### SWEZ University Sleep-Wake-Epilepsy-Centre Bern







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**Interdisciplinary treatment, research and teaching** SWEZ – University Sleep-Wake-Epilepsy-Centre Bern







healthy good night's sleep is essential for the body to rest and recover from daily activities. This enables us to not only engage in social interactions with others but also to function during the day on a mental and emotional level. Sleep disorders affect more than 10% of the population bringing healthcare costs to a rise. Not only having serious impact on the individuals health but it can also impair intellectual abilities, school performances and quality of life in general. *The University Sleep-Wake-Epilepsy-Centre in Bern(SWEZ)* deals with diagnosing, treating and researching disorders related to sleep, wakefulness and consciousness. The SWEZ also contributes to distributing and sharing the gained knowledge. *The Centre is a working platform consisting of neurologists,* epileptologists, pulmonologists, psychiatrists, pediatricians, psychosomaticists, psychologists, biologists, pharmacists, engineers and physics who collaborate with one another. This allows the healthcare professionals to provide accurate and rapid care for individually tailored diagnoses and needed treat*ments. The interaction between clinical and experimental* research allows newly generated insights and ideas to be put into practice without unnecessary delays. The BENESCO (the Bern Network for Epilepsy, Sleep, and consciousness) promotes cooperation between SWEZ and other Centre's in Switzerland. *This initiative brings our consortium recognition for promoting* best clinical practice, teachings and research on the international stage.

#### **Prof. Claudio Bassetti**

Chairman and Head of the Department of Neurology Chairman of the Board of Trustees of SWEZ and BENESCO

### The orchestra in the brain – the complexity of sleep, wakefulness and related disorders

e sleep. We doze, take a nap, enjoy a snooze. Yet what exactly is sleep? Is it a brief death, with death being a period of extended sleep, as Plato believed? The state in which we are both present and absent at the same time is a source of fascination for humankind. It has preoccupied poets, thinkers and medical specialists alike. Hippocrates, the most famous physician of all, realised that "both sleep and insomnolency, when immoderate, are bad". It is this very interplay between sleep and wakefulness that forms the focus of attention at the Sleep-Wake-Epilepsy-Centre (SWEZ). Its director, Prof. Claudio Bassetti, explains further: "Sleep is a complex state," he says. "Sleep and wakefulness are produced in the brain, and many sleep-wake disorders arise due to something in the brain not being quite right." Bassetti is Chairman of the Department of Neurology at Inselspital and of the Board of Trustees of SWEZ. For the benefit of non-experts, he has come up with a comprehensible metaphor: "Like the instruments in an orchestra, the various parts of the brain all have a part to play in the sleep-wake cycle, but with no conductor setting the tempo or bringing in each part."

Somnology, the scientific study of sleep, is a relatively young discipline covering sleep research and sleep medicine. In 1862, the German physician Ernst Kohlschütter became the first person to describe different depths of sleep in his work "*Messung der Festigkeit des Schlafes*" ("Measuring the soundness of sleep"). The first sleep "bible" was then published in Russia in 1892 by Maria Manasseina. In the 1920s, neurologist Hans Berger developed the technique of electroencephalography (EEG) in Jena. EEG recording now forms an important part of polysomnography (PSG) analyses. This combines EEG recording during sleep with other physiological parameters (e.g. heart rhythm, breathing, oxygen saturation in the blood, muscle tension, leg and eye movements) and makes it possible to conduct a precise analysis of sleep. The 1950s saw the discovery of the REM phase (rapid eye movement: the phase in which

### "If we do not sleep, we die."

the sleeping person's body is paralysed but their brain is active). Inselspital got involved in somnology at an early stage: in the 1950s, Prof. Robert Isenschmid began carrying out recordings during sleep in the EEG unit in the Department of Neurology. Prof. Matthias Gugger (pulmonology), Prof. Christian Hess (neurology) and his successors Prof. Claudio Bassetti and Prof. Johannes Mathis have been pioneering interdisciplinary sleep medicine in Bern since the 1980s. Inspired by a study visit to Edinburgh, Gugger was an important driving force behind sleep medicine and introduced CPAP therapy to Switzerland as a management for sleep apnoea. Bassetti initiated experimental research on animals in Bern.

Nowadays, the various phases of sleep – falling asleep, light sleep, deep sleep and REM sleep – are well

#### From 1952

First EEG recordings during sleep: following the discovery of electroencephalography (EEG) in 1929, Prof. Robert Isenschmid carries out recordings during sleep for the first time in the EEG unit at Inselspital in 1952. This marks the start of modern sleep studies in Bern.

#### 1982

First polysomnography (PSG) recordings: Prof. Christian Hess and Prof. Johannes Mathis (from 1984) carry out the first PSG recordings in the EEG facilities. This combination of EEG recording during sleep with other physiological parameters makes it possible to conduct a differentiated analysis of sleep.

#### 1990

Switzerland's first interdisciplinary sleep laboratory: a room in the EEG unit is converted into a sleep laboratory. Under the leadership of pulmonologist Prof. Matthias Gugger, who helped pioneer CPAP therapy in Switzerland, and neurologist Prof. Claudio Bassetti, joint consultations are offered to patients. This interdisciplinary cooperation is the first of its kind in Switzerland.

#### 1997

Interdisciplinary cooperation extended to include psychiatry: starting from 1997, neurologists (Prof. Johannes Mathis) and psychiatrists (Prof. Bogdan Radanow, later Dr. Wolfgang Schmitt) offer joint interdisciplinary consultations for patients with insomnia (neuropsychiatric sleep clinic). Prof. Claudio Bassetti organises the first Bern Sleep Symposium.

#### 2009

Collaboration extended to include neuropaediatrics: in 2009, Inselspital starts offering sleep medicine services for children too.

#### 2012

A boost for sleep medicine and research: Inselspital elects Prof. Claudio Bassetti, former President of the European Sleep Research Society, as Physician-in-Chief and Chairman of the Department of Neurology and appoints Prof. Antoine Adamantidis.

#### Today

The new, expanded Sleep-Wake-Epilepsy-Centre is a world leader in its field.

Patients, researchers and staff alike benefit from the strong focus on interdisciplinary teamwork and networking between neurology, pulmonology, psychiatry, neuropaediatrics and other specialist areas.

tigated. Sleep is vital, that much is clear: if we do not sleep, we die. "Even simple creatures enter sleep-like states," says Bassetti. Sleep plays a fundamental role for our brain, organism, mental health and performance.

"Everything we learn is consolidated in our sleep," explains Katharina Henke, a professor of neuropsychology, adding that sleeping also helps us to make important decisions: "The decisions we make consciously have already been made unconsciously beforehand. Unconscious decisions are also readjusted while we sleep." It therefore really is a good idea to "sleep on it" before finalising an important decision. It has also been proved that we absorb and consolidate newly acquired knowledge in our sleep. Does this mean it is also possible to learn a language, for example, while sleeping? This is the question Henke is exploring in her research (see project example 1, p. 11).

#### Sleep-wake disorders - a widespread phenomenon

Sleep-wake disorders are a genuinely widespread phenomenon. A quarter of the Swiss population suffers from sleep disorders, while eight out of 100 people in Switzerland take medication to help them sleep. This is corroborated by figures from the Swiss Health Survey carried out by the Federal Statistical Office in 2012. As they grow older, around 60% of men and 40% of women snore. Snoring also affects roughly 10% of

"Microsleep is the cause of up to 20% of serious road traffic accidents in Switzerland."

#### children.

Sleep disorders can have a serious impact on the health of those affected. If a person suffers from sleep-related breathing disorders, insomnia or restless legs syndrome, for example, this can lead to cardiovascular diseases (e.g. stroke), high blood pressure, impotence and various other health problems.

However, sleep disorders can also have an effect on those not directly affected by them. For instance, nodding off momentarily during the day, a phenomenon known as microsleep, is the cause of up to 20% of serious road traffic accidents in Switzerland, according to Prof. Johannes Mathis. Epileptics are also well aware of the importance of sleep: sleep deprivation increases their chances of having a seizure, says Prof. Kaspar Schindler, Head of Epileptology and Managing Director of SWEZ. Finally, sleep disorders can also signal the development of a neurological or psychiatric disorder.

#### There are around 90 different sleep-wake disorders

Sleep-wake disorders vary considerably in terms of their causes and effects. Specialists distinguish between some 90 different sleep-wake disorders, which are roughly divided into four groups:

• Insomnia or reduced sleep: an inability to fall asleep or sleep through the night. Possible causes include environmental influences, stressful situations, substances such as alcohol and caffeine, sleeping pills or psy-*Continues on page 10* >





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chostimulants such as cannabis or amphetamines taken over a long period, sleep-wake rhythm disorders such as restless legs syndrome, physical illnesses, breathing disorders or psychological conditions such as anxiety and depression.

