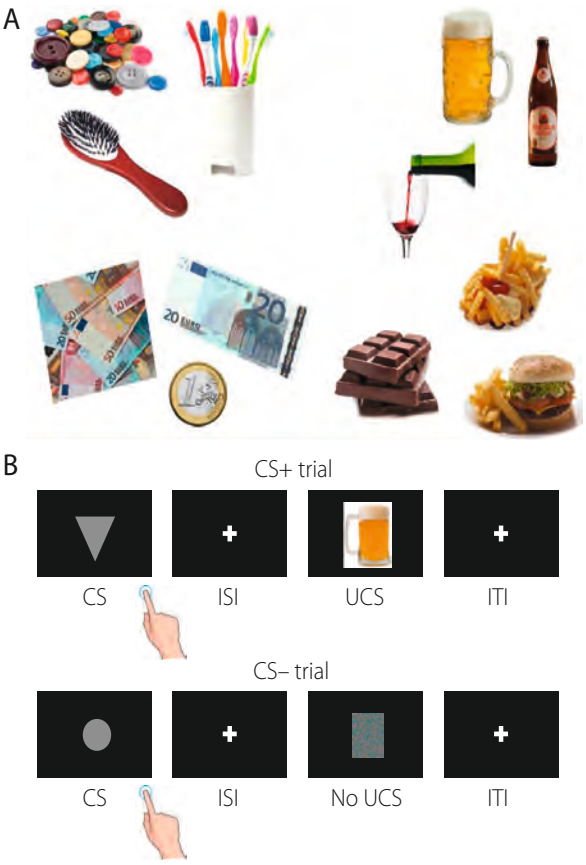

Figure 5.5.3 (A) Example stimuli used as unconditioned stimuli (UCS) with four different categories: neutral household items, secondary reinforcer (money), alcoholic beverages, and high-calorie food. (B) Example trials in the Pavlovian Conditioning paradigm: In a CS+ trial a repeated pairings between an initially neutral geometric figure (Conditioned Stimuli = CS) and pictures of one of the four different reinforcer types (US) is established. In CS– trials the CS is followed by a scrambled, imperceptible picture.

5.5.4 Response inhibition and dimensions of impulsivity

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Impulsivity is a multidimensional construct and has been suggested as a potential endophenotype for several psychiatric disorders especially substance use disorder (Ersche et al., 2012, Science, 335, 601–604). Response inhibition is thought to be one dimension of impulsivity and can be measured with a Stop Signal Task. However, there is contrasting evidence how different self-reported dimensions of impulsivity can be linked to behavioural and neurobiological measures. To this extent, 52 healthy individuals scoring either high or low on the self-report questionnaire Barratt Impulsiveness Scale (BIS-11, Patton et al., 1995, J Clin Psychol, 51, 768–774) were investigated using functional magnetic resonance imaging while performing a reward-modulated Stop Signal Task (Boehler et al., 2012, Cognition, 125, 498–503).

Behaviourally, response inhibition (measured by the SSRT) revealed no group difference with regard to the overall BIS-11 score. A multiple regression analysis with the SSRT as dependent variable showed that only the UPPS subscore *Urgency* (Whiteside et al., 2001, Pers Individ Dif, 30, 669–689) explained response inhibition performance ($p = 0.044$). This UPPS subscore *Urgency* revealed a negative correlation with BOLD signal in the right inferior frontal gyrus—a key region activated during response inhibition (Fig. 5.5.4). Thus, *Urgency* might be related to a weaker activation of network structures that are crucial for response inhibition. Successful rewarded stop trails revealed a prominent activation of the ventral striatum and this activation was only related to better response inhibition performance in subjects with low *Urgency* scores.

Response inhibition performance was found to be related to the impulsivity dimension *Urgency*, which focuses on the negative outcomes of actions. This subdimension was related to neuronal signals during cancellation of a prepotent action and reward feedback processing. This may be relevant for subjects suffering from substance use disorders with higher overall impulsivity measures and deficits in response inhibition.

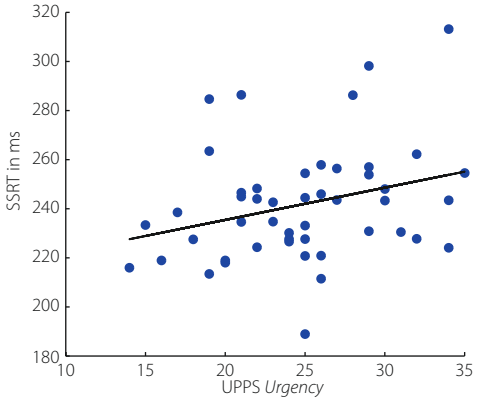

Figure 5.5.4.1 The UPPS subdomain *Urgency* showed a positive correlation with the SSRT ($r = 0.29$; $p < 0.05$), indicating that more impulsive individuals showed reduced response inhibition abilities.

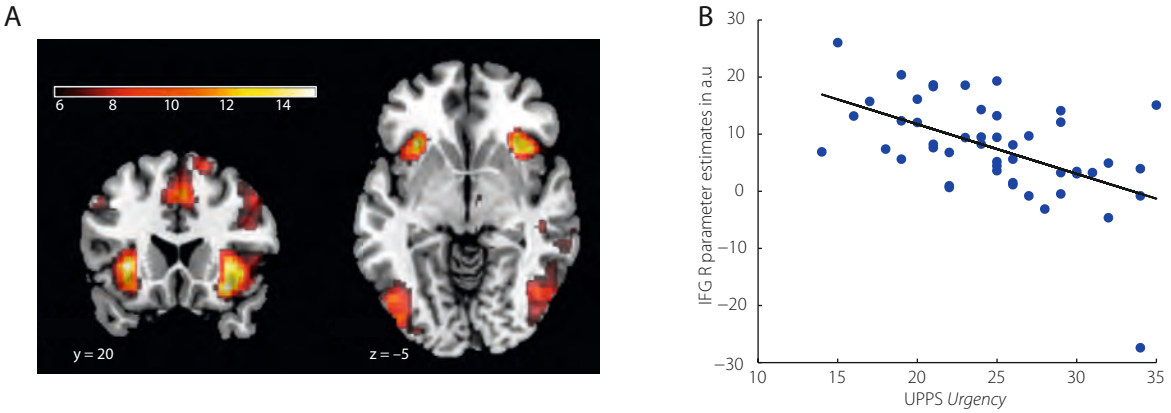

Figure 5.5.4.2 (A) Main Effect of 'Stop–Go' showing the inhibition network (FWE corrected for the whole brain, $p < 0.05$); (B) There was a negative correlation between the individual UPPS *Urgency* score and the BOLD signal in the right inferior frontal gyrus for the contrast 'Stop–Go' (FWE corrected for ifg main effect of 'Stop–Go', $p < 0.05$); parameter estimates extracted from the main effect of task at $x = 38$; $y = 28$; $z = –8$).

Effect of D-cycloserine on extinction learning in healthy controls

5.5.5

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A failure of extinction in the appetitive domain has been suggested as a common mechanism in addiction (Kalivas et al., 2005, Neuron, 45, 647–650). Extinction can be defined as a form of inhibitory learning that suppresses a previously learned association and is conceptualized as the formation of a separate extinction memory rather than just forgetting (Peters et al., 2009, Learn Mem, 16, 279–288). The extinction of alcohol-related cues and instrumental behaviour could be a major contribution to reduce relapse with a great demand for pharmacological strategies to improve extinction learning in alcohol use disorder. The NMDA-receptor partial agonist D-cycloserine (DCS) has been shown to facilitate extinction learning in preclinical and some clinical studies (Myers and Carlezon, 2012, Biol Psychiatry, 71, 947–955). Therefore, we developed a task to study the effect of DCS on extinction learning in healthy controls on three consecutive days in a randomized, placebo-controlled study. We use a classical (Pavlovian) extinction task with positive and negative monetary outcomes as unconditioned stimuli (US) and an instrumental extinction task with both positive and negative monetary reinforcement (see Fig. 5.5.5) to test if D-cycloserine enhances extinction learning in healthy controls. On a neuronal level we expect DCS to modulate learning signals in structures like striatum, hippocampus, amygdala, and prefrontal areas.

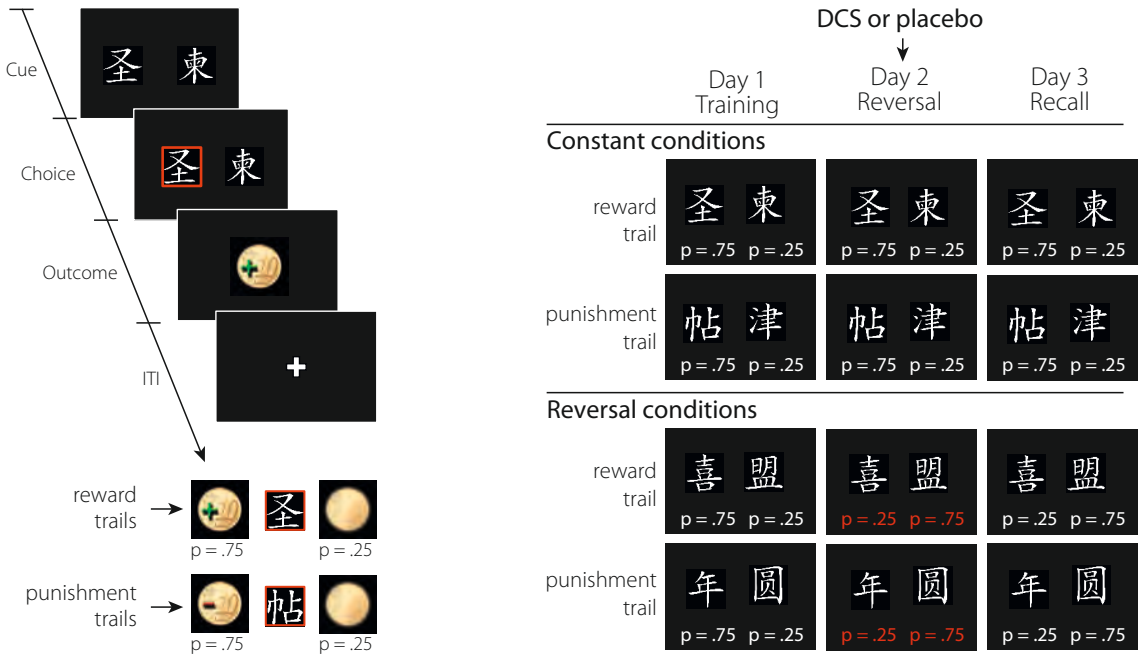

Figure 5.5.5 Left panel: A representative trial of the probabilistic instrumental learning task. Right panel: On the first day, subjects learn pairing of stimuli with monetary rewards; on the second day, they randomly receive either 50 mg DCS or placebo 60 min before the experiment. After medication, learned contingencies are partly reversed in order to assess the capacity of extinction learning in previously rewarded stimuli. On the third day, we assess consolidation of the acquired extinction memory without any further changes in contingencies.

Congresses, Workshops, and Symposia

2013 Schlagenhauf, F. (April) *Reward, salience and dopamine in schizophrenia patients*. Symposium. 21th European Congress of Psychiatry EPA, Nice, France.

Publications

Articles

Beck, A., Wüstenberg, T., Genauck, A., Wrase, J., Schlagenhauf, F., Smolka, M. N., Mann, K., & Heinz, A. (2012). Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. *Archives of General Psychiatry, 69*(8), 842–852.

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5.6
Max Planck Research Group "Early Social Development"

Infancy is the time of life during which enormous changes take place—the 'helpless' newborn seems almost a different creature from the inquisitive, walking, and talking 1-year-old. During this formative life period, infants develop in an intensely social world filled with other people and one of the most important tasks they face is to develop skills that help them interact with others and understand others' social behaviour. In the Early Social Development Group, we study the early emergence of the social and affective competencies that enable infants to interact with others. By using non-invasive and child-friendly methods such as electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), and eye-tracking technology, we examine changes in infant brain function while important social developmental milestones are achieved. We study these developmental processes across a range of situations in which infants can glean social and emotional information from various different sources such as faces, voices, biological motion, and touch. Moreover, we aim to understand how social development varies across infants and what factors give rise to such individual differences. Our research programme represents an integrated multi-method approach that provides a unique window into the infant mind.

Physiological and behavioural responses reveal human infants' sensitivity to pleasant touch

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Caregiving touch has been shown to be essential for the growth and development of human infants. However, the mechanism that underpins infants' sensitivity to pleasant touch is still poorly understood. In human adults, a subclass of unmyelinated peripheral nerve fibres has been identified to respond preferentially to medium velocity soft brushing, similar to parental stroking (Löken et al., 2009, Nat Neurosci, 12, 5, 547–548). It has been theorized that this privileged pathway for pleasant touch is used for close affiliative interactions, especially between caregivers and infants. To test whether human infants are sensitive to pleasant touch, we examined arousal (heart rate) and engagement (gaze shifts and duration of looks) to varying velocities of brushing (slow, medium, and fast) in 9-month-old infants. The current results revealed that only when stroked at medium velocity, (i) infants' heart rate decelerated, reflecting greater parasympathetic activity and indicative of a decrease in arousal, and (ii) infants' behavioural engagement with the stroking object (brush) increased, indicative of an increased engagement and interest in the stroking object. Our analysis further revealed that the greater the caregiver's sensitivity to social touch, the greater the infant's selective physiological response to medium-velocity touch. This shows that there is variation in infants' responsiveness to pleasant touch and suggests that such individual differences

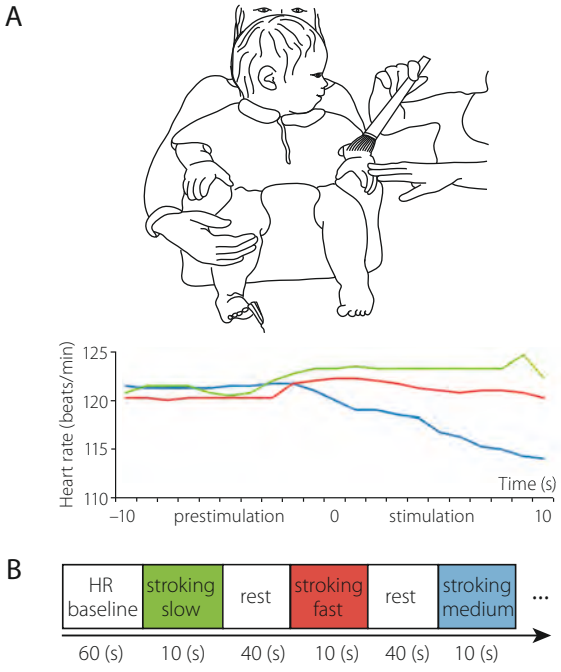

Figure 5.6.1.1 Study design. (A) A graphical representation of the experimental setup showing the infant seated within a "Bumbo" seat placed on the lap of the parent facing the distractor film displayed on a monitor. The experimenter is seated beside the infant so as to most easily stroke the non-dominant dorsal forearm with an artist's paintbrush at one of three set velocities (slow: 0.3 m/s, medium: 3 m/s, and fast: 30 m/s). A response in arousal is measured by a special infant pulse oximeter probe placed on the big toe of the right foot. A trace of an individual infant's heart rate response before (10 s pre-stimulation) and during (10 s stimulation) stroking (slow: green; medium: red; fast: blue) showing a marked deceleration during medium velocity stimuli. (B) Protocol of pseudo-randomized stroking stimuli and rest events.

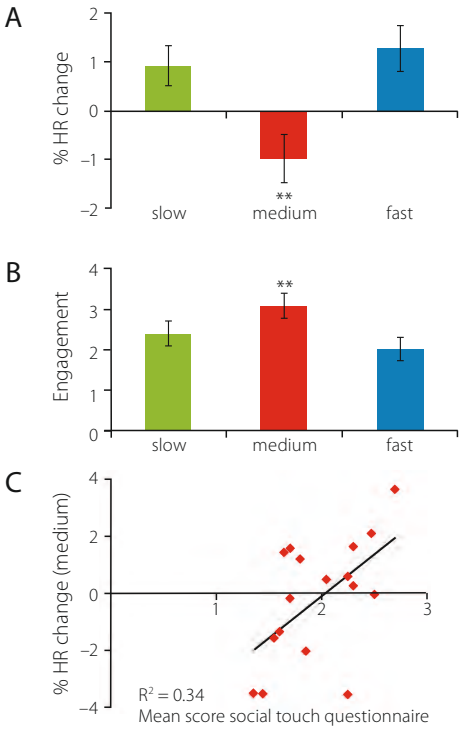

Figure 5.6.1.2 Physiological and behavioural responses to three set velocities of stroking. (A) Mean percentage heart rate (HR) change across conditions. (B) Engagement with the paintbrush as measured by duration of gazes divided by the frequency of shifts. Error bars represent standard error. ** indicate two-tail significance $p < 0.05$. (C) Correlation between mean percentage heart rate change in the medium velocity condition and the individual mean score on the Social Touch Questionnaire. Note that lower scores indicate greater preference for social touch.

might be attributed to differences in the primary caregiver's sensitivity to social touch. Our results provide physiological and behavioural evidence for the view that the sensitivity to pleasant touch emerges early in development and therefore plays an important role in regulating human social interactions.

5.6.2 The neural correlates of perceptually conscious and unconscious processing of facial expressions in human infants

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The detection of others' emotional facial expressions is of critical importance for adaptive social behaviour. In human adults, it has been shown that emotional facial expressions are processed without conscious awareness and that conscious and unconscious emotion processing is related to distinct brain processes (Smith, 2012, Cereb Cortex, 22, 1748–1760). However, it is not known whether this ability of the human brain arises early in ontogeny. In the present event-related brain potential (ERP) study, we examined the brain responses of 7-month-old infants in response to subliminally (50 and 100 ms) and supraliminally (500 ms) presented happy and fearful facial expressions (the selection of stimulus duration is based on infant face visibility thresholds, see Koudier et al., 2013, Science, 340, 376–380). Furthermore, we assessed whether the neural processing is associated with infants' behaviourally expressed perceptual sensitivity, as measured by the Infant Behavioral

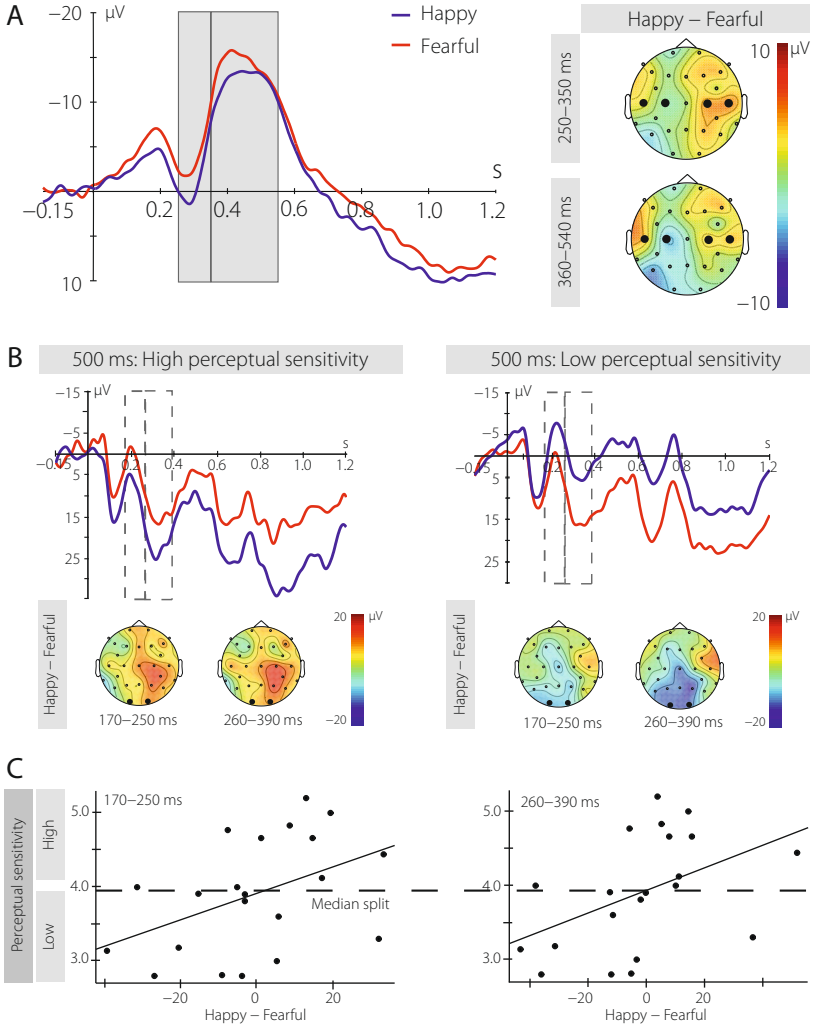

Figure 5.6.2 Event-related brain potentials (ERPs) at centro-temporal and occipital electrodes. (A) The mean ERP response at T7, C3, C4, and T8 is shown; significant differences in the response to happy and fearful faces were observed during the time windows marked in grey. The topographical representations show the distribution of the difference between happy and fearful in the two time windows which reached significance. (B) The ERP response at O1 and O2 for the high and low Perceptual Sensitivity groups are depicted separately, showing the difference between happy and fearful in the 500-ms condition. The topographical representations show the distribution of the difference between happy and fearful in the two time windows of interest, which are marked by dashed lines. (C) The correlation between the difference between happy and fearful (at O1 and O2 in the 500-ms condition) and Perceptual Sensitivity is shown.

Questionnaire (Garstein & Rothbart, 2003, Infant Behavior and Development, 26,1, 64–86). Our results revealed that infants' brain responses (Pb and Nc) over anterior electrodes distinguished between emotions irrespective of stimulus duration, whereas the discrimination between emotions at posterior electrodes (N290 and P400) only occurred when faces were presented supraliminally (above threshold). This suggests that early in development the human brain not only detects unconsciously presented emotional facial expressions, but also that the neural processes associated with conscious and unconscious emotion processing differ in a similar manner as shown in adults. Interestingly, our data further suggest that the brain processing of emotional facial expressions differs across infants depending on their behaviourally shown perceptual sensitivity.

Tuning the developing brain to emotional body expressions

5.6.3

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Reading others' emotional body expressions is an essential social skill. Adults recognize emotions from human body movements alone, without seeing the face or hearing the voice of the other person, as demonstrated by using point-light displays (PLDs) of body expressions (Atkinson et al., 2004, Perception, 33, 717–746). However, it is unclear when in development infants become sensitive to emotions expressed in body motions. We examined the development of processing emotional body expressions by measuring event-related brain potentials (ERPs) in 4- and 8-month-old infants. Infants were presented with video clips of point-light body movements of fearful and happy expressions presented in two orientations, upright and inverted. The analysis revealed a significant main effect of orientation in the time range of 200 to 400 ms at fronto-central electrodes in 8-month-

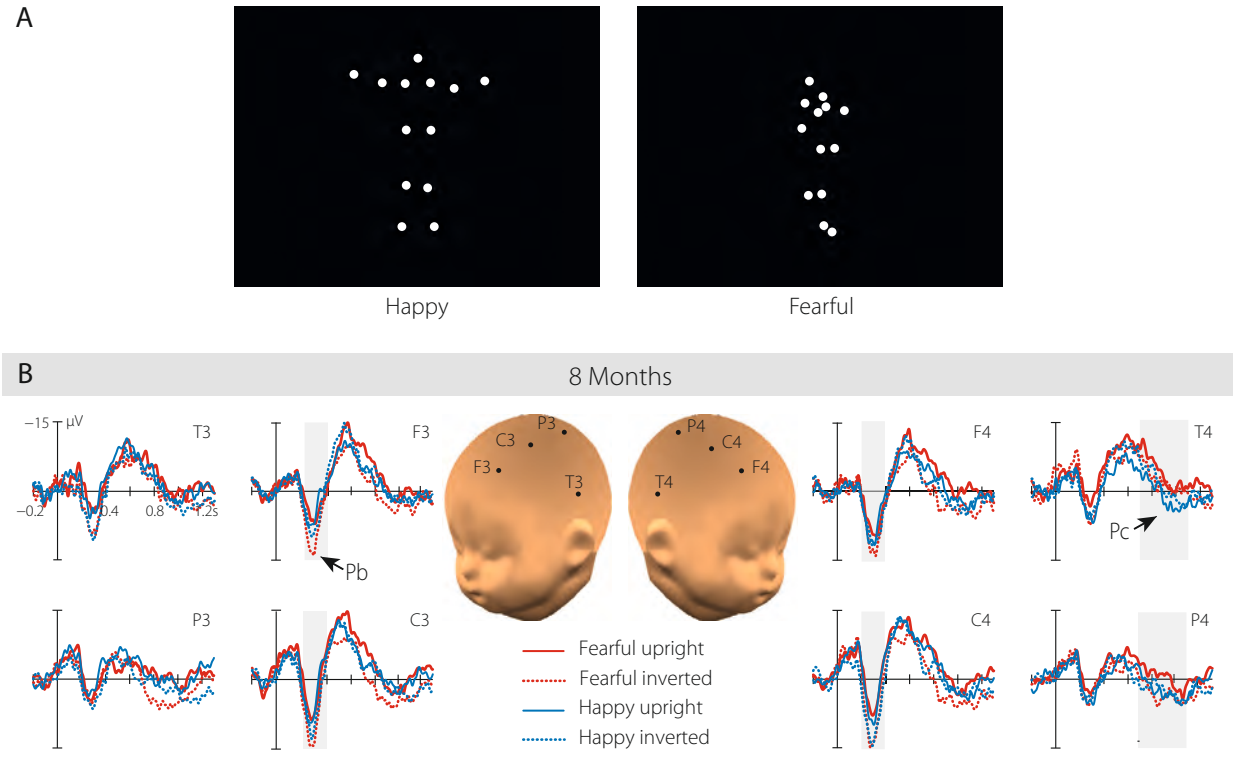

Figure 5.6.3 Stimuli examples and event-related brain potentials (ERPs). (A) This figure provides an example of the PLD stimuli. The figure shows two still frames taken at the maximum of the emotional expression. (B) This figure shows the ERP responses time-locked to the stimulus onset in 8-month-old infants elicited by fearful and happy point-light body expressions. The time windows during which significant differences were observed are marked in grey.

old infants. In the time range of 700 to 1100 ms the analysis showed a significant difference between emotions at right temporo-parietal electrodes. This effect of emotion was (a) specific to the upright orientation, because no differences between emotions were found when the stimuli were inverted, (b) lateralized to the right hemisphere, since no significant differences between emotions was observed in the left hemisphere, and (c) seen only in the older infants, while 4-month-olds showed no differences between emotions in either hemisphere. These findings suggest that the infant brain becomes tuned to configural differences in emotional body expressions between 4 and 8 months of age, and are in line with work demonstrating that infants' perception of facial and vocal expressions of emotion undergoes similar developmental tuning during this period.

5.6.4 Individual differences in infants' neural sensitivity to emotional body expressions: The role of temperament and maternal empathy

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During the first year of life, infants develop the ability to detect and sensitively respond to emotional signals conveyed to them by others (Leppänen & Nelson, 2009, Nat Rev Neurosci, 10, 37–47). Despite the well-mapped developmental emergence of emotion perception in infancy, very little is known about how infants differ in their neural sensitivity to emotional signals and what factors contribute to such differences. In the current study, we examined the role of infant temperament and maternal empathy in the neural processing of happy and fearful emotional body expressions in 8-month-old infants by measuring event-related brain potentials (ERPs). With regard to infant temperament, our results revealed that the tendency to approach novel objects was positively correlated with infants' neural sensitivity to fearful expressions, while fearfulness was negatively correlated with infants' neural sensitivity to fearful expressions. Maternal empathic concern was associated with infants' neural discrimination between happy and fearful expressions, with infants of more empathetically concerned mothers showing greater neural sensitivity to fearful compared to happy expressions. Our results further revealed that indi-

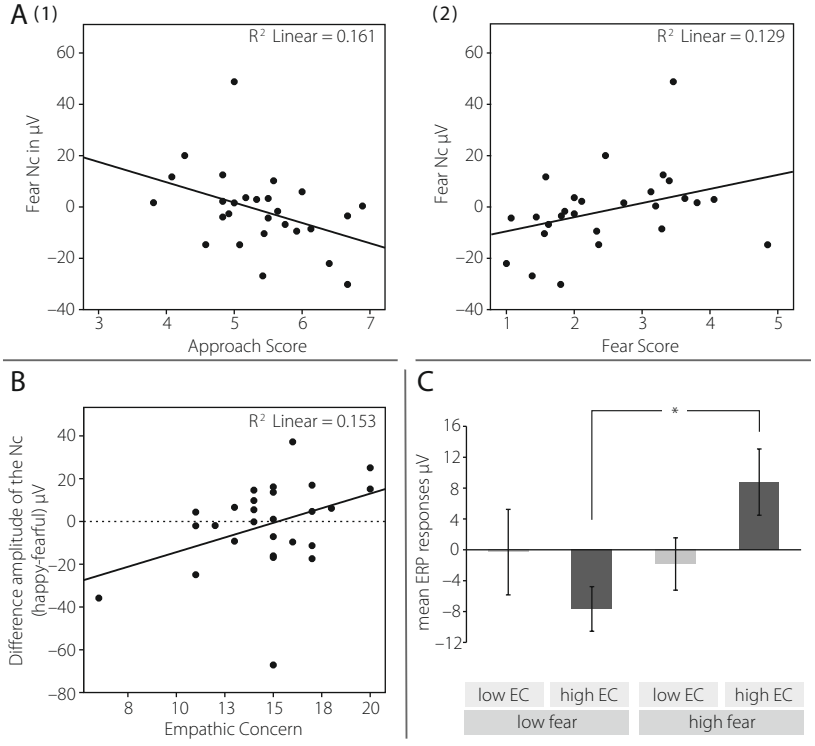

Figure 5.6.4 (A) Infant Temperament: This figure reveals that both differences in 1) infants' tendency to approach novelty and in 2) infants' fearfulness correlated with differences in brain response to fearful body expressions. (B) Maternal Empathy: This figure shows that differences in maternal empathic concern significantly correlated with differences in the brain responses to fearful and happy body expressions. (C) Interactions between infant temperament and maternal empathy: This figure reveals a significant two-way interaction between the between-subjects factors infant fearfulness (high versus low fearfulness) and maternal empathy (high versus low empathic concern) regardless of the emotional body expression watched by the infants.

vidual differences in the neural sensitivity to emotional information are explained by an interaction between infant temperament and maternal empathic concern: Infants in the low fearful group with mothers scoring high in empathic concern showed more sensitive neural responses to emotions, while infants in the high fearful group with mothers scoring high in empathic concern showed less sensitive neural responses to emotions. Taken together, these findings support the notion that the way in which infants respond to emotional signals in the environment is fundamentally linked to their temperament and maternal empathic traits.

