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UNIVERSITÄT BERN

CLINICAL NEUROSCIENCE BERN

Dear CNB members,

With the CNB Newsletter, we intend to inform you about upcoming CNB events, ongoing projects and give insights into the research topics of selected CNB members. In this edition we look back on the Brainweek 2022 and are looking forward to the Annual Meeting 2022 which will take place on September 9th.

We are pleased to present the research group of Prof. Dr. Claudia M. Roebers, as well as the research group of Prof. Dr. med. vet. Daniela Schweizer and introduce you to the new research group around Dr. med. Gerd Tinkhauser.
Please also note that we are updating and upgrading the CNB-Website, so please feel free to contact Ms. Noémi Allet (noemi.allet@unibe.ch) if you want to make changes on your research group-site (e.g. add photos, videos, members etc.).

We hope you enjoy reading the May 2022 edition.

Prof. Dr. Sebastian Walther
President CNB

① Brainweek Bern

Monday, 14th of March 2022 – Thursday, 17th of March 2022

Monday, 14th of March 2022
Moderation: Prof. Dr. med. Sebastian Walther
Sponsor of the day: Fragile Bern
On Monday the two talks were about consciousness from the neurologist and the philosophical points of view:

"Consciousness – the neurologists perspective"
PD Dr. Dr. Frédéric Zubler (EEG specialist for comatose patients)
Dr. Zubler introduced the anatomical systems that provide wakefulness and consciousness. Furthermore, he discussed how physicians test consciousness in clinical practice, for instance when subjects are brought to the emergency room after stroke or accidents. Finally, he mentioned multiple ways of brain damage and how they can change perception or consciousness. The audience was very interested and had excellent questions.

"Philosophical Zombies and the mystery of consciousness"
Prof. Dr. Vera Hoffmann-Kolss (theoretical philosophy)
Moderation: Prof. Dr. med. Sebastian Walther
Prof. Hoffmann-Kolss introduced the change of definitions of consciousness in philosophy. Her talk focused specifically on the subjective experience which can only be approximated but not reliably measured with the current neuroscience methods. In order to explain this problem, she introduced the audience to a thought experiment including zombies. Again, this talk was exciting and stimulated much discussion with the audience.

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Tuesday, 15th of March 2022
Moderation: Prof. Dr. Tobias Nef
Sponsor of the day: Cerebral
On Tuesday we had two talks about how our consciousness works, from psychological and psychedelic points of view:

"Remembering – from conscious to unconscious"
Prof. Katharina Henke (cognitive Neuroscientist)
In her talk about remembering and recalling of things, Prof. Henke showed us many ways how our brains trick us into remembering things we did not see and not recalling things correctly. She introduced us to the Hippocampus and what consequences one might face in case of hippocampal lesions. She also elaborated upon the mechanism of episodic memory. Finally the audience was much engaged in the questions and answers session.

"How do psychedelics work?"
PD Dr. Katrin Preller (Neuropsychologist)
In PD Dr. Katrin Preller's lecture we learned how different psychedelics work on our consciousness, how they influence our perception and behaviour. Further-more, in the informative and exciting lecture PD Dr. Preller explained, how those psychedelics can change psychotherapy. After the talk, numerous questions were asked and interesting topics were discussed.

The Swiss Brain League has awarded the 2022 Research Prize. The Swiss Brain League Research Prize 2022, endowed with 20,000 Swiss francs, goes to the research group of Professor Antoine Adamantidis and Professor Claudio Bassetti of the Center for Experimental Neurology at the Inselspital Bern. Congratulations!

