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## **The exciting migraine brain: towards neurophysiological prediction of migraine attacks**

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# Chapter 1

## General introduction





## Migraine

Migraine is a common, disabling brain disorder, characterized by recurrent attacks of headache associated with nausea and/or vomiting and hypersensitivity to sensory inputs like light (photophobia) and sound (photophobia).<sup>1</sup> Migraine attacks by definition last between 4 and 72 hours, and present with severe, often unilateral, pulsating headache.<sup>1</sup> Migraine is divided in two main subtypes: migraine without aura and migraine with aura; in about one-third of migraine patients, the headache is for the majority of attacks preceded by transient neurological symptoms (the migraine aura), mostly consisting of visual disturbances but sometimes also concerning motor or speech impairments.<sup>2</sup> The prevalence of migraine is different between men and women; in western countries, at least 12% of the general population suffers from recurrent migraine attacks, of which more than two-thirds are women mainly in the age of 35-50 years.<sup>3</sup> The worldwide impact of migraine on the quality of life is substantial,<sup>4</sup> making migraine the second leading cause of years lived with disability.<sup>5</sup> The median attack frequency is 1-2 per month and the median attack duration is one day; at least 10% of the patients have weekly attacks of 2-3 days each. Since the last revision of the International Classification of Headache Disorders,<sup>1</sup> migraine is divided into two subgroups based on the number of monthly migraine days and monthly headache days: patients with *episodic migraine* have fewer than 15 days of headache per month, patients with *chronic migraine* experience at least 15 headache days per month of which at least 8 migraine days.<sup>6</sup> Treatment of migraine remains challenging, with both acute and prophylactic treatment seldom resulting in complete remission of symptoms and often causing bothersome physical and cognitive side effects.<sup>7</sup> Ineffective treatment of episodic migraine using acute medication could even lead to chronification of migraine.<sup>8</sup>

Patients with migraine have an increased risk to develop comorbid disorders like depression and epilepsy, and vice versa.<sup>9,10</sup> Not only in adults,<sup>11</sup> but also in children with juvenile myoclonic epilepsy, migraine was more prevalent than in the general population.<sup>12</sup> Some antiepileptic drugs are also effective in the treatment of migraine,<sup>13</sup> in particular those that act by reducing neuronal excitability, suggesting shared mechanisms involving network hyperexcitability underlying attack initiation in migraine and epilepsy.<sup>13,14</sup> Also, mutations that underly a rare monogenic form

of migraine can cause epilepsy,<sup>15</sup> which can be modelled in animals and has indicated hyperexcitability as key mechanism.<sup>16</sup> Lastly, shared features of cortical excitability that were identified in people with migraine or epilepsy<sup>17</sup> further point to shared disease and treatment mechanisms involving disturbances in neuronal network excitability.

The combination of the unpredictable recurrence of migraine attacks, the migraine-related complaints in between and during attacks, side effects of migraine drugs and migraine comorbidities contribute to a substantial burden to people with migraine. While various clinical studies investigated whether in migraine functional processing in brain networks including the cortex is altered, no consistent results were obtained. With respect to structural abnormalities, only minor changes were found, in particular for migraine with aura.<sup>18</sup> Both clinical and experimental studies of migraine are hampered by the fact that clinical symptoms in migraine are largely subjective, which underscores the need of a reliable biological marker of migraine susceptibility, and clinical animal models of migraine with recurring attacks.

### **Phases of the migraine attack**

Migraine is a cyclical disease, where the headache occurs in episodes. Traditionally, four different phases are distinguished in a migraine attack.<sup>19</sup>

The premonitory, or prodromal, phase is characterized by a variety of symptoms; the most frequently reported premonitory symptoms are fatigue, weariness, phonophobia, yawning, stiff neck, gastrointestinal symptoms, mood and cognitive changes, temperature change, smell and taste distortion, and food craving.<sup>20,21</sup> The duration of the prodromal phase varies amongst patients and ranges from a few hours until one to two days.<sup>22</sup>

The aura phase occurs in about one in three migraine patients, and is characterized by transient neurological aura symptoms and ranges from 5 until 60 minutes.<sup>19</sup> The aura phase usually precedes the headache phase, but could also overlap with the start of the headache phase.<sup>23</sup> The visual aura is the most prevalent type of aura, with symptoms varying from simple flashes, lights to fortification scotoma ('zig-zag

patterns') or complex hallucinations. Other aura symptoms such as sensory, motor or speech disturbances rarely occur without coexisting visual disturbances.<sup>2</sup>

The headache phase is characterized by a moderate to severe, often unilateral throbbing headache, accompanied by nausea, vomiting and photo- and phonophobia, that typically lasts between 4 and 72 hours when no rescue medication is used. The headache can be aggravated by mild physical activity, and many patients require bedrest during an attack.<sup>24</sup>