Exclusive breastfeeding duration and emotion perception: Evidence for a "positivity bias" in both mothers and infants

5.6.5

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Much research has recognized the importance of maternal behaviour in the early development and programming of the mammalian offspring's brain (Weaver et al., 2004, Nature Neuroscience, 7, 8, 847–854). Exclusive breastfeeding (EBF) plays a particularly prominent role in promoting healthy brain and cognitive development in human children (Mortensen et al., 2002, J Am Med Assoc, 287, 2365–2371). However, surprisingly little is known about the influence of EBF on social and emotional development in infancy. Moreover, whether breastfeeding might also impact maternal emotion perception has yet to be determined.

In the current studies, we examined whether and how the duration of EBF impacts the neural processing of emotional signals by measuring electro-cortical responses (infant negative component (Nc)) to body expressions in 8-month-old infants, and whether EBF duration impacts emotion recognition in mothers in a dynamic morphed faces task. Our results revealed that the sensitivity to emotional expressions differed as a function of the duration of EBF in both infants and mothers. Specifically, infants who had been exclusively breastfed longer showed an increased neural sensitivity to positive (happy) body expressions, while infants who had less EBF experience showed an increased neural sensitivity to negative (fearful) body expressions. Furthermore, we found a specific correlation of reaction time to happy faces and EBF duration in mothers, suggesting that mothers with greater EBF have a heightened sensitivity to happiness. These findings suggest that EBF and the associated psychological and hormonal changes critically shape the way in which infants and mothers respond to emotional signals, providing evidence for a "positivity bias" in which both parties are tuned to the processing of positive, prosocial emotional expressions.

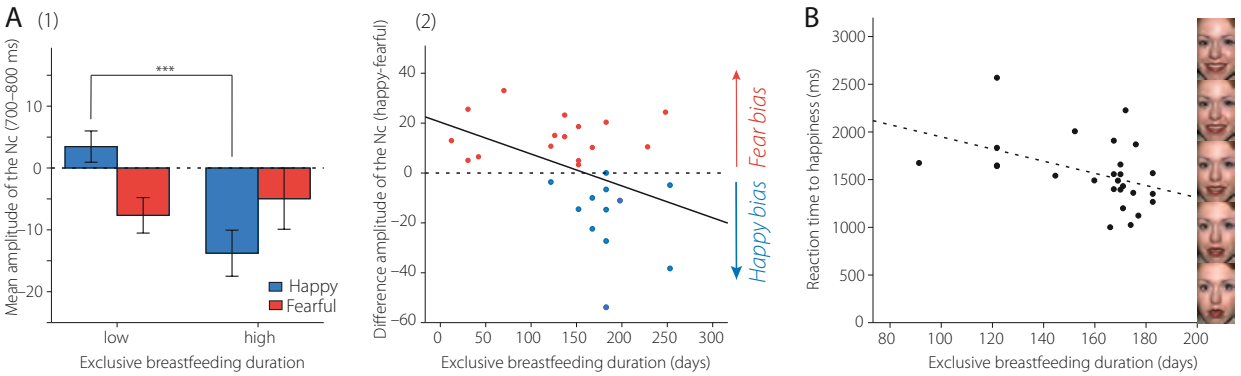

Figure 5.6.5 Perceptual sensitivity to happiness in infants and mothers. (A) Infants with a longer duration of EBF display an increased attentional allocation to happiness as witnessed through the Infant Nc at right fronto-central electrodes. (A1) Interaction of EBF duration and emotion. (A2) A difference score was computed in order to correlate Nc amplitude in response to happy-fearful expressions with duration of EBF. As days of EBF increase, an attentional bias for fear shifts to one for happiness. (B) With increased duration of EBF in mothers, reaction time to dynamic facial morphs of happiness is reduced, suggesting a lower threshold of intensity required to recognize the emotion.

5.6.6 Matching auditory and visual speech cues: The role of social processes in phoneme learning

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Social information seems to play a crucial role during infants' native language attunement (Kuhl et al., 2003, PNAS, 100, 9096–9101), but research on social influences on early language learning is limited. So, the current study asked how the interactive behaviour of mother and infant influences audio-visual phoneme learning. We tested 5.5- to 6-month-olds' ability to categorize native vowels in an audio-visual matching task. In addition, we videotaped mothers freely playing with their infants to assess mothers' speech style (measured by pitch characteristics, the amount of vocal play, and the amount and length of speech utterances) and the interactive behaviour of mother and infant (measured by mutual attention, imitation behaviour, and mothers' sensitivity to infants' interest), and assessed infants' vocal productivity, perceptual sensitivity, and duration of orientation (measured by the IBQ). Results show that infants' sensitivity to the congruency between auditory and visual speech cues is positively correlated with mothers' use of vocal play and imitation, and with infants' vocal productivity and attention allocation. Our results suggest that social processes related to contingent responding, in particular imitation and vocal play that likely play a key role in mimicking infants' babbling, helps infants to associate auditory and visual speech cues. Moreover, infants that babble more and are better able to focus their attention might have a further learning advantage by eliciting more contingent responses from their mothers.

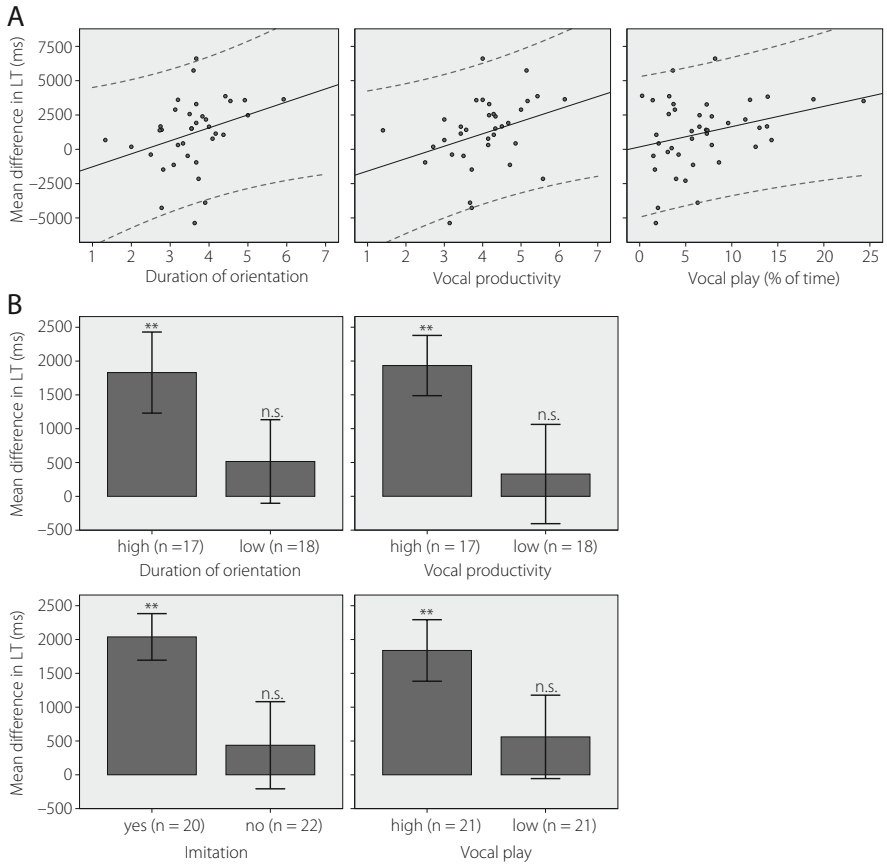

Figure 5.6.6 Mean difference in looking time (LT) to matching vs mismatching trials in the audio-visual matching task. (A) Plotted against infants' duration of orientation and vocal productivity scores, and against the percentage of time that mothers used vocal play during the free play session. The continuous line depicts the linear regression line, the dotted lines indicate the 95% confidence interval. (B) Dependent on infants' duration of orientation and vocal productivity scores and mothers' imitation and vocal play behaviour (groups formed by median split). Error bars indicate +/- 1 SE.

Congresses, Workshops, and Symposia

Grossmann, T. (June). *Social Perception in Infancy: A Neuroscience Perspective*. Symposium, International Conference on Infant Studies, Minneapolis, MN, USA. **2012**

Grossmann, T. (October). *Early Social Development*. Workshop, Internationales Wissenschaftsforum Heidelberg, Germany. **2013**

Degrees

Habilitation Theses

Grossmann, T. *Developing social minds: A neuroscience perspective*. University of Heidelberg, Germany. **2012**

Appointments

Grossmann, T. (2012). *Privatdozent*. Department of Psychology, University of Heidelberg, Germany. **2012**

Grossmann, T. (2013). *Assistant Professor in Developmental Psychology*. Department of Psychology, University of Virginia, VA, USA. **2013**

Awards

Grossmann, T. *Early Career Award*. International Society on Infant Studies (ISIS), USA. **2012**

Grossmann, T. *Visiting Scholarship*. Institute for Advanced Studies, Israel. **2013**

Publications

Book Chapters

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5.7 Otto Hahn Group "The Neural Bases of Intonation in Speech"

Traditionally taken as a conventionally coded string of symbols transferring information between sender and receiver (Bühler, 1934/1999, Stuttgart: G. Fischer), language is increasingly recognized as an intentional action (Grice, 1957, Philos Rev, 66, 377–388) that communicates—advertently or inadvertently—the speaker's inner motivations and goals and, thus, modifies the behaviour of the interlocutor (Searle, 1969, Cambridge: Cambridge University Press). Effective social interaction requires the understanding of these communicative functions of speech, i.e. the so-called speech acts, behind the coded meaning. The Otto Hahn Group focuses on prosody, for example, the soothing, warning, or blaming sound of the speaker's voice, as one cue that often conveys the communicative function of an utterance. The key question of the group is: Which neural machinery allows humans to use and understand these prosodic cues during language comprehension? The principal research strategy guiding the group is first to identify—and interrogate in laboratory tasks—the basic acoustic properties of vocal tone that qualify a set of communicative acts derived from speech act theory (Searle, 1969), and then to systematically use these acoustic cues to specify the neurocognitive architecture involved when humans comprehend the function and meaning conveyed by speech prosody. At a later stage, the group's work will turn towards the exploration of individual differences (e.g. musicality, empathy) and situational factors (e.g. social dominance of the speaker) that may shape the function of the network. The methods portfolio includes behavioural, neuroimaging, and brain stimulation techniques in healthy and patient populations. The following projects were conducted during the post-doctoral phase of the Otto Hahn Award spent in the Voice Neurocognition Laboratory at the University of Glasgow (UK), preceding and preparing the group's establishment in July 2013. The three showcased projects address the communicative function of pitch modulations in speech and argue for a dorsal auditory-to-(pre)motor pathway as neural basis of a putative motor simulation mechanism that aids the understanding of prosodic meaning in speech.

5.7.1 Understanding meaning in prosodic pitch contour

Sammler, D.[1,2], Bestelmeyer, P. E. G.[1,3], & Belin, P.[1,4,5]

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[3] School of Psychology, Bangor University, Gwynnedd, United Kingdom
[4] BRAMS, Université de Montréal & McGill University, Montréal, QC, Canada
[5] Institut des Neurosciences de La Timone, CNRS & Aix-Marseille Université, Marseille, France

Pitch contour is one aspect of speech prosody that determines the communicative function and meaning of an utterance (Kohler, 1991, In K. J. Kohler (Ed.), Studies in German Intonation, AIPUK 25, pp. 295–360, Kiel:IPDS; Pierrehumbert & Hirschberg, 1990, In P. R. Cohen, J. Morgan, and M. E. Pollack (Eds.), Plans and Intentions in Communication and Discourse (SDF Benchmark Series in Computational Linguistics), pp. 271–311, MIT Press). In the simplest case, the falling or clearly rising vocal pitch at the end of a sentence signals that the speaker either names an object or rather asks for it (i.e. basic speech acts according to Searle, 1969). The present fMRI study assessed the neural mechanisms that allow us to understand prosodic pitch contour as statement (naming) or question (asking). Participants were instructed to categorize the prosodic meaning (statement or question) of single-word utterances that varied along a pitch contour continuum from falling to rising (experimental task) obtained through auditory morphing (Kawahara, 2006, Acoust Sci Technol, 27, 349–353). In an analogous control task, participants categorized the word-initial consonant of the same utterances that varied along a phoneme continuum from /bear/ to /pear/ (Fig. 5.7.1.1). Categorization of prosodic meaning induced stronger activity than the control task in the posterior STS (pSTS), laryngeal premotor cortex (PMC), and dorsal inferior frontal gyrus (IFG) of the right hemisphere. Diffusion-weighted imaging suggested the arcuate fascicle (AF) as plausible anatomical connection between these brain areas (Fig. 5.7.1.2). The pSTS has been implicated in the processing of non- and paralinguistic meaning, e.g. in music (Steinbeis, & Koelsch, 2008, PLoS One, 3(5), e2226) and emotional prosody (Grandjean, Sander, Pourtois, Schwartz, Seghier, et al., 2005, Nat Neurosci, 8, 145–146) and the recognition of a speaker's communicative intention (Noordzij, Newman-Norlund, de Ruiter, Hagoort, Levinson, & Toni, 2009, Front Hum Neurosci, 3:14). Interestingly, the activation of laryngeal PMC and IFG fits with a motor simulation mechanism, i.e. the conversion of the perceived falling or rising pitch contour into simulated laryngeal gestures. Together with the right AF, the observed set of brain areas may represent the neural basis for an auditory-to-motor mapping of pitch patterns that aids the recognition of the speaker's vocal action and thus the comprehension of prosodic meaning.

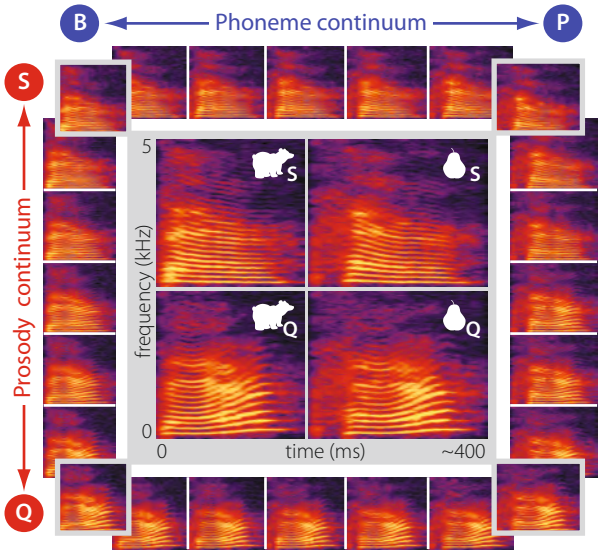

Figure 5.7.1.1 The words "bear" and "pear" spoken as statement (S) or question (Q) (central panel) were used as starting points for auditory morphing to construct stimulus continua along 2 dimensions: prosody (vertical) and word-initial phoneme (horizontal).

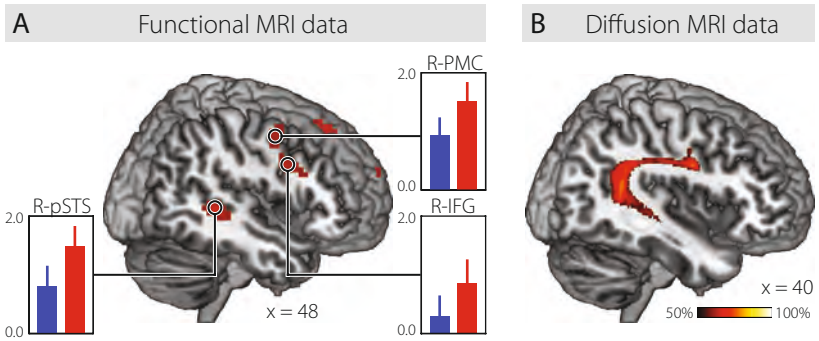

Figure 5.7.1.2 (A) Categorization of prosody (red) compared to word-initial phoneme (blue) evoked stronger brain activity in right fronto-temporal brain areas. (B) Visualization of the dorsal pathway connecting these areas. The heat map indicates the percentage of participants (minimum 50%) who showed fibres in the respective voxels.

Prosody perception in the right laryngeal premotor cortex: A TMS study

5.7.2

Sammler, D.[1,2], Belin, P.[1,3,4], & Grosbras, M.[1]

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[4] Institut des Neurosciences de La Timone, CNRS & Aix-Marseille Université, Marseille, France

Prosody perception is known to typically involve superior temporal and inferior frontal brain areas (Meyer, Steinhauer, Alter, Friederici, & von Cramon, 2004, Brain Lang, 89, 277–289; Schirmer; & Kotz, 2006, Trends Cogn Sci, 10, 24–30). Interestingly, a recent fMRI study carried out by our group (5.7.1) found additional involvement of the right laryngeal premotor cortex (PMC) during a prosodic categorization task (statement vs question). This activation was interpreted as reflecting simulated laryngeal movements that may feed back into temporal areas, tuning-up prosodic comprehension. The present repetitive transcranial magnetic stimulation (rTMS) study tested if the right laryngeal PMC (as part of a larger motor simulation system most likely also including IFG, pSTS, and the arcuate fascicle) indeed augments prosodic comprehension. We assessed participants' performance in categorizing single-word utterances in terms of prosody (statement vs question; experimental task) or word-initial consonant (/bear/ vs /pear/; control task) after application of 15 minutes of low frequency (1 Hz) rTMS over right laryngeal PMC, compared to their performance after 15 minutes of sham stimulation. The TMS-induced temporary downregulation of the right laryngeal PMC led to a performance decrease that was specific to prosodic comprehension, while leaving phoneme categorization unaffected. This result suggests a right (pre)motor contribution to vocal pitch perception in speech, most likely via simulated laryngeal gestures to identify rising or falling pitch contours. Overall, the present study lends further support for motor simulation as a neural mechanism in aiding the understanding of prosodic meaning in speech.

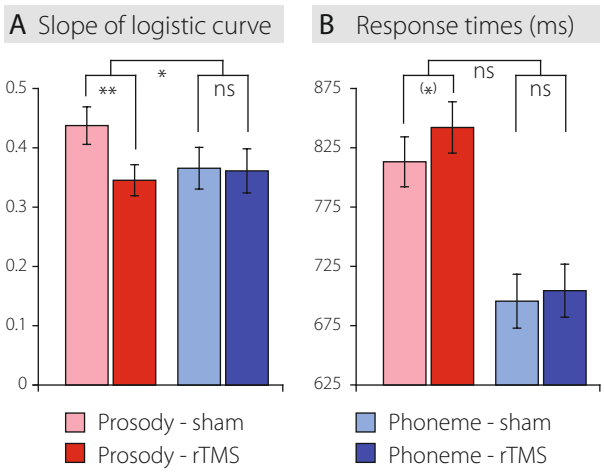

Figure 5.7.2 In the prosodic categorization task (statement vs question), the slope of the logistic curve (A) became shallower and response times (B) longer after rTMS (compared to sham stimulation) over right laryngeal premotor cortex, indicating a temporary reduction of prosodic comprehension. No such effect was observed in the control task to categorize the word-initial phoneme (/b/ vs /p/; for a description of the stimuli, see Fig. 5.7.1.1).

5.7.3 The role of the right dorsal pathways in prosody processing

Sammler, D.[1,2], Cunitz, K.[1], Gierhan, S. M. E.[1,3], Anwander, A.[1], Adermann, J.[4], Meixensberger , J.[4], & Friederici, A. D.[1,3]

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[4] Department of Neurosurgery, University Hospital Leipzig, Germany

A growing number of studies focus on the functional roles of white matter fibre bundles such as the arcuate (AF) and superior longitudinal fascicle (SLF) connecting fronto-temporal "language-areas" in the left hemisphere. While the roles of these pathways gain increasing clarity (Friederici, & Gierhan, 2013), the roles of the homologue right-hemispheric tracts have received less attention (but see study 5.7.1). The present case study lends first support for the functional role of the right dorsal pathways in processing prosody (pitch) in speech. Oedemas infiltrating white matter tracts can cause functional deficits without damaging the fibre bundle, which allows for a complete reversibility of dysfunctions after oedema reabsorption (Bizzi, Nava, Ferre, Castelli, Aquino, Ciaraffa, et al., 2012, Cortex, 48, 255–272). We tested prosodic perception (experimental task) and auditory syntactic comprehension (control task), pre- and postsurgically (-24 and +135 days), in one male patient (43 years, right-handed) with a right parietal peritumoural vasogenic oedema infiltrating the dorsal pathways (Fig. 5.7.3A). The prosodic task (thought to involve the right dorsal pathways) required the detection of incongruent prosodic pitch drops signalling closure at non phrase-final sentence positions (Eckstein, & Friederici, 2006, J Cogn Neurosci, 18, 1696-1711). The syntactic task (known to involve the intact left dorsal pathway) tested the comprehension of sentences with canonical and non-canonical word order (Gierhan, 2013). Compared to 10 matched healthy controls, the patient showed presurgical deficits and postsurgical recovery in detecting the prosodic incongruities, while his performance in syntactic language comprehension was unimpaired in both test sessions (Fig. 5.7.3B). These data suggest a functional role of the right dorsal pathways in prosody (pitch) in speech, in line with study 5.7.1.

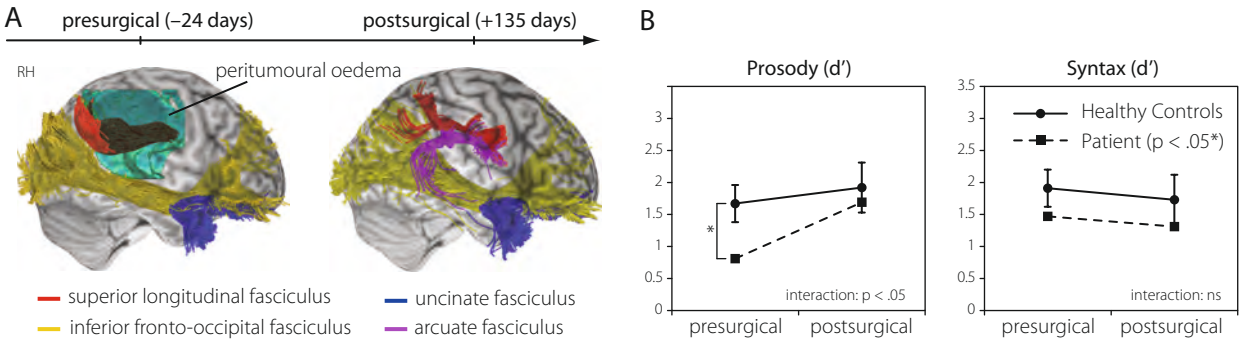

Figure 5.7.3 (A) Presurgically, the peritumoural oedema (green) invaded the dorsal pathway but was entirely reabsorbed in the postsurgical session after tumour resection. Note that the arcuate fascicle (pink) was not "absent" before surgery but tractography was hindered due to low FA values in the oedema. (B) The patient showed presurgical deficits and postsurgical recovery in the prosody task compared to controls (left), but performed equally well in both sessions in the syntax task (right).

Congresses, Workshops, and Symposia

2013

Sammler, D. (March). *CCNi workshop on Diffusion-weighted imaging*. Centre for Cognitive Neuroimaging (CCNi) & Institute of Neuroscience and Psychology (INP), University of Glasgow, United Kingdom.

Publications

Articles

Merrill, J., Sammler, D., Bangert, M., Goldhahn, D., Lohmann, G., Turner, R., & Friederici, A. D. (2012). Perception of words and pitch patterns in song and speech. *Frontiers in Psychology, 3*:76. doi:10.3389/fpsyg.2012.00076.

Sammler, D., Koelsch, S., Ball, T., Brandt, A., Grigutsch, M., Huppertz, H.-J., Knösche, T. R., Wellmer, J., Widman, G., Elger, C. E., Friederici, A. D., & Schulze-Bonhage, A. (2013). Co-localizing linguistic and musical syntax with intracranial EEG. *NeuroImage, 64*, 134–146.

Sammler, D., Novembre, G., Koelsch, S., & Keller, P. E. (2013). Syntax in a pianist's hand: ERP signatures of "embodied" syntax processing in music. *Cortex, 49*(5), 1325–1339.

6 Methods & Development Units

6.1 Methods and Development Unit "Nuclear Magnetic Resonance"

Head

Professor Dr Harald E. Möller

Senior Researchers and PostDocs

Dr Ilona Henseler (*)
Dr Štefan Holiga (39)
Anna Kosatschek
Dr Christian Labadie (37)
Dr Leonie Lampe
Dr Jöran Lepsien
Dr Toralf Mildner
PD Dr Karsten Müller
Dr habil. André Pampel
Daniel-Paolo Streitbürger
Dr Chao Xu (37) (*)

Guest Researchers

Dr Thies Jochimsen (30) (*)
Samer Samalekh (38)

Secretarial and Technical Staff

Nancy Muschall
Reiner Hertwig
Mandy Jochemko
Anke Kummer
Roland Müller
Torsten Schlumm
Manfred Weder (*)
Simone Wipper

PhD Students

Maria Guidi (8)
Dr Štefan Holiga (19) (PhD since 09/2013)
Laurentius Huber
Kathrin Lorenz (19, 30)
Henrik Marschner (37)
Miguel Martínez Maestro (8)
Riccardo Metere (8)
Manoj Shrestha
Daniel-Paolo Streitbürger
Dr Sabrina Trapp (**) (PhD since 12/2012)

Former PhD Students

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Daniel-Paolo Streitbürger	PostDoc in this unit
Dr Sabrina Trapp	Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Visiting Research Fellows

PD Dr Robert Jech	Clinic for Neurology, Charles University Prague, Czech Republic

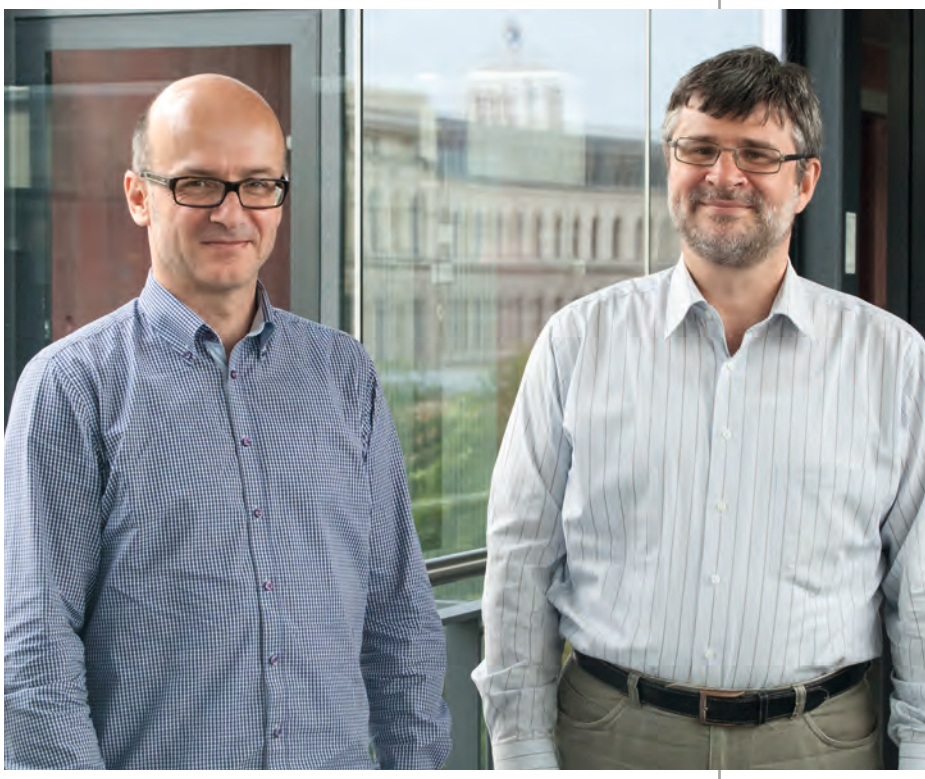
(7) Elekta Instruments, Inc. (industry)
(8) European Union 7th Framework Programme
(13) German Federation of Industrial Research Associations (AiF)
(14) German Research Foundation (DFG)
(19) IMPRS NeuroCom, Leipzig, Germany
(21) Leipzig University of Applied Sciences (HTWK), Germany(22) Leipzig Research Center for Civilization Diseases (LIFE) funded by European Union and State of Saxony
(30) University of Leipzig, Germany
(37) Helmholtz Association, Germany
(38) The German-American Fulbright Program
(39) Parkinson's Disease Foundation (PDF), USA
(45) La Fundación Caja Madrid, Spain

(*) Left the institute during 2012/2013
(**) Left the unit during 2012/2013

6.2 Methods and Development Unit "MEG and EEG – Cortical Networks and Cognitive Functions"

Heads

Dr habil. Thomas R. Knösche
Dr Burkhard Maess



PhD Students

Jae-Hyun Cho (14)
David Moreno-Dominguez (45) (**)
Mirco Fuchs (21)
Seung-Goo Kim (19)
Dr Fahimeh Mamashli (19) (*)
(PhD since 07/2013)
Dominic Portain (14)
Till Riffert (7) (*)
Jan Schreiber (**)
Manh Nguyen Trong (8, 13) (*)
Peng Wang (19)

Technical Staff

Ralph Schurade (13, 30)
Hermann Sonntag
Yvonne Wolff

Visiting Research Fellows

Kentaro Ono (*)

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Dr Fahimeh Mamashli	Harvard Medical School, Boston, MA, USA
Till Riffert	Zalando GmbH, Berlin, Germany
Jan Schreiber	Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
Manh Nguyen Trong	GAMPT mbH – Company for Applied Medical Physics and Technique, Merseburg, Germany

Former Visiting Research Fellows

Kentaro Ono	Career-Path Promotion Unit for Young Scientists, Kyoto University, Japan

6.1
Methods and Development Unit "Nuclear Magnetic Resonance"

Imaging physics and image-processing have continued to constitute the backbone of our research. As in previous years, these fields have been complemented by selected applications that allow the study of specific biomedical questions. Currently, new international collaborations are being initiated in the EU-funded Marie-Curie networks 'TRANSACT' and 'HiMR'.

Methodological work has mutually benefited from joint projects with the Department of Neurophysics—most notably in hardware development and investigations of cerebral blood supply. Of common interest is the use of printed circuit boards for the fabrication of radiofrequency coils. An example is a transceiver coil for post-mortem animal brain that allowed stable operation during days of continuous scanning at high duty cycle (6.1.1). With regard to pulse-sequence developments, previously introduced strategies employing centre-out echo-planar trajectories were expanded to cylindrical spatial encoding for 3D imaging with input from colleagues at Duke University (6.1.2). Arterial spin labelling has been a topic of research in our group for some time now. Recent progress with this includes the refinement of the MATISSE experiment to map arterial transit times (6.1.5). Collaborations with the University of Sheffield and the MPI for Biological Cybernetics in Tübingen were initiated to study blood volume changes in the animal brain.

A cooperation with Charles University in Prague on the application of functional imaging to reliably assess motor symptoms in Parkinson's disease turned out to be particularly fruitful. Concepts to control for movement performance and to integrate clinical scores into task-based studies were introduced (6.1.3), while resting-state experiments yielded information on connectivity related to different treatments (6.1.4).

