Birgit Frauscher – Michael Prize 2019

Dr. Frauscher's research awarded with the Michael Prize 2019 focused on the study of the important interactions between epileptic activity and sleep as well as the development of normative values in the awake and sleeping human brain. For her research, she exploited the method of stereo-electroencephalography which offers the unique opportunity to directly record neuronal activity in humans. In the work "Facilitation of epileptic activity during sleep is mediated by high amplitude slow waves", Dr. Frauscher and colleagues challenged the paradigm that it is non-rapid eye movement (NREM) sleep itself, which activates epileptic activity during sleep, but that it is in fact specific transients present during, the so-called *sleep slow oscillations* which activate epileptic activity. In physiological conditions, sleep slow oscillations are known to orchestrate sleep rhythms. The research team found that epileptic activity is enhanced during these oscillations. Furthermore, they found that pathological high-frequency oscillations, which are a novel marker of the epileptic focus show a specific coupling to these slow oscillations. This is important, as high-frequency oscillations are not only pathological in nature, but they occur also in physiological conditions. So far, the two entities could not be sufficiently separated. We showed that the coupling to slow waves might in fact contribute to do so. Interestingly, the timing of the coupling was suggestive of synchronization rather than hyperexcitability as underlying mechanism for the activation of epileptic activity during sleep (Frauscher B. et al., Brain 2015). A continuation of this research direction confirmed these first findings in a large cohort of 45 patients (von Ellenrieder et al., Epilepsia 2016). Moreover, the authors were able to show distinct sleep-homeostatic properties of physiological versus pathological high-frequency oscillations (von Ellenrieder et al., NeuroImage Clin 2017). In contrast, episodes with highest desynchronization as present during REM sleep with rapid eye movements had lowest rates of epileptic activity (Frauscher et al., Epilepsia 2016).

Research into sleep and epilepsy demonstrated further that presence of sleep spindles, one of the main characteristics of NREM sleep stage N2 is a sign of physiology as shown in the example of the hippocampus. In the work "Interictal Hippocampal Spiking Influences the Occurrence of Hippocampal Sleep Spindles", Frauscher and colleagues showed that hippocampal sleep spindles are a physiological phenomenon which rate is reduced in temporal lobe epilepsy and which rate is dependent on interictal spiking (Frauscher et al., Sleep 2016). Whether reduced hippocampal spindle rates cause memory problems in temporal lobe epilepsy is an open question.

The most recent line of research established normative values during wakefulness and sleep in the intracranial EEG ("Atlas of the normal intracranial electroencephalogram: neurophysiological awake activity in different cortical areas"). This work presents the first atlas on physiological intracranial EEG activity across the different states of vigilance and for normal versus high frequencies (Frauscher B. et al., Brain 2018; Frauscher B. et al., Ann Neurol 2018; von Ellenrieder et al., 2019 under review). This research demonstrated region-dependent variability in EEG activity across the different states of vigilance using quantitative EEG measures. It further showed that deep-seated brain structures show spectral peaks which differ from the baseline EEG. Finally, it shows that there is a huge heterogeneity in rates of high-frequency oscillations, which can reach high values in primary eloquent cortical areas. These baseline values will be of great importance to better disentangle between physiological and pathological brain activity.

The conducted work contributed to the understanding of the interactions between sleep and epilepsy investigating sleep microstructure elements and to create an atlas of physiological brain activity. The findings of the enhancing and suppressing mechanisms of the different sleep microstructural elements might open the avenue to interesting new developments for drugs for patients with epilepsy. The development of an atlas of normal physiological intracranial EEG activity can be exploited to differentiate normal from pathological brain activity, which is a novel approach that has never been utilized in the context of intracranial EEG before. Moreover, data can be used as direct measurements for validation of the various non-invasive mapping procedures. The results of this work are directly translatable to clinical practice, and they might be extremely valuable for improving surgical treatment options for the 30% of patients with drug-resistant epilepsy, as they have potential to better delineate the epileptic focus and to develop better non-invasive evaluation methods being able to avoid the use of intracranial electrodes in a subgroup of patients (currently approximately 20% of patients undergoing subsequent epilepsy surgery need intracranial EEG evaluation).