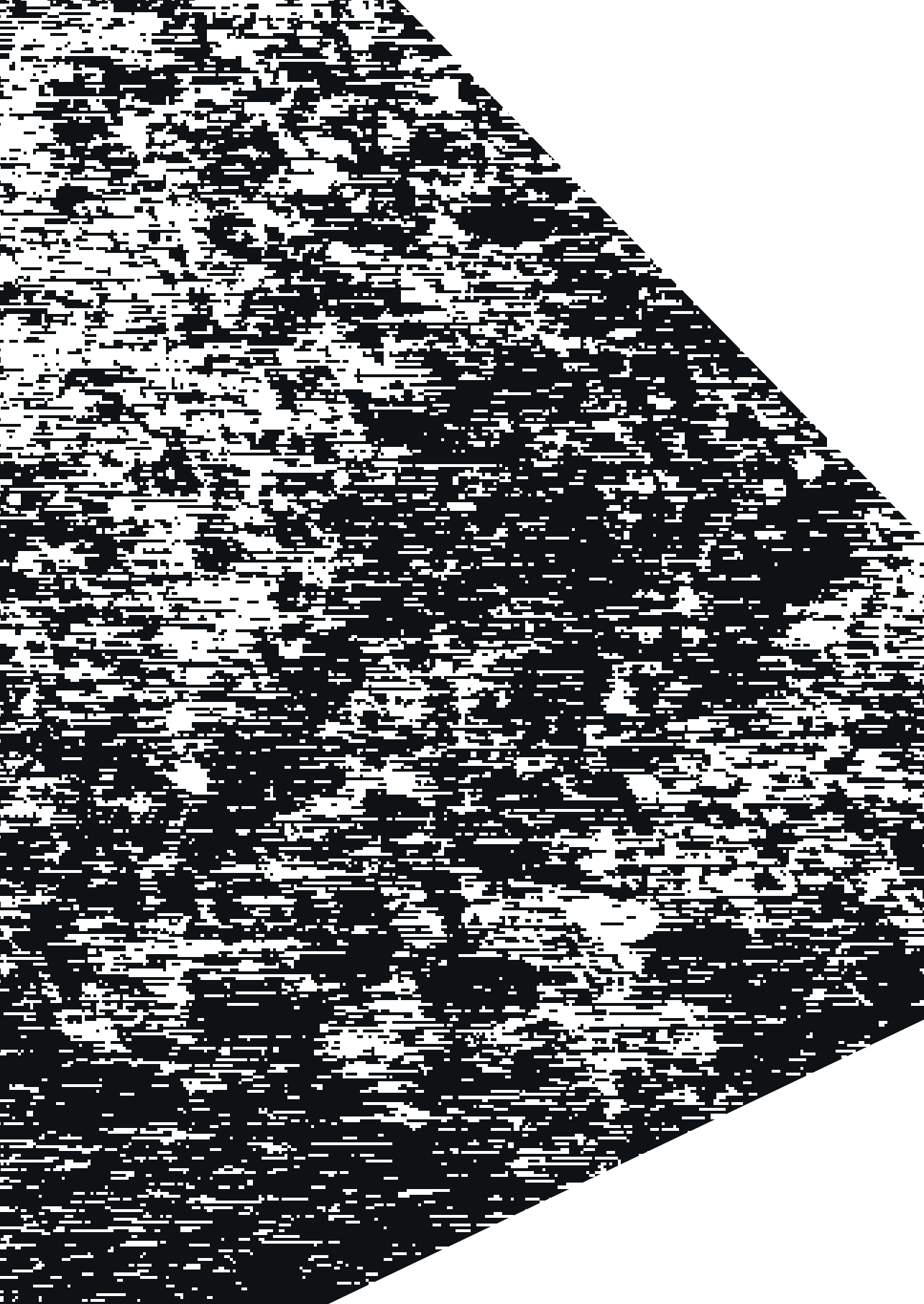
The exciting migraine brain: towards neurophysiological prediction of migraine attacks

Perenboom, M.J.L.



Chapter 7

General discussion

General discussion

The ability to predict the timing of a migraine attack would reduce the burden of migraine substantially, and open up new horizons for short-term preventive therapies. The fact that only few studies have focused on identifying functional markers of attack initiation in migraine is probably a reflection of the challenges to measure brain activity from a migraine patient while he or she develops a spontaneous attack. Migraine patients often indicate that certain *external* triggers specifically enhance the chance of developing an attack.[1,2] When tested in a clinical laboratory setting, however, it has always proven difficult to initiate an attack with supposedly reliable, patient-specific triggers like visual stimulation or physical exercise.[3,4] Elaborate neuroimaging and neurophysiology studies that aimed to dissect *internal* mechanisms contributing to the initiation of a migraine attack identified specific rises in brain activity during early phases of migraine attacks in the hypothalamus,[5] sensory cortex,[6] or visual cortex.[7] Applying such measurements on a daily basis for an early warning of an impending attack, preferably in a home setting, seems impracticable or even impossible.

The original research idea for this thesis was to combine longitudinal neurophysiological recordings with visual stimulation or transcranial magnetic stimulation, with the aim to identify neurophysiological features with predictive value for an upcoming migraine attack. This idea was based on the theory that in several biological systems, the speed by which a system recovers from a short perturbation is reduced when the system is nearing a tipping point, i.e., in our case a migraine attack onset.[8] However, we first had to develop a 'toolbox' of functional methods that are easy to apply over the migraine cycle with sufficient reproducibility, that allow measuring changes in brain excitability. Only after development of such methods, it is feasible to identify neurophysiological features indicative of an impending migraine attack. To this end, we developed and tested different techniques that allow to measure longitudinal changes in (cortical) responsivity in migraine. Firstly, we developed and applied the Leiden Visual Sensitivity Scale (**Chapter 2**). Secondly, we tested the applicability of several visual stimulation paradigms, including the visual chirp stimulation, in combination with EEG recordings, in a migraine mouse model (**Chapter 3**), and next validated the

usefulness of the same visual chirp stimulation in migraine patients (**Chapter 4**). Lastly, we studied transcranial magnetic stimulation evoked potentials (TEPs) and EEG phase clustering in migraine with aura and epilepsy (**Chapters 5 and 6**).

