

ID: U-OP-01**BrainLinks-BrainTools-Methods and Tools for Neural Engineering**

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Diseases and disorders of the brain like epilepsy, stroke, Alzheimer's and Parkinson's disease, mood and anxiety disorders, addiction and traumatic brain injury affect millions of persons worldwide, restrict their participation in work and social life and decrease their quality of life, dramatically. In Europe, the costs of treating these patients have exceeded even the sum of costs to treat cancer and cardiovascular diseases. Diagnosis, therapy and rehabilitation of these diseases needs interventions with the brain to collect neuronal signals, understand pathophysiological changes and propose new treatment options to record neural activity, identify states of the brain and overwrite "wrong" signal patterns when necessary.

The BrainLinks-BrainTools Cluster of Excellence focus its research on the development of methods and tools to probe the brain and to investigate the behaviour of neuronal networks after stroke, in epilepsy, in movement and mood disorders and in paralyzed subjects. Probe technologies that needed to get developed to probe the brain on the single cell level as well as the network level have been developed over the last years. They include electrical as well as optical approaches and allow non-destructive analysis of the anatomy and morphology of brain regions, intracortical as well as epicortical recording of electrical signals over more than one hundred channels and optical interaction with genetically modified nerve cells in the field of optogenetics. Electronic circuitry has been developed to integrate functionality in smallest low noise and low power systems to amplify smallest nerve signals. Signal processing needs to go beyond clinical diagnosis methods in both, non-invasive and invasive settings, to obtain robust and reliable information about brain states that is necessary to drive assistive devices and deliver closed-loop therapies.

ID: U-OP-02**Controlling Bessel beams for optophysiology**

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Deep optogenetic stimulation currently requires physical penetration of the the brain either by optical fibres or by neuro probes comprising optical waveguides. In our project we aim to avoid harmful damage as far as possible by using the self-reconstructing properties of propagation invariant beams, so-called Bessel beams, to penetrate the brain with light only.

Bessel beams are generated by conical lenses or mirrors (axicons) which are illuminated with collimated laser light. The self-interfering conical wavefront then forms a ring pattern with a strong central maximum which, in contrast to classical lenses, does not provide one single focal spot but an extended focal zone along the optical axis. When a scattering object is brought into this focal zone, the Bessel beam is first strongly disturbed but reconstructs itself further down the optical axis.

We will use these features to develop controlled optophysiological interfaces without penetrating the brain tissue. This lightweight stimulation device integrates an array of nine blue laser diodes with miniaturized optical elements and a depth control for the Bessel beams to individually address different regions in the brain.

As first results, we found that Bessel beams can be generated by edge-emitting laser diodes which intrinsically do not provide a circular spot and suffer from astigmatism. These laser diodes provide a wavelength of 450 nm which is close to the maximum sensitivity of Channel Rhodopsin-2 at 473 nm. For depth control, we developed a liquid crystal-based ring aperture that allows to select defined sections of the Bessel beam. The miniature axicons and collimation lenses will be produced with a novel rapid prototyping process relying on laser structuring and molding.

ID: U-OP-03**MEMS-based micro-optical tools for optogenetic applications**

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In order to gain a more detailed understanding of the interaction within and among neural networks and consequently to analyze brain dysfunction it is requested to not only record neuronal activity but also actively interact with neuronal tissue at a high spatial and temporal resolution. Aside from basic research this is also true for clinical applications of neurotechnology for the treatment of neurological disorders such as Parkinson's disease and epilepsy as well as the restoration of sensory and motor functions. Optogenetics, i.e. the well controlled interaction with genetically modified neurons using light, has emerged over the past decade as the most innovative method in experimental neuroscience that also provides new perspectives for future clinical applications of neurotechnology. Aside from biological aspects addressing the development of light sensitive molecules, i.e. opsins, and their controlled expression in neurons, a key technological challenge targets the development of implantable, miniaturized light sources combined with recording electrodes.