Photo by Marco Zanoni

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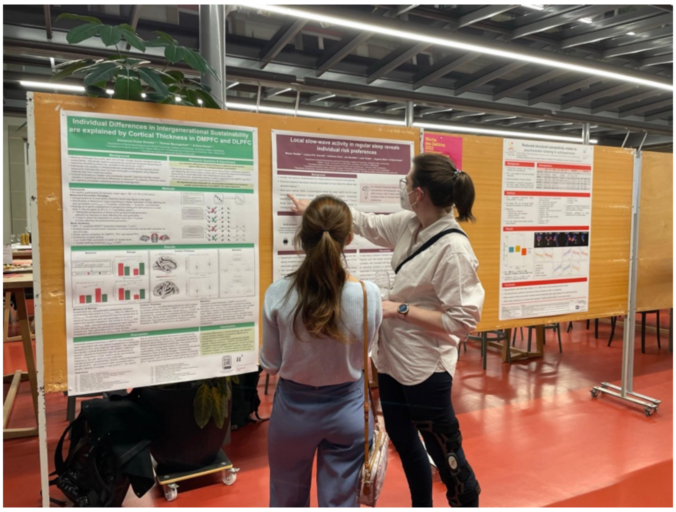
Wednesday, 16th of March 2022

"Le Scaphandre et le Papillon"

The input lecture from Prof. Dr. Thomas König to the film "Butterfly and diving bell" at the Kino Rex introduced the spectators to the locked-in syndrome. He also talked about the chances of EEG-science and how the interface between brain and computer can help patients to communicate with their relatives.

CNB Poster Session

On Wednesday, the Poster Session took place at the UniS. It was a great event for students to learn how to present their poster in front of a live audience. It was also a great possibility to engage with others, exchange ideas and learn more about other fields of research. There was also delicious food and some drinks, which made the event quite enjoyable for all attendees. A big Thank you to all poster presenters! We're looking forward seeing you next year!
Mark your calendar for the next Poster Session: Wednesday, 15th of March 2023.



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Thursday, 17th of March 2022
Panel discussion "News on the Topic: Life with Dementia"
Introduction: Prof. Dr. Sebastian Walther
Panel discussion: PD Dr. Jessica Peter, Prof. Dr. Tobias Nef, Prof. Dr. Claudio Bassetti, Marco Zysset
Moderation: Regula Zehnder (SRF)

On Thursday 75 spectators attended the different short-talks about research on dementia, its consequences and new chances for patients and relatives. Afterwards, a lively discussion took place, with many options to ask questions and receive valuable answers by the experts. The audience was very diverse, with questions coming from affected people and relatives, but also from students and other interested people. Mrs. Zehnder was able to guide the questions and the discussion, so that all experts could answer but also Mr. Zysset, who is a relative of someone with dementia provided valuable insights to the daily struggles but also on the bright sides of this illness.

The next Brainweek Bern will take place from the 13th to the 16th of March 2023. The program and further informations will be published on the Brainweek homepage: www.brainweekbern.ch. You also find the programs and impressions from past events on that site.