The post-headache phase (also called postdromal or recovery phase) is typically characterized by decreased cognitive functioning, mood changes, drowsiness and tiredness. The postdromal phase is present in most migraine patients and can last from several days to one week.<sup>25</sup>

In addition to the symptoms related to the attack, migraine patients suffer from various types of complaints in periods between attacks, such as enhanced sensitivity to light.<sup>26</sup> Thus, the clinical manifestations of migraine are not limited to the headache episodes, which makes migraine a disease with a fluctuating representation of symptoms of which headache is only one.<sup>27</sup> The start of the 'migraine attack' remains elusive, and has been suggested to represent a tipping point in brain dynamics.<sup>28</sup> Any technique and readout parameter that can reliably indicate and/or explain the mechanisms underlying the onset of a migraine attack, opens up a new possibility for studies into migraine attack prediction and prevention. In this thesis, we focus on the development of a 'toolbox' of methods and paradigms aimed at identifying functional markers that can help predict an impending migraine attack.

## Migraine pathophysiology

Although the pathophysiological mechanisms for the different phases of a migraine attack are extensively studied in experimental models, little is known about how and why attacks actually begin in a patient.<sup>19</sup> Several mechanisms seem to contribute to migraine attack susceptibility, each with a distinct time scale (Figure 1). First, genetic predisposition, that may cause dysfunction of ion channels or transporters and subsequent neuronal hyperexcitability, can underlie lifelong disease

susceptibility.<sup>29</sup> Second, fluctuating factors like stress and relaxation, circadian and hormonal rhythms that all influence brain activity may temporarily increase the susceptibility to develop an attack.<sup>30,31</sup> Finally, patient-specific attack triggers – such as certain types of food, or extensive exercise – could be an additional mechanism leading to the migraine attack onset.<sup>22,32</sup>

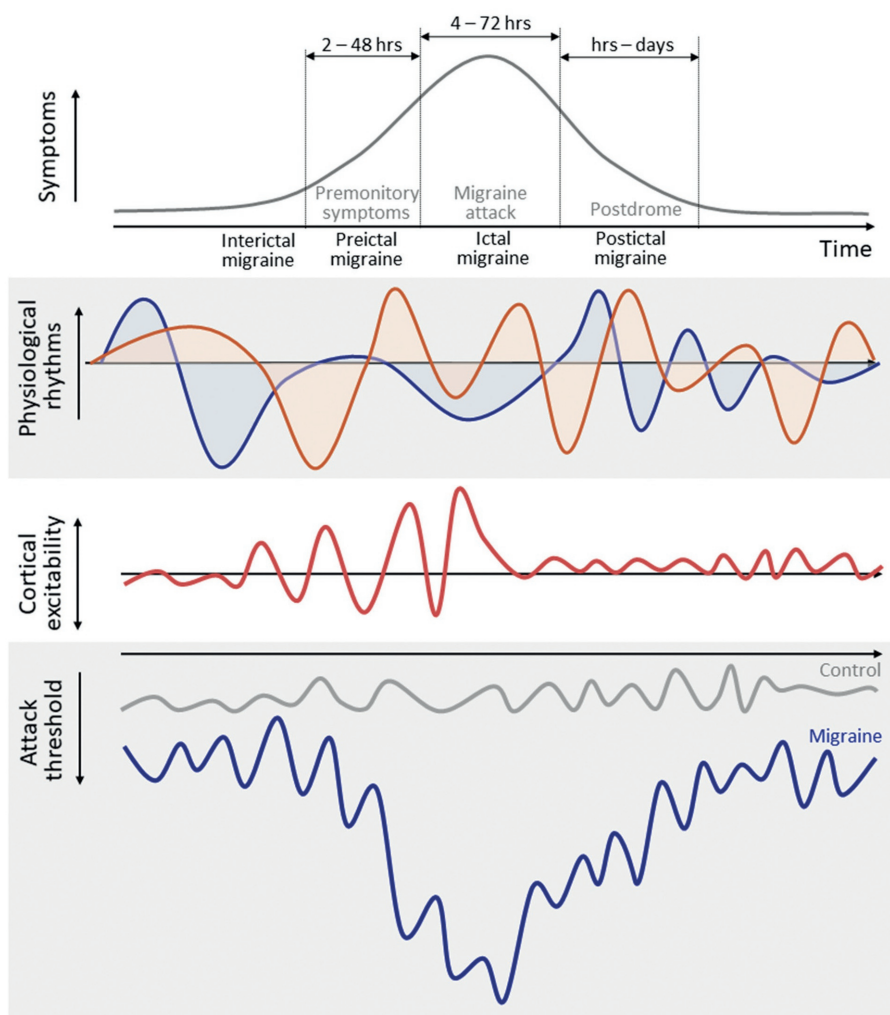
The genetic component of migraine has evidence in the hereditary predisposition demonstrated in family and twin studies, and population research.<sup>33</sup> Large genome-wide association studies indicated the involvement of multiple gene variants in the susceptibility to migraine, which (besides several variants linked to vascular function) include variants in genes associated with ion channel activity.<sup>33,34</sup> Genetics studies on the rare migraine form of (familial) hemiplegic migraine (FHM) identified three causal genes: *CACNA1A* (FHM1), *ATP1A2* (FHM2), and *SCN1A* (FHM3), which all encode proteins that affect ion activity in the brain.<sup>9</sup> At the cellular level, as shown by mouse studies for the cortex, a consequence of each of the three FHM mutations is that the release and concentration of the excitatory neurotransmitter glutamate in the synaptic cleft is enhanced, leading to increased neuronal excitability.<sup>9,16</sup>

