The exciting migraine brain: towards neurophysiological prediction of migraine attacks

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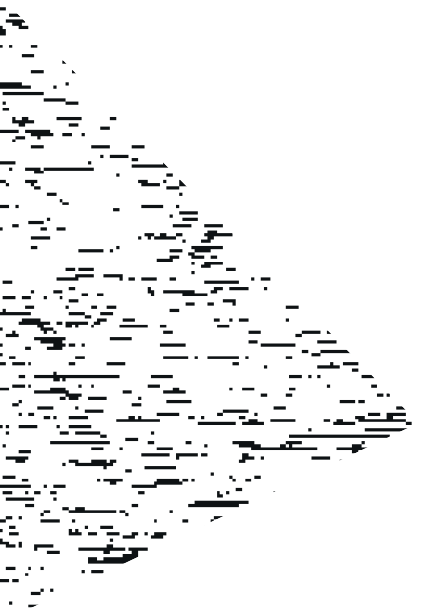
Appendices



Summary

The aim of this thesis was to identify functional biomarkers for migraine attack prediction based on neurophysiological readout parameters. Migraine is a paroxysmal brain disorder, whereby attacks of headache and associated neurological symptoms like nausea, vomiting and enhanced sensitivity to light and sound, are separated by periods without attacks. About one-third of people with migraine experience visual aura features, like expanding fortification spectra and/or scotoma's, before and during the start of the headache. In the International Classification of Headache Disorders, the number of headache and migraine days per month determines if a patient is considered as either episodic or chronic. Patients experiencing at least 15 headache days per month, of which at least 8 are migraine days, are classified as suffering from chronic migraine. It remains an enigma exactly when and why migraine attacks start. It has been hypothesized that episodic alterations in brain excitability may be an important factor in the initiation and cyclic recurrence of migraine attacks. The main focus of this work, therefore, was on the development of methodologies to measure brain excitability over the migraine cycle, with special emphasis on identifying changes in excitability of the visual system and the occipital cortex. Applying such measures over the course of a migraine cycle could help elucidate factors that initiate the migraine attack, and might lead to better (or better timing of) preventive measures. The research described in this thesis is divided into two parts. The **first part** reports on the development and application of several methodologies to measure excitability of the visual system including the cortex in migraine patients and a migraine mouse model. The **second part** consists of two studies employing transcranial magnetic stimulation (TMS) in combination with concurrent electroencephalography (EEG) recordings to provide direct measures of cortical excitability in migraine and epilepsy.

Part I focuses on visual system excitability as target for readouts that could help in predicting or indicating an upcoming migraine attack. Migraine patients often report (inter)ictal hypersensitivity to light, and visual pseudo hallucinations are the dominant symptom of a migraine aura. This suggests that migraine attack initiation

may involve fluctuations in responsivity of the visual system including the occipital cortex. Several methods can be used to examine occipital cortical excitability. Visual stimulation with flashes of light could be used to perturb the visual system in humans but also rodents, whereby the evoked potentials (VEPs) are evident in EEG recordings from the occipital cortex. In migraine patients, such measurements can be combined with subjective assessments of visual sensitivity. We developed a questionnaire to quantify self-reported sensitivity to light and patterns. In addition, for humans and for mouse migraine models, we developed several visual stimulation paradigms to be combined with EEG measurements.

Enhanced sensitivity to light (photophobia) and patterns is common in migraine and can – certainly when it is reported as painful – be regarded as visual allodynia. **Chapter 2** describes the development, validation and application of the Leiden Visual Sensitivity Scale (L-VISS), a 9-item questionnaire to assess sensitivity to light and patterns, with its content based on scientific literature and patient interviews. Construct validity (i.e., does the questionnaire measure what it aims to be measuring) was confirmed by comparing L-VISS scores to two behavioral tests. The light discomfort threshold was lower, whereas the pattern glare score was higher, with increased L-VISS scores. Comparing migraine subtypes (with versus without aura, chronic versus episodic) and states (during or outside an attack) between and within large groups of participants showed that L-VISS scores were increased for migraine with aura versus migraine without aura, for chronic versus episodic migraine, and during versus in between attacks. This pattern of increased visual sensitivity may reflect dynamics in cortical hyperexcitability between migraine subtypes and states, as also indicated by neurophysiological studies. The L-VISS has potential to be used in large-scale longitudinal assessments of sensitivity to light and patterns in patients, as it is quick to apply and not dependent on any recording technology. Besides, it could be used in conjunction with more elaborate neurophysiological recordings of visual cortex activity to provide a subjective assessment of changes in visual system excitability over the migraine cycle.