• Hypersomnia or "increased sleep" gives rise to symptoms such as sleeping for longer periods at night, feeling a constant need to sleep or repeatedly nodding off during the day. An extreme form of this is narcolepsy, a condition which causes excessive sleepiness during the day. Other patients with hypersomnia find they wake up a lot during the night or suffer a variety of seizures, which is confirmed in the sleep laboratory. Sleep-related breathing disorders and a lack of sleep are also common causes of daytime sleepiness.

• Parasomnias are uncontrollable patterns of behaviour during sleep, such as sleepwalking, sleep paralysis or REM sleep behaviour disorder.

• Disturbances in a person's circadian sleep-wake rhythm or "displaced sleep", e.g. due to jet lag or shift work (sleep-wake rhythm disorders).

#### From bench to bedside and back

Findings and insights from other research centres are also pooled together in Bern: the Bern Network for Epilepsy, Sleep and Consciousness (BENESCO) encompasses scientists and clinicians from the University of Bern, the University of Fribourg, the Neurocenter of Southern Switzerland in Lugano, and Klinik Barmelweid in Aargau who specialise in sleep medicine, epilepsy and consciousness. The network shares research results, runs seminars for young researchers and promotes the transfer of knowledge into routine clinical practice as quickly as possible with the aim of improving patient diagnosis and treatment.

At Inselspital, the distance "from bench to bedside and back" is exceptionally short: fundamental research is carried out in very close proximity to clinical research and has a direct impact on the care and treatment provided to patients (see project examples, p. 11). The work of Prof. Antoine Adamantidis offers a good example of this: as a biologist, he conducts experimental research on animals at Inselspital. Using optogenetic methods, he investigates the brain activity of mice and rats to find out "how sleep occurs in the brain" (p. 19, p. 38). The findings from Adamantidis' experiments are channelled directly into clinical treatment. They provide important insights for minimally invasive (stereotactic) treatment of Parkinson's disease, epilepsy and other conditions. Stereotactic operations can now be performed with extreme precision and they in turn supply vast quantities of data that can be used to support research.

#### Strictly interdisciplinary

Sleep and sleep disorders are complex: in the words of Claudio Bassetti, "Sleep medicine is a recapitulation of the entire spectrum of medicine". Certain sleep disorders can also be early indicators of serious diseases: involuntary violent movements during sleep and falling out of bed could be a sign of Parkinson's disease, restlessness and the urge to move when going to sleep (sundowning) could point to Alzheimer's, and insomnia could be a symptom of depression or schizophrenia. It is because of the complexity of sleep and its countless possible disorders that the neurologists, pul-

### "At SWEZ, patient care and treatment benefit from the close link between fundamental and clinical research."

monologists, psychiatrists, psychologists, neuropaediatricians, pharmacists and physiologists working at SWEZ have adopted the following maxim: sleep medicine absolutely must be practised on an interdisciplinary basis.

The various specialists at Inselspital therefore work closely together, run joint clinics and collaborate on research. Results from investigations in the sleep laboratory are discussed collectively to ensure that patients and the doctors treating them benefit from expertise from all disciplines. SWEZ offers a wide range of clinics and various outpatient and inpatient sleep-wake tests and analyses for adults and children suffering from all kinds of sleep-wake disorders.

Adamantidis reiterates something that other colleagues of his have also highlighted: "Somnology in Bern is perfect. What we can do here is what every researcher and every clinician dreams of."

#### Project example 1: Verbal learning during sleep

Very few studies have been carried out on learning verbal information during sleep. However, there is evidence that the hippocampus, which enables us to learn verbally while we are awake, is also very active during non-rapid eye movement (NREM) sleep. We therefore believe that people can learn new information and store it in their long-term memory during NREM sleep. It is a well-known fact that the hippocampus stabilises what we have learned during the previous day during the NREM sleep phase at night. Our hypothesis is that those sleep parameters that trigger this memory stabilisation process while we sleep are also responsible for enabling us to learn new verbal information via headphones during NREM sleep. Our experiments involve taking EEG recordings from hippocampal macro- and microelectrodes on patients with temporal lobe epilepsy. These recordings shed light on the role of hippocampal sharp-wave ripples and cortical slow oscillations in the stabilisation during sleep of information learned previously while in a state of wakefulness and the acquisition of verbal information during sleep. The results will provide information to substantiate memory theories and help to improve the diagnosis and treatment of memory disorders. *Prof. Katharina Henke* 

#### Project example 2: Sleep-wake rhythms and the functions of sleep

The functions of sleep are still not fully understood. However, its primary functions are believed to be memory consolidation and optimisation of synaptic brain plasticity.

The neuronal substrates of sleep and wake states are the subject of intensive research.

Our main focus is on the neuronal networks that control sleep-wake states and brain plasticity. We combine a range of technologies in this research, including *in-vivo* electrophysiology and optogenetics (p. 19). Our work, which is supported by the Swiss National Science Foundation (SNSF), has particularly identified hypothalamic networks that play a key role in regulating wakefulness and REM sleep, in conjunction with other subcortical and cortical structures. The ultimate aim of our work is not only to identify the neuronal substrates of sleep-wake rhythms but also to gain important insights into consciousness and the control of innate and goal-oriented behaviour. From a translational perspective, we integrate our work into the interrelationships between sleep disorders and neurological and psychiatric diseases. As part of the Sleep-Wake-Epilepsy-Centre team, we study the regenerative and restorative effects of sleep on brain plasticity, e.g. during the recovery period after a stroke. *Prof. Antoine Adamantidis* 

#### Project example 3: The role of sleep in functional recovery after a stroke

Studies show that healthy sleep improves neuronal and functional recovery following a stroke. We are currently carrying out three SNSF-funded research projects on sleep and strokes. The first is investigating whether sleep apnoea treatment for acute stroke patients involving adaptive servo-ventilation therapy reduces the volume of the infarct and has a positive effect on the clinical course of the condition (p. 24). The second focuses on the influence of sleep disorders on the recurrence of strokes and other cardiovascular diseases within two years. The third project is being run in collaboration with the University of Zurich and the University of Milan. Using animal models of stroke and human studies, it aims to get to the bottom of the relationship between the neuronal repair mechanisms following a stroke and sleep-wake rhythm and to boost neuronal recovery after a stroke through brain stimulation in animals and humans. Through our research, we want to gain a more comprehensive understanding of the mechanisms involved in neuronal recovery after a stroke and thus develop new treatment concepts for stroke patients. *Prof. Claudio Bassetti* 

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Bern Network for Epilepsy, Sleep and Consciousness (BENESCO) Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel AG) Clinical Neuroscience Bern (CNB)

#### CLINIC

## Close links: how SWEZ works for referring doctors and patients

SWEZ offers a range of interdisciplinary clinics. Doctors can refer patients with suspected sleep-wake or consciousness disorders or epilepsy directly to the clinics or for additional investigations. However, the SWEZ secretary's office also serves as a single point of contact for all referrals. This saves patients from having to make repeated trips for various assessments. It also means they can benefit from the expert knowledge and care of a variety of specialists on site within a reasonable period of time.

#### **Multidisciplinary clinics**

At the neuropulmonary sleep clinic, patients with sleepwake disorders (e.g. daytime sleepiness, parasomnias, restless legs syndrome, sleep-related breathing disorders and insomnia) receive advice from consultant neurologists and pulmonologists at the same time, making it the only clinic in Switzerland to provide such a service.

Patients who have complex problems getting to sleep or sleeping through the night or who are suffering from sleep-wake rhythm disorders attend the neuropsychiatric sleep clinic, where they are seen by a consultant psychiatrist and a consultant neurologist at the same time (and, if necessary, a chronobiologist). During these clinic sessions, the medical experts investigate both the organic and the mental and psychosocial causes and components of the patient's condition in greater detail.

The pulmonology CPAP clinic, which is where sleep apnoea patients are admitted and monitored under positive pressure ventilation overnight, was set up in 1990. Meanwhile, the children's clinic has been running a neuropaediatric clinic since 2009. Younger children are admitted to the children's hospital if necessary. Epilepsy patients have their own epilepsy clinic, and in many cases an EEG can be carried out on the same day. In unclear cases, this is sometimes followed by a sleep deprivation or long-term EEG. Vigilance tests and driving simulators are used, with or without EEG co-registration, for assessing the fitness of neurological patients (including patients with sleep-wake disorders and epilepsy) to drive.

#### State-of-the-art investigation methods

At the clinics, the SWEZ medical experts determine the indications for further investigations. The most important method of investigation used is polysomnography, which is carried out in the SWEZ sleep laboratory (or in the children's clinic in the case of children of pre-school age). Respiratory polygraphy, which focuses purely on examining nocturnal breathing, is provided by pulmonologists on both an inpatient and an outpatient basis. During the day, investigations are conducted at SWEZ for the purpose of measuring daytime sleepiness and patients' ability to stay awake in spite of this problem. Actigraphy is offered as an outpatient service for measuring physical activity over one to two weeks in order to provide objective documentation of a patient's sleepwake rhythm. The driving simulator is mainly used for investigations on patients suffering from daytime sleepiness, to help determine whether or not they are fit to drive.

