The onset of the migraine attack

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Chapter 1.

General introduction and aims of this thesis

Migraine

Migraine is a common, multifactorial neurovascular disorder characterized by recurrent, disabling attacks of severe and often unilateral headaches, accompanied by symptoms of photophobia, phonophobia, nausea and vomiting [1, 2]. In one third of patients, transient neurological symptoms, called migraine aura, precede the headaches [3]. When untreated, migraine attacks can last for several hours up to several days, and pose a large burden on patients especially when the attack frequency is high [4-6]. Migraine is a multiphasic disorder. The premonitory phase is the phase preceding the headache phase and - if present - the aura phase, and is considered to be the first phase of a migraine attack. Although the mechanisms behind the migraine headache and aura symptoms are reasonably well understood, the triggering mechanisms for the initiation of migraine attacks are unknown [7]. In recent decades, accumulating evidence has shifted the emphasis away from the vascular theory of migraine towards mechanisms of central nervous system activation originating from deeper brain regions such as the hypothalamus and the brainstem. These regions may play a pivotal role in the early phases of the migraine attack, as is suggested by evidence from preclinical, clinical, biochemical and imaging studies [8, 9].

Clinical symptoms during the four phases of a migraine attack

During the course of a migraine attack cycle, up to four different phases can be distinguished: i) the premonitory (or prodromal) phase; ii) the aura phase; iii) the headache phase; and iv) the postdromal phase. Clinically, there is great variability in phenotype between patients as is reflected by the large clinical heterogeneity over all the different phases of the migraine cycle. A more detailed overview of each of these four phases I will describe below.

The premonitory phase

The duration of the premonitory phase varies between patients and ranges from 2-72 hours before the aura and/or migraine headache starts [10]. In this phase a variety of general, non-specific, non-headache symptoms can occur, which are usually rather consistent within patients. These symptoms may provide an early warning signal for the upcoming migraine headache. The most frequently reported premonitory symptoms include fatigue, mood and cognitive changes, gastrointestinal symptoms, neck pain, yawning, temperature change, smell and taste distortion, food craving and appetite changes. Many of these symptoms are assumed to be of hypothalamic origin [11-14].

Despite being recognised in the literature for decades [15, 16], the pathophysiological relevance of premonitory symptoms and their clinical implications have been largely neglected [15]. It is unknown when and where in the brain functional or metabolic changes occur in the premonitory phase nor what these exactly are. In addition, there are no validated screening instruments for premonitory symptoms and they have a very subjective character, all hampering studying them properly. Exact prevalence rates therefore remain difficult to assess. Based on the scarce literature, it is estimated that over 80% of migraine patients experience a minimum of one premonitory symptom [3, 17].

The aura phase

The aura phase is present in approximately 30% of migraine patients [1, 18, 19] and is characterized by transient neurological deficits with a duration ranging from 5 until 60 minutes, of which at least one has a unilateral localization. In the majority of patients (75%), aura symptoms last for less than 30 minutes, and only 5% has auras lasting longer than 4 hours [20-22]. In migraine with aura patients, not every migraine headache needs to be preceded by an aura. Detailed prospective diary study work has shown that at least one of three auras last over an hour in up to 26% of patients [23].

The aura is considered the clinical correlate of cortical spreading depolarisation (CSD: formerly known as cortical spreading depression; see also section Neurobiology of migraine). Based on the specific cortical regions involved, several different aura symptoms can be distinguished: i) visual symptoms; ii) sensory symptoms; iii) aphatic speech disturbances; and iv) motor symptoms. The visual aura is the most common aura symptom, reported by 80-90% of patients with migraine with aura. Visual symptoms can vary from simple flashes or dots to fortification spectra (positive phenomena), scotomas (negative phenomena) or complex hallucinations with metamorphopsias [3]. Sensory symptoms usually are paraesthesias, which occur in 30% of patients with migraine with aura and show a preferential cheiro-oral distribution. Aphatic speech disturbances (17%) and motor weakness (10%) are less common. When patients experience multiple aura symptoms, their occurrence follows a specific temporal sequence that can be explained by the pathway the wave of depolarisation spreads over the cortex: visual, sensory, aphatic speech and then motor symptoms [24, 25]. Although the aura phase usually directly precedes the headache phase, a short delay between the end of the aura phase and the beginning of the headache can occur: a recent study has demonstrated that the overlap of aura and headache phases is more common rather than the exception [26]. The classification of migraine into subtypes is based on the presence of aura symptoms (see Table 1).

