Migraine Alleviation

A Novel Treatment Approach and the Mechanisms Investigated Using Multimodal Neuroimaging

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Abstract (English) *

This project investigates a novel approach to abort migraine attack. The approach targets at hyper-electrical activity in the brain at the front wave of cortical spreading depression (CSD) - thought to cause migraine aura. By applying a mild mechanical stimulation to the head, the brain tissue is stretched and the electrical activity is decreased according to mechanical-electrophysiological experimental data, canceling out the hyper-electrical activity before CSD spreads. A proof-of-concept pilot study shows the approach is effective and safe. In this project, an in-depth investigation of the underlying mechanisms and its effectiveness in a larger volunteer group will be explored before it can be introduced as a new therapy for migraine alleviation. The project includes two major parts: mechanical part (the Swedish team) involves head injury biomechanics and numerical simulations of electrophysiological effect caused by the mechanical stimulation for optimal targeting; functional investigation (the XX team) using multimodal neuroimaging techniques (simultaneous EEG-EOG-fMRI) and a novel technique for eye movement. New mechanisms of migraine will be uncovered by the introduction of above new technologies and critical for the development of new therapy options in the future. Further, the new critical time window identified from this project will promote the effectiveness of other therapies by ensuring the treatment provided within this time window.

Popular scientific description (Swedish)*

Migrän är en mycket vanlig kronisk neurologisk sjukdom som påverkar 10% av befolkningen över hela världen och är för närvarande den 6:e ledande orsaken till sjukdomsrelaterad funktionsnedsättning. En miljon människor lider av migrän i Sverige och förekomsten av migrän i Kina är högre än 9%. Migränattack präglas av återkommande huvudvärk och ca 30% har en aurafas före starten av huvudvärken. Under aurafasen har patienter oftast visuella hallucinationer och ser fläckar av ljus, zigzag-linjer (scintillationer) och områden med visuell förlust (scotom), som kan orsaka säkerhetsproblem speciellt om man får migränattack under bilkörning. Trots några läkemedel och icke-läkemedelsterapi som för närvarande finns tillgängliga, söker endast personer med svår migrän medicinskt stöd. Många söker inte behandling på grund av den frustrerande ineffektiviteten av behandlingarna som finns tillgängliga. För tillfället finns det inget botmedel mot migrän vilket gör det till en kronisk sjukdom som påverkar livskvaliteten för dem som lider av migrän under hela deras livstid. Nytt tillvägagångssätt för migränlindring behövs. Studier har visat konkreta bevis på att visuella hallucinationer av migränaura är relaterade till kortikal spridingsdepression (eng. cortical spread depression (CSD)) som kännetecknas av abnorm elektrisk avfyrning av neuronerna. CSD har sedan dess varit ett mål för att utveckla nya terapier. Detta projekt syftar till att undersöka ett nytt tillvägagångssätt med hjälp av mekanisk stimulering för att avbryta migränauran och efterföljande huvudvärk. Tillvägagångssättet riktar sig mot den hyperelektriska aktiviteten i hjärnregionen vid den främre vågen av CSD. Genom att applicera en mild mekanisk stimulering mot huvudet sträcker sig hjärnvävnaden och den elektrofysiologiska aktiviteten minskas enligt experimentella data, vilket avbryter den hyperelektriska aktiviteten innan CSD vågen sprider sig och därmed avbryter migränauran. Pilotförsök av konceptet har visat att tillvägagångssättet är effektivt och säkert. I detta projekt kommer en fördjupad undersökning av de underliggande mekanismerna och dess effektivitet i en större volontärgrupp att undersökas innan den kan introduceras som en ny behandling för migränlindring. Projektet innehåller två huvuddelar: 1. Mekaniska delen (görs av det svenska forskarlaget) som undersöker hjärnbiomekaniken som orsakas av mekanisk stimulering och hur det förändrar hjärnans elektrofysiologiska aktivitet - att användas för optimal inriktning mot CSD; 2. Funktionell delen (görs av XX) använder samtidig EEG-fMRI och en ny för ögonrörelse. Resultaten från ovan beskrivna forskningsaktiviteter kommer att ge en god grund för effektiviteten av det föreslagna tillvägagångssättet. Genom detta samarbetsarbete, som består av experter från huvudskadebiomekanik, samt experter inom EEGfMRI, MR-fysik och kliniker kommer, förutom införandet en ny metod för migrän-lindring, ny kunskap om migrän utvecklas genom projektet genom att introducera nya teknologier av samtidig EEG-fMRI (för närvarande en Modalitet som används), och av ögonrörelse. Detta kommer även att främja effektiviteten hos andra migränbehandlingar och främja migränforskning i bredare bemärkelse. Särskilt har det nya sättet att fånga ögonrörelse under migränattacker sina unika fördelar vad gäller att fånga de oförutsägbara migränattackerna som är omöjliga att detektera med konventionella tillvägagångssätt. Slutligen kommer det kritiska tidsfönstret som identifieras från detta projekt att främja effektiviteten hos andra terapier om de tillhandahålls inom tidsfönstret.