Substantial effort has been directed towards quantitative structural imaging, supported by the Helmholtz Alliance 'ICEMED'. Work related to T_1 relaxographic imaging was expanded by an approach from computational chemistry in a joint effort with Lyon. Results indicate reduced mobility of water in a hydration layer on the surface of myelin membranes (6.1.7). Limitations in magnetization-transfer imaging are due to time-consuming experiments as well as computationally demanding data analysis. Simultaneous accelerations in both image acquisition and analysis were achieved by using artificial neural networks for parameter mapping (6.1.6). Finally, a thorough evaluation of voxel-based morphometry with support from Lausanne revealed significant impact upon changing the RF coil, pulse sequence, and image resolution, which is likely to introduce systematic bias (6.1.8).

A transceiver RF coil based on PCB design for imaging tissue specimen

6.1.1

Müller, R.[1], Pampel, A.[1], Mildner, T.[1], Marschner, H.[1], & Möller, H. E.[1]

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

With printed circuit boards (PCBs), an inexpensive and reproducible design of radiofrequency (RF) coils is achieved with sub-millimetre precision. 3D structures are obtained by appropriate arrangement of standard 2D boards. This principle was used to build an efficient quadrature transceiver coil for imaging tissue specimen on a human 3T scanner. It consists of two perpendicular Helmholtz pairs with venting slots and openings for air circulation. Each loop was pre-tuned by fixed capacitors, connected in series for balanced feeding. Additional trimmer capacitors and the feeding coaxial cable were placed exactly midway between the loops. Inductive coupling between the perpendicular Helmholtz pairs can be neglected. Differential-mode sheath waves were aperiodically suppressed by adding a few resistors between the shields of the two coaxial cables. The unloaded *Q* was 350 with isolation of both coil pairs by > 20 dB. No detuning was observed during continuous scanning for several days. The temperature in an agar phantom increased by 6 K after 1 hour of RF heating (3640° pulses, *TR* 30 ms), compared to 16 K obtained with a linearly polarized coil. Tissue samples were embedded in 50-mm acrylic spheres, filled with Fomblin.

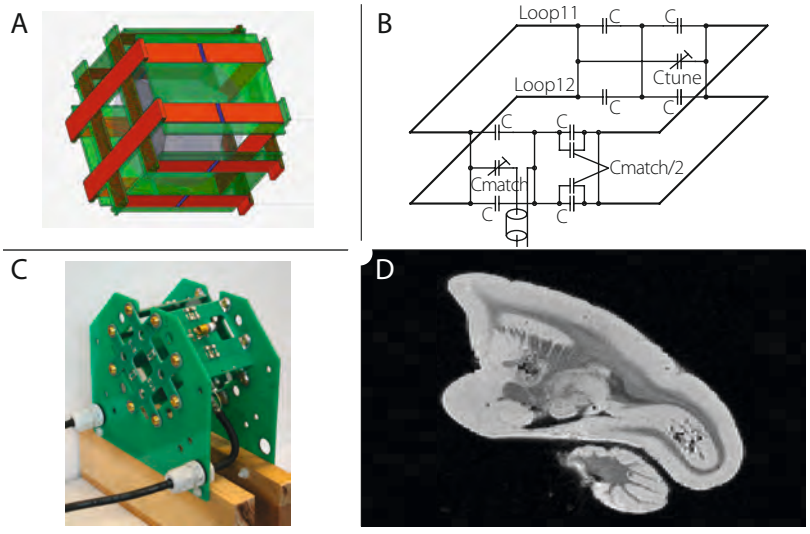

Figure 6.1.1 (A) Simplified HFSS (Ansys, Pittsburgh, PA) coil model used in simulations showing quadric copper loops (66 × 66 mm^2; 10 mm wide, 35 µm thick) in red, FR4 PCB basic material in green, ports in blue, and a homogeneous load in grey colour. (B) Matching and tuning circuits of one Helmholtz pair. (C) Final coil made from three types of boards; removable brass screws permit access to the interior space. (D) Image of a post-mortem marmoset brain (3D FLASH; α 60°, *TE/TR* 30/300 ms, 200 µm isotropic voxels).

3D centre-out echo-planar imaging with cylindrical encoding

6.1.2

Shrestha, M.[1], Mildner, T.[1], Schlumm, T.[1], Robertson, S. H.[2], & Möller, H. E.[1]

[1] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2] Center for In Vivo Microscopy, Duke University Medical Center, Durham, NC, USA

The recently introduced DEPICTING technique allows rapid acquisition of high-resolution 2D images at ultra-short echo time (*TE*) by double-shot *k*-space sampling along centre-out trajectories. This method was adapted to obtain a 3D centre-out EPI variant with cylindrical encoding offering the same intrinsic advantages, that is, ultra-short *TE* independent of the matrix size. Phase correction, Cartesian regridding and distortion correction are three major steps of the image reconstruction procedure. A single template scan without phase blips is used for phase correction of all spokes based on a linear fit of the phase differences of adjacent lines in hybrid space. For correction of geometrical distortions, a separate B_0 field-map scan (3D multi-echo FLASH) is acquired. Multi-frequency gridding of the data is then performed separately for every off-resonance frequency provided by the field map, and the specific frequency index in every voxel is selected for Fourier transform along the

k_x- and k_y-axes. Conventional Kaiser-Bessel gridding was implemented to interpolate Cartesian grid points. The algorithm is based on the original work of O'Sullivan with an in-house C++ implementation. Potential applications include time-of-flight angiography and 3D cine MRI using dynamically updated *k*-space trajectories.

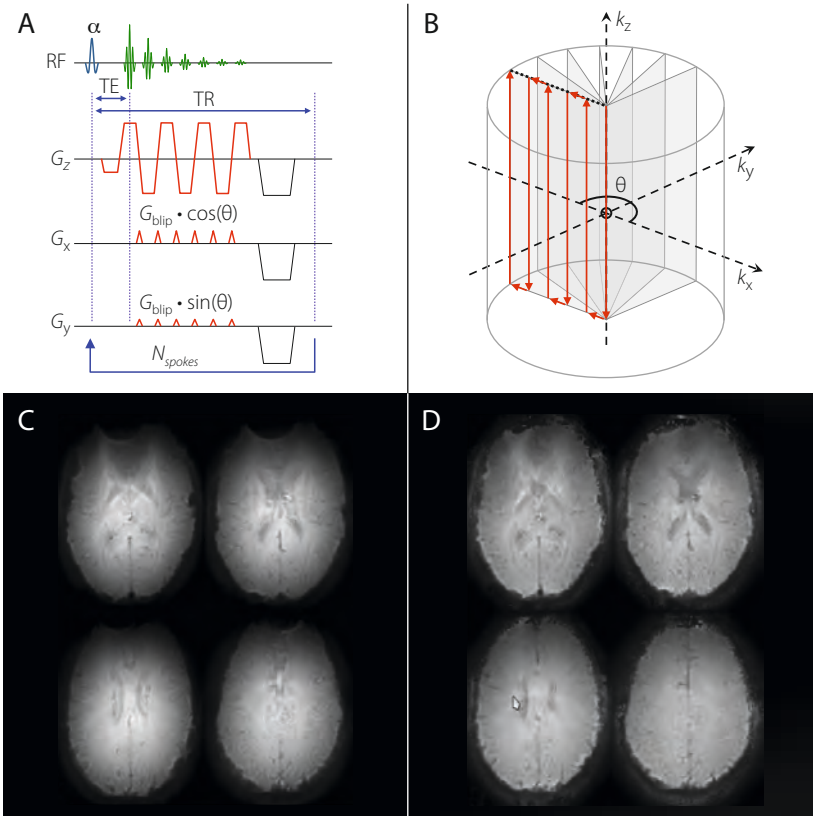

Figure 6.1.2 Schematic pulse sequence diagram (A), sampling trajectory of a single spoke in the cylinder of acquired *k*-space data (B), and phase-corrected images recorded from a healthy volunteer (α 24°, *TE/TR* 2.8/95 ms, 1.5-mm isotropic voxels) without (C) and with (D) multi-frequency distortion correction.

6.1.3 Personalising fMRI protocols for studying neural substrates of motor deficits in Parkinson's disease

Holiga, Š.[1], Möller, H. E.[1], Sieger, T.[2], Schroeter, M. L.[1,3], Jech, R.[2], & Mueller, K.[1]

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

Functional magnetic resonance imaging (fMRI) employing motor paradigms has been extensively used to assess the pathological state of Parkinson's disease (PD) motor circuitry. Interestingly, the results appear to be conflicting. We hypothesize that failure to consider the substantial disease heterogeneity might cause discrepant results in population-based studies or even invalidate interpretations. Accordingly, we propose means to account for both intra- and inter-subject variability. At the intra-individual level, two approaches of hemodynamic modelling of a simple finger-tapping task (blocked design) were compared, either by a boxcar function or by considering actual movement performance recorded by an MRI-compatible sensory glove. Notably, novel models incorporating patients' movement significantly outperformed conventional modelling in sensitivity to detect brain activity. We thus advocate controlling for performance during task-based motor experiments. Further, clinical measures of PD were assessed at the inter-individual level by incorporating Unified PD rating scale (UPDRS) scores in the group fMRI models. A strong relationship between patients' fMRI response and specific UPDRS components was discovered; calling for consideration of such measures in fMRI studies either as correlates or confounding factors.

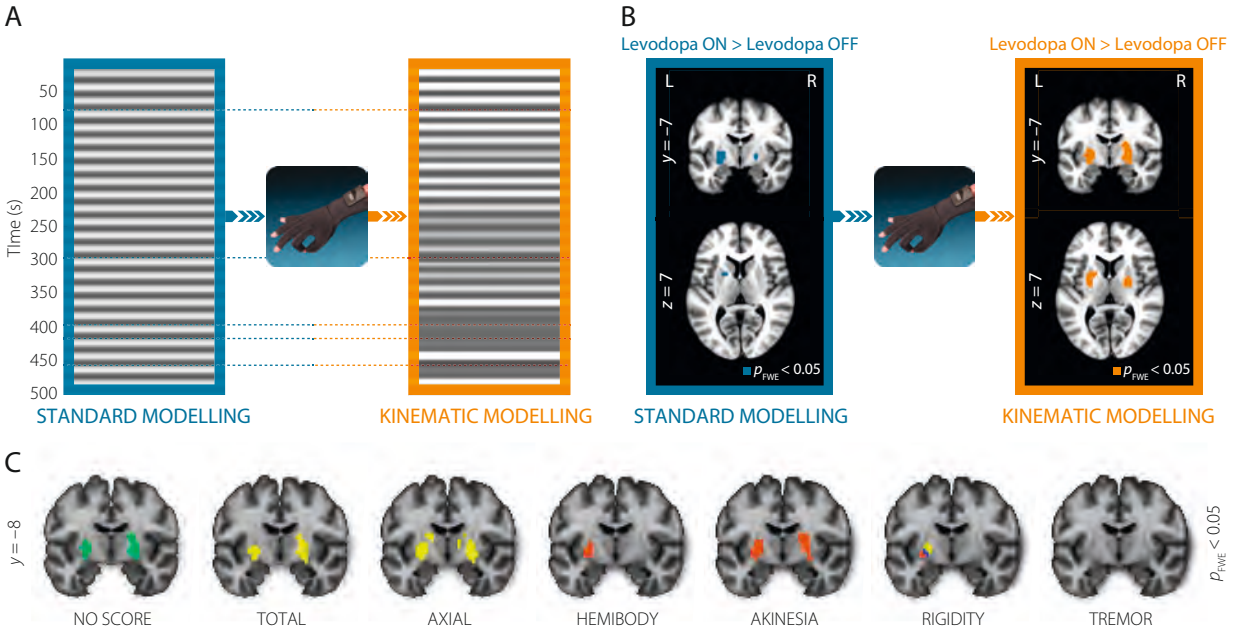

Figure 6.1.3 (A) Comparison of a conventional and personalised kinematic model utilising glove recordings. Amplitude and temporal deviations from an idealised paradigm (classified as errors in standard model) are clearly visible in the latter model. (B) Comparison of repeated-sessions' group response to levodopa treatment calculated using conventional and kinematic modelling. (C) Effect of UPDRS sub-scores in group response to levodopa. Green colour shows conventional results without score, while yellow and red colours show variable results for specific scores used for correlations or confounds in factorial model, respectively, accounting for a large amount of heterogeneity in the population sample.

6.1.4

Connectivity changes in Parkinson's disease when switching treatment from levodopa to deep brain stimulation

Mueller, K.[1], Holiga, Š.[1], Möller, H. E.[1], Schroeter, M. L.[1,2], Vymazal, J.[3], Růžička, F.[4,5], Urgošík, D.[4,5], Růžička, E.[4], & Jech, R.[4]

[1] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2] Clinic for Cognitive Neurology, University Hospital Leipzig, Germany
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[4] Department of Neurology and Centre of Clinical Neuroscience, Charles University in Prague, Czech Republic
[5] Department of Stereotactic and Radioneurosurgery, Na Homolce Hospital, Prague, Czech Republic

Levodopa medication and deep brain stimulation (DBS) are favoured methods for treating motor symptoms of Parkinson's disease (PD). While both approaches lead to improved clinical symptoms, little is known about changes in brain function upon switching treatment. We used resting-state functional magnetic resonance imaging (fMRI) at 1.5 T to study functional connectivity in patients before and after bilateral implantation of DBS electrodes in the subthalamic nucleus (STN). Examinations were performed in the first session (i.e. without DBS) after oral administration of 250/25 mg levodopa/carbidopa. In the second session, 1–3 days after surgery, scanning was performed during DBS from an external stimulator outside the magnet bore after levodopa effects had worn off. The results demonstrate a differential effect of both treatments on functional-connectivity patterns in motor networks. An increased eigenvector centrality (EC), used as a measure of 'connectedness', was observed in premotor cortex (PMC) contralateral to the site of STN stimulation. This increase was accompanied by connectivity alterations between PMC and cerebellar regions. While these observations contribute to understanding different treatment mechanisms, they still reflect all aspects from treatment switching including effects due to lesions from electrode implantation.

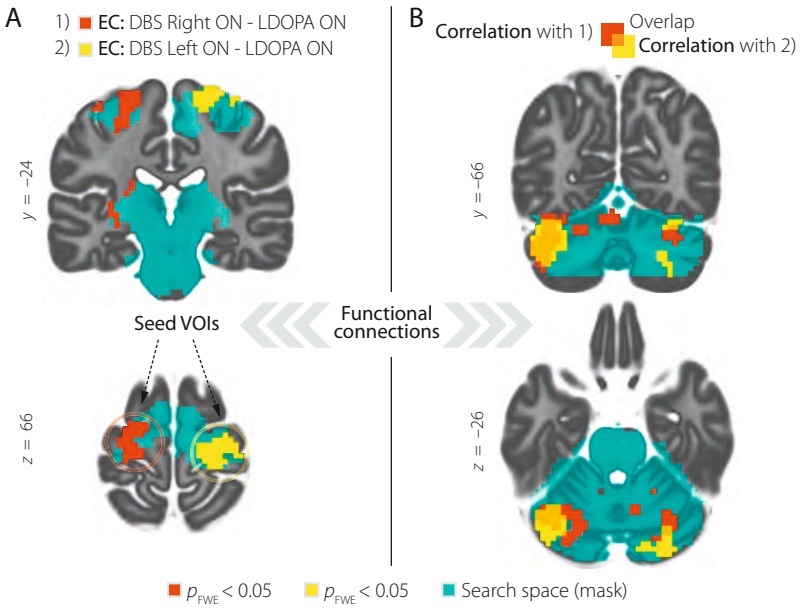

Figure 6.1.4 Differential effects of levodopa medication and DBS on functional connectivity in motor networks affected by PD (13 PD patients; Hoehn-Yahr stages II-III, 11 males, age 52.8 ± 6.9 years, first signs of PD with 40.2 ± 6.0 years, levodopa treatment for 9.5 ± 3.1 years). (A) Significant differences of eigenvector centrality (EC) when comparing levodopa treatment and unilateral DBS of the left (yellow colour) and right subthalamic nucleus (red colour). (B) The increased EC in the left and right premotor cortex is due to an increased connectivity with cerebellar areas, predominantly in the left hemisphere.

6.1.5 The contribution of large-calibre vessels in arterial transit time mapping

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[2] Faculty of Physics and Earth Sciences, University of Leipzig, Germany

Recently, we introduced the MATISSE technique for the model-independent quantification of arterial transit times, δ_a. It directly measures the shift and signal change ($\Delta S/S$) of an amplitude-modulated arterial-spin labelling time series between a label position in a brain-feeding artery (e.g. at the neck) and the imaging slice. Further information on the contribution of large-calibre vessels was obtained from applying flow-weighting (FW) gradients. Areas of short δ_a and elevated $\Delta S/S$ were observed in the insular cortex due to large-calibre branches of the medial cerebral artery. In the posterior brain, δ_a was elevated compared to anterior territories, which agrees well with previous work. Areas with highest δ_a values represent borders between perfusion territories and are of clinical relevance as they are prone to "watershed" infarctions. Upon application of FW, prominent hot spots in the $\Delta S/S$ map almost completely vanished, and δ_a increased on average by about 600 ms. This was evident in the corresponding time courses by a shift to the right and a roughly halved amplitude. Another observation was a slight asymmetry of the modulation at the position of the imaging slice. This is likely due to the combined contribution from several arterial trajectories in the same voxel causing a spread of δ_a.

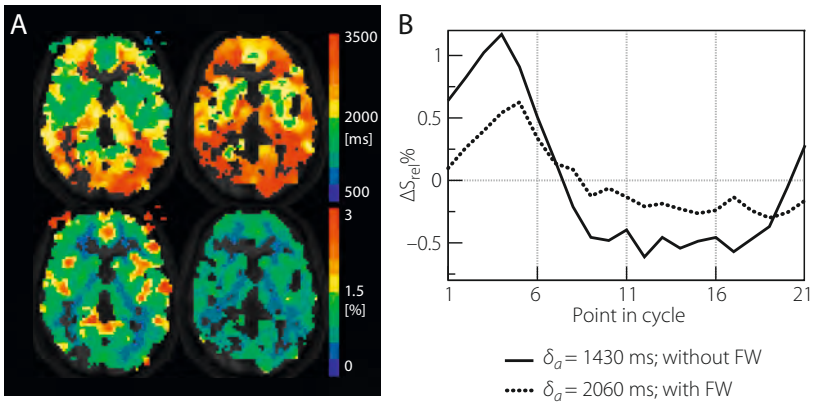

Figure 6.1.5 (A) Colour-coded axial maps of δ_a (top) and $\Delta S/S$ (bottom) recorded without (left) and with (right) FW (*b*-factor of 4 s/mm²). (B) Averaged signal time courses obtained in a region close to the putamen with (solid line) and without (dashed line) FW.

Estimation of magnetization-transfer parameters from sparsely sampled *in vivo* data using artificial neural networks

6.1.6

Marschner, H.[1], Pampel, A.[1], Neumann, J.[1,2], & Möller, H. E.[1]

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Information on macromolecules, which are not directly visible using magnetic resonance imaging, can be obtained from quantitative magnetization transfer (qMT) experiments. Quantification is typically based on the binary spin-bath model which considers a liquid (water) pool and a semi-solid (macromolecular) pool with pool sizes, relaxation times, and exchange rate constants as free fitting parameters. A drawback is that the necessity for multipoint data acquisition, with variation of offset frequencies and radiofrequency (RF) power in pulsed saturation of the semi-solid pool and for multi-parameter fitting, is time consuming. For acceleration, artificial neural networks (ANNs) were trained to estimate parameter maps from sparsely sampled data. An iterative reduction and optimization method for selecting the sampling points was applied to analyse the effect of a reduced sampling space on the obtained precision. The ANNs were trained on data from three healthy volunteers and then tested on data from four other subjects. The analysis showed that only five sampling points were sufficient for most parameters without degradation of the quality. Thus, scanning could be accelerated by a factor of two or more. An additional benefit was the reduction in computation time to less than 2 s per slice and parameter.

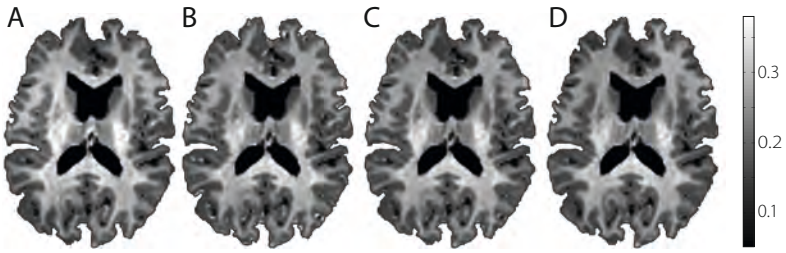

Figure 6.1.6 Parameter maps of the fraction of macromolecular pool size relative to the normalized liquid pool size, which is typically the focus of interest in qMT experiments. Shown are results from experiments (19 MT-prepared FLASH scans with variation of the offset frequency and RF power) in a healthy volunteer, obtained with conventional fitting (A) and from ANN estimations using a subset of 10 (B), 8 (C), and 5 (D) experimental data points.

Investigation of water exchange in compact myelin – results from computational chemistry

6.1.7

Labadie, C.[1], Allouche, A.-R.[2], Aubert-Frécon, M.[2], & Möller, H. E.[1]

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[2] Institut Lumière et Matière, Université Claude Bernard Lyon I, France

The interpretation of longitudinal water relaxation in the human brain is related to assumptions on the exchange of water between the confined environment of compact myelin and other spaces. Fast exchange is assumed in the two-pool model of magnetization transfer between membranes and water, whereas slow exchange suggests the distinct observation of myelin water with a short T_1 (shutter-speed model). To study the effect of membranes on water mobility, we employed computational chemistry. A pseudo-myelin arrangement of galactosylcerebroside and cholesterol was optimized by a semi-empirical self-consistent field method and replicated with opposing head groups. A water molecule was then translated parallel to the membrane surface or reoriented. Corresponding changes in the heat of formation were 3.5–4 kcal/mol near the head groups but negligible in the centre region. This suggests that water diffusion in myelin is slow due to dipolar and van-der-Waals interactions with lipids in a 0.7-nm hydration layer on the membrane surface. Diffusion is further hindered in the bulk space between membranes by a pattern of obstacles formed by proteins. The proposed slow diffusion of myelin water is consistent with experiments in freezing tissue and compatible with a distinct T_1 fraction as recently established by longitudinal relaxographic imaging.

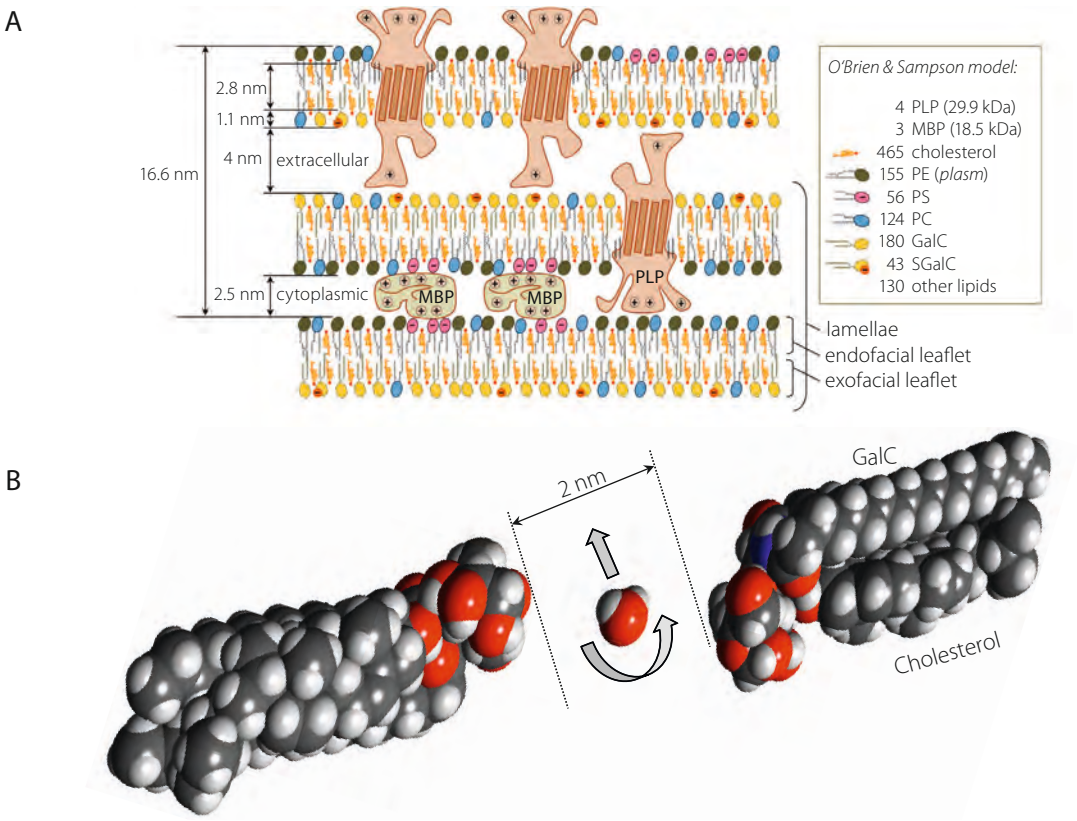

Figure 6.1.7 (A) In compact myelin, cytoplasmic or extracellular water needs to either permeate the membranes or circumferentially diffuse into the space separating membranes to reach outer spaces. (B) Pseudo-myelin with opposing arrangements of galactosylcerebroside (GalC) and cholesterol. An included water molecule was randomly translated and reoriented, and the heat of formation of the resulting system of 417 atoms was estimated.

6.1.8 Impact of image acquisition on voxel-based-morphometry investigations of age-related structural brain changes

Streitbürger, D.-P.[1], Pampel, A.[1], Krueger, G.[2], Lepsien, J.[1], Schroeter, M. L.[1,3], Mueller, K.[1], & Möller, H. E.[1]

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While voxel-based morphometry (VBM) is becoming increasingly popular for assessing structural brain changes, little is known about effects of the image acquisition parameters on the results. For systematic evaluation, grey matter density (GMD) changes associated with aging were investigated by three VBM approaches and a variety of T_1-weighted 3D acquisitions. Statistical tests revealed significant effects from the receiver coil, pulse sequence, and image resolution on estimated age-related GMD changes in cortical and subcortical regions. Potential tissue classification and segmentation advantages were obtained for the MP2RAGE sequence as compared to MP-RAGE. The 32-channel coil generally outperformed the 12-element matrix coil, with more benefit for MP2RAGE. Further improvement can be expected from higher resolution if the loss in sensitivity is accounted for, e.g. by scanning at 7 T. The direct comparison of different VBM approaches revealed widespread differences in resulting aging effects, most likely due to differences in using spatial priors to estimate the probability of grey matter. Use of inconsistent acquisition parameters in VBM analyses is likely to introduce systematic bias. Overall, acquisition protocol changes require careful adaptations of the VBM analysis strategy before a generalized conclusion can be drawn.

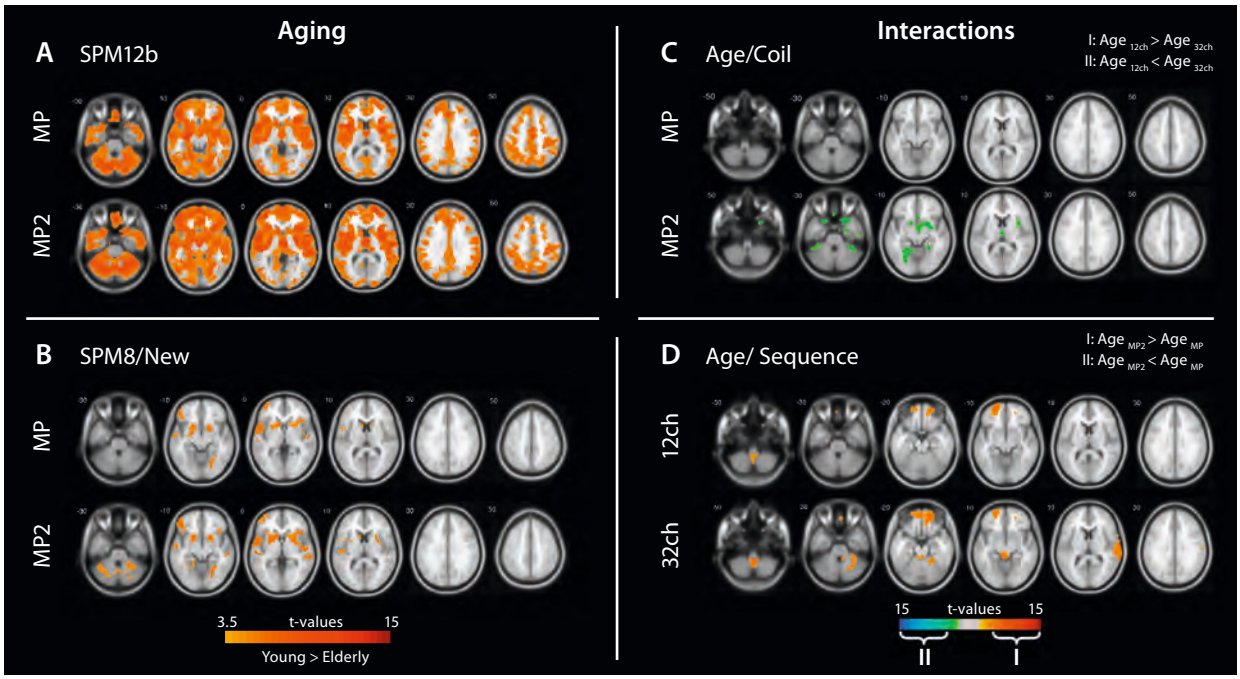

Figure 6.1.8 Two-sample *t*-test results ($p < 0.05$ FWE) demonstrating aging effects observed with MP-RAGE and MP2RAGE and VBM processing with SPM 12b (A) and SPM 8 (with routine "new segment") (B). Red colour scales indicate higher GMD in young (22.3 ± 1.1 years) compared to elderly subjects (71.8 ± 1.9 years). Note that drastically reduced GMD changes were obtained with 'SPM8/new'. Interaction effects ($p < 0.05$ FWE) of age and receiver coil (12-element matrix vs 32-channel array coil) (C) and of age and imaging sequence (MP-RAGE vs MP2RAGE) (D) indicate more pronounced GMD changes for MP2RAGE in acquisitions with the 32-channel coil and for MP2RAGE as compared to MP-RAGE.

Congresses, Workshops, and Symposia

2012 Möller, H. E. (January–December). *Magnetic Resonance Methods in Brain Research*. Seminar. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

2013 Möller, H. E. (January–December). *Magnetic Resonance Methods in Brain Research*. Seminar. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Möller, H. E. (December). *TRANSACT Workshop on Introductory MRS Topics*. Workshop. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Degrees

PhD Theses

2012 Trapp, S. *Untersuchungen der Effekte und Mechanismen selektiver Aufmerksamkeitsausrichtung im Arbeitsgedächtnis [Investigations on effects and mechanisms of selective orienting of attention in working memory]*. University of Leipzig, Germany.

