Homeostatic Mechanisms in Cluster Headache

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Members of the assessment committee:

Professor Stefan Evers, University of Münster

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Chair of the defence ceremony:

Professor Gitte Moos Knudsen, University of Copenhagen

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Table of Contents

Original Publications

This thesis is comprised of results from the following works and a coherent review. The included publications all concern cluster headache as a disorder of homeostasis and are divided into studies investigating sleep and chronobiology (I-IV), studies of therapeutic manipulation of peripheral structures and their interaction with central systems (V-VII) and studies of the autonomic nervous system's role in cluster headache pathology (VIII-X). The review summarizes findings, relates them to the body of existing literature and presents a novel model for understanding cluster headache.

I. Barloese M.C.J., Haddock B., Lund N., Petersen A., Jensen R.H. **Chronorisk in cluster headache: A tool for individualized therapy?** Cephalalgia, 2018.[1]

II. Lund N., Barloese M.C.J., Petersen A., Haddock B., Jensen R.H., **Chronobiology differs between men and women with cluster headache, clinical phenotype does not.** Neurology, 2017.[2]

III. Barloese M.C.J., Beske R., Petersen A., Haddock B., Lund N., Jensen R.H. **Episodic and chronic cluster headache: Differences in family history, traumatic head injury and chronorisk**. Headache, 2019.[3]

IV. Lund N., Snoer A.H., Petersen A.S., Beske R.P., Jennum P.J., Jensen R.H., Barloese M.C.J. **Disturbed sleep in cluster headache is not the result of transient processes associated with the cluster period.** European Journal of Neurology, 2018.[4]

V. Jürgens T.P.*, Barloese M.C.J.*, May A., Láinez J.M., Schoenen J., Gaul C., Goodman A.M., Caparso A., Jensen R.H., **Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache.** Cephalalgia, 2017.[5]

VI. Barloese M.C.J.*, Jürgens T. P.*, May A., Lainez J. M., Schoenen J., Gaul C., Goodman A. M., Caparso A., Jensen R. H. **Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months**. The Journal of Headache and Pain, 2016.[6]

VII. Barloese M.C.J., Petersen A., Stude P., Jürgens T., Jensen, R.H., May A. **Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry.** The Journal of Headache and Pain, 2018.[7]

VIII. Barloese M.C.J. **A Review of Cardiovascular Autonomic Control in Cluster Headache**. Headache, 2016.[8]

IX. Barloese M.C.J., Mehlsen J., Brinth L., Lundberg H. I. S., Jennum P. J., Jensen R. H. **Reduced Baroreflex Sensitivity in Cluster Headache Patients**. Headache, 2015.[9]

X. Barloese M.C.J., Petersen A. S., Guo S., Ashina M., Mehlsen J., Jensen R. H. **Sphenopalatine ganglion stimulation induces changes in cardiac autonomic regulation in cluster headache**. Clinical Physiology and Functional Imaging, 2018.[10]

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The dedicated staff of The Danish Headache Center is a unique community and I must thank my colleagues there, especially Drs. Petersen and Lund. Without their help, feedback and camaraderie the projects would not have succeeded. I also thank the Danish Center for Sleep Medicine, serendipitously colocalized at Rigshospitalet-Glostrup. Its dedicated staff and its leader, Professor Poul Jennum, were invaluable during the demanding sleep investigations, a cornerstone of my PhD-thesis on which this dissertation builds.

I am thankful to my colleagues at the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet-Glostrup and Frederiksberg and Bispebjerg Hospitals, specifically Drs. Mehlsen and Haddock, for their expert help in investigating autonomic function and developing tools to characterize chronobiology. I thank my colleagues at Hvidovre Hospital for providing a scientifically stimulating work environment and the many interesting scientific discussions we have had.

I thank my wife for her love, support and patience. Having listened to a continuous stream of presentations and musings on the topic, she has by now become an expert on cluster headache. Lastly, I thank my mother and father for their continued love and support in large and small matters and for giving me the upbringing and opportunities from which I have benefitted tremendously.