1 Purpose and aims

1.1 Background

Migraine is a *chronic neurological disease* characterized by recurrent headaches accompanied by nausea, vomiting, and hypersensitivity to light, sound, and smell influencing 10% of people all around the world and is the 6th leading cause of disease related disability and about 30% has aura (see **Figure 1** image modified based on[1]) and literature of CSD theory.[2]. In the *U.S.*, more than 38 million people suffer from migraine[3], and over 1 million reported in *Sweden*[4]. In *China*, the prevalence of migraine is higher than 9%[5,6]. Among migraineurs, about 30% have *visual* aura phase precede the onset of headache including spots of light, zigzag lines (scintillations) and regions of visual loss (scotomas)[7], although a small portion have other types of aura such as *sensory* aura. Substantial evidences from animal models also human volunteers have shown migraine visual aura is related to Cortical Spreading Depression (CSD) (see Reviews[8,9]). CSD is like the passage of a hyperelectricity storm over the cortex, the surface of the brain. The storm front arrives as a wave of *increased electrical discharg*e (causes the visual scintillations at the beginning of the aura) that starts at a particular spot and spreads gradually outward over the cortex). After the wave passes, electrical activity in the area behind is *significantly reduced* (responsible for the missing or dark area of vision, the *scotoma*).

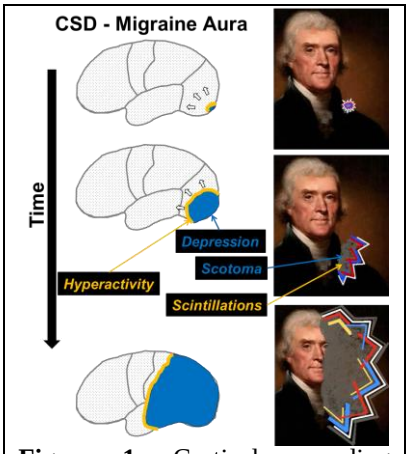

Figure 1: Cortical spreading depression (CSD) propagation imaged by fMRI is related to the symptoms of migraine aura reported by migraineurs. Wavefront of CSD (area under the thick yellow line) has increased electrical activity, followed by decreased activity once the wave has passed (blue area).

Hadjikhani et al. (2001)[10] provided definite evidence for the occurrence (both spatial and temporal) of CSD and migraine aura using high-field strength functional magnetic resonance imaging (fMRI) capturing visual aura in a migraine volunteer with predictable attack triggers. *Studies show CSD also plays an important role in migraine without aura (MoA)*[11]. Consequently, interrupting the abnormal brain electrical activity in CSD has been a target attempting to abort migraine attack in both MA and MoA[12].

Notwithstanding, the mechanisms for migraine is still unclear reflected by the little progress made in the therapeutic options available in the last two decades. Recent advances investigating different aspects of migraine urges that migraine should be viewed as a *complex brain network disorder* involves multiple cortical, subcortical and brainstem regions to account for the pain and the wide constellation of symptoms characterizing the attack[11].

Despite the few existing treatment options, only severe migraineurs seek for medical support. Drug is often with serious side effects and not always effective (Sec. 2.1). Single Transcranial Magnetic Stimulation (sTMS) as a promising therapeutic option approved by FDA, only works 37%[13] and varies in

[1] Dr. Craig Blackwell Migraine 2: Clinical https://www.youtube.com/watch?v=jduJpQCc5ao&t=176s
[2] Vos T et al (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386(9995):743.
[3] http://migraineresearchfoundation.org/about-migraine/what-is-migraine/migraine-disease-and-its-impact/
[4] The Swedish Migraine Association. http://www.w-h-a.org/index.cfm/spKey/member_organisations.sweden_svenska_migr_nf_rbundet_.html
[5] Yu S et al (2012) The prevalence and burden of primary headaches in China: a population based door to door survey. Headache 52:582-91.
[6] Wang X et al (2015) The Prevalence and Awareness of Migraine Among University Students in Harbin, China. J Oral Facial Pain Headache 29 (4).
[7] Schain AJ et al (2017) Cortical Spreading Depression Closes Paravascular Space and Impairs Glymphatic Flow: Implications for Migraine Headache. J Neurosci 37(11):2904-15.
[8] Charles AC and Baca SM (2013) Cortical spreading depression and migraine. Nat Rev Neurol 9:637-644
[9] Ayata C (2010) Cortical spreading depression triggers migraine attack: pro. Headache 50(4):725-30.
[10] Hadjikhani N et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. PNAS 98(8):4687-92.
[11] Puledda F et al (2017) An update on migraine: current understanding and future directions. J Neurol 20:1-9.
[12] Costa C et al (2013) Cortical spreading depression as a target for anti-migraine agents. J Headache Pain 14(1):62.
[13] Bhola R et al (2015) Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program. J Headache Pain 16(1):51.

