How to target inter-regional phase synchronization with dual-site Transcranial Alternating Current Stimulation
Large-scale synchronization of neural oscillations is a key mechanism for functional information exchange among brain areas. Dual-site Transcranial Alternating Current Stimulation (ds-TACS) has been recently introduced as non-invasive technique to manipulate the temporal phase relationship of local oscillations in two connected cortical areas. While the frequency of ds-TACS is matched, the phase of stimulation is either identical (in-phase stimulation) or opposite (anti-phase stimulation) in the two cortical target areas. In-phase stimulation is thought to synchronize the endogenous oscillations and hereby to improve behavioral performance. Conversely, anti-phase stimulation is thought to desynchronize neural oscillations in the two areas, which is expected to decrease performance. Critically, in- and anti-phase ds-TACS should only differ with respect to temporal phase, while all other stimulation parameters such as focality and stimulation intensity should be matched to enable an unambiguous interpretation of the behavioral effects. Using electric field simulations based on a realistic head geometry, we tested how well this goal has been met in studies, which have employed ds-TACS up to now. Separating the induced electrical fields in their spatial and temporal components, we investigated how the chosen electrode montages determined the spatial field distribution and the generation of phase variations in the injected electric fields. Considering the basic physical mechanisms, we derived recommendations for an optimized stimulation montage. The latter allows for a principled design of in- and anti-phase ds-TACS conditions with matched spatial distributions of the electric field. This knowledge will help cognitive neuroscientists to design optimal ds-TACS configurations, which are suited to probe unambiguously the causal contribution of phase coupling to specific cognitive processes in the human brain.
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**Centre-surround organization of fast sensorimotor integration in human hand area**

Using the short-latency afferent inhibition (SAI) paradigm, transcranial magnetic stimulation (TMS) of the primary motor hand area (M1HAND) can probe how sensory input from limbs modulates corticomotor output in humans. Here we applied a novel TMS mapping approach to chart the spatial representation of SAI in human hand-knob. We hypothesized SAI is somatotopically expressed in M1HAND depending on both the site of peripheral electrical nerve stimulation and the cortical spot targeted by TMS within M1HAND. The left index or little finger was stimulated 23 ms before focal single-pulse TMS of the right M1HAND. Using frameless stereotaxy, we applied biphasic-TMS pulses at seven stimulation positions above right M1HAND and recorded the motor evoked potentials (MEPs) from relaxed left first-dorsal-interosseous (FDI)
and abductor-digiti-minimi (ADM) muscles. Homotopic stimulation of the finger close to the muscle targeted by TMS revealed a somatotopic expression of afferent inhibition matching the somatotopic representation of unconditioned MEPs (homotopic SAI). Conversely, heterotopic stimulation of a finger distant to the muscle targeted by TMS induced short-latency afferent facilitation (SAF) of MEPs in M1HAND. Like homotopic SAI, heterotopic SAF was somatotopically expressed in M1HAND. Together, the results provide first-time evidence that fast sensorimotor integration involves centre-inhibition and surround-facilitation in human M1HAND.

General information
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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, Copenhagen University Hospital
Authors: Dubbioso, R. (Ekstern), Raffin, E. (Ekstern), Karabanov, A. (Ekstern), Thielscher, A. (Intern), Siebner, H. R. (Ekstern)
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Comparing TMS perturbations to occipital and parietal cortices in concurrent TMS-fMRI studies—Methodological considerations

Neglect and hemianopia are two neuropsychological syndromes that are associated with reduced awareness for visual signals in patients' contralesional hemifield. They offer the unique possibility to dissociate the contributions of retinogeniculate and retino-colliculo circuitries in visual perception. Yet, insights from patient fMRI studies are limited by heterogeneity in lesion location and extent, long-term functional reorganization and behavioural compensation after stroke. Transcranial magnetic stimulation (TMS) has therefore been proposed as a complementary method to investigate the effect of transient perturbations on functional brain organization. This concurrent TMS-fMRI study applied TMS perturbation to occipital and parietal cortices with the aim to 'mimick' neglect and hemianopia. Based on the challenges and interpretational limitations of our own study we aim to provide tutorial guidance on how future studies should compare TMS to primary sensory and association areas that are governed by distinct computational principles, neural dynamics and functional architecture.

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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, Max-Planck-Institute for Biological Cybernetics  
Authors: Leitao, J. (Ekstern), Thielscher, A. (Intern), Tuennerhoff, J. (Ekstern), Noppeney, U. (Ekstern)  
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Background Tumor treating fields (TTFields) are increasingly used in the treatment of glioblastoma. TTFields inhibit cancer growth through induction of alternating electrical fields. To optimize TTFields efficacy, it is necessary to understand the factors determining the strength and distribution of TTFields. In this study, we provide simple guiding principles for clinicians to assess the distribution and the local efficacy of TTFields in various clinical scenarios. Methods We calculated the TTFields distribution using finite element methods applied to a realistic head model. Dielectric property estimates were taken from the literature. Twenty-four tumors were virtually introduced at locations systematically varied relative to the applied field. In addition, we investigated the impact of central tumor necrosis on the induced field. Results Local field "hot spots" occurred at the sulcal fundi and in deep tumors embedded in white matter. The field strength was not higher for tumors close to the active electrode. Left/right field directions were generally superior to anterior/posterior directions. Central necrosis focally enhanced the field near tumor boundaries perpendicular to the applied field and introduced significant field non-uniformity within the tumor. Conclusions The TTFields distribution is largely determined by local conductivity differences. The well conducting tumor tissue creates a preferred pathway for current flow, which increases the field intensity in the tumor boundaries and surrounding regions perpendicular to the applied field. The cerebrospinal fluid plays a significant role in shaping the current pathways and funnels currents through the ventricles and sulci towards deeper regions, which thereby experience higher fields. Clinicians may apply these principles to better understand how TTFields will affect individual patients and possibly predict where local recurrence may occur. Accurate predictions should, however, be based on patient specific models. Future work is needed to assess the robustness of the presented results towards variations in conductivity.
Sensitivity analysis of magnetic field measurements for magnetic resonance electrical impedance tomography (MREIT)