Resumé (Danish summary)

Klyngehovedpine er en særdeles smertefuld lidelse. Anfaldenes smerteintensitet og hyppighed udgør en stor belastning både for patient og omgivelser, og særligt i sin kroniske variant er diagnosen en klinisk udfordring. I den klassiske beskrivelse af hovedpinen har fokus forståeligt været på anfaldene, men nyere forskning har afdækket en række andre manifestationer som ikke er undersøgt tilstrækkeligt. Disse omfatter påvirket homeostase inklusiv forstyrrelse af autonom- og søvnregulering samt en symptomatologi der udviser forudsigelige fluktuationer.

Kronobiologi er en videnskabelig disciplin som beskæftiger sig med den tidsmæssige organisering af fysiologiske og patologiske processer. Den har hidtil ikke spillet en stor rolle i hovedpineforskning til trods for at flere hovedpinelidelser udviser betydelig forudsigelighed i anfaldsforekomsten. Denne forudsigelighed har været genstand for sporadisk interesse siden firserne og har, sammen med tilbøjeligheden til at anfald opstår fra søvn, formet opfattelsen af klyngehovedpine som en søvn-relateret lidelse med stærke kronobiologiske træk. Tidligere studier har foreslået et tæt, endda kausalt, forhold med bestemte søvnfaser og -fænomener hvilket dog synes usandsynligt når nyere resultater medtages.

De kranielle, autonome symptomer som ledsager anfaldene er grundigt karakteriseret og indgår i de diagnostiske kriterier. Bedre forståelse af den anatomisk-fysiologiske baggrund for deres opståen har ført til udvikling af højteknologiske behandlingsmuligheder i form af målrettet neuromodulation. I modsætning hertil står det mangelfulde kendskab til interaktionen mellem perifere og centrale elementer i patofysiologien, herunder den forstyrrede homeostatiske regulering. Disse forstyrrelser udgør ofte ikke et klinisk problem men repræsenterer en mulighed for bedre at forstå interaktionen mellem kronobiologi, søvn og autonom regulering. De ti studier som præsenteres i nærværende disputats blev udført med det formål at øge vores forståelse af disse uafklarede aspekter af klyngehovedpine.

Hovedfundene kan skitseres således:

Studie I-IV: Et nyt værktøj til avanceret analyse af anfaldsforekomsten blev udviklet og anvendt. Klyngehovedpine er udtalt kronobiologisk i sin kliniske præsentation hvor anfaldene opstår forudsigeligt og ofte om natten. I modsætning til manifestationen af de enkelte anfald varierer anfaldsrytmen mellem subtyperne. Hvor den kroniske variant udviser en ultradian 5-timers oscillation, er den dominerende frekvens i episodisk klygehovedpine en langsommere, circadian 24-timers oscillation. Anfaldsrytmen er associeret med flere faktorer herunder køn. Tidligere hovedtraumer og familiær disposition er hyppigere i kronisk klyngehovedpine. Familiær klyngehovedpine har en markant øget risiko for natlige anfald i sammenligning med sporadisk klyngehovedpine. Der er en udtalt forstyrrelse af søvnen som ikke ophører med klyngens udgang.

Studie V-VII: Neuromodulation rettet mod ganglion sphenopalatina kan anvendes terapeutisk og medfører nedsat anfaldsfrekvens og akut anfaldslindring. Effekten er reproducérbar, stabil og genfindes i forskellige populationer. Fra at være kroniske patienter igennem flere år er der ca. 1/3-del af de behandlede patienter der oplever anfaldsfri perioder og egentlig konvertering til den episodiske variant.

Studie VIII-X: Litteraturgennemgangen med fokus på systemiske autonome forandringer i klyngehovedpine viste at emnet har været underkastet sporadisk videnskabelig opmærksomhed tidligere. Autonom regulering er påvirket i klyngehovedpine og det autonome respons på stimuli og barorefleksfølsomheden er nedsat. Ved påvirkning af kendte perifere patologiske mekanismer er det muligt at fremkalde ændringer i det autonome nervesystems funktion.

Analysen af ovenstående fund nødvendiggør nytænkning hvad angår involveringen af anatomiske kerner og netværk i hjernestammen og mellemhjernen. Fundene understøtter involvering af et komplekst netværk af kerner og der præsenteres en ny model for klyngehovedpine. Denne model kombinerer kronobiologi og homeostatisk regulering med udgangspunkt i hovedpinen. På baggrund af disse fund kan der opstilles en række muligheder for fremtidig forskning:

1. Kronoterapi skal videreudvikles. Forud for dette bør der foretages en kortlægning af døgnvariation i metabolisme af de anvendte forebyggende medikamenter. Det er sandsynligt, at inddragelse af kronoterapeutiske principper kan øge effektiviteten og/eller mindske bivirkningerne.