Xu, C. *Exploring novel magnetic resonance imaging markers for ischemic stroke in the application of vessel size imaging and amide proton transfer imaging*. Charité University Medicine Berlin, Germany.

2013 Labadie, C. *Gradient-echo pulse sequence development for phase sensitive magnetic resonance imaging: Application to the detection of metabolites and myelin water in human brain white matter*. University Claude Bernard Lyon I, France.

Holiga, Š. *Personalizing functional magnetic resonance protocols for studying neural substrates of motor deficits in Parkinson's disease*. University of Leipzig, Germany.

Awards

2012 Holiga, Š. *Trainee Award*. International Society for Magnetic Resonance in Medicine (ISMRM), Melbourne, Australia.

Huber, L. *Trainee Award*. International Society for Magnetic Resonance in Medicine (ISMRM), Melbourne, Australia.

2013 Holiga, Š. *Magna cum Laude Merit Award*. International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, UT, USA.

Holiga, Š. *Trainee Award*. International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, UT, USA.

Huber, L. *Magna cum Laude Merit Award*. International Society for Magnetic Resonance in Medicine (ISMRM), Salt Lake City, UT, USA.

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Index of Published Figures

Figure 6.1.3 (A) (B)
Holiga, S., Möller, H. E., Sieger, T., Schroeter, M. L., Jech, R., & Mueller, K. (2012). Accounting for movement increases sensitivity in detecting brain activity in Parkinson's disease. *PLoS One, 7*(5): e36271. doi:10.1371/journal.pone.0036271

Figure 6.1.3 (C)
Holiga, S., Mueller, K., Möller, H. E., Sieger, T., Schroeter, M. L., Vymazal, J., Růžička, E., & Jech, R. (2013). Motor matters: Tackling heterogeneity of Parkinson's disease in functional MRI studies. *PLoS One, 8*(2): e56133. doi:10.1371/journal.pone.0056133

6.2 Methods and Development Unit "MEG and EEG – Cortical Networks and Cognitive Functions"

In this group, we develop and evaluate methods that help to interpret non-invasive brain measurements in terms of structural and functional features of the brain. More specifically, work focuses on the identification of functional and structural networks by means of MEG/EEG, functional MRI, and diffusion MRI. Additionally, we aim to elucidate the relationship between structure and function, especially by means of neural modelling. Because in human research we are restricted to non-invasive measurements most of the time, the amount of information is limited and gaining insight into intracranial processes involves solving non-unique inverse problems. Such problems are riddled with the necessity to make sensible assumptions about the processes to be recovered.

The most widely used non-invasive brain measurement methods are electroencephalography (EEG) and magnetoencephalography (MEG), which provide us with real-time fingerprints of the electrical brain activity. The measured potentials and fields are the direct and immediate consequence of the electrical currents due to neuronal activity. However, the spatial sensitivity is limited—each recording is a weighted superposition of contributions from the entire brain. The methodological challenge lies in the decomposition of the superimposed effects, while taking into account the complex physical structure of the head. Source reconstruction methods seek to solve the associated inverse problem by combining EEG/MEG data with additional knowledge or sensible assumptions in a meaningful way, in order to obtain an estimate of the spatio-temporal activation pattern in the brain. This area is still under massive development and new algorithms are continuously being proposed. For example, in one study, we investigate the usefulness of a type of algorithm that takes into account the assumption of temporal smoothness (6.2.1). Another approach that has gained considerable popularity in recent years is dynamic causal modelling (DCM). Here, mathematical models of neural populations linked by axonal connections are used to constrain the dynamics of neural activity. In a methodological study, we propose a novel variant of this model that offers a more realistic laminar structure of a local neural circuit and, most importantly, incorporates short-term synaptic plasticity (6.2.2). In an application study, DCM is used to elucidate the process of using predictive information in language processing (6.2.3). When there is little ground for making sensible assumptions about the sources, and/or the data are rather noisy, for example because averaging over many trials is not possible, spatial filters can be an effective means of extracting meaningful information from EEG/MEG data. We propose an efficient virtual channel approach based on independent component analysis and multivariate linear regression and evaluate this method with single-trial MEG and EEG data from a speech experiment (6.2.4). An alternative to the use of EEG/MEG for the non-invasive characterization of brain function is functional MRI (fMRI). While this method less clearly reflects the source

dynamics, it allows for an accurate spatial localization within voxel precision. We use this technique to investigate neural correlates of musical experience and visuomotor synchronization (6.2.5).

The structural organization of brain networks can be investigated non-invasively by diffusion MRI (dMRI). This technique yields, on a voxel basis, a direction dependent MRI signal attenuation that, at least in the white matter, can be attributed to the course of nerve fibre populations. The precise qualitative and quantitative reconstruction of the local fibre configuration (local model), the tracking of the course of fibre pathways throughout the white matter (tractography), and the establishment of the connection scheme (connectome) of the brain give rise to inverse problems and constitute substantial methodological challenges. In one study we propose a novel technique to reconstruct the local fibre configuration and parameterize it in a meaningful way. This enables us to derive meaningful metrics that, on a voxel-by-voxel basis, describe certain aspects of local fibre architecture such as fibre collinearity or white matter complexity (6.2.6). In a second study, we develop a new tractography method that combines the advantages of probabilistic and global tractography techniques and offers an elegant way to map dMRI-derived metrics to a particular connection between two well-defined brain areas (6.2.7). As local model specification and tractography form inverse problems and therefore heavily depend on additional assumptions, validation of algorithms is a crucial issue. We use manganese tracing in an animal model to assess the performance of a representative selection of state-of-the-art algorithms and draw specific and general conclusions on their strengths and weaknesses (6.2.8). For the definition of the connectome, it is not only important to characterize the connections but also to define the elements between which the connections are considered. This requires the parcellation of the brain into functionally meaningful areas. In the context of the connectome it makes sense to use connectivity as the prime criterion for parcellation: Parts of the cortex that are similarly connected to the rest of the brain may be considered to belong to the same area. However, this similarity pattern turns out to be rather complicated, rendering any single subdivision of the cortex into areas that are not very representative. We therefore propose a hierarchical parcellation scheme to more completely account for the function-anatomical organization of the cortex (6.2.9).

Spatio-temporal regularization in linear distributed source reconstruction from EEG/MEG – a critical evaluation

6.2.1

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Potentially, the high temporal resolution of EEG/MEG data offers a way to improve source reconstruction estimates by using temporal constraints on source time courses. Here we investigated the performance of spatio-temporal regularization (STR) in a linear estimation approach by systematically comparing it to simple filtering of the data or of the reconstructed current density. The widely used sLORETA algorithm was adapted for STR and generally used for source reconstruction. For the STR method we applied a constraint that penalises solutions outside a narrow frequency band of interest. STR and filtering approaches were evaluated with respect to spatial localization error and accuracy of the reconstructed source time courses in single and double dipoles scenarios with oscillating source waveforms. We performed extensive computer simulations of EEG data, and varied parameter settings (noise levels and regu-

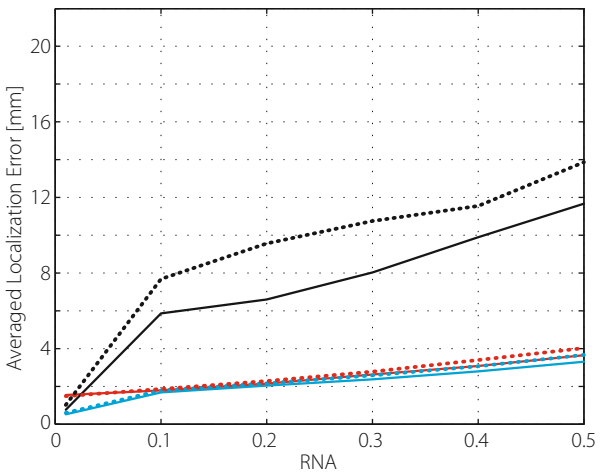

Figure 6.2.1 Localization errors for frontal tangential (dotted) and radial (solid) sources, averaged over 100 trials with independent noise realizations, with different relative noise amplitudes (RNA). Black lines: sLORETA, red lines: sLORETA with prior temporal filtering, blue lines: sLORETA with STR.

larization parameters) for all algorithms. For verification, we also used data from MEG phantom measurements. In the investigated scenarios, there was no evidence for any superiority of STR-based methods over purely spatial algorithms applied to temporally filtered data (see Fig. 6.2.1). In addition, the results clearly show that the performance of STR strongly depends on the choice of regularization parameters.

6.2.2 A realistic neural mass model of the cortex with laminar-specific connections and synaptic plasticity – evaluation with auditory habituation

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Based on neural masses, we propose a biologically realistic local cortical circuit model (LCCM). It implements important functional aspects of the brain, which are not part of previous neural mass models: (1) activity dependent synaptic plasticity and (2) realistic inter-laminar connectivity between neural populations (see Fig. 6.2.2). We demonstrate the potential of the LCCM with auditory habituation. The model parameters were determined using Bayesian inference. We showed that: (1) apart from the major serial excitatory information route (layer 4 to layer 2/3 to layer 5/6) a parallel "short-cut" pathway (layer 4 to layer 5/6) exists, (2) while the excitatory signal flow from the pyramidal cells to the inhibitory interneurons appears to be more intra-laminar, the inhibitory signal flow seems to be both intra- and inter-laminar, and (3) the connections habituate asymmetrically, i.e. stronger for forward connections (from layer 4 to layer 2/3) than for backward connections (from Layer 5/6 to layer 4). Our evaluation demonstrates that the novel features of the LCCM make a real difference for mechanistic explanations of brain function. Their incorporation into mass models links them to macroscopic data (like EEG or MEG) in human experiments. Our LCCM may therefore be a valuable building block for future realistic models of human cognitive function.

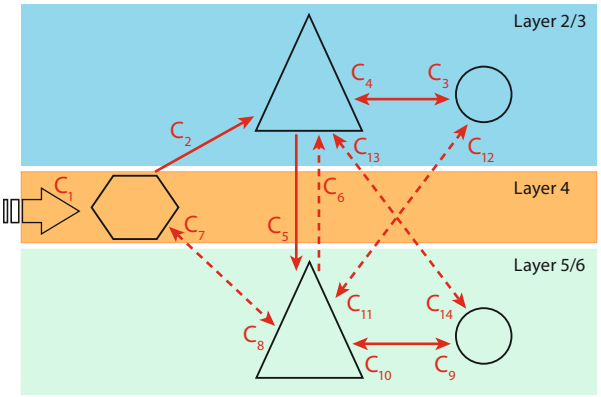

Figure 6.2.2 Neural mass model for a cortical source with excitatory interneurons (hexagon), superficial/deep pyramidal cells (triangles), and superficial/deep inhibitory interneurons (circles). Solid connections are known from literature, dotted ones are uncertain.

6.2.3 Benefits of prediction formation in speech perception

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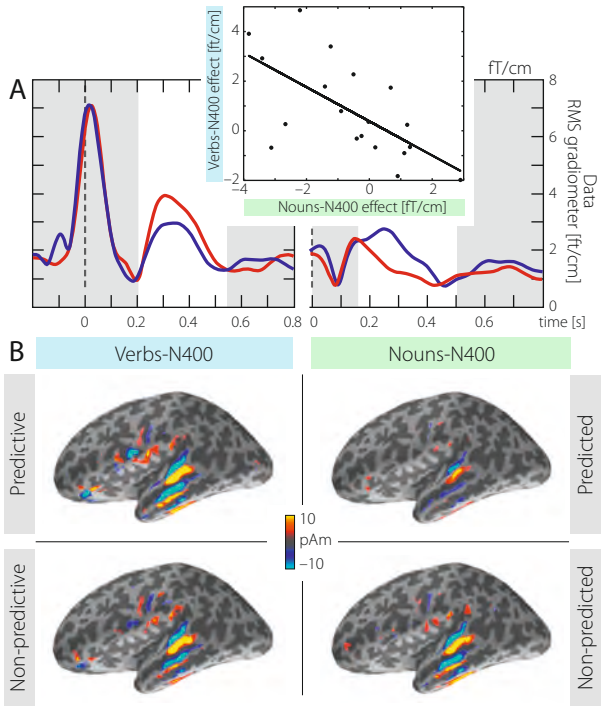
The human brain naturally forms internal representations of the external world. As these representations evolve, the brain forms expectations, allowing reduced processing towards the highly predictable. Adopting this *predictive coding* perspective for complex cognitive functions like language, the dynamics of the neural response as measured should gradually reflect the varying predictive associations that exist between successive words in a sentence. Here we use magnetoencephalography (MEG) and dynamic causal modelling (DCM) to describe precisely this transfer of predictive language information across hierarchical processing stages in the human brain. In simple German sentences, we selected verbs which were either highly predictive for the occurrence of a following noun or not. Going beyond the expected reduced N400-like activity for highly *predicted* nouns (Fig. 6.2.3A right), we demonstrate that the setting up of a predictive context can be observed in increased neu-



ral activity and information flow while processing highly *predictive* (i.e. informative) verbs (Fig. 6.2.3A left). Effects were inversely correlated across participants (Fig. 6.2.3A insert), demonstrating a direct relation between formation of and benefit from prediction. In addition, distribution and polarity of the brain activity relevant to the N400 support our interpretation (Fig. 6.2.3B). Further employing Bayesian model comparisons, we show that both noun and verb effects are best explained by hierarchical networks which incorporate a bilateral, widely distributed set of cortical regions plus one deep, subcortical region.

Figure 6.2.3 Grand average results: (A) Root mean squared values of the gradiometer channels for verb (left) and nouns (right) and both sentence types. Correlation between the mean amplitudes of the white windows is displayed in the insert. (B) Minimum norm (L2) results of the two sentence types for both verbs and nouns projected to the surface normal (negative values show currents which point inwards).

Efficient spatial filter approach permits single-trial decoding of speech items from M/EEG recordings

6.2.4

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Neural oscillations in the auditory cortex might be entrained by amplitude modulations of ongoing speech and have been proposed to subserve speech comprehension by adjusting neuronal excitability to linguistic speech rhythms (e.g. Peelle & Davis, 2012, Front Psychol, 3:320). Here, we conducted an efficient virtual channel approach to assess cortical speech tracking from M/EEG measurements while participants listened to sentences.

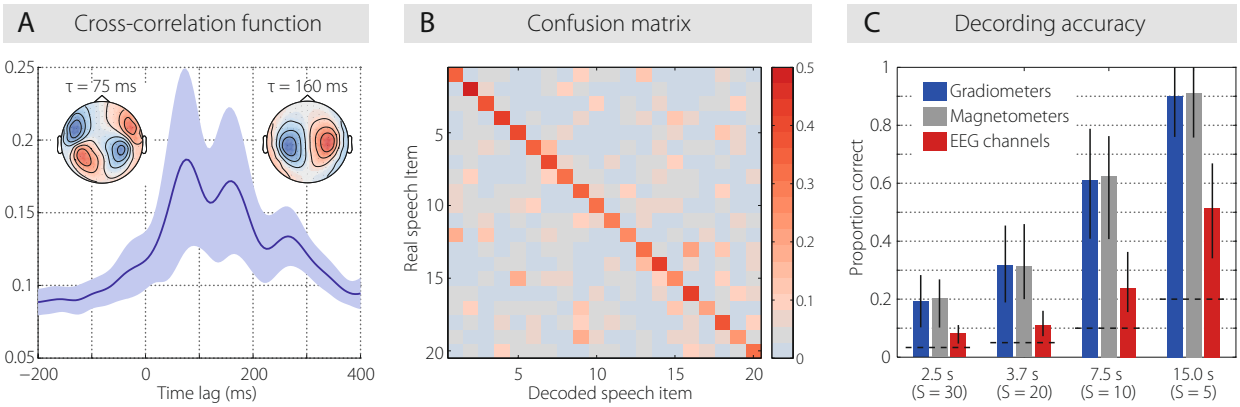

Figure 6.2.4 Grand average results across participants (n = 33). (A) Mean cross-correlation function (with standard deviation) between the virtual channel and the real speech envelopes in the training set. Insets show the back-projected magnetic field topographies (red: outgoing) corresponding to peak correlations. (B) Grand average confusion matrix of speech decoding (set size S = 20, item length L = 3.7 s, chance level = 0.05, 300 bootstrap replications per participant, filters based on magnetometer recordings). (C) Median decoding accuracy (with IQR) across participants for different sensor types used to form the virtual channel (same L and S as in B). Chance level is indicated by dashed horizontal lines.

By employing independent component analysis and multivariate linear regression we optimized spatial filter weights such that the projected M/EEG signal (*virtual channel*) maximally covaried with the acoustic speech envelope. Back-projected sensor topographies reveal a pattern similar to one of bilateral activity at the primary auditory cortices (Fig. 6.2.4A). To investigate the reliability of our approach the precomputed filters were utilized in a decoding experiment on an independent subset of the data. Speech envelopes could be partially reconstructed and thus speech items of a few seconds correctly identified well above chance level from a variety of single-trial measurements (Fig. 6.2.4B,C). In summary, the method effectively suppressed background activity and provided a hypothesis-driven data reduction of high-dimensional M/EEG measurements.

6.2.5 Keeping an eye on the conductor: Neural correlates of musical experience and visuo-motor synchronization

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For musicians in an orchestra, synchronized playing with a conductor is necessary to achieve an optimal performance. Previous studies have reported a cortico-subcortical network underlying synchronization with sounds or flashes. However, it remains unclear how precisely musicians synchronize with a conductor's gestures and which brain areas are needed for this.

We conducted a functional magnetic resonance imaging (fMRI) experiment with nonmusicians and musicians who regularly play music with a conductor. Participants were required to tap the rhythm they perceived from movies displaying either a conductor's gestures or a swinging metronome with two different speeds of presentation (Fast: starting at 120bpm; Slow: starting at 90bpm). When tapping with a conductor, musicians performed tapping more precisely than nonmusicians and the fMRI results showed greater activity in the medial part of the left superior frontal gyrus (SFG) in musicians than in nonmusicians (Fig. 6.2.5). The SFG activity correlated with the number of hours of playing music with a conductor and the accuracy of the tapping. On the contrary, tapping with the metronome did not show any effect of musical experience, either behaviourally or in the brain activity. The observed differences in the conductor condition suggest that musicians may develop a special ability for social interaction to synchronize with the conductor while playing music.

Figure 6.2.5 The brain areas showing significantly larger activation in musicians, compared to nonmusicians, while tapping with the conductor.

6.2.6 Beyond fractional anisotropy: Extraction of bundle-specific structural metrics from crossing fibre models

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Diffusion MRI allows for the non-invasive inference of microstructural properties of brain white matter. Voxels may contain complex fibre configurations, which cannot be described by the diffusion tensor model. In many cases, multi-compartment models offer a useful parameterization of the complex fibre architecture, but are rid-

dled with fitting and model selection problems. On the other hand, spherical deconvolution generates fibre orientation density functions (fODF) without any explicit model assumptions. However, as the fODF is represented by spherical harmonics, it does not yield any directly interpretable model parameters. We propose a technique that combines the advantages of both approaches: First the fibre configuration is modelled as fODF represented by spherical harmonics, and then each of the peaks is parameterized separately using a Bingham distribution in order to characterize the underlying bundle. From the Bingham distributions, we capture first and second order statistics of the fibre orientations, from which we derive metrics for the parametric quantification of fibre bundles. We propose meaningful relationships between these metrics and the underlying microstructural properties. The metrics are compared to the conventionally used fractional anisotropy (FA) and it is demonstrated how they may contribute to the increase of specificity of the characterization of microstructural properties.

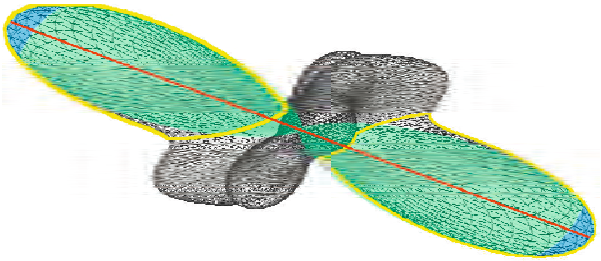

Figure 6.2.6 The Bingham fit. Grey: fODF; red: maximum direction of the largest peak; green: Bingham distribution fitted using a small neighbourhood of the maximum direction (blue).

Plausibility Tracking: A method to evaluate anatomical connectivity and microstructural properties along fibre pathways

6.2.7

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Plausibility Tracking is a novel global tractography method. It estimates the most plausible pathway between two areas in the brain, modelled as a spline curve. Plausibility Tracking combines the advantages of some existing tractography methods: from probabilistic tractography, the more complete connectivity pattern, and from global tractography, the relative robustness against local noise and error propagation. In addition, it provides reliable local directions all along the fibre pathways. This is of special importance because it enables the efficient use of direction dependent indices from diffusion MRI in tract-based analysis schemes.

Here, we propose a framework for the assessment and comparison of diffusion-derived tissue properties. Its main ingredients are Plausibility Tracking, atlas-guided parameterization of the tracts and the use of advanced bundle-specific indices describing fibre density, fibre spread, and white matter complexity (Fig. 6.2.7). The new method is evaluated using real data. We show that it allows for a more specific interpretation of the white matter's microstructure, as compared to classical methods based on rotationally invariant indices derived from the diffusion tensor.

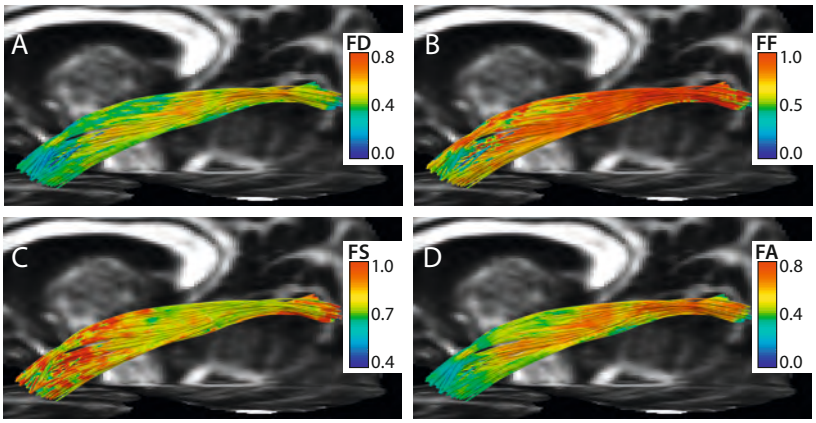

Figure 6.2.7 Indices mapped onto the inferior longitudinal fasciculus of a representative subject. (A) Fibre density (FD); (B) Fibre fraction (FF); (C) Fibre spread (FS); (D) Fractional anisotropy (FA).

6.2.8 Validation of tractography – comparison with manganese tracing

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We evaluated a representative selection of white matter tractography methods based on diffusion-weighted magnetic resonance imaging (dwMRI) data using invasive manganese tracing in pigs. Tractography and tracing were first compared on a voxel-wise basis. In a second step, a more qualitative assessment was performed to examine to what extent particular fibre tracts and target regions were reached. The voxel-wise agreement turned out to be very limited. In contrast, the qualitative assessment showed that tractography is capable of finding the major fibre tracts, although there was some variation among the methods (see Fig. 6.2.8). Importantly, however, many false positive connections were found. It was not possible to achieve high sensitivity (i.e. few false negatives) and high specificity (i.e. few false positives) at the same time. These problems mainly originated from regions with complex fibre arrangements or high curvature, such as the centrum semiovale, and could not be easily resolved by sophisticated local models alone. We conclude that the main challenge in making tractography a truly useful and reliable tool in brain research and neurology lies in the acquisition of better data. In particular, we believe that the main route to improvement is the increase of spatial resolution, under preservation of the signal to noise ratio.

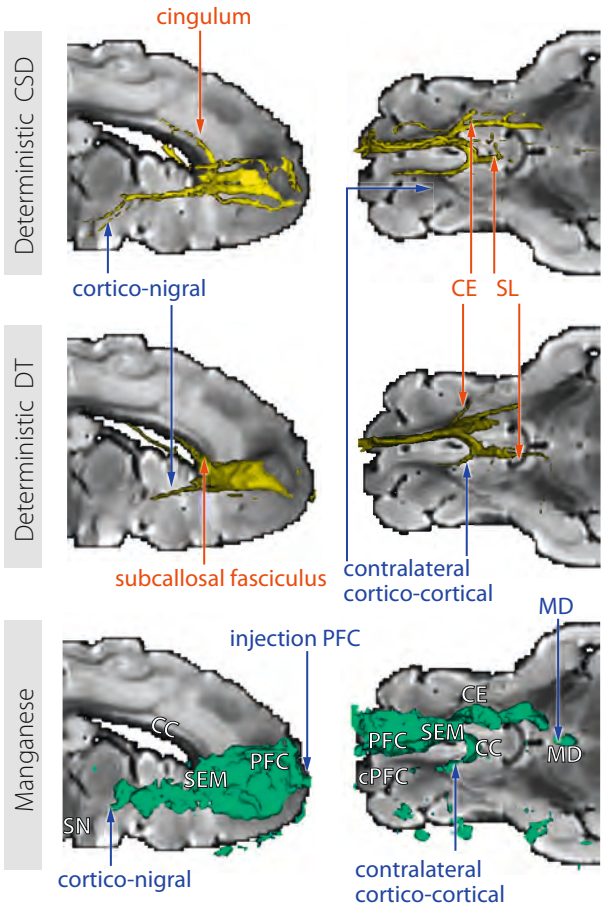

Figure 6.2.8 Connectivity of right PFC, reconstructed using manganese tracing and tractography. Thresholded tracts are surface-rendered. True positive tracts are labelled in blue, false positive ones in red. For reference, slices of a T2 image are used. Abbreviations: PFC, prefrontal cortex; cPFC, contralateral prefrontal cortex; SEM, centrum semiovale; CC, corpus callosum; SN, substantia nigra; CE, external capsule; MD, mediodorsal thalamus; SL, nucleus septalis lateralis; DT, diffusion tensor; CSD, constrained spherical deconvolution.

6.2.9 Whole-brain connectivity-based hierarchical parcellation

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There is common consensus in modern neuroscience that brain function is based on networks and that connectivity is therefore crucial for brain function. Therefore, the delineation of functional brain areas on the basis of connectivity should lead to highly relevant brain maps. Long-range connectivity can be estimated *in vivo* using diffusion magnetic resonance imaging (dMRI) and tractography. Previous methods are typically often limited to small regions of grey matter, and/or try to find a predefined number of areas. However, in most cases a parcellation dividing the brain into a finite number of areas does not adequately represent the function-ana-

tomical organisation of the brain. Here, we propose hierarchical clustering to overcome these limitations and achieve whole-brain parcellation. We demonstrate that agglomerative hierarchical clustering well encodes the information of the underlying structure at all granularity levels in a hierarchical tree. An optimal tree building and processing pipeline is proposed that reduces tree complexity with minimal information loss. We demonstrate that these trees can be used to compare the function-anatomical organization of different subjects' cortices and how to extract parcellations from them. Our novel approach allows for a more complete representation of the real underlying structure and successfully tackles the challenge of whole-brain parcellation.

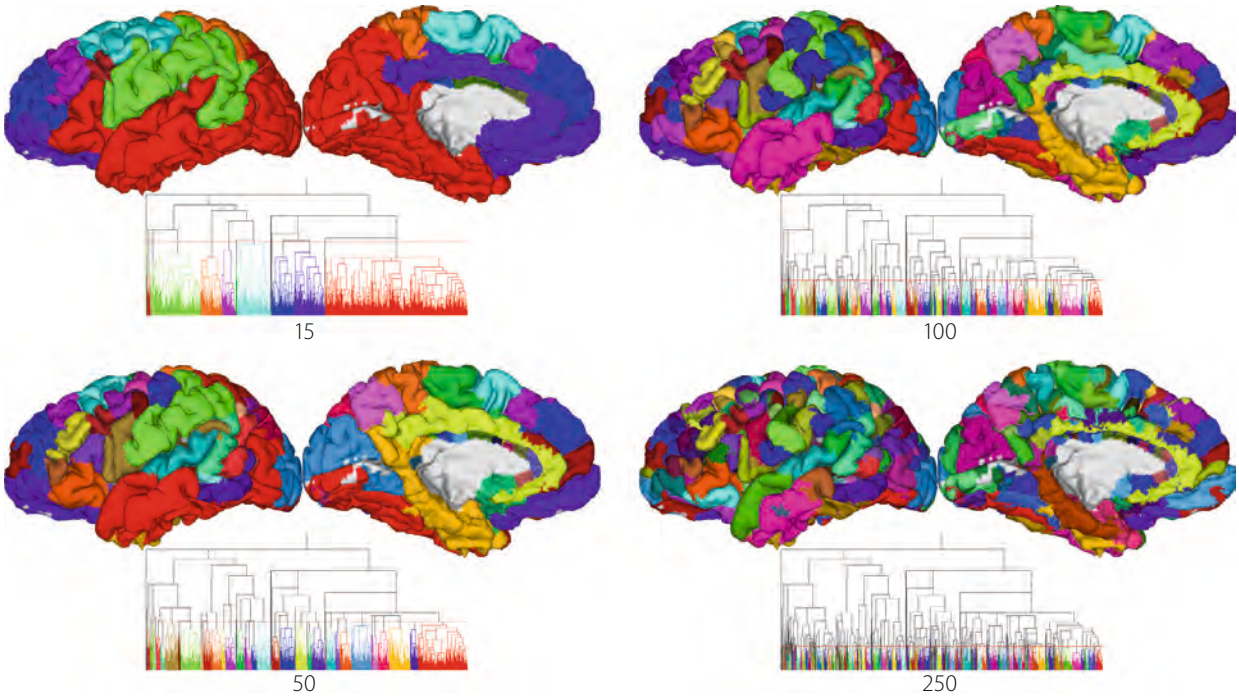

Figure 6.2.9 Parcellations extracted from the hierarchical tree of the left hemisphere of a healthy volunteer using the horizontal cut algorithm. The numbers indicate the predefined number of clusters. The red horizontal lines in the trees denote the cutting level.

Congresses, Workshops, and Symposia

2012 Haueisen, J., & Knösche, T. R. (September). *Field modeling in the human head.* Symposium on 46th DGBMT Annual Conference, Jena, Germany.

Maess, B. (May). *Fieldtrip Training Course. Workshop.* Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

2013 Haueisen, J., & Knösche, T. R. (September). *6th International Summerschool on Biomedical Engineering – Multimodal integration of brain measurements in research and clinical practice.* Havana, Cuba.