All investigation results are discussed in a joint report involving all sleep specialists as a basis for recommending the best possible treatment for each patient. If it is not possible to control an epilepsy patient's seizures with medication, the next step is to investigate whether this patient is a suitable candidate for surgery: in many cases, for instance, the part of the brain responsible for triggering seizures can be surgically removed without any negative consequences. However, this requires extensive assessments performed over several days in the telemetry unit, which can sometimes involve electrodes being implanted directly into the brain.

# Basic and advanced training in sleep medicine, epileptology and related disorders

Initial, further and advanced training is an essential part of the activities of SWEZ and is among the core tasks undertaken by any university hospital department. At SWEZ, junior doctors receive basic further training in epileptology and sleep-wake medicine. This makes them eligible to obtain Swiss federal certificates in electroencephalography (EEG) and sleep medicine.

#### Sleep and EEG fellows

SWEZ also offers in-depth clinical further training in sleep medicine and epileptology for advanced staff, coupled with research as part of a one-year fellowship programme. It is the first institution in Switzerland to provide training for sleep fellows specifically in line with the European Sleep Research Society's (ESRS) somnology certification. EEG fellows learn skills such as how to evaluate intracranial EEG recordings and carry out detailed analyses of the semiology of epileptic seizures.

#### International Postgraduate Advanced Course

The demand for highly qualified experts in the field of sleep, consciousness and related disorders is increasing. To meet this demand, the University of Bern - together with the Università della Svizzera italiana in Lugano has developed with the support and patronage of the European Sleep Research Society (ESRS) postgraduate advanced courses (certificate [CAS], diploma [DAS] and master [MAS] of advanced studies) in sleep, consciousness and related disorders.

The courses will start in 2018 and are designed for professionals already working in the corresponding area of medicine, or for graduates wishing to embark on a career in these fields.

### Bernese sleep-wake-days and epilepsy and EEG symposium

The SWEZ offers traditionally the yearly symposiums for sleep medicine and epilepsy and EEG for a further training of medical and scientific specialists. The Bernese sleep-wake-days take place every automn and the epilepsy and EEG symposium every spring. For dates and programs please visit www.swez.ch.



INTERNATIONAL POSTGRADUATE ADVANCED COURSES (CAS, DAS, MAS) IN SLEEP, CONSCIOUSNESS AND RELATED DISORDERS

Course direction Prof. Claudio Bassetti (Director), Past-President ESRS Prof. Mauro Manconi (Co-Director) Prof. Kaspar Schindler (Co-Director)



Bassetti CL, Peigneux P, Dogas Z (2014). ESRS European Sleep Medicine Textbook. Blackwell.

CLINICAL RESEARCH

### Clinical research in sleep medicine, epileptology and related disorders

Beside of initial, further and advanced training, clinical research on humans is also an essential part of the activities of SWEZ and is among the core tasks undertaken by any university hospital department.

#### **Clinical research**

Clinical research focuses on the following key areas:

1) The cardio- and cerebrovascular and metabolic consequences of sleep-related breathing disorders (SRBDs) and other sleep disorders (p. 24). Bern is leading the way on the international stage in researching the links between SRBDs and strokes.

2) Diagnosing, investigating the causes of and treating narcolepsy and neurogenic hypersomnias (p. 34). The best screening test for narcolepsy (the Swiss Narcolepsy Scale) was developed in Bern. SWEZ experts are currently testing, for example, the hypothesis that narcolepsy could be caused by a faulty immune defence and treated with new drugs.

3) The link between sleep-wake disorders and the development, progression and rehabilitation of neurological diseases such as stroke, Parkinson's disease, epilepsy and dementia (p. 11, p. 36). SWEZ experts are investigating the conditions under which sleep, an increase in sleep, and sleep deprivation have a beneficial or adverse effect on neuroplasticity. This is now being done with the aid of high-resolution sleep EEG meth-

ods and by carrying out sleep studies on Parkinson's patients before and after deep brain stimulation.

4) Diagnosis, treatment and impact on quality of life of patients with restless legs syndrome, also including cases during pregnancy.

5) Diagnosing and investigating the causes of complex behavioural disorders during sleep, such as sleepwalking and REM sleep behaviour disorders, and differentiating them from nocturnal epileptic seizures.

6) Gaining a better understanding of the dynamics of epileptic seizures by taking extra- and intracranial EEG recordings and analysing them using mathematical methods, such as those developed in physics for studying complex systems (p. 49).

7) To develop EEG based biomarkers that help to improve diagnosis and prognosis in comatose patients.

8) Testing the effects of sleepiness and interictal epileptiform activity on the ability to drive safely by using EEG recordings in a driving simulator.

#### PUBLICATIONS FROM CLINICAL RESEARCH

Dauvilliers Y, Bassetti CL, Lammers GJ, et al (2015). *Pitolisant versus placebo or modafinil in patients with narcolepsy*. Lancet Neurol 12: 1068-75.

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Steimer A, Zubler F, Schindler K. *Chow-Liu* trees are sufficient predictive models for reproducing key features of functional networks of periictal EEG time-series. Neuroimage. 2015 Sep;118:520-37. Ponz A, Khatami R, Poryazova R, Werth E, Boesiger P, Schwartz S, Bassetti CL (2010). *Reduced amygdala activity during aversive conditioning in human narcolepsy.* Ann Neurol 67: 394-8.

Schreier DR, Roth C, Mathis J. Subjective perception of sleepiness in a driving simulator is different from that in the Maintenance of Wakefulness Test. Sleep Med. 2015 Aug;16(8):994-8.





### How does sleep occur in the brain? Why do we sleep?

The Centre for Experimental Neurology (*Zentrum für experimentelle Neurologie*, ZEN) was set up by Prof. Claudio Bassetti in 2012 and has been headed up by Prof. Antoine Adamantidis since 2013. The centre's researchers investigate molecular and cellular brain mechanisms and neuronal circuits involved in normal brain activity and activity disturbed due to illness (e.g. neurological diseases, epilepsy, sleep and consciousness disorders). The (inter)national cooperation between clinical and experimental researchers is intended to forge links between animal and human research. The researchers focus on the neuronal substrate of sleep-wake states, the function of sleep, the mechanisms involved in rehabilitation after a stroke and the neuronal networks at work in cases of epilepsy.

#### Optogenetics

What makes ZEN stand out from other experimental research institutions is its multidisciplinary research team and use of state-of-the-art technologies. The latest laboratory tools for molecular, cellular and behavioural research methods include gene expression analysis, genetically modified mouse models, *in-vitro/vivo* electrophysiology, behavioural phenotyping and optogenetics.

The ZEN laboratory boasts a high level of expertise in the fields of optogenetics and high-density electrophysiology in animal models. Optogenetics uses

PUBLICATIONS FROM EXPERIMENTAL RESEARCH

Adamantidis A, Zhang F, Aravanis AM, Deisseroth K & de Lecea L (2007). Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 450, 420–424.

Pace M, Baracchi F, Gao B, Bassetti C. Identification of sleep-modulated pathways involved in neuroprotection from stroke. Sleep 2015; 38: 1707-18

Carter ME, de Lecea L & Adamantidis A (2013). *Functional wiring of hypocretin* 

*and LC-NE neurons: implications for arousal.* Frontiers in behavioral neuroscience 7, 43.

Colby-Milley J, Cavanagh C, Jego S, Breitner JC, Quirion R & Adamantidis A (2015). Sleep-wake cycle dysfunction in the TgCRND8 mouse model of alzheimer's disease: from early to advanced pathological stages. PloS one, 10, e0130177.

Hodor O, Palchykova S, Baracchi F, Noain D, Bassetti CL (2014). Baclofen facilitates sleep, neuroplasticity, and recovery from stroke in

light-sensitive molecules, e.g. channelrhodopsin-2 (ChR2) or halorhodopsin (NpHR), to activate or deactivate genetically predetermined circuits in the brain in a targeted way with millisecond-long flashes of light of specific wavelengths. ZEN uses this technology to "pause and play back the symphony of the brain" and to find out which networks in the brain have a role to play in wakefulness, NREM and REM sleep.

ZEN combines optogenetics with electrophysiological technologies – the same ones used in clinical research and patient treatment (in the case of sleep, wake and consciousness disorders or epilepsy). This makes it possible not only to "conduct the orchestra", but also to "listen" to the orchestra in the brain of sleeping or ill animals.

In an effort to reinforce its multidisciplinary strategy, ZEN is currently also taking human clinical data into consideration when planning experimental research projects. To this end, the experts at ZEN are working with animal models of human diseases such as stroke, dementia and narcolepsy.

The research carried out at ZEN helps to generate a better understanding of the pathophysiological mechanisms of sleep, epilepsy and consciousness disorders, which could lead to improved treatments for neurological diseases in the long term.

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Jego S, Glasgow SD, Herrera CG, Ekstrand M, Reed SJ, Boyce R, Adamantidis A, et al. (2013). Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. Nature neuroscience 16, 1637–1643.