2. Mekanistiske studier af klyngehovedpine, især hvor der forsøges provokation, kan med fordel inkorporere kronobiologisk tænkning. Den øgede sårbarhed over for anfald på bestemte tidspunkter af døgnet og året bør kortlægges, og forsøget planlægges i forhold til dette.

3. Neuroradiologien og –fysiologien er et felt som udvikler sig hurtigt, og de forskellige modaliteter kan hver især anvendes til at afdække varierende aspekter af patologien bag klyngehovedpine. Med kendskab til involvering af centre og netværk indblandet i reguleringen af autonom funktion, kronobiologi og søvnregulering, samt de muligheder der eksisterer for at manipulere disse, kan man forsøge at uddissekere deres relative betydning i klyngehovedpines komplekse og gådefulde symptomatologi.

Summary

Cluster headache is an exceptionally painful primary headache disorder. The severity and frequency of the attacks are a massive burden for the patients and their surroundings, especially in the chronic variant, and constitute a considerable clinical challenge. The research focus has rightly been on the attacks themselves, however, it is becoming clear that a range of manifestations have previously not been dealt with sufficiently. These include clear signs of disturbed homeostasis including perturbation of sleep and autonomic regulation and a symptomatology with predictable fluctuations.

Chronobiology, the study of the temporal organization of physiological and pathological processes, has hitherto only been incorporated superficially in headache research, despite several of the disorders exhibiting clear, predictable patterns. The distinct rhythms which cluster headache attacks exhibit have been the object of sporadic interest since the eighties and together with a predilection for attacks to occur during sleep, have shaped the concept of a chronobiological, sleep-related headache disorder. Previous studies suggested a close, even causal, relationship with rapid-eye-movement sleep and sleep apnea but recent findings, including those presented herein, contradict such theories.

The cranial autonomic symptoms which accompany cluster headache attacks are well-characterized and form part of the diagnostic criteria. A better understanding of their anatomical and physiological background, along with technological developments, have led to the development of new treatments in the form of targeted neuromodulation. The interaction between peripheral and central elements of the pathophysiology is not understood and the systemic autonomic alterations are not well-described. These autonomic alterations mostly do not represent a clinical problem but do offer an opportunity to better understand the interplay between chronobiology, sleep and autonomic regulation. The ten studies presented herein were undertaken with the aim of improving the understanding of these under-developed aspects of cluster headache.

The main findings can be summarized as follows:

Studies I-IV: A novel tool to investigate attack occurrence was developed and used. Cluster headache is clearly chronobiological in its clinical manifestation with predictability of attack occurrence which has a nocturnal predilection. The rhythmicity varies between the subtypes with the chronic variant exhibiting faster 5-hour oscillations and the episodic slower 24-hour oscillations. These oscillations are associated with a number of factors including sex. Traumatic head injury and family history are more common in chronic cluster headache and familial cluster headache dramatically increases the risk of attacks occurring at night. There is a pronounced disturbance of sleep which does not normalize outside of the bout.

Studies V-VII: Neuromodulation of the sphenopalatine ganglion is effective and leads to decreased attack frequency and acute headache relief. The effect is reproducible and stable over 24 months. From being chronic through several years, roughly 1/3 of patients begin to experience attack-free periods following treatment, effectively converting to the episodic subtype.

Studies VIII-X: The literature review revealed that systemic, particularly cardiac, autonomic functioning in cluster headache has previously conjured sporadic scientific curiosity. There is a blunting of cardiac autonomic reactivity and reduced baroreflex sensitivity. By manipulating known peripheral cluster headache pathways, it is possible to induce subclinical changes in systemic autonomic regulation.

The analysis of the above findings necessitates a novel way of thinking about cluster headache pathology at the level of the brainstem and midbrain. The findings dictate involvement of a complex network of anatomical nuclei in the presented model for cluster headache. This model fuses chronobiological thinking with homeostatic regulation in the setting of headache. In the wake of the presented findings future research opportunities present themselves:

Firstly, chronotherapy must be developed further. This could be preceded by mapping of the metabolism of known preventive medications. It is likely that adherence to chronotherapeutic principles can improve effectiveness and/or decrease side-effects of these drugs.