The migraine headache is preceded by the premonitory phase, which is hypothesized to start in the hypothalamus.<sup>19,27</sup> Already before the presence of headache, neuroimaging demonstrated specific activation of the hypothalamus.<sup>36</sup> Common premonitory symptoms such as tiredness, yawning and concentration problems, and often reported migraine attack triggers like lack of sleep, stress and food deprivation are likely under control of the hypothalamus.<sup>19</sup> Also, several of the fluctuating factors involved in attack susceptibility, like circadian and hormonal rhythms, point toward hypothalamic involvement in the onset of a migraine attack.<sup>27</sup>

Visual aura symptoms are most likely caused by the phenomenon of cortical spreading depolarization (CSD).<sup>9</sup> Based on experimental studies in rodents, CSD is a propagating depolarizing wave of electrophysiological neuronal and glial hyperactivity, followed by depression of the formerly hyperactive neurons. When induced in the occipital (visual) cortex, CSD spreads frontally across the cortex. The speed of the depolarizing wave front is about 2–4 mm per minute, while the

subsequent neuronal depression might last several minutes to an hour.<sup>37,38</sup> The variety in the presentation of aura symptoms correlates with different cortical activation patterns, as demonstrated by neuroimaging.<sup>39</sup> Direct measurement of CSD during the aura phase is notoriously difficult. First, because of the unpredictability of attacks, and second, because the slow DC-features characteristic of a CSD are difficult to reliably identify from scalp EEG.<sup>40,41</sup> Using blood oxygen level-dependent (BOLD) neuroimaging as an indirect brain activity measure during the visual aura phase of migraine patients, brain activation patterns reflecting the predicted spreading and depolarizing nature of CSD were observed.<sup>42</sup> Using magneto-encephalography, a comparison of neurophysiological activity features during an induced (by visual pattern stimulation) and spontaneous visual aura with brain activity during rest showed spreading potential shifts indicative of CSD in the occipital cortex.<sup>43</sup>

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**Figure 1.** Migraine is a paroxysmal disorder, characterized by unpredictable recurrent attacks of headache and associated symptoms. The susceptibility to develop an attack is likely affected by the periodicity of several physiological rhythms (e.g., circadian, hormonal) and external factors (e.g., food intake, stressors) as well as a lower overall attack threshold due to genetic predisposition. Cortical excitability varies over the migraine cycle, and is likely affected by the underlying physiological rhythms as well as the acute impact of external factors on brain activity. The start of an attack might thereby be caused by the combination of patient-specific ‘migraine triggers’ in combination with a lowered threshold. (Figure based on Stankewitz & May (2009)<sup>30</sup> and Peng & May (2019)<sup>35</sup>)

The migraine headache is thought to result from activation of the trigeminovascular system, which involves dural nociceptive trigeminal afferents from trigeminal ganglion sensory neurons, and brainstem centers and thalamocortical areas involved in processing head pain.<sup>19</sup> The neurological symptoms that accompany a migraine headache, like photophobia, phonophobia and allodynia, appear to be the result of sensitization of neurons in and around the thalamus.<sup>19,44</sup> Which factors underlie the activation of the trigeminovascular system during a spontaneous migraine attack remains an enigma. Based on experimental studies, several factors can activate the trigeminovascular system at the dural level. These factors include the build-up of diffusible substances such as extracellular  $K^+$ , release of vasoactive mediators such as calcitonin gene-related peptide (CGRP)<sup>9</sup> as well as inflammatory mechanisms.<sup>19,45</sup> In animal experiments, CSD was demonstrated to be capable of activating the trigeminovascular system,<sup>46</sup> involving a neuroinflammatory response leading to activation of trigeminal afferents.<sup>47</sup> In addition or alternatively, CSD may also directly contribute to headache initiation via cortico-trigeminal projections.<sup>19</sup> In migraine without aura, where the presence of CSD is not indicated as in the aura phase, a ‘silent aura’ in subcortical brain regions might trigger the headache phase.<sup>44</sup> Also in the absence of a spreading depolarization, however, it is possible that overall hyperexcitability in neurons within the trigeminovascular system might lower the threshold for activating head pain pathways resulting in an attack.