The headache phase

The migraine headache phase is characterized by a moderate to severe, often unilateral headache with a throbbing or pulsating character with a duration from several hours up to several days when untreated [2]. The headache is considered disabling by patients, who usually need to lie down during the headache [2, 27]. Accompanying gastrointestinal symptoms, such as nausea, vomiting, abdominal pain and diarrhea, are very common. Nausea and vomiting are being reported by 70-90% of patients. These symptoms are very consistent over time in different migraine attacks and interfere with the patients' ability to take their oral medication in 30-40% [11]. Symptoms of sensory hyperexcitability include photophobia, phonophobia and osmophobia and are experienced frequently as well.

The postdromal phase

After the headache phase has subsided, postdromal symptoms can be experienced that can last from several days up until one week [28]. More than 80% of patients report at least one postdromal symptom: a stiff neck, tiredness, weakness, mood changes and cognitive difficulties are the most common symptoms [13, 29, 30]. Mild residual head discomfort, light-headedness, and gastro-intestinal symptoms are frequently reported as well [29, 30]. As there

is some overlap in premonitory and postdromal symptomatology, it is suggested that these symptoms may have been present during the entire attack, but were overshadowed by the aura symptoms, the severe headache, nausea and vomiting [28]. Most patients (93%) return to normal within 24 hours after the headache resolves. The duration of the postdromal phase is not associated with migraine headache severity [13].

Migraine classification

Defining migraine patients and migraine attacks has been difficult, because of both the variability of migraine symptoms between patients, and the variability between recurrent attacks within the same patient. The introduction of the International Classification of Headache Disorders (ICHD) in 1988 has standardised the diagnosis of migraine, enabling more accurate epidemiologic studies, more accurate patient selection for clinical trials, scientific research, and for diagnosis in healthcare. Currently, the third edition is the prevailing classification system [2]. According to the ICHD, two subtypes of migraine can be distinguished based on the presence of aura symptoms (Tables 1.1 and 1.2).

Table 1: Classification of migraine without aura (1.1) and migraine with aura (1.2) according to the International Classification of Headache Disorders 3 criteria [2].

1.1 Migraine without aura			
A.	At least 5 attacks [1] fulfilling criteria B-D		
B.	Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) [2,3]		
C.	Headache has at least 2 of the following 4 characteristics:	1.	Unilateral location
		2.	Pulsating quality
		3.	Moderate or severe pain intensity
		4.	Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D.	During headache at least one of the following:	1.	Nausea and/ or vomiting
		2.	Photophobia and phonophobia
E.	Not better accounted for by another ICHD-3 diagnosis		

Notes

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks, should be coded 1.5.1 *Probable migraine without aura*.
2. When the patient falls asleep during a migraine attacks and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).

1.2 Migraine with aura		
A.	At least 2 attacks [1] fulfilling criteria B and C	
B.	One or more of the following fully reversible aura symptoms [2]:	1. Visual 2. Sensory 3. Speech and/or language 4. Motor [3] 5. Brainstem 6. retinal
C.	At least 2 of the following 4 characteristics:	1. At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession 2. Each individual aura symptom lasts 5-60 minutes[1] 3. At least one aura symptom is unilateral[4] 4. The aura is accompanied, or followed within 60 minutes, by headache
D.	Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded	