In the BrainLinks-BrainTools Cluster of Excellence, we develop microoptical tools for optogenetic research. Key requirements to be achieved are a compact system layout, biocompatibility as well as long-term stability for chronic animal experiments. This is achieved among others by integrating electrooptical components, i.e. light-emitting diodes and laser diode chips, packaged for instance in hermetic micro housings based on silicon and glass. In order to achieve a high flexibility in positioning these optical tools during implantation, we apply optical waveguides based on silicone rubber and other polymers. The paper will introduce penetrating as well as surface probes for a localized optical stimulation and simultaneous electrical recording of neural tissues. It will analyze innovative wafer-level fabrication technologies of hermetic micro housings applying thinned glass wafers patterned by wet etching and reflow, and glass substrates with integrated beam shaping elements such as microlenses realized using dry etching.

ID: U-OP-04**Developments for the next generation of brain probes**

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Intervention with the brain needs technical probes that allow to either monitor the desired target tissue or region or modify the excitation of the targeted nerve cells in a predefined manner. Different technological approaches have become success stories over the last decade depending on the intended use. Reliability and adaptivity by redundancy or by active switching elements led to broad acceptance of microdevices with increased functionality compared to the single or multiple wire approach. Flexible, polyimide-based electrodes arrays with about 250 channels have been chronically implanted to investigate network interaction over large distances and between different brain areas by means of field potentials. Signal quality remained stable over more than a year in preclinical implantations. So far, percutaneous plugs have been used to select electrodes of interest and record data. In the meantime, telemetric systems that integrate multiplexing, recording and stimulation capabilities have been developed that allow fully implantable systems with inductive energy supply and data exchange. Silicon-based shaft electrodes have become the gold standard for intracortical single unit recording. The integration of electronic circuitry together with a large number of electrode sites led to the “electronic depth control” (EDC) in which in vivo tracing of nerve signals can be done by electronic electrode switching. Flexible intracortical probes complement the silicon approach and showed only little scar formation in chronic use. They need either an insertion tool or stiff, resorbable coatings for implantation. For deep brain structures, different designs have to be developed. Hybrid approaches combining existing clinical probe technology with microsystems allow for increased spatial resolution of recording and stimulation as well as potential to integrate biochemical sensor. Preclinical trials are successful but translation into medical devices and clinical practice is not yet in sight.

ID: U-OP-05**Achievements and trends of CMOS-assisted neural recording interfaces**

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Investigating the human brain and understanding its neuronal communication is one of the prominent tasks of modern neuroscience. The ongoing technological improvement of microsystem technologies thereby offers an increased measurement precision that allows for the transition from non-invasive procedures (e.g. EEG), over intracranial approaches (e.g. ECoG), towards the electrophysiological characterization of single neurons in-vivo. The small size of neurons between 4 and 100 μm requests not only for the miniaturization of tools, but the fast response of a single neuron in contrast to the averaged answer of a large brain area requires improvements in signal processing. Modern tools thus have to process local field potentials (LFPs) as well as action potentials (APs), and should be able to separate these two frequency bands of interest.

This work will address recent advances in implantable active neural recording interfaces. It will present some of the most prominent tools and will discuss their respective achievements, e.g. in terms of area, channel count, or overall functionality. It will furthermore describe how modern CMOS technologies are used by the BrainLinks-BrainTools Cluster of Excellence to maintain an optimal signal quality and cope with micro motions of the implant or plastic reorganization of the brain, i.e. discussing the concept of electronic depth control (EDC). EDC combines the high spatial resolution of neuron-sized electrodes with the processing power of CMOS electronics. Challenges of such CMOS probes with active assistance arise from the fact that each recording site has to be equipped with a gain stage consuming very little area. This work will therefore finally present CMOS circuit techniques for area-efficient implementations of analog signal-processing features and name possible future trends for CMOS-assisted neural interfaces.

ID: U-OP-06**Beyond Slow Waves: Non-Invasive High-Gamma Mapping in an Optimized EEG Lab**