② Selected Research Groups

Research Group Cognitive Development

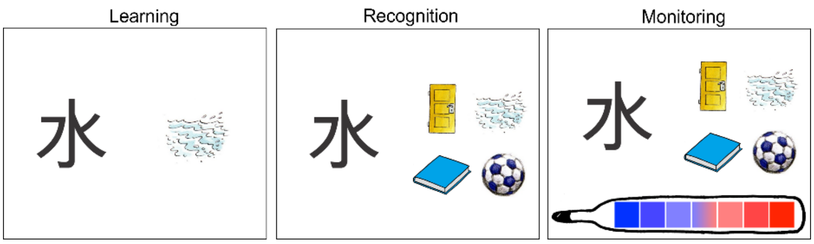
Prof. Dr. Claudia M. Roebers

Institute of Psychology
Unit Developmental Psychology

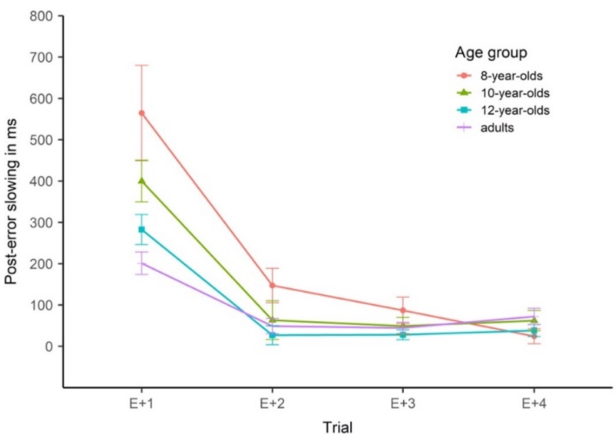
Uncertainty is ubiquitous in our lives. When shopping for groceries after forgetting the list on the kitchen counter, when getting ready for an overseas trip (do I have my passport with me?), or when writing an exam, our ability to recognize uncertainty is vital. The importance of monitoring holds not only for adults but also for children. Being able to experience and accurately report different levels of uncertainty („I am uncertain on which platform my train leaves!“) and certainty („I am very sure I answered that question correctly!“) has repeatedly been found to be associated with academic success, self-regulated learning skills, and productive social interactions, independent of age. I have been researching the development of the so-called monitoring and control processes for nearly 20 years, trying to understand when and how these monitoring skills develop, what factors drive improvements over time, and how these skills can be improved.
In a theoretical and empirical review of the literature, I have suggested to conceptually integrate monitoring processes researched in two – so far - unrelated domains. The one domain is cognitive control or, in broader terms, executive functioning. Here, monitoring is central whenever individuals face a cognitive conflict and are to decide as fast and as accurately as possible. Monitoring then includes both the reactive control (when an error has occurred to slow down subsequent responses to avoid future errors; i.e., post-error slowing) and proactive control (when a task is perceived as difficult, high in cognitive conflict, to take a slower task approach to maintain a high level of task performance; i.e., fine-tuned modulations of reaction times). In cognitive neuroscience studies, electrophysical markers of error processing are typically the error-related negativity (ERN/Ne), a fast response (50-150 ms after a response), and the error positivity (Pe), a positive deflection peaking around 200-500 ms post-error, localized to the anterior cingulary cortex. While the concept of error monitoring and post-error slowing has attracted much research interest in the adult literature (both on the behavioral and the electrophysiological level), only a few research groups within developmental psychology have yet addressed the role of monitoring in the context of executive function development.
The other domain is metacognitive monitoring researched in perception, learning, and memory. Here, monitoring is being investigated in its own right. Based on monitoring (“How sure am I to remember this detail in the upcoming test?”, “How sure am I that I got this answer correct?” – with judgments given on Likert scales, (a)), individuals select a task approach, differentially allocate study time, engage in self-testing or re-studying, and/or terminate learning efforts. However, if monitoring is not accurate, difficulties in self-regulated learning are the consequence. The role of monitoring for academic success is well-established for university and secondary school students. However, only a handful of research groups investigate kindergarten and primary school children’s ability to monitor performance accurately.
Concerning monitoring in cognitive control, we have shown that monitoring is already present in primary school children in the form of substantial post-error slowing (b). The depicted pattern of results generates across different cognitive conflict tasks documenting coarser response speed adjustments in younger compared to older children and adults. We are currently running a training study in which young primary school and kindergarten children are repeatedly confronted with cognitive conflict tasks and given feedback when they committed an error. We want to explore whether and to what extent we can improve their monitoring, i.e., decrease their exaggerated post-error slowing.

A consistently replicated pattern of results of metacognitive monitoring in children's learning is that younger compared to older children significantly overestimate their performance. Even when they err, they give high confidence ratings indicating that they are "very sure that their answer was correct". In the course of primary school, this overconfidence slowly but surely decreases. However, what still poses severe problems until secondary school and beyond, is the ability to act on monitoring: when given the option to withdraw a previously given answer (or to opt-out a question), monitoring processes are not fully taken into account. In a large-scale study we found too high confidence in objectively incorrect answers (c).
In both domains, that is, when investigating monitoring within cognitive control and metacognition and learning, we find evidence that time plays a crucial role for accurate monitoring. Young children's still developing inhibitory control skills impede their monitoring as they rather jump on an answer than carefully consider the task's rules or the alternatives before selecting a response. Yet, when giving low confidence judgments indicating uncertainty, the choice latencies of these lower metacognitive judgments are longer compared to high confidence ratings, even in kindergarten children (d). We have further established that carefully considering which answer to give (higher choice latencies in a recognition test) can serve as a valid cue to inform and improve monitoring. Interestingly, children's use of such a cue increases with age (e; compare upper (2nd graders) and lower graph (4th graders), underscoring that time is a driving force for developmental improvements in monitoring. Future work will show whether and how we can educate young children to take their time and reflect on certainty before giving answers.