Boyce R, Glasgow SD, Williams S, Adamantidis AR. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 2016; 352: 812-6 An expert team of neurologists, psychologists and psychiatrists advises patients with sleep or sleep-wake rhythm disorders: Prof. Roland von Känel, Dr. Vivien Bromundt, Prof. Christoph Nissen, Dr. Heidemarie Gast, Dr. Wolfgang Schmitt, Dr. Simone Duss, Prof. Johannes Mathis (from left to right).



#### **INSOMNIA AND SLEEP-WAKE RHYTHM DISORDERS**

### WHEN SLEEP IS ELUSIVE OR SLEEP-WAKE RHYTHMS ARE DISTURBED

Insomnia is the most common type of sleeping disorder. It has a variety of causes and can develop in different ways. If it persists, insomnia also gives rise to unfavourable reaction and behavioural patterns, which require specific treatment. The close cooperation between the individual disciplines at SWEZ makes it possible to determine the causes of the problem quickly. This teamwork particularly comes into its own when there are several factors at play in a case of insomnia. The process begins with diagnosis through extensive investigation, testing and a targeted assessment in the sleep laboratory, with the primary focus being on treating the cause of the insomnia. If specific sleep medicine interventions are required, these can be carried out at SWEZ. The specialists at SWEZ also help to put patents in touch with local therapy providers at their request.

SWEZ offers advice on medicinal options and provides cognitive behavioural therapy one-to-one or in groups. Supplying patients with sound information about important sleep hygiene rules and how to put them into practice forms the basis for the therapy process. This is supplemented by additional evidence-based modules. Treatments are carried out on an outpatient basis, either as a short-term intervention or over a longer period in the case of severe disorders or psychiatric comorbidity. Inpatient treatment is also available. In future, the option of internet-based therapy will also be offered in partnership with the Institute of Psychology at the University of Bern.

Further core areas covered by SWEZ include diagnosing and treating sleep-wake rhythm disorders. These are treated using specific chronobiological approaches (e.g. targeted application of melatonin and light). Additional behavioural therapy is also essential when dealing with these disorders and is available at SWEZ. Dr. Wolfgang Schmitt



#### INTERDISCIPLINARY COOPERATION Psychiatry

Primary insomnia, sleep-wake rhythm disorders Dr. Wolfgang Schmitt Neurology Insomnia in the context of sleep-wake rhythm disorders Prof. Johannes Mathis Dr. Heidemarie Gast Dr. Vivien Bromundt Dr. Simone Duss **Neuropaediatrics** Insomnia and sleep-wake rhythm disorders in children Dr. Susi Strozzi Child and youth psychiatry Leila Tarokh, PhD **Psychosomatic** medicine Prof. Roland von Känel

Your contact Dr. Wolfgang Schmitt



#### **SLEEP-RELATED BREATHING DISORDERS**

### THE VARIOUS CAUSES OF BREATHING DISORDERS AT NIGHT

Sleep-related breathing disorders are becoming an increasingly important focal area, partly due to the growing prevalence of these conditions and partly because of an improvement in the diagnosis and treatment methods available. Aside from classic obstructive sleep apnoea, the wide range of pathological causes of sleep-related breathing problems also includes disorders of the central respiratory drive and hypoventilation syndromes with acute or chronic respiratory failure. The latter can be triggered by an impaired respiratory pump or pulmonary changes. Since nocturnal breathing disorders are so diverse, dealing with them requires a thorough investigation and plenty of experience.

From a diagnostic point of view, the top sleep investigation method on offer is polysomnography, which is carried out in the SWEZ sleep laboratory with routine capnography. Small portable systems offering multichannel analysis, i.e. respiratory polygraphy, and wrist devices such as the WatchPAT are available in the pulmonology outpatient department. Screening systems and oximetry are also used to monitor established ventilation and oxygen therapies. In addition to analysing sleep at night, the pulmonary medicine specialists at SWEZ provide the full range of functional investigations such as pulmonary function testing, measuring the respiratory pump, blood gas analyses and assessing cardiopulmonary performance. If required, sleep endoscopies are also carried out under propofol sedation in the bronchoscopy unit to examine the upper airways. Clinical research in this area focuses on aspects such as the influence of sleep-related breathing disorders on the organism and new treatment concepts. By carrying out comprehensive investigations, our experienced team can offer patients the best possible treatment on a case-by-case basis depending on the underlying pathology. Dr. Sebastian R. Ott and Dr. Anne-Kathrin Brill



**INTERDISCIPLINARY** COOPERATION **Pulmonary medicine** Prof. Thomas Geiser Sleep and respiratory medicine Prof. Matthias Gugger Dr. Sebastian R. Ott Dr. Anne-Kathrin Brill Daniela Wyss Paediatric pulmonology Dr. Carmen Casaulta Prof. Philipp Latzin Neurology Prof. Claudio Bassetti

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### AN UNDERESTIMATED CARDIOVASCULAR RISK FACTOR

Dr. Sebastian R. Ott , Prof. Claudio Bassetti

leep-related breathing disorders are common and set to become even more widespread. In spite of this, however, they are underdiagnosed. This is because those affected rarely notice themselves that their breathing is impaired during sleep and subjective symptoms such as tiredness and sleepiness during the day are rather vague. Early diagnosis and treatment are important for dealing with these conditions. Sleep-related breathing disorders, especially obstructive sleep apnoea (OSA), have been attracting increasing interest in connection with cardio- and cerebrovascular diseases and metabolic disorders.

There is, to some extent, a bidirectional relationship between sleep-related breathing disorders and the concomitant or secondary diseases associated with them. Patients with OSA often suffer from obesity, diabetes, arterial hypertension and lipid metabolic disorders, all of which are known to be risk factors for vascular diseases. On the other hand, however, obesity and diabetes are risk factors for sleep-related breathing disorders. There is clear evidence that OSA is an independent risk factor for the development of certain diseases, such as arterial hypertension, heart failure and stroke (the specialists in Bern are at the forefront of international research in this area)1-7. Patients with untreated OSA therefore have a significantly increased risk of suffering cardio- and cerebrovascular events and diseases, a risk that can be reduced through effective treatment of the breathing disorder.

Investigating the links between sleep-related breathing disorders and cardiovascular diseases is one of the core areas of clinical research at SWEZ. For instance, our research has demonstrated that patent foramen ovale (PFO), a fault left over from embryonic development that affects around 25% of the population, has an effect on the severity of OSA and endothelial function. Closing a PFO in OSA patients leads to a significant drop in the apnoea-hypopnoea index, the oxygen desaturation index and pulmonary arterial pressure <sup>8,9</sup>.

Two of the studies being conducted at SWEZ with support from the Swiss National Science Foundation (SNSF) are examining the influence of sleep appoea and its treatment on the course of events following a stroke. The SAS CARE study has not only been investigating the prevalence and evolution of sleep-related breathing disorders in the acute phase following a stroke, but also been using a randomised approach to explore the effect of APAP therapy during the sub-acute phase on the secondary prevention of vascular events<sup>10</sup>. Another large randomised controlled study (eSATIS) is looking into the influence of early treatment for breathing disorders in the acute phase of a stroke on the course of the acute stage. The findings gained from interdisciplinary clinical research at SWEZ help to improve our understanding of the relationships between sleep-related breathing disorders and numerous internal medical and neurological secondary diseases.

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#### **NON-INVASIVE VENTILATION (NIV)**

### ACHIEVING SUCCESS THROUGH INDIVIDUALLY TAI-LORED THERAPY AND CARE

As a highly effective way of treating sleep-related breathing disorders, non-invasive ventilation (NIV) is one of the key areas of expertise covered by the Department of Pulmonary Medicine. Using this method, it is possible to deal with the obstruction in the upper airway while relieving the respiratory pump and improving the gas exchange at the same time.

Aside from choosing the right equipment and accessories on a case-specific basis, key factors in ensuring the success of this treatment include optimal adjustment of the NIV settings, professional training for patients, and quick and straightforward follow-up care. This is made possible thanks to a wide variety of masks, state-of-the-art therapeutic devices and aids, and a proficient team with many years of experience and good links with equipment providers and the Swiss Lung Association. The available treatment options range from simple positive pressure ventilation (CPAP and APAP) for cases of obstructive sleep apnoea or adaptive servo-ventilation for central breathing disorders through to volume- or pressure-controlled ventilation as treatment for neuromuscular diseases or respiratory failure with a different cause. Ventilation is usually provided via nose or face masks, although invasive ventilation via tracheostomy is also possible. In addition, the pulmonology ward is equipped for complex ventilation and weaning settings. Patients can also be provided with mouthpiece ventilation during the day, additional oxygen, batteries, speaking valves and suction pumps. Alternatives to NIV therapy, such as prognathic mouthguards, surgery and pacemaker implantations, are also explored and assessed. Pulmonological sleep research activities focus particularly on optimising the design and fit of ventilation masks with a view to further developing the range of treatments on offer. Dr. Anne-Kathrin Brill



#### COOPERATION Pulmonary medicine Prof. Thomas Geiser Sleep and respiratory medicine Prof. Matthias Gugger Dr. Sebastian R. Ott Dr. Anne-Kathrin Brill Daniela Wyss Paediatric

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Your contacts **Prof. Matthias Gugger Dr. Sebastian R. Ott Dr. Anne-Kathrin Brill** 

#### DAYTIME SLEEPINESS AND FALLING ASLEEP AT THE WHEEL

### TAKING RISK ALONG FOR THE RIDE – THAT FATAL MOMENT OF SLEEP

According to Swiss authorities, 1 to 3% of all traffic accidents in Switzerland are caused by falling asleep at the wheel. This figure stands in strong contrast to the 10 to 30% estimate given by scientific studies. Sleep deprivation due to work or social activities is the most common factor causing people to momentarily doze off at the wheel. However, daytime sleepiness can also be caused by sedative drugs or sleep disorders. Since the symptoms of sleepiness can usually be perceived it is important to raise awareness among drivers of risk factors and ways to counter this problem.

