Migraine biochemistry and visual snow

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General introduction

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General introduction

The first part of this thesis focuses on migraine and the value of biochemical studies to unravel migraine pathophysiology. Migraine is a disease that has been recognized since ancient times. It is a disorder that affects a large portion of the population. Over the last decades more and more is known about its pathophysiology. However, we are still in need for new treatment options for migraine as the current treatment options are not effective enough in many patients. Knowledge on biochemical differences between persons with and without migraine may shed important light on underlying disease mechanisms and may provide possible new targets for treatment.

Visual snow, the topic of the second part, in contrast to migraine, is a rather "novel" disease entity of which hardly anything is known, but it is believed to be associated with migraine. Given their partly overlapping disease characteristics, with presumably underlying hyperexcitability of the brain in both conditions, part two challenges to investigate the relationship between migraine and visual snow and hypothesizes how similarities between visual snow and migraine may aid to further unravel migraine pathophysiology.

Migraine

Migraine is one of the most common brain disorders. It is characterized by recurrent attacks of severe, often unilateral, headaches that are accompanied by photophobia, phonophobia, and/or nausea and vomiting.[1] Migraine attacks can last from several hours to multiple days. In one-third of patients attacks are preceded by additional transient neurological symptoms, the so-called migraine aura.[2,3] Auras typically and most frequently consist of visual symptoms but can also affect sensory function and speech, or even motor function.[2]

The global disease burden caused by migraine is high.[4] Lifetime prevalence is 33% in women and 13% in men. Some 25% of migraineurs have two or more attacks per month.[3] Preventive drugs are effective - defined as reducing the average attack frequency by 50% - in only half of the patients. Pharmacological mechanisms of the drugs are poorly understood.[5] Clearly, there is a need for better, targeted drugs. The past few years, progress has been made with the development of new treatments aimed at CGRP. Both small molecule antagonists of the CGRP receptor have been studied, and monoclonal antibodies against CGRP itself or its receptor. However, even with these newly and specifically designed migraine treatments there is still a large group of patients which are unresponsive.[6] Thus, although much progress has been made in unravelling the underlying mechanisms that play a role during migraine attacks, it remains an enigma how attacks are initiated and what makes patients susceptible to develop migraine attacks.[7] A better understanding of migraine

pathophysiological triggers and early markers of attacks can hopefully lead to novel drug targets and, ultimately, improved treatment options for patients who are unresponsive to the current drug treatment possibilities.

Clinical characteristics

A classic migraine attack consists of four phases.[7]

The premonitory phase. Many patients report that they experience symptoms in the 72 hours preceding the aura and/or the migraine headache. A wide variety of symptoms has been described, but most common are concentration problems, tiredness, stiff neck, craving for food, and yawning.[8] Presence of premonitory symptoms predicted a migraine attack with 72% accuracy in a diary study.[9]

The aura phase. Approximately one in three migraineurs experiences this phase in their attacks.[3] The aura consists of transient neurological symptoms that typically last between 5 and 60 minutes. Most patients report visual symptoms, but sensory symptoms, such as paraesthesia's, and aphasic symptoms, and even motor symptoms may also occur.[2] Classic visual phenomena are scotoma´s and/or fortification spectra which start in one part of the visual field and generally expand. Originally it was thought that the aura phase ends before the migraine headache starts, but 73% of patients report that headache already started during the aura.[10]

The headache phase. A unilateral, throbbing or pulsating headache develops with moderate to severe intensity. Routine physical activity often aggravates the headache. Many patients additionally complain of nausea up to vomiting and/or photophobia and phonophobia. The headache lasts between 4 and 72 hours.

The postdrome phase. This phase has not been extensively studied.[7] Patients report symptoms similar to the premonitory phase.[11] One hypothesis is that premonitory symptoms persist through the entire migraine attack and are continuing after the headache has already subsided, but this requires further research.[7] The postdrome phase can last up to two days.