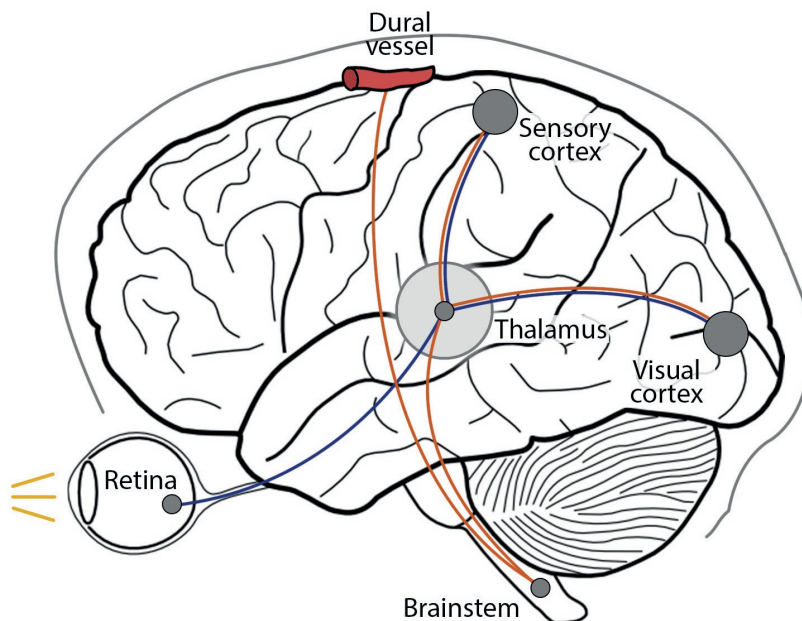
## Visual sensitivity in migraine

Multiple symptoms related to the migraine attack are linked to the visual system. For instance, visual stimuli such as flashing lights or striped patterns are commonly reported by patients to be triggers of a migraine attack.<sup>48,49</sup> Interictally, migraine patients with and without aura reported more optical illusions when looking at striped patterns, the so-called ‘pattern glare’, in comparison to healthy controls,<sup>50</sup> and also moving imagery was processed differently by migraineurs.<sup>51</sup> During and in between attacks, more than half of migraine patients experience enhanced sensitivity to light, i.e. ‘photophobia’.<sup>26</sup> Photophobia is one of the diagnostic criteria of migraine, not only in migraine with aura but also in migraine without aura.<sup>1</sup> Lastly, the migraine aura, when present, is almost always at first visual.<sup>52</sup>

Hyperexcitability of the visual cortex is suggested to underlie the visual sensitivity,<sup>53</sup> and may also prime the initiation of CSD.<sup>18</sup>

In between attacks, the visual cortex of migraine patients showed a more pronounced response, as measured by position emission tomography (PET), to stimulation by light compared to controls, that was even further enhanced by additional painful heat stimulation.<sup>54</sup> Such enhanced responsivity may be even more specific for migraine with aura patients, indicated by an increased BOLD activity in response to visual stimulation.<sup>55</sup> With similar study methods, it was shown that in migraine with aura, visual cortex activation also correlated positively with visual discomfort and photophobia.<sup>56</sup> In the pre-ictal phase, patients experiencing photophobia showed a larger enhancement of visual cortex activity (measured by PET) compared to patients with no photophobia symptoms.<sup>57</sup> During the attack, low intensity light stimulation which did not activate the cortex interictally induced measurable increases in BOLD activation of the visual cortex, and, to a lesser extent, also after headache relief.<sup>58</sup>