different clinical trials[14]. There is still no cure for migraine. Indeed, many migraineurs do not seek medical care due to ineffective treatment, leaving on average, every day at least *24 million* people in the European Union and North America suffering migraines, making the condition one of the most disabling and expensive medical complaints worldwide[15]. ***New approaches for migraine alleviation and further studies on the mechanisms is needed, and this project tackles both*** - to introduce a new treatment approach for migraine alleviation and to investigate the underlying neurophysiological mechanisms using novel multimodal neuroimaging techniques.

1.2 A new treatment approach for migraine alleviation

According to CSD theory, the wavefront of CSD has an ***increased electrical activity*** at migraine attack. Then an approach can ***decrease the electrical activity*** at attack should be able stop CSD before it propagates to a larger area of the cortex thus to abort a migraine attack. *In vitro* stretching of brain tissue has shown to decrease brain electrical activity and up to 8.1% stretch is completely reversible[16], meaning a mild mechanical stimulation to stretch the brain tissue can modulate brain electrical activities. By linking above evidences, we propose a *new treatment approach for migraine alleviation by applying a mild mechanical stimulation based on the following new hypothesis.*

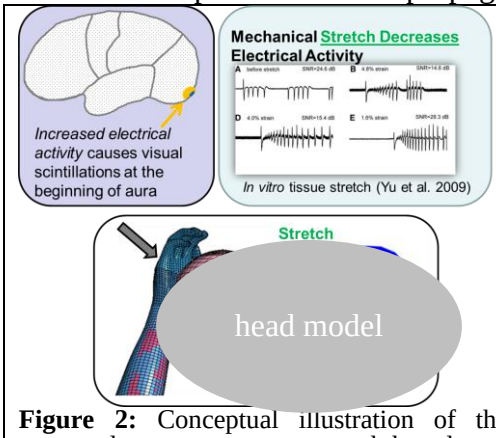

Figure 2: Conceptual illustration of the proposed new treatment approach based on a new hypothesis targeting at the wavefront of CSD. Apply a mild mechanical stimulation (e.g. self-hit) to the head to induce a mechanical stretch of brain tissue thus decreases the brain electrical activity to compensate the increased electrical activity at the wavefront of CSD. Note the color slice of brain tissue stretch is a conceptual illustration from another study with a different impact loading not related to this project.

The new hypothesis: the wavefront of CSD has increased brain electrical activity, when apply a mild mechanical stimulation to the head, the brain tissue deforms (stretching, compression, shearing etc.), and the stretching of tissue in turn decreases the activity and compensates the hyperelectric wavefront, therefore abort a migraine attack (see Figure 2). CSD although is more clearly related to migraine with aura, it also found to play an important role in migraine without aura. Thus, the mechanical approach is expected to work in both MA and MoA based on the same mechanism.

As part of the hypothesis:

- *A critical time window* exists for the mechanical stimulation to be effective. The intervention has to be applied as early as possible when only a small cortical area is affected (as shown in Figure 2, upper left) before CSD spreads. The reason for an early intervention is because CSD spreads at a relatively fast velocity about 3 mm/min[10], when the affected cortical area grows, it will be out of the capacity for the mild stimulation to induce sufficient mechanical stretch, thus decreasing in brain electrical activity, to cancel out the abnormal electrical activity at the wavefront of CSD. The ***critical time window is to be determined from this project and is hypothesized to be super early even less than a few seconds*** (see *Preliminary results* for evidence of this assumption).
- The *magnitude* of the brain tissue stretch during the mild stimulation should be "benign" – sufficient to interrupt the abnormal electrical activity and functionally reversible as a stretch up to a threshold will cause traumatic brain injury[17].
- The *location* of the mild stimulation to the head should target at inducing a stretching in the brain tissue at the wavefront of CSD. Figure 2 illustrates location at parietal eminence of the head, which is reported to be effective in one individual with visual aura (related to the visual cortex in the occipital lobe).

[14] Lipton RB et al (2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 9(4):373-80.
[15] Ferrari MD et al (2015) Migraine pathophysiology: lessons from mouse models and human genetics. Lancet Neurol 14(1):65-80.
[16] Yu Z et al (2009) Monitoring hippocampus electrical activity in vitro on an elastically deformable microelectrode array. J Neurotrauma 26(7):1135-45.
[17] About 22% reported in Kang WH et al (2015) Alterations in hippocampal network activity after in vitro traumatic brain injury. J Neurotrauma 32(13):1011-9.