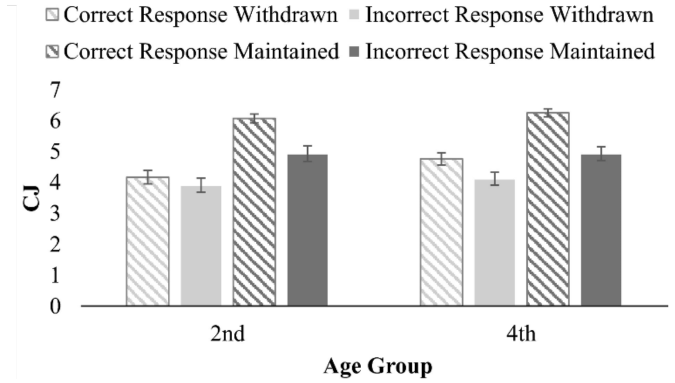
a) Measuring Monitoring Judgments in the Context of a Learning Task



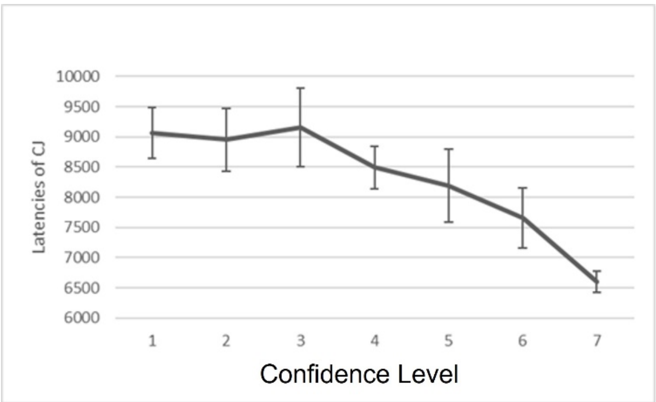
b) Age-related differences in Error Monitoring (Post-Error Slowing)
– from Dubravac, Roebers, & Meier, 2022



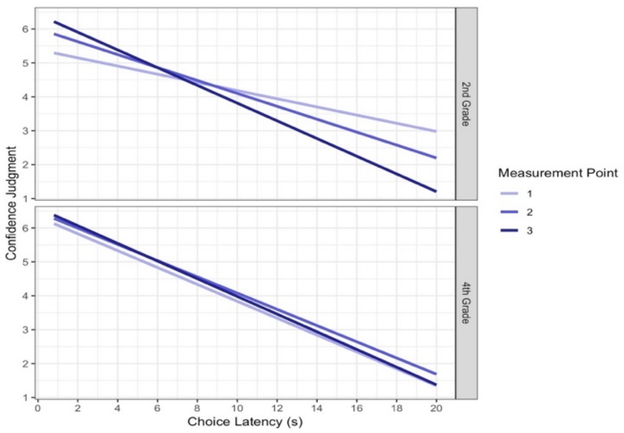
C) Confidence Judgments for Correct and Incorrect Answers in a Memory Test as a Function of Age Group (2nd vs. 4th graders) – from Bayard, van Loon, Steiner, & Roebers, 2021



d) Latencies of Confidence Judgments in Kindergarten Children – from Kaelin & Roebers, 2020



e) The Predictive Power of Choice Latencies in a Recognition test for Primary School Children's Monitoring (cue utilization) – from Roebers, Meier, Bayard, Steiner, & van Loon, 2019



Recent Publications on Children's Monitoring:

- Bayard, N., van Loon, M., Steiner, M. & Roebers, C. M. (2021). Developmental improvements and persisting difficulties in elementary school children`s metacognitive monitoring and control skills: Cross-sectional and longitudinal perspectives. Child Development, 92, 1118-1136.