Notes

1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 x 60 minutes.
2. Usually, a headache with the features of migraine without aura follows the aura symptoms. Less common, the headache is without migraineous features, or even is absent. Most patients who have attacks of migraine with aura also report attacks of migraine without aura [2]
3. The very rare hemiplegic migraine, a form of migraine with aura characterized by a transient hemiplegia that may last from several minutes to hours or even days, is considered to be the most severe subtype of the migraine spectrum [31].
4. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Especially for the purpose of large-scale epidemiologic and genome-wide association studies, large numbers of migraine patients (and non-migraine individuals) are to be included in order to obtain reliable study data. Accurate and easy-to-use screening instruments, based on the International Headache Society's criteria [2], are of utmost importance. Screening questionnaires or web-based tools can be feasible for this purpose, as has been shown in the past in the Genetic Epidemiology of Migraine study [32]. They, however, necessitate validation within every population in which they are used.

Epidemiology and burden of disease

Migraine is a public health problem of great impact on both the patient and society. In western countries, the overall one-year migraine prevalence in the general population is at least 12 percent, and its epidemiologic profile has remained stable over the past decades [27, 32-34]. Two-thirds of migraine patients are women, in which the one-year prevalence is 16-18% in comparison to a prevalence of 6-8% among men [35]. The lifetime prevalence of migraine

is up to 33% in women and up to 13% in men [32]. The median attack frequency is 1-2 attacks per month and the median attack duration is one day. More than 10% of migraine patients have weekly attacks lasting for 2-3 days each. The burden of migraine therefore is high. It is associated with deteriorated health-related quality of life and lost productivity, with a large impact on migraine patients and their families [6, 33, 34]. The World Health Organization (WHO) has rated migraine as the sixth most prevalent disorder globally, the condition with the second most years lived in disability, and the most disabling of neurologic disorders [6, 36, 37]. Furthermore, WHO has also ranked migraine as the most costly neurologic disorder in the European Union [37]. Although the epidemiological profile has remained stable, the rankings increase over time[7].

Migraine attack susceptibility, modulating and trigger factors

Every person can have a migraine attack. An individual is considered a migraine patient according to the criteria of the International Headache Society only after five attacks of migraine without aura, or after 2 attacks of migraine with aura [2]. Both between and within patients, attack frequency varies and depends on genetic susceptibility, intrinsic and extrinsic factors that modulate the so-called excitability threshold, and trigger factors that can initiate a new migraine attack[7, 9].

Attack susceptibility

As suggested by clinical practice, there is a strong genetic component in migraine [7]. Population-based family studies have shown that direct family members of migraine patients have an increased risk of having migraine in comparison to relatives of matched controls [38], with the risk being the highest for relatives of migraine with aura patients [7]. In addition, twin studies have revealed significantly higher pairwise concordance rates of migraine in monozygotic versus dizygotic twins [39]. In the small subset of patients with familial hemiplegic migraine, mutations in ion channel genes cause a lifelong susceptibility to migraine in this monogenic form [40]. In the majority of patients with migraine without aura or migraine with aura (excluding the hemiplegic migraine subset), genome wide association studies have revealed several distinct genomic loci associated with migraine, which show enrichment for genes expressed in vascular and smooth muscle tissue [41-43]. The exact pathways involved are still topic of extensive research[7].

Cortical and non-cortical hyperexcitability

In recent years it has been suggested that an altered neuronal excitability of the cortex, subcortical structures and/or trigeminal neurons are underlying mechanisms for migraine susceptibility. There is accumulating evidence for increased glutamergic transmission as one of the underlying pathways. Glutamate is the major excitatory neurotransmitter in the Central Nervous System and is implicated in several mechanisms related to migraine, including trigeminovascular activation, central sensitization and cortical spreading depolarization [44]. The hypersensitivity to light (photophobia), to sounds (phonophobia), odours (osmophobia) and touch (allodynia) are considered to result from central sensitisation, a condition in which dorsal horn nociceptive neurons exhibit enlargement of

their receptive fields, increased synaptic strength and increased excitability [45]. For allodynia, there is large body of evidence endorsing this hypothesis. For the other hypersensitivities, this mechanism is suggested [46]. It has been suggested that migraine may be considered as a brain state of altered excitability [45]. A clear biochemical correlate for the neurobiological cascade leading from enhanced excitability via modulating or triggering factors to a new migraine attack has not been elucidated yet and is dearly needed.