Secondly, mechanistic studies of cluster headache, especially those where provocation of attacks is attempted could incorporate chronobiological thinking. The increased susceptibility to attacks at certain times of the day and year should be mapped and provocation attempts be made in accordance with this.

Lastly, neuroimaging is a field advancing at a staggering pace and different modalities can be wielded to clarify various aspects of cluster headache pathology. Using such methods and incorporating knowledge of involvement of centers of cardiac autonomic-, chronobiological- and sleep regulation and known ways to manipulate these, we can attempt to dissect their overall contribution to the complex symptomatology of this enigmatic headache disorder.

Abbreviations

ANS	Autonomic nervous system
BP	Blood pressure
BRS	Baroreflex sensitivity
CAS	Cranial autonomic symptoms
CH	Cluster headache
eCH	Episodic cluster headache
cCH	Chronic cluster headache
CSF	Cerebrospinal fluid
DBS	Deep brain stimulation
ECG	Electrocardiogram
fCH	Familial cluster headache
HC	Hemicrania continua
HCRT	Hypocretin
HF	High frequency (-nu – normalized units)
HR	Heart rate
HRV	Heart rate variability
HUTT	Head-up tilt table test
ICHD	International Classification of Headache Disorders
LF	Low frequency (-nu – normalized units)
MEQ	Morningness-Eveningness Questionnaire
NREM	Non-rapid eye movement
NTS	Nucleus of the solitary tract
ONS	Occipital nerve stimulation
OSA	Obstructive sleep apnoea
PAG	Periaqueductal grey
PBN	Parabrachial nucleus
PH	Paroxysmal hemicrania
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
REM	Rapid eye movement
RRi	Interval between R-waves in the electrocardiogram
SCN	Suprachiasmatic nucleus
SPG	Sphenopalatine (pterygopalatine) ganglion
SPGS	Sphenopalatine (pterygopalatine) ganglion stimulation
SSN	Superior salivatory nucleus
SUNCT	Short-lasting, unilateral, neuralgiform headache with conjunctival injection
TAC	Trigeminal autonomic cephalalgia
THI	Traumatic head injury
TCC	Trigeminal cervical complex

Introduction

Headache is a major public health issue affecting >10% of the world's population and is the main neurological cause of years lived with disability.[11] Regardless, it remains underrecognized, underdiagnosed and undertreated[12,13] with significant economic[14] and personal consequence.[15,16] Cluster headache (CH) is a primary headache disorder which affects 0.1% of the population and is the most frequent of the trigeminal autonomic cephalalgias (TACs).[17,18] Characterized by unilateral headache, often arising from sleep, the crises are interspersed by periods of pain freedom. The severity of the pain is indisputable and it ranks among the worst described by modern medicine, cited as being worse than childbirth, kidney stones and multiple limb fractures.[19,20] The 15-180 min. attacks can occur up to eight times a day and the accompanying cranial autonomic symptoms (CAS) are appreciably more pronounced than in any other headache disorder.[21,22] In the attack state, the patient is agitated and unable to remain still.[21] Of the TACs, CH has the longest attack duration but the lowest daily frequency (Figure 1).[21,23] CH dichotomizes into an episodic and chronic variant defined by the duration of the remission periods.