In this discussion, the findings presented in this thesis are placed in a broader context and suggestions are provided for future work aimed at identifying and understanding functional features of migraine attack onset.

Visual sensitivity and cortical excitability

In this thesis we identified features of abnormal visual processing in the migraine brain, evidenced from (i) the increased visual sensitivity in migraine, especially in the ictal state and further enhanced in migraine with aura and chronic migraine, as measured by the L-VISS questionnaire (**Chapter 2**), (ii) altered interictal TEP responses at the visual cortex (**Chapter 5**), and (iii) specific pre-ictal enhancement of visual responsivity in response to chirp stimulation (**Chapter 4**). Our findings point to hyperexcitability of visual cortical networks, and using a subjective outcome instrument as the L-VISS may provide a more simple approach to assess (clinical symptoms of) abnormal visual cortical excitability. In contrast to the used VEP and TMS measures, however, our L-VISS measures do not provide direct insight in underlying neuronal network mechanisms. Subjective measures of visual sensitivity in its different forms (like perception of luminance, contrast, color, motion and orientation[9]) are not a substitute for objective, but more elaborate, measures of cortical excitability using neuroimaging or neurophysiology. Indications of enhanced visual system activation during the interictal period based on subjective measures of visual sensitivity with questionnaires (**Chapter 2**), or psychophysical tests concerning visual motion, contrast or orientation sensitivity in migraine,[10,11] will have increased value when being supported by findings from neurophysiology and neuroimaging studies.

With magnetic resonance imaging, photophobia as measured by questionnaires positively correlated with blood oxygen-level dependent activation in the visual cortex interictally,[12,13] and positron emission tomography activation levels were also extra enhanced in migraine patients experiencing photophobia compared to patients without this symptom.[14] With a psychophysical approach, enhanced

contrast perception in the interictal period in migraine has been related to excessive cortical GABA-ergic inhibition in between attacks, which would reduce in the pre-ictal phase, thus resulting in more excessive excitation.[15]. Also in schizophrenia patients, performance in a psychophysical contrast increment tasks has been correlated to levels of the inhibitory neurotransmitter GABA as measured with magnetic resonance spectroscopy.[16] To further explore the underlying mechanisms of visual sensitivity as measured by the L-VISS questionnaire or other psychophysical measures, combined research including neuroimaging or neurophysiology would be a next step.

After publication, the L-VISS questionnaire has been applied in other patient groups with possible alterations in cortical excitability.[17,18] People with Visual Snow Syndrome, a condition where continuous visual distortions like TV-static are present in the entire visual field, report a level of visual burden (as measured by L-VISS) comparable to migraine patients during the attack, irrespective of comorbid migraine.[17] Other studies had shown that contrast and luminance increment thresholds are altered in those patients, suggestive of elevated visual cortex excitability in Visual Snow Syndrome.[19] In patients with the chronic pain syndromes fibromyalgia or chronic regional pain syndrome (CRPS), visual discomfort as measured by L-VISS was increased with regards to controls or patients with other chronic pain like back pain or ostheoarthritis.[18] In CRPS and fibromyalgia, but not in the other pain conditions studied, hypersensitivity to bright light and flashing stimuli was previously reported, possibly as a result of central sensitization.[18] The increased levels of visual sensitivity in those disorders could be another, still indirect, hint of the link between visual sensitivity and cortical excitability.

Recently, a couple of longitudinal studies employed measurements of visual sensitivity across the migraine cycle using on-screen image presentations. Afterimage duration was increased in individual migraine patients during the attack compared to interictal measurements, while 48 and 24 hours before attack onset the averaged afterimage duration showed a non-significant positive trend.[20] The detection of contrast increments, but not luminance increments, improved in patients two days (but not one day) before the attack.[15] This effect was mainly reported on a group level, but was also highly patient-specific; contrast perception was enhanced either before or during the attack depending on the subject. Lastly,

the threshold for detecting vertical coherent motion improved from two days before to two days after the attack.[9] These findings, based on subjective psychophysical experiments, illustrate that within-patient differences in visual processing may lead to individual 'attack predictors'. With a questionnaire like the L-VISS, such patient-specific differences in visual sensitivity could also be tracked. The subjective nature of such instruments, however, still allows for the presence of a learning effect and personal bias in the interpretation of these tests. Parallel future neurophysiological and neuroimaging studies would be required to identify whether patient-specific changes in visual processing occur towards and during attack onset.

Translational research for identification and understanding of migraine attack biomarkers

In this thesis, we studied the visual chirp stimulation, a promising neurophysiological method for migraine attack prediction, in a migraine mouse model (**Chapter 3**) as well as in migraine patients (**Chapter 4**). A translational approach helps to unravel the mechanistic underpinnings of functional differences between migraine patients and headache-free control subjects, and has identified neuronal hyperexcitability as key feature contributing to migraine-related functional changes.[21,22] The influence of genetic background on neurophysiological findings in migraine,[23] is controlled for in animal experiments by studying comparable stimulation paradigms as are used in patient studies. Also, more invasive recordings at *in vitro* (e.g., neuronal) and *in vivo* level (e.g., single cell, local fields potentials and intracranial EEG) could be conducted with relevant mouse models.