Purpose: Clinical use of magnetic resonance electrical impedance tomography (MREIT) still requires significant sensitivity improvements. Here, the measurement of the current-induced magnetic field (DBz,c) is improved using systematic efficiency analyses and optimization of multi-echo spin echo (MESE) and steady-state free precession free induction decay (SSFP-FID) sequences. Theory and Methods: Considering T1, T2, and T2 relaxation in the signal-to-noise ratios (SNRs) of the MR magnitude images, the efficiency of MESE and SSFP-FID MREIT experiments, and its dependence on the sequence parameters, are analytically analyzed and simulated. The theoretical results are experimentally validated in a saline-filled homogenous spherical phantom with relaxation parameters similar to brain tissue. Measurement of DBz,c is also performed in a cylindrical phantom with saline and chicken meat. Results: The efficiency simulations and experimental results are in good agreement. When using optimal parameters, DBz,c can be reliably measured in the phantom even at injected current strengths of 1 mA or lower for both sequence types. The importance of using proper crusher gradient selection on the phase evolution in a MESE experiment is also demonstrated. Conclusion: The efficiencies observed with the optimized sequence parameters will likely render in-vivo human brain MREIT feasible.

General information
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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, University of Tubingen
Authors: Göksu, C. (Intern), Scheffler, K. (Ekstern), Ehses, P. (Ekstern), Hanson, L. G. (Intern), Thielscher, A. (Intern)
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Scopus rating (2008): SJR 2.382 SNIP 1.512
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The impact of large structural brain changes in chronic stroke patients on the electric field caused by transcranial brain stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) are two types of non-invasive transcranial brain stimulation (TBS). They are useful tools for stroke research and may be potential adjunct therapies for functional recovery. However, stroke often causes large cerebral lesions, which are commonly accompanied by a secondary enlargement of the ventricles and atrophy. These structural alterations substantially change the conductivity distribution inside the head, which may have potentially important consequences for both brain stimulation methods. We therefore aimed to characterize the impact of these changes on the spatial distribution of the electric field generated by both TBS methods. In addition to confirming the safety of TBS in the presence of large stroke-related structural changes, our aim was to clarify whether targeted stimulation is still possible. Realistic head models containing large cortical and subcortical stroke lesions in the right parietal cortex were created using MR images of two patients. For TMS, the electric field of a double coil was simulated using the finite-element method. Systematic variations of the coil position relative to the lesion were tested. For TDCS, the finite-element method was used to simulate a standard approach with two electrode pads, and the position of one electrode was systematically varied. For both TMS and TDCS, the lesion caused electric field "hot spots" in the cortex. However, these maxima were not substantially stronger than those seen in a healthy control. The electric field pattern induced by TMS was not substantially changed by the lesions. However, the average field strength generated by TDCS was substantially decreased. This effect occurred for both head models and even when both electrodes were distant to the lesion, caused by increased current shunting through the lesion and enlarged ventricles. Judging from the similar peak field strengths compared to the healthy control, both TBS methods are safe in patients with large brain lesions (in practice, however, additional factors such as potentially lowered thresholds for seizure-induction have to be considered). Focused stimulation by TMS seems to be possible, but standard TDCS protocols appear to be less efficient than they are in healthy subjects, strongly suggesting that TDCS studies in this population might benefit from individualized treatment planning based on realistic field calculations.

General information
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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, Copenhagen University Hospital, Max-Planck-Institute for Biological Cybernetics, Aarhus University, University of Oxford
Authors: Minjoli, S. (Ekstern), Saturnino, G. B. (Ekstern), Blicher, J. U. (Ekstern), Stagg, C. J. (Ekstern), Siebner, H. R. (Ekstern), Antunes, A. (Ekstern), Thielscher, A. (Intern)
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Transcranial magnetic stimulation of right inferior parietal cortex causally influences prefrontal activation for visual detection

For effective interactions with the environment, the brain needs to form perceptual decisions based on noisy sensory evidence. Accumulating evidence suggests that perceptual decisions are formed by widespread interactions amongst sensory areas representing the noisy sensory evidence and fronto-parietal areas integrating the evidence into a decision variable that is compared to a decisional threshold. This concurrent transcranial magnetic stimulation (TMS)-fMRI study applied 10 Hz bursts of four TMS (or Sham) pulses to the intraparietal sulcus (IPS) to investigate the causal influence of IPS on the neural systems involved in perceptual decision-making. Participants had to detect visual signals at threshold intensity that were presented in their left lower visual field on 50% of the trials. Critically, we adjusted the signal strength such that participants failed to detect the visual stimulus on approximately 30% of the trials allowing us to categorise trials into hits, misses and correct rejections (CR). Our results show that IPS-relative to Sham-TMS attenuated activation increases for misses relative to CR in the left middle and superior frontal gyri. Critically, while IPS-TMS did not significantly affect participants' performance accuracy, it affected how observers adjusted their response times after making an error. We therefore suggest that activation increases in superior frontal gyri for misses relative to correct responses may not be critical for signal detection performance, but rather reflect post-decisional processing such as metacognitive monitoring of choice accuracy or decisional confidence.
Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives

Non-invasive transcranial brain stimulation (NTBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (TCS) are important tools in human systems and cognitive neuroscience because they are able to reveal the relevance of certain brain structures or neuronal activity patterns for a given brain function. It is nowadays feasible to combine NTBS, either consecutively or concurrently, with a variety of neuroimaging and electrophysiological techniques. Here we discuss what kind of information can be gained from combined approaches, which often are technically demanding. We argue that the benefit from this combination is twofold. Firstly, neuroimaging and electrophysiology can inform subsequent NTBS, providing the required information to optimize where, when, and how to stimulate the brain. Information can be achieved both before and during the NTBS experiment, requiring consecutive and concurrent applications, respectively. Secondly, neuroimaging and electrophysiology can provide the readout for neural changes induced by NTBS. Again, using either concurrent or consecutive applications, both "online" NTBS effects immediately following the stimulation and "offline" NTBS effects outlasting plasticity-inducing NTBS protocols can be assessed. Finally, both strategies can be combined to close the loop between measuring and modulating brain activity by means of closed-loop brain state-dependent NTBS. In this paper, we will provide a conceptual framework, emphasizing principal strategies and highlighting promising future directions to exploit the benefits of combining NTBS with neuroimaging or electrophysiology.
Efficiency Analysis of Magnetic Field Measurement for MR Electrical Impedance Tomography (MREIT)