- The *resting-state neural activity* of the migraineurs differs for different subtypes of migraine thus allow classifying subtype of migraine using multimodal neuroimaging, which then can guide optimal individual treatment.

1.3 Objectives

We have initiated a *proof-of-concept pilot* study and the results show the brain tissue stretch induced by an effective mild stimulation is sufficient to decrease the electrical activities while safe enough for complete reversible neuronal functions (see ***Preliminary results***). However, an in-depth investigation of the underlying mechanisms is needed before it can be used as an effective and safe therapeutic option for migraine alleviation.

Based on the preliminary investigations, the current project aims at:

- **Investigate the effectiveness of the approach in a larger group of migraineurs.** To answer following questions: what is the *critical time window* for the approach to be effective? Does effective impact force magnitude differ among migraineurs? Should the location be different for different subtypes of migraineurs (e.g. visual or sensory aura)? What is the biomarker to predict the effectiveness of the approach in an individual patient?
- **Investigate the mechanisms of migraine in general** by introducing novel multimodal neuroimaging. A migraine classification model will be built based on the features from neuroimaging
- **Investigate the underlying electrophysiological mechanisms of the proposed treatment approach** with the developed techniques from above, the onset time of the wavefront of CSD will be obtained in EOG and modeled as regressor in the simultaneously recorded functional MRI signal. The dynamic process will be revealed firstly for the treatment approach
- **Multiphysics modeling of CSD** to guide the use of the proposed approach targeting at a required brain area specific for different subtypes of migraine

2 Survey of the field and envisioned advances in this project

2.1 Treatment alternatives for migraine

A range of ***drugs*** has been considered for migraine for both treatment and prevention, which is usually classified as two major groups, one is painkiller to comfort the headache phase and the other is preventive drug that were originally developed for treating other types of brain disorder, such as antidepressant, anti-epilepsy drugs. Triptans, a drug has an effect or making blood vessels constrict and has been shown its effectives in migrant treatment[11]. Preventive medications don't always stop headaches completely, and some drugs cause serious side effects plus preventative drugs often need to take daily doses. *In China*, a number of studies have shown acupuncture can reduce migraine headache and alleviate migraine (see Review paper[18]). However, the effectiveness of this approach remains inconclusive.

A few ***noninvasive stimulation options*** exist including supraorbital stimulation (Cefaly), vagus nerve stimulation (gammaCore) and single-pulse transcranial magnetic stimulation (SpringTMS)[19]. Among these, sTMS based on the principle to interrupt the abnormal hyperactivity in CSD[20,21] - has shown to be effective for some patients to abort progression of the attack in clinical trials[13,14]. Interestingly, in both trials, the patients were instructed to use sTMS as early as possible: "We instructed patients to begin treatment ***as soon as possible*** after aura began and always within 1 h of aura onset"[13], and "Initiate treatment ***as early as possible*** when patient first experiences symptoms of migraine, including pain and/or aura symptoms"[13]. However, neither study offered an explanation on *how early* or the reasoning behind.

According to our hypothesis (Sec. 1.2), a *critical time window* exists for the proposed mechanical stimulation to be effective. Similarly, sTMS and other therapies based on the same principle as our proposed approach – targeting at CSD to interrupt the abnormal electrical activity – should also have a *critical time window* for it to be more effective. The instructions of early treatment for sTMS seem to

[18] Ning et al (2017) Research progress of fMRI study on pain – related brain networks of patients with migraine. Liaoning Journal of Traditional Chinese Medicine 44(1): 204-6. *(In Chinese)*
[19] Miller S et al (2016) Neurostimulation in the treatment of primary headaches. Pract Neurol 16(5): 362-375.
[20] Lipton RB, Pearlman SH (2010) Transcranial magnetic simulation in the treatment of migraine. Neurotherapeutics 7(2):204-12.
[21] Barker AT, Shields K (2017) Transcranial Magnetic Stimulation: Basic Principles and Clinical Applications in Migraine. Headache 57(3):517-24.

support the *critical time window* we proposed here and will determined in this project. Then if the patients use sTMS within the *critical time window*, the effectiveness is expected to be significantly increased. Despite it might be difficult for sTMS to be used super early with a few seconds, same with other therapy options. In this regard, the mild mechanical stimulation approach e.g. with a mild self-hit proposed in this project has its unique advantage over other therapy device even with the same effectiveness.

