MED MEDIZINISCHE FAKULTÄT

Forschungsbericht 2019

Institut für Medizinische Psychologie

INSTITUT FÜR MEDIZINISCHE PSYCHOLOGIE

Leipziger Straße 44, 39120 Magdeburg
Tel. 49 (0)391 67 21800, Fax 49 (0)391 67 21 803
imp@med.ovgu.de

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 hirngeschädigte Patienten
- Gesichtsfelddiagnostik, Eye-tracking und elektrophysiologische Evaluierung von Gebieten des Residualsehens
- Untersuchung der Lebensqualität bzw. Beeinträchtigung von Aktivitäten des täglichen Lebens bei hirngeschädigten Patienten, insbesondere Sehbeeinträchtigungen nach Läsionen der zentralen Sehbahn
- Untersuchung von Mechanismen visueller Plastizität bei behavioraler Intervention mit visueller Restitutionstherapie und non-invasiver Elektrostimulation mit EEG und VEP
- Computersimulation der Plastizität im visuellen Kortex/Prädiktoren der Erholung von Sehfunktionen

Arbeitsgruppe Verhaltensneurowissenschaften

- Untersuchung der neuroanatomischen Korrelate
- Pharmakologische Behandlung dieser teilerblindeten Tiere mit verschiedenen therapeutischen Ansätzen
- Repetitive transkorneale Elektrostimulation zur Restitution des Sehvermögens bei Ratten
- In vivo Neuronales Imaging
- Elektrophysiologische Parameter zur Quantifizierung von Sehvermögen und Neuroplastizität
- Erforschung der Blut-Hirn-Schrankenpassage von Nanopartikeln im Zusammenhang mit ZNS Pharmakotherapie Toxizitäts- Molekularbiologische in vitro Versuche zu Nanopartikeleekte

4. METHODIK

Neuropsychologie

- Neurovisuelle Rehabilitation hirngeschädigter Patienten mit Sehbeeinträchtigungen mit visuellem Restitutionstraining (Vision Restoration Therapy, VRT), repetitiver transorbitaler alternating current stimulation (rtACS) und transcranial direct current stimulation (tDCS) zur Behandlung von Patienten mit Sehnervschädigung (Optikusneuropathie), Glaukom (grüner Star) und Schlaganfall
- Evaluation und Entwicklung von Verfahren der Lebensqualität des Sehens
- Messung weiterer 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

Verhaltensneurowissenschaften

- Behandlung von teilerblindeten Tiere mit verschiedenen optischen Reizen zur schnelleren und besseren Wiederherstellung ihrer Sehfähigkeit. Dies erlaubt die Erforschung von Sehnervschädigung (Optikusneuropathie), Glaukom (grüner Star) und Schlaganfall
- 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
- Drugs Technology, Moskau, Russland, Dr. S. Gelperina
- Elvire Vaucher, Ecole d'optométrie, University of Montreal, Canada
- Fakultät für Informatik (OvGU), Prof. Dr. Kruse / Christian Möwes
- Helsinki University Central Hospital (HUCH), Department of Neurology, Prof. Turgut Tatlisumak
- Hochschule Magdeburg-Stendal (FH), Fachbereich IWO, Studiengang Statistik, Prof. Köhler
- Institut für Neuropathologie, Prof. Mawrin
- 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
- Nencki Institute of Experimental Biology, Polish Academy of Sciences, Department of Neurophysiology, Prof. Wioletta Waleszczyk
- Photonscore GmbH, Dr. Yury Prozakov
- University of Crete, Heraklion, Griechenland, Prof. A. Tsatsakis

6. FORSCHUNGSPROJEKTE

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Zheng Wu
Förderer: Haushalt - 16.11.2015 - 31.12.2019

A global view of vision loss: global brain network reorganization after optic nerve lesions

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 - 31.12.2019

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
Projektbearbeitung: Mohamed Tawfik
Förderer: Haushalt - 01.02.2016 - 31.12.2019

Polymeric nanoparticles targeting the CNS: between the new PVP NPs crossing the BBB and siRNA-PBCA NPs for glaucoma treatment

In the last two decades, polymeric nanoparticles such PBCA, PLGA and PLA NPs have been extensively studied for brain drug delivery due to their biodegradable and biocompatible proprieties. We now studied polymeric NPs produced from Poly-vinyl-pyrrolidone (PVP NPs) as a new nano-carrier-system and studied their ability to pass the blood-brain-barrier (BBB) after systemic administration.