Modulating and triggering factors

Intrinsic and extrinsic modulating factors include stress, relaxation, fatigue, prophylactic treatment [47] and hormonal fluctuations [48,49]. Collectively these factors may lead to a state in which the brain is more susceptible to developing a new migraine attack [50]. Trigger factors are defined as any factor that on exposure or withdrawal leads to a development of a migraine attack [51]. It can nevertheless be difficult to clearly distinguish between modulating factors and trigger factors. Extensive lists of potential modulators / trigger factors for the onset of a new migraine attack have been described in literature, including stress, nutritional factors, sleep changes, changes in circadian rhythm, atmospheric factors, sex hormones and pharmacological compounds (such as glyceryl trinitrate, PACAP, sildenafil) [52-67]. Methodological issues in assessing trigger factors, premonitory symptoms and self-prediction have hampered correct interpretation of the association with occurrence of migraine attacks [67, 68]. Observational (mainly questionnaire) studies have often suggested strong associations between possible trigger factors and the attack onset, but these correlations have rarely been confirmed in prospective or interventional studies. I will briefly discuss some of these factors below.

Stress

Migraine patients report stress and negative emotions both as modulators and trigger factors for a new attack [13, 69, 70]. There is some evidence suggesting headache severity and duration in migraine patients are correlated to the cortisol response to a stressor [71]. Interestingly, the sudden absence of perceived stress might also be relevant, as timing of migraine headaches in the weekend is a clear clinical observation [72].

Sleep and circadian rhythmicity

Sleep and sleep deprivation play a role in migraine: sleep is considered an effective means to alleviate the migraine headache; attacks of migraine may occur during or shortly after either nocturnal or diurnal sleep; sleepiness may emerge during various phases of the migraine attack [73, 74], and sleep deprivation is associated with the onset of migraine attacks [28, 75]. Polysomnographic findings of sleep disturbances can be found in nights preceding migraine attacks [76]. Several studies have suggested that migraine attacks show seasonal and circadian periodicity [77-81], implicating chronobiological, probably hypothalamic-mediated mechanisms in the triggering and initiation of migraine attacks.

Sex hormones

Migraine prevalence and the frequency, duration and severity of migraine attacks are highly dependent on age, gender and, in women, events which are associated with marked fluctuations in female reproductive hormones [32, 82, 83]. The prevalence of *active* migraine,

defined as at least one attack in the previous year, shows a bell-shaped pattern across lifetime in both sexes. In the fertile period, three times more women (24%) than men (8%) have active migraine and their attacks are on average more frequent, longer, and more severe [32, 83]. Additional evidence that sex hormones might modulate migraine risk and activity comes from a range of other clinical and experimental observations. Higher migraine prevalence rates were reported among obese individuals [84], when starting oestrogen therapy in male-to-female transsexuals [85], or when having certain polymorphisms in sex hormone receptor genes [86]. Migraine is less prevalent after testosterone administration in women with migraine [87]. Attack frequency or prevalence rates vary after starting or stopping of oral contraceptives [88], with menstrual cycle-related changes in oestrogen levels [40, 89], and due to gender-related differences or experimental manipulation of sex hormone levels in rat transgenic mouse models [40, 90].

Pharmacological factors

A variety of pharmacological compounds are known for their ability to provoke migraine or migraine-like headache attacks and can be considered pharmacological models of migraine [91]. These compounds include glyceryl trinitrate (nitroglycerin), PACAP, and sildenafil [92, 93]. They can be used as models to study mechanisms responsible for migraine in humans, and to explore the mechanisms of action of existing and future anti-migraine drugs. The most often used is the nitroglycerin provocation model which has sufficient information on reproducibility and reliability available [94]. Infusion of nitroglycerin results in an immediate type of headache unrelated to aura symptoms in both healthy volunteers and migraine patients and a 4-6 hours delayed migraine attack in about 50% of migraine patients (range 20% - 80%), but not in healthy volunteers [95-97]. The nitroglycerin model is commonly used, as the induced attacks are very similar to the genuine attack, including the premonitory symptoms and response to acute [94] and prophylactic [98] treatment [91, 96, 99]. It is also a reliable and reproducible model that has been critically evaluated by several independent groups.