The mutant mice used for the VEP experiments in **Chapter 3** harbor an R192Q mutation that in patients causes familial hemiplegic migraine type 1 (FHM1). The mutation causes a gain of presynaptic neuronal $Ca_V2.1$ channel function that was demonstrated to lead to enhanced glutamatergic neurotransmission in the cortex.[24,25] Those Ca^{2+} channels play a key role in thalamocortical oscillatory activity, as absence of $Ca_V2.1$ channels showed reduced gamma-band power in *in vitro* and *in vivo* experiments.[26] FHM1 mutant mice showed entrainment of cortical oscillatory activity up to 40 Hz, as evidenced by an enhanced EEG response power to chirp stimulation in beta- and lower gamma-band (**Chapter 3**). This observation

adds to the literature pointing towards enhanced thalamocortical excitability in a migraine-susceptible brain.[27] In our mouse study, especially the combination of local field recordings and subdural EEG recordings allowed us to point to a role of neural network interactions outside of the visual cortex, as local neuronal activity during chirp stimulation was absent above 15 Hz, whereas in the EEG recordings entrainment was present up to 40 Hz (**Chapter 3**). In the same mouse model, females were shown to be most susceptible to induction of cortical spreading depolarization (CSD),[28] the neural correlate of the migraine aura. Our preliminary observation that EEG responses to visual chirp stimulation appeared larger (but not significantly so) interictally in female migraine patients (**Chapter 4**) is an interesting lead for further translational research.

In migraine patients, beta-gamma band responses to chirp stimulation were previously reported to be increased interictally,[29] whereas our experiments in migraine patients showed this enhancement only for pre-ictal recordings (**Chapter 4**). Our translational findings (**Chapter 3**) support the link between enhanced cortical excitability[22,30] and increased chirp responsivity in migraine, while our clinical findings (**Chapter 4**) suggest a transient pre-ictal, but not interictal, rise in responsivity. Compared to previous reports of interictal increases in EEG responsivity to visual stimulation in beta-gamma band frequencies,[29,31,32] our findings could differ due to selection of participants experiencing at least on migraine episode per month. As cortical excitability measured in migraine patients differs with the attack frequency, within episodic migraine[33] and between episodic and chronic migraine[34] (as also indicated in **Chapter 2**) a comparison between groups of patients with different attack frequencies could provide more insight into possible frequency related differences in EEG responses to visual chirp stimulation.

To further our mechanistic insights in brain disorders, the recent development of 'lab-on-a-chip' methods to study, e.g., the effect of ion channel deficiencies at a neuronal (and even vascular) level are exciting. *Ex vivo* cellular models using brain slices or neuronal cultures based on stem-cells derived from migraine patients can help to elucidate the role of glutamatergic versus GABA-ergic inhibitory neurons in altered brain excitability in migraine[35] and, by comparison to *in vivo* animal models, roles of larger-range brain connectivity. Cortical dynamics are being studied with 'brain-on-a-chip' models with thalamic and hippocampal input,[36] and epileptic

seizures could already be modelled with a modular approach to mimic functionally connected (human) neural networks.[37] On the side of visual input, several advances are made in 'eye-on-a-chip' models, with focus on retinal or cornea models to study ophthalmic disorders.[38] The combination of these different models can provide a first step towards unraveling functional features of the entire chain of visual processing, in line with future visions of a 'human-on-a-chip'.[39] In migraine research, however, factors like individual external attack triggers and the combination of systemic fluctuations possibly underlying an attack, are highly unlikely to be mimicked in *ex vivo* research. In this light, *in vivo* animal research will remain an important link between *ex vivo* research in cellular models, and human patient studies, to bridge the knowledge gaps between single cell responses, local interactions and visual system responsivity.

The value of TMS-EEG measurements in migraine attack prediction and prevention

Transcranial magnetic stimulation as a method to probe cortical excitability has been applied in migraine and epilepsy in various ways. Here, we focused specifically on the direct measurement of cortical responses using concomitant EEG recordings. In **Chapter 5**, we showed frontal and occipital decreases in the N100 peak of the TMS evoked potentials for migraine patients with aura in the interictal phase compared to controls, but no differences in phase clustering over stimuli for any of the studied EEG response frequency bands. In people with epilepsy, relative phase clustering was enhanced when no anti-epileptic medication (typically directed at reducing excitability) was used (**Chapter 6**), but not when such medication was used, nor in controls or migraine patients with aura. In line with the findings at the group level, in a single subject with epilepsy, we demonstrated an inversely proportional relationship between medication dosage and phase synchronization.

In contrast to our TMS-EEG findings in migraine patients (with aura; **Chapters 5 and 6**), altered EEG phase synchronization in relation to visual stimulation was reported for migraine (with and without aura) patients, indicating altered excitability of the visual cortex.[40,41] The effect, however, was not similar in both subgroups of migraine; phase synchronization was enhanced in the alpha band in

migraine without aura, whereas it was decreased in the beta band in migraine with aura.[40] In photosensitive epilepsy, increased phase synchrony to flash stimuli was measured in the EEG gamma band right before the occurrence of the light-induced epileptic discharge.[42] This synchronization could be indicative of an increased propensity to neural entrainment. Although we measured a similar propensity of enhanced synchronization involving the gamma-band using visual chirp stimulation in migraine (**Chapter 4**), direct stimulation (over electrode Cz at the center of the scalp) of cortical neurons by magnetic stimulation did not result in entrainment in the visual cortex (**Chapters 5 and 6**). The absence of such synchronization effects with TMS in migraine with aura points to different underlying mechanisms, including region and frequency specific effects, and between subgroups of patients. Future studies incorporating groups of migraine with and without aura (compared to controls), and utilizing multiple stimulation frequencies and synchronization measures are necessary to provide additional insight in phase clustering and its relationship to cortical excitability in migraine.

Over the migraine cycle, various motor responses after TMS, measured by electromyography (EMG), were altered pre-ictally compared to interictal measurements,[33,43] and also differed during and after an attack.[33] Those responses were also altered in interictal migraine patients compared to controls, in line with our findings obtained by EEG for cortical instead of motor activity (**Chapter 5**). In epilepsy, seizure susceptibility is suggested to be reflected in changes in TMS-induced motor responses up to 24 hours before the seizure.[44,45] TMS-EEG could be an addition to this repertoire of tests not only for epilepsy but also for migraine. Unlike visual stimulation (**Chapter 4**), such tests involving daily magnetic stimulation seem currently only suitable in a clinical setting and are thus mainly of interest for research purposes rather than supporting individual attack prediction.