A "blackout" can be caused by many disorders (i.e., epileptic seizure, cardiac syncope, or briefly falling asleep) and requires a comprehensive investigation. In addition to our epileptologists and sleep medicine specialists, SWEZ has the technical facilities required to evaluate patients, such as long-term EEG monitoring, wakefulness tests and other vigilance tests, including driving simulators.

Our goal is to correctly diagnose and treat patients' conditions while informing them of their personal responsibility when they are behind the wheel. This informative discussion, which is particularly important for those taking sedating drugs must be documented in the patient's medical records. Professional drivers with daytime sleepiness, motorists with a prior accident as a result of momentarily falling asleep at the wheel, and patients at risk should have their daytime sleepiness analysed objectively in the sleep laboratory. Physicians in Switzerland have the right to report non-compliant drivers to authorities, but are not obliged to do so. Teamwork between primary care providers and specialists at SWEZ is essential to avoid premature reporting of motorists to the licensing office and instead focusing on effective driver rehabilitation. Prof. Johannes Mathis



#### INTERDISCIPLINARY COOPERATION Neurology Prof. Johannes Mathis Neuropsychology Prof. Klemens Gutbrodt

Your contact Prof. Johannes Mathis



### CONCEPT OF SLEEPINESS – INDUCED ACCIDENTS & DRIVING REHABILITATION

Prof. Johannes Mathis, Dr. David Schreier, Prof. Klemens Gutbrod

p to 15% of the population in industrialised countries suffer from excessive daytime sleepiness (EDS) <sup>1</sup>. Based on scientific evidence, sleepiness is the underlying cause in up to 20% of motor vehicle accidents<sup>2,3</sup> and 50% of drivers admitted to have been driving while sleepy at least once in the past year<sup>4</sup>.

Sleepiness induced accidents primarily occur during the night and secondarily in the early afternoon<sup>5.</sup> It is difficult to understand and accept the high incidence of sleepiness induced accidents even though sleepiness at the wheel can be recognised before driving is impaired by the well-known signs such as "tunnel vision", prolonged reaction time, and lane deviations.

#### Concept behind the sleepiness induced accidents

The process leading to a sleepiness induced accident consists of 1) EDS with its social and medical aetiologies, 2) perception and judgement of sleepiness at the wheel, 3) inaccurate and risky behaviour while continuing to drive despite being sleepy, ultimately resulting in a high risk of accident occurrence<sup>6</sup>. Research on many causes of daytime sleepiness is vast, whereas rather limited knowledge is available on the perception and judgement of sleepiness at the wheel and risky behaviour while sleepy.

We have recently shown that many healthy individuals can fall asleep under the condition of a maintenance of wakefulness test without prior signalling of their subjective sleepiness<sup>7,8</sup>.

In contrast, this is not the case in a driving condition where all subjects signalled their sleepiness before their first microsleep in all trials<sup>8</sup>. If we can assume that a driver is able to detect his or her sleepiness before a microsleep occurs it is of utmost importance to educate the patient about the risk and legal and financial consequences of a sleepiness induced accident as well as of effective countermeasures such as coffee and napping.

#### Driving rehabilitation

The most common aetiologies of daytime sleepiness, e.g. sleep apnoea syndrome or narcolepsy, can be treated sufficiently to allow patients to continue to drive. Therefore, driving rehabilitation consisting of the most effective treatment, based on an optimal diagnostic assessment battery, is feasible. A rehabilitation programme with driving simulator sessions could be used as sleepiness perception training and to minimize risk-taking behaviour in sleepy condition. Finally, built-in driving assistant systems will provide additional possibilities to judge impaired driving performance. In a project funded by the commission for technology and innovation of the Swiss Government (CTI), we aim to devise such a driving assistant system to accurately detect sleepiness and automatically detect and predict microsleeps in collaboration with an industrial partner. The sanctioning assessment of fitness to drive in sleepy patients should always be performed after driving rehabilitation. A battery of tests such as the maintenance of wakefulness test, driving simulators, reaction time and eventually neuropsychological tests should then be combined with clinical judgement.

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#### **RESTLESS LEGS SYNDROME**

### LEGS WITH AN IRRITATING LIFE OF THEIR OWN

Restlessness associated with uncomfortable sensations in the legs that intensify during periods of inactivity, in the evenings and at night, and are relieved by physical activity of any kind: these are the main diagnostic criteria for what can be reliably diagnosed as restless legs syndrome (RLS). Periodic leg movements occurring during sleep and/or low doses of dopaminergic compounds improving symptoms are factors that make a diagnosis of this condition even more certain. The latest diagnostic approach includes a severity criterion based on the impact of the condition on the patient's quality of life.

However, even if all these criteria are met, it is important to rule out diseases that can imitate the characteristics of RLS (known as RLS mimics), or that could cause RLS, known as "secondary RLS". Differential diagnoses include, for example, muscle cramps at night, polyneuropathies and agitated depression. Differentiating between RLS and RLS mimics, investigating the causes of secondary RLS, and treating augmentation or multiple comorbidities all require interdisciplinary teamwork between sleep medicine experts, pain specialists, neurophysiologists and psychiatrists, which is precisely what SWEZ offers. Symptoms must be treated with medication if physical methods prove insufficient, particularly in the absence of secondary causes of RLS such as iron deficiency. Dopamine agonists, pregabalin or gabapentin and opiates are the main drugs of choice for RLS. These medications are often selected on the basis of comorbidities. For example, patients with an additional anxiety disorder tend to find pregabalin effective, while those with severe neuropathic pain are more likely to require gabapentin or opiates, and dopamine agonists are usually used to treat idiopathic RLS without any comorbidity. Intermittent use of L-dopa drugs may be employed in cases with mild or intermittent

#### SYMPTOMS. Prof. Johannes Mathis

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#### INTERDISCIPLINARY COOPERATION Neurology

Prof. Johannes Mathis Prof. Claudio Bassetti Markus Schmidt, MD, PhD Dr. Ulf Kallweit **Psychiatry** Dr. Wolfgang Schmitt

Your contact Prof. Johannes Mathis

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#### THE BRAIN, BRAIN DISEASES AND SLEEP

### SUDDENLY OVERCOME WITH SLEEP

Sleep-wake disorders are a common phenomenon in most neurological diseases. Primary neurological sleep-wake disorders include, for example, narcolepsy and idiopathic or periodic hypersomnia.

Narcolepsy is a chronic condition that affects 0.5-1 out of 2,000 people and has a disruptive effect on sleep-wake regulation. The five main symptoms associated with this disease are chronic daytime sleepiness/attacks of falling asleep, cataplexy, hypnagogic hallucinations, sleep paralysis and fragmented sleep at night. There is increasing evidence of an immune-mediated mechanism at work in cases of narcolepsy, resulting in a loss of hypocretin cells in the hypothalamus. In addition to genetic factors, various possible environmental influences and an autoimmune origin have been identified as triggers for the development of this disease.

Narcolepsy is diagnosed on the basis of a patient's medical history, sleep medicine analyses and laboratory tests. Aside from advice on how to modify behaviour to mitigate this specific condition and help with managing it, the therapeutic approach for dealing with narcolepsy primarily involves medicinal treatment strategies. The differential diagnosis of daytime sleepiness covers an extremely wide range of sleep-wake disorders. These include sleep apnoea syndrome, behaviour-related sleep deprivation and psychiatric illnesses. Daytime sleepiness also occurs in association with many neurological diseases, such as Parkinson's. The interdisciplinary approach adopted by SWEZ ensures that high-quality differential diagnoses and optimal treatments are provided for conditions with daytime sleepiness as their main symptom. As a nationally and internationally recognised centre for narcolepsy, SWEZ offers many years of experience and exceptional expertise in diagnosing, treating and researching this condition. Prof. Claudio Bassetti, Dr. Ulf Kallweit



#### INTERDISCIPLINARY COOPERATION Neurology Diagnosis and

treatment of adult narcolepsy patients Prof. Claudio Bassetti Dr. Ulf Kallweit Prof. Johannes Mathis Markus Schmidt, MD, PhD **Neuropaediatrics** Diagnosis and treatment of paediatric narcolepsy patients Dr. Susi Strozzi **Psychiatry** Treatment of

psychiatric comorbidities and psychiatric differential diagnosis Dr. Wolfgang Schmitt **Pulmonary medicine** Treatment of internal medical comorbidities and internal medical/ pulmonary differential diagnosis Dr. Sebastian R. Ott

Your contact Prof. Claudio Bassetti

### NARCOLEPSY – A NEUROIMMUNOLOGI-CAL DISEASE

Dr. Ulf Kallweit, Prof. Claudio Bassetti

n the case of narcolepsy (with cataplexy), hypocretin (also known as orexin) has a key role to play: the condition is associated with the destruction of hypocretin cells in the hypothalamus, resulting in a measurable loss of hypocretin in the cerebrospinal fluid<sup>1</sup>. Hypocretin is particularly important for maintaining stable sleep and wakeful states.