Degrees

PhD Theses

2013 Mamashli, F. *Investigating prediction in semantic processing.* University of Leipzig, Germany.

Awards

2012 Moreno-Dominguez, D. (2012). *Doctoral Fellowship.* FAZIT-Stiftung, Frankfurt/Main, Germany.

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7 Former Departments and Groups

Department of Psychology and Research Group "Infant Cognition and Action"

Director Emeritus

Professor Dr Wolfgang Prinz

Group Leader

Professor Dr Moritz M. Daum (*)

PhD Students

Manja Attig (*)
Dr Thomas Dolk (19) (*) (PhD since 07/2013)
Dr Anja Gampe (*) (PhD since 02/2013)
Christina Jung (23)
Anne Keitel (née Melzer) (15)
Andrea Walter (14)
Caroline Wronski (*)

Secretaries and Technical Staff

Nancy Muschall (**)
Susanne Starke
Janette Studniczka (*)
Kerstin Träger (**)

Former Researchers and PhD Students

Manja Attig
Research Assistant, National Educational Panel Study (NEPS), University of Bamberg, Germany

Dr Thomas Dolk
PostDoc, Human Sciences Faculty, University of Potsdam, Germany

Dr Anja Gampe
Assistant, Department of Developmental Psychology, University of Zurich, Switzerland

Caroline Wronski
PhD student, Department of Developmental Psychology, University of Zurich, Switzerland

Max Planck Research Group "Music Cognition and Action"

Group Leader

Professor Dr Peter E. Keller

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Dr Merle T. Fairhurst-Menuhin (**)

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Dr Giacomo Novembre (19) (*) (PhD since 07/2013)
Nadine Pecenka (*)
Marie Ragert (née Uhlig) (19) (*)
Vassilis Sevdalis (*)
Maria Christine van der Steen (8)

Guest Researchers

Rasmus König, M. Mus.

Technical Staff

Jan Bergmann (*)
Kerstin Träger (**)

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Dr Annerose Engel	PostDoc, Social Brain Lab, Netherlands Institute of Neuroscience, Amsterdam, the Netherlands PostDoc, IDOR - D'Or Institute for Research and Education, Rio de Janeiro, Brazil
Dr Merle T. Fairhurst-Menuhin	Max Planck Research Group "Early Social Development"
Dr Giacomo Novembre	Research Lecturer, MARCS Institute, University of Western Sydney, Australia
Nadine Pecenka	Praxis 57plus, Lenzburg, Switzerland
Marie Ragert	Maternity leave
Vassilis Sevdalis	Scientific Staff, Institute of Psychology, German Sport University Cologne, Germany

(8) European Union 7th Framework Programme
(14) German Research Foundation (DFG)
(15) University of Leipzig, Germany
(19) IMPRS NeuroCom, Leipzig, Germany
(23) MaxNetAging Research School, Germany

(*) Left the institute during 2012/2013
(**) Left the group during 2012/2013

Max Planck Research Group "Body and Self"

Group Leader

Dr Simone Schütz-Bosbach

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Dr Antje Gentsch (16, 31) (*) (PhD since 05/2012)
Dr Sylvia Hach (*)
Dr Luca F. Ticini (14) (*)
Dr Carmen Weiß (31) (PhD since 07/2013)

PhD Students

Dr Nadine Diersch (23) (*) (PhD since 05/2013)
Dr Esther Kühn (19) (*) (PhD since 03/2013)
Barbara Vogt (*)

Technical Staff

Jeanine Auerswald (**)
Jan Bergmann (*)

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Dr Nadine Diersch	PostDoc, Social Brain in Action Laboratory, Bangor University, Wales, United Kingdom
Dr Antje Gentsch	Postdoctoral Research Associate, Division of Psychology and Language Sciences, University College London, United Kingdom
Dr Sylvia Hach	Research Fellow, Memory Lab, University of Auckland, Australia
Dr Esther Kühn	Postdoctoral Fellow, Institute of Cognitive Neuroscience, University College London, United Kingdom (June – December 2013)
	PostDoc, Department of Neurology, Max Planck Institute for Human and Cognitive Brain Sciences, Leipzig (since 12/2013)
Dr Luca F. Ticini	Research Associate, University College London, United Kingdom
Barbara Vogt	Completion period

(1) Alexander von Humboldt Foundation, Germany
(8) European Union 7th Framework Programme
(15) Graduate Programme "Function of Attention in Cognition", University of Leipzig/funded by German Research Foundation (DFG)
(16) Berlin School of Mind and Brain, Humboldt University Berlin, Germany
(19) IMPRS NeuroCom, Leipzig, Germany
(23) MaxNetAging Research School, Germany
(25) Canadian Institute of Health and Parkinson Society, Canada
(26) Postdoctoral Grant from Spanish Government
(31) Volkswagen Foundation, Germany
(34) Programm Beatriu de Pinos, Generalitat de Catalunya, Spain
(63) Erasmus Mundus Student Exchange Network in Auditory Cognitive Neuroscience, European Commission

(*) Left the institute during 2012/2013
(**) Left the group during 2012/2013

Minerva Research Group "Neurocognition of Rhythm in Communication"

Group Leader

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Dr Christian Obermeier (14)
Dr Patricia E. Román (26) (*)
Dr Michael Schwartze (14) (*)

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Eleanor Harding (*)
Hao Tam Ho (14) (*)
Iris Nikola Knierim (19) (*)
Dr Franziska Knolle (née Grimm) (19) (*)
Dr Paula M. Roncaglia-Denissen (23) (*)
Ellen Schüßler (15)
Mary Elizabeth Sutherland (63) (*)
Laura Verga (8)
Artyom Zinchenko (19)
Dr Patricia Garrido-Vásquez (25) (*)

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Maria Jakuszeit (*)
Anika Stockert

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Dr Michael Schwartze	School of Psychological Sciences, University of Manchester, United Kingdom

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Dr Patricia Garrido-Vásquez	Cognitive Neuroscience of Perception and Action, Philipp University Marburg, Germany
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Dr Franziska Knolle (née Grimm)	Study of Medicine, Technical University Dresden, Germany
Mary Elizabeth Sutherland	Department of Psychology, McGill University, Montreal, QC, Canada

Former Visiting Research Fellows

Professor Carrie Jackson	Department of Germanic and Slavic Languages, Pennsylvania State University, PA, USA

7.1 Department of Psychology and Research Group "Infant Cognition and Action"

Cognition and Action

The research programme of the former Department of Psychology addressed relationships between cognition and action. The department was closed in September 2010 when Wolfgang Prinz retired. At that time the majority of associated researchers left the institute and most experimental projects had to be concluded. Nevertheless, some research activities continued, allowing former researchers to carry on their work in new places and in new positions, finishing their Leipzig projects and publishing major outcomes. One major research activity that continued beyond the closing date of the department was the former "Baby Lab". This was established as a Research Group on "Infant Cognition and Action" for two more years and headed by Moritz Daum, with Wolfgang Prinz as close collaborator (see below).

Parallel to ongoing experimental work, two major book projects came to a close during the reporting period. The first addresses the emergent field of Action Science, providing an overview of the current theoretical and methodological landscape (Wolfgang Prinz, Miriam Beisert, & Arvid Herwig, Eds.). The second is a German textbook on experimental research in the action domain (edited by Wolfgang Prinz).

Infant Cognition and Action

The former Research Group "Infant Cognition and Action" came to a close in July 2012 when Moritz Daum took over the chair of Developmental Psychology at the University of Zurich. The overarching theme of the research group was to address the roots of infants' perception of their social world. There were three major questions: 1) How do infants develop an understanding of others' actions? 2) When do infants start to perform their own actions? And, as a consequence, 3) when do infants start to engage in cooperative and communicative activities with social interaction partners? The specific focus of the research was the development of the (neuro)cognitive mechanisms underlying action perception, which we approached from different directions.

The first and major line of research focused on the mechanisms underlying infants' action perception. The processing timeline of infants' action perception includes a number of component processes operating at different processing stages. When observing an agent performing an action, the observer first has to identify the agent and the directedness of his or her behaviour. Upon identification, the observer generates an expectation about the future behaviour of the agent, which results in the shift of attention in the direction of the expected action continuation. Finally, upon completion, the action outcome is evaluated and compared to the previously generated action expectation. These expectations that are built at various instances throughout the processing timeline can be measured using a variety of dependent variables such as saccadic reaction times (see 7.1.1) or anticipatory looking or imitation (see 7.1.3).

The second line of research addresses the interrelation between action and language. Much is known about the onset and development of both domains in isolation,

however little is known about how the emerging symbolic system of language interacts with the previously developed embodied system of action perception. The aim of this line of research is to chart the ways in which the onset of an explicit symbolic system (i.e. language) impacts on the early understanding of the behaviour of others (see 7.1.2).

The third major line of research focuses on the selective implementation of observed behaviour into self-performed actions via imitation. Infants selectively imitate actions according to observed intentions and situational constraints. In previous studies (e.g. Beisert et al., 2012; Buttelmann, Zmyj, Daum, & Carpenter, 2013; Zmyj, Buttelmann, Carpenter, & Daum, 2010, J Exp Child Psychol, 106, 208–220; Zmyj, Daum, Prinz, Nielsen, & Aschersleben, 2012), we explored how socially relevant characteristics such as age, competence, and cultural background, as well as low-level attentional characteristics, impact on the likelihood of an action being imitated. In more recent studies, we explored how the two processes involved in imitation, the perception and the reproduction of actions, are related over development (see 7.1.3).

The research conducted in the group investigated the above aspects of action perception and its interplay with action control by means of different paradigms and methods such as measuring looking time and heart rate, the analysis of infants' eye movements using an eye-tracking system, and the analysis of infants' imitation of observed actions. In collaboration projects, we examined infants' action perception using neurophysiological measures such as EEG and NIRS.

Mechanisms of action perception: Development of pointing perception in infancy

7.1.1

Daum, M. M.[1], Ulber, J.[1,2], & Gredebäck, G.[3]

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[2] Department of Developmental and Comparative Psychology, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany
[3] Department of Psychology, Uppsala University, Sweden

One important component process of infants' action perception is the modulation of covert once a stimulus that contains directional information (e.g. an agent performing an action directed towards a goal) has been identified (e.g. Posner, 1980, Q J Exp Psychol, 32, 3–25). Previous research has shown that goal-directed grasping actions cause such shifts of covert attention beginning around halfway through the first year of life (Daum & Gredebäck, 2011a, Exp Brain Res, 2, 113–126; Wronski & Daum, subm). Such shifts of covert attention can be assessed via reaction times either measured in a button-press task (Daum & Gredebäck, 2011b, Int J Mind Br Cogn, 2, 113–126) or via saccadic reaction times (e.g. Daum & Gredebäck, 2011a).

In the present study (Daum, Ulber, & Gredebäck, 2013) we applied a spatial cueing paradigm to assess the development of infants' perception of pointing actions. In particular, we aimed to investigate the interplay of verbal and non-verbal communication with respect to infants' perception of pointing gestures, and to find out to which extent a pointing gesture needs to be embedded in a communicative context in order to be interpreted as directed towards a distal goal object. Infants were presented with still images of pointing hands (cue) in combination with an acoustic stimulus. In four conditions, the communicative content of this acoustic stimulus was manipulated from being human and referential ("Look!

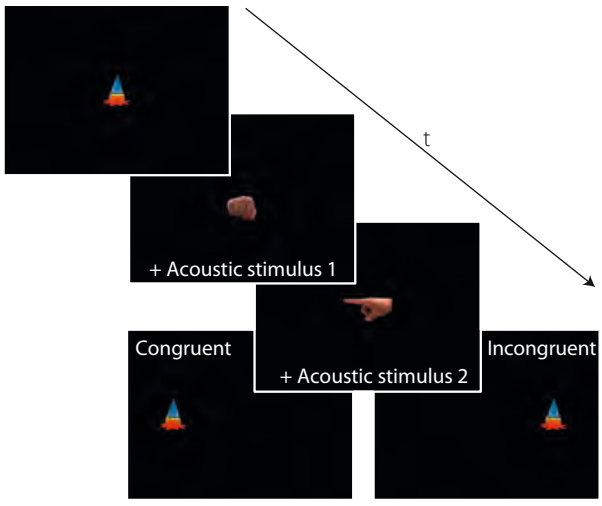

Figure 7.1.1 General paradigm used in Experiments 1 and 2. The acoustic stimuli used in the four conditions were verbal communicative speech (acoustic stimulus 1: "Look!", acoustic stimulus 2: "There!"), reversed speech (similar to "Kool", "Ereht"), an artificial sound, and no acoustic stimulus at all.

There!") over human and non-referential to artificial or absent. Saccadic reaction times (SRTs) from the cue to a peripheral target were measured as an indicator of the modulation of covert attention. A significant cueing effect (facilitated SRTs for congruent compared to incongruent trials) was only present in a condition with additional communicative and referential speech. In addition, the more human and communicative the acoustic stimulus was, the greater the size of the cueing effect. This indicates a beneficial effect of verbal communication on the perception of non-verbal communicative pointing gestures, emphasizing the important role of verbal communication in facilitating social understanding across domains. These findings additionally suggest that human and communicative (ostensive) signals are not qualitatively different from other less social signals but just quantitatively the most attention grabbing amongst a number of other signals.

7.1.2 Interrelation of language and action: Enactment is beneficial for verb learning in toddlers

Gampe, A.[1], Brauer, J.[1], & Daum, M. M.[1]

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

A number of previous findings have revealed that in adults, language and actions are part of a common representational system (Barsalou, 2008, Annu Rev Psychol, 59, 617–645; Fischer & Zwaan, 2008, Q J Exp Psychol, 61, 825–850). However, less is known about whether, and how, the onset of language has an effect on infants' processing of observed actions; in other words, whether a child's action representation is modified once the child acquires knowledge about how the action is labelled and whether a common representational system is established at the onset of language or whether it develops in line with a child's increasing linguistic experience. In the present research project, we addressed the question to what extent the enactment of a novel action supports the acquisition of a related novel action word. Recent findings suggest that in adults' second language acquisition, learning a novel word is enriched by enactment (Macedonia & Knösche, 2011, Mind Brain Educ, 5, 196–211). In the present study (Gampe, Brauer, & Daum, subm.), we investigated the extent to which action production also helps to acquire the first language. In a simple word-learning study 24-, 30- and 36-month-old children learned the labels of *path actions*, where a means object was moved towards an end object, and *manner actions* in which an action was performed in a specific way. The children were presented with these two actions in one of two conditions: In the *passive condition*, the children only observed the experimenter executing the action. In the *active condition*, the children additionally executed the action themselves. In a subsequent test phase, the children were presented with the word they just learned and were asked to execute the respective action. The results showed that path actions were learned in all age groups irrespective of condition. They further revealed that 36-month-olds learned the labels of manner actions in both conditions, whereas 30-month-olds were only able to learn the labels in the active condition. At 24 months manner actions could not be learned in either condition. The execution abilities of children in the active condition were correlated to their verb learning success. Taken together, these findings provide evidence for an interrelation between language and action on

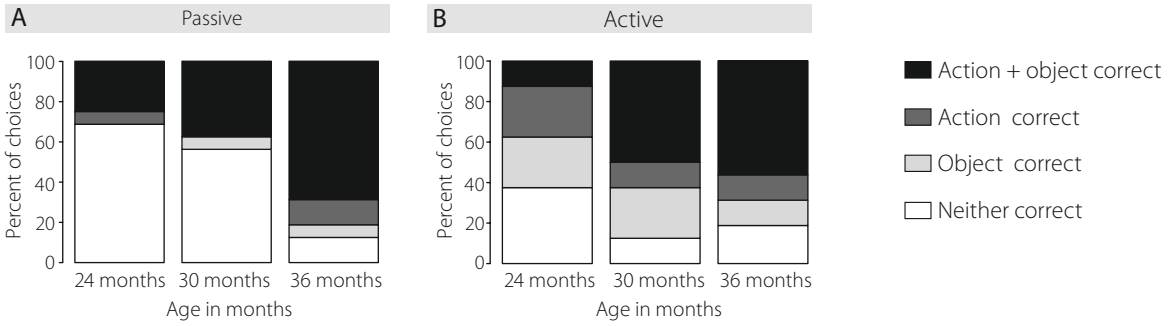

Figure 7.1.2 The learning pattern in the manner actions in the two conditions and the three age groups. Children at the ages of 24 and 30 months acquired more partly correct semantic concepts (only object or only motion correct) in the active condition of the manner actions than in the passive condition.

two levels. First, enactment is beneficial for learning the words for actions that are primarily defined by their motion characteristics. Second, the ability to reproduce an action seems to be a prerequisite for the learning of the respective action word.

Implementation of observed actions into one's own actions: Temporal and functional relationships between action prediction and imitation

7.1.3

Gampe, A.[1], Prinz, W.[1], & Daum, M. M.[1]

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

One of the fundamental mechanisms of the transmission of knowledge is imitation (e.g. Tomasello, 1999, The cultural origins of human condition, Harvard University Press). Imitation leads to the acquisition of new skills and knowledge about both the physical and the social world. To acquire new skills, two processes are involved. First, an observer perceives another person performing an action. Then, the observer reproduces this perceived action. The connection between these two processes is still a matter of debate (e.g. correspondence problem, Brass & Heyes, 2005, Trends Cogn Sci, 9, 489–495).

In the present study (Gampe, Prinz, & Daum, subm.), we explored the long-term developmental course of the perception and the reproduction of an action. In particular, we investigated the temporal and functional relationships between the prediction and the imitation of two novel actions (more familiar hammering or less familiar pulling) in children between 12 and 30 months old. The children were first presented with a video of a complex multi-step action while their eye movements were measured using eye-tracking technology. They were then given the opportunity to reproduce the previously observed action. We analyzed the frequency of children's anticipatory gaze shifts (i.e. how often a child's gaze arrived at the goal of the action before the action was completed) as well as the proficiency of their action reproduction. The results showed that the frequency of anticipatory gaze shifts was correlated with the repro-

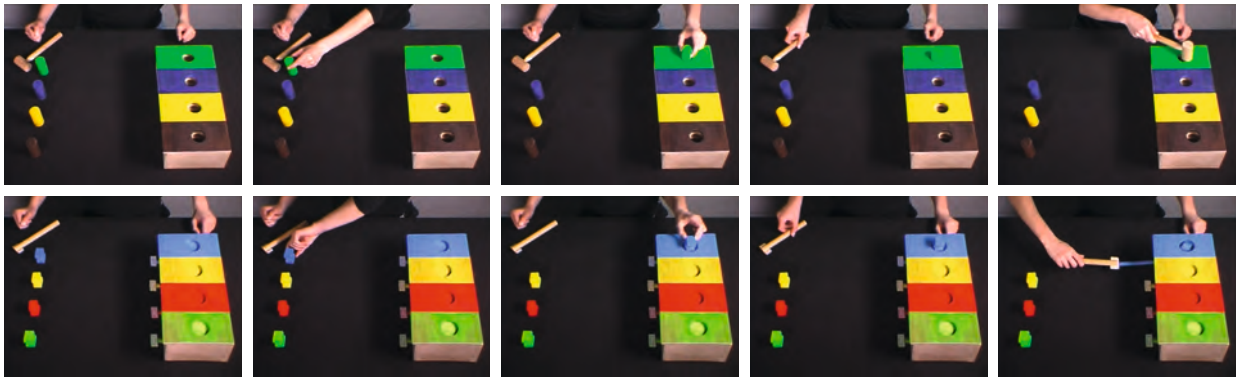

Figure 7.1.3.1 Stimulus Material used for the hammering action (upper row) and the pulling action (lower row). Each key frame depicts one of the steps: starting frame, Step 1) grasping the block, Step 2) putting the block onto the box, Step 3) grasping the tool, and Step 4) using the tool to put the block into the box.

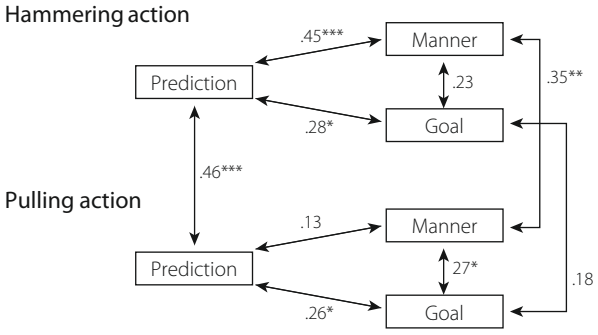

Figure 7.1.3.2 Results of partial correlational analyses between action prediction and action imitation, controlling for age. *p < .05, **p < .01, ***p < .001.

duction of the action. This indicates that with respect to a functional relationship, the prediction of an action goal was correlated with the imitation of the action goal. Further, this relation differed between the two action types. In the more familiar hammering action, goal prediction was correlated with the imitation of both the goal of the action and the specific manner to achieve it. In the less familiar pulling action, goal prediction was only related to the imitation of the goal but not the manner. With respect to the temporal relation, the results show that developmental trajectories of prediction and imitation differ. In the more familiar hammering action, the development of the prediction of the actions preceded the development of the imitation of the same action. In the less familiar pulling action, in contrast, action prediction and imitation followed the same developmental trajectories. These results are the first to show that the prediction of the goal of an observed action is related to the subsequent imitation of the same action. In fact, one might even interpret the present data as indicating that action perception in the sense of goal prediction can be used as a predictor of whether and how well a child will imitate the observed action.

Congresses, Workshops, and Symposia

Daum, M. M. (April–July). *Action Colloquium – Summer Semester.* Colloquium. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. **2012**

Prinz, W., & Schneider, W. X. (July). *Perception and Action: In Search of Linkage Principles.* Workshop. Centre for interdisciplinary Research (ZiF), Bielefeld, Germany. **2013**

Degrees

PhD Theses

Dolk, T. *A referential coding account for the social Simon effect.* University of Leipzig, Germany. **2013**

Gampe, A. *The developmental interrelations of action representations in early childhood.* University of Zurich, Switzerland.

Walter, A. *The role of goal representations in action control.* University of Leipzig, Germany.

Appointments

Daum, M. M. *Professor for Developmental Psychology.* University of Zurich, Switzerland. **2012**

Awards

Prinz, W. *Franz Emanuel Weinert Award.* German Psychological Society (DGPs). **2012**

Publications

Books and Book Chapters

Daum, M. M., & Aschersleben, G. (in press). Experimentelle Handlungsforschung: Die ontogenetische Perspektive. In W. Prinz (Ed.), *Experimentelle Handlungsforschung: Kognitive Grundlagen der Wahrnehmung und Steuerung von Handlungen*. Stuttgart: Kohlhammer.

Daum, M. M., & Prinz, W. (2012). Body and action representations for integrating self and other. In V. Slaughter, & C. A. Brownell (Eds.), *Early development of body representations* (pp. 267–286). Cambridge, UK: Cambridge University Press.

Elsner, B., & Prinz, W. (2012). Psychologische Modelle der Handlungssteuerung. In H.-O. Karnath, & P. Thier (Eds.), *Kognitive Neurowissenschaften* (3rd ed., pp. 367–375). Berlin: Springer.

Herwig, A., Beisert, M., & Prinz, W. (2013). Action science emerging: Introduction and Leitmotifs. In W. Prinz, M. Beisert & A. Herwig (Eds.), *Action science: Foundations of an emerging discipline* (pp. 1-34). Cambridge, MA: MIT Press.

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Prinz, W. (2012). *Open minds: The social making of agency and intentionality*. Cambridge, MA: MIT Press.

Prinz, W. (2012). Subjektivität zwischen Natur und Kultur. In C. Ammer, & A. Lindemann (Eds.), *Hirnforschung und Menschenbild* (pp. 53–84). Leipzig: Evangelische Verlagsanstalt.

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Prinz, W. (2013). *Selbst im Spiegel: Die soziale Konstruktion von Subjektivität*. Berlin: Suhrkamp.

Prinz, W. (Ed.). (in press). *Experimentelle Handlungsforschung: Kognitive Grundlagen der Wahrnehmung und Steuerung von Handlungen*. Stuttgart: Kohlhammer.

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Articles

Aschersleben, G., Henning, A., & Daum, M. M. (2013). Discontinuities in early development of the understanding of physical causality. *Cognitive Development, 28*(1), 31–40.

Atmaca, S., Stadler, W., Keitel, A., Ott, D. V. M., Lepsien, J., & Prinz, W. (2013). Prediction processes during multiple object tracking (MOT): Involvement of dorsal and ventral premotor cortices. *Brain and Behavior*. Advance online publication. doi: 10.1002/brb3.180

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Dietrich, S., Prinz, W., & Rieger, M. (2012). Vision-to-event and movement-to-event coordination in an unimanual circling task. *Experimental Brain Research, 218*(2), 237–246.

Dittrich, K., Dolk, T., Rothe-Wulf, A., Klauer, C., & Prinz, W. (2013). Keys and seats: Spatial response coding underlying the social Simon effect. *Attention, Perception, & Psychophysics, 75*(8), 1725-1736.

Dolk, T., Hommel, B., Prinz, W., & Liepelt, R. (2013). The (not so) Social Simon effect: A referential coding account. *Journal of Experimental Psychology: Human Perception and Performance, 39*(5), 1248–1260.

Dolk, T., Liepelt, R., Prinz, W., & Fiehler, K. (2013). Visual experience determines the use of external reference frames in joint action control. *PLoS One, 8*(3): e59008. doi:10.1371/journal.pone.0059008

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Index of Published Figures

Figure 7.1.1
Daum, M. M., Ulber, J., & Gredebäck, G. (2013). The development of pointing perception in infancy: Effects of communicative signals on covert shifts of attention. *Developmental Psychology*, *49*(10), 1898–1908.

7.2
Max Planck Research Group "Music Cognition and Action"

The broad aim of the former Max Planck Research Group on Music Cognition and Action (MCA) was to investigate the behavioural and brain bases of human interaction in musical contexts. Our research employed performers in diverse ensembles—piano duos, choral groups, jazz combos, and gamelan musicians—but our most rigorous research efforts were directed towards ensemble performance in the tradition of Western classical music. This approach was motivated by the assumption that, when considered as a microcosm of human interaction, ensemble performance is a fruitful domain in which to study the dynamics of interpersonal coordination and nonverbal communication under controlled conditions.

A theoretical framework addressing the psychological processes and factors that influence the quality of interpersonal coordination during musical ensemble performance guided the research agenda pursued by the group (Keller, in press). The core of this framework consists of three cognitive-motor skills that allow a performer to anticipate, attend, and adapt to the actions of co-performers in real time. The framework accounts for how these three skills interact with one another, as well as with social-psychological factors (e.g. variables related to personality) and the performer's knowledge about the music and familiarity with co-performers (see Fig. 7.2). The project descriptions that follow document recent discoveries concerning these links and the neural processes and structures that support them.

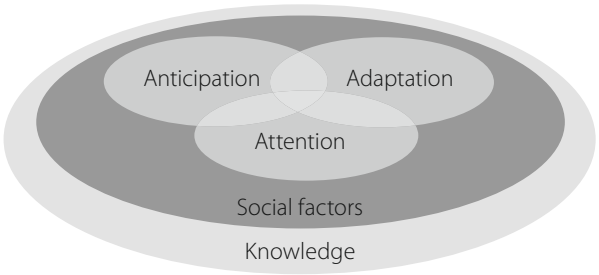

Figure 7.2 Components of a theoretical framework for musical ensemble performance.

7.2.1 Motor simulation and the coordination of self and other in real-time joint action

Novembre, G.[1], Ticini, L. F.[1,2], Schütz-Bosbach, S.[1], & Keller, P. E.[1]

[1] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2] Wellcome Laboratory of Neurobiology, University College London, United Kingdom

Interpersonal coordination during cooperative joint action, as exemplified by musical ensemble performance, requires the integration of simultaneous self- and other-related behaviour. The current project (Novembre et al., in press) investigated whether this function is underpinned by motor simulation, i.e. the capacity to represent a perceived action in terms of the neural resources required to execute it. We tested this hypothesis in a musical duet experiment wherein on-line brain stimulation (double-pulse Transcranial Magnetic Stimulation, dTMS) was employed to interfere with motor simulation of a virtual partner's part.

Pianists played the right-hand part of piano pieces in synchrony with a recording of the left-hand part, which had (Trained) or had not (Untrained) been practised beforehand. It was assumed that training a part enhances its simulation. The task required the pianists to adapt to tempo changes in the left-hand part that, in critical conditions, were preceded by dTMS delivered over the right primary motor cortex. We compared the accuracy of tempo adaptation following dTMS or sham stimulations across Trained and Untrained conditions.

Results indicated that dTMS impaired tempo adaptation accuracy only in the Trained condition, that is, when the pianists had practised the recorded parts beforehand and were hence more likely to simulate them. This interference effect was modulated by social-cognitive predispositions: The magnitude of the effect was greater in empathic individuals possessing a strong tendency to adopt others' perspectives (see Fig. 7.2.1). These findings suggest that motor simulation provides a functional resource for the temporal coordination of one's own behaviour with others in dynamic social contexts.

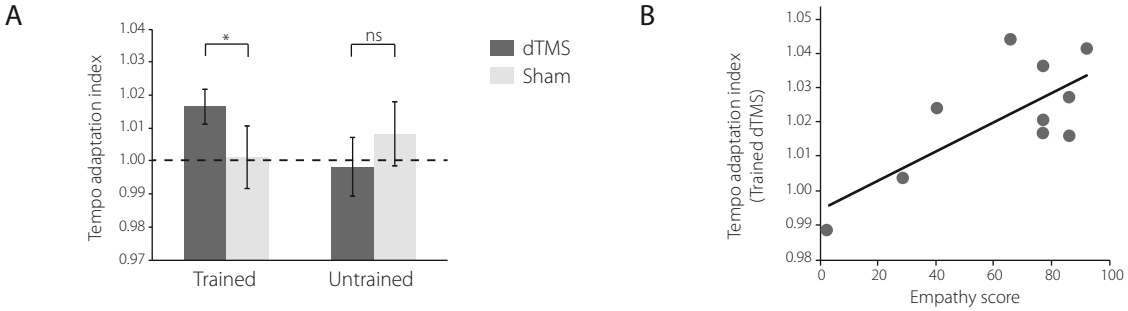

Figure 7.2.1 (A) Average tempo adaptation indices following tempo changes in Training (Trained vs Untrained) and TMS (dTMS vs. Sham) conditions. The dashed horizontal line indicates 1 (perfect adaptation), while values above or below 1 indicate that performance tempo was too slow or too fast, respectively. *P < 0.05, ns P > 0.05; (B) Scatterplot displaying the positive correlation between the adaptation indices from the Trained-TMS condition and perspective taking scores from an empathy questionnaire.

7.2.2 Segregation and integration of auditory streams when listening to multi-part music

Ragert, M.[1], Fairhurst, M. T.[1], & Keller, P. E.[1]

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

Our environment is typically replete with mixtures of sounds. Auditory stream segregation is a process that allows us to differentiate concurrent sound sources and thereby to make sense of the scene we are experiencing. This process is not always straightforward: A combination of auditory stream segregation and integration may be necessary in order to analyze the relationship between streams, and thus perceive a coherent auditory scene. This is the case, for example, when performing or listening to ensemble music.