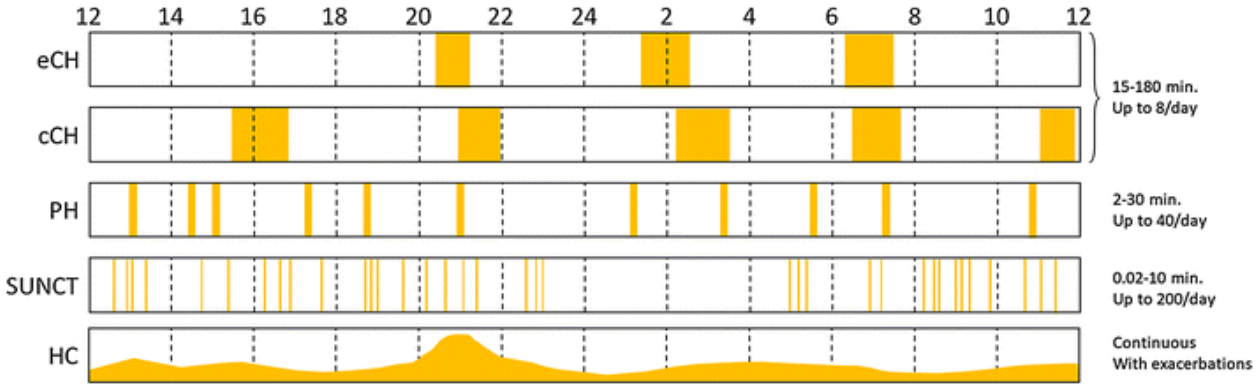

Figure 1: Patterns of pain. The yellow areas indicate typical attack durations, frequencies and pain intensities within a 24-hour period of the different trigeminal autonomic cephalalgias. eCH – episodic cluster headache, cCH – chronic cluster headache, PH – paroxysmal hemicrania, SUNCT – short-lasting, unilateral, neuralgiform headache with conjunctival injection, HC – hemicrania continua. Reproduced with permission from Springer Nature.

The bulk of the CH phenotype can be encompassed in a triad of characteristics:

1) Severe unilateral headache
2) Predictable attack occurrence with nocturnal predilection
3) Altered autonomic functioning

During CH attacks the trigeminal-autonomic reflex is activated with increased cranial parasympathetic outflow, effectuated by the superior salivatory nucleus (SSN) in the brainstem.[19] Whether peripheral or central mechanisms initiate the pain in CH is a long-standing debate.[24] The primary theory behind a central origin for the attacks revolves around a dysfunctional descending, homeostatic control of trigeminal pain and demonstration of activation of an area in, or proximate to, the posterior hypothalamus by H_2O^{15}-PET/CT[25] along with other findings[26,27] seemed to confirm already existing suspicions of the area's relatively specific involvement in CH. However, subsequent studies indicate that while the hypothalamus, in broad terms, is likely a key structure, CH pathology involves a network of central and peripheral structures, seemingly without one being pivotal or a "cluster generator".[28–30] Homeostasis is the state of continued maintenance of an internal milieu conducive to health and as a brain-hormone and neuronal integrator the hypothalamus controls numerous functions

including pain perception, body temperature, sleep, hunger, thirst as well as the autonomic nervous system (ANS).

Within the past decades advances in our understanding of headache pathology, along with technological progress, particularly within the field of medical devices, have been instrumental in expanding the therapeutic armamentarium. Not only have these developments allowed for better treatment, they have also provided new ways to study CH. In lieu of readily available and specific biomarkers, autonomic function and the timewise manifestation of symptoms can be characterized to provide insight into hypothalamic, diencephalic and brainstem functioning.

This dissertation focuses on chronobiology, autonomic regulation and interaction with peripheral structures with an a priori hypothesis of disturbed homeostatic regulation in CH. Chronobiology, neuromodulation and autonomic regulation will be covered and introduced below in the context of headache.

Chronobiology and Sleep in CH

Chronobiology is the study of how biological processes organize temporally and are entrained by so-called zeitgebers (time cues). In 1729 Jean-Jacques d'Ortous de Mairan described persisting opening and closing of the leaves of the *Mimosa pudica* in the absence of sunlight and is credited with being first to scientifically describe a chronobiological rhythm.[31] Since then, chronobiology has advanced greatly. The tripartite model describing circadian systems encompasses 1) inputs, 2) an internal oscillator and 3) outputs.[32] The main internal oscillator is the hypothalamic suprachiasmatic nuclei (SCN) which generates near 24-hour oscillations entrained by dedicated retinal cells.[33,34] Additionally, accumulation of hypnogenic substances in the brain ensures that a night with a lack of sleep is followed by subsequent, compensatory increased sleep duration. These two systems, the circadian oscillator and the sleep-wave homeostat, govern our sleep-wake rhythms (reviewed by Dijk and Lockley[35]).