Several pathophysiological processes might underlie photophobia and other forms of visual sensitivity.<sup>44</sup> Visually-impaired migraine patients, who were capable of detecting light but had severe retinal rod-cone degeneration, still reported exacerbation of the migraine headache by light.<sup>59</sup> This led to the discovery, in rats, of dura-sensitive thalamic neurons that are indirectly responsive to light via input received from photosensitive retinal ganglions cells containing the photoreceptor melanopsin. These dura-sensitive and light-responsive thalamic neurons project further towards somatosensory and visual cortices, thereby representing an integration of light and painful stimuli (Figure 2).<sup>59</sup> In migraine patients, specific colors of light were found to either enhance (blue, red) or decrease (green) the headache pain, and visual flash stimulation with green light resulted in significantly smaller responses than stimulation with red and blue light flashes.<sup>60</sup> In rats, the light-responsive thalamic neurons were driven to a lesser extent by green compared to white, blue and red light, pointing towards an important role of the trigeminovascular system in visual sensitivity.<sup>60</sup> In addition, reversal of photophobia has been reported in several studies on efficacy of migraine drugs. Drugs that are able to abort migraine headache usually reverse photophobia, which suggests a shared mechanism involving activation of the trigeminovascular system.<sup>61</sup>



**Figure 2.** Neuronal pathways processing responses of the retina to light converge onto pathways processing pain signals from the dura towards the thalamus. This convergence proposedly worsens the migraine headache by projection of these thalamic neurons to somatosensory cortices involved in pain perception. In a similar way, enhanced sensitivity to light during a migraine attack might result from the same convergence, as thalamic neurons also project to visual cortices involved in the perception of light. (Figure based on work by Nosedá et al. (2011)<sup>61</sup>)

## Cortical excitability in migraine

An important hypothesis concerning mechanisms underlying migraine is the theory that the excitability of the cortex is specifically enhanced,<sup>30,53</sup> which may be most pronounced for the visual cortex given the often visual nature of the aura.<sup>42</sup> As for the rest of the brain, cortical excitability is affected by factors that influence neuronal function such as the balance in neuronal ion concentrations and the functioning of neuronal and astrocytic ion channels or transporters.<sup>62</sup> Intrinsic enhancement of neuronal excitability in migraine is likely to have a genetic basis, which is evident for the FHM mutations that are linked to dysfunctional ion channels which cause a

disturbed balance between glutamatergic and GABAergic transmission.<sup>18,63</sup> When measured using magnetic resonance spectroscopy, indeed enhanced glutamate levels,<sup>64,65</sup> and elevated levels of GABA have been measured in the brain of migraine patients.<sup>66</sup>

Several approaches have been developed to study in which way abnormal excitability of the cortex may play a role in migraine and the initiation of attacks, using neurophysiological, neuroimaging, metabolomic and animal model approaches.<sup>53</sup>

### **The FHM1 mutant mouse model to study cortical hyperexcitability in migraine**

Animal models are valuable tools to explore mechanisms of cortical dysfunction in the context of migraine. Translational approaches include the introduction of human pathogenetic mutations, such as the mutations in the three FHM genes *CACNA1A*, *SCN1A* and *ATP1A2*, and investigating the neuronal, network and behavioral consequences in transgenic mouse models.<sup>16,29</sup> FHM1 mice displaying the gain-of-function missense mutation R192Q in the *Cacna1a* gene encoding a subunit of neuronal voltage-gated Cav2.1 Ca<sup>2+</sup> channels show enhanced susceptibility to experimentally induced CSD.<sup>67,68</sup> This CSD susceptibility could be explained by an enhanced glutamatergic transmission resulting from the effect of the R192Q mutation on increasing presynaptic calcium-influx in glutamatergic neurons.<sup>69</sup> At the morphological level, FHM1 mutant mice display altered axonal and dendritic morphology in the sensorimotor cortex, with larger axonal boutons and a higher percentage of highly excitable mushroom-type dendritic spines, which are densely populated with excitatory NMDA receptors compared to wild-type, suggesting stronger and more excitable synapses.<sup>70</sup> With respect to modelling effects of migraine triggers, the CSD susceptibility in FHM1 R192Q mutant mice (but not in wild-type controls) was specifically enhanced by an acute administration of the stress hormone corticosterone,<sup>71</sup> possibly resembling patient reports of stress as attack trigger.<sup>72</sup> Also, in line with clinical photophobia symptoms in patients,<sup>73</sup> FHM1 mutant mice showed signs of light aversion that could reflect an increase in visual system responsivity.<sup>74</sup>

## Neurophysiological techniques to investigate cortical excitability

Electroencephalography (EEG) is the measurement of electrical activity generated by neurons firing action potentials. With electrodes on the scalp, several cortical rhythms are distinguished, which are related to sleep stages and levels of arousal; these rhythms are named delta ( $< 4$  Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz) and gamma ( $> 30$  Hz).<sup>75</sup> The activity levels in those frequency bands, as well as the relationship between activities in different frequency bands (cross-frequency coupling) or between different regions of the cortex (connectivity analysis), are studied as possible indicators of neurological disease presence or severity.<sup>76–78</sup> EEG has an excellent temporal resolution (milliseconds) while the spatial resolution is, due to filtering effects of the skull, low compared to neuroimaging methods like magnetic resonance imaging or position emission topography. However, when compared to those techniques, EEG is much more easy and quicker to apply in both clinical and research setting.<sup>79</sup> With automated parameter extraction like peak amplitude or band power, a blinded EEG analysis of different groups is possible, circumventing the large inter-observer variability present in traditional EEG analysis with visual determination of those parameters.<sup>80</sup>

