MED MEDIZINISCHE FAKULTÄT

Forschungsbericht 2021

Institut für Medizinische Psychologie

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1. LEITUNG

Prof. Dr. med. habil. B.A. Sabel, Ph.D. (geschäftsführender Leiter)

2. HOCHSCHULLEHRER/INNEN

Prof. Dr. med. habil. B.A. Sabel, Ph.D.

3. FORSCHUNGSPROFIL

Arbeitsgruppe Neuropsychologie

- Durchführung klinischer Prüfungen zur Etablierung non-invasiver Elektrostimulation
- Entwicklung und Validierung computergestützter Diagnose-und Therapieverfahren für Patienten mit Sehbehinderungen nach Hirnschädigung oder Augenerkrankungen (z.B. Glaukom, Sehnervschädigung)
- Gesichtsfelddiagnostik, Eye-tracking und elektrophysiologische Untersuchung von Gebieten des Residualsehens
- Untersuchung der Lebensqualität bzw. Beeinträchtigung von Aktivitäten des täglichen Lebens bei Sehbeeinträchtigungen nach Augenerkrankungen oder Läsionen der zentralen Sehbahn
- Untersuchung von Mechanismen visueller Plastizität bei behavioraler Intervention mit visueller Restitutionstherapie, Augenbewegungstraining, oder nicht-invasiver Elektrostimulation
- Computersimulation der Plastizität im visuellen Kortex/Prädiktoren der Erholung von Sehfunktionen

Arbeitsgruppe Verhaltensneurowissenschaften

- Untersuchung neuroanatomischer Korrelate von neuronaler Schädigung und Erholung
- Pharmakologische Behandlung von Versuchstieren mit verschiedenen therapeutischen Ansätzen
- Repetitive transkorneale Elektrostimulation zur Restitution des Sehvermögens bei Ratten
- In vivo neuronales Imaging retinaler Ganglienzellen
- Erforschung der Blut-Hirn-Schrankenpassage von Nanopartikeln im Zusammenhang mit ZNS Pharmakotherapie Toxizitäts- Molekularbiologische in vitro Versuche zu Nanopartikeleffekten

4. METHODIK

Neuropsychologie

- Neurovisuelle Rehabilitation von Patienten mit Sehbeeinträchtigungen mittels visuellem Restitutionstraining (Vision Restoration Therapy, VRT), repetitiver transorbitaler alternating current stimulation (rtACS) und transcranial direct current stimulation (tDCS) bei Sehnervschädigung (Optikusneuropathie), Glaukom (grüner Star) oder Schlaganfall
- Evaluation und Entwicklung von Verfahren der Lebensqualität des Sehens
- Messung visueller Funktionen (Kontrastsehen, Dynamisches Sehen, Lesegeschwindigkeit usw.)
- Gesichtsfeld-Messung mit Perimetrie (Tübinger Automatik Perimeter, Twinfield Oculus), Computerkampimetrie (High Resolution Perimetry)

- Augenbewegungsmessung (Eyetracking): Tobii ET1750, ClearView (Tobii Technology AB, Sweden), Eyelink1000
- EG & visuell evozierte Potentiale: 128 Channel Geodesic EEG System 300, BrainVision Recorder und BrainVision Analyzer Dynamische, vaskuläre Regulationsmessung mit dem DVA (Dynamic vessel analyzer)

Verhaltensneurowissenschaften

- In Vivo Confocal Neuroimaging (ICON) bei Nagern
- Ex vivo wholemount Präparat
- In vivo Modell zur transcornealen Wechselstromstimulation der Ratte (unter Narkose und frei beweglich) Messung von Tiefen-EEG und Visuell Evozierten Potentialen (VEP) in chronisch implantierten Ratten unter Narkose und freibeweglich
- In vitro molekularbiologische Untersuchungsmethoden zu Neuroprotektionsmechanismen (Zellkultur, Westernblot, Absorptionsspektrophotometrie; Histologie)

5. KOOPERATIONEN

- Amphion, Skolkovo Innovation Center, Russland, Prof. M. Shitlmann
- Catholic University of Rome and IRCCS S. Raffaele Pisana, Prof. Paolo M. Rossini
- Chinese Academy of Sciences, Inst. Automation, Prof. Dr. He
- Drugs Technology, Moskau, Russland, Dr. S. Gelperina
- Elvire Vaucher, Ecole d'optométrie, University of Montreal, Canada
- Fakultät für Informatik (OVGU), Prof. Dr. Nürnberger
- Helsinki University Central Hospital (HUCH), Department of Neurology, Prof. Turgut Tatlisumak
- Institut für Verfahrenstechnik (OvGU), Prof. van Wachem / Dr. Hintz
- Institute of Psychology, Russian Academy of Science, Moscow State University, Dr. A. Gorkin
- Leibnitz Institut für Neurobiologie (LIN), Dr. Werner Zuschratter
- Photonscore GmbH, Dr. Yury Prozakov