MREIT is an emerging method to measure the ohmic tissue conductivities, with several potential biomedical applications. Its sensitivity depends on the magnitude of the applied current, which is limited to 1-2 mA in the human brain [1, 2]. This renders in-vivo applications challenging. Here, we aim to analyze and optimize the efficiency of two MREIT pulse sequences for in-vivo brain imaging.
Enhancing predicted efficacy of tumor treating fields therapy of glioblastoma using targeted surgical craniectomy: A computer modeling study

Objective: The present work proposes a new clinical approach to TTFields therapy of glioblastoma. The approach combines targeted surgical skull removal (craniectomy) with TTFields therapy to enhance the induced electrical field in the underlying tumor tissue. Using computer simulations, we explore the potential of the intervention to improve the clinical efficacy of TTFields therapy of brain cancer. Methods: We used finite element analysis to calculate the electrical field distribution in realistic head models based on MRI data from two patients: One with left cortical/subcortical glioblastoma and one with deeply seated right thalamic anaplastic astrocytoma. Field strength was assessed in the tumor regions before and after virtual removal of bone areas of varying shape and size (10 to 100 mm) immediately above the tumor. Field strength was evaluated before and after tumor resection to assess realistic clinical scenarios. Results: For the superficial tumor, removal of a standard craniotomy bone flap increased the electrical field strength by 60-70% in the tumor. The percentage of tissue in expected growth arrest or regression was increased from negligible values to 30-50%. The observed effects were highly focal and targeted at the regions of pathology underlying the craniectomy. No significant changes were observed in surrounding healthy tissues. Median field strengths in tumor tissue increased with increasing craniectomy diameter up to 50-70 mm. Multiple smaller burr holes were more efficient than single craniectomies of equivalent area. Craniectomy caused no significant field enhancement in the deeply seated tumor, but rather a focal enhancement in the brain tissue underlying the skull defect. Conclusions: Our results provide theoretical evidence that small and clinically feasible craniectomies may provide significant enhancement of TTFields intensity in cerebral hemispheric tumors without severely compromising brain protection or causing unacceptable heating in healthy tissues. A clinical trial is being planned to validate safety and efficacy.
Evaluation of a Modified High-Definition Electrode Montage for Transcranial Alternating Current Stimulation (tACS) of Pre-Central Areas

Objective: To evaluate a modified electrode montage with respect to its effect on tACS-dependent modulation of corticospinal excitability and discomfort caused by neurosensory side effects accompanying stimulation. Methods: In a double-blind cross-over design, the classical electrode montage for primary motor cortex (M1) stimulation (two patch electrodes over M1 and contralateral supraorbital area) was compared with an M1 centre-ring montage. Corticospinal excitability was evaluated before, during, immediately after and 15 minutes after tACS (10 min., 20 Hz vs. 30 s low-frequency transcranial random noise stimulation). Results: Corticospinal excitability increased significantly during and immediately after tACS with the centre-ring montage. This was not the case with the classical montage or tRNS stimulation. Level of discomfort was rated on average lower with the centre-ring montage. Conclusions: In comparison to the classic montage, the M1 centre-ring montage enables a more focal stimulation of the target area and, at the same time, significantly reduces neurosensory side effects, essential for placebo-controlled study designs.

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Reaching with the sixth sense: Vestibular contributions to voluntary motor control in the human right parietal cortex

The vestibular system constitutes the silent sixth sense: It automatically triggers a variety of vital reflexes to maintain postural and visual stability. Beyond their role in reflexive behavior, vestibular afferents contribute to several perceptual and cognitive functions and also support voluntary control of movements by complementing the other senses to accomplish the movement goal. Investigations into the neural correlates of vestibular contribution to voluntary action in humans are challenging and have progressed far less than research on corresponding visual and proprioceptive involvement. Here, we demonstrate for the first time with event-related TMS that the posterior part of the right medial intraparietal sulcus processes vestibular signals during a goal-directed reaching task with the dominant right hand. This finding suggests a qualitative difference between the processing of vestibular vs. visual and proprioceptive signals for controlling voluntary movements, which are pre-dominantly processed in the left posterior parietal cortex. Furthermore, this study reveals a neural pathway for vestibular input that might be distinct from the processing for reflexive or cognitive functions, and opens a window into their investigation in humans. (C) 2015 The Authors. Published by Elsevier Inc.
Transcranial electric stimulation (TES) is an emerging technique, developed to non-invasively modulate brain function. However, the spatiotemporal distribution of the intracranial electric fields induced by TES remains poorly understood. In particular, it is unclear how much current actually reaches the brain, and how it distributes across the brain. Lack of this basic information precludes a firm mechanistic understanding of TES effects. In this study we directly measure the spatial and temporal characteristics of the electric field generated by TES using stereotactic EEG (s-EEG) electrode arrays implanted in cebus monkeys and surgical epilepsy patients. We found a small frequency dependent decrease (10%) in magnitudes of TES induced potentials and negligible phase shifts over space. Electric field strengths were strongest in superficial brain regions with maximum values of about 0.5 mV/mm. Our results provide crucial information of the underlying biophysics in TES applications in humans and the optimization and design of TES stimulation protocols. In addition, our findings have broad implications concerning electric field propagation in non-invasive recording techniques such as EEG/MEG.
Transcranial brain stimulation: closing the loop between brain and stimulation: closing the loop between brain and stimulation