Headache and sleep coalesce at physiological, anatomical and clinical focal points.[36–40] Except for the very rare hypnic headache, of the primary headaches, CH arguably has the closest relationship with sleep and the international classification of sleep disorders lists CH as a "sleep-related headache".[41] Since the 70's two main concepts have been fostered: CH as a rapid eye movement (REM)-sleep associated disorder and CH as a obstructive sleep apnea (OSA) -related disorder.[42–48] Yet, although sleep in CH patients certainly is altered towards the pathological, modern polysomnography (PSG) studies are not in agreement and thus the theories have not been verified convincingly.[4,49,50] Further, epidemiological research indicates that the sleep disturbances do not follow a bout-remission pattern.[51] Lastly, in the past two decades a link between sleep and pain in the form of the hypothalamic neuropeptide hypocretin (HCRT) has garnered interest.[52] The relevance for CH is apparent from its documented effects on arousal, sleep[53] and descending modulation of trigeminal pain processing.[54–56] The concentration of HCRT-1 is reduced in the cerebrospinal fluid (CSF) of CH patients[57] and there is an ongoing debate of genetic association.[58,59]

Some predictability in the fluctuation of symptom intensity is not uncommon in disease and recognizing this can facilitate prompt and correct diagnosis. Administration of therapy according to fluctuating symptoms, pharmacodynamics and -kinetics is known as chronotherapy,[60] a concept only sparsely investigated in CH.[61] This is puzzling given the pronounced chronobiological symptom manifestation[60,62–66] and that treatments for CH, including verapamil,[67] lithium,[68] valproate[69] and melatonin[70] all affect circadian rhythms.[71]

Neuromodulation in Cluster Headache

Neuromodulation has a two-thousand-year history: Scribonius Largus, court physician to the Roman emperor Claudius, experimented with electrical discharges from torpedo fish to treat various ailments from gout to headache.[72] It became apparent that subjecting tissues to electric current can induce therapeutic effects. In its modern refinement, the targeted, precise administration of titrated currents has given otherwise refractory CH patients new hope.[73,74] Around the year 2000 deep brain stimulation (DBS) of an area in or proximate to the posterior hypothalamus was initially trialed resulting in substantial reductions of attack severity and frequency.[75,76] Later, occipital nerve stimulation (ONS) was used to treat similar patient populations with similar results.[77–79] The latest addition is in the form of non-invasive vagal nerve stimulation (nVNS).[80]

The observation of ipsilateral CAS during headache attacks has motivated therapeutic targeting of the sphenopalatine (pterygopalatine) ganglion (SPG) as the primary parasympathetic ganglion of the cranium for over a hundred years.[81,82] SPG stimulation (SPGS) using a transbuccal approach was pioneered by Tepper and Ansarinia[83,84] and on-demand SPGS became feasible when an implantable microstimulator was developed. The device is inserted transorally and activated by remote control (Figure 2). Being powered inductively, the lack of batteries reduces the need for surgical revisions.[85]

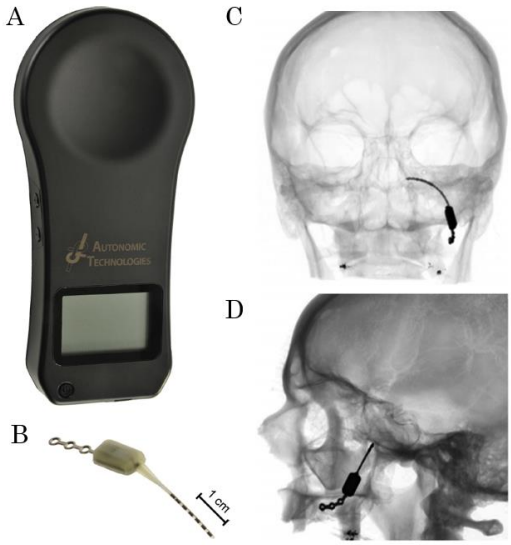

Figure 2: The sphenopalatine ganglion stimulation system remote control (A) and microstimulator (B). The device is depicted on digitally reconstructed coronal (C) and sagittal (D) radiographs with inserted models.[85]*Reproduced with permission from Elsevier.*

Apart from providing a much welcomed, minimally invasive treatment alternative for CH patients, SPGS also allowed for new ways of studying pathomechanisms. Therapeutic blocking is achieved using high frequency (HF, 80-180 Hz) stimulation whereas experimental activation and increased parasympathetic outflow is induced using low frequency (LF, 5-20 Hz) stimulation.[83,84] Using DBS, ONS, vagal nerve stimulation and SPGS, therapeutic neuromodulation has been achieved targeting both central and peripheral structures[74] and in the context of disturbed homeostasis,[86] stimulation of central and peripheral structures has been shown to alter autonomic responses in patients.[87,88] The question arose whether peripheral stimulation, specifically SPGS, affects systemic autonomic regulation.