Classification

Migraine is classified according to the International Classification of Headache Disorders (ICHD).[12] Diagnosis is made on history taking. Sometimes additional investigations are necessary, but only to exclude secondary causes of headache. There are no imaging markers or blood tests to (accurately) diagnose migraine.

According to the ICHD there are two main types of migraine: migraine without aura and migraine with aura (Table 1). A diagnosis of migraine without aura is made when

a patient has experienced 5 or more attacks without aura, whereas for a diagnosis of migraine with aura a patient needs 2 or more attacks that involve an aura. Many migraine with aura patients also have attacks without aura.[3] Some patients experience an aura without the headache, so co-called typical aura without headache .[13]

Table 1. Classification of migraine without aura and migraine with aura (ICHD-3 criteria[12])

Migraine without aura	
A.	At least five attacks fulfilling criteria B-D
B.	Headache attacks lasting 4 – 72 hours (untreated or unsuccessfully treated)
C.	Headache has at least two of the following four 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

Migraine with aura	
A.	At least two attacks fulfilling criteria B and C
B.	One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal
C.	At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache
D.	Not better accounted for by another ICHD-3 diagnosis.

Also relevant for this thesis is the subtyping of episodic versus chronic migraine. According to criteria of the ICHD[12], a patient has chronic migraine when headaches occur on 15 or more days per month for at least 3 months of which at least 8 of the headache days are migraine days (i.e. headache fulfilling migraine criteria). A patient has episodic migraine when headache days are less frequent. Patients with episodic migraine have a clear "interictal state" when they have headache-free days and an "ictal state" when they are in one of the four phases (premonitory/aura/headache/postictal) of the migraine attack. For patients with chronic migraine, it is more difficult to make this distinction

since many of them experience almost daily headaches. An important cause of the daily headaches is the overuse of acute medication leading to medication-overuse headache, which is likely present in the majority of chronic migraine patients.[14] After withdrawal from acute medication during two to three months the number of headache days is reduced by 50% in most patients.[15]

Migraine pathophysiology

Migraine headache is caused by activation of the trigeminovascular system.[1,7] This system consists of the nociceptive trigeminal afferents that surround cranial blood vessels and project via the trigeminal ganglion to the trigeminal nucleus caudalis in the brainstem. Pain signals are then transmitted to the thalamus via ascending pain pathways and finally cortical areas. The long duration of the migraine headache could be due to sensitisation of the trigeminal afferents. Accompanying symptoms such as allodynia, photophobia and phonophobia can also be explained by activation and sensitisation of neurons along the ascending pain pathways and in the thalamus.[7]

Migraine aura is regarded to be caused by 'cortical spreading depolarization' (CSD), a wave of electrophysiological hyperactivity followed by a wave of inhibition. Spreading depolarization describes a phenomenon characterized by intense neuronal and glial depolarization that classically starts in the occipital - visual - cortex and slowly (~3 mm/min) propagates frontally, until it "encounters a less sensitive part of the brain" and stops or redirects, thus explaining the wide variety of aura patterns patients report.[1,7,16] After the initial wave, affected neurons can be depolarized for several minutes up to an hour.[16] Therefore, originally the term 'cortical spreading depression' was used although the term depolarization is now advocated.[1]

It is not clear what initiates the aura and the headache. Genetic predisposition definitely plays an important role, as shown in family, population, and twin studies.[17] Discovery of so-called 'FHM genes' has led to the concept that the migraine brain is hyperexcitable and therefore more vulnerable to a CSD.[18] Familial hemiplegic migraine (FHM) is a rare monogenetic subtype of migraine with auradefined by transient hemiparesis during the aura phase. In most patients FHM is caused by pathogenic mutations in either the *CACNA1A* (FHM1), the *ATP1A2* (FHM2) or the *SCN1A* (FHM3) gene.[19] All three genes code for proteins involved in ion transport across neuronal and glial cell membranes, and FHMmutations, at least based on cellular studies, all lead to increased concentrations of the excitatory neurotransmitter glutamate in the synaptic cleft (at least in the cortex).[18] Additional functional studies in transgenic FHM mice, which express human pathogenic mutations, indeed showed a reduced CSD-triggering threshold, enhanced speed and enhanced propagation of CSDs compared to wild-type mice.[18] In the mutant mice CSDs also reaches the motor cortex, explaining the hemiplegia.[20] From experiments