6. FORSCHUNGSPROJEKTE

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Dr. rer. nat. habil. Mirela Bîlc
Förderer: Haushalt - 01.10.2021 - 30.09.2023

Home-based microcurrent therapy for visual field defects in glaucoma - A controlled multicenter clinical trial

The overall aim of the current project is to investigate the efficacy and safety of long-term treatment of glaucoma by transorbital alternating current stimulation with a home-stimulation device (SASm). We hypothesize that tACS home-stimulation significantly improves vision and associated biomarkers compared to sham-controls. Our secondary aim is exploratory, namely to investigate possible mechanisms of action. The current study will be a double blind, parallel group interventional study. Participants (N=30) will be randomized to one of two intervention arms: (1) arm 1 – intervention group receiving tACS; (2) arm 2 – placebo group receiving sham (no tACS, only phosphene threshold measured at study entry). The primary endpoint of this clinical investigation is a mixed endpoint as follows: (i) Improved detection accuracy in super-threshold high resolution perimetry (HRP) or improved near-threshold Humphrey Visual Field Index following active tACS stimulation compared to sham, as documented by relative change over baseline.

According to our goal of investigating the long-term tACS efficiency, participants will undergo 30 stimulation sessions. Endpoints will be assessed before, immediately after and 12 weeks after the intervention. To our knowledge, this would be the longest stimulation duration and follow-up period investigating the effect of tACS. It would allow us not only to collect information on long-term effects, but also to compare it with short-term interventions (i.e., 10 days). The study will be considered completed after the last follow-up measurement of the

last patient.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Shuting Li
Förderer: Haushalt - 13.10.2020 - 12.10.2023

Microsaccades, vision restoration and brain network reorganization in glaucoma patients and effects of EYE YOGA therapy

Understanding how the human brain reversibly generates and loses normal vision, through a complex interaction of neural activity at multiple spatial and temporal scales, is a grand challenge for modern neuroscience. Recent theoretical advances have argued that vision deteriorates when the balance between integrated and differentiated neural activity is affected. However, accurately tracking these changes in brain dynamics remains a key research challenge with potentially wide-ranging applications, and is complicated by the significant individual variability in the trajectory along which vision is deteriorated and alleviated.

We propose to study the effects of EYE YOGA, which is a "low tech but high concept" solution with an enormous potential to revolutionize visual rehabilitation by offering an alternative, behavioral technique that is easy to use in the patients´ home environment. We expect that this very simple technique which everyone can practice at home (even normally sighted people) can help improve vision related function. By way of reducing the tension eye muscle and facial tissues, synchronizing brain network interactions, and by possibly improving blood flow, we expect EYE YOGA to be established as an ancient, yet novel and very effective vision rehabilitation method to improve vision by reducing fogginess and increasing acuity.

This project will help change the mind of the research and clinical community. It is time to start looking at mechanisms of vision loss beyond the eye such as brain network plasticity. We should consider follow a more holistic approaches to treat low vision and blindness by making use of modern technology in combination with ancient methods of healing.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Yi Liang
Förderer: Haushalt - 01.12.2019 - 31.10.2022

Microsaccade alteration in primary open-angle glaucoma and the effects in treatment induced by noninvasive transorbital Alternating Current Stimulation for vision restoration

Glaucoma is a progressive optic neuropathy associated with degeneration of retinal ganglion cells and their axons, which has an impact on complex daily behaviors, such as driving, walking, and eye-hand coordination, which may be affected by visual field defects (VFDs). Little is known about the underlying nature of the functional mechanisms influencing impairment from VFDs, but it seems likely that worsening of eye movements may play a role in this process.
Microsaccades (MS) are a kind of fixational eye movement. They play a significant role in counteracting foveal and peripheral fading. MS can be measured precisely with reliable parameters in recent years. Because of their important role in normal vision, it is reasonable to assume that MS are also affected in glaucoma patients.
Noninvasive, repetitive transorbital alternating current stimulation (rtACS), as a new method to enhance neuronal function both in normal subjects and in patients with some residual vision, was proved effective and safe in the treatment of glaucoma. Based on the theory about the role of MS in vision fixation it was of importance to investigate that whether MS could be one of the significant cause of the efficacy of vision restoration as induced by rtACS.
Therefore, the aim of this study will be to determine whether microsaccadic eye movements are altered in glaucoma patients and whether there are changes of MS-related parameters during the treatment for vision restoration induced by rtACS.