PURPOSE OF REVIEW: To discuss recent strategies for boosting the efficacy of noninvasive transcranial brain stimulation to improve human brain function. RECENT FINDINGS: Recent research exposed substantial intra- and inter-individual variability in response to plasticity-inducing transcranial brain stimulation. Trait-related and state-related determinants contribute to this variability, challenging the standard approach to apply stimulation in a rigid, one-size-fits-all fashion. Several strategies have been identified to reduce variability and maximize the plasticity-inducing effects of noninvasive transcranial brain stimulation. Priming interventions or paired associative stimulation can be used to ‘standardize’ the brain-state and hereby, homogenize the group response to stimulation. Neuroanatomical and neurochemical profiling based on magnetic resonance imaging and spectroscopy can capture trait-related and state-related variability. Fluctuations in brain-states can be traced online with functional brain imaging and inform the timing or other settings of transcranial brain stimulation. State-informed open-loop stimulation is aligned to the expression of a predefined brain state, according to prespecified rules. In contrast, adaptive closed-loop stimulation dynamically adjusts stimulation settings based on the occurrence of stimulation-induced state changes. SUMMARY: Approaches that take into account trait-related and state-related determinants of stimulation-induced plasticity bear considerable potential to establish noninvasive transcranial brain stimulation as interventional therapeutic tool.
Where does TMS Stimulate the Motor Cortex? Combining Electrophysiological Measurements and Realistic Field Estimates to Reveal the Affected Cortex Position: Combining Electrophysiological Measurements and Realistic Field Estimates to Reveal the Affected Cortex Position

Much of our knowledge on the physiological mechanisms of transcranial magnetic stimulation (TMS) stems from studies which targeted the human motor cortex. However, it is still unclear which part of the motor cortex is predominantly affected by TMS. Considering that the motor cortex consists of functionally and histologically distinct subareas, this also renders the hypotheses on the physiological TMS effects uncertain. We use the finite element method (FEM) and magnetic resonance image-based individual head models to get realistic estimates of the electric field induced by TMS. The field changes in different subparts of the motor cortex are compared with electrophysiological threshold changes of 2 hand muscles when systematically varying the coil orientation in measurements. We demonstrate that TMS stimulates the region around the gyral crown and that the maximal electric field strength in this region is significantly related to the electrophysiological response. Our study is one of the most extensive comparisons between FEM-based field calculations and physiological TMS effects so far, being based on data for 2 hand muscles in 9 subjects. The results help to improve our understanding of the basic mechanisms of TMS. They also pave the way for a systematic exploration of realistic field estimates for dosage control in TMS.

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Authors: Bungert, A. (Ekstern), Antunes, A. (Ekstern), Espenhahn, S. (Ekstern), Thielscher, A. (Intern)
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Bringing transcranial mapping into shape: Sulcus-aligned mapping captures motor somatotopy in human primary motor hand area

Motor representations express some degree of somatotopy in human primary motor hand area (M1HAND), but within-M1HAND corticomotor somatotopy has been difficult to study with transcranial magnetic stimulation (TMS). Here we introduce a “linear” TMS mapping approach based on the individual shape of the central sulcus to obtain mediolateral corticomotor excitability profiles of the abductor digiti minimi (ADM) and first dorsal interosseus (FDI) muscles. In thirteen young volunteers, we used stereotactic neuronavigation to stimulate the right M1HAND with a small eight-shaped coil at 120% of FDI resting motor threshold. We pseudorandomly stimulated six targets located on a straight mediolateral line corresponding to the overall orientation of the central sulcus with a fixed coil orientation of 45° to the mid-sagittal line.
(STRAIGHT-450 FIX) or seven targets in the posterior part of the crown of the central sulcus following the bending of the central sulcus (CURVED). CURVED mapping employed a fixed (CURVED-450 FIX) or flexible coil orientation producing always a current perpendicular to the sulcal wall (CURVED-900 FLEX). During relaxation, CURVED but not STRAIGHT mapping revealed distinct corticomotor excitability peaks in M1HAND with the excitability maximum of ADM located medially to the FDI maximum. This mediolateral somatotopy was still present during tonic contraction of the ADM or FDI. During ADM contraction, cross-correlation between the spatial excitability profiles of ADM and FDI was lowest for CURVED-900 FLEX. Together, the results show that within-M1HAND somatotopy can be readily probed with linear TMS mapping aligned to the sulcal shape. Sulcus-aligned linear mapping will benefit non-invasive studies of representational plasticity in human M1HAND.

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Authors: Raffin, E. (Ekstern), Pellegrino, G. (Ekstern), Di Lazzaro, V. (Ekstern), Thielscher, A. (Intern), Siebner, H. R. (Ekstern)
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Concurrent TMS-fMRI Reveals Interactions between Dorsal and Ventral Attentional Systems

Adaptive behavior relies on combining bottom-up sensory inputs with top-down control signals to guide responses in line with current goals and task demands. Over the past decade, accumulating evidence has suggested that the dorsal and ventral frontoparietal attentional systems are recruited interactively in this process. This fMRI study used concurrent transcranial magnetic stimulation (TMS) as a causal perturbation approach to investigate the interactions between dorsal and ventral attentional systems and sensory processing areas. In a sustained spatial attention paradigm, human participants detected weak visual targets that were presented in the lower-left visual field on 50% of the trials. Further, we manipulated the presence/absence of task-irrelevant auditory signals. Critically, on each trial we applied 10 Hz bursts of four TMS (or Sham) pulses to the intraparietal sulcus (IPS). IPS-TMS relative to Sham-TMS increased activation in the parietal cortex regardless of sensory stimulation, confirming the neural effectiveness of TMS stimulation. Visual targets increased activations in the anterior insula, a component of the ventral attentional system responsible for salience detection. Conversely, they decreased activations in the ventral visual areas. Importantly, IPS-TMS abolished target-evoked activation increases in the right temporoparietal junction (TPJ) of the ventral attentional system, whereas it eliminated target-evoked activation decreases in the right fusiform. Our results demonstrate that IPS-TMS exerts profound directional causal influences not only on visual areas but also on the TPJ as a critical component of the ventral attentional system. They reveal a complex interplay between dorsal and ventral attentional systems during target detection under sustained spatial attention.
Determinants of the electric field during transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) causes a complex spatial distribution of the electric current flow in the head which hampers the accurate localization of the stimulated brain areas. In this study we show how various anatomical features systematically shape the electric field distribution in the brain during tDCS. We constructed anatomically realistic finite element (FEM) models of two individual heads including conductivity anisotropy and different skull layers. We simulated a widely employed electrode montage to induce motor cortex plasticity and moved the stimulating electrode over the motor cortex in small steps to examine the resulting changes of the electric field distribution in the underlying cortex. We examined the effect of skull thickness and composition on the passing currents showing that thinner skull regions lead to higher electric field strengths. This effect is counteracted by a larger proportion of higher conducting spongy bone in thicker regions leading to a more homogenous current over the skull. Using a multiple regression model
we could identify key factors that determine the field distribution to a significant extent, namely the thicknesses of the cerebrospinal fluid and the skull, the gyral depth and the distance to the anode and cathode. These factors account for up to 50% of the spatial variation of the electric field strength. Further, we demonstrate that individual anatomical factors can lead to stimulation “hotspots” which are partly resistant to electrode positioning. Our results give valuable novel insights in the biophysical foundation of tDCS and highlight the importance to account for individual anatomical factors when choosing an electrode montage. (C) 2015 Elsevier Inc. All rights reserved.
Modeling the effects of noninvasive transcranial brain stimulation at the biophysical, network, and cognitive level