in animals there is compelling evidence for a link between CSD and activation of the trigeminovascular system.[21–23] Regarding the underlying molecular mechanism for this link, there is data showing that activation of neuronal Panx1 channels leads to release of HMGB1 protein upon a CSD event, subsequently leading to parenchymal neuroinflammation and stimulation of astrocytes in the glia limitans, which then release inflammatory mediators that can activate the trigeminal afferents and cause head pain.[24] Molecules such as K^+, nitric oxide (NO) and H^+ that are additionally released upon a CSD might also stimulate trigeminal afferents.[20] Furthermore, it is thought that CSD may also activate the trigeminovascular system via direct cortico-trigeminal projections.[7,25]

Several important questions remain unanswered. It is not known what triggers a CSD in patients with migraine with aura. Furthermore, in humans, a spontaneous CSD has not been demonstrated unequivocally except for the capture by advanced neuroimaging of less than a handful events.[26] CSD has typically been described after cortical injury and not spontaneously.[27,28] More importantly, the CSD theory lacks a compelling explanation for patients that experience migraine without aura, although it has been proposed that spreading depolarizations may occur subcortical and asymptomatic, but evidence for such 'silent auras' is essentially lacking.[7]

Another proposed theory is that migraine attacks start earlier and deeper in the brain, namely in the hypothalamus.[7,29] One good argument for this theory is that the premonitory phase and its symptoms such as yawning, frequent urination, thirst, food craving and mood changes point to the hypothalamus.[7] Neuroimagingstudies in humans also point tohypothalamic activation prior to aura or headache manifestations of a migraine attack.[29] Furthermore, the hypothalamus is closely linked to the trigeminovascular system, brainstem nuclei implicated in migraine, and the thalamus, and plays a key role in periodicity. It is not known which molecular mechanisms would cause paroxysmal hypothalamic dysfunction in migraine.

Migraine pathophysiology in relation to biochemical studies

Biochemical measurements in multiple body fluids – most relevant are cerebrospinal fluid (CSF), blood, and urine – have already contributed to our understanding of migraine pathophysiology.

First, the discovery of altered plasma levels of serotonin (5-HT) and its metabolite 5-HIAA in migraineurs was important for the development of so-called 'triptans'.[30] 5-HT_1 receptor agonists (primarily targeting 5-HT_{1B} and 5-HT_{1D} subtypes) are effective in aborting a migraine attack in many patients, when taken early in the headache phase. 5-HT receptors are abundantly expressed in the various components of the trigeminovascular system.[11] Triptans currently are the main class of acute migraine medication, that is in addition

to ordinary pain killers such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). However, the overuse of triptans (≥ 10 days per month) and ordinary pain killers or NSAIDS (≥ 15 days per month) or combination (≥ 10 days per month) can result in medication-overuse and is the main risk factor for developing chronic migraine.[14]

Second, elevated levels of calcitonin gene-related peptide (CGRP) were found in the external jugular vein during migraine attacks, compared to headache-free intervals;[31] although there has been discussion whether this is the case, since results could not be replicated in another study even though the same assay was used.[32] CGRP is a neuropeptide that is released from trigeminal afferent fibers upon activation. It is released together with other neuropeptides and mediators and can lead to sustained activation and sensitization of trigeminal afferents.[33] There is increasing evidence that CGRP has additional central sites of action; for instance CGRP is likely to act as an important neurotransmitter in the trigeminal nucleus caudalis.[33,34] In humans, intravenously administered CGRP was shown to provoke a migraine without aura-like attack in both patients with migraine with aura (57% success) and migraine without aura (67% success), but not in healthy controls.[35] Currently, antibodies against CGRP or its receptor and small molecules targeting the CGRP system are being investigated as preventive and acute migraine drugs and have shown to be effective[36], so these classes of drugs are entering the domain of clinical practice.