External perturbations of the brain using different modalities (e.g. visual, auditory or somatosensory stimuli) generate synchronized electrical activity that can be recorded as evoked potentials using scalp EEG. Altered neurophysiological activity in response to perturbations could possibly be used as biomarker of migraine type (with or without aura) or as predictor of an impending migraine attack.<sup>28,81</sup> Due to its ease-of-use and excellent temporal resolution, EEG is a useful tool to study the effect of such perturbations in migraine patients.

## Quantitative EEG changes in migraine patients

The study of EEG rhythms in the absence of any external perturbation (‘resting-state’) is named quantitative EEG. Early studies (reviewed by Sand<sup>82</sup>) remained inconclusive regarding the effect of migraine and migraine phase on e.g. peak frequency, band power and hemispheric symmetry.<sup>82,83</sup> More recently, reduced alpha power in the occipital cortex for migraine without aura was reported.<sup>84</sup> Another resting-state study demonstrated, in the interictal phase for patients with migraine without aura, reduced EEG power and reduced coherence in the delta,

alpha, beta and gamma bands, except for an increased delta, alpha and beta connectivity in the fronto-occipital network.<sup>85</sup> In a group of patients with migraine, an increased theta power in all cortical regions, and increased delta power in the fronto-central region was demonstrated; this effect was more pronounced in patients without compared to with aura.<sup>86</sup> Overall, results appear to vary depending on the parameter that is derived from the EEG recordings, which indicates that quantitative EEG parameters are inadequate as reliable readout of cortical excitability.

### **Visual evoked potential changes in migraine patients**

The functioning of the visual system including the cortex can be studied non-invasively by recording the electrophysiological response to visual stimulation to the eye, the so-called visual evoked potential (VEP), using scalp EEG. The VEP represents the summation of electrical potentials recorded over the scalp, mirroring the neurophysiological activation along the visual pathway from retina up to the visual cortex.<sup>79</sup> Visual stimulation can be presented to people using flashes of light or patterned stimuli such as a shifting black-and-white checkerboard-like pattern. Besides application to human subjects, the VEP response can be used to study visual system functioning in animal models, for instance in freely-behaving mice, allowing invasive EEG recordings to study the evoked responses also locally within the cortex.<sup>87</sup>

The averaged EEG response to multiple transient stimuli (the ‘single VEP’) consists of multiple positive and negative peaks in the EEG trace, of which the amplitude and latency have been studied as potential markers of altered cortical excitability in migraine.<sup>88,89</sup> Lack of habituation to repeated visual stimulation has long been considered a hallmark of altered cortical excitability in migraine.<sup>90</sup> Whereas healthy controls showed a decreasing VEP response after about 600 repeated stimuli, the VEP response of migraine patients remained stable.<sup>79,91</sup> However, lack of repeatability of those results in studies with a blinded study design challenged the concept of ‘lack of habituation’ as migraine biomarker.<sup>80,92</sup>

A repetitive visual stimulus presented at a frequency above ~3.5 Hz generates a stationary (‘steady-state’ or ‘photic drive’) neurophysiological response consisting of the stimulation frequency and multiples of the stimulation frequency (harmonics) in the EEG signal. Enhanced photic drive for several stimulation frequencies (but

mainly between 10 and 30 Hz) was reported interictally for migraine, at the stimulated frequency<sup>93–95</sup> or at harmonic frequencies.<sup>96,97</sup> Combining multiple frequencies in one stimulation paradigm, by presenting light flashes at increasing frequency (the so-called ‘chirp’ stimulation) showed an interictal increased EEG response for 18–26 Hz stimulation, but not above or below those frequencies.<sup>98</sup> With similar stimulation frequencies, the synchronization and connectivity of EEG responses showed different responses in migraine with versus without aura, with specifically increased cortical activation in patients with aura.<sup>99</sup>

Alterations in responsivity to visual stimulation are considered to be related to alterations in cortical excitability, but it remains debated whether changes are caused by hypo- or hyperexcitability.<sup>100,101</sup> EEG activity reflects the summation of a population of inhibitory and excitatory neurons, often obscuring the underlying pathophysiological processes.<sup>101</sup> In addition, by using VEPs not only cortical but also subcortical responses, and their interactions, are measured. More direct measures of cortical excitability are therefore required to provide direct insight in changes in cortical excitability in migraine.