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Analysis of high-gamma cortical brain responses occurring in conditions such as during voluntary movement has, for a long time, been in the domain of intracranial EEG recordings. In the BrainLinks-BrainTools Cluster of Excellence, we develop novel, optimized non-invasive EEG methods that allow to measure high-gamma responses with unprecedented clarity. To this aim we have set up an optimized EEG Lab. The technical EEG Setup comprises (1.) Active shielding: optimized for frequencies from DC - 10 kHz (-30 dB to -50 dB), shielded window, ventilation & cable feedthrough (2.) Suitable amplifiers: high-resolution (24 bits/sample) and low-noise ($<0.6 \mu\text{V RMS}$ 0.16-200 Hz, $<1.5 \mu\text{V RMS}$ 0.16-3500 Hz), 5 kHz sampling rate, (3.) Eye tracking: EyeLink 1000Plus, binocular 500 Hz, resolution $<0.01^\circ\text{RMS}$, (4.) Full optical decoupling: All devices (amplifiers, eye tracking, communication, etc.) battery powered and communicate via optic fiber and (5.) High-density EEG: up to 480 shielded EEG channels (here: 128 channels). With this setup, we were able to show contralateral movement-related high gamma responses during a visuomotor-Reaction-Time Task (~60-90 Hz) which was also single-trial decodable. Especially clear high-gamma responses were found during foot movement. Finally, for the first time, we were also able to demonstrate error-related high gamma responses, located above the frontal midline. Together these findings show that non-invasive EEG has a much greater potential for detecting high-gamma band responses than previously thought. Our findings open a new window on this physiologically important frequency range of cortical activity, and enables brain-computer interfacing (BCI) studies in the high gamma range that are complementary to intracranial studies, or may be helpful in planning clinical trials with BCI implants.

U-PP-01**Epidural Recordings of Auditory Evoked Potentials in Cochlear Implant Users – First Cases**

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On the long term it is desirable for cochlear implant (CI) users to control their device in a closed loop via brain signals. A possible application is the active or passive selection of speech coding strategies or preprocessing algorithms. A promising approach is the use of auditory evoked potentials (AEP) and previous studies have shown the possible suitability of auditory paradigms [1]. However, these investigations are based on non-invasive signal acquisition which requires the use of additional EEG electrodes mounted on the users scalp [2]. For CI users in an everyday life application it is more convenient to use implanted electrodes for recording the signals. Further it is to be expected that invasively recorded signals are of higher quality and are less effected by movement artefacts. Permanently implanted electrodes would also allow for a monitoring of maturation of the auditory system following the CI implantation. First invasive recordings within CI surgeries were already done in the early years of CIs [3]. However, under the influence of anesthesia cortical potentials cannot be recorded reliably.

In this pilot project we investigate the feasibility of implanting epidural electrodes temporally during the CI surgery and the possibility to record AEPs in the course of several days when the patient is awake again. After a few days the epidural electrodes are removed.

Currently the first data sets are obtained with three patients showing promising results. The recorded potentials were compared to the clinical standard recordings using adhesive electrodes. Cortical evoked response audiometry (CERA) depicted clearer N100 waves which were also visible at lower stimulation intensities. Furthermore, the signal was less disturbed by artefacts.

Altogether the approach is feasible, safe and well tolerated by the patients, and the AEP waves can be clearly seen.

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ID: U-PP-02**Cost-effective, high-channel-count system for impedance spectroscopy**

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The electrode impedance of brain-machine-interfaces to neural tissue strongly depends on electrode material, surface roughness and exposed electrode area. Time-resolved impedance monitoring of electrodes submersed in saline solution serves as a first indicator of their long-term stability and provides information on the potential onset of their degradation. We present a novel high-channel-count test system of minimal size (80x80x50 mm³) enabling impedance spectroscopy at frequencies between 350 Hz and 95 kHz. The setup is of modular design suitable for the online control of long-term test sequences via internet. It relies on the integrated circuit chip AD5933 (Analog Devices, USA) to generate the sinusoidal measurement signals of 20 mV_{pp}, and to amplify and digitize the respective response current. A 128-channel system variant was validated using known resistors and capacitors as well as combinations thereof, and compared against two commercial systems, i.e. the 64-channel nanoZ (White Matter LLC, USA) and CompactStat (Ivium Technologies, The Netherlands). Absolute impedance values at 1 kHz in the range of up to 2 MOhm revealed differences to the analytical model of up to 10% for the CompactStat, nanoZ and our new system. Measured phase shifts matched to analytically expected results, showing an offset of about 2° for both, the commercial systems and our device. The novel impedance spectroscopy system outperforms commercial systems with respect to channel count, in particular since the system design allows for future expansion well beyond the currently available 128 measurement channels. Results of neural probes characterized with the novel system at frequencies between 350 Hz and 10 kHz match those measured with the CompactStat. At higher frequencies however, we observed small offsets of about 15 kOhm. We started gathering plausible long-term characterization results of various neural probes established in our lab and expect to gain deeper insights into potential degradation mechanisms.