Neurobiology of migraine

As laid out in the International Classification of Headache Disorders 3 criteria, migraineous symptoms are not just restricted to headache pain, but include a wide variety of sensory and homeostatic symptoms throughout the course of a migraine attack [2]. Sensory symptoms include hypersensitivity to light stimuli (photophobia), acoustic stimuli (phonophobia), olfactory stimuli (osmophobia) or tactile stimuli (allodynia). Symptoms that reflect a disruption of the normal homeostasis include altered sleep, altered feeding behaviour, changes in mood and in water homeostasis. These different clinical symptoms seem to be driven by particular underlying pathophysiological mechanisms [7].

The interictal period

Evidence from electrophysiological and imaging studies has suggested that the migraine brain differs from the non-migraine brain in function and structure also in the interictal period, i.e. between two migraine attacks. Interictal studies with auditory evoked potentials

[100] or with the nociceptive blink reflex [101] suggested that the migraine brain over-responds [7]. Interictal imaging studies showed alterations in grey matter volume and hypometabolism in pain processing areas [102-108]. Biochemically, abnormal patterns of hypothalamic hormonal secretion were found interictally in the serum of chronic migraine patients, including decreased nocturnal prolactin peaks, increased cortisol concentrations, a delayed nocturnal melatonin peak and lower melatonin concentrations [109]. Several other studies also found increased interictal levels of prolactin, LH and FSH levels and decreased interictal cortisol levels [110]. In CSF studies increased levels of LH, FSH and prolactine and hypocretin were detected [110-112]. Overall, both increased and decreased levels of hormones were detected.

In summary, the brain of migraine patients differs subtly from non-migraine individuals in structure and functioning even outside attacks.

The premonitory phase

The clinically heterogeneous pattern of premonitory symptoms has led to the hypothesis that some of these symptoms, such as yawning, frequent urination, thirst, mood changes food intake, craving and alterations in the sleep-wake cycle [7, 12], might be hypothalamic in nature, in which the neurotransmitters dopamine [113], vasopressin [114] and the orexins [115] play a key role. The underlying pathophysiologic mechanisms of the premonitory phase have only been studied scarcely, mostly due to the technical and logistic challenges of predicting spontaneous migraine attacks. Neuroimaging studies have provided some insight in timing and anatomical localisation of functional changes, but relevant mechanisms still need to be elucidated. In patients with provoked premonitory symptoms, Maniyar et al. found blood flow increases in the posterior hypothalamus [116]. Later, Stankewitz et al. found pre-ictal normalisation of the interictally reduced activation of spinal trigeminal nuclei, that further increased during the headache phase. A correlation with clinical premonitory symptoms was not found [117]. Finally, in a fMRI study scanning a single patient every morning for 30 days, altered hypothalamic blood flow coupled with brain stem nuclei was found 24 hours before pain onset in three captured spontaneous migraine attacks [118]. Although Denuelle et al. were the first to capture hypothalamic involvement in acute migraine attacks, they only focussed on the headache phase [119].

The aura phase

Aura symptoms, defined by transient neurological deficits preceding or just overlapping with the headache phase in migraine, have a believed experimental correlate which is the cortical spreading depolarisation (CSD), a steady wave of depolarising neuroglial membranes. This was first described in 1944 by Leão, who studied the rabbit cortex and suggested CSD to be the neurobiological substrate of the clinical migraine aura [120], mainly since CSD and aura have similar rates of propagation (3mm/minute) [121]. Later studies detecting blood flow changes and blood oxygenation levels confirmed this assumption [120-123]. Taken together, these studies point to CSD as the underlying mechanism in the visual aura in migraine [7]. Whether aura symptoms can occur independently (and induce further symptoms, including headache) or are related to earlier changes elsewhere in the brain as part of a bigger cascade of events, remains unresolved.