The Autonomic Nervous System

Through the opposite actions of sympathetic and parasympathetic signalling the autonomic nervous system (ANS) anticipates and orchestrates responses to external challenges.[89] As stated, during CH attacks the characteristic unilateral CAS result from amplified cranial parasympathetic outflow and diminished sympathetic.[19] Although sometimes present in other headaches, and perhaps underrecognized in these,[90] they are most pronounced in the TACs[24] and when elicited by pain or other noxious stimuli are referred to as the trigeminal-autonomic reflex.[91] These features and their semi-dependent relation to pain[92–98] have been studied extensively but still their place in the series of events leading to attacks remains undetermined.[24]

Although acknowledged in the literature, including in historical accounts,[99,100] the systemic autonomic changes in CH are sparsely investigated. That systemic autonomic homeostasis is altered in CH rests on four observations:

1. Attacks arise during times of parasympathetic dominance and are suppressed during times of sympathetic dominance.[101,102]
2. Dramatic fluctuations in autonomic regulation have been observed during attacks.[103–105]
3. Systemic autonomic functioning in CH patients is altered between attacks.[106–108]
4. Affected hormones,[109] altered antinociceptive control,[110] neurophysiological and anatomical changes[111] suggest involvement of centres of autonomic control.

Like CAS, whether these systemic changes are epiphenomena or integral to the disease process is unclear. In light of the chronobiological features and suspected generalized homeostatic disturbance, studying downstream phenomena such as the regulation of the ANS will add to our understanding of CH pathophysiology.

Aims

The ambition for the presented studies was to investigate CH pathology and therapy with an a priori hypothesis of CH being a syndrome of disturbed homeostatic regulation in terms of chronobiology, sleep and peripheral and systemic autonomic regulation.

Specifically:

1. To investigate sleep, chronobiology and bout-related pathological changes using epidemiological and neurophysiological methods in a large population of episodic (eCH) and chronic (cCH) CH patients as well as identify potential differences between subgroups (I-IV).
2. To study the acute and preventive effects of neuromodulation targeting the SPG (V-VII).
3. To characterize autonomic function in CH generally and during stimulation of the SPG (VIII-X).

Methods

The Danish Cluster Headache Survey (I, II, III)

Studies I, II and III are based on data obtained in The Danish CH Survey, described in detail in the respective articles and in other publications.[2,51,112] The first publication from this dataset included 275 patients and 145 controls[51] which expanded to 351 patients in I and II and 400 in III. The Danish CH Survey consisted of questions covering phenotype, treatment, burden, sleep, work, lifestyle and physical activity. It also contained other validated questionnaires including The Pittsburgh Sleep Quality Index (PSQI),[113] and The Morningness-Eveningness Questionnaire (MEQ).[114] The included studies are mainly based on sections of the survey on phenotype, attack timing and headache history, including traumatic head injury (THI). Patients first completed the questionnaire and afterwards underwent an in-person or telephone interview where missing answers and ambiguities were addressed.

Standard statistical methods were used to compare differences in chronorisk and demographics (*t*-test, Mann-Whitney U-) as well as MEQ (ANOVA). Category distributions were compared using χ^2- and Fisher exact test and logistic regression predicted odds ratios and 95%-confidence intervals for cCH patients for predictors (familial CH (fCH), THI, THI prior to onset, smoking, age>49, sex). Linear regression was used to describe cluster occurrence and daylight hours. In II, analysis of differences in rhythmicity was done by converting reported attacks to probability distributions and calculating prominence for a given hour. Higher prominence than the 2 preceding hours was identified as peak time. These were then compared using a *t*-test. The Likert scale (0-4) was used for graduating pain intensity.