ID: U-PP-03**Piezoelectric effect of PVDF and PVDF-TrFE scaffolds**

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In neural tissue engineering piezoelectric polymers are being investigated as potential scaffolds for supporting nerve regeneration processes. Electrospun scaffolds from polyvinylidene-fluoride (PVDF) and with trifluoroethylene PVDF-TrFE are very promising because of their proven biocompatibility and piezoelectric properties, which can possibly stimulate cell ingrowth with their electrical activity upon mechanical deformation. This work reports the characterizing of the piezoelectric effect of electrospun PVDF and PVDF-TrFE scaffolds in response to mechanical loading.

Scaffolds were produced via electrospinning from PVDF and PVDF-TrFE both with concentration of 10, 15, 20 and 30 wt% dissolved in N,N-dimethylformamide and acetone (6:4). In the process flow rates of 1-2 ml/h and voltages of 20-24 kV were applied to produce aligned fibers. The electrospinning time was 30 min that led to scaffolds' thickness of 50 to 70 μm . The piezoelectric response of the scaffolds was induced using an impact testing machine (BOSE-Electroforce-LM1-Test-Bench). Impact forces of 1 to 15 N were applied.

Electrospun PVDF and PVDF-TrFE scaffolds with different concentrations exhibited an piezoelectric responses that varied according to the applying impact load. PVDF-TrFE scaffolds showed increased and reproducible piezoelectric effect in the range 10-150 mV as compared to pure PVDF ones. The mechanically induced electrical impulses range in the pure PVDF scaffolds was between 7 mV and 80 mV. The results were recorded in response to impact forces from 1 to 15 N. Increasing the polymer concentration led to enhanced piezoelectric effect.

The results demonstrate the possibility of producing electrospun PVDF and PVDF-TrFE scaffolds, as nerve guidance, with controllable piezoelectric responses depending on the polymer concentration and applied mechanical load. That can in turn stimulate Schwann cell ingrowth and axonal elongation. Future experiments are scheduled to evaluate this piezoelectric response in more detail in organotypic cell culture models in vitro and rat sciatic nerve repair models in vivo.

ID: U-PP-04**3D Visualization of intraoperative stimulation test results for better target selection in DBS surgery**

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Despite an increasing use of deep brain stimulation (DBS), the fundamental mechanisms underlying therapeutic and adverse effects as well as the optimal stimulation site remain largely unknown. The aim of the present study was to develop a method to correlate electric field simulations for intraoperative stimulation tests with quantitatively evaluated symptom improvement and patient specific anatomy to estimate the optimal stimulation site.

One essential tremor patient, bilaterally implanted in the ventro-intermediate nucleus (Vim) has been included. Preoperatively Vim and its anatomic neighbors were manually outlined according to spontaneous MRI contrasts using the commercial planning software from where the structures could be exported via a specifically designed interface. During the intervention, intraoperative stimulation tests were performed on two trajectories per hemisphere (8 positions per trajectory). The change in tremor at each stimulation position compared to baseline was evaluated using a 3-axis accelerometer. Based on accelerometer data, two stimulation amplitudes (low and high improvement) were identified per position and corresponding electric-field isosurfaces (0.2V/mm) were simulated. As each voxel in the region of interest may be part of several isosurfaces -each surface depicting one amplitude responsible for one improvement in tremor- the voxel was assigned to the isosurface representing the minimum improvement using Matlab. Data were imported into Paraview (VTK based 3D visualization software). Color-coded minimum 3D-improvement maps were visualized on the patient's MR images together with the manually outlined anatomical structures. The resulting visualization was evaluated by clinicians.

The software allowed 3D visualization as well as orthographic slices parallel to the trajectory. Clinicians confirmed that it enables the identification of the most effective stimulation areas with respect to the anatomy. This new concept based on quantitative symptom evaluation, electric field simulations, and patient specific anatomical data will allow the analysis of a high amount of intraoperative data which might help to elucidate the mechanism of action of DBS.