Using the blood-retina-barrier (BRB) as a surrogate of the BBB, we utilized in-vivo confocal neuroimaging (ICON) for live retinal imaging and compared our results with ex-vivo wholemount retina preparation. By loading NPs with fluorescent agents and using double/triple fluorescent labeling protocols for ex-vivo wholemount retinae, we were able to observe the distribution of NPs in the vessels and the parenchyma of the retina.

PVP NPs loaded with 1, 1'-dioctadecyl-3, 3, 3', 3'-tetramethylindocarbocyanine perchlorate (DIL), a substitute for hydrophobic drugs, were found to be able to cross the BRB when linked with 5(6)-carboxyfluorescein diacetate N-succinimidyl ester (CFSE) which accumulated in retinal tissues within 10 min after injection.

Apart from the PVP NPs, PBCA NPs was also used to study the inhibition of retinal ganglion cells apoptosis when loaded with caspase-3-siRNA after intravitreal injection. The cells survival was tracked for 21 and 41 days post- optic nerve crush (ONC) also using ICON as it allows repetitive real-time imaging for the same rat. The results have shown a lower cell death after treatment (-35%) in comparison with the control group (-56%). Furthermore, ex-vivo wholemount retina has been successfully performed to study the RGCs morphology changes on higher cellular level with better magnification.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Jiahua Xu
Förderer: Haushalt - 01.10.2015 - 31.10.2020

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: Qing You
Förderer: Haushalt - 01.10.2014 - 31.12.2019

Drug delivery with polybutylcyanoacrylate nanoparticles to the retina, brain and main organs of rats

Because the blood-brain barrier (BBB) is an obstacle for drug-delivery, carrier systems such as polybutylcyanoacrylate (PBCA) nanoparticles (NPs) have been studied. Yet, little is known of how physiochemical features such as size, surfactants and surface charge influence BBB passage in vivo. We used a rat model of in vivo imaging of the retina - which is brain tissue and can reflect the situation at the BBB - to study how size and surface charge determine NPs ability to cross the blood-retina barrier (BRB). The result showed that for poloxamer 188-modified, DEAE-dextran-stabilized PBCA NPs, decreasing the average zeta-size from 272 nm to 172 nm by centrifugation reduced the BRB passage of the NPs substantially. Varying the zeta potential within the narrow range of 0 15 mV by adding di erent amounts of stabilizer revealed that 0 mV and 15 mV were less desirable than 5 mV which facilitated the BRB passage. Then we removed and imaged the retina of the rats ex vivo to observe the detailed location of the NPs in retina tissue. Similar as the in vivo result, the NPs with larger zeta-size and 5 mV surface charge accumulated more in the vessel wall and in retina ganglion cells. Interestingly, the NPs with 0 mV surface charge accumulated unevenly in vessel wall and some agglomerates attached on the surface of the vessel wall. We also collected blood, brain, heart, kidneys, liver, lungs and spleen of the rats. The biological distribution of NPs in blood and brain is comparable to the results of in vivo imaging of blood vessel and retina tissue. Thus, minor changes in design of nanocarriers can alter physicochemical parameters such as size or zeta potential, thus substantially influencing NPs biological distribution in vivo.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Wanshu Zhou
Förderer: Haushalt - 01.01.2018 - 31.10.2021

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
Förderer: Haushalt - 02.08.2013 - 31.01.2019

Microsaccades in normal vision and in hemianopia after stroke

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.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Jiaqi Wang
Förderer: Haushalt - 01.09.2016 - 31.08.2019

Psychosomatic factors in the vision restoration

Objective: To study whether psychosomatic factors including age, gender, personality traits, chronic stress levels and Flammer syndrome signs a ect the degree of vision restoration in patients with glaucoma or non-glaucoma vision loss.

Methods: Total of 30 patients with glaucoma or non-glaucoma vision loss, aged from 20 to 86 years old are asked to complete psychological questionnaires: The NEO Five-Factor Inventory-3 (NEO-FFI), Trier Inventory for Chronic Stress (TICS), Type D scale (DS-14) and Flammer syndrome questionnaires within two years after the application of repetitive transorbital alternating current stimulation (rtACS) 10 days in SAVIR-Center.

The study will unveil if age, gender and chronic stress influence vision restoration. We expect that patient's recovery better if they have less neuroticism and more conscientiousness and openness. Also, the Flammer syndrome might have a negative influence on visual restoration of visual field index in the worse eye.

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Dr. Andrea Wetzel
Kooperationen: Photonscore GmbH, Dr. Yury Prozakov; Leibnitz Institut für Neurobiologie (LIN), Dr. Werner Zuschratter
Förderer: EU - EFRE Sachsen-Anhalt - 01.01.2019 - 31.12.2021

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.