2.2 CSD computational modeling of CSD stopping and propagation

Computational models of CSD have been developed attempting to support the design of novel therapies targeting at CSD, which dates back to 1970s (see Review[22]). More recently, Dahlem et al[23,24] developed a macroscopic computational model of CSD described by differential equations of reaction-diffusion. Remarkably, it is capable of reproducing the particular spatio-temporal CSD pattern observed using high-field functional magnetic resonance imaging (fMRI)[10] and reported visual defects[25].

Studies have also shown cortical geometry (shape, curvature) influences the propagation of CSD waves. Pocci et al (2010)[26] using a simplified 2D model showed how sharp bends naturally blocked the wave propagation. In a personalized approach to migraine aura treatment, Dahlem et al (2015)[27] used Gaussian curvature of the cortex computed from MRI data to identify potential targets for neuromodulation. Towards this direction, a serial studies by Kroos et al. [28 , 29] advanced CSD modeling by developing patient-specific multiscale models of the whole cortex and include diffusion tensor imaging for a more realistic modeling of CSD. Solve the differential equations on such complex domain is only possible with numerical approaches; in above studies[23,24,28,28] ***Finite Element (FE) Method*** was used (Figure 3).

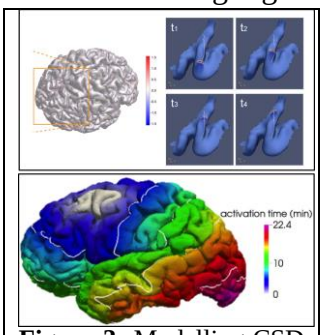

Figure 3: Modelling CSD propagation based on realistic geometry of the cortex surface. Image modified based on[27] (upper) and [28] (lower).

In this project, we will couple the mechanical stimulation to the state-of-the-art CSD models, and study which location should be stimulated to achieve a required brain tissue stretching targeting at the wavefront of CSD. Since wavefront of CSD is expected to be different for different subtypes of migraine (e.g. sensory aura CSD is likely to be initiated at sensory lobe, and visual aura at visual cortex), such a model will guide the location of stimulation for different subtypes of migraine. For this purpose, we will first develop an approach to extend the current state-of-the-art 2D (only included cortex surface domain) CSD models into 3D solid domain of the entire head thus allows coupling of the mechanical effect to study alterations of electrical activity induced by the intervention. See Sec. 3.2.2 for details for the approach.

2.3 Eye movement during migraine attack

Migraine aura typically begins as a small geometric pattern, known as a *fortification pattern*, somewhere in the visual field, which then expands overs a short period of time, around 20 minutes is a typical time period. Pöppel (1973)[30] reported that *eye movements shifted fortification patterns* by the angle of eye

[22] Miura RM et al (2007) Cortical spreading depression: an enigma. Eur Phys J Spec Top 147:287-302.
[23] Dahlem MA (2013) Migraine generator network and spreading depression dynamics as neuromodulation targets in episodic migraine. Chaos 23 (4):046101.
[24] Dahlem MA, Isele TM (2013) Transient localized wave patterns and their application to migraine. J Math Neurosci 3:7
[25] Dahlem MA, Hadjikhani N (2009) Migraine aura: retracting particle-like waves in weakly susceptible cortex. PLoS One 4(4):e5007.
[26] Pocci C et al (2010) Numerical study of the stopping of aura during migraine. InESAIM: Proceedings 2010 (Vol. 30, pp. 44-52). EDP Sciences.
[27] Dahlem MA et al (2015) Cortical hot spots and labyrinths: why cortical neuromodulation for episodic migraine with aura should be personalized. Front Comput Neurosci 9:29.
[28] Kroos JM et al (2016) Geometry Shapes Propagation: Assessing the Presence and Absence of Cortical Symmetries through a Computational Model of Cortical Spreading Depression. Front Comput Neurosci 10.
[29] Kroos JM et al (2017) Patient-specific computational modeling of cortical spreading depression via diffusion tensor imaging. Int J Numer Method Biomed Eng doi: 10.1002/cnm.2874. [Epub ahead of print]
[30] Pöppel E (1973) Fortification illusion during an attack of ophthalmic migraine. Implications for the human visual cortex. Naturwissenschaften 60: 554–555.

movement, which was then confirmed by more extensive studies by Jung (1979)[31]. Further, Jung (1979) observed that induced nystagmus influences the fortification spectra. During migraine aura, the *fortification pattern* develops naturally from a small to larger area visual hallucinations[32]. If eye movement can change the fortification patterns shown in above studies, ***then the change in the fortification patterns should be related to eye movement or pupil sizes at different phases of migraine aura.*** The changes in eye movement may be small; the question is how to detect such subtle changes. Indeed related to this issue, Koban et al (2016)[33] assessed pupil sizes in migraine patients with aura during migraine attacks. The results showed pupil size did not differ significantly between migraine pain period, painless period and healthy controls. However, due to the preparation time, when patients were measured, the aura phase already passed and which could explain their findings. This is due to the nature of the approach that did not allow them to capture the migraine aura phase.