Projektleitung:	Prof. Dr. Bernhard Sabel
Projektbearbeitung:	Dr. Andrea Wetzel
Kooperationen:	Leibnitz Institut für Neurobiologie (LIN), Dr. Werner Zuschratter; Photonscore GmbH, Dr. Yury Prozakov
Förderer:	EU - EFRE Sachsen-Anhalt - 01.01.2019 - 31.07.2022

Research and Development of a Single Photon Counting "In Vivo Cam" for Diagnosis

This collaborative project aims the research and development of an innovative, highly sensitive, in vivo camera for diagnosis of eye disorders. A prototype of this single photon counting camera (LINCam) has been developed by our collaborators from Photonscore GmbH. This camera is able to detect auto-fluorescence in live cells in vitro with very low light intensity ($<$50 mW/cm^2) and without any additional labelling of the cells. These preliminary observations are very promising for our aim to detect eye disorders in rats and patients in vivo through fluorescence lifetime imaging by time-correlated single-photon counting (FLIM) as a very mild procedure. In order to employ this technique in vivo, we would like to benefit from our experience in 'in vivo confocal neuroimaging' (ICON). This well-established method was first described by Sabel et al. Nature Medicine, 1997 and can be used to detect pre-labelled retinal ganglion cells in narcotised rats. Initial comparison of both techniques will help us to determine parameters for in vivo imaging optimisation with the new camera. Therefore, subcellular changes need to be identified, the survival of sensitive cells such as neurons needs to be monitored and long term imaging effects need to be defined under normal and pathological conditions. Further development of a user friendly software tool will finally lead to the production of an EYECam prototype, which should not just be usable for basic research on eye structures in animals, but also as prototype for an eye diagnosis system usable for future patients.

Projektleitung:	Prof. Dr. Bernhard Sabel
Projektbearbeitung:	Wanshu Zhou
Förderer:	Haushalt - 01.01.2018 - 31.10.2022

Effect of vascular dysregulation in glaucomatous vision restoration

Hypothesis: Mental stress can cause vascular dysregulation (unregulated vascular diameter, flow velocity, and vessel dynamics) in the brain and retina, and an impaired dynamic vessel response will prevent vision restoration that can be induced by transorbital alternating current stimulation (tACS). By correlating the dynamic vessel response (vascular dysregulation, VDR) and stress levels in patients and studying their influence on the degree of vision recovery in glaucoma patients, We hope to uncover if patients with a regulated vascular response can recover their vision while those with vascular dysregulation cannot. This study will help to better understand and treat optic nerve damage, for example after glaucoma, or optic neuropathy and vision loss (hemianopia) after stroke.

Projektleitung:	Prof. Dr. Bernhard Sabel
Projektbearbeitung:	Jiahua Xu
Förderer:	Haushalt - 01.10.2015 - 31.12.2021

Prediction of vision recovery rate after stroke based brain graph network and deep neural networks

This multidisciplinary project draws from the fields of neurology, informatics and medical engineering research to develop a new method for the prediction and diagnostics of visual dysfunctions after visual system damage. The final goal is to find methods to improve vision after optic nerve damage, for example after glaucoma or optic neuropathy, and for stroke. About $^1/_3$ of all stroke patients' su er posterior artery territory damage which leads to visual impairments (hemianopia) which decreases of life quality. Less is known about the mechanism of how brain works with the neurons which managed to survive and how the brain could recover and which kinds of treatments are useful. According to the "residual vision activation theory", visual functions can in

part be activated and restored because some residual structures are usually spared after damage. EEG is an electrophysiological monitoring method to record electrical activity of the brain. Brain stimulation was a typically noninvasive common method to treat the brain injuries for lot of clinical applications, here 24 patients were assigned into three groups and accepted the brain stimulation therapy for ten days, resting state EEG data was recorded while patients kept eyes closed in a no task condition, the data was preprocessed and resourced into a 3D brain model, brain connectivity were analyzed on power and phase as well as the correlation with HRP data, the di erent areas will be marked for next step machine learning. Deep neural network (deep learning) can allow us to gain lots of insight based on its high performance with undefined features. Therefore, we combine the deep learning technology and brain graph network to make prediction how the brain recovers following brain stimulation treatment. Generally, this topic would be highlighted by the integrated technologies such brain imaging and deep learning, the result could be referred as an alternatively way to help the stroke patients in their daily life.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Zheng Wu
Förderer: Haushalt - 16.11.2015 - 31.12.2021