The observed effect of medication which alters brain excitability on TMS induced phase clustering in one epilepsy patient (**Chapter 6**), emphasizes that another potential clinical application of TMS-EEG in migraine is the prediction of an individual's response to preventive medication.[46,47] Clinically, medication responsiveness can only be established when a period of at least three times the usual interval between attacks has passed without attacks. In epilepsy, attacks are usually easy to count (unless the patient is unaware of seizures) and are preventively treated

even when their frequency is low (e.g., two per year), hence this may require a long period of observation. In migraine, other issues hamper the clinical evaluation of preventive medication. The number of attacks per month is more difficult to register for migraine patients, as attacks vary in severity and duration. Furthermore, epilepsy preventives induce complete remission more often than migraine preventives. Therefore, migraine patients find it difficult to assess the overall effectiveness of their preventive medication. Objective measures to predict medication efficacy by assessing the inhibitory/excitatory balance in the brain could therefore be of great clinical benefit when preventing migraine attacks. In epilepsy, an increased TMS-EMG resting motor threshold, induced with anti-epileptic medication, was positively correlated with seizure reduction after one year.[48] With TMS-EEG, based on single and paired-pulse stimulation a distinction between anti-epileptic medication responders and non-responders could be made with 80% accuracy (compared to 92% accuracy for differentiating patients from controls).[49] In migraine, some older studies associated altered in phosphene thresholds with the prophylactic effects of e.g. beta-blockers or anti-epileptic medication on cortical excitability.[50,51]

Predicting migraine attacks requires longitudinal studies

Most studies in migraine focus on differences between measurements in migraine patients during the interictal phase and control subjects, with a wide variety of measurement modalities and readouts. Methods from neuroimaging, neurophysiology, neurochemistry and psychophysiology are applied to provide insights in the 'trait' of migraine, i.e., in which way differs the physiology (and psychology) of a migraine patient compared to people without the disease.[22,52] For insight in the start of the migraine attack, we are more interested in the 'state' of the migraine patient, i.e., in which way differs the physiology (and psychology) of an individual with migraine during the different phases of the migraine attack.

Different theories and frameworks regarding the onset of the migraine attack co-exist in scientific literature, most of which focus either on changes in cortical excitability,[8,53] or changes in subcortical brain activation levels.[5,54] The onset of the migraine attack is hypothesized to be related to a 'critical transition' in brain

dynamics.[8] In a similar way, EEG-based signatures of epileptic seizure susceptibility showed paroxysmal critical transitions before an attack based on the concept of critical slowing down over short (minutes) and longer (hours to days) timescales.[55] As the tipping point of this transition is approached, the migraine attack threshold lowers and smaller triggers are sufficient to start the attack.[8] Based on the theory of early-warning signals for critical transitions,[56] the recovery rate to small perturbations (like flashes of light) decreases as the tipping point (the migraine attack onset) is eminent.[57] Our findings support the view that brain excitability, including that of the cortex, fluctuates over the migraine cycle (**Chapters 2 and 4**). This fluctuation combines with (and may be caused by) effects of other physiological rhythms that are related to factors like (lack of) sleep, stress and hormonal levels. The combined impact of these changes on brain function could cause a migraine patient to have a temporarily lower attack threshold. A trigger like a flashing light, a change in external stressors or intake of certain food that normally would not initiate a migraine attack, could in case of a lower attack threshold start a cascade of brain activation leading to the migraine headache.[8] For instance, a reduction in stress level (i.e., relief after stress) appeared to be a specific trigger for headache initiation in certain patients.[58] The concept that relief after chronic stress could lower the attack threshold has been supported by pre-clinical findings in the FHM1 mouse model.[59] In the cortex, a lower threshold as result of hyperexcitability can also result in a migraine aura by initiation of a cortical spreading depolarization.

For longitudinal studies over the migraine cycle, the reproducibility of EEG read-outs within a participant should be high for consistent *intra*-individual comparisons (**Chapter 4**). Several findings of altered interictal cortical excitability, however, could not be reproduced in other, blinded, study designs.[60,61] Multiple reasons for this lack of *inter*-individual reliability are proposed, like differences in stimulation parameters (e.g., intensity, frequency and duration) and read-out parameters (e.g., block amplitude, synchronization, habituation, et cetera), but also timing with respect to the previous or next migraine attack, differences in medication or comorbidities, and (relatively) low number of patients in studies.[22,61] It could be possible that for different individuals, different stimulation paradigms and read-outs need to be combined to meet this criterium. Therefore, already during the development of biomarkers that could be used as early-warning signals for an

impending migraine attack, this longitudinal reproducibility should be taken into account by repeatedly measuring the same patients – preferably over multiple attacks – before conclusions can be drawn. As outlined in the next paragraphs several promising recent developments including home EEG recordings and the rise of data analysis using artificial intelligence are leading the way towards such studies.

Future directions in migraine attack prediction

The prediction of an impending migraine attack with a simple home test would be valuable for patients on several levels.[8,62] It provides patients with the possibility to manage their lives around the paroxysmal nature of the disease, and helps in timing the use of pre-emptive prophylactic medication to avert attacks, as well as acute medication to suppress or shorten the headache phase. From a research perspective, new avenues for therapeutic targets and drug development could open up when it becomes easier to study patients with more elaborate methods like neuroimaging in research labs or hospitals during the premonitory or early headache phase.