### **Transcranial magnetic stimulation as a tool to study cortical excitability**

Another way to study excitability of the (visual) cortex is by directly exciting cortical neurons with a magnetic pulse over the scalp, a method known as transcranial magnetic stimulation (TMS), while measuring the response in muscular activity using electromyography (EMG) or cortical activity using EEG.<sup>102</sup> The magnetic pulse activates neurons to a depth of up to 2 cm below the skull, so the technique is limited to influencing activity of superficial layers of the cortex. Focal stimulation is achieved using a figure-of-eight coil, while the use of a circular coil activates the cortex more diffusely.<sup>103</sup>

When applied over the motor cortex, triggered motor cortical neurons subsequently activate spinal motor neurons resulting in a motor evoked response (MEP) that is measurable by EMG.<sup>104</sup> While the peaks and latencies of the MEP are highly variable within and between participants, the lowest stimulation intensity at which an MEP is induced – the resting motor threshold (RMT) – is often used as a reflection of motor cortex excitability.<sup>17</sup> Interictally, patients with migraine with and without aura, as well as patients with familial hemiplegic migraine, showed similar RMT

values compared to controls.<sup>90,105,106</sup> However, when using stepwise increasing stimulation intensities (a so-called input-output curve), enhanced MEP responses were seen in patients with migraine with and without aura, specifically for higher stimulation intensities, indicative of motor cortex hyperexcitability.<sup>107,108</sup>

Applying TMS over the visual cortex results in the induction of magnetophosphenes, which are visually perceptible flashes and patterns of light and color. The minimum stimulation intensity necessary to induce phosphenes is inversely related to the level of visual cortex excitability,<sup>109</sup> and could as such be used as subjective marker of hyperexcitability.<sup>110</sup> Combining several studies in a meta-analysis, it appears the phosphene threshold was reduced in migraine with and without aura with circular coil stimulation, whereas focal stimulation only demonstrated an increased phosphene prevalence in migraine with aura.<sup>111</sup>

As both cortical and subcortical pathways contribute to the MEP, the RMT is not a direct measure of motor cortical excitability,<sup>112</sup> and TMS-evoked magnetophosphenes represent a subjective readout. To measure cortical excitability objectively or in behaviorally silent areas (i.e., without measurable motor or visual response), TMS can be combined with EEG.<sup>113</sup> The TMS-evoked potential (TEP) consists of several positive and negative peaks which are reproducible within participants.<sup>114,115</sup> In healthy subjects, distinct peaks have been assessed to specifically reflect network activity influenced by excitatory or inhibitory networks based on observed effects of neuroactive drugs.<sup>116,117</sup> In conditions with implied altered cortical excitability like epilepsy<sup>118,119</sup> and schizophrenia,<sup>120</sup> TEP responses were demonstrated as possible biomarker of changes in cortical excitability. In migraine, the combination of TMS with concurrent EEG has not yet been described.

## Changes in cortical network excitability over the migraine cycle

Surprisingly, there have been relatively few studies on the development of parameters reflecting the onset of migraine attacks. Any technique that can reliably predict or explain the mechanisms behind attack onset in migraine opens up new targets for studies into migraine attack prevention. To be able to study fluctuations

in cortical excitability over the migraine cycle, ideally the same patients are each monitored at multiple timepoints. To circumvent the difficulty of predicting the migraine attack, some studies have focused on multiple randomly timed measurements in the same patients, which afterwards could be timed to the nearest attack.<sup>121,122</sup> Another method is to study female patients with periodic menstrual migraine, in whom attacks often coincide with the menstrual phase.<sup>123,124</sup>

One of the earliest attempts to study neurophysiological changes before a migraine attack used a slow cortical potential change, the contingent negative variation (CNV) that is evident in EEG recordings following a ‘warning’ sound and subsequent ‘test’ sound followed by a motor response (button press). During the 24-48 hours prior to the onset of a migraine attack, an increase in the characteristic negative EEG amplitudes of the repeated CNV had a predictive value for attack onset.<sup>125</sup> Another study confirmed this finding, and uncovered that the differences in CNV amplitude and habituation over repeated stimuli was at its maximum compared to non-migraineurs in a window of 24 hours prior to the attack.<sup>126</sup> Using TMS-EMG, in the 48 hours before an attack, repeated motor responses to TMS were found to be facilitated suggestive of enhanced network excitability and predisposition to attack triggers, whereas during and in the 48 hours after the attack the responses showed a pattern of suppression suggestive of enhanced network inhibition.<sup>127</sup> In line with these findings, the photic drive to visual stimulation at 12 Hz increased in migraine patients in the same 48-hour time window before an attack.<sup>128</sup> Using resting-state EEG, increased hemispheric asymmetry (alpha and theta bands) and decreased (alpha and theta) or increased (delta band) EEG power demonstrated that 36 hours, but not 72 hours, before an attack migraine patients showed altered brain activity compared to controls; those differences are proposed to be indicative of fluctuating cortical activity over the migraine cycle, possibly caused by thalamocortical dysfunction.<sup>129</sup>