Third, the discovery of the FHM genes, but also other basic science research, suggests that glutamate plays an important role in migraine pathophysiology.[1] Glutamate is the main excitatory neurotransmitter in the brain and increased concentrations in migraine could explain a lower threshold for CSD.[18] However, biochemical results in migraine have been conflicting.[37,38] Furthermore, other neurotransmitters are also relevant for neuronal excitability such as gamma-aminobutyric acid (GABA) and glutamine.[39]

Hypothesis and aim

The leading hypothesis for the research described in the first part of this thesis is that the susceptibility to develop migraine attacks is somehow reflected at the biochemical level. That is, already outside the attack the biochemical profile of a person with migraine is different from that of a person without migraine. It is likely that – besides serotonin, CGRP and glutamate – additional metabolites show differences between patients and healthy subjects. The aim of this part of the thesis is to identify these metabolites to further unravel migraine pathophysiology. This will not only be relevant for the development of new drug targets but also for the diagnosis and disease prognosis of migraine patients. Ideally, the metabolites or 'biomarkers', can also aid clinicians in choosing the correct treatment for their patients.

Methods particularly relevant for this thesis

The studies described in this thesis primarily focus on the CSF. Although blood is easier to collect, blood foremost contains biochemical information that reflects what happens in the entire organism. CSF on the other hand, being closer to the brain, likely better reflects biochemical processes occurring in the brain.[40] As migraine is a brain disease, CSF should therefore be the preferred body fluid for discovery studies on migraine biomarkers. To have improved understanding of the biochemical processes relevant to migraine pathophysiology, one ideally measures multiple metabolites instead of one single molecule. Advances in the field of *metabolomics* have made this possible. Using techniques such as mass-spectrometry one can measure up to dozens of metabolites simultaneously in the same sample.[41,42] This is in sharp contrast with older measurement techniques, such as enzyme-linked immune sorbent assay (ELISA) or radio-immuno-assay (RIA) that target one specific molecule often using most of a precious sample.[41] Especially when samples are scarce – as is the case for CSF because it needs to be collected via lumbar puncture – it is undesirable to use large sample sizes to measure only a few metabolites. Metabolomics made it possible to measure multiple metabolites, not only raising the chance of finding a candidate biomarker, but also leading to a better understanding of involved metabolic networks. Ideally, multiple metabolites show alterations in disease versus control samples, pointing towards specific disease pathways.[43] Metabolomics has already led to promising discoveries in diabetes,[44] atherosclerosis,[45] and cancer.[46] Researchers of brain disorders are also beginning to apply metabolomics with interesting results in epilepsy,[47] mild cognitive impairment,[48] and Alzheimer's disease.[49] However, metabolomics has not yet been applied in migraine studies.

Metabolomic techniques also have disadvantages. Foremost, extensive validation is necessary before a method can be applied in a study. Ideally, for each metabolite the optimal sample and measurement condition must be developed. Also, for each metabolite, rigorous validation procedures are needed before quantification is considered reliable.[50] Since optimal conditions can vary between metabolites, researchers are forced to choose between metabolites, that is reliable quantification of certain metabolites at the cost of reliability of another metabolites.[51] However, for our research purpose (searching for candidate biomarkers), the advantages outweigh the disadvantages. We focussed on reliable quantification of amine molecules,[52] since relevant neurotransmitters such as glutamate and GABA are amines. Ideally, precursors and degradation products of these metabolites are also quantified in the same metabolomics run. The results of our work on CSF measurements in migraine are described in this thesis.