Home EEG recordings

Recording brain signals in a home environment used to be limited to small-scale, often recreative, EEG systems with a limited number of electrodes in e.g. a headband. Systems developed for this purpose demonstrated the potential for research applications by recording event-related potentials after auditory stimulation, although especially the signal-to-noise ratio warrants improvement.[63] More elaborate scalp EEG systems with a cap with 10 or more electrodes and direct connection to a smartphone could provide more information, although home application could be more bothersome due to the number of electrodes. Comparing data obtained with an open source smartphone-based system to a standard clinical EEG system, both used for recordings in a hospital setting, showed that epileptiform abnormalities were correctly captured when the smartphone-based EEG recordings were analyzed manually by neurologists, albeit with lower sensitivity than with the standard EEG recordings in the same patients.[64] To train patients to use comparable systems themselves in a home setting with the aim of consistent, longitudinal data generation is one of the challenges that have to be overcome. Easier-to-use EEG

systems could mitigate the inconsistent application of for instance the EEG cap, with mobile in-ear EEG electrodes integrated in a headphone providing a possible solution.[65]

In migraine, a promising longitudinal application of home EEG applying a commercial device with electrodes over the frontal cortex was recently published.[62] Resting state brain waves and image-induced event-related potentials were recorded daily for 14 days, with patients doing all the necessary setup themselves. Based on diary input, recordings were categorized into interictal, pre-ictal (<24 hrs before an attack), ictal or post-ictal (<48 hrs after an attack) phases. Decreased theta power, increased relative beta power, and decreased event-related potential amplitude were present in the 24 hours before an attack and during the attack, compared to interictal recordings in the same patients. In another pilot study, patients were recorded at least five times per week over several weeks with a similar commercial EEG device, while receiving an auditory oddball task. Prediction of attack likelihood improved with one or two (short) tests in the pre-ictal phase, where induced EEG responses differed from *a priori* defined template EEG activity.[66] The relationship between the changes in EEG features observed in these longitudinal recordings and possible underlying changes in cortical excitability remains to be determined.

To efficiently implement longitudinal home recordings of EEG activity in patients, several difficulties that were indicated in those recent longitudinal studies with large, at-home, patient involvement (like setting up the EEG recordings without help of a researcher)[62,66] need to be addressed in further research. Firstly, no within-patient repeatability could be tested, and when multiple recordings in the same phase were available in the same patient only the measurement with highest quality of data was used. Secondly, for a single daily measurement participants had to record at least 20 minutes of brain activity, which could be a large burden in a home setting. Still, data quality was relatively low, as just 20-30% (7-11 out of 35, depending on the paradigm) of participants had enough artifact-free recordings in all migraine phases.[62] A quicker stimulation with high signal to noise ratio, like the visual chirp stimulation (**Chapter 4**) could improve data quality issues. Thirdly, the division of phases in 24 hours blocks for the statistical analysis still averages brain activity that might change on an hour-level towards an impending attack. Daily neuroimaging measurements showed that up to 48 hours before an attack the brain's activity is

already altered.[5] Especially an easy-to-use method like EEG could shed further light on the relevant time scale of attack prediction, possibly in combination with psychophysical visual tests,[9] or questionnaires (**Chapter 2**).

Resting-state recordings of brain activity and artificial intelligence

In this thesis, we studied the brain's response to external perturbations. From the ongoing EEG activity (so-called 'resting-state' EEG), however, a wealth of additional information about the brain's functioning including disease propensity could also be extracted. Standard quantitative EEG analyses in migraine did not provide a clear biomarker for disease presence or phase of the migraine cycle.[67] With the advent of artificial intelligence methods to be applied to large EEG datasets, several new directions of study become available.[68]

Firstly, with machine learning methods, classification patterns that otherwise may go undetected could be distinguishable, by combining multiple – hundreds – of EEG-based features, and also data from e.g. questionnaires and patient headache diaries, in a single model.[69] For example, when classifying pain phenotypes using standard quantitative EEG features, multiple comparison correction limited the amount of features that could be taken into account. With a machine learning classification algorithm, hundreds of EEG features over multiple frequency bands and electrode locations were combined in one model, demonstrating the possibility of pain phenotype classification that was not feasible with the traditional combination of statistics and feature extraction.[70] Due to the number of features and the non-linear nature of the model, it was unfortunately not possible to study which parameters carried the largest distinctive load.[70]

Secondly, non-standard features can be extracted automatically from the raw EEG signal using a subset of machine learning, i.e., deep learning methods like convolutional neuronal networks. Using such methods, the gender of a subject could be predicted based on EEG signals only; reverse-engineering of the sex-specific features revealed that fast beta activity and its spatial distribution were main attributes.[71] With a large database of EEG recordings of people with migraine and controls, similar big data analyses could yield insights that are not attainable in smaller studies like presented in this thesis. The clinical relevance of the predictive

ability of newly detected EEG features should be in balance with the amount of intra- and interpatient recordings necessary to detect the feature(s). As observed in longitudinal recordings in people with epilepsy, features indicative of an impending migraine attack with a large individual effect size (high predictive value within a patient) could be more relevant than standard clinical neurophysiological features with a larger group effect size but smaller individual effect.[72]

Thirdly, 'deep learning' methods could aid in the prediction of migraine attacks by building patient-specific models that take into account individual variation in activity within and across brain areas. Deep learning methods are able to extract ('learn') relevant features from large datasets with examples, like EEG recordings with the corresponding migraine phase, without explicit definition of EEG features by a researcher. Within-patient epileptic seizure detection using longitudinal scalp EEG, recorded with a wearable setup, indicated that patient-specific models can be effective for individual seizure prediction.[73] Interestingly, a more general seizure prediction model, developed on EEG data from multiple patients, could easily be adapted to a personalized attack prediction model using transfer learning (i.e., adapting a general model by partly retraining it with a smaller amount of extra data).[73] After an initial model development phase on a large dataset containing longitudinal EEG data from many patients (20 or more), for other patients personalized predictive models could possibly be developed. Short EEG recordings (up to a couple of minutes) could then suffice in training such individualized predictors based on the general model, instead of needing multiple patient-specific, longitudinal EEG recordings (resting state and/or evoked EEG responses) to build a personalized model.[73] Applying such an approach to migraine attack prediction could direct future studies towards the development of a general EEG-based attack onset model, that is adaptable to individual differences in brain activity (including responses to triggers) towards the next attack.