3 Project description and mode of cooperation

3.1 Project overview

The project consists two major parts (Figure 4):

- **Biomechanical Study** *of the consequences of mild mechanical stimulation (e.g. self-hit) to the head. Mechanical Simulation* to study the brain tissue deformation (stretch, compression, shearing etc.) based on the measured force (see *Sec. 3.2.1 and Preliminary Results*) and location (from video kinetics). Secondly, M*ultiphysics Modeling of CSD wave* and investigate how and where mechanical stimulation to be applied to target the hyperelectric CSD wavefront.
- **Functional Study** using multimodal neuroimaging including *EEG-EOG, fMRI* to capture brain activity at *interictal phase, ictal phase (natural without intervention) and ictal phase (with intervention).*The functional study of migraine mechanisms *in general* involves local volunteers (Group 1 without intervention of the proposed treatment approach), will be used to develop a migraine classification model based on the features from multimodal neuroimaging. The techniques developed here will then be used for Group 2 with intervention to investigate the underlying neurophysiological mechanisms of the proposed treatment approach. The biomechanical study and functional data measured from this intervention Group 2 will be integrated, together with self-reported effectiveness to develop a **Guideline** for optimal treatment, which will then be disseminated to the project website to recruit more **Online Volunteers.** With eye movement data and intervention effectiveness collected from hundreds of online volunteers, critical time window and a novel objective diagnostic/prognostic tool for migraine will be developed.

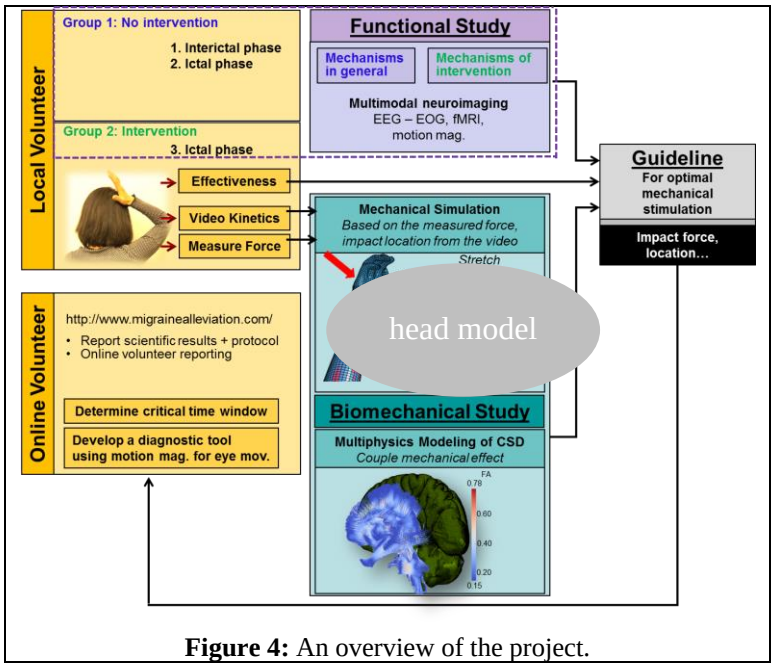

Figure 4: An overview of the project.

3.2 Methodologies and approaches

The methodologies and approaches to be used for each task identified in Figure 4 are described as following.

[31] Jung R (1979) Translocation of cortical migraine phosphenes through eye movements and vestibular stimulation. Neuropsychologia 17: 173–185.
[32] Schott GD (2007). Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration. Brain130(6):1690-703.
[33] Koban Y et al (2016) Intraocular pressure and ocular biometric parameters changes in migraine. BMC Ophthalmology 16(1):70.

3.2.1 Impact force during the mild mechanical stimulation

Pressure film will be used to measure the contact pressure then integrate over the contact area to obtain the impact force. Pressure film is a paper-like sensor and contains two layers, one liquid bubble layer and a layer with dye. Under pressure loading the bubbles break and stain the dye layer. The liquid bubble layer is manufactured so that the amount of breaking bubbles is proportional to the applied pressure, thus causing a color density proportional to the applied pressure[34]. Fuji pressure film has been shown effective in a number of biomechanics studies, e.g. to measure hip/knee impact force[35,36,37] and during boxing[38]. Our ***Preliminary results*** show it's effective in measuring the impact force during the mild self-hit and we will continue use the developed technologies in this project to measure contact forces in more volunteers during the intervention. From the quantified force, the volunteer will also get a sense how much force should be applied for an effective mechanical stimulation.