Nowadays, it is believed that a neuroimmunological pathological mechanism is responsible for destroying the hypocretin cells. The haplotype HLA-DQB1\*0602 has been found to be present in more than 98% of people suffering from narcolepsy with cataplexy. The HLA (human leukocyte antigen) system forms part of the immune system.

Various studies have reported a link between certain infections (streptococcal infections, H1N1 viruses) or the H1N1 vaccine Pandemrix® and the onset of narcolepsy. The theory put forward is that a faulty immune response to certain specific environmental factors (e.g. streptococci) occurs in patients with a certain genetic disposition (HLA, etc.). The similarity between certain surface components of streptococci and hypocretin cells leads to a cross-reaction, causing the immune system to identify hypocretin cells as «foreign» and therefore attack them<sup>2</sup>.

Our own research results have supported this concept of an immune-mediated (possibly autoimmune) disease.

### Causal and symptomatic treatment

At the moment, there is no causal treatment available for narcolepsy, partly because the underlying pathological mechanism has not yet been fully explained. Trials involving immunoglobulins have only shown a lasting improvement in symptoms – objectively speaking –

in a few individual cases. It seems conceivable that causal (probably immunomodulatory) therapeutic approaches will be developed in future based on further knowledge gained from neuroimmunological research.

At the moment, narcolepsy is treated using various symptomatic therapies, mainly involving the use of stimulants (e.g. modafinil, methylphenidate) or anticataplectic drugs (e.g. sodium oxybate).

#### Histamine treatment with pitolisant

One new symptomatic treatment option involves using pitolisant.

Various recent studies indicate changes in histamine and histamine cells in cases of narcolepsy.

We compared the histamine levels in the cerebrospinal fluid of narcolepsy patients and other people who suffer from severe daytime sleepiness with those of healthy people not experiencing sleepiness. The sleepy patients were found to have lower histamine levels <sup>3</sup>.

Activating the histamine neurons via the histamine H3

receptor increases wakefulness. Studies have successfully tested the effectiveness of pitolisant, an inverse agonist of the histamine H3 receptor, as a treatment for daytime sleepiness in cases of narcolepsy<sup>4</sup>.

Pitolisant is currently only used as part of what is known as a «compassionate use» programme.

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### SLEEP BOOSTS MEMORY AND PREVENTS DEMENTIA

Dr. Simone Duss, Prof. Katharina Henke

hy do we sleep? Sleep researchers still have no clear answer to this question. Sleep takes up around a third of our lives and occurs in all living creatures. It therefore cannot be considered a dispensable luxury - it must play an important role in the development and regeneration of our bodies and brains. One aspect of sleep that has been well-researched is its function of embedding information we have learned in our memory. Currently, scientific discussions are also focusing on the role of sleep in clearing harmful metabolites from the brain. This article briefly outlines why these research findings could in future be beneficial for people with brain damage or dementia.

Studies show that sleep helps to firmly root what we have learned during the day in our memory so that it is easier for us to recall it the following day. There are two theories on how this memory consolidation might be achieved, both of which are substantiated by findings from animal and human research. The active memory system consolidation theory suggests that the neurons in the hippocampus and the cerebral cortex that were particularly active when new information was being learned are reactivated during deep sleep<sup>1</sup>. This reactivation strengthens the connections between these neurons, thus facilitating our ability to recall the information the next day. The synaptic homeostasis theory states that the neurons that were active in the daytime regenerate during sleep<sup>2</sup>. In this process, connections between nerve cells that were particularly active during the day are maintained while weaker connections perish. Information that has been learned well is thus stored in the long-term memory, and the regeneration process makes us receptive to learning new content again. The fact that sleep boosts our ability to acquire and remember new knowledge has significant implications for neurorehabilitation following a brain injury<sup>3</sup>.

After suffering a stroke, for example, many patients face the challenge of relearning lost or impaired language or motor skills. Which sleep-related mechanisms are important for relearning of lost or impaired functions and for successful rehabilitation following a stroke is subject of our research (SNSF Sinergia project of the Universities of Bern, Zurich and Milan).

Current research in animals and humans has produced some fascinating findings: metabolites that accumulate in the brain during the day and that can have harmful effects are cleared away more quickly during sleep than when we are awake<sup>4</sup>. This also applies to the protein beta-amyloid, which increasingly builds up in the brains of people with Alzheimer's disease. Does this mean that sleep counteracts neurodegeneration? And does poor sleep - something that often affects Alzheimer's patients - foster the deterioration of memory associated with this disease? This hypothesis is supported by findings from a research group at the University of California, Berkeley: those healthy study participants with the most beta-amyloid deposits in the frontal lobe of the brain experienced the least deep sleep and produced the worst results in terms of memory performance on the following day<sup>5</sup>. Whether and how sleep promotes the clearance of metabolites in the brain is something experts at SWEZ are investigating as part of a SNSF project led by Prof. Roland Kreis from the Department of Clinical Research at the University of Bern.

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Using brain perfusion imaging, it is possible to make areas of the brain in which beta-amyloid deposits have accumulated indirectly visible. The blue areas indicate parts of the brain where the cerebral blood flow is restricted (due to beta-amyloid deposits and changes in the metabolism of the brain).



### THE CEREBRAL MECHA-NISMS OF ACTION OF SLEEP AND WAKEFUL-NESS

Beyond the structure, function and disorders of sleep

#### Prof. Antoine Adamantidis

leep and wakefulness consist of both ultradian (i.e. shorter than the 24hour day) and circadian (i.e. corresponding to the 24-hour day) periods. Wakefulness is a conscious state in which our ability to perceive and interact with our surroundings is maintained. Sleep is usually divided into two phases -NREM or slow-wave sleep and REM sleep – which can be distinguished from one another and from the state of wakefulness using the techniques of EEG (electroencephalography) and EMG (electromyography).

One of the biggest challenges in neuroscientific research is the task of identifying the neuronal networks that regulate sleep and wakefulness. In the past few decades, researchers have pinpointed neuronal clusters whose activity correlates with these respective states. These include numerous systems that promote wakefulness, which are spread throughout the brain (hypocretin/orexin, norepinephrine, serotonin, histamine



Brain oscillations in the brain of a mouse during sleep.

and acetylcholine). Networks active during NREM sleep contain thalamocortical connections and inhibitory neurons of the anterior hypothalamus. while certain connections in the lateral hypothalamus (MCH) and brain stem are predominant in REM sleep<sup>1,2</sup>. One of the key research objectives is to investigate the function of these networks in terms of inducing, maintaining and terminating NREM and REM sleep or wakefulness.

Another fundamental aim is to develop an understanding of the purpose of sleep. Possible functions include helping brain structures to mature, consolidating learning and memory, and enabling the metabolisation of breakdown products («brain clearance») <sup>3</sup> (p. 36). These functions may be performed differently in each phase of sleep.

The new research strategy combining optogenetics (p. 19), genetically manipulated mouse models, and in-vivo/vitro electrophysiology has highlighted new aspects of sleep-wake cycles, including with regard to memory consolidation. These research approaches will help to shed light on the mechanisms of the sleep-wake cycle in healthy brains and those affected by a pathological condition, and to generate an understanding of sleep disorders in connection with neurological diseases such as stroke, epilepsy, Alzheimer's, Parkinson's, schizophrenia, attention deficit disorder and depression<sup>4</sup>.