- Buehler, F. J., Van Loon, M. H., Bayard, N. S., Steiner, M. & Roebers, C. M. (2021). Comparing metacognitive monitoring between native and non-native speaking primary school students. Metacognition & Learning, 16, 749-768.

- Dubravac, M., Roebers, C. M., & Meier, B. (2022). Age-related qualitative differences in post-error cognitive control adjustments. British Journal of Developmental Psychology.

- Kaelin, S., & Roebers, C. M. (2020). Time-based measures of monitoring in association with executive functions in kindergarten children. Zeitschrift für Psychologie, 228, 244-253.

- Roebers, C. M., van Loon, M. H., Buehler, F. J., Bayard, N. S., Steiner, M., & Aeschlimann, E. A. (2021). Exploring psychometric properties of children's metacognitive monitoring. Acta Psychologica, 220, 103399.

- Roebers, C. M. (2017). Executive function and metacognition: Towards a unifying framework of cognitive self-regulation. Developmental Review, 45, 31 – 51.

- Roebers, C. M., Kälin, S., & Aeschlimann, E. A. (2020). A comparison of non-verbal and verbal indicators of young children's metacognition. Metacognition & Learning, 15, 31-49. doi: 10.1007/s11409-019-09217-4

- Roebers, C. M., Kälin, S., & Aeschlimann, E. A. (2020). A comparison of non-verbal and verbal indicators of young children's metacognition. Metacognition & Learning, 15(1), 31-49. doi: 10.1007/s11409-019-09217-4

- Roebers, C. M., Mayer, B., Steiner, M., Bayard, N., & Van Loon, M. (2019). The role of children`s metacognitive experiences for cue utilization and monitoring accuracy: A longitudinal study. Developmental Psychology, 55, 2077-2089. doi:10.1037/dev0000776

Clinical Neuroscience Vetsuisse

Dr. Julien Guevar Dip EVCN

Prof. Dr. med. vet. Daniela Schweizer Dip ECVDI

Division of Surgery and Division of Clinical Radiology, Dept. of Clinical Veterinary Medicine, Vetsuisse Faculty Bern

The group clinical neuroscience Vetsuise encompasses a lot more than only one research group and one research group leader and we group researchers from neurology, neuroradiology as well as neurosurgery all together under this name. While we care for mainly dogs and cats with neurological disorders in everyday clinical practice, we conduct research to improve the diagnosis and treatment of such diseases. The areas of interest within the research group are manifold, encompassing imaging of epilepsy in cats and dogs, biomechanical investigation on the spine as well as diagnosis and treatment of disc disease in dogs, imaging CSF flow disturbances in dogs and still the imaging features of various brain disease and their correlation to histopathology. To some part evolving from these various interests, a research focus is now neuronavigation.

For many years, neuronavigation has allowed neurosurgeons around the globe to bring high precision surgery to patients requiring brain or spinal surgery. The technology has not only made these procedures safer but also much more accurate. It is now the gold standard in neurosurgery, being used multiple times a day for many different types of neurosurgery procedures. The strength of the system resides in the ability for the surgeon to visualize on screen the real-time location of the instruments relative to the anatomical region being operated on. Whether it be a brain lesion to biopsy, a brain tumor to remove or a screw to be perfectly placed into a vertebra, the surgeon can observe the procedure progress in real-time during the surgery, making sure the trajectory used is safe and accurate. But how did they do it before neuronavigation?