3.2.2 Finite element (FE) head models for mechanical simulation and multiphysics CSD simulation

FE head models will be used in this project in two different aspects: simulate mechanical deformation in the brain due to impact, and simulate the CSD wave with mechanical effects added. Advanced human head models based on FE Method have proven to be a powerful tool and is widely used in studying traumatic brain injury in automobile industry and sport head injury. FE models allow including detailed brain anatomy such as falx, tentorium, bridging vein thus make it possible to study the deformation of brain tissue due to an external hit to the head. Head models have shown brain tissue deforms in a complicated and inhomogeneous manner, stretched at some area, and compressed or sheared at other area depending on the magnitude and location of the impact.

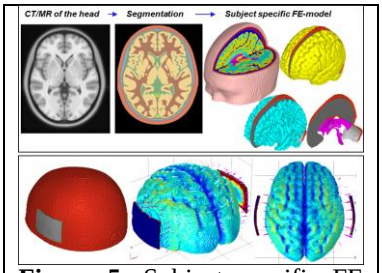

Figure 5: Subject specific FE head model with detailed anatomical structures for an adult head (upper) and finite element simulation of electrical field with electrode paddings. These models will be used and refined in this project.

In this project, we will first develop an approach to extend the current state-of-the-art 2D (only included cortex surface domain) CSD models into 3D solid domain to couple the mechanical effect and study which location should be stimulated to achieve a required brain tissue stretching targeting at the wavefront of CSD. Especially we will focus on the critical time window to explore why critical time window exists before it's too late to stop a migraine attack. The output from neuroimaging measurement and volunteer test (eye movement, fMRI, EEG-EOG) from the XX team will provide data to evaluate and verify the model.

Finite element head model has been used in the Preliminary proof-of-concept study and will be refined further in this project to include more anatomical details. Knowledge on FEM head modeling, brain biomechanics, multiphysics modeling (Figure 5) already developed provide pre-prerequisite for carrying out this task.

3.3 Innovative aspects, the identified risks and contingency plans

The innovative aspect of the project includes risks and difficulties, which are identified as following.

Identified risks	Impact	Anticipated solutions and considerations

[34] Liggins AB (1996) The practical application of Fuji Prescale pressure-sensitive film. Optical measurement methods in biomechanics 173-89.
[35] Rupp JD et al (2007) Characterization of knee impacts in frontal crashes. In the 20th International Technical Conference on the Enhanced Safety of Vehicles (ESV), Lyon, France 2007 Jun 18.
[36] Sparks DR et al (2005) Contact pressures in the flexed hip joint during lateral trochanteric loading. J Orthop Res 23(2):359.
[37] Li N et al (2013) Comparison of impact force attenuation by various combinations of hip protector and flooring material using a simplified fall-impact simulation device. J Biomech 46(6):1140-6.
[38] Loosemore M et al (2015) Unique method for analysing pressure distribution accross the knuckles during boxing. PeerJ PrePrints3:e917v1

Difficult to capture migraine attack since migraine attack is in unpredictable	High	Migraine attack although unpredictable, many migraineurs do know what can trigger their migraine attack, e.g. temperature, sports. In a previous study, migraine attack was triggered in a migraineur by playing basketball then lying in an fMRI scanner prepared for the attack which allowed researchers to capture 2 attacks (out of 3 attempts) before, during and after migraine attack[10]. However, recognizing the difficulty, following aspects are considered in the project: (a) volunteer test will be done in parallel in both Sweden and China, especially in Sweden one individual with known triggering factor of temperature has agreed to take part; (b) In the planed research tasks especially for the XX team, only a small number of tests need to be performed during attack, thus limits the number of tests needed for a successful completion of the project; (c) EEG-EOG is movable and can be wearing for a longer time than staying in fMRI for triggered cases, and a larger number of triggered case will be recorded by EEG-EOG; (e) Project website allows larger number of volunteers taking part, which is important for the determination of critical time window and effectiveness of the treatment approach, also ensures enough data for developing a diagnostic/prognostic tool based on eye movement; (f) Mechanical test for force and Video kinetics can be done any time (not necessarily during attack). The volunteer will be instructed to mimic the force he/she applied during the attack, allowing quantifying a typical force applied. The measured force will then serve as input to numerical head impact simulation to see sufficient to cause sufficient interruption in the electrical activity to cancel migraine aura attack. Design in this way, migraineurs can participate in the test any time, make it possible to evaluate the effectiveness of the approach in a larger group of migrainurs, and get information on where works + how much force works for different type of migraine.
Effectiveness of the novel approach for migraine without aura	Moderate	Majority of studies on CSD shows it is more related to migraine with aura, also the preliminary results shows the proposed approach is effective in an individual with migraine aura. The hypothesis that this approach work is based on the studies found that CSD also plays a role in migraine without aura. So whether or not this approach effective for MoA or not should be investigated. However, this is not critical for the progress of this project due to other identified novel tasks irrespective to this risk;