Noninvasive transcranial brain stimulation (NTBS) is widely used to elucidate the contribution of different brain regions to various cognitive functions. Here we present three modeling approaches that are informed by functional or structural brain mapping or behavior profiling and discuss how these approaches advance the scientific potential of NTBS as an interventional tool in cognitive neuroscience. (i) Leveraging the anatomical information provided by structural imaging, the electric field distribution in the brain can be modeled and simulated. Biophysical modeling approaches generate testable predictions regarding the impact of interindividual variations in cortical anatomy on the injected electric fields or the influence of the orientation of current flow on the physiological stimulation effects. (ii) Functional brain mapping of the spatiotemporal neural dynamics during cognitive tasks can be used to construct causal network models. These models can identify spatiotemporal changes in effective connectivity during distinct cognitive states and allow for examining how effective connectivity is shaped by NTBS. (iii) Modeling the NTBS effects based on neuroimaging can be complemented by behavior-based cognitive models that exploit variations in task performance. For instance, NTBS-induced changes in response speed and accuracy can be explicitly modeled in a cognitive framework accounting for the speed-accuracy trade-off. This enables to dissociate between behavioral NTBS effects that emerge in the context of rapid automatic responses or in the context of slow deliberate responses. We argue that these complementary modeling approaches facilitate the use of NTBS as a means of dissecting the causal architecture of cognitive systems of the human brain.

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Authors: Hartwigsen, G. (Ekstern), Bergmann, T. O. (Ekstern), Herz, D. M. (Ekstern), Angstmann, S. (Ekstern), Karabanov, A. (Ekstern), Raffin, E. (Ekstern), Thielsercher, A. (Intern), Siebner, H. R. (Ekstern)
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On the importance of electrode parameters for shaping electric field patterns generated by tDCS

Transcranial direct current stimulation (tDCS) uses electrode pads placed on the head to deliver weak direct current to the brain and modulate neuronal excitability. The effects depend on the intensity and spatial distribution of the electric field. This in turn depends on the geometry and electric properties of the head tissues and electrode pads. Previous numerical studies focused on providing a reasonable level of detail of the head anatomy, often using simplified electrode models. Here, we explore via finite element method (FEM) simulations based on a high-resolution head model how detailed electrode modeling influences the calculated electric field in the brain. We take into account electrode shape, size, connector position and conductivities of different electrode materials (including saline solutions and electrode gels). These factors are systematically characterized to demonstrate their impact on the field distribution in the brain. The goals are to assess the effect of simplified electrode models; and to develop practical rules-of-thumb to achieve a stronger stimulation of the targeted brain regions underneath the electrode pads. We show that for standard rectangular electrode pads, lower saline and gel conductivities result in more homogeneous fields in the region of interest (ROI). Placing the connector at the center of the electrode pad or farthest from the second electrode substantially increases the field strength in the ROI. Our results highlight the importance of detailed electrode modeling and of having an adequate selection of electrode pads/gels in experiments. We also advise for a more detailed reporting of the electrode montages when conducting tDCS experiments, as different configurations significantly affect the results.

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Transcranial Magnetic Stimulation: An Automated Procedure to Obtain Coil-specific Models for Field Calculations

Background: Field calculations for transcranial magnetic stimulation (TMS) are increasingly implemented online in neuronavigation systems and in more realistic offline approaches based on finite-element methods. They are often based on simplified and/or non-validated models of the magnetic vector potential of the TMS coils.

Objective: To develop an approach to reconstruct the magnetic vector potential based on automated measurements.

Methods: We implemented a setup that simultaneously measures the three components of the magnetic field with high spatial resolution. This is complemented by a novel approach to determine the magnetic vector potential via volume integration of the measured field.

Results: The integration approach reproduces the vector potential with very good accuracy. The vector potential distribution of a standard figure-of-eight shaped coil determined with our setup corresponds well with that calculated using a model reconstructed from x-ray images.

Conclusion: The setup can supply validated models for existing and newly appearing TMS coils.