EEG studies in migraine patients show conflicting results indicating hypo- or hyperexcitability of the visual system. This can be caused by large inter-interindividual variation, differences in visual stimulation techniques and paradigms used, or intra-individual dynamics within the migraine cycle. To

understand the neuronal mechanisms underlying previously observed EEG features in patients, we strived to bridge the gap between the indirect measurements of visual system excitability by scalp EEG in patients and precise neurophysiological measurements in rodent models. In **Chapter 3** we studied EEG responses to visual stimulation in mice by combining local intracortical recording electrodes with simultaneous cortical surface EEG recordings. For clinical translation, we used transgenic mice carrying the human pathogenic R192Q missense mutation in the *Cacna1a* gene that causes familial hemiplegic migraine type 1 (FHM1). The *Cacna1a* gene encodes the α_{1A} subunit of presynaptic voltage-gated $Ca_V2.1$ Ca^{2+} channels, with the FHM1 R192Q mutation resulting in enhanced glutamatergic transmission and hyperexcitability. In freely-behaving transgenic and wild-type (control) mice, we investigated common clinical and newly developed visual stimulation paradigms consisting of flashes of light. FHM1 mutant mice displayed faster visual evoked potential responses following stimulation at varying intensities. The initial negative peak had a decreased amplitude with less neuronal suppression compared to controls. Flash light stimulation consisting of increasing stimulation frequencies between 10 and 40 Hz (the 'chirp' paradigm) showed enhanced photic drive in the beta-gamma bands (15–40 Hz). These results revealed a context-dependent enhancement of visual cortex excitability in the FHM1 mouse model. We hereby demonstrated that measurement of VEPs in transgenic mice can be applied to better understand changes in visual system responsivity in migraine.

One technique to study visual cortex excitability is the photic driving response in the EEG, as we also applied in the FHM1 mouse model in Chapter 3. In **Chapter 4**, we explore the use of the same 'chirp' visual stimulation paradigm to assess visual system responsivity including cortical excitability in migraine patients. Measurements were made in between attacks (interictal) and just before the next attack (pre-ictal). Using light flashes at increasing stimulation frequency, 'chirp' stimulation allows comparison of responsivity at various driving frequencies and related harmonic frequencies, which emerge in the EEG at multiples of the stimulation frequencies. This method thereby provides a quick way to examine photic driving over a range of stimulation frequencies. Our results showed that chirp readouts were repeatable over days to months, as demonstrated by repeated within-subject measurements. Interictally, responses to chirp stimulation were comparable

between controls and patients with migraine with and without aura. The 8 pre-ictal measurements (3 with, 5 without aura), which were recorded within 48 hours of an impending migraine attack, demonstrated an increased harmonic response in the beta band (22–32 Hz). Visual chirp stimulation proved a simple and reliable technique with potential to detect changes in visual cortex responsivity associated with the onset of migraine attacks.

Part II focuses on direct measurements of cortical excitability in migraine patients, in contrast to the indirect measurements with the L-VISS questionnaire or VEP recordings applied in the patient study in Part I. Visual stimulation is processed not only in the visual cortex, but also in pathways involving the retina, thalamus and superior colliculi. As such, VEP readouts are not only processed cortically, but also subcortically, thereby reflecting the excitability of the visual system as a whole. By employing transcranial magnetic stimulation (TMS) over the scalp with concordant EEG recordings, cortical excitability can be evaluated directly by studying TMS-evoked cortical responses. The TMS evoked potential (TEP) has been shown to be affected in conditions with implied underlying changes in cortical excitability like epilepsy and schizophrenia. **Chapter *5*** describes the first study investigating TMS evoked potentials in patients with migraine. Stimulation with a circular coil over the vertex, at stimulation intensities around the resting motor threshold, was applied to migraine patients with aura (in between attacks) and controls matched on sex, gender and resting motor threshold. Sham coil stimulation was employed to control for possible confounding effects of auditory and somatosensory activations by TMS. In migraine with aura, TEP waveforms were decreased in amplitude around the N100 peak at frontal and occipital electrodes. Decreased N100 peak amplitude is indicative of reduced cortical $GABA_B$-ergic inhibition, expanding previous – indirect – observations of cortical hyperexcitability in migraine.

Migraine and epilepsy are comorbid paroxysmal neurological disorders associated with altered cortical excitability. In **Chapter *6***, we investigated EEG phase clustering indices in response to transcranial magnetic stimulation in migraine with aura and juvenile myoclonic epilepsy patients, to identify potential functional biomarkers related to migraine with aura, epilepsy, or both disorders. Phase clustering in

response to TMS was significantly different between epilepsy (without medication) and controls. In one participant with epilepsy, the strength of phase clustering was inversely correlated with the dosage of antiepileptic medication. In migraine with aura, phase clustering did not differ from controls, indicating that the tendency for altered phase clustering is not shared between migraine and epilepsy.

Chapter 7 provides a general discussion of this thesis, with considerations for future clinical and preclinical translational research into migraine attack prediction using neurophysiological methods.