The headache phase

The headache in migraine is considered to be due to activation of the trigeminovascular system (TGVS). The brain itself is insensate, but pial, arachnoidal and dural vessels are richly innervated by nociceptive large non-myelinated (C) and thinly myelinated (Aβ) fibers from mainly the ophthalmic division of the trigeminal nerve [7, 124]. The axon terminals of these fibers contain vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A and pituitary adenylate cyclase-activating peptide (PACAP) [125, 126], which upon release after stimulation cause vasodilatation of dural and pial vessels [125, 127]. The convergence of sensory inputs from intracranial and extracranial structures explains the distribution of migraine headache pain over the frontal and temporal regions as well as involvement of occipital and high cervical areas [128]. All nociceptive information is relayed via ascending projections to brainstem and diencephalon areas involved in pain processing. Activation of these regions is considered to contribute to the perception of headache pain in migraine, and to account for autonomic, cognitive, endocrine and affective symptoms occurring over the course of a migraine attack [7].

More recent is the appreciation that the hypothalamus also is involved in the control of pain [129] and the attack initiation of primary headaches [77, 130, 131]. As early as 1989, Lance already hypothesized that both internal and external stimuli may initiate a migraine attack via hypothalamic activation and its downstream connections with brainstem nuclei [16]. The hypothalamus has reciprocal connections with many structures involved in nociceptive processing: descending projections to the superior salivatory nucleus, where they affect autonomic regulation, and modulate trigeminovascular nociceptive processing at the spinal level [7]. Orexinergic peptides [115] and somatostatin [132] from the posterior hypothalamus, $GABA_a$-ergic projections from the paraventricular hypothalamic nucleus [133], as well as inhibitory dopaminergic projections from the A11 hypothalamic nucleus [134, 135] can modulate dural- and cutaneous evoked trigeminovascular transmission. A changed function of any of these hypothalamic regions may result in altered processing of nociceptive inputs that sustain or modulate migraine headache. It might also trigger activation of previously silent trigeminovascular neurons correlating with attack initiation. The hypothalamus also regulates many other important processes involved in homeostasis, such as feeding, sleep/wake and stress. An altered function of the hypothalamus may also result in many of the accompanying symptoms in a migraine attack [136].

Together with data from concomitant hypothalamic activation in both nitroglycerin-triggered [116] and spontaneous [119] migraine attacks, the evidence mentioned above suggests that brainstem and hypothalamic structures are crucial for migraine pathophysiology and might also reflect the clinical heterogeneity in migraine attacks [7].

The postdromal phase

This phase follows the end of the headache phase and can persist for hours or days when the patient is free of headache but has not fully returned to feeling normal. As mentioned before, there is some overlap in premonitory and postdromal symptomatology [28], but up to date no imaging of neurobiological studies have been reported focusing on this phase of the migraine cycle.

The onset of the migraine attack; a multi-modal approach into modulating and trigger factors

As presented, there are many different modulating and triggering factors involved in migraine attack susceptibility. Some of these are, on both clinical and pre-clinical grounds, hypothesised to be associated with possible altered functioning of hypothalamic nuclei during the premonitory phase and possibly early headache phase of the migraine attack. This thesis describes the onset of the migraine attack and its modulating and trigger factors. Since it is not feasible to elaborate on all, I will focus on some modulating or triggering mechanisms in both spontaneous and nitroglycerin-induced migraine attacks in this thesis using a multi-modal approach. I will distinguish the three different parts 'Clinical aspects and modulators', 'Imaging aspects' and 'Biochemical aspects'.

Clinical aspects and modulators (Part I)

Large scale epidemiological and genetic studies require inclusion of large numbers of migraine patients and non-migraine control subjects. In chapter two, the validity of a new self-administered migraine questionnaire is described.