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Organisations: Department of Informatics and Mathematical Modeling, Department of Applied Mathematics and Computer Science, Cognitive Systems, Department of Electrical Engineering, Center for Magnetic Resonance, Copenhagen University Hospital
Authors: Madsen, K. H. (Intern), Ewald, L. (Ekstern), Siebner, H. R. (Ekstern), Thielscher, A. (Intern)
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A key region in the human parietal cortex for processing proprioceptive hand feedback during reaching movements

Seemingly effortless, we adjust our movements to continuously changing environments. After initiation of a goal-directed movement, the motor command is under constant control of sensory feedback loops. The main sensory signals contributing to movement control are vision and proprioception. Recent neuroimaging studies have focused mainly on identifying the parts of the posterior parietal cortex (PPC) that contribute to visually guided movements. We used event-related TMS and force perturbations of the reaching hand to test whether the same sub-regions of the left PPC contribute to the processing of proprioceptive-only and of multi-sensory information about hand position when reaching for a visual target. TMS over two distinct stimulation sites elicited differential effects: TMS applied over the posterior part of the medial intraparietal sulcus (mIPS) compromised reaching accuracy when proprioception was the only sensory information available for correcting the reaching error. When visual feedback of the hand was available, TMS over the anterior intraparietal sulcus (aIPS) prolonged reaching time. Our results show for the first time the causal involvement of the posterior mIPS in processing proprioceptive feedback for online reaching control, and demonstrate that distinct cortical areas process proprioceptive-only and multi-sensory information for fast feedback corrections.
Connectivity between Right Inferior Frontal Gyrus and Supplementary Motor Area Predicts After-Effects of Right Frontal Cathodal tDCS on Picture Naming Speed

Background: Cathodal transcranial direct current stimulation (tDCS) of the right frontal cortex improves language abilities in post-stroke aphasic patients. Yet little is known about the effects of right frontal cathodal tDCS on normal language function. Objective/hypothesis: To explore the cathodal tDCS effects of the right-hemispheric homologue of Broca's area on picture naming in healthy individuals. We hypothesized that cathodal tDCS improves Picture naming and that this effect is determined by the anatomical and functional connectivity of the targeted region. Methods: Cathodal and sham tDCS were applied to the right inferior frontal gyrus in 24 healthy subjects before a picture-naming task. All participants were studied with magnetic resonance imaging at pre-interventional baseline. Probabilistic tractography and dynamic causal modeling of functional brain activity during a word repetition task were applied to characterize anatomical and functional connectivity. Results: Subjects named pictures faster after cathodal relative to sham tDCS. The accelerating effect of tDCS was explained by a reduced frequency of very slow responses. tDCS-induced acceleration of Picture naming correlated with larger volumes of the tract connecting the right Broca's area and the supplementary motor area (SMA) and greater functional coupling from the right SMA to the right Broca's area. Conclusions: The results support the notion that the after-effects of tDCS on brain function are at least in part determined by the anatomical and functional connectivity of the targeted region.
Design of a New MR Compatible Haptic Interface with Six Actuated Degrees of Freedom

Functional magnetic resonance imaging is an often adopted tool to study human motor control mechanisms. Highly controlled experiments as required by this form of analysis can be realized with haptic interfaces. Their design is challenging because of strong safety and MR compatibility requirements. Existing MR-compatible haptic interfaces are restricted to maximum three actuated degrees of freedom. We propose an MR-compatible haptic interface with six actuated degrees of freedom to be able to study human brain mechanisms of natural pick-and-place movements including arm transport. In this work, we present its mechanical design, kinematic and dynamic model, as well as report on its model-based characterization. A novel hybrid control scheme for the employed ultrasonic motors is introduced. Preliminary MR compatibility tests based on one complete actuator-sensor module are performed. No measurable noise is found and thus, bidirectional compatibility of the six DoF interface can be expected.

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Authors: Ergin, M. A. (Ekstern), Kühne, M. (Ekstern), Thielscher, A. (Intern), Peer, A. (Ekstern)
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Applying electric field modeling to TMS motor mapping

Realistic field calculations in transcranial neurostimulation promise a better insight into the position and extent of the affected brain areas and improve the spatial specificity of stimulation. This is underlined by recent work that demonstrated a strong influence of individual gyral geometry on the strength and distribution of the induced electric field [1]. The field calculations are based on fundamental laws of electrodynamics and rely on conductivity model of individual heads, which are based on segmented structural MR images. For the wider application and the general acceptance of electric field modeling for neurostimulation, two steps seem essential: — a demonstration that the simulated fields correlate with observable effects of neurostimulation (e.g. behavioral or electrophysiological). That is, the simulated fields contribute accurate and relevant information to the experiments; integration electric field modeling into regular TMS experiments in a user-friendly way.

Methods and results.— We demonstrate the integration of the Simulation for Non-Invasive Brain Stimulation (SimNIBS, www.simnibs.de) software package with neuronavigation tools for TMS (VISOR from ANT). The coil position and orientation for each TMS pulse is saved by VISOR. These coil positions are automatically converted into the SimNIBS format and used to carry out Electric field simulations for each coil position.

First results from TMS-motor mapping show how the simulated Electric fields can be correlated with the motor evoked potentials of individual muscles.

Conclusion.— These results demonstrate that advanced Electric field simulations can be applied routinely in experiments involving TMS. In addition, the application to TMS-motor mapping allows validating these simulations in a brain system that is well characterized.
Effects of Parietal TMS on Visual and Auditory Processing at the Primary Cortical Level - A Concurrent TMS-fMRI Study

Accumulating evidence suggests that multisensory interactions emerge already at the primary cortical level. Specifically, auditory inputs were shown to suppress activations in visual cortices when presented alone but amplify the blood oxygen level–dependent (BOLD) responses to concurrent visual inputs (and vice versa). This concurrent transcranial magnetic stimulation–functional magnetic resonance imaging (TMS-fMRI) study applied repetitive TMS trains at no, low, and high intensity over right intraparietal sulcus (IPS) and vertex to investigate top-down influences on visual and auditory cortices under 3 sensory contexts: visual, auditory, and no stimulation. IPS-TMS increased activations in auditory cortices irrespective of sensory context as a result of direct and nonspecific auditory TMS side effects. In contrast, IPS-TMS modulated activations in the visual cortex in a state-dependent fashion: it deactivated the visual cortex under no and auditory stimulation but amplified the BOLD response to visual stimulation. However, only the response amplification to visual stimulation was selective for IPS-TMS, while the deactivations observed for IPS- and Vertex- TMS resulted from crossmodal deactivations induced by auditory activity to TMS sounds. TMS to IPS may increase the responses in visual (or auditory) cortices to visual (or auditory) stimulation via a gain control mechanism or crossmodal interactions. Collectively, our results demonstrate that understanding TMS effects on (uni)sensory processing requires a multisensory perspective.

