MED MEDIZINISCHE FAKULTÄT

Forschungsbericht 2018

Institut für Medizinische Psychologie

INSTITUT FÜR MEDIZINISCHE PSYCHOLOGIE

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1. Leitung

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

2. HochschullehrerInnen

Prof. Dr. med. habil. B.A. Sabel, Ph.D.
PD Dr. rer. nat. habil. P. Henrich-Noack

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 Psychoneurobiologie

- Untersuchung der neuroanatomischen Korrelate
- Pharmakologische Behandlung von teilerblindeten Tiere mit verschiedenen therapeutischen Ansätzen
- Repetitive transcorneale 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 Nanopartikeleffekten

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
- EEG & visuell evozierte Potentiale: 128 Channel Geodesic EEG System 300, BrainVision Recorder und BrainVision Analyzer

Psychoneurobiologie

- 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
- Nencki Institute of Experimental Biology, Polish Academy of Sciences, Department of Neurophysiology, Prof. Wioletta Waleszczyk
- University of Crete, Heraklion, Griechenland, Prof. A. Tsatsakis

6. Forschungsprojekte

Projektleitung: Prof. Dr. Bernhard Sabel
Projektbearbeitung: Zheng Wu
Förderer: Haushalt - 16.11.2015 - 30.09.2019

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 aects 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 dierent 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 eciency. 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 - 30.09.2019

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 eects. 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

Nanoparticle Development and Application for Brain Damage and Disease

The main objectives of the project:

1. Studying the pharmacokinetic of the blood-retina barrier (BRB) passage and the distribution of Polyvinylpyrrolidone Nanoparticles (PVP NPs) under normal and pathological conditions using ICON, ex-vivo wholemount retina and triple labelling techniques.

1. Studying the dynamic changes in the vessel diameter under normal and pathological conditions and correlate the data with the results obtained from previous experiments (BRB passage).

A newly developed PVP-NP design (PVP-DIL-FITC-NPs) was successfully tested for BRB passage and delivered the incorporated active compound (fluorescent marker) into the retina parenchyma. Moreover, mechanistically these data support the hypothesis that the surface characteristics of NPs are decisive for BRB passage. Interestingly, the dierent kinetic of NPs at the BRB was associated with a dierent localization of the NPs in the blood components (blood cells). When investigating the BRB integrity under pathological conditions it was revealed that within a time-window of 1-2 hours after optic nerve crush the vessels in the retina are not impaired or altered. This was true for both conditions of NPs accumulation in the vessel walls and for NPs BRB passage and confirmed by the standard marker FITC-dextran. Next period of time, we will characterize the distribution of the successful PVP-DIL-FITC-NPs on a cellular level and measure systemic distribution. The second objective is to using the Retina Vessel Analyser (RVA) to investigate the vessel dynamic under short and long-term retinal damage and correlate the results with data of cell death, BRB impairment and nanoparticulate transport dynamics at the BRB.

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 multi-disciplinary 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 suer 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 dierent 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 - 30.06.2019

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 dierent 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
Projektbearbeitung: Ying Gao
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 dierent 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 aect 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: Dr. Petra Henrich-Noack
Förderer: EU - ERA Net, Joint Programm - 01.03.2016 - 28.02.2018

Nanopartikel für ZNS Applikationen, Diagnostik und Ophthalmologie

Mit unserem Netzwerk möchten wir perspektivisch ein Internationales Exzellenz Service Center für Nanoparticle Design and Testing for Life-Science aufbauen.
Im Bereich Nanomedizin ist die Wirkstoffverabreichung bei neurologischen Indikationen ein besonderer Schwerpunkt da das Gehirn - im Gegensatz zu peripheren Organen - durch die Blut-Hirn Schranke (BHS) abgeschottet ist. Unser russischer Partner wird Nanopartikel (NP) Prototypen entwickeln, die Neuroprotektiva und Diagnostika schützen und über die BHS in die Gehirnzellen transportieren. Am Institut für Medizinische Psychologie ist die Technik des in vivo neuro-imagings (ICON) entwickelt worden, mit der man die BHS-Passage von NP live beobachten kann. Diese Methode ist zuverlässiger, informativer, schneller und günstiger als andere Verfahren. Allerdings war bisher keine quantitative Pharmakokinetik möglich. Da dieser Punkt Voraussetzung für eine professionelle Bewertung eines nanopartikulären Arzneimittelträgersystems ist, wird die entsprechende Bildverarbeitungssoftware im Rahmen unsere Kooperation von arivis entwickelt und getestet. Unser vierter Partner (ToxPlus) stellt die Expertise im Bereich Toxizitätsbewertung.

7. Eigene Kongresse, wissenschaftliche Tagungen und Exponate auf Messen

5 th 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 Zeitschriftenaufsaetze

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Evaluation of toxicity and neural uptake in vitro and in vivo of superparamagnetic iron oxide nanoparticles
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Cross-cultural supervision in cognitive-behavioral therapy - a case study
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Dissertationen

Voigt, Nadine; van Wachem, Berend [GutachterIn]; Sabel, Bernhard [GutachterIn]
Evaluierung pharmakokinetischer und toxikologischer Determinaten von Nanopartikeln mittels in vivo Neuroimaging
Magdeburg, 2018, XIV, 111 Blätter, Illustrationen;
[Literaturverzeichnis: Blatt 87-96]