Visual snow

Clinical characteristics

Visual snow is characterized by the continuous presence of countless small dots in the entire visual field.[53] Patients often describe it as "tv static from a detuned analogue television" since the dots are flickering on and off. Severity of the snow can vary during the day, but symptoms are never fully absent. Visual snow is regarded a separate disease since 2014.[53] Earlier reports often referred to the snow as a form of 'persistent migraine aura', likely because many patients have a history of migraine with aura.[54–59] However, in visual snow classic migraine features such as scintillating scotomas and fortification spectra are absent.[12,53,57] Furthermore, migraine auras often start unilaterally and expand,[59] whereas patients with visual snow generally report that disturbances in the entire visual field without spatial expansion.[53] Little is known about the epidemiology of visual snow, but it is considered quite rare. Age at onset is often in the early twenties. Visual snow occurs equally frequent in men and women.[53]

Classification

Diagnosis of visual snow is made after exclusion of secondary causes of pan-field visual disturbances, such as lesions in the visual pathway and retina. Ophthalmic and neurological examinations are generally normal.[53] Most patients report additional visual symptoms: palinopsia, enhanced entopic phenomena (excessive floaters or blue field entoptic phenomena, spontaneous photopsia), photophobia and nyctalopia. Therefore, it was proposed that visual snow is part of a clinical syndrome ('visual snow syndrome').[53] The syndrome criteria are reported in Table 2.

Visual snow pathophysiology

It is hypothesized that cortical hyperexcitability plays a role in visual snow, as also proposed for migraine with aura.[58] Theoretically the visual disturbances can be attributed to bilateral retinal pathology, but this seems unlikely since ophthalmological examinations and electro-retinograms are normal in patients with visual snow.[53] Visual snow is therefore generally considered a cortical problem.

In a magneto-encephalography study in six patients with persistent migraine aura (of which two were likely visual snow presentations) all cases had increased hyperexcitability of the visual cortex compared to migraine patients.[58] Another study using [^{18}F]-2-fluoro-2-de-oxy-D-glucose positron emission tomography (PET) showed hypermetabolism in the lingual gyrus, an area that modulates visual processing, in visual snow patients compared to healthy controls.[60] The same area was shown to be involved in migraine studies on photophobia.[61,62] However, because 14 of the 17 visual snow patients from the PET study also had comorbid migraine it remains unknown what differentiates between

visual snow, photophobia and migraine.[60]

Table 2. Proposed diagnostic criteria for visual snow syndrome [53]

Visual snow syndrome		
A.	Patient sees visual snow: dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.	
B.	Presence of at least two additional visual symptoms of the four following categories:	
	(i)	Palinopsia. At least one of the following: afterimages (different from retinal after images[a]) or trailing of moving objects.
	(ii)	Enhanced entoptic phenomena.[b] At least one of the following: excessive floaters in both eyes, excessive blue field entoptic phenomenon, self-light of the eye, or spontaneous photopsia.
	(iii)	Photophobia
	(iv)	Nyctalopia (impaired night vision)
C.	Symptoms are not consistent with typical migraine visual aura.	
D.	Symptoms are not better explained by another disorder.[c]	

[a] Palinopsia may be visual after-images and/or trailing of moving objects. Visual after-images are different from retinal after-images, which occur only after staring at a high-contrast image and are in complementary colour.
[b] These phenomena, arising from the structure of the visual system itself, include excessive floaters in both eyes, excessive blue field entoptic phenomenon (uncountable little grey/white/black dots or rings shooting over the visual field of both eyes when looking at homogeneous bright surfaces such as the blue sky), self-lighting of the eye (coloured waves or clouds perceived when closing the eyes in the dark) and spontaneous photopsia (bright flashes of light).
[c] Normal ophthalmology tests (corrected visual acuity, dilated-pupil fundoscopy, visual field examination and electroretinography) and no intake of psychotropic drugs.