Multidisciplinary research in a university medical center

A multidisciplinary approach towards migraine attack prediction, as described in this thesis, with a combination of clinical and translational studies with a focus on state-of-the-art data analytics, is important to bring together knowledge in the

different fields studying the origins of migraine. Within a university medical center, there is wide-spread clinical, medical and biological expertise; the addition of technical expertise provides opportunities in, amongst others, data analytics, and hardware and software design for stimulation and recording. With the emergence of overlapping, multidisciplinary study fields like biomedical engineering, clinical technology and technical medicine, researchers working as intermediaries between patients, clinicians, biologists and engineers will be better equipped to balance different visions on e.g. patient burden, clinical and biological relevance, technical implementation and, preferably, also make the sum more than its parts. Challenges in patient recruitment and measurements, stimulus design and data analysis would benefit from such a combined approach by selecting the right discipline for each step – while maintaining oversight of all developments.

The success of a multidisciplinary approach is not a given. Complex research questions, like the origin of the migraine attack, have to be solved at the cross-borders between the patient, the doctor, and a technical environment.[74] By being open to each other's viewpoints and qualities, expectations between researchers, medical doctors and patients can be managed and resources allocated; the so-called 'discipline openness' challenge.[74] For instance, while many recordings and burdensome stimulations might improve the availability of (EEG) data, the patient's involvement will probably be more difficult to ensure. As seen in migraine research, new methods to perturb and probe the brain's activity emerge on a regular basis, shining new light (sometimes literally) on the enigma at hand. Where this tendency to accumulate, by adding more techniques to a toolbox with each newly involved discipline, possibly leads to more publications, the step to better integrate and compare those techniques might lead to more insight.

While connecting people, data and health systems,[75] all involved disciplines should put the patient first. Especially in migraine, with a disease burden that stretches beyond the headache phase, a home test for an impending attack should be easy to do for the patient – possibly by subtracting as much technology as possible to get a simple yet effective home test.[76] How much technology could be subtracted is one of the next challenges.

References

1. Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, et al. Premonitory symptoms in migraine - An electronic diary study. *Neurology*. 2003;60(6):935–40.
2. Schoonman GG, Evers DJ, Terwindt GM, Van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: A questionnaire study in 461 patients. *Cephalalgia*. 2006;26(10):1209–13.
3. Hougaard A, Amin FM, Amin F, Hauge AW, Ashina M, Olesen J. Provocation of migraine with aura using natural trigger factors. *Neurology*. 2013;80(5):428–31.
4. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A*. 2001;98(8):4687–92.
5. Schulte LH, Mehnert J, May A. Longitudinal Neuroimaging over 30 Days: Temporal Characteristics of Migraine. *Ann Neurol*. 2020;87(4):646–51.
6. Mykland MS, Bjørk MH, Stjern M, Sand T. Alterations in post-movement beta event related synchronization throughout the migraine cycle: A controlled, longitudinal study. *Cephalalgia*. 2018;38(4):718–29.
7. Bjørk M, Stovner LJ, Hagen K, Sand T. What initiates a migraine attack? Conclusions from four longitudinal studies of quantitative EEG and steady-state visual-evoked potentials in migraineurs. *Acta Neurol Scand Suppl*. 2011;124(191):56–63.
8. Scheffer M, van den Berg A, Ferrari MD. Migraine Strikes as Neuronal Excitability Reaches a Tipping Point. Sommer C, editor. *PLoS One*. 2013;8(8):e72514.
9. Shepherd AJ. Tracking the migraine cycle using visual tasks. *Vis*. 2020;4(2):23.
10. Nguyen BN, McKendrick AM, Vingrys AJ. Abnormal inhibition-excitation imbalance in migraine. *Cephalalgia*. 2016;36(1):5–14.
11. Battista J, Badcock DR, McKendrick AM. Center-surround visual motion processing in migraine. *Investig Ophthalmol Vis Sci*. 2010;51(11):6070–6.
12. Cucchiara B, Datta R, Aguirre GK, Idoko KE, Detre J. Measurement of visual sensitivity in migraine: Validation of two scales and correlation with visual cortex activation. *Cephalalgia*. 2015;35(7):585–92.
13. Huang J, Zong X, Wilkins A, Jenkins B, Bozoki A, Cao Y. FMRI evidence that precision ophthalmic tints reduce cortical hyperactivation in migraine. *Cephalalgia*. 2011;31(8):925–36.
14. Maniyar FH, Sprenger T, Schankin C, Goadsby PJ. Photic hypersensitivity in the premonitory phase of migraine - a positron emission tomography study. *Eur J Neurol*. 2014;21(9):1178–83.
15. McKendrick AM, Chan YM, Vingrys AJ, Turpin A, Badcock DR. Daily vision testing can expose the prodromal phase of migraine. *Cephalalgia*. 2018;38(9):1575–84.
16. Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD, et al. GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *J Neurosci*. 2010;30(10):3777–81.
17. Eren OE, Ruscheweyh R, Straube A, Schankin CJ. Quantification of photophobia in visual