4 Significance

The proposed treatment approach after identifying the critical factors (force, location, critical time window) for its effectiveness in a larger group of volunteer tests will

- prove to be a non-cost, safe and instant treatment approach to abort migraine attack

Besides offering a new approach for migraine alleviation,

- the *critical time window* identified from this project
  - will explain why sTMS has to be applied *as soon as possible* [52] to be more effective since as both sTMS and the proposed approach is essentially based on the same principle – to interrupt the abnormal brain electrical activities
  - will bring awareness of the critical importance of *super-early* treatment intervention within this critical time window possibly of several seconds, thus to largely promote the effectiveness of other therapy treatments targeting at interrupting CSD propagation

Further, regardless of the proposed treatment approach:

- new knowledge on migraine in general will be developed through introducing of novel multimodal neuroimaging techniques.
- multiphysics modeling of CSD extended to 3D solid domain instead of current existing models with only cortex surfaces will be ready to for studying, besides the mechanical effects in this project, other Multiphysics interventions such as electrical, magnetic intervention or drug effects

[52] As reported in earlier studies, see Sec. 2.1.

5 Preliminary results

A *proof-of-concept* study has been initiated supported by a pilot fund from KTH Innovation between 2017 Feb – May. ***The aims of this pilot project*** were to

- quantify the force applied to the head during a mild self-hit to the head in an individual
- evaluate the brain tissue deformation during the mild hit using numerical models
  - Is the stretch in the brain sufficient to cause electrical activity changes in the brain?
  - Any potential risk to cause traumatic brain injuries?
- apply ethical permission for further volunteer test

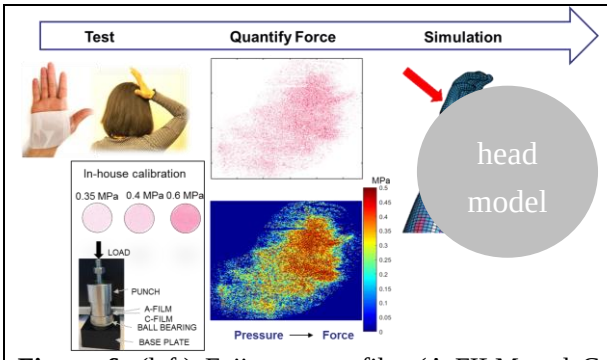

Figure 6: (left) Fuji pressure film (A-FILM and C-FILM layers) was attached to the hand and a mild self-hit coloured the pressure film proportional to the applied pressure. Through an in-horse calibration using dynamic compression test machine Instron E3000 with known applied force, color density is related to pressure by polynomial interpolation. (middle) Then pressure distribution during the impact is quantified by relating the obtained film color density with the calibration result. Integrating the pressure over area gave the impact force (331 Newton for this test). (right) The obtained force is applied to the head from the impact of a hand and arm to simulate brain tissue stretching.

Figure 6 shows the procedure and the obtained preliminary result for one test. The measured force to the head was 331 newton during a self-inflicted hit in an individual. Different tests of the same individual show the impact force ranged between 300 – 500N [53]. Subsequent numerical head simulation shows under such forces the brain tissue is stretched between 2.5% and 5.0%, sufficient to change electrical activity according to in vitro experimental brain tissue stretching reported earlier[16] while far less to cause concussion (threshold for concussion is between 20%-30% (see Kleiven (2007)[54] and references therein). Also note that the stretching magnitude is similar to the one found in previous volunteer studies (2%-5%) conducted in Bayly's group[55,56], where healthy volunteers' heads were subjected to mild impacts in a MRI scanner to measure the brain deformation using a tagged MRI technique.

To summarize, the proof-of-concept study shows

- the mechanical stimulation to the brain tissue by a mild self-hit to the head cause sufficient stretching of brain tissue to cause electrical changes in the brain,
- brain deformation during an effective aborting-aura self-inflicted hit is safe and far from causing potential injuries to the brain. Similar loadings to the head reported in previous health volunteers further support such loading is safe
- Ethical permission will be applied to perform this project.

The technologies developed in this pilot study will be used in this project and the envisioned advances have been described in the proposal.

[53] Compared with several thousand newton of loading to the head measured in boxing by Walilko TJ et al. (2005) Biomechanics of the head for Olympic boxer punches to the face. Br J Sports Med 39(10):710-9.
[54] Kleiven S (2007) Predictors for traumatic brain injuries evaluated through accident reconstructions. Stapp Car Crash J 51:81.
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