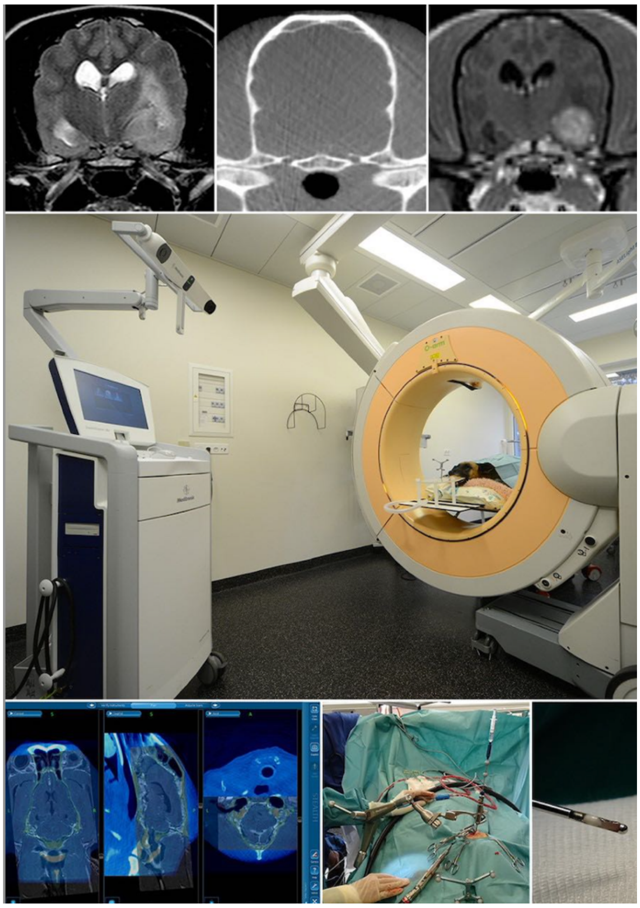
Well, they did it like we do in veterinary surgery: a little less accurately. This in a way is a bit of an irony when considering that some of the small animal patients weigh less than 1kg and have surgical targets less than 3mm wide.

However, the Vetsuisse small animal hospital in Bern is in the top 5 veterinary establishment in the world to benefit from this high standard equipment and for more than ten years, clinical researchers have been applying the technology to diagnose brain lesions in dogs. Accurate diagnosis of brain lesions is of course paramount prior to embarking into therapeutics options to help pets afflicted by central nervous system disorders to live longer.

While the technique of stereotactic brain biopsy is well established in humans, we have encountered several problems in our animal patients that make life difficult for us. These problems start with the strongly developed masticatory muscles that lie over the skull and hamper the rigid attachment of a stereotactic frame or C-clamp directly to the skull. Not to forget that some of the dog breeds and cats have such a thin skull bone that no great forces can be applied. For these reasons, it seems safer not to attach the reference for navigation as well as the guide for the drill or biopsy needle to the skull itself, but to attach the head via a bite plate and the instruments to the surgical table.

This also helps to make the procedure less dependent on skull size (Bernhardiner versus Chihuahua) and shape (French Bulldog versus Dachshound). As the owners of our patients often hesitate whether to subject their protégé to such diagnostic procedures and such a financial effort for a diagnosis, we try to perform brain biopsies with as little time and expenses as possible. This means one general anaesthesia for the diagnostic imaging and then a second anesthesia for the navigated brain biopsy. For this purpose, we are currently using a mobile cone beam CT, with which images of the head are taken in the operating theatre with the reference for navigation. The cone beam CT is linked to the navigation system so that the images are registered automatically and the biopsy can then be planned on the computer based on the planning of the fusion of MRI and cone beam CT and taken directly afterwards. Using this method of intraoperative computed tomography-based automated registration in combination with the frameless brain biopsy system, we achieve median needle placement error of 1.8 mm for the piriform lobe and 1.53 mm for the thalamus in dogs. In cats, the calculated median needle placement error was 0.79 mm for the piriform lobe target site and 1.29 mm for the thalamic target site with an overall diagnostic yield of 96.4% and a diagnostic accuracy of 94.4%.