snow syndrome: A case-control study. *Cephalalgia*. 2020;40(4):393–8.
18. Ten Brink AF, Proulx MJ, Bultitude JH. Validation of the Leiden Visual Sensitivity Scale and Visual Discomfort Scale in Chronic Pain Conditions. *Perception*. 2021;50(5):399–417.
19. McKendrick AM, Chan YM, Tien M, Millist L, Clough M, Mack H, et al. Behavioral measures of cortical hyperexcitability assessed in people who experience visual snow. *Neurology*. 2017;88(13):1243–9.
20. Luedtke K, Schulte LH, May A. Visual processing in migraineurs depends on the migraine cycle. *Ann Neurol*. 2019;85(2):280–3.
21. Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AMJM. Migraine pathophysiology: Lessons from mouse models and human genetics. *Lancet Neurol*. 2015;14(1):65–80.
22. Tolner EA, Chen S-PP, Eikermann-Haerter K. Current understanding of cortical structure and function in migraine. *Cephalalgia*. 2019;39(13):1683–99.
23. Lisicki M, Ruiz-Romagnoli E, D'Ostilio K, Piedrabuena R, Giobellina R, Schoenen J, et al. Familial history of migraine influences habituation of visual evoked potentials. *Cephalalgia*. 2017;37(11):1082–7.
24. Tottene A, Conti R, Fabbro A, Vecchia D, Shapovalova M, Santello M, et al. Enhanced Excitatory Transmission at Cortical Synapses as the Basis for Facilitated Spreading Depression in CaV2.1 Knockin Migraine Mice. *Neuron*. 2009;61(5):762–73.
25. Vecchia D, Tottene A, van den Maagdenberg AMJM, Pietrobon D. Mechanism underlying unaltered cortical inhibitory synaptic transmission in contrast with enhanced excitatory transmission in CaV2.1 knockin migraine mice. *Neurobiol Dis*. 2014;69:225–34.
26. Llinás RR, Choi S, Urbano FJ, Shin HS. γ-Band deficiency and abnormal thalamocortical activity in P/Q-type channel mutant mice. *Proc Natl Acad Sci U S A*. 2007;104(45):17819–24.
27. Coppola G, Ambrosini A, Di Clemente L, Magis D, Fumal A, Gérard P, et al. Interictal abnormalities of gamma band activity in visual evoked responses in migraine: an indication of thalamocortical dysrhythmia? *Cephalalgia*. 2007;27(12):1360–7.
28. Eikermann-Haerter K, Dileköz E, Kudo C, Savitz SI, Waeber C, Baum MJ, et al. Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. *J Clin Invest*. 2009;119(1):99–109.
29. Gantenbein AR, Sandor PS, Goadsby PJ, Kaube H. Chirp stimulation: H-response short and dynamic. *Cephalalgia*. 2014;34(7):554–8.
30. Vecchia D, Pietrobon D. Migraine: a disorder of brain excitatory–inhibitory balance? *Trends Neurosci*. 2012;35(8):507–20.
31. Nyrke T, Kangasniemi P, Lang a. H. Difference of steady-state visual evoked potentials in classic and common migraine. *Electroencephalogr Clin Neurophysiol*. 198973(4):285–94.
32. Chorlton P, Kane N. Investigation of the cerebral response to flicker stimulation in patients with headache. *Clin Electroencephalogr*. 2000;31(2):83–7.
33. Cosentino G, Fierro B, Vigneri S, Talamanca S, Paladino P, Baschi R, et al. Cyclical changes of cortical excitability and metaplasticity in migraine: evidence from a repetitive transcranial magnetic stimulation study. *Pain*. 2014;155(6):1070–8.
34. Chen WT, Wang SJ, Fuh JL, Lin CP, Ko YC, Lin YY. Persistent ictal-like visual cortical excitability in chronic migraine. *Pain*. 2011;152(2):254–8.

35. Wendling F, Gerber U, Cosandier-Rimele D, Nica A, De Montigny J, Raineteau O, et al. Brain (Hyper)Excitability Revealed by Optimal Electrical Stimulation of GABAergic Interneurons. *Brain Stimul*. 2016;9(6):919–32.
36. Brofiga M, Pisano M, Callegari F, Massobrio P. Exploring the contribution of thalamic and hippocampal input on cortical dynamics in a brain-on-a-chip model. *IEEE Trans Med Robot Bionics*. 2021;3(2):315-27.
37. Pelkonen A, Mzezewa R, Sukki L, Ryynänen T, Kreutzer J, Hyvärinen T, et al. A modular brain-on-a-chip for modelling epileptic seizures with functionally connected human neuronal networks. *Biosens Bioelectron*. 2020;168:112553.
38. Peng Z, Zhou L, Wong JKW, Chan YK. Eye-on-a-chip (EOC) models and their role in the future of ophthalmic drug discovery. *Expert Rev Ophthalmol*. 2020;15(5):259–61.
39. Edington CD, Chen WLK, Geishecker E, Kassis T, Soenksen LR, Bhushan BM, et al. Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies. *Sci Rep*. 2018;8(1):1–18.
40. De Tommaso M, Stramaglia S, Marinazzo D, Trotta G, Pellicoro M. Functional and effective connectivity in EEG alpha and beta bands during intermittent flash stimulation in migraine with and without aura. *Cephalalgia*. 2013;33(11):938–47.
41. Angelini L, Tommaso M De, Guido M, Hu K, Ivanov PC, Marinazzo D, et al. Steady-State Visual Evoked Potentials and Phase Synchronization in Migraine Patients. *Phys Rev Lett*. 2004;93(3):038103.
42. Parra J, Kalitzin SN, Iriarte J, Blanes W, Velis DN, Lopes da Silva FH. Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception? *Brain*. 2003;126(5):1164–72.
43. Neverdahl JP, Omland PM, Uglem M, Engstrøm M, Sand T. Reduced motor cortical inhibition in migraine: A blinded transcranial magnetic stimulation study. *Clin Neurophysiol*. 2017;128(12):2411–8.
44. Badawy R, Macdonell R, Jackson G, Berkovic S. The peri-ictal state: cortical excitability changes within 24 h of a seizure. *Brain*. 2009;132(4):1013–21.
45. Wright MASY, Orth M, Patsalos PN, Smith SJM, Richardson MP. Cortical excitability predicts seizures in acutely drug-reduced temporal lobe epilepsy patients. *Neurology*. 2006;67(9):1646–51.
46. Ziemann U, Reis J, Schwenkreis P, Rosanova M, Strafella A, Badawy R, et al. TMS and drugs revisited 2014. *Clin Neurophysiol*. 2015;126(10):1847–68.
47. Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS–EEG. *Clin Neurophysiol*. 2019;130(5):802–44.
48. Badawy RAB, Macdonell RAL, Berkovic SF, Newton MR, Jackson GD. Predicting seizure control: Cortical excitability and antiepileptic medication. *Ann Neurol*. 2010;67(1):64–73.
49. Kimiskidis VK, Tsimpiris A, Ryvlin P, Kalviainen R, Koutroumanidis M, Valentin A, et al. TMS combined with EEG in genetic generalized epilepsy: A phase II diagnostic accuracy study. *Clin Neurophysiol*. 2017;128(2):367–81.
50. Gerwig M, Niehaus L, Stude P, Katsarava Z, Diener HC. Beta-blocker migraine prophylaxis affects the excitability of the visual cortex as revealed by transcranial magnetic stimulation. *J Headache Pain*. 2012;13(1):83–9.