In the third and fourth chapter, the focus is on several clinical aspects of modulating or triggering factors in migraine. The distribution of chronotypes, circadian timing of migraine attacks, sleep quality and effect of sleep disturbances on migraine are assessed in chapter three. As is unclear whether the severity of restless legs syndrome (RLS) in migraine differs from non-migraine RLS patients and whether sleep quality is affected differently by RLS in this group, we assess this in a study described in the fourth chapter.

Whether or not migraine patients have a higher risk of getting post-dural puncture headache than controls is an unanswered question. In a prospective, CSF biochemical profiling study, the differences in the occurrence of post-dural puncture headache between migraine patients and non-migraine individuals are studied and presented in the fifth chapter. The effects of perceived stress (for the planned lumbar puncture in an experimental setting) on migraine attack frequency in the migraine patients are assessed as well.

In chapter six the cardiovascular effects of nitroglycerin in migraine patients and non-migraine control subjects are studied. Nitroglycerin is a compound known to be able to trigger migraine-like headache in susceptible individuals [94]. The chapter describes an experimental study assessing the possible differences in effects on systemic cardiovascular parameters between migraine patients and non-migraine individuals after intravenous nitroglycerin infusion.

Imaging aspects (Part II)

As mentioned earlier, data from imaging studies have suggested hypothalamic involvement in the premonitory phase of the migraine attack [116, 117, 119]. Part II describes an experimental setting in which hypothalamic metabolites are studied, both interictal and during nitroglycerin-induced attacks. We compare hypothalamic activation after oral ingestion of a glucose solution in the interictal and pre-ictal phase between migraine patients and non-migraine control subjects using functional MRI in chapter seven.

Biochemical aspects (Part III)

Part III focusses on several biochemical factors that are involved in migraine attack susceptibility. Migraine prevalence and the frequency, duration and severity of migraine attacks are highly dependent on age, gender and, in women, events which are associated with marked fluctuations in female reproductive hormones [32, 82, 83]. In males with migraine, however, this has never been studied before. Therefore, in the first chapter of Part III baseline levels of female sex hormones are compared between male migraine patients and male non-migraine control subjects (chapter eight). Furthermore, the levels of these hormones are longitudinally measured within the migraine group in the days prior to the next migraine attack, including the premonitory and headache phases as described in chapter nine. In chapter ten, the development and validation are described of a human capsaicin model to enable assessment of salivary CGRP secretion.

Aims of this thesis

There are several different modulating or triggering factors that play a role in migraine attack susceptibility and I will focus on several of these mechanisms in both spontaneous and nitroglycerin-induced migraine attacks using a multi-modal approach. Therefore, the aims of the thesis are as follows:

1. To assess the validity of a web-based questionnaire to diagnose migraine and migraine aura (Part I; chapter 2)
2. To study the distribution of chronotypes and circadian timing of attacks in migraine patients, and to assess sleep quality and the effect thereof on migraine attack susceptibility (Part I; chapter 3)
3. To study the prevalence and severity of restless legs syndrome in migraine patients, and assess the interference with sleep quality (Part I; chapter 4)
4. To study the incidence of post-dural puncture headache in migraine patients, and the possible role of perceived stress on new migraine attacks (Part I; chapter 5)
5. To assess migraine-specific effect of intravenous nitroglycerin infusion on systemic cardiovascular parameters (Part I; chapter 6)
6. To assess hypothalamic activation after an oral glucose challenge in migraine patients interictally, and during the premonitory phase of both nitroglycerin-induced and spontaneous attacks (Part II; chapter 7)
7. To assess levels of sex hormones in relation to migraine susceptibility in males, and to study changes in these levels prior to the migraine attack (Part III; chapter 8)
8. To study trigeminovascular cyclicity in women with menstrually related migraine (Part III; chapter 9)
9. To develop a human capsaicin model to quantitatively assess salivary calcitonin gene-related peptide (CGRP) secretion (Part III; chapter 10)

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