Hallucinogen Persisting Perception Disorder and visual snow syndrome

For the thesis it is important that the term 'Hallucinogen Persisting Perception Disorder' (HPPD) is also introduced. The DSM-V diagnosis HPPD is used to describe visual complaints after illicit drug use. Although this diagnosis was originally reserved for flashback to the initial hallucinogenic trip, it is now also used to describe visual snow and other persistent visual symptoms that started after the intake of illicit drugs.[63] Primarily hallucinogens, such as ecstasy (XTC), lysergic acid diethylamide (LSD) and hallucinogen mushrooms, have been reported by patients as the trigger for their visual snow. Although these patients are excluded from previous studies on visual snow *syndrome* (see Table 2; footnote *c*) they report the exact same symptoms, including other symptoms associated with visual snow such as halos and palinopsia.[63] The reports suggest that hallucinogenic drug use is a potential risk factor for developing visual snow (although not the only risk factor since there are patients with visual snow who never used hallucinogenic drugs[53] and that visual snow is also reported in young children of whom it is unlikely that they used hallucinogens[64]). It will be important to known whether migraine is prevalent in patients with HPPD and visual snow. The hypothesis of hyperexcitability has been postulated in HPPD research, although this has not been investigated in much detail.[65]

Hypothesis and aim

The evidence discussed above suggests migraine and visual snow may share pathophysiological mechanisms underlying the visual symptoms. Since symptoms are continuously present in patients with visual snow these symptoms are easier to study – for example with functional neuroimaging – than the unpredictable attacks of migraine auras. It would therefore be interesting to include visual snow in future migraine studies. However, first more evidence is needed to determine if there is indeed a close relationship between both disorders. The second part of this thesis therefore aims to better describe the clinical relationship between migraine and visual snow.

Outline of this thesis

Part I of this thesis focuses on migraine, a paroxysmal brain disorder where visual disturbances occur in about one-third of patients as part of the migraine attack ('the migraine aura'). This part aims to discover biochemical alterations in CSF and blood in patients with migraine, that is in patients with aura and without aura. Special focus will be on investigating neurotransmitters given the evidence that cortical hyperexcitability seems to play an important role in migraine pathophysiology. **Part II** focuses on visual snow, a brain disorder with continuous visual disturbances in which cortical hyperexcitability could also play a role. This part aims to better describe the presumed clinical relation of visual snow with migraine. If there is a strong relation with migraine, visual snow could teach us more about potentially shared mechanisms involving cortical hyperexcitability.

Part I: Migraine, a brain disorder with paroxysmal visual disturbances

Chapter 2 describes a systematic review and meta-analysis of biochemical studies in CSF and blood of migraine patients. This chapter summarizes the most profound biochemical findings as well as strengths and limitations of previous studies. **Chapter 3** includes an observational study on the incidence of post-dural puncture headache, the major complication when collecting CSF. This study investigates which needles have the lowest risk for this complication. In **Chapter 4** we investigated amine profiles in CSF and blood from interictal patients (i.e. outside the attack) with migraine with aura (N = 99) and migraine without aura (N = 98) and compared those with amine profiles of healthy volunteers (N = 96). Several important neurotransmitters implicated in migraine pathophysiology such as glutamate and GABA, are amines.

Part II: Visual snow, a brain disorder with continuous visual disturbances

First, in **Chapter 5**, literature on visual symptoms in migraine is reviewed, including visual snow. Next, **Chapter 6** investigates migraine prevalence in population with

visual snow syndrome as well as the effect of treatment with commonly used migraine aura preventives, such as lamotrigine, valproate and topiramate. In addition, other comorbidities associated with migraine and visual snow are studied. **Chapter 7** investigates migraine prevalence in patients with visual snow triggered after intake of hallucinogenic drugs (HPPD). It is hypothesized that especially migraine patients - with their increased baseline excitability – are at risk of developing further changes in excitability after use of hallucinogens.

Finally, **Chapter 8**, provides a general discussion of this thesis, with considerations for future research on migraine biochemistry and visual snow.

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