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#### **PAEDIATRIC SLEEP**

### WHEN YOUNG CHILDREN SIMPLY CAN'T SLEEP

Sleep disorders are common in children and young people. The disorders and sleep-related illnesses that are known to affect adults can also occur during childhood and adolescence. Even at a young age, obstructive sleep apnoea syndrome, mainly caused by tonsillar hypertrophy, is the most common organic cause of restless night's sleep. Sleep disorders triggered by negative associations with going to sleep or inconsistent parenting are the most common behaviour-related disorders amongst young children, with poor sleep hygiene and delayed sleep-phase syndrome occurring most frequently amongst adolescents. Secondary effects of sleeping disorders, such as problems at school, social adjustment disorders, obesity or systemic inflammatory responses must be avoided by means of appropriate therapy. The age-specific characteristics of sleep mean that symptoms, causes and courses of treatment can vary significantly between children and adolescent patients and those of adult age. It is therefore important for children and young people with sleep disorders to be under the care of a team of specialists who are extremely well-versed in the physiology and development of sleep. SWEZ runs a special sleep clinic for children and young people, in which a team of neuropaediatricians, paediatric pulmonologists and child and youth psychiatrists work together on an interdisciplinary basis. They also cooperate closely with colleagues who specialise in adult sleep medicine, paediatric surgery and ENT medicine. Depending on the age of the children concerned, sleep studies are carried out either in the children's clinic where the pediatric clinical consultations are performed, or in the SWEZ sleep laboratory. This ensures that children, young people and their families receive the appropriate care for their age. Dr. Susi Strozzi



INTERDISCIPLINARY COOPERATION Neuropaediatrics Dr. Susi Strozzi Paediatric pulmonology Dr. Carmen Casaulta Child and youth psychiatry Dr. Christian Wüthrich Neurology Prof. Johannes Mathis

Your contact Dr. Susi Strozzi

### SLEEP AND MENTAL HEALTH DURING ADOLESCENCE

Leila Tarokh, PhD

S leep and psychiatric disorders are closely interrelated and have a mutual effect on one another. Sleep-related factors are included in the official diagnostic criteria for a variety of mental illnesses, such as depression, post-traumatic stress disorder or even generalised anxiety disorder. 50 to 80% of patients with psychiatric conditions suffer from chronic sleep disorders. The most common problems are difficulties getting to sleep or sleeping through the night.

There is increasing evidence that sleep disorders increase the risk of developing a psychiatric disorder or promote the onset of such conditions. For instance, a number of studies have shown that individuals who suffer from insomnia are at a higher risk of becoming depressed.

Sleep and mental health are also closely linked during adolescence. Various psychiatric illnesses begin even at this early stage in life and are accompanied by changes in sleep behaviour, in the same way as in adulthood. For example, a study of adolescents undergoing inpatient treatment revealed that 95% of them showed atypical sleep behaviour <sup>1</sup>.

Sleep undergoes fundamental changes during adolescence. One of the clearest examples of this is a 40% or so reduction in low-frequency waves with high amplitudes within a short period of time - just a few years<sup>2</sup>. At the same time, there is a noticeable, behaviour-related decrease in sleep duration. This is due to a tendency amongst adolescents to go to bed later and later while still getting up at the same time. In addition, problems with sleeping become more frequent at this age. In one study, for example, 26% of young people aged between 12 and 18 indicated that they have trouble going to sleep, while 31% reported having difficulty sleeping through the night on at least one occasion within the previous two weeks<sup>3</sup>.

The development of sleep and sleep disorders from adolescence through to adulthood varies significantly from one individual to another. A better understanding of the influencing factors at work is therefore crucial. What triggers changes in a person's normal sleep architecture, and when and why do sleep disorders arise during adolescence? To find answers to these questions, we are currently conducting a study on twins in an attempt to unravel the genetic and environmental influences on sleep physiology (measured using EEG monitoring) and behaviour in young people (measured using actigraphy).

As part of SWEZ, our aim is not only to describe the change in sleep amongst healthy adolescents, but also to venture beyond this and develop a better understanding of the effect of psychiatric illnesses on sleep. To this end, we carry out a wide range of analyses using techniques such as sleep and wake EEG, fMRI, actigraphy, cognitive tests and surveys based on self-assessment and external evaluation. By investigating the sleep of both healthy adolescents and those with psychiatric disorders and their ability to function at various levels, we hope to play a part in improving the treatment options available. Adolescence could be an ideal time for intervention, as patterns of behaviour only develop slowly at this stage and early interventions could potentially have a positive impact on the progression of various diseases. Interventions based on sleep offer hitherto untapped potential for developing resilience during adolescence and add to the range of therapies available to young people with psychiatric illnesses.

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Alarming things sometimes happen in dreams. Painting what they have dreamed can help people come to terms with these bizarre impressions. Prof. Johannes Mathis talks to a patient about her nocturnal experiences.

#### **DREAMS AND PARASOMNIAS**

### BED AS A CRIME SCENE: HOW REAL DRAMAS SOMETIMES PLAY OUT DURING SLEEP

When we dream, our thought processes carry on in our sleep. Dreams are often bizarre because the temporal and spatial connection between thoughts and fragments of memory become separated while we slumber. This dissociation between brain areas active during sleep and wakefulness leads to unusual patterns of behaviours during sleep, known as parasomnias. Most people dream regularly, even if they cannot remember doing so. Visual impressions are more common than acoustic ones during dreams, whereas other sensory phenomena, such as tactile sensations, smells or tastes, are rare. However, around half of our dreams are accompanied by emotional content. The triggered emotions may be happy ones, but they can also include anger, anxiety or stress.

During REM sleep, inhibition of the muscles at the spinal cord level prevents dream enacting behaviour. In the absence of this mechanism, movements occur corresponding to dream contents. Aggressive dreams can cause those experiencing them to injure themselves or others, which raises difficult legal questions in the case of criminal offences committed during sleep. "Attacks" by sleeping people involving complex behaviours or even sexual assaults on sleeping partners and aggression with or without wild dreams, require an interdisciplinary investigation. Such events could be triggered by epileptic seizures, psychiatric disorders or parasomnias. At SWEZ, such cases are discussed on an interdisciplinary basis amongst epileptologists, sleep medicine specialists, psychiatrists and, if necessary, Inselspital legal experts. REM sleep behaviour disorder can be an early sign of certain brain diseases, such as Parkinson's. An interplay between parts of the brain associated with wakefulness and sleep is also believed to occur in sleepwalking, where rationality and memory are largely absent even though the motor skills of the individual are working relatively well. Prof. Johannes Mathis



#### INTERDISCIPLINARY COOPERATION Neurology

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### EPILEPTOLOGY AND ASSESSMENTS PRIOR TO EPILEPSY SURGERY SURGICAL INTERVENTION IS NO LONGER THE EXCEPTION

Epilepsy is a pathologically altered chronic condition of the brain that increases the probability of epileptic seizures occurring. There are numerous possible causes of epilepsy, ranging from genetic malfunctions at the ion channel level to post-traumatic changes in the brain. Epilepsy is therefore one of the most common chronic neurological diseases. The high priority given to this condition in day-to-day clinical activities is due not only to the striking prevalence of epilepsy in Switzerland (it affects some 100,000 patients), but also - more importantly - to the extremely dangerous nature of epileptic seizures. A single seizure can be fatal. The primary aim of epilepsy treatment is therefore to ensure that patients are completely free from seizures while enjoying the best possible quality of life. This ambitious goal can only be achieved with an optimal treatment programme that combines drug-based medication and non-pharmacological therapies and is adapted to the individual patient concerned. All such types of treatment are available at SWEZ, which offers an exceptionally wide range of non-pharmacological methods in particular. The option of investigations involving extra- and intracranial long-term EEG video monitoring prior to epilepsy surgery is especially worth highlighting in this regard. The aim of these comprehensive recordings is to precisely locate the epileptogenic part of the brain and to assess whether this can be surgically removed without any negative neurological consequences. Another option is detailed sleep analysis, which provides the basis for detecting and successfully treating any existing conditions that increase the risk of seizures, such as sleep apnoea syndrome. Likewise, the uniquely close cooperation between epileptologists and sleep medicine specialists at SWEZ often also makes it possible to improve daytime sleepiness in epilepsy patients who are free from seizures, thereby enhancing their quality of life. Prof. Kaspar Schindler



**INTERDISCIPLINARY** COOPERATION Neurology Epileptological assessments, including EEG Prof. Kaspar Schindler Neurosurgery Electrode implantation, epilepsy surgery Prof. Claudio Pollo Neuroradiology Functional and structural imaging Prof. Roland Wiest Neuropsychology Pre- and post-operative neuropsychological assessments Dr. Dörthe Heinemann **Psychiatry** Pre- and post-operative psychiatric evaluation Dr. Wolfgang Schmitt **Neuropaediatrics** Diagnosis and treatment for epileptic children Dr. Susi Strozzi

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### TRANSLATIONAL EPILEPTOLOGY AND INTRACRANIAL EEG

Prof. Kaspar Schindler

social burden Epilepsy is characterized by a persistent state of the brain that

predisposes to the occurrence of transiently uncontrolled neuroglial activity, which manifests as epileptic seizures. Epileptic seizures may be deadly and the unpredictability of their occurrence exerts constant stress on the patient. In Switzerland 1% of the population suffers from epilepsy and up to 10% have an epileptic seizure during lifetime. Epilepsy is thus one of the most prevalent neurologic disorders.