In the present project (Ragert et al., in press), we used functional magnetic resonance imaging to examine the relative roles, and neural underpinnings, of these listening strategies—segregation vs integration—in the context of multi-part musical stimuli. We compared a real human performance of a piano duet (which contained temporal asynchronies between parts) and a synthetic stimulus of the same duet (without asynchronies) in an attentive listening paradigm that required the simultaneous segregation and integration of auditory streams. The relative contributions of integration and segregation were investigated by asking listeners to assess the leader-follower relationship between parts of the duet as we manipulated the degree to which an attended part led either structurally (attend melody vs attend accompaniment) or temporally (asynchronies vs no asynchronies between parts).

Behavioural results indicated that the relationship between parts was biased towards perceiving the conventional structural hierarchy in Western music, in which the melody generally leads (dominates) the accompaniment. Furthermore, listeners' assessments were found to vary as a function of both cognitive load, as reflected in difficulty ratings, and the interaction of the temporal and the structural relationship factors. The fMRI data (see Fig. 7.2.2) indicated that varying the temporal relationship between parts—a salient cue for stream segregation—elicited distinct patterns of neural activity in the planum temporale. By contrast, integration processes employed when listening to both the temporally separated performance stimulus and the temporally fused synthetic stimulus resulted in increased activation of the intraparietal sulcus. These results support the hypothesis that the planum temporale and intraparietal sulcus are key structures underlying the mechanisms of auditory stream segregation and integration, respectively.

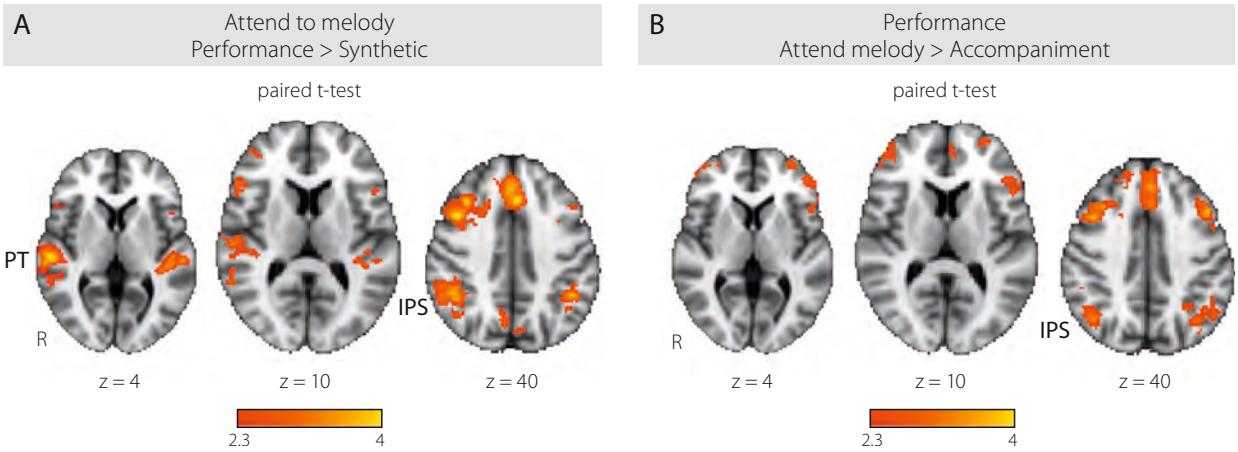

Figure 7.2.2 FMRI contrast results (P = 0.05 corrected) for (A) attending to melody in the performance stimulus relative to the synthetic stimulus and (B) when listening to the performance stimulus attending to melody relative to attending to accompaniment. PT = planum temporale; IPS = intraparietal sulcus.

The ADaptation and Anticipation Model (ADAM) of sensorimotor synchronization

7.2.3

van der Steen, M. C.[1], & Keller, P. E.[1]

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

Environments characterized by rhythmic events—as encountered in musical ensemble performance—require the precise yet flexible timing of movements. Sensorimotor synchronization (i.e. the temporal coordination of an action with events in a predictable external rhythm) is a fundamental human skill that contributes to optimal sensorimotor control in daily life. There is a long tradition of research on sensorimotor synchronization focusing on adaptive error correction mechanisms that support the synchronization of periodic movements (e.g. finger taps) with events in regular pacing sequences. The results of recent studies have additionally highlighted the importance of anticipatory mechanisms that support temporal prediction in the context of sensorimo-

tor synchronization with sequences containing tempo changes.
This ongoing project investigates the interactive roles of adaptation and anticipatory mechanisms in sensorimotor synchronization with ADAM: an ADaptation and Anticipation Model (van der Steen & Keller, 2013). ADAM combines reactive error correction processes (adaptation) with predictive temporal extrapolation processes (anticipation) motivated by the computational neuroscience concept of internal models. Computer simulations and experimental manipulations based on ADAM are used to validate its architecture, and to demonstrate its viability as a platform for exploring the mechanisms that underlie adaptation and anticipation in sensorimotor synchronization.

7.2.4 Social communicative functions of music

König, R.[1], & Keller, P. E.[1]

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

Music is a human communicative art that may have deep biological roots. Long before humans evolved the capacity to sing and dance together in groups, other animals—such as crickets, frogs, fireflies, and fiddler crabs—engaged in synchronous group behaviour. These synchronous displays, produced by males in order to attract migrating females, are termed the "beacon effect".
The current project investigated whether a similar effect characterizes human musical behaviour. The voices of members of the St Thomas Boys' Choir in Leipzig, one of the world's premier choral ensembles, were recorded with head-worn microphones as they performed a short concert programme three times: first with an all-male audience, then with female peers in the audience, and finally with an all-male audience again (see Fig. 7.2.4). The boys in the choir were 12–19 years of age, and the female peers were aged 15–16. Acoustic analyses of the recordings revealed that older boys (aged 16–19) increased the energy in a high frequency band (2500–3500 Hz) within the voice's spectrum in the presence of the females. As this frequency band, known as the "singers' formant", adds brilliance and carrying power to the voice, this finding is consistent with a beacon effect.

Figure 7.2.4 The St Thomas Boys' Choir during the recording session (Photo: Markus Eckardt).

Congresses, Workshops, and Symposia

Kotz, S. A., & Keller, P. E. (September). *EBRAMUS Workshop on Music and Language: Structure, Rhythm and Prosody.* Workshop. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. **2012**

Degrees

PhD Theses

Novembre, G. *Action-perception coupling in the musician's brain: What is it good for?* University of Leipzig, Germany. **2013**

Appointments

Novembre, G. *Research Lecturer.* MARCS Institute, University of Western Sydney, Australia. **2013**

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Wöllner, C., Deconinck, F. J. A., Parkinson, J., Hove, M. J., & Keller, P. E. (2012). The perception of prototypical motion: Synchronization is enhanced with quantitatively morphed gestures of musical conductors. *Journal of Experimental Psychology: Human Perception and Performance, 38*(6), 1390–1403.

7.3
Max Planck Research Group "Body and Self"

The Research Group "Body and Self", which officially concluded its work at the end of 2012, completed a number of studies in cooperation with the Max Planck Institute for Human Cognitive and Brain Sciences between 2012 and 2013. These studies were funded by the Max Planck Society, Deutsche Forschungsgemeinschaft (DFG), and Volkswagen Foundation (VW-Stiftung). In our last period of work at the MPI, we focused on sensorimotor-based markers of action attribution and their relation to conscious experience of authorship for actions (7.3.1), the neural correlates of authorship ascription (7.3.2) as well as visual self-body identification (7.3.3). Finally, we aimed to identify the neural network underlying interoceptive bodily awareness (7.3.4), and, last but not least, we investigated changes in the neural representation of observed actions in the aging body and brain (7.3.5).

7.3.1 Agency in the sensorimotor system and its relation to explicit action awareness

Weiss, C.[1], Tsakiris, M.[2], Haggard, P.[3], & Schütz-Bosbach, S.[1]

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[2] Department of Psychology, Royal Holloway University of London, Egham, United Kingdom
[3] Institute of Cognitive Neuroscience, University College London, United Kingdom

Previous work suggests that a basic registration of agency (i.e. experience of generating and controlling one's own actions) might be embedded in low-level, sensorimotor representations of actions. Specifically, it was shown that corticospinal excitability in response to observed actions was decreased if the actions were linked to oneself, whereas it was increased if the actions were linked to another person (Schütz-Bosbach, Mancini, Aglioti, & Haggard, 2006, Curr Biol, 16, 1830–1834). The present project firstly sought to confirm this finding and secondly aimed to investigate whether or not the hypothesized low-level, sensorimotor representation is linked to high-level, explicit representation of agency (i.e. a level at which judgments of agency are formed). To this end, participants performed simple manual movements while receiving visual feedback thereof. The degree of agency over the visually-displayed movement was manipulated by varying the degree of its temporal correspondence with the movement participants actually executed (see Fig. 7.3.1.1). Corticospinal excitability (i.e. motor-evoked potentials to single-pulse TMS) was recorded as a low-level, sensorimotor measure of agency. In addition, participants verbally judged whether or not the observed movement corresponded to the movement they executed as a high-level, explicit measure of agency. In line with the idea of a sensorimotor embedment of agency, corticospinal excitability varied with the degree of temporal correspondence between observed and executed movement (see Fig. 7.3.1.2A). Moreover, a substantial covariation between corticospinal excitability and verbal judgments was found (see Fig. 7.3.1.2B). This suggests that explicit agency judgments could be directly based on information within the sensorimotor system.

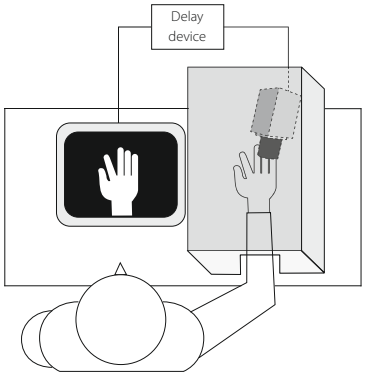

Figure 7.3.1.1 Experimental setup. Participants sat comfortably in front of a horizontally aligned monitor. Their right hand was hidden from direct view, placed inside a box positioned on the right side of the monitor. Participants had to perform abduction movements of their right index finger. These movements were filmed vertically from above and projected on the monitor in front of participants either in approximate real time or delayed by 100, 200, or 300 ms.

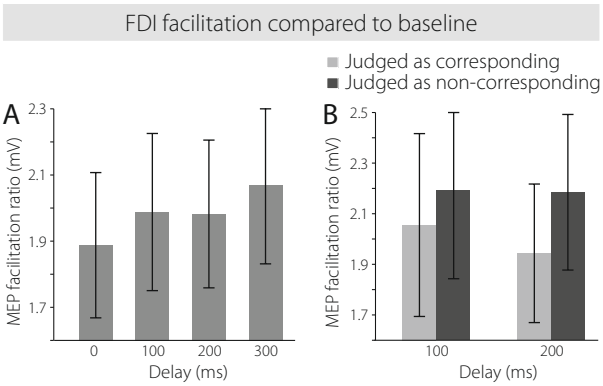

Figure 7.3.1.2 Results: Mean motor-evoked potentials (MEPs) of the first dorsal interosseus (FDI; index finger muscle) were normalized to a pre-recorded fixation baseline (MEP facilitation ratio) for each participant. Figure 7.3.1.2A shows the means and standard errors of the averaged MEP facilitation ratios of FDI as a function of the delay of the visual movement feedback (0, 100, 200, or 300 ms). A significant increase of MEPs with increasing delay of the visual movement feedback (i.e. decreasing temporal correspondence of observed as compared to executed movement) was found. Figure 7.3.1.2B shows the means and standard errors of the averaged MEP facilitation ratios of FDI as a function of the delay of the visual movement feedback (100 or 200 ms) and participants' correspondence judgment (observed movement judged as corresponding vs non-corresponding as compared to executed movement). No significant difference between MEPs in the 100- and 200-ms delays was found. Importantly, however, MEPs were significantly increased if participants judged the observed movement as corresponding to their executed movement as compared to when they judged it as non-corresponding.

Posterior parietal activity shapes agent-specific responses in the human motor system

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Successful social interaction demands the ability to recognize 'who' is the agent of an observed action. To investigate where and how the brain computes this assignment, we combined online single-pulse (spTMS) and offline repetitive transcranial magnetic stimulation with a modified version of the 'rubber hand illusion' in which participants observed hand actions that were illusorily attributed either to the self or to another individual (Fig. 7.3.2.1). While spTMS-induced motor-evoked potentials (MEP) measured the state of the motor system during action observation, either continuous or intermediate (sham) theta-burst stimulation (cTBS and imTBS) were applied over the left inferior parietal lobe in order to investigate its causal contribution to self and other action attribution. The results showed an owner-specific pattern of activation for the muscle not involved in the observed action (ADM; Fig. 7.3.2.2A): MEP were facilitated when the hand observed was illusorily attributed to the self versus the other individual. The MEP recorded from the muscle involved in the observed action (FDI) showed agent-specific activations during sham imTBS: MEP were facilitated during the observation of actions attributed to the other individual, whilst they were suppressed during observation of self-attributed actions (Fig. 7.3.2.2B). Interestingly, when the left inferior parietal region was virtually and transiently lesioned with cTBS, the participants selectively lost agent-specific responses whilst those MEP associated with limb ownership could be measured. These results suggest that action attribution in the motor system arises from parietal neural computations that provide fundamental neural signals for social differentiation.

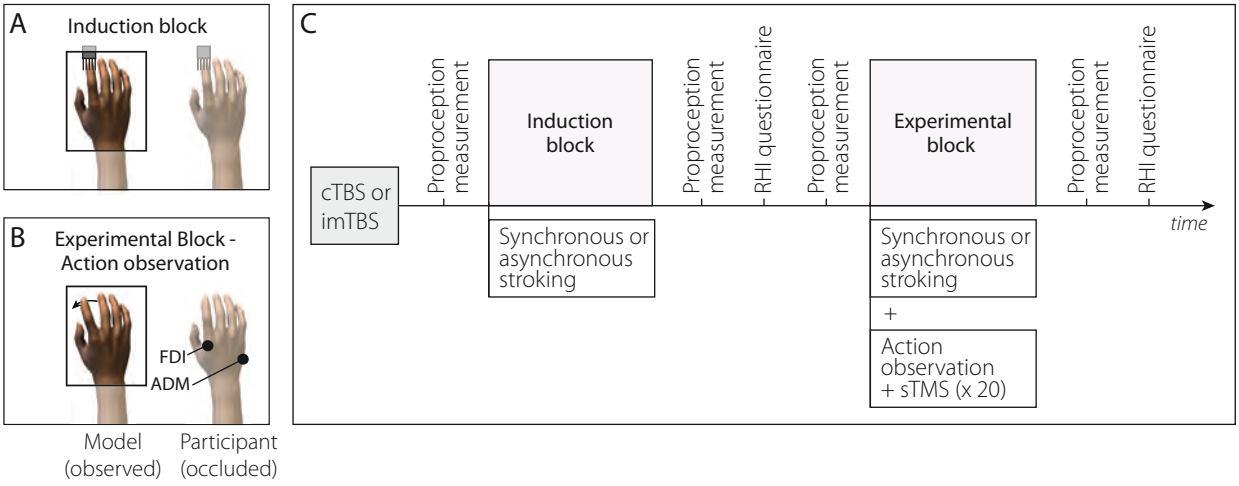

Figure 7.3.2.1 Experimental Setup: We assessed the role of parietal cortex in attributing observed actions attributed either to the self or to another agent by applying inhibitory or sham TBS (cTBS, imTBS) over this brain area while participants illusorily attributed (or not) a model's hand to their own body, by means of the Rubber Hand Illusion (RHI). Participants rested their right hand hidden from view in a box while they observed the model's right hand. Synchronous or asynchronous brushstrokes were applied to the participants' and the models' right index fingers by two identical paintbrushes mounted on computer-controlled motors (A; Induction Block, IB). Only synchronous stroking induced the RHI. In an Experimental Block (EB), the models made unpredictable index finger abductions and the participant received a single TMS pulse (sTMS) over the left motor cortex shortly after observing the model's action (B). Measures of ownership (proprioceptive drift and RHI questionnaire, right panel) assessed implicit and explicit ownership of the model's hand. STMS-induced motor-evoked potentials (MEPs) were recorded from the FDI (index finger abductor) and ADM (little finger abductor) muscles to investigate the effect of parietal TBS on the facilitation of the motor system while observing self or other attributed actions.

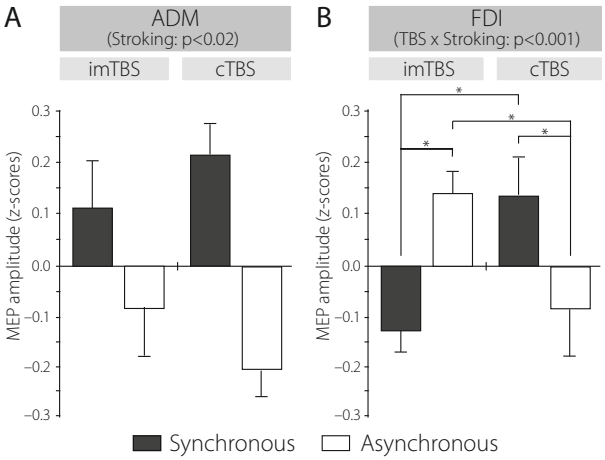

Figure 7.3.2.2 Cortical Excitability of ADM (A) and FDI (B) muscles after action observation in each Stroking and TBS condition. Data represent the average MEP size (z-scores) in each condition (Mean + S.E.M.).

7.3.3 Decoding visual representations of self- and other bodies in the human brain

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Previous fMRI studies on visual self-other distinction mainly focused on investigating regional activation differences. In contrast, here, we aimed to study where in the brain information on the identity of one's own versus other bodies is encoded in terms of differential patterns of activation. Participants viewed stimuli depicting their own, a familiar, and an unfamiliar other body. Multivariate pattern classification was employed to pairwise decode the identities. Areas differentially encoding self- versus familiar other bodies were found in the right posterior cingulate cortex and the left ventromedial prefrontal cortex. Both areas have been suggested to be part of a multimodal "core-self" network (Northoff, Heinzel, de Greck, Bermpohl, Dobrowolny, & Panksepp, 2006, NeuroImage, 31, 440–457). Decoding of self versus unfamiliar other was possible in frontal and subcortical regions of which several appear to be involved in processing self-relevant information, like the left middle frontal gyrus (Kjaer, Nowak, & Lou, 2002, NeuroImage, 17, 1080–1086). Finally, we were able to decode familiar- versus unfamiliar other bodies in the right temporo-parietal junction area. It is thought to provide a multimodal detection mechanism for deviance from expectation (Sperduti, Delaveau, Fossati, & Nadel, 2011, Brain Struct Funct, 216, 151–157), which may enable the detection of unfamiliarity.

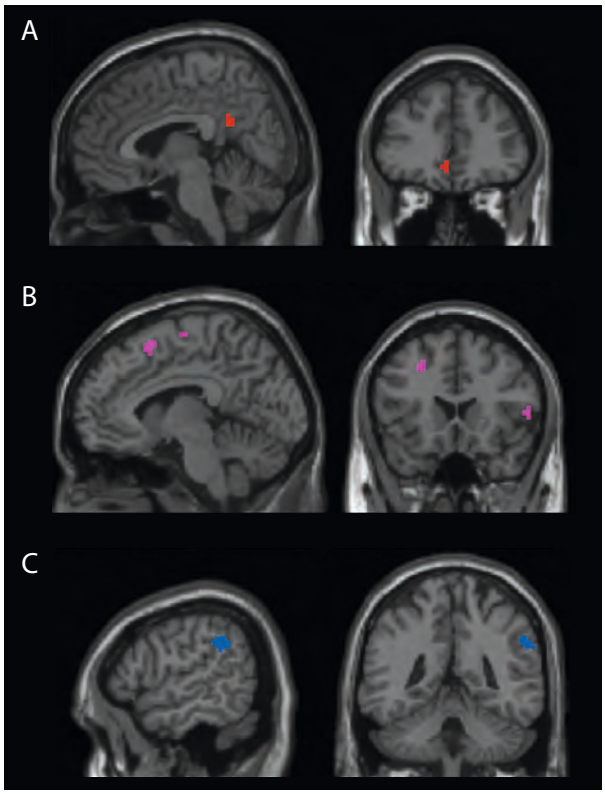

Figure 7.3.3 Results of pairwise identity decoding analyses. (A) Self- versus familiar other bodies; (B) Self- versus unfamiliar other bodies; (C) Familiar other versus unfamiliar other bodies ($p < 0.0001$ voxelwise threshold, minimum cluster size 5 voxels, cluster correction threshold $p < 0.001$).

How experts feel their body from the inside: The somatomotor system but not the insula mediates interoceptive awareness in high-perceivers

7.3.4

Kuehn, E.[1], Mueller, K.[1], Lohmann, G.[1], & Schütz-Bosbach, S.[1]

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The ability to consciously perceive inner bodily signals, such as one's own heartbeat, has been assigned an important role in the emergence of bodily and self-awareness. For a long time, interoceptive awareness (IA) has been assumed to be mediated by the right anterior insula cortex. Recent evidence, however, indicates that also the somatosensory cortices are critically involved in heartbeat detection. The present study aimed to systematically characterize the neuronal correlates of IA. We investigated two groups of participants that either showed high or low levels of IA as accessed by heartbeat counting. Both groups underwent two fMRI sessions where they either concentrated on their own heartbeat (IA), or on externally generated tones (exteroceptive awareness, EA). We show that during IA compared to EA, high-perceivers display (i) higher activity levels in somatomotor areas, and (ii) decreased network centrality of the right posterior insula. In addition, high-perceivers showed higher network centrality in somatomotor areas during rest compared to low-perceivers. Taken together, our results support the assumption that the right anterior insula is not the sole cortical substrate mediating IA, but that high-perceivers particularly make use of their somatosensory cortices when detecting their own heartbeat signals.

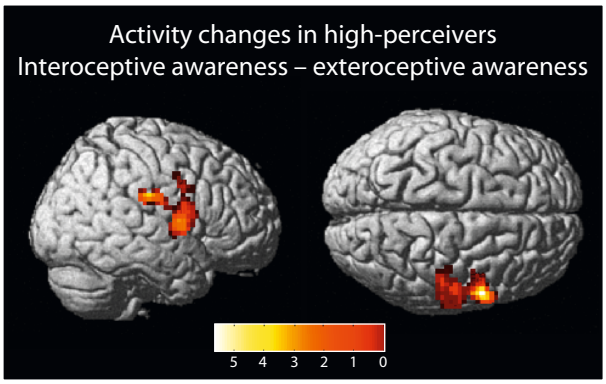

Figure 7.3.4 Brain activity changes during interoceptive versus exteroceptive awareness in high-perceivers. When high-perceivers concentrated on their own heartbeat, compared to concentrating on external tones, they showed significantly higher activity in the right precentral cortex and the right rolandic operculum. This cluster also spanned the secondary somatosensory cortex (S2). Functional data are displayed on the lateral and axial views of the SPM template brain (threshold: $p \leq 0.001$ at voxel level, $k \geq 5$, cluster-level corrected at FDR, $p \leq 0.05$).

Action prediction in younger versus older adults: Neural correlates of motor familiarity

7.3.5

Diersch, N.[1,2], Mueller, K.[1], Cross, E. S.[1,3,4], Stadler, W.[1,5], Rieger, M.[1,6], & Schütz-Bosbach, S.[1]

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[6] Institute for Psychology, Medical Sciences & Management Department, UMIT – The Health and Life Sciences University, Hall/Tyrol, Austria

According to prominent conceptualizations of motor cognition, the observation of another person performing an action automatically activates an internal representation of how the observer's body would perform the same action. This allows us to predict observed actions. In line with this, neuroimaging studies frequently demonstrate a remarkable overlap between brain regions recruited during action execution and action ob-

servation. To date, however, it remains largely unknown how the neural representation of observed actions changes with advancing age. Using fMRI, we investigated age-related changes in neural activation patterns during the observation of actions that were partly occluded at critical time points and varied in their degree of motor familiarity. The continuation of the action sequences was temporarily manipulated and participants were asked to judge the temporal coherence of the observed action continuations. The results indicate that older adults are less efficient in exploiting their sensorimotor system to generate predictions about observed actions. Older adults showed greater recruitment of the visual cortex no matter whether the observed actions were familiar or not. If the actions were familiar, older adults recruited an additional cluster in the right hippocampus extending to the caudate. Thus, neural selectivity in relevant brain regions seems to decrease with advancing age which might result in an altered representation of observed actions in older compared to younger adults.

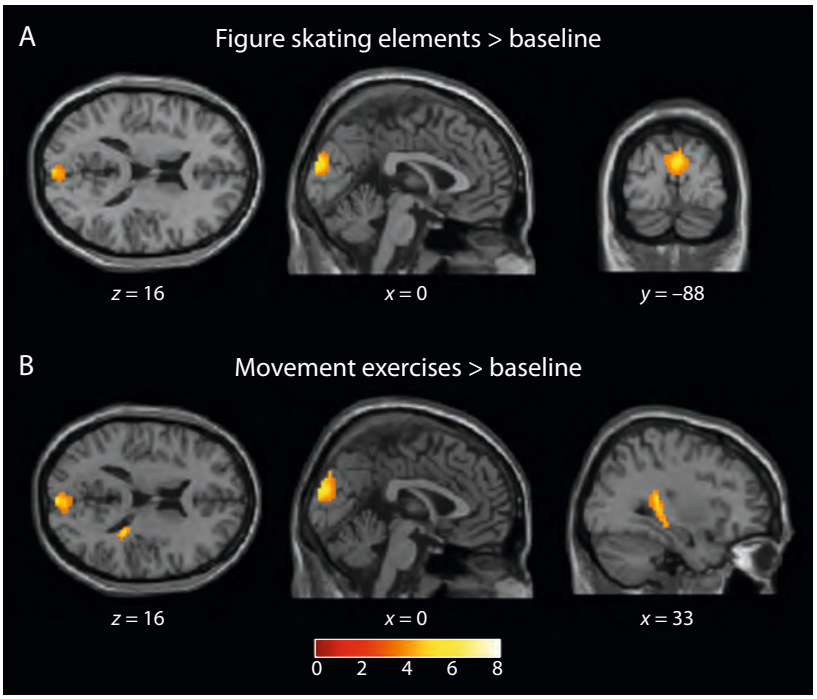

Figure 7.3.5 Brain regions more activated in older adults compared to younger adults during the prediction of unfamiliar actions (i.e. figure skating elements; (A) and familiar actions (i.e. simple movement exercises; (B) compared to baseline ($p < 0.05$, FWE corrected).

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Weiss, C., Tsakiris, M., Haggard, P., & Schütz-Bosbach, S. (2013). Agency in the sensorimotor system and its relation to explicit action awareness. *Neuropsychologia*. Advance online publication. doi:10.1016/j.neuropsychologia.2013.09.034

Index of Published Figures

Figure 7.3.1.1, Figure 7.3.1.2
Weiss, C., Tsakiris, M., Haggard, P., & Schütz-Bosbach, S. (in press). Agency in the sensorimotor system and its relation to explicit action awareness. *Neuropsychologia.*

Figure 7.3.5
Diersch, N., Mueller, K., Cross, E. S., Stadler, W., Rieger, M., & Schütz-Bosbach, S. (2013). Action prediction in younger versus older adults: Neural correlates of motor familiarity. *PLoS One,* 8(5): e64195. doi:10.1371/journal.pone.0064195

7.4 Minerva Research Group "Neurocognition of Rhythm in Communication"

Understanding adaptive yet complex human behaviour necessitates a thorough and detailed understanding of principles guiding such behaviour. We have therefore focused our research on four key questions within our conceptual framework: (1) What is the impact of prediction (type 'what' and temporal 'when') on sensory, multisensory, and integrative cognitive processes? (2) What are the consequences of uncertainties or unexpected outcomes in these processes? (3) Which networks support these processes? (4) What are the consequences of impairment in the system(s) underlying these processes? Our interactive research was pursued by a team of undergraduate and post-graduate students, post-doctoral researchers, and colleagues utilizing behavioural and electrophysiological/oscillatory measures and s/fMRI (3T and 7T) in healthy and clinical (Parkinson's disease, focal basal ganglia, and cerebellar lesion patients) populations.

For example, we investigated how subjectively perceived binary rhythms in equitone sequences relate to internal fluctuations of attention found in the alpha frequency range (8–12 Hz) to illuminate the contribution of sensorimotor systems to temporal processing (7.4.1). By means of symptom-lesion mapping, we explored the contribution of the basal ganglia to optimal temporally predictive behaviour (7.4.2). In collaboration with colleagues (Neuropsychology, Cortical Networks and Cognitive Function, University of Jena), we isolated potential microstructural subdivisions in the caudate nucleus with diffusion MRI, substantiating their contribution to cortico-subcortico-cortical loops relevant for adaptation and reactive control (7.4.3). Lastly, in collaboration with the Department of Neurophysics we studied the role of the basal ganglia in stimulus incompatibility with probabilistic expectations leading to conflict (7.4.4). This series of studies highlights the critical impact of subcortical structures on predictive adaptation and reactive control in human cognitive behaviour.

7.4.1 Subjective rhythmization in healthy young and older adults and basal ganglia lesion patients: Evidence from alpha oscillations

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[2] School of Psychological Sciences, University of Manchester, United Kingdom

When listening to identical tones in an equitone sequence we perceive some tones as more salient than others. This sensation, termed subjective rhythmization, seems to be based on a binary rhythm of strong and weak beats and has been related to internal increases in attention in audition that are seen as brain oscillatory changes (relative increase in the alpha band (8–12 Hz)). We further pursued this phenomenon in two experiments with young and elderly volunteers and patients with focal lesions in the basal ganglia to explore whether this form of internal attention varies as a function of age and whether the basal ganglia are critically involved in its modulation. Our findings indicate that differences in alpha band oscillations reflect subjective rhythmization as evident in the relative alpha enhancement for perceptually strong as compared to weak tones (Fig. 7.4.1) and provide further support for the Dynamic Attending Theory (Large & Jones, 1999). The topographical distributions of the alpha enhancement suggest the involvement of sensorimotor and attention areas involved in temporal-processing (e.g. bilateral SMA, left IPL). Aging may generally weaken this effect, whereas lesions within the basal ganglia may abolish it completely.