More recently, we have been evaluating the use of the navigation for spinal surgeries and more particularly to place screws in the cervical and thoracolumbar vertebrae of miniature breed like chihuahua or Pomeranians, those who fits in one's hand. The tiny size of these patients vertebral column makes the use of this technology particularly attractive for the intraoperative safety. Another attractive aspect of neuronavigation is its coupling to minimally invasive spinal procedures. This will allow veterinary neurosurgeons to use stabilization techniques similar to what is being use in human neurosurgery yet with very small surgical approaches. The anatomy of course differs between man and dogs, but great variations do also occur between breeds of dogs, making this precision technology especially attractive. Our research has shown that when using neuronavigation for stabilization procedures of the spine in dogs, small deviations did occur when comparing a planned screw corridor trajectory to the navigated result. The mean (SD) entry point deviations of the drilling corridor were 0.3mm (0.8mm) lateral, 1.3mm (0.8mm) ventral and 0.7mm (1.8mm) caudal. The mean (SD) exit points deviations were 0.8mm (1.9mm) lateral, 0.02mm (0.9mm) dorsal, 0.7mm (2.0mm) caudal. We are now very keen to study how to convert routine spinal surgeries to a new safer level with the use of navigation. In the end, man's best friend is also allowed to benefit from man's safest and most accurate technologies.



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Neurophysiology and Adaptive Neuromodulation in Movement Disorders

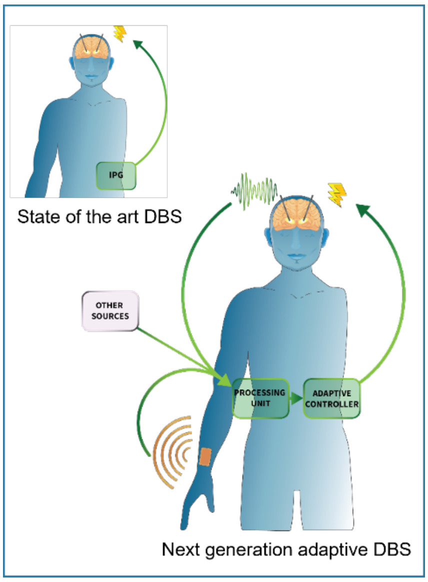
Gerd Tinkhauser, MD, PhD

Parkinson's Disease and Movement Disorders Center;
Center for Experimental Neurology, Dept. of Neurology and DBMR, Inselspital, Bern University Hospital, University of Bern.

My research group follows a multidisciplinary approach ranging from clinical observation to electrophysiology and neuro-engineering. The goal is to advance the understanding of neurophysiology in the context of movement disorders and to develop novel Deep Brain Stimulation (DBS) paradigms.

DBS is an established therapy that alleviates symptoms in patients with movement disorders, such as Parkinson's disease (PD). The major limitation of DBS, as it is currently applied in clinics, is that stimulation can only be delivered continuously at a constant rate, and it cannot be adjusted in real-time to the fluctuating nature of symptoms and neurophysiological states present in patients. The consequences of such continuous stimulation are stimulation-induced side effects or insufficient symptom control. So, how can we improve this therapy? Over the last years, evidence linking brain and peripheral signals to motor symptoms steadily increased. This led to the first-in-human trials using closed-loop adaptive Deep Brain Stimulation (aDBS) for PD patients. aDBS is a novel neuromodulation therapy in which the delivery of stimulation is dynamically controlled in real-time by a feedback-signal measured from the brain or other signal sources (as depicted in the figure). First results using this patient-tailored stimulation approach are promising with efficient symptom control and less side-effects.

My research group is working on several lines surrounding the aDBS precision medicine technology. Our goals include an advanced understanding of neurophysiological biomarkers to guide stimulation, the development of aDBS control algorithms and to leverage the clinical implementation of aDBS. To achieve this, we study movement disorders patients implanted with neurostimulators and apply a broad range of methods including intra-, post-operative and long-term brain signals recordings of intra- and extracranial signals, multimodal sensor-based symptom assessments, behavioural tasks, stimulation and medication protocols, spectral anatomical mapping, statistical signal analyses and machine learning approaches.