#### **Demand for biomarkers** It is known that epileptogen-

esis, that is the pathologic processes rendering a brain epileptic - for example after trauma or stroke-, often takes months to years. There is an urgent need for biomarkers that identify those patients who are most likely to develop epilepsy in order to test novel prophylactic treatment strategies aimed at interfering with epileptogenesis. Once epilepsy has developed we know that many seizures are not adequately remembered by the patients. Therefore seizure counts by patients, which is most often used as outcome measure in current treatment studies, are not reliable. Thus it is mandatory to develop novel biomarkers that allow to efficiently and accurately monitor persons at risk for or patients suffering from epilepsy.

#### Ambulatory Monitoring

An important goal at SWEZ-SITEM (p. 54) will be to develop, test and apply innovative methods and devices that assess and modulate the electric activity of the human brain by extra- and intracranial probes. Intracranial EEG in particular provides data with unrivaled signal to noise ratio and allows sophisticated quantiative eeg analysis such as application of methods from network science (Figure X).

Specific signal features will be evaluated as biomarkers for the risk of seizure occurrence and to unravel seizure dynamics (p. 49), i.e. how epileptic seizure start, propagate and terminate. Their use for detecting epileptogenesis and for monitoring treatment effects in an ambulatory setting has the potential to revolutionize the way epilepsy patients are treated in the future.



Functional networks derived from interseizure iEEG signals. Directed connectivity between all pairs of iEEG signals (left) recorded from a patient suffering from pharmaco-resistent right temporal lobe epilepsy is represented by a matrix (middle). This connectivity matrix is then used to construct and visualize the functional network shown on the right, where nodes represent iEEG signals and arrows the direction and strength of their connectivities. The pathologic right temporal lobe is characterized by strongly increased connectivities.

### THE DYNAMICS OF EPILEPTIC SEIZURES

Prof. Kaspar Schindler

he defining characteristic of epilepsy is the spontaneous and unpredictable occurrence of seizures. To improve the diagnosis and treatment of epilepsy, it is crucial to gain a better understanding of the dynamics of epileptic seizures. To this end, experts at SWEZ are investigating the intracranial EEG signals recorded during pre-operative investigations using modern quantitative analytical methods such as those developed in physics for studying complex systems<sup>1</sup>.

A representative example of this type of analysis is pictured on the bottom right. The top half of the picture shows an intracranial EEG signal from the region where the seizure originates. It is clear to see how the amplitudes initially increase and then decrease again towards the end of the seizure. The bottom half features the spectrogram of this signal, which helps to record rapid oscillations. Rapid oscillations typically occur shortly after the start of a seizure and are an excellent biomarker for epileptogenic brain tissue<sup>2</sup>.

The yellow line superimposed onto the spectrogram shows the extent to which the EEG signal pictured is synchronised with all the other EEG signals. It is clear that the synchronisation is weakest during the rapid oscillations and only increases as the sei-

zure progresses, reaching its peak at the end of the seizure. These analyses support a new concept, which has also been co-developed over the past few years by the SWEZ research group, whereby pathologically altered parts of the brain are disconnected at the start of an epileptic seizure and then resynchronised with the rest of the brain during the course of the seizure. The increase in synchronisation helps to bring the seizure to an end<sup>3</sup>.

As this example shows, quantitative EEG analyses help to develop a better understanding of the pathophysiological principles behind the origin, distribution and termination of epileptic seizures. However, these analyses also enable the experts at SWEZ to characterise the epileptogenic areas of the brain more objectively, thus putting them in a better position to plan surgical treatment for epilepsy. Mathematical analyses of intracranial EEG signals are a prime example of the translational and systems-oriented research carried out at SWEZ with the overriding aim of improving patient treatment.



Literature: <sup>1</sup>Rummel C, Goodfellow M, Gast H, et al, Schindler K (2013). A systems-level approach to human epileptic seizures. Neuroinformatics 11:159–73. <sup>2</sup> Jiruska P, de Curtis M, Jefferys JG, et al, Schindler K (2013). Synchronization and desynchronization in epilepsy: controversies and hypotheses. J Physiol 591:787–97. <sup>3</sup> Zubler F, Steimer A, Gast H, Schindler KA (2014). Seizure termination. Int Rev Neurobiol 114:187–207.



### ANNEXE NETWORKS BERN NETWORK FOR EPILEPSY, SLEEP AND CONSCIOUSNESS (BENESCO) A national platform for scientific exchange

Innovative research relies on networking, interdisciplinary teamwork and training and continuing education for students and doctoral students. With this in mind, the Bern Network for Epilepsy, Sleep and Consciousness (BE-NESCO) was founded in 2013 on the initiative of Bernbased researchers and clinicians also working for SWEZ and ZEN.

#### Promoting an interdisciplinary approach

BENESCO aims to support multidisciplinary and translational research on animals and humans in the domain of epilepsy, sleep and consciousness, and to promote the transfer of knowledge between fundamental and applied research in this area. Regular meetings are held to provide an opportunity for scientific exchange between what currently amounts to 20 research groups from the fields of neurology, pulmonary medicine, biology, psychiatry and psychology. These events also include lectures designed to further the training and continuing education of young researchers. BENESCO organises a Winter Research Meeting and an Alpine Sleep Summer School. The Winter Research Meeting serves as a platform for scientific exchange between the 20 research groups involved in the network and for developing joint projects. The Summer School is aimed at



providing training and continuing education opportunities for young scientists and clinicians with an interest in sleep medicine.

### BENESCO boasts more than 22 ongoing SNSF projects

The group leaders and members of BENESCO work at institutions such as the Universities of Bern and Fribourg, the Inselspital Bern, the Neurocenter of Southern Switzerland in Lugano, and the centers for sleep medicine in Aargau, Lucerne and Solothurn (Clinic Barmelweid, KSM Lucerne, ISZ Solothurn). Their research is largely funded by the Swiss National Science Foundation (SNSF), their own institutions or endowments. More than 22 SNSF projects are currently being carried out by BENESCO research groups.

Further information: BENESCO Winter Research Meeting (www.benesco.ch) ASSS Alpine Sleep Summer School (www.sleep-summer-school.ch)



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#### ANNEX: NETWORKS SWISS INSTITUTE FOR TRANSLATIONAL AND ENTREPRENEURIAL MEDICINE (SITEM-INSEL)

### Translational and Entrepreneurial Medicine for disorders of sleep, epilepsy and consciousness

The aim of the newly founded Swiss Institute for Translational and Entrepreneurial Medicine (SITEM-insel), which will be located on the Insel Campus, is to establish, operate and develop a National Center of Excellence for Translational Medicine and Entrepreneurship in Bern. Here translational medicine denotes the modern, process-oriented discipline that aims to translate new findings and products resulting from industrial development and basic research into clinical applications. It seeks to professionalize the essential interaction between basic science researchers, clinicians, regulatory bodies and investors. The SWEZ-SITEM-team will be strongly engaged in building all of these three approaches, motivated by the increasing prevalence of neurologic disorders.

#### The Threat of Neurologic Disorders

Neurologic disorders cause direful individual suffering and they impose a tremendous economic burden on a progressively overaged society. One important reason for the devastating effects of most neurologic disorders is their chronic time course. On one hand, once a neurologic disorder manifests it may persist for many years or even the rest of the patient's life. On the other hand, a seemingly sudden manifestation may emerge from pathophysiologic processes that have been evolving for a long time period and might have been averted by early treatment.

#### The Need for New Technology

To better understand the dynamics of neurologic disorders, we urgently need new devices that generate "big data" recorded over long time periods. For practical and economic reasons such data cannot be recorded at hospitals. This new type of data acquisition has to be implemented in the natural environment of patients or persons at risk to develop a neurologic disorder.

#### The Translational Future of Neurology

The future of neurology will depend on successful translational research. New biomedical devices have to be developed that record and analyse biomarkers that allow early diagnosis, swift treatment and accurate monitoring of the interventions effects. These devices have to be tested in model systems and in controlled environments, before they are applied under real-world conditions. The SWEZ-SITEM-team strives for enabling this translation of new neuro-medical devices from the lab to the patients environment to better monitor disorders of sleep, epilepsy and consciousness.

#### SWEZ SITEM TEAM MEMBERS

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#### ANNEX: NETWORKS CLINICAL NEUROSCIENCE BERN (CNB)

### Interdisciplinary collaboration is pivotal to success in neuroscience research

Clinical Neuroscience Bern is an interdisciplinary consortium of research groups from different fields. The main purpose is to connect neuroscientific researchers, promote research quality, and increase the clinical impact at Bern.

### Promote knowledge, communication, collaboration

Established by the faculties of medicine and human science in 2004, Clinical Neuroscience Bern will further pursue its aim to promote knowledge, communication and collaboration between related fields of neuroscience. At present, it includes more than 150 researchers involved in clinical and translational neuroscience in a variety of disciplines such as neurology, psychiatry, psychology, neurosurgery, neuroradiology, neurophysiology, neurobiology and neurogenetics. Interested scientists from other faculties are also welcomed.

#### More than 50 Research Groups

Currently, 66 research group leaders and more than 50 research groups are involved in clinical and cognitive neuroscience. Through functional, goal-oriented cooperation,

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they contribute to the diversity and strength of the network.

Further information: www.neuroscience.unibe.ch

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