51. Mulleners WM, Chronicle EP, Vredeveld JW, Koehler PJ. Visual cortex excitability in migraine before and after valproate prophylaxis: A pilot study using TMS. *Eur J Neurol*. 2002;9(1):35–40.
52. Goadsby PJ, Holland PR, Martins-oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine – A disorder of sensory processing. *Physiol Rev*. 2017;97:553–622.
53. Stankewitz A, May A. The phenomenon of changes in cortical excitability in migraine is not migraine-specific--a unifying thesis. *Pain*. 2009;145(1–2):14–7.
54. Peng KP, May A. Migraine understood as a sensory threshold disease. *Pain*. 2019;160(7):1494–501.
55. Maturana MI, Meisel C, Dell K, Karoly PJ, D'Souza W, Grayden DB, et al. Critical slowing down as a biomarker for seizure susceptibility. *Nat Commun*. 2020;11(1):1–12.
56. Scheffer M, Bascompte J, Brock W a, Brovkin V, Carpenter SR, Dakos V, et al. Early-warning signals for critical transitions. *Nature*. 2009;461(7260):53–9.
57. Veraart AJ, Faassen EJ, Dakos V, van Nes EH, Lürling M, Scheffer M. Recovery rates reflect distance to a tipping point in a living system. *Nature*. 2012;481(7381):357–9.
58. Lipton RB, Buse DC, Hall CB, Tennen H, Defreitas T a, Borkowski TM, et al. Reduction in perceived stress as a migraine trigger: testing the "let-down headache" hypothesis. *Neurology*. 2014;82(16):1395–401.
59. Balkaya M, Seidel JL, Sadeghian H, Qin T, Chung DY, Eikermann-Haerter K, et al. Relief Following Chronic Stress Augments Spreading Depolarization Susceptibility in Familial Hemiplegic Migraine Mice. *Neuroscience*. 2019;415:1–9.
60. Omland PM, Uglem M, Hagen K, Linde M, Tronvik E, Sand T. Visual evoked potentials in migraine: Is the "neurophysiological hallmark" concept still valid? *Clin. Neurophysiol*. 2016;127(1):810–816.
61. Cosentino G, Fierro B, Brighina F. From different neurophysiological methods to conflicting pathophysiological views in migraine: A critical review of literature. *Clin Neurophysiol*. 2014;125(9):1721–30.
62. Martins IP, Westerfield M, Lopes M, Maruta C, Gil-da-Costa R. Brain state monitoring for the future prediction of migraine attacks. *Cephalalgia*. 2020;40(3):255–65.
63. Badcock NA, Mousikou P, Mahajan Y, De Lissa P, Thie J, McArthur G. Validation of the Emotiv EPOC® EEG gaming systemfor measuring research quality auditory ERPs. *PeerJ*. 2013;2013(1):e38.
64. Mckenzie ED, Lim ASP, Leung ECW, Cole AJ, Lam AD, Eloyan A, et al. Validation of a smartphone-based EEG among people with epilepsy: A prospective study. *Sci Rep*. 2017;7.
65. Sintotskiy G, Hinrichs H. In-ear-EEG–a portable platform for home monitoring. *J Med Eng Technol*. 2020;44(1):26–37.
66. Shahaf G, Kuperman P, Bloch Y, Yariv S, Granovsky Y. Monitoring migraine cycle dynamics with an easy-to-use electrophysiological marker—A pilot study. *Sensors (Switzerland)*. 2018;18(11).
67. Magis D, Vigano A, Sava S, D'Elia TS, Schoenen J, Coppola G. Pearls and pitfalls: Electrophysiology for primary headaches. *Cephalalgia*. 2013;33(8):526–39.
68. Roy Y, Banville H, Albuquerque I, Gramfort A, Falk TH, Faubert J. Deep learning-based

electroencephalography analysis: A systematic review. *J Neural Eng*. 2019;16(5):37.
69. Bzdok D, Altman N, Krzywinski M. Points of Significance: Statistics versus machine learning. *Nat Methods*. 2018;15(4):233–4.
70. Levitt J, Edhi MM, Thorpe R V., Leung JW, Michishita M, Koyama S, et al. Pain phenotypes classified by machine learning using electroencephalography features. *Neuroimage*. 2020;223:117256.
71. Van Putten MJAM, Olbrich S, Arns M. Predicting sex from brain rhythms with deep learning. *Sci Rep*. 2018;8(1):1–7.
72. Kuhlmann L, Lehnertz K, Richardson MP, Schelter B, Zaveri HP. Seizure prediction — ready for a new era. *Nat Rev Neurol*. 2018;14(10):618–30.
73. Page A, Shea C, Mohsenin T. Wearable seizure detection using convolutional neural networks with transfer learning. *Proc - IEEE Int Symp Circuits Syst*. 2016;2016:1086–9.
74. Grönqvist H, Olsson EMG, Johansson B, Held C, Sjöström J, Lindahl Norberg A, et al. Fifteen challenges in establishing a multidisciplinary research program on eHealth research in a university setting: A case study. *J Med Internet Res*. 2017;19(5):e7310.
75. Bardhan I, Chen H, Karahanna E. Connecting systems, data, and people: A multidisciplinary research roadmap for chronic disease management. *MIS Q Manag Inf Syst*. 2020;44(1):185–200.
76. Adams GS, Converse BA, Hales AH, Klotz LE. People systematically overlook subtractive changes. *Nature*. 2021;592(7853):258–61.