7. EIGENE KONGRESSE, WISSENSCHAFTLICHE TAGUNGEN UND EXPONATE AUF MESSEN

5th International Symposium "Low Vision and the Brain" (you see with your eyes AND with your brain); 30.11.-02.12.2018; Berlin

8. VERÖFFENTLICHUNGEN

BEGUTACHTETE ZEITSCHRIFTENAUFSÄTZE

Bikson, Marom; Esmaeilpour, Zeinab; Adair, Devin; Kronberg, Greg; Tyler, William J.; Antal, Andrea; Datta, Abhishek; Sabel, Bernhard A.; Nitsche, Michael; Loo, Colleen; Edwards, Dylan; Ekhtiari, Hamed; Knotkova, Helena; Woods, Adam J.; Hampstead, Benjamin M.; Badran, Bashar W.; Peterchev, Angel V.
Transcranial electrical stimulation nomenclature
Brain stimulation - New York, NY [u.a.]: Elsevier, Bd. 12.2019, 6, S. 1349-1366
[Imp.fact.: 6.919]

Cattaneo, Zaira; Ferrari, Chiara; Schiavi, Susanna; Alekseichuk, Ivan; Antal, Andrea; Nadal, Marcos
Medial prefrontal cortex involvement in aesthetic appreciation of paintings - a tDCS study
Cognitive processing - Heidelberg : Springer, Bd. 20.2019, insges. 12 S.
[Imp.fact.: 1.233]

Sabel, Bernhard A.; Abd Hamid, Aini Ismafairus Binti; Borrmann, Carolin; Speck, Oliver; Antal, Andrea
Transorbital alternating current stimulation modifies BOLD activity in healthy subjects and in a stroke patient with hemianopia - a 7 Tesla fMRI feasibility study
International journal of psychophysiology - Amsterdam [u.a.]: Elsevier Science, 2019;
[Imp.fact.: 2.407]

Singh, Aditya; Erwin-Grabner, Tracy; Maldonado, Roberto Goya; Antal, Andrea
Transcranial magnetic and direct current stimulation in the treatment of depression - basic mechanisms and challenges of two commonly used brain stimulation methods in interventional psychiatry
Neuropsychobiology - Basel : Karger, Bd. 78.2019, insges. 11 S.
[Imp.fact.: 1.675]

Singh, Aditya; Erwin-Grabner, Tracy; Sutcliffe, Grant; Antal, Andrea; Paulus, Walter; Maldonado, Roberto Goya
Personalized repetitive transcranial magnetic stimulation temporarily alters default mode network in healthy subjects
Scientific reports - [London]: Macmillan Publishers Limited, part of Springer Nature - Bd. 9.2019, Art.-Nr. 5631, insges. 12 S.
[Imp.fact.: 4.011]

Turi, Zsolt; Csifcsák, Gábor; Boayue, Nya Mehnwolo; Aslaksen, Per; Antal, Andrea; Paulus, Walter; Groot, Josephine; Hawkins, Guy E.; Forstmann, Birte U.; Opitz, Alexander; Thielscher, Axel; Mittner, Matthias
Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 min in young healthy adults
European journal of neuroscience - Oxford [u.a.]: Wiley, Bd. 50.2019, 8, S. 3261-3268
[Imp.fact.: 2.784]

You, Qing; Hopf, Talea; Hintz, Werner; Rannabauer, Stefan; Voigt, Nadine; Wachem, Berend; Henrich-Noack, Petra; Sabel, Bernhard A.
Major effects on blood-retina barrier passage by minor alterations in design of polybutylcyanoacrylate nanoparticles
Journal of drug targeting - Abingdon: Taylor & Francis Group, Bd. 27.2019, 3, S. 338-346;
[Imp.fact.: 3.277]

You, Qing; Sokolov, Maxim; Grigartzik, Lisa; Hintz, Werner; Wachem, Berend; Henrich-Noack, Petra; Sabel, Bernhard A.
How nanoparticle physicochemical parameters affect drug delivery to cells in the retina via systemic interactions
Molecular pharmaceutics - Washington, DC: American Chemical Society, Bd. 16.2019;
[Imp.fact.: 4.396]

NICHT BEGUTACHTETE ZEITSCHRIFTENAUFSÄTZE

Sabel, Bernhard A.; Antal, Andrea; Sabel, Kornelia
Die ganzheitliche Behandlung von Glaukom und anderen Sehverlusten - Komplementär, individualisiert und evidenzbasiert
Natur-Heilkunde-Journal: Medizin, Praxis, Wissenschaft - Kulmbach: Mediengruppe Oberfranken, Bd. 21.2019, 10, S. 4-8