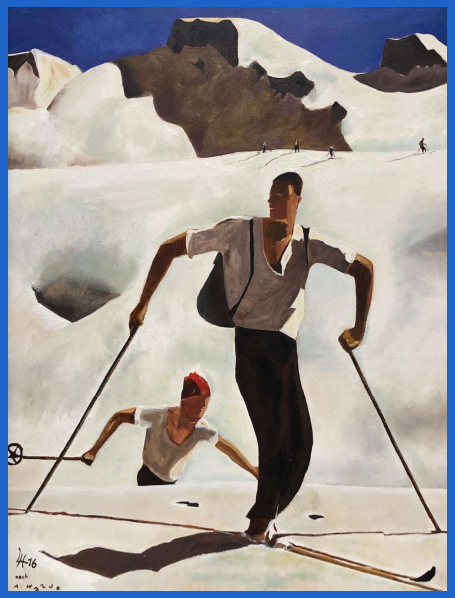
FACULTY OF MEDICINE AND HEALTH SCIENCES

NEUROPHYSIOLOGICAL CHARACTERISTICS OF DRUG RESISTANT EPILEPSY PATIENTS AND RESPONSE TO VAGUS NERVE STIMULATION



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Summary

Epilepsy affects over 50 million people worldwide. In 30% of patients with epilepsy seizure freedom cannot be achieved with antiepileptic drugs (AEDs). These **drug resistant epilepsy (DRE) patients** represent a particular vulnerable subgroup. When patients are considered unsuitable candidates for epilepsy surgery, they may be treated with **vagus nerve stimulation (VNS).** With VNS treatment more than 50% of DRE patients achieve a significant reduction in seizure frequency (>50% seizure reduction), but up to one third of patients do not respond to VNS. This thesis was conducted to investigate eligible neurophysiological parameters related to the mechanism of action of VNS – the so called **vagal afferent network**. These neurophysiological parameters could serve as predictive biomarkers and guide the pre-stimulation evaluation in the future.

In the first study, three neurophysiological parameters related to the vagal afferent network were evaluated and correlated with VNS response:

1.the cognitive evoked potential P3b, 2. heart rate variability (HRV), the variation of the time interval between consecutive heart beats, and **3. sleep** in particular sleep stages. We demonstrated that VNS responders had a higher amount of deep sleep (NREM3), significantly lower P3b amplitudes and significantly lower (high frequency power) HF HRV parameters prior to treatment. These findings suggest that the vagal afferent network shows variations between epilepsy patients and that these differences are related to treatment response.

In the second study, we investigated pre-ictal HRV parameters in DRE patients with focal seizures in correlation to VNS response. We found that VNS non-responders were characterized by a decrease in HRV parameters in the pre-ictal phase of focal seizures.

Based on the data of these two studies, we hypothesize that VNS responders are characterized by a higher amount of NREM3, a lower level of P3b amplitude, lower HF HRV (inter-ictal) and a preserved seizure-related autonomic balance.

In a third study, pre-ictal HRV in generalized seizures of DRE patients diagnosed with **Lennox-Gastaut syndrome** was investigated. In this study we found a significant sudden pre-ictal increase in HF HRV, a parasympathetic overdrive, in both VNS responders and VNS non-responders. This pre-ictal para-sympathetic overdrive was described in previous case reports in the event that led to **sudden unexpected death in epilepsy (SUDEP).** Further studies involving larger sample sizes are necessary to evaluate this potential biomarker for individual SUDEP risk determination.

Conclusions

- Drug resistant epilepsy patients show differences in neurophysiological investigations that are related to response to VNS.
- The integration of neurophysiological and neuroimaging techniques in a comprehensive model may allow individual VNS response prediction in the future.

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Curriculum Vitae

Stephanie Hödl became a licensed neurologist at the Johannes Kepler University Hospital (Linz, Austria) in 2011. She later joined the Department of Neurology at Ghent University Hospital in November 2011. In the following years, she subspecialized in epilepsy and sleep medicine. In addition to having a clinical position as staff member at the Department Neurology, she started a research position at the faculty of Medicine and Health Sciences, Ghent University. She became a certified expert in sleep medicine in 2017. She is (co)author of several A1 publications.

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