In patients with periodic menstrual migraine, an increased EEG power in delta and theta frequency bands, increased alpha asymmetry and enhanced early CNV amplitude were observed in the 1-4 days before an attack, when compared to measurements in the same patients after the attack.<sup>122</sup> In a neuroimaging study of migraine patients (with and without aura), an increased BOLD activity in the spinal trigeminal nuclei during nociceptive stimulation is in line with a rise in excitability

towards the next migraine attack, also in subcortical regions.<sup>130</sup> Expanding on this work, when a patient with migraine without aura was examined over 30 consecutive days, clear cyclical patterns of increased BOLD activity in the visual cortex following painful stimulation was visible before and immediately after the three captured migraine attacks.<sup>36</sup> Again, the response to nociceptive stimuli was specifically enhanced 24 hours prior to the headache onset, and normalized after the attack. These cortical and subcortical changes in brain activity were proposed to reflect an increased susceptibility of the migraineous brain to precipitating factors and the neurophysiological readiness to generate an attack.<sup>36,122,130</sup>

Subjective complaints in the phase preceding migraine attacks have also been studied to help predict attacks. A lot of clinical studies have assessed these premonitory symptoms,<sup>20,21</sup> and some studies tried to predict a migraine attack based on detection of premonitory symptoms.<sup>131</sup> Nevertheless, none succeeded at finding a premonitory parameter that was reliable and precise enough to be used as a predictive indicator for the onset of migraine attacks. Therefore, further research is needed to identify easy-to-use and reliable predictive readouts for migraine attacks.

## Scope and outline of this thesis

The aim of this thesis was to investigate the initiation phase of migraine attacks based on neurophysiological outcome parameters. The main focus of the work was on the development of methodologies to measure cortical excitability dynamics over the migraine cycle. The research described in this thesis is divided into two parts. **Part I** describes the development of measurements of visual cortex excitability in migraine patients and a transgenic migraine mouse model. We developed a questionnaire to assess visual allodynia in patients, and combined preclinical and clinical studies to develop several visual stimulation paradigms in combination with EEG measurements. **Part II** describes applications of transcranial magnetic stimulation (TMS) with concurrent EEG recordings in people with migraine or epilepsy. TMS-EEG measures the direct neuronal response to stimulation over the whole cortex, rather than the indirect activation of the visual cortex in response to visual stimulation. We studied the TMS-evoked potential and phase clustering of those potentials as possible disease biomarkers.

## Part I: Visual system excitability as migraine attack predictor

**Chapter 2** describes the development, validation and application of the ‘Leiden Visual Sensitivity Scale’ (L-VISS), a questionnaire to assess visual allodynia. This tool has potential use in longitudinal assessments of a patient’s sensitivity to light and patterns, as it is quick to apply and not dependent on any recording technology. Besides, it could be used in conjunction with more elaborate (e.g., neurophysiological) recordings to provide a personalized (subjective) assessment of changes in cortical excitability over the migraine cycle.

**Chapter 3** describes the translational application of common and newly developed visual stimulation paradigms during EEG recordings in a migraine mouse model. To bridge the gap between measurements of surface EEG in patients and direct neuronal network measurements in animal models, we studied the effect of the FHM1 missense mutation R192Q, that leads to enhanced glutamatergic neurotransmission, on visual cortex responsivity using visual evoked potential recordings.

In **Chapter 4**, we explore the use of the ‘chirp’ visual stimulation to measure cortical excitability in migraine patients. Using light flashes at increasing stimulation frequency, chirp stimulation allows comparison of responsivity at various driving frequencies and related harmonic frequencies. We applied this stimulation paradigm in groups of migraine patients with and without aura in the interictal and pre-ictal phases, to study the effect of migraine aura and migraine phase on cortical excitability.

## Part II: TMS-EEG, a novel method to measure cortical excitability in migraine

**Chapter 5** described the application of transcranial magnetic stimulation (TMS) with concurrent EEG to enable comparison of TMS-evoked potentials between migraine with aura and controls, as direct measure of cortical excitability. In **Chapter 6**, differences in TMS-induced EEG ‘phase clustering’ were investigated in migraine with aura and juvenile myoclonic epilepsy, to explore the potential of this EEG feature as a biomarker of genetic generalized epilepsy or migraine with aura.

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

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