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Authors: Leitao, J. (Ekstern), Thielscher, A. (Intern), Werner, S. (Ekstern), Pohmann, R. (Ekstern), Noppeney, U. (Ekstern)
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Scopus rating (2014): SJR 4.815 SNIP 2 CiteScore 6.86
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TMS field modelling-status and next steps

In the recent years, an increasing number of studies used geometrically accurate head models and finite element (FEM) or finite difference methods (FDM) to estimate the electric field induced by non-invasive neurostimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial weak current stimulation (TCS; e.g., Datta et al., 2010; Thielscher et al., 2011). A general outcome was that the field estimates based on these more realistic models differ substantially from the results obtained with simpler head models. This suggests that the former models are indeed needed to realistically capture the field distribution in the brain. However, it is unclear how accurate even these more advanced models are and, in particular, to which extent they allow predicting the physiological outcome of stimulation. An experimental validation of the novel methods for field calculation is thus necessary.

Focusing on motor cortex stimulation by TMS, our goal is to explore to which extent the field estimates based on advanced models correlate with the physiological stimulation effects. For example, we aim at testing whether interindividual differences in the field estimates are also reflected in differences in the MEP responses. This would indicate that the field calculations accurately capture the impact of individual macroanatomical features of the head and brain on the induced field distribution, in turn strongly supporting their plausibility. Our approach is based on the SimNIBS software pipeline (www.simnibs.de) that allows for the automatic creation of accurate head models from structural and diffusion-weighted magnetic resonance images (MRI) (Windhoff et al., 2011). This enables us to perform field calculations for multiple subjects, as required in neuroscientific studies. We substantially improved the software in order to improve its usability in a group analysis. At the moment, we are performing field calculations and are acquiring motor mapping data in a group of subjects for a systematic comparison of both data sets. I will give an overview on the status of the SimNIBS project. I will start by summarizing the key findings on how the individual brain anatomy shapes the electric field induced by TMS (Thielscher et al., 2011; Opitz, 2011). The putative link between the modeling results and basic physiological TMS effects is highlighted. I will then introduce the novel features of SimNIBS that include the import of coil positions from neuronavigation systems, improved support for diffusion-weighted MRI and transformation of the estimated fields into MNI space for group analysis. Preliminary results on the comparison between field estimates and motor mapping data will be presented. To summarize, field estimates based on accurate head models have already proven highly useful for a better understanding of the biophysics of non-invasive brain stimulation. The improved software tools now allow for systematic tests of the links between the estimated fields and the physiological effects in multi-subject studies. This will give the knowledge needed, e.g., for a more accurate spatial targeting of specific
brain areas by TMS.

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Authors: Thielscher, A. (Intern)
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Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.572 SNIP 0.437 CiteScore 2.61
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BFI (2011): BFI-level 1
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BFI (2009): BFI-level 1
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Web of Science (2009): Indexed yes
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Scopus rating (2008): SJR 0.258 SNIP 0.33
Scopus rating (2007): SJR 0.32 SNIP 0.206
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Electric field calculations in brain stimulation: The importance of geometrically accurate head models

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Authors: Thielscher, A. (Intern), Opitz, A. (Ekstern), Will, S. (Ekstern), Windhoff, M. (Ekstern)
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Scopus rating (2003): SJR 0.165 SNIP 0.456
Scopus rating (2002): SJR 0.244 SNIP 0.456
Scopus rating (2001): SJR 0.174 SNIP 0.381
Scopus rating (2000): SJR 0.235 SNIP 0.505
Scopus rating (1999): SJR 0.213 SNIP 0.637
The optimal application of TMS is still severely hampered by technical restrictions of current neuronavigation systems. Firstly, studies combining TMS with functional neuroimaging increasingly demonstrate that TMS affects networks rather than isolated regions. These network effects might contribute to the observed behavioural or peripheral electrophysiological stimulation effects. However, neuronavigation systems only visualize the directly stimulated area underneath coil rather than networks. Secondly, recent modelling studies demonstrated that field estimates based on realistic head models differ markedly from those obtained with simplified spherical head models. Notably, when considering figure-8 coils, the field peak can be shifted away from a position directly underneath the coil centre (as currently visualized by neuronavigation systems). We present a cooperative development effort that aims at enabling future neuronavigation systems to take the factors 'connectivity' and 'realistic field shape' into account during online visualization. The overarching goal is to increase the specificity and reproducibility of stimulation effects both on the intra- and interindividual level. Diffusion-weighted magnetic resonance imaging (DWI) can be used to estimate in-vivo the individual anatomical connectivity in patients and healthy subjects. We will highlight advanced schemes for the connectivity estimation based on probabilistic orientation distribution functions [1]. In addition, we will present novel techniques to visualize the resulting connectivity estimates in real-time. Second, we will give an overview over the state-of-the-art in field calculations for TMS based on finite-element methods and discuss concepts to incorporate the knowledge gained with these realistic but time-consuming methods into the online visualization of neuronavigation systems [2]. Both techniques in combination will allow for a more accurate selection of the desired target region and will for the first time allow the optimal targeting of an area based on its connectivity profile.

Individual anatomical connectivity visualization and improved field predictions in neuronavigation for TMS
The neural mechanisms of reliability weighted integration of shape information from vision and touch

Behaviourally, humans have been shown to integrate multisensory information in a statistically-optimal fashion by averaging the individual unisensory estimates according to their relative reliabilities. This form of integration is optimal in that it yields the most reliable (i.e. least variable) multisensory percept. The present study investigates the neural mechanisms underlying integration of visual and tactile shape information at the macroscopic scale of the regional BOLD response. Observers discriminated the shapes of ellipses that were presented bimodally (visual–tactile) or visually alone. A 2×5 factorial design manipulated (i) the presence vs. absence of tactile shape information and (ii) the reliability of the visual shape information (five levels). We then investigated whether regional activations underlying tactile shape discrimination depended on the reliability of visual shape. Indeed, in primary somatosensory cortices (bilateral BA2) and the superior parietal lobe the responses to tactile shape input were increased when the reliability of visual shape information was reduced. Conversely, tactile inputs suppressed visual activations in the right posterior fusiform gyrus, when the visual signal was blurred and unreliable. Somatosensory and visual cortices may sustain integration of visual and tactile shape information either via direct connections from visual areas or top-down effects from higher order parietal areas.