Spacetime in the Brain: rapid brain network reorganization in visual processing and recovery

Purpose: Although it is known that optic nerve damage, for example after glaucoma or optic neuropathy, a *local* event, alters *global* functional connectivity networks (FCN) in the brain resting state, it is unknown if and how visual deprivation a ects the dynamics of transient and rapid brain FCN changes. The synchronization between brain regions is essential for the integration between visual and non-visual modalities in time and space, and if a patient detects - or fails to detect - visual stimuli is rather variable and may depend on the FCN response to visual stimuli.

Methods: In patients with optic nerve damage (n=19) and healthy subjects (n=14), the ability to detect super-threshold stimuli was related to parameters of the "event related network analysis (ERNA) based on graph theory immediately following successful (hits) or unsuccessful stimulus detections (misses). Graph-based features of transient and dynamically synchronized networks where described following stimulus onset to compare di erent visual field states of normal and partially damaged visual field sectors (areas of residual vision, ARVs).

Results: Compared to controls, hits in the *intact* visual field sector in patients where associated with connectivity topology changes characterized by less cluster, but more large scale connections with low e ciency. In areas of residual vision, hits in patients evoked a network dynamic change with weaker node strength and less clustering, shorter characteristic path length and poorer small-world-ness than hits in their intact field. These rapid FCN topology changes happened primarily in high alpha and beta band in the late "cognitive processing stage (300-600 ms).

Conclusion: Patients with optic nerve damage have a weaker processing balance of functional integration and segregation during the cognition which reduces local and global information interactions. FCN fluctuations are thus a physiological correlate of response variability of visual functions and network modulation might be a possible target for modulating visual performance.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Enqi Zhang
Förderer: Haushalt - 01.10.2015 - 31.03.2022

In vivo visualization different kinetic of active compound encapsulated in PLGA nanoparticles at the blood-retinal barrier

US Food and Drug administration (FDA) approved product poly (lactic-co-glycolic acid) nanoparticles (PLGA NP) have a huge potential as drug delivery systems, for imaging and diagnostic methods. Here, with In vivo Confocal Neuroimaging (ICON) we visualize in real time the biodistribution of fluorescent nanoparticles in vessels

of the retina by microscopic evaluation of the distribution of the fluorescence. When working with Rhodamine123 (Rho123) labelled PLGA NPs we observed disappearance of the fluorescence within the first 15 minutes after injection. However, with 1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate (DiI) labelled poly (lactic-co-glycolic acid) nanoparticles showed more long-lasting e ects. The final result showed that fluorescent signal of the hydrophobic marker DiI can last for more than 1.5 hours in blood vessels which are significantly longer than for the hydrophilic Rho123, although Rho123 as well as DiI-labelled PLGA NP were clearly visible a significant fluorescent signal in the retina vessels from shortly after injection up to approximately 5 min later. In the case of Rho123-labelled PLGA NP application, no fluorescent was detectable at later time-points 15 min, but clearly visible fluorescent lining of the vessels can be seen for more than 2 hours after injection of DiI-loaded PLGA NP. By quantification of the fluorescent signal in the retina blood vessel we created a temporal-spatial map of the active ingredients distribution. With this work we contribute to a better understanding of the causal relationship between design of nanoparticulate carrier systems and their distribution at the blood-retinal barrier (BRB), which will be helpful for future drug development projects for the treatment of optic nerve damage, for example after glaucoma or optic neuropathy.

Projektleitung: Prof. Dr. Bernhard Sabel
Förderer: Stiftungen - Sonstige - 01.05.2020 - 31.03.2023

Microsaccades in normal vision and in glaucoma and its treatment with eye movement training

Microsaccades are fast, jerk-like eye movements that happen once or twice per second. They are profoundly involved in visual perception. Microsaccades show also high clinical relevance e.g. alterations of microsaccades can cause symptoms such as diplopia, reduced visual acuity and blurred vision, which are reported in a series of ophthalmological and neurological diseases. The study addresses if microsaccade and microsaccade-related potentials are stable in normal aging. This explores the usefulness of microsaccades as a potential biomarker to monitor and better understand di erent diseases with oculomotor symptoms.

7. VERÖFFENTLICHUNGEN

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DISSERTATIONEN

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