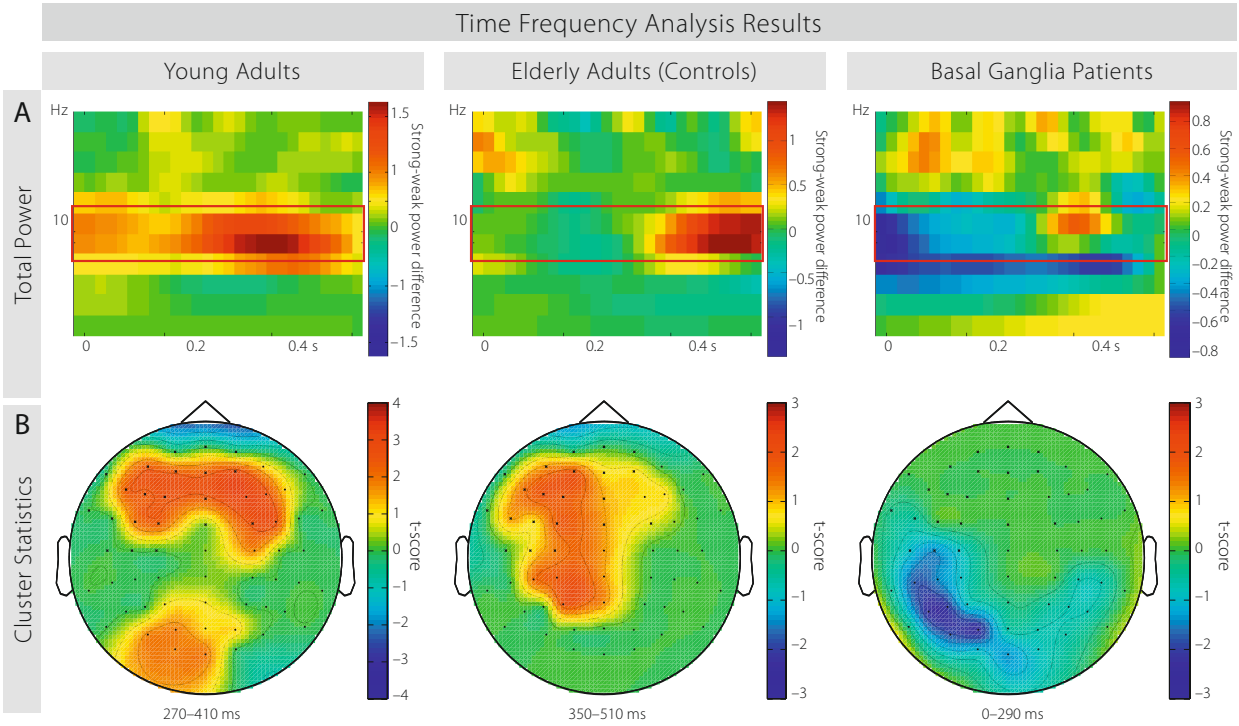

Figure 7.4.1 (A) Total power differences (STRONG-WEAK) between standard tone 5 (STRONG) and standard tone 6 (WEAK). (B) Topographic plots for significant statistical differences ($p < .025$) between standard tone 5 (STRONG) and standard tone 6 (WEAK). All significant clusters are situated in the alpha band (8–12 Hz).

Lesion-symptom mapping of temporal processing impairment in basal ganglia patients

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While the advent and continuous improvement of functional neuroimaging has rendered lesion-symptom mapping partly obsolete, the method still generates insight into structure-function mapping. Here, a joint approach provides the opportunity to combine the high temporal resolution of electroencephalography (EEG) with the high spatial resolution of structural magnetic resonance imaging (sMRI). Patients with focal basal ganglia lesions (N = 30) and healthy controls used the temporal structure of an auditory stimulus sequence to optimize predictive cognitive behaviour. During EEG, participants listened to 'oddball sequences', silently counting the number of rare deviant sinusoidal tones (300 ms, 660 Hz) presented among frequent standard tones (300 ms, 600 Hz). Regular sequences employed a stable inter-stimulus-interval of 600 ms (maximal predictability), whereas irregular sequences employed a random interval (200–1000 ms). Compared to controls, patients display selective impairments in early sensory (e.g. P50) and later attention-dependent event-related potentials (e.g. P3b) indicative of less efficient use of predictable temporal structure. By means of Voxel-based Lesion-Symptom Mapping (VLSM; Bates, Wilson, Saygin, Dick, Sereno, et al., 2003, Nat Neurosci, 6, 448–450) we used these data to establish detailed structure-function relations. The results suggest a fine-grained functional and anatomical differentiation within the basal ganglia, consistent with its proposed role in perceptual temporal processing and the predictive adaptation of behaviour (Schwartze et al., 2012).

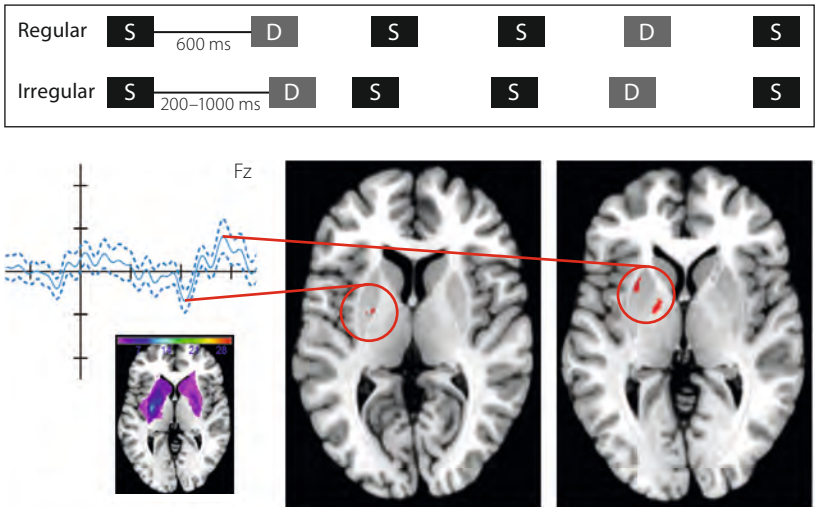

Figure 7.4.2 Experimental paradigm and results. Patients with basal ganglia lesions and healthy controls listened to temporally regular (inter-stimulus-interval 600 ms) and irregular (inter-stimulus-interval 200–1000 ms) stimulus sequences (upper panel), consisting of standard (S) and deviant tones (D). Patients and controls differ in the event-related potential (ERP) response to deviant tones. More specifically, patients do not differentiate between deviants embedded in regular and irregular temporal structure. This lack of differentiation (i.e. the effect size of components such as the P50 or the N100, which was obtained by subtracting irregular from regular responses) can be used as a "symptom" in VLSM, which identifies regions of the basal ganglia that are critically involved in this specific type of behaviour (lower panel).

7.4.3 The internal and external connectivity structure of the caudate nucleus

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[2] School of Psychological Sciences, University of Manchester, United Kingdom
[3] Hans Berger Clinic for Neurology, Jena University Hospital, Friedrich Schiller University Jena, Germany

The caudate nucleus (CN) of the striatum receives information from multiple cortical regions and transmits it back to the neocortex via the globus pallidus (GP) and the thalamus. The structure has therefore been functionally related to a number of higher cognitive functions. While there is ample evidence on the functional and connectional differentiation of the caudate nucleus, less is known about its potential microstructural subdivisions. However, this latter aspect is critical for local information processing. We used diffusion MRI, a non-invasive *in vivo* method that has great potential for the exploration of the brain structure-behaviour relationship to characterize the local fibre structure in grey matter of the CN and report novel evidence of a functionally relevant structural tri-partition along the anterior-posterior axis of this region. More specifically, the anterior section, with primarily anterior-posterior fibre directions, is connected with lateral and medial prefrontal cortices (BA 10, 11, 47), while the middle section, containing the radial fibres, features connections to the entire prefrontal cortex (Fig. 7.4.3). Furthermore, the connectivity of the CN subregions is in line with connectivity evidence from earlier invasive studies in animal models and histological validation using polarized light imaging (PLI) confirms these results and corroborates the notion that cortico-subcortico-cortical loops involve microstructurally differentiated regions in the caudate nucleus.

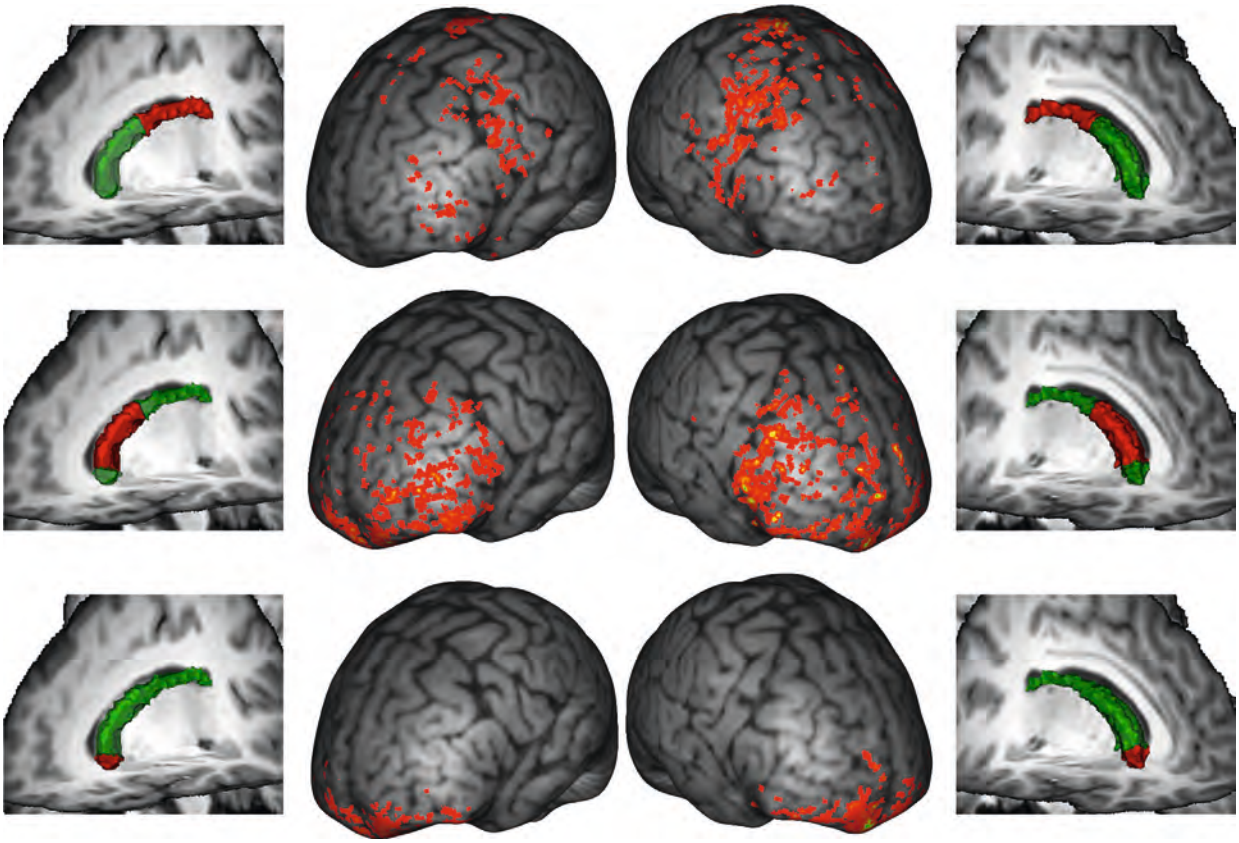

Figure 7.4.3 Cortical targets of fibres originating in the caudate subregions. Centre columns: Cumulative projection sites from all subjects, overlaid to T1 image of one subject (brain surface distance map). Outer columns: Surfaces of caudate nuclei (green) and respective subregion (red) for one subject.

Dorsomedial striatum involvement in cognitive control and conflict modulation

Mestres-Missé, A.[1,2], Bazin, P. L.[2], Trampel, R.[2], Turner, R.[2], & Kotz, S. A.[1,2]

[1] School of Psychological Sciences, University of Manchester, United Kingdom
[2] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Using ultra-high-field high-resolution functional magnetic resonance imaging (7T-fMRI), the aim of this research was to study the involvement of the basal ganglia in modulating conflict and its resolution. The working hypothesis is that the basal ganglia play a critical role when a stimulus is incompatible with probabilistic expectations, thus creating conflict, which, in turn, requires cognitive control mechanisms to inhibit a salient response, implement retrospective re-evaluation in search of the origin of conflict and a solution, and, if possible, discharge an alternative that solves the conflict. Here conflict can be manipulated by using incorrect and ambiguous stimuli. While ambiguous stimuli create a conflict but at the same time provide a resolution by means of a less common but meaningful option, incorrect stimuli are simply wrong (no alternative to render stimuli meaningful). This hypothesis was tested in a series of two experiments: Mestres-Missé et al. (2012) studied conflict that arose from structural ambiguity, that is, the same sequence could be interpreted as having two different structures (syntactic ambiguity); the present investigation focused on local ambiguity, that is, the structure remains the same, but individual elements can have more than one interpretation (semantic ambiguity).

Mestres-Missé et al. (2012) reported a rostro-caudal gradient of cognitive control within the dorsomedial striatum mirroring the described anterior–posterior cognitive control hierarchy in prefrontal cortex (Koechlin, Ody, & Kouneiher, 2003, Science, 302, 1181–1185; Badre, 2008, Trends Cogn Sci, 12, 193–200; Badre & D'Esposito, 2009, Nat Rev Neurosci, 10, 659–669) (see Fig. 7.4.4B). The present investigation tested local semantic ambiguity. The results reveal the involvement of the anterior dorsomedial striatum in conflict modulation (Fig. 7.4.4A) and highlight the importance of fronto-striatal systems in modulating conflict and its resolution.

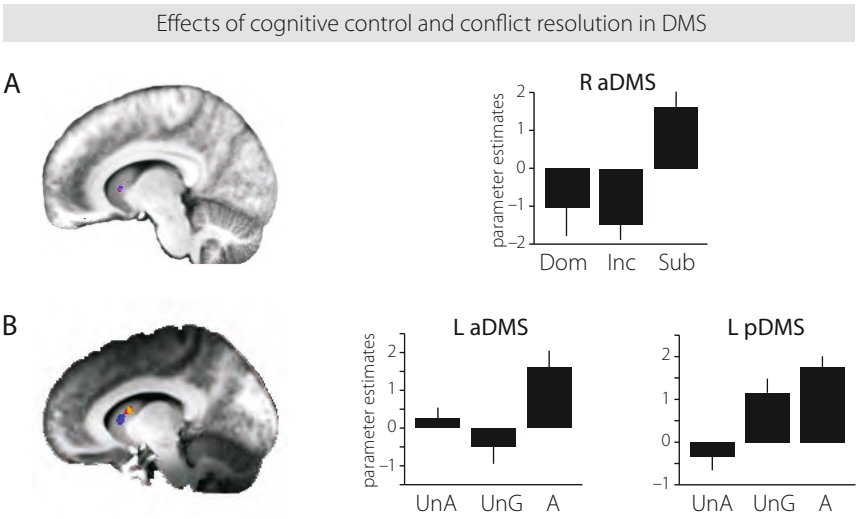

Figure 7.4.4 Functional imaging results and group-average beta values for the different sentence conditions in the dorsomedial striatum (DMS). (A) Group-average comparisons and parameter estimates for the semantic ambiguity experiment; left: overlapping (magenta) activation of the right aDMS, from the contrast 'subordinate minus dominant' (red) and 'subordinate minus incongruent' (blue). (B) Group-average comparisons and parameter estimates for the previous syntactic ambiguity experiment (Mestres-Missé et al., 2012); left: overlapping (orange) activation of the left pDMS, from the contrast 'ambiguous minus unambiguous' (red) and 'ungrammatical minus unambiguous' (green); and activation of the left aDMS, from the contrast 'ambiguous minus ungrammatical' (blue). Note the larger activation in dorsomedial striatum for subordinate/ambiguous conditions (high conflict/cognitive control) which reflects high-level cognitive processes. Abbreviations: aDMS, anterior dorsomedial striatum; pDMS, posterior dorsomedial striatum; Dom, dominant; Inc, incongruent; Sub, subordinate; UnA, unambiguous; UnG, ungrammatical; A, ambiguous.

Congresses, Workshops, and Symposia

2012 Keller, P., & Kotz, S. A. (September). *Music and Language: Structure, Rhythm and Prosody.* Workshop. Max Planck Institute for Human and Cognitive Brain Sciences, Leipzig, Germany.

Kotz, S. A., & Schwartze, M. (May). *A question of time: Subcortico-cortical interactions in speech processing.* Symposium. 1st Conference of the European Society for Cognitive and Affective Neuroscience (ESCAN), Marseille, France.

2013 Schröger, E., & Kotz, S. A. (March). *Hören wir in die Zukunft? Zur Rolle von Prädiktionen in der auditiven Informationsverarbeitung.* Symposium on 57th Annual Meeting of the German Section of the International Federation of Clinical Neurophysiology (DGKN), Leipzig, Germany.

Degrees

PhD Theses

2012 Garrido Vásquez, P. *Emotion processing in Parkinson's disease: The role of motor symptom asymmetry.* University of Leipzig, Germany.

Jessen, S. *Emotion perception in the multisensory brain.* Free University of Berlin, Germany.

Knolle, F. *Knowing what's next: The role of the cerebellum in generating predictions.* University of Leipzig, Germany.

Rothermich, K. *The rhythm's gonna get you: ERP and fMRI evidence on the interaction of metric and semantic processing.* University of Potsdam, Germany.

Schwartze, M. *Adaptation to temporal structure.* University of Potsdam, Germany.

2013 Roncaglia-Denissen, P. M. *Age of acquisition or individual differences: What drives ambiguity resolution?* University of Potsdam, Germany.

Publications

Books and Bookchapters

Garrido-Vásquez, P. (2012). Emotion processing in Parkinson's disease: The role of motor symptom asymmetry (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 137*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

Jessen, S. (2012). Emotion perception in the multisensory brain (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 140*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

Knolle, F. (2012). Knowing what's next: The role of the cerebellum in generating predictions (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 142*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

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Kotz, S. A., Rothermich, K., & Schmidt-Kassow, M. (2012). Sentence comprehension in healthy and brain-damaged populations. In M. Faust (Ed.), *The Handbook of the Neuropsychology of Language: Vol. 2. Language processing in the brain: Clinical populations* (pp. 760–777). New York: Wiley-Blackwell.

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Schwartze, M. (2012). Adaptation to temporal structure (Doctoral dissertation). *MPI Series in Human Cognitive and Brain Sciences: Vol. 138*. Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

Articles

Flasskamp, A., Kotz, S. A., Schlegel, U., & Skodda, S. (2012). Acceleration of syllable repetition in Parkinson's disease is more prominent in the left-side dominant patients. *Parkinsonism & Related Disorders, 18*(4), 343–347.

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Hove, M. J., Fairhurst, M. T., Kotz, S. A., & Keller, P. E. (2013). Synchronizing with auditory and visual rhythms: An fMRI assessment of modality differences and modality appropriateness. *NeuroImage, 67*, 313–321.

Jakuszeit, M., Kotz, S. A., & Hasting, A. S. (2013). Generating predictions: Lesion evidence on the role of left inferior frontal cortex in rapid syntactic analysis. *Cortex, 49*(10), 2861–2874.

Jessen, S., & Kotz, S. A. (2013). On the role of crossmodal prediction in audiovisual emotion perception. *Frontiers in Human Neuroscience, 7*:369. doi:10.3389/fnhum.2013.00369.

Jessen, S., Obleser, J., & Kotz, S. A. (2012). How bodies and voices interact in early emotion perception. *PLoS One, 7*(4): e36070. doi:10.1371/journal.pone.0036070.

Kanske, P., & Kotz, S. A. (2012). Auditory affective norms for German: Testing the influence of depression and anxiety on valence and arousal ratings. *PLoS One, 7*(1): e30086. doi:10.1371/journal.pone.0030086.

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Opitz, B., & Kotz, S. A. (2012). Ventral premotor cortex lesions disrupt learning of sequential grammatical structures. *Cortex, 48*(6), 664–673.

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Paulmann, S., Jessen, S., & Kotz, S. A. (2012). It's special the way you say it: An ERP investigation on the temporal dynamics of two types of prosody. *Neuropsychologia, 50*(7), 1609–1620.

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Roncaglia-Denissen, M. P., Schmidt-Kassow, M., Heine, A., Vuust, P., & Kotz, S. A. (2013). Enhanced musical rhythmic perception in Turkish early and late learners of German. *Frontiers in Psychology, 4*:645. doi:10.3389/fpsyg.2013.00645.

Roncaglia-Denissen, M. P., Schmidt-Kassow, M., & Kotz, S. A. (2013). Speech rhythm facilitates syntactic ambiguity resolution: ERP evidence. *PLoS One, 8*(2): e56000. doi:10.1371/journal.pone.0056000.

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Schwartze, M., Farrugia, N., & Kotz, S. A. (2013). Dissociation of formal and temporal predictability in early auditory evoked potentials. *Neuropsychologia, 51*(2), 320–325.

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Spielmann, M., Schröger, E., Kotz, S. A., Pechmann, T., & Bendixen, A. (2013). Using a staircase procedure for the objective measurement of auditory stream integration and segregation thresholds. *Frontiers in Psychology, 4*:534. doi:10.3389/fpsyg.2013.00534.

Stahl, B., Henseler, I., Turner, R., Geyer, S., & Kotz, S. (2013). How to engage the right brain hemisphere in aphasics without even singing: Evidence for two paths of speech recovery. *Frontiers in Human Neuroscience, 7*:35. doi:10.3389/fnhum.2013.00035.

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Index of Published Figures

Figure 7.4.3
Kotz, S. A., Anwander, A., Axer, H., & Knösche, T. R. (2013). Beyond cytoarchitectonics: The internal and external connectivity structure of the caudate nucleus. *PLoS One, 8(7):* e70141. doi:10.1371/journal.pone.0070141.

Neuroscience of Communication: Function, Structure, and Plasticity

International Max Planck Research School

The International Max Planck Research School on Neuroscience of Communication: Function, Structure, and Plasticity (IMPRS NeuroCom) is an interdisciplinary PhD programme which was originally initiated by the Max Planck Institute for Human Cognitive and Brain Sciences (MPI CBS). The school is based at the MPI CBS and the University of Leipzig (UL), and also involves the Max Planck Institute for Evolutionary Anthropology (MPI EVA) in Leipzig, and the Institute of Cognitive Neuroscience (ICN) at University College London, UK. The IMPRS NeuroCom is a project mainly funded by the Max Planck Society and the MPI CBS but also by the UL. The official inauguration of the IMPRS NeuroCom was on 15 October 2009. The school strengthens the already existing, close working relationship between all participating institutions and enables its students to benefit from the joint knowledge and resources.

Students of the 2012 Cohort

PhD students and projects

Module I: Verbal Communication: Language (since 2009)

Student	Project	Project Stage
Bianco, Roberta	What is beyond a pianist's hand? Syntactic-based prediction of forthcoming musical motor acts	progressed
Fengler (née Hubert), Anja	Recursion during language development	final
Girlich, Sarah	Verb acquisition in German-speaking children: Evidence from various methods	final
Hellbernd, Nele	The neural bases of prosody in speech acts	orientation
Janska, Anna Christina	Investigating the structure of the perceptual vowel category	final
Knierim, Iris Nikola	Rules don't come easy: Investigating feedback-based learning of rules in the language domain	submitted
Dr Knolle (née Grimm), Franziska	Knowing what's next: The role of the cerebellum in generating predictions	completed

Kraft, Indra	Neuroanatomical correlates of developmental dyslexia in young children – an MRI study	progressed
Krause, Carina Denise	Higher-order syntax processing in the aging brain – a tDCS-fMRI study	progressed
Kroczek, Leon	Topdown influences during language processing	orientation
Marzecová, Anna	Temporal expectancy, auditory cognition, and cognitive control	progressed
Roswandowitz, Claudia	Voice and speech recognition abilities in patient and control groups	progressed
Schell, Marianne	The neural representation of language and mathematics	progressed
Spielmann, Mona	Maturation of auditory streaming in adolescence	final
Winkler, Marina	Infant artificial language learning investigated with combined EEG – NIRS	progressed
Wöstmann, Malte	Compensating for degraded speech: Cognitive mechanisms	progressed

Module II: Non-Verbal Communication: Action and Interaction (2009–2012) *

Student	Project	Project Stage
Dr Dolk, Thomas	A referential coding account for the Social Simon Effect	completed
Goltz, Dominique	Attentional modulation of somatosensory processes	final
Dr Kühn, Esther	Open body maps – primary somatosensory cortex activity during touch observation described with 7 Tesla fMRI	completed
Dr Novembre, Giacomo	Action-perception coupling in the musician's brain: What is it good for?	completed
Ragert (née Uhlig), Marie	Cognitive mechanisms underlying perception and production of polyphonic music	submitted

* For reasons of faculty member retirement or relocation, the structure and research focus of Module II, in particular, has changed considerably. This was formerly named "Non-verbal Communication: Action and Interaction" but it is now "Foundation of Social Cognition and Emotions".

Module II: Foundation of Social Cognition and Emotions (since 2012)

Student	Project	Project Stage
Krol, Kathleen Marie	The hormonal modulation of emotion perception across motherhood	progressed
Lumma, Anna-Lena	Investigating intra-individual and interindividual change patterns in subjective, affective, and cognitive experiences throughout a one-year longitudinal mental training study	progressed
Valk, Sofie	The structural architecture of social cognitive networks	progressed
Zinchenko, Artyom	Affective control and prediction formation in multisensory integration	progressed

Module III: Neuroscience: Basic and Clinical (since 2009)

Student	Project	Project Stage
Freigang, Claudia	Processing of auditory objects in older adults in the acoustic free field	submitted
Dr Gräf, Susanne	(-)-[18F]NCFHEB-PET in Alzheimer's disease: Relationship between nicotinic receptor availability and cognition	completed
Hardikar, Samyogita	A genetic approach to gustatory processing	progressed
Hoyer (née Rambow), Jana	Neurovegetative coupling in a high risk sample of essential hypertension in a stress paradigm	final
Jakobsen, Estrid	Functional neuroanatomy of the human somatomotor cortex: Microstructural and functional mapping with ultra-high-field magnetic resonance imaging	progressed
Dr Krönke, Klaus-Martin	Learning by doing? Gesture-based word-learning and its neural correlates in healthy volunteers and patients with residual aphasia	completed
Polyakova, Maryna	Neural correlates of affective and cognitive dysfunctions	progressed
Reiter, Andrea Maria Franziska	Behaviours running out of control – failure of behavioural adaptation in psychopathology	progressed
Sarrou, Mikaella	Audiovisual interaction in the localization of stationary and moving objects	progressed
Schaare, Herma Lina	Neurocognition of vascular risk factors	progressed
Dr Stahl, Benjamin	Treatment of non-fluent aphasia through melody, rhythm, and formulaic language	completed
Strotmann, Barbara Maria	The human habenula: Structure, function, and connectivity	submitted

Module IV: Methods: Physics of Neuroimaging and Computational Neuroscience (since 2009)

Student	Project	Project Stage
Hämäläinen, Janne	Identification and analysis of individual brain responses	cancelled
Dr Holiga, Štefan	Personalizing fMRI protocols for studying neural substrates of motor deficits in Parkinson's disease	completed
Kim, Seung-Goo	The topological alteration of the cortical networks in musicians with absolute pitch	progressed
Lorenz, Kathrin	Parameters of the human cerebral blood supply observed by arterial spin labelling techniques	progressed
Dr Mamashli, Fahimeh	Investigating prediction in semantic processing	completed
Philips, Stefan	Speedup and extension of global brain tractography	final
Teichmann, Christoph	Improving Bayesian methods for unsupervised natural language structure induction	submitted
Wang, Peng	Parameter estimation of neural mass model	submitted

Third IMPRS NeuroCom Summer School, 10–12 July 2013, Leipzig

Faculty

Module I: Verbal Communication: Language (since 2009)

Professor B. Comrie (since 2009) MPI EVA, Dept. of Linguistics	Professor T. Pechmann (since 2009) UL, Dept. of Linguistics
Professor A. D. Friederici (since 2009) MPI CBS, Dept. of Neuropsychology	Dr D. Sammler (since 2013) MPI CBS, OHG "Neural Bases of Intentional Speech"
Professor J. Jescheniak (since 2009) UL, Dept. of Cognitive Psychology	Professor E. Schröger (since 2009) UL, Dept. of Cognitive and Biological Psychology
Professor S.A. Kotz (since 2009) MPI CBS, Dept. of Neuropsychology, and University of Manchester, UK	Professor K. von Kriegstein (since 2012) MPI CBS, MPRG "Neural Mechanisms of Human Communication"
Dr J. Obleser (since 2012) MPI CBS, MPRG „Auditory Cognition"	

Module II: Non-Verbal Communication: Action and Interaction (2009–2012)

Professor P.E. Keller (2009 - 2012) MPI CBS, MPRG "Music Cognition and Action" (now: University of Western Sydney, Australia)	Dr S. Schütz-Bosbach (2009-2012) MPI CBS, MPRG "Body and Self"
Professor E. Lieven (2009 - 2012) MPI EVA, Dept. of Developmental and Comparative Psychology (now: University of Manchester, UK)	Professor M. Tomasello (2009-2012) MPI EVA, Dept. of Developmental and Comparative Psychology
Professor M. Müller (2009 - 2012) UL, Dept. of Experimental Psychology and Methods	

Module II: Foundation of Social Cognition and Emotions (since 2012)

Dr J. Call (since 2012) MPI EVA, Wolfgang Köhler Primate Research Center	Dr D. S. Margulies (since 2012) MPI CBS, MPRG "Neuroanatomy & Connectivity"
Dr M. Carpenter (since 2012) MPI EVA, Dept. of Developmental and Comparative Psychology	Professor M. Schroeter (since 2012) UL, Day Clinic of Cognitive Neurology, and MPI CBS, Dept. of Neurology
Dr T. Grossmann (since 2012) MPI CBS, MPRG "Early Social Development"	Professor T. Singer (since 2012) MPI CBS, Dept. of Social Cognition and Emotions

Module III: Neuroscience: Basic and Clinical (since 2009)

Professor I. Bechmann (since 2012) UL, Institute for Anatomy	Professor R. Rübsamen (since 2009) UL, Dept. of General Zoology and Neurobiology
Professor J. Claßen (since 2012) UL, Dept. of Neurology	Dr F. Schlagenhauf (since 2012) MPI CBS, MPRG „Cognitive and affective control of behavioural adaption“
Dr S. Geyer (since 2009) MPI CBS, Dept. of Neurophysics	Professor P. Schönknecht (since 2009) UL, Clinic and Polyclinic of Psychiatry
Professor U. Hegerl (since 2009) UL, Clinic and Polyclinic of Psychiatry	Professor A. Villringer (since 2009) MPI CBS, Dept. of Neurology
Professor H. Obrig (since 2009) UL, Day Clinic of Cognitive Neurology, and MPI CBS, Dept. of Neurology	Professor K. von Klitzing (since 2009) UL, Clinic and Polyclinic of Children and Youth Psychiatry

Module IV: Methods: Physics of Neuroimaging and Computational Neuroscience (since 2009)

Professor M. Bogdan (since 2012) UL, Dept. of Computer Engineering	Dr B. Maess (since 2009) MPI CBS, “MEG and EEG – Cortical Networks and Cognitive Functions” Unit
Professor J. Haase (since 2009) UL, Dept. of Magnetic Resonance of Complex Quantum Solids	Professor H. E. Möller (since 2009) MPI CBS, “Nuclear Magnetic Resonance” Unit
Professor G. Heyer (since 2009) UL, Dept. of Natural Language Processing	Dr K. Müller (since 2009) MPI CBS, “Nuclear Magnetic Resonance” Unit
Professor M. Hlawitschka (since 2012) UL, Dept. of Scientific Visualisation	Dr G. Lohmann (2009-2012) MPI CBS, Dept. of Neurophysics (now: MPI for Biological Cybernetics and University Clinic Tuebingen, Germany)
Professor D. Huster (since 2012) UL, Dept. of Medical Physics and Biophysics	Dr A. Pampel (2009-2012) MPI CBS, “Nuclear Magnetic Resonance“ Unit
Professor S. Kiebel (since 2012) MPI CBS, Dept. of Neurology, and Dept. of Neurology, University Clinics Jena	Professor G. Scheuermann (since 2009) UL, Dept. of Image Processing
Dr T. Knösche (since 2009) MPI CBS, “MEG and EEG – Cortical Networks and Cognitive Functions“ Unit	Professor R. Turner (since 2009) MPI CBS, Dept. of Neurophysics

Note. MPRG = Max Planck Research Group; OHG = Otto Hahn Group

IMPRS NeuroCom

The IMPRS NeuroCom focuses on the functional, structural, and neural plasticity foundations of the neuroscience of communication through an integrative and interdisciplinary approach. The overriding goal of this programme is to train PhD students in the multidisciplinary aspects of cognition, psychology, and neuroscience involved in different levels of communicative action, and to introduce specific research themes within this broad area of academic endeavour. Besides introducing behavioural methodology, the programme draws on powerful modern neuroimaging techniques such as functional and structural MRI, EEG, MEG, NIRS, and TMS, with the aim of understanding the brain in its complexity and functionality. There is permanent constructive exchange between neuroscientific methodologies and cognitive science, which is supported by the infrastructure and the facilities of the school. PhD projects, teaching, and supervision are organized in the following four modules:

Module I: Verbal Communication: Language (since 2009)

Module II: Non-Verbal Communication: Action and Interaction (2009–2012)

Module II: Foundation of Social Cognition and Emotions (since 2012)

Module III: Neuroscience: Basic and Clinical (since 2009)

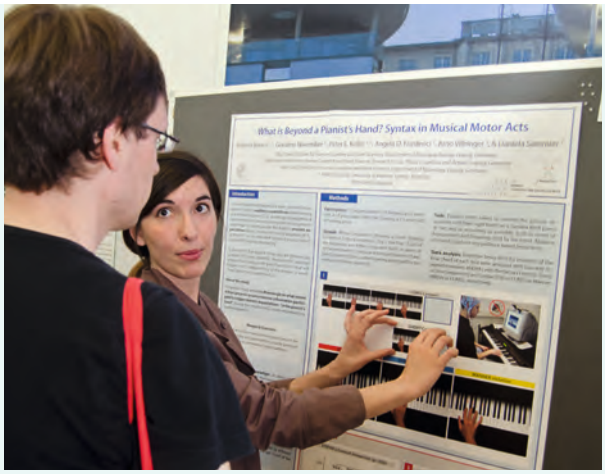
Module IV: Methods: Physics of Neuroimaging and Computational Neuroscience (since 2009)

The most crucial event in 2012/2013 was the evaluation of the IMPRS NeuroCom on 12 March 2013. Katrin Amunts (Research Centre Jülich, Germany), Sharlene Newman (Indiana University, USA), David Norris (Radbound University, the Netherlands), and Henrik Walter (Charité – University Medicine Berlin, Germany) were the external experts for the evaluation. NeuroCom received very positive feedback, and after the recommendation of the IMPRS commission in November 2013 the Max Planck Society invited NeuroCom to apply for a second funding period covering 2015–2021.