General information
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Uncovering a Context-Specific Connectional Fingerprint of Human Dorsal Premotor Cortex

Primate electrophysiological and lesion studies indicate a prominent role of the left dorsal premotor cortex (PMd) in action selection based on learned sensorimotor associations. Here we applied transcranial magnetic stimulation (TMS) to human left PMd at low or high intensity while right-handed individuals performed externally paced sequential key presses with their left hand. Movements were cued by abstract visual stimuli, and subjects either freely selected a key press or responded according to a prelearned visuomotor mapping rule. Continuous arterial spin labeling was interleaved with TMS to directly assess how stimulation of left PMd modulates task-related brain activity depending on the mode of movement selection. Relative to passive viewing, both tasks activated a frontoparietal motor network. Compared with low-intensity TMS, high-intensity TMS of left PMd was associated with an increase in activity in medial and right premotor areas without affecting task performance. Critically, this increase in task-related activity was only present when movement selection relied on arbitrary visuomotor associations but not during freely selected movements. Psychophysiological interaction analysis revealed a context-specific increase in functional coupling between the stimulated left PMd and remote right-hemispheric and mesial motor regions that was only present during arbitrary visuomotor mapping. Our TMS perturbation approach yielded causal evidence that the left PMd is implicated in mapping external cues onto the appropriate movement in humans. Furthermore, the data suggest that the left PMd may transiently form a functional network together with right-hemispheric and mesial motor regions to sustain visuomotor mapping performed with the left nondominant hand.
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ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.954 SNIP 1.876
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 6.053 SNIP 1.871
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 6.567 SNIP 1.9
Scopus rating (2007): SJR 6.034 SNIP 1.928
Scopus rating (2006): SJR 5.863 SNIP 1.924
Scopus rating (2005): SJR 5.793 SNIP 1.978
Scopus rating (2004): SJR 5.862 SNIP 1.973
Scopus rating (2003): SJR 5.949 SNIP 2.054
Scopus rating (2002): SJR 5.972 SNIP 1.986
Scopus rating (2001): SJR 5.811 SNIP 2.051
Scopus rating (2000): SJR 6.158 SNIP 2.126
Scopus rating (1999): SJR 6.803 SNIP 2.248
Original language: English
DOIs:
Source: dtu
Source-ID: n:oai:DTIC-ART:biosis/365883147::17978
Publication: Research - peer-review › Journal article – Annual report year: 2012

Projects:

**Highly Sensitive Magnetic Sensing of Neural Activity**
Department of Electrical Engineering
Period: 01/02/2016 → 31/01/2019
Number of participants: 4
PhD Student:
- Karadas, Mürsel (Intern)
Supervisor:
- Andersen, Ulrik Lund (Intern)
- Hanson, Lars G. (Intern)
Main Supervisor:
- Thielcher, Axel (Intern)

**Financing sources**
Source: Internal funding (public)
Name of research programme: Forskningsrådsfinansiering
Project: PhD

**Combining ultrasound brain stimulation with MR imaging**
Department of Electrical Engineering
Period: 15/12/2015 → 14/12/2018
Number of participants: 4
PhD Student:
- Pasquinelli, Cristina (Intern)
Supervisor:
Hanson, Lars G. (Intern)
Lee, Hyunjoo Jenny (Ekstern)
Main Supervisor:
Thielscher, Axel (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Institut stipendie (DTU)
Project: PhD

Decreasing the spatial uncertainty in non-invasive brain stimulation, EEG and MEG based on advanced head modelling

Department of Applied Mathematics and Computer Science
Period: 15/10/2015 → 14/10/2018
Number of participants: 4
Phd Student:
Nielsen, Jesper Duemose (Intern)
Supervisor:
Madsen, Kristoffer Hougaard (Intern)
Thielscher, Axel (Intern)
Main Supervisor:
Hansen, Lars Kai (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

MR Imaging of Weak Electric Currents

Department of Electrical Engineering
Period: 01/09/2014 → 31/08/2017
Number of participants: 6
Phd Student:
Göksu, Cihan (Intern)
Supervisor:
Hanson, Lars G. (Intern)
Main Supervisor:
Thielscher, Axel (Intern)
Examiner:
Petersen, Esben Thade (Intern)
Bieri, Oliver (Ekstern)
Ider, Yusuf Ziya (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Early detection of response to treatment in cancer by Hyperpolarized Metabolic MR

Department of Electrical Engineering
Period: 01/01/2014 → 23/08/2017
Number of participants: 7
Phd Student:
Eldirdiri, Abubakr (Intern)
Supervisor:
Hanson, Lars G. (Intern)
Kjær, Andreas (Intern)
Main Supervisor:
Ardenkjær-Larsen, Jan Henrik (Intern)
Examiner:
Thielscher, Axel (Intern)
Mayer, Dirk (Ekstern)
McLean, Mary A. (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: Forskningsrådsfinansiering

Relations
Publications:
Monitoring Cancer Response to Treatment with Hyperpolarized $^{13}$C MRS
Project: PhD

Motion-insensitive Magnetic Resonance Imaging
Department of Electrical Engineering
Period: 01/12/2012 → 16/03/2016
Number of participants: 6
Phd Student:
Andersen, Mads (Intern)
Supervisor:
Madsen, Kristoffer Hougaard (Intern)
Main Supervisor:
Hanson, Lars G. (Intern)
Examiner:
Thielscher, Axel (Intern)
Bowtell, Richard William (Ekstern)
Ringgaard, Steffen (Ekstern)

Financing sources
Source: Internal funding (public)
Name of research programme: ErhvervsPhD-ordningen VTU
Project: PhD