<u>Characterisation of neurophysiological symptom biomarkers:</u> A key activity of my group is the characterisation of putative neurophysiological biomarkers to guide more advanced DBS paradigms. PD is characterised by fluctuating motor and neuropsychiatric symptoms and the optimal DBS control algorithm should be patient-tailored and as comprehensive as possible to include this broad symptom spectrum. We are therefore dissecting motor and non-motor circuitries and determine the dynamic interaction of both domains using neurophysiological recordings combined with motor-psychological profiling, behavioural tasks, sensor technology and neuroimaging.

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Clinical-spectral-spatial topography: The library of symptom-specific brain signal biomarkers is spanning a wide range of spectral frequencies. Nowadays recordings from brain activity in patients implanted with DBS electrodes can be performed with high spatial resolution. Here we investigate the clinical-spectral topography of symptom biomarkers in the DBS target structures, e.g. subthalamic nucleus. Dissecting this spectral segregation can be used to inform the optimal electrode placement during DBS surgery, DBS programming and enables a more differentiated feedback signal selection for aDBS.

Ambulatory neurophysiological and behavioural monitoring: In the past, neurophysiological recordings in movement disorders patients were limited to hospital settings, while the period in-between remained a "black box". Recent advances in hardware technology allow to link long-term neurophysiological recordings with wearable technology and digital logs. This opens-up new opportunities to contextualise clinical symptom fluctuation, medication effects and circadian rhythms in the out of the hospital- real life– setting. For these projects, we are working with 'Rune Labs', a company hosting a health data platform for novel neurostimulators. Such an approach in which clinical decision and treatment adjustments could be based on objective neurophysiological measures would have a remarkable clinical impact.

Translation of adaptive neuromodulation in clinical practice: As these novel and promising technologies evolve, the level of complexity increases in parallel. A neurostimulator that controls the temporal fluctuation of neurophysiological states – in contrast to conventional continuous stimulation - requires specific control algorithms that expand the parameter space that needs to be adjusted. To make sure that these technologies remain user-friendly and are not overwhelming our clinical routines, we are working on clinical-electrical assessment and automatization strategies to facilitate the adjustments of future aDBS algorithms.

The current members of the lab are Alberto Averna, PhD (Neuro-Engineer, Postdoc), Elena Bernasconi, MSc (Engineer, PhD Student), Laura Alva, MD (Clinician-Scientist), Mario Sousa, MD (clinical PhD Student, co-supervised, Krack/Tinkhauser) and Katrin Petermann (DBS engineer, Biostatistician). In addition to various international partners, we have a strong local network with experts from various disciplines such as neurology (Prof. Krack and Team), neurosurgery (Prof. Pollo and team), DBS-Imaging (Dr. Nyguen and team), experimental neurology (Prof. Adamantidis and groups), and links to the Neuro-Tec/Sitem platform (Prof. Schindler, Prof. Nef, Prof. Bassetti) to facilitate academic-industry interaction.

Our future goals This research field progresses in parallel to the technical capabilities of neurostimulators. Brain-sense capable neurostimulators (devices that can stimulate and record brain activity from the implanted electrodes) entered the market 2 years ago and are now regularly implanted in our patients. This has already revolutionized the field as it allows recording brain signals in chronically implanted patients, while before we were restricted to recordings during DBS surgery in the operating room. In the upcoming years the neurostimulators will be updated to access aDBS control paradigms and the research focus of my team will at that time expand toward clinical aDBS trials. Similarly, the use of aDBS will be of interest not only for movement disorders but also for other indications such as obsessive compulsive disorder and depression.
I believe that this exciting and multifaceted research will evolve faster, both locally and internationally, if experts across disciplines join forces, therefore exchanges and collaborations are welcome.

Contact: gerd.tinkhauser@insel.ch

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③ Upcoming events

9. September 2022	Annual Meeting “Precision Medicine in clinical neuroscience”
13th-16th March 2023	Brainweek Bern
15th March 2023	CNB Poster Session with Apéro

For any inquiries, please contact:

Noémi Allet

noemi.allet@unibe.ch