Another important event was the second recruitment of doctoral students in 2012. In comparison to the first recruitment in 2009, the number of applications increased by approximately 50% (from 184 to 285). This was mainly due to the substantially increased profile of the IMPRS NeuroCom, both nationally and internationally. Admission to the programme was highly competitive, meaning that fewer than 10% of applicants were offered a position in the graduate school. In autumn 2012, 21 up-and-coming, excellent young scientists from a wide cross-section of the student community started their PhD projects at NeuroCom. The wide variety of the students' professional backgrounds enables them to benefit from shared knowledge and resources.

From 10–12 July 2013, the third IMPRS NeuroCom Summer School took place at the MPI CBS in Leipzig, comprising three full international science days supported by high-ranking scientists and around 200 interdisciplinary participants from all over the world. Excellent lectures, courses, and workshops offered participants the

Hands-on Brain Anatomy Course



Third IMPRS NeuroCom Summer School, 10–12 July 2013, Leipzig

chance to immerse themselves in the neurosciences and to experience scientific expertise on a high level. During exciting sessions on *Predictive Brain*, *Neuroanatomy & Connectomics*, *Motor Learning*, and *Sleep*, as well as scientific workshops and poster sessions, the participants had the opportunity to discuss their research projects, gain experience, get ideas, and establish contacts for possible future research collaborations.

The programme combines opportunities for outstanding research with excellent teaching to ensure that students are highly qualified for a successful career in relevant areas of Neuroscience. Courses held in 2012/2013 included lectures covering modules on Neuroscience, Methods, and Verbal Communication, conducted by the IMPRS faculty from all involved institutions in Leipzig. In addition, an intensive Matlab course was provided to allow the students to develop and broaden their programming skills, which are essential for implementing new methods of analyzing brain data. In a unique 3-day event, students participated in a brain anatomy course that included practical hands-on sessions as well as a series of lectures given by guest researcher Professor Dr Rudolf Nieuwenhuys. In order to assist students in developing and broadening essential research skills, NeuroCom organized a course *Communication and presentation in the academic context: How to be confident and persuasive*. Furthermore, international students were encouraged and financially supported to participate in German language courses.

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Third IMPRS NeuroCom Summer School, 10–12 July 2013, Leipzig

Guest Professor R. Nieuwenhuys (left) with Professor Robert Turner

Index of Names

A

Ackermann, A. *88*
Adermann, J. *222*
Allouche, A.-R. *233*
Altvater-Mackensen, N. *164, 216*
Anwander, A. *32, 54, 58, 76, 81, 130, 144, 154, 222, 244, 245, 246, 282*
Arélin, K. *17, 33, 38, 42*
Atkinson, A. P. *213*
Attig, M. *252*
Aubert-Frécon, M. *233*
Auerswald, J. *54, 254*
Axer, H. *282*

B

Babayan, A. *17*
Bacha-Trams, M. *54, 55, 80*
Bahlmann, J. *61*
Baird, B. *162, 198*
Bareither, I. *17, 29*
Bar, M. *18*
Barth, C. *17*
Barth, U. *54*
Bazin, P.-L. *127, 130, 135, 140, 141, 142, 143, 144, 196, 283*
Bechmann, I. *293*
Becker, C. *127, 299*
Becker, R. *187*
Belin, P. *220, 221*
Benoit, C.-E. *255*
Bergmann, J. *253, 254*
Bernhardt, B. C. *88, 89, 92, 95, 98, 101, 104, 112, 113, 119*
Berson, J. *162*
Bestelmeyer, P. E. G. *220*
Bialojan, A. *127*
Bianco, R. *17, 164, 288*
Bird, G. *112*
Bisenius, S. *17*
Bitzer, S. *17, 40*
Blankenburg, F. *40*
Blank, H. *160, 168, 172*
Blank, R. *298*
Blüher, M. *32*
Bobovnikov, N. *54*
Bochow (née Zube), C. *88*
Böckler, A. *88, 92, 104*
Boehler, N. *206*
Boesch, C. *80*
Bogdan, M. *293*
Bogler, C. *274*
Boltze, J. *77, 78*
Bolz, M. *88*
Bonhage, C. E. *54, 61*
Borch Petersen, E. *161*
Bornemann, B. *88, 104, 119*
Böthel, H. *54*
Böttcher, C. *164*
Böttger, J. *162, 195*
Brauer, J. *54, 72, 74, 75, 76, 77, 258*
Breakspear, M. *189, 190*
Budnik, U. *127*
Burkhardt, F. *299*
Burmann, I. *33*
Buschmann, T. *162*
Busch, N. *29*
Busse, F. *32*
Bzdok, D. *37*

C

Cafiero, R. *54, 74*
Callard, F. *162, 199*
Call, J. *118, 292*
Carpenter, M. *292*
Chaumon, M. *29*
Cho, J.-H. *227*
Chwiesko, C. *37*
Ciupek, M. *17*
Claßen, J. *20, 293*
Clevert, L. *17, 18*
Cohen, N. *18*
Comrie, B. *292*
Conde, V. *17, 20, 21*
Cozatl, R. *197, 299*
Craddock, C. *34, 162*
Cross, E. *275*
Cunitz, K. *54, 75, 222*

D

Dahncke, R. *300*
Dannhauer, M. *227, 241*
Daum, M. M. *7, 252, 257, 258, 259, 261*
De Caso, I. *162*
Deco, G. *190*
Demey, M. *23*
Démonet, F. *80*
Demoucron, M. *23*
Deserno, L. *163, 203, 204, 205, 206*
Deubel, F. *300*
Dhital, B. *126, 127, 130, 132, 134*
Diaz Menendez, B. *172*
Diersch, N. *254, 275, 277*
Dietrich, A. *17*
Dinse, H. R. *187, 188*
Dinse, J. *127, 140, 141, 142, 143, 153, 154*
Dolk, T. *252, 261, 273, 289*
Dollmeyer, D. *300*
Draganski, B. *18*
Dreyer, M. *17*
Dukart, J. *42*
Dyrby, T. B. *246*
Dziobek, I. *114*

E

Eichner, C. *127, 133, 154*
Eickhoff, S. B. *37*
Eisner, F. *180*
Emmrich, F. *77*
Endres, M. *34*
Engel, A. *253*
Engen, H. *88, 104, 107, 108*
Engert, V. *88, 93, 94, 104*
Erbey, M. *17*
Erb, J. *161, 180*

F

Fairhurst-Menuhin, M. T. *164, 211, 253, 266*
Farkas, A. *54*
Farrugia, N. *255*
Fasano, F. *133*
Federbusch, M. *17*
Fehr, E. *100*
Felber, M. J. *54, 55, 243*
Fengler (née Hubert), A. *54, 55, 73, 288*
Fiebach, C. J *61*
Fiebach, J. *34, 36*
Flake, K. *2, 298*
Forneck, J. *115*
Forschack, N. *17, 27*
Förstl, S. *18*
Forstmann, B. U. *130*
Franke, R. *298*
Franz, A.-K. *17*
Freigang, C. *290*
Freyer, F. *161, 187, 188, 189*
Friedel, E. *207*
Friederici, A. D. *5, 6, 50, 58, 59, 60, 62, 63, 64, 65, 66, 68, 72, 73, 74, 75, 76, 77, 78, 80, 222, 242, 244, 292*
Friedrich, M. *54*
Frisch, S. *42*
Frith, U. *112*
Fritz, T. *17, 23*
Fuchs, M. *227*
Fukuda, Y. *163*

G

Gählsdorf, C. *163, 207*
Gampe, A. *252, 258, 259, 261*
Garrido-Vásquez, P. *255, 284*
Gast-Sandmann, A. *298*
Gaudrain, E. *166*
Gauthier, C. *127, 154*
Gentsch, A. *254, 277*
Geyer, S. *127, 130, 140, 141, 142, 144, 145, 153, 293*
Ghosh, S. *200*
Gierhake, D. *34*
Gierhan (née Bihler), S. M. E. *54, 55, 58, 80, 222*
Giot, O. *23*
Girbarth, J. *17*
Girlich, S. *288*
Goense, J. *131*
Golchert, J. *162, 199*
Goltz, D. *17, 289*
Gorgolewski, K. J. *162, 196, 198, 200*
Goucha, T. B. *54, 62*
Goulas, A. *162, 194*
Gräf, S. *290*
Grant, J. A. *88, 104, 108, 119*
Graupner, S. *299*
Gredebäck, G. *257*
Greiner, M. *54, 299*
Grellmann, C. *17*
Grigutsch, M. *54, 177, 243*
Groba, A. *24*

Grodd, W. *22*
Grosbras, M. *221*
Grosse Wiesmann, C. *54*
Grossmann, T. *7, 54, 55, 164, 211, 212, 213, 214, 215, 216, 217, 292*
Grunert, H. *88*
Gryga, M. *17*
Guidi, M. *226*
Gundlach, C. *17, 26*
Gunter, T. C. *54, 68, 75*
Gutekunst, S. *54*
Guthke, T. *18*

H

Haase, J. *293*
Hach, S. *254*
Haggard, P. *272*
Hahn, J. *300*
Halfpaap, J. *17*
Hämäläinen, J. *54, 55, 291*
Hanel, P. *33*
Hardikar, S. *17, 23, 290*
Harding, E. *255*
Haspelmath, M. *80*
Haueisen, J. *248*
Haueis, P. *162*
Haufe, S. *160*
Haushofer, J. *100*
Hayd, H. *299*
Haynes, J.-D. *23, 274*
Heck, F. *80*
Hegerl, U. *144, 145, 293*
Heidemann, R. M. *81, 127, 133, 154*
Heinz, A. *204*
Heinze, H.-J. *163, 205, 206*
Heissler, J. *115*
Hellbernd, N. *164, 288*
Helle, L. *242*
Hellrung, L. *17*
Henry, M. J. *161, 175, 176, 177, 178, 179, 180*
Henseler, I. *64, 226*
Henze, G. *298*
Herbst, M. *135*
Herrmann, B. *161, 175, 177, 179, 243*
Herrmann, C. *182*
Hertwig, R. *226*
Herzig, S. *18*
Heuer, K. *54*
Heyer, G. *293*
Hilbert, A. *31*
Hildebrandt, L. *88, 104, 117*
Hillebrand, P. *17*
Hirotani, M. *54*
Hlawitschka, M. *293*
Hoff, L. *17*
Hoffmann, F. *88, 98, 114*
Hofmann, M. *88*
Ho, H. T. *255*
Holiga, Š. *38, 226, 230, 231, 236, 291*
Hollmann, M. *17, 18*
Hoppe-Graff, S. *80*
Horstmann, A. *17, 30, 31, 32, 41, 42, 206*
Hoyer (née Rambow), J. *17, 290*
Huber, L. *127, 131, 134, 154, 226, 236*
Hummitzsch, C. *17*
Hupfer, E. *300*
Huster, D. *293*
Hutchison, R. M. *194*
Huys, Q. J. M. *203*

I

Ihme, K. A. *33*
Iliopoulos, F. *17*
Ivanov, D. *126, 127, 131, 133, 134, 153, 154*

J

Jackson, C. *255*
Jakobsen, E. *127, 162, 195, 290*
Jakuszeit, M. *17, 255*
Janska, A. C. *288*
Jech, R. *226, 230, 231*
Jentzsch, T. *18*
Jeon, H.-A. *54, 65*
Jescheniak, J. *292*
Jessen, S. *164, 212, 284*
Jiang, J. *160*
Jirsa, V. K. *186, 187, 190*
Jochemko, M. *226*
Jochimsen, T. *226*
Johst, B. *17*
Jung, C. *252*
Jungehulsing, J. G. *36*
Junghanns, B. *298*

K

Kaiser, R. *253*
Kalberlah, C. *17*
Kaminski, E. *17*
Kaminski, J. *17*
Kanaan, A. *162*
Kanske, P. *33, 88, 92, 104, 115, 119*
Kappes, C. *160*
Kastner, L. *17, 31*
Kästner, T. *88*
Keitel (née Melzer), A. *252*
Keller, H. *80*
Keller, P. E. *7, 253, 266, 267, 268, 269, 284, 292*
Kelly, E. *298*
Kennerley, A. *131*
Ketscher, C. *17, 299*
Kharabian, S. *17*
Kiebel, S. J. *17, 18, 40, 42, 167, 168, 172, 293*
Kim, S.-G. *227, 291*
Kipping, J. A. *17, 19, 22*
Kirschbaum, C. *93*
Kirsche, K. *54*
Kirsten, H. *77, 78*
Klein (née Werrmann), K. *54*
Kleinsorge, M. *127*
Klein, T. *17*
Klimecki, O. M. *88, 89, 92, 106, 119*
Klose (née Schober), L. *17*
Knierim, I. N. *255, 288*
Knight, Y. *17*
Knock, S. *161*
Knolle (née Grimm), F. *255, 284, 288*
Knoll, L. J. *54, 55, 80*
Knösche, T. R. *7, 227, 241, 242, 244, 245, 246, 248, 282, 293*
Koch, K. I. *54*
Kögler, C. *127, 134*
Kohlhoff, E. *17*
Köhne, S. *114*
Kok, B. E. *88, 104*
König, R. *253, 268*
Koopmans, P. J. *133*
Korsawe, H. *299*
Kosatschek, A. *226*
Kotz, S. A. *7, 54, 55, 64, 81, 255, 269, 280, 281, 282, 283, 284, 292*
Kozlov, M. *127, 148, 149, 150, 152*
Kraft, I. *54, 77, 289*
Kratzsch, J. *38*
Krause, C. D. *17, 54, 289*
Kreitewolf, J. *160, 166*
Kretzschmar, S. *298*
Krieger, S. *126, 127, 131, 136, 154*
Kroczek, L. *54, 68, 289*
Krol, K. M. *164, 214, 215, 290*
Krönke, K. M. *17, 290*
Krueger, G. *234*
Kube, J. *17, 31*
Kühn, E. *17, 254, 275, 277, 289*
Kuhnt, J. *17*
Kumar, V. *22*
Kummer, A. *226*
Kunke, D. *161*

L

Labadie, C. *226, 233, 236*
Lachmann, U. *17, 18*
Laird, A. R. *37*
Lämmel, E. *241*
Lampe, L. *226*
Lange, A. *298*
Lehmann, S. *54*
Leiberg, S. *89, 92, 106*
Leman, M. *23*
Lepsien, J. *32, 131, 226, 234*
Leuze, C. *126, 127, 130, 153*
Liebau, G. *17*
Liebig, S. *298*
Lieven, E. *292*
Lipka, H. *299*
Liptrot, M. *246*
Lohmann, G. *127, 275, 293*
Löken, L. *211*
Long, X. *17, 28, 34*
Lorenz, K. *226, 232*
Lorenz, N. *88, 291, 299*
Luettgau, L. *163*
Lumma, A.-L. *88, 104, 290*
Lützkendorf, R. *133*
Lv, Y. *17, 34*

M

Macedonia, M. *160, 169*
Macher, K. *17*

Maclaren, J. *135*
Maess, B. *7, 167, 179, 227, 242, 243, 244, 248, 293*
Maess, E. *299*
Maestro, M. M. *226*
Makuuchi, M. *54, 55, 59*
Mamashli, F. *227, 242, 248, 291*
Männel, C. *54, 78*
Margulies, D. S. *6, 22, 28, 33, 34, 36, 162, 194, 195, 196, 198, 199, 200, 292*
Marinos, D. *54, 55*
Markovic, D. *17*
Marou, V. *162*
Marschhauser, A. *18, 54*
Marschner, H. *226, 229, 233*
Marzecová, A. *289*
Mathar, D. *17, 30*
Mathias, S. R. *160, 170*
Mattingley, J. *80*
Mayer, K. M. *160, 169*
McCall, C. *88, 104, 117*
McGettigan, C. *161*
McIntosh, A. R. *186, 187, 190*
Meemken, M.-T. *17*
Meinhold, A. *298*
Meixensberger , J. *222*
Melzer, Y. *88*
Mendes, N. *88, 89, 118, 162*
Mendil, L. *17*
Menendez, B. D. *160*
Menger, R. *17*
Mentzel, J. *17*
Merrill (née Groh), J. *54, 55, 80*
Mestres-Missé, A. *54, 55, 255, 283*
Metere, R. *226*
Meyer, L. *54, 60, 73, 78, 80*
Meyer, M. *133*
Miao, Q. *127*
Mietke, A. *130*
Mildner, T. *226, 229, 232*
Milham, M. *162*
Miller, R. *93*
Missana, M. *54, 55, 164, 213, 214*
Mittag, B. *17, 299*
Model, K. *298*
Moeller, S. *299*
Möller, H. E. *7, 32, 131, 144, 226, 229, 230, 231, 232, 233, 234, 236, 293*
Moreno-Dominguez, D. *162, 200, 227, 246, 248*
Morys, F. *17*
Mueller, J. L. *54, 55, 61, 66, 81*
Mueller, K.-R. *25*
Müller, B. *77*
Müller, D. *134*
Müller, K. *32, 38, 42, 226, 230, 231, 234, 275, 293*
Müller, M. M. *26, 27, 292*
Müller, R. *148, 226, 229*
Murzik, E. *88*
Muschall, N. *226, 252, 299*

N

Naethe, K. *298*
Naito, E. *80*
Nakamura, A. *244*
Naor, N. *18*
Neef, L. *54*
Neubert, S. *88*
Neumann, J. *17, 30, 31, 37, 41, 206, 233*
Nguyen Trong, M. *227*
Niederhausen, H. *88*
Nierhaus, T. *17, 25, 26, 27, 28*
Niessen, M. *23*
Nieuwenhuys, R. *295*
Niven, A. *295, 298*
Nolte, G. *188*
Norris, D. G. *133*
Novembre, G. *253, 266, 269, 289*

O

Obermeier, C. *255, 280*
Obleser, J. *6, 24, 60, 161, 175, 176, 177, 178, 179, 180, 182, 242, 292*
Obrig, H. *17, 18, 24, 42, 293*
Okon-Singer, H. *17, 18, 33, 41, 42*
Ono, K. *227, 244*
Otte, A. *298*
Otto, N. *88*
Ovadia-Caro, S. *17, 36*

P

Paasche, K. *298*
Pampel, A. *33, 134, 226, 229, 233, 234, 293*
Pampus, N. *88*
Papagno, C. *80*
Park, H. *17, 40*
Pecenka, N. *253*
Pechmann, T. *292*
Peelle, J. *161*
Perani, D. *76*
Peter, A. *127, 299*
Petrides, M. *162, 194*
Petzold, F. *127*
Pfeuffer, J. *133*
Philips, S. *291*
Pleger, B. *17, 19, 32, 41, 42*
Plessow, F. *93*
Polyakova, M. *290*
Pool, J. *162*
Portain, D. *227*
Pössel, M. *17*
Preusser, S. *17*
Prinz, W. *252, 259, 261*
Proulx, T. *162*
Przyrembel, M. *88, 119*

Q

Quinque (née Weig), E. M. *17, 42*

R

Radenbach, C. *163*
Ragert (née Uhlig), M. *253, 266, 289*
Ragert, P. *17, 19, 20, 21, 24, 66, 273*
Rajhans, P. *164, 214*
Ramasamy, M. *54*
Reck, A. *298*
Regel, S. *54, 64, 80*
Regenbrecht, F. *18*
Regenthal, R. *33*
Reiche, M. *300*
Reimann, K. *127, 130*
Reimer, E. *127, 134*
Reinacher, M. *161, 188, 192*
Reinelt, J. *17*
Reiter, A. M. F. *163, 205, 290*
Ricard, M. *106*
Richter, L. *17*
Richter, M. *17*
Riedel, P. *160*
Rieger, M. *275*
Riffert, T. *227, 244, 245*
Ritter, P. *6, 160, 186, 187, 188, 189, 190, 192*
Rivera, D. S. *127, 134, 148, 153*
Rivera, G. *197, 299*
Rjosk, V. *17*
Röbbig, J. *17, 33*
Roberts, J. A. *189*
Robertson, S. H. *229*
Roggenhofer, E. *17, 18, 42*
Rohr, C. *17*
Rolle, K. *298*
Román, P. E. *255*
Roncaglia-Denissen, P. M. *255, 284*
Rook, C. *17*
Rossi, S. *17, 18*
Roswandowitz, C. *160, 289*
Rothermich, K. *284*
Roy, D. *160, 190*
Rübsamen, R. *293*
Ruby, F. J. M. *88, 89*
Rufener, K. *161*
Rügen, C. *54*
Rullmann, M. *17*
Ruschel, M. *17, 127*
Růžička, E. *231*
Růžička, F. *231*

S

Sacher, J. *17, 33, 38, 42*
Samalekh, S. *226*
Sammler, D. *7, 164, 220, 221, 222, 223, 292*
Sarrou, M. *290*
Schaadt, G. *54, 77*
Schaare, H. L. *17, 290*
Schäfer, A. *17, 19, 33, 127, 130, 134, 140, 142, 143*
Schall, S. *160, 167*
Scharinger, M. *161, 175, 178, 179*
Schelinski, S. *160*
Schell, M. *54, 289*
Scheuermann, G. *293*
Schindler, S. *127, 144, 145*
Schipke, C. S. *54, 80*
Schirner, M. *160, 186, 187*
Schlagenhauf, F. *6, 163, 203, 204, 205, 206, 207, 208, 293*
Schlichter, C. *298*

Schlumm, T. *226, 229*
Schmidl, L. *298*
Schmidt, C. *54*
Schmidt-Duderstedt, H. *298*
Schmidt, F. M. *145*
Schmidt, L. *127, 144*
Schmorde, P. *298*
Schmude, I. *298*
Schneider, W. X. *261*
Schnitzler, T. *17, 24*
Schönfelder, S. *115*
Schönknecht, P. *144, 145, 293*
Schorch, T. *54*
Schreiber, J. *17, 54, 227, 244, 245*
Schrimpf, A. *17*
Schröder, C. *298*
Schroeter, M. L. *17, 18, 32, 37, 38, 41, 42, 230, 231, 234, 292*
Schröger, E. *80, 284, 292*
Schücking, B. *80*
Schuetz-Bosbach, S. *275*
Schulz, J. *127, 135*
Schumann, J. *17*
Schurade, R. *195, 227*
Schüßler, E. *255*
Schütz-Bosbach, S. *7, 254, 266, 272, 273, 274, 275, 277, 292*
Schwartze, M. *255, 281, 284*
Schwartz, J. *161*
Sehm, B. *17, 19, 21, 24, 26, 66*
Seifert, S. *17*
Setsompop, K. *133*
Sevdalis, V. *253*
Sewerin, S. *17, 21*
Shrestha, M. *226, 229*
Sieger, T. *230*
Siegert, T. *127, 135*
Sigala, R. *160, 190*
Silani, G. *112*
Simmank, J. *17*
Singer, T. *5, 6, 86, 92, 93, 94, 95, 98, 99, 100, 101, 104, 106, 107, 108, 112, 113, 114, 117, 118, 119, 292*
Sjoerds, Z. *163*
Skeide, M. A. *54, 72, 77, 80*
Skottnik, L. *104*
Smallwood, J. M. *88, 89, 94, 95, 119, 162, 198, 199, 200*
Song, J. *160*
Sonntag, H. *227*
Spielmann, M. *289*
Stadler, W. *275*
Stahl, B. *126, 127, 153, 290*
Starke, S. *252, 299*
Stasch, S. *17*
Steele, C. J. *17, 20*
Steinbeis, N. *88, 98, 99, 100, 101, 114, 118*
Steinbrink, J. *28*
Stelzer, J. *28, 126, 127*
Stemmler, G. *33*
Stiers, P. *194*
Stockart, A. *17*
Stockert, A. *255, 281*
Strauß, A. *161, 178*
Strauß, M. *144, 145*
Streicher, M. N. *126, 127, 134, 136, 141, 153*
Streitbürger, D.-P. *38, 42, 226, 234*
Strotmann, B. *127, 290*
Strotseva-Feinschmidt, A. *54, 75*
Stüber, C. *127, 130, 153, 154*
Studniczka, J. *252, 299*
Stuke, K. *17*
Sutherland, M. E. *255*
Syrbe, R. *300*

T

Tardif, C. *127, 142, 143, 154*
Taskin, B. *28*
Taubert, M. *17, 19, 21, 22, 42*
Teichmann, C. *291*
Thiel, F. *17, 18*
Thiel, S. *17*
Thöne-Otto, A. *18*
Ticini, L. F. *254, 266, 273*
Tidwell, L. F. *17, 18*
Tomasello, M. *292*
Träger, K. *88, 252, 253*
Trampel, R. *127, 131, 133, 134, 136, 140, 144, 145, 153, 283*
Trapp, S. *17, 226, 236*
Trautwein, F.-M. *88, 92, 104, 119*
Triebkorn, P. *161*
Trümper, M. *54, 299*
Tsakiris, M. *272*
Tudorascu, D. *18*
Türke, E. *127*
Turner, R. *2, 5, 8, 124, 127, 130, 131, 132, 133, 134, 135, 136, 140, 141, 142, 143, 144, 145, 148, 149, 150, 152, 153, 283, 293, 295*
Tusche, A. *88, 95, 104*
Tydecks, S. *88*

U

Ulber, J. *257*
Ulbrich, H. *17*
Uludag, K. *127*
Urchs, S. *162*
Urgošík, D. *231*

V

Valk, S. L. *88, 104, 112, 113, 290*
Vallar, G. *80*
van der Meer, E. *36*
van der Steen, M. C. *253, 267*
Vavatzanidis, N. K. *54, 81*
Verga, L. *255*
Vidaurre, C. *25*
Viehweger, A. *54*
Vignotto, M. *17*
Villringer, A. *5, 6, 12, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 36, 38, 41, 42, 206, 293, 295*
Villringer, K. *34, 36*
Vissiennon, K. *54*
Vogt, B. *254, 274*
Voigt, G. *17*
Vollmann, H. *20, 21*
von Klitzing, K. *293*
von Kriegstein, K. *6, 160, 166, 167, 168, 169, 170, 172, 292*
Vymazal, J. *231*

W

Wähnert, M. D. *127, 141, 142*
Wähnert, P. *141*
Wald, L. L. *133*
Walter, A. *252, 261, 294*
Wang, P. *227, 242, 291*
Waszak, F. *273*
Watanabe, A. *162*
Weder, M. *226*
Weicker, J. *17*
Weinbrenner, D. *54, 55*
Weiß, C. *254, 272, 277*
Weiß, M. *126, 127, 140, 141*
Weissman, D. *162*
Werner, T. *298*
Wessa, M. *115*
Wharton, S. *127*
Wiedemann, A. *17*
Wilbertz, T. *163, 206*
Wilcke, A. *77, 78*
Wilfling, D. *127*
Wilsch, A. *161, 179*
Winkler, M. *54, 289*
Winter, B. *34*
Wipper, S. *226*
Wittenburg, L. *88*
Witte, O. W. *20, 21*
Wladimirow, E. *127*
Woestmann, M. *161*
Wolff, Y. *227*
Wolf, R. *17*
Wolters, C. H. *241*
Woost, T. *17*
Wöstmann, M. *289*
Wrede, K. *17*
Wronski, C. *252*
Wu, C.-Y. J. *54*
Wuttke, M. *54*

X

Xiao, Y. *54*
Xu, C. *226, 236*

Y

Yildiz, I. B. *17, 18, 169*
Yongming, L. *23*

Z

Zaccarella, E. *54, 63*
Zaitsev, M. *135*
Zeidler, W. *88*
Zenker, N. *299*
Ziesche, A. *17*
Zinchenko, A. *255, 290*
Zurborg, S. *88*

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