Gaussian Modelling and Spectral Analysis

Multimodal Gaussian models were applied to 24-hour chronorisk distributions with the aim of better describing the observed patterns in attack occurrence and developing objective methods of comparing these in subgroups. The method and its limitations are detailed in I. Concisely, it involves three separate analyses, Gaussian modelling, spectral analysis and comparison of attack risk at individual hours (Figure 3), which together allow evaluation of attack timing and regularity. Power spectra were not compared using any statistical test.

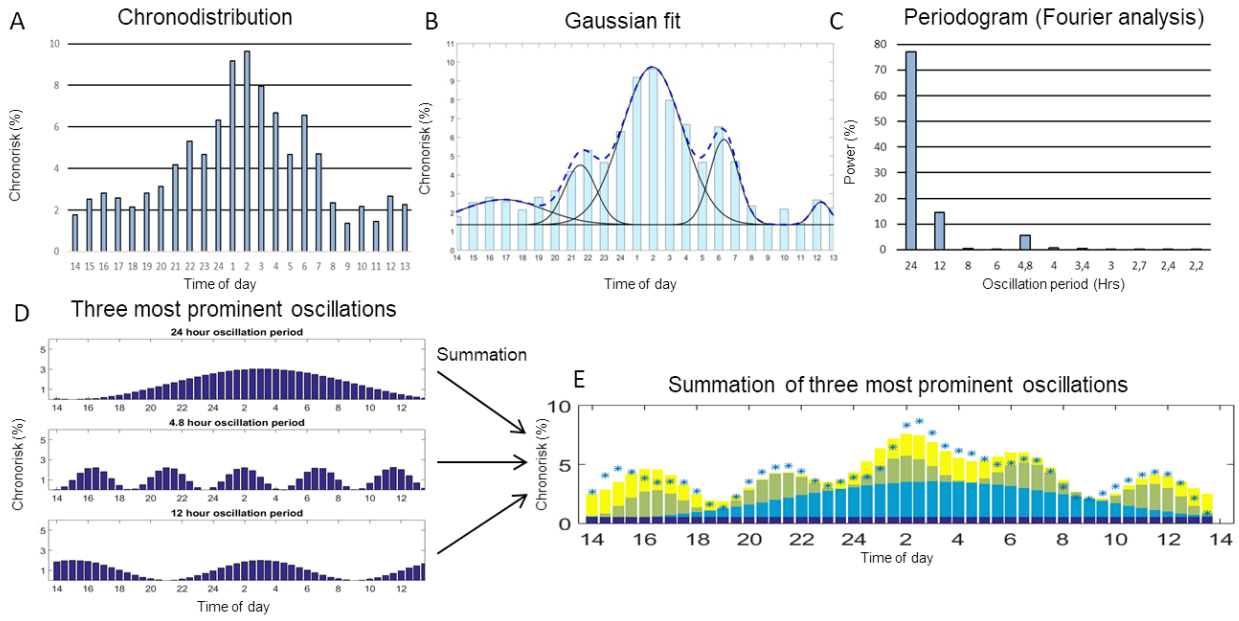

Figure 3: Schematic overview of the chronorisk analyses including the relative risk of an attack occurring during a particular hour (A). A multimodal Gaussian model was applied to this distribution producing (B). The Fourier analysis revealed circadian (24 hour) and ultradian (<24 hour) oscillations (C), the three most prominent of which are extracted (D) and summed in (E). Reproduced with permission from Sage Publishing.

The sleep studies (IV)

Patients entered the study and underwent PSG in two inclusion periods. In the first inclusion period participants were cCH and eCH patients with ongoing attacks (bout). The dataset was augmented in a second inclusion period in which patients who had already participated were invited to repeat the sleep study in the remission phase. Also, new patients, who had not participated before were invited to undergo sleep studies in both remission and bout. Controls were BMI-, age- and sex-matched. All studies were conducted at Rigshospitalet-Glostrup, Danish Center for Sleep Medicine according to the standards of The American Academy of Sleep Medicine (electroencephalogram, electro-oculogram, electromyography (submentalis, tibialis anterior), electrocardiography, air flow, respiratory effort, blood oxygenation and video recording). Patients from the first inclusion period underwent recording for two nights, patients from the second inclusion period and controls underwent recording for one night. 30-sec epochs were scored by sleep technicians and the final assessment was made by senior doctors according to The International Classification of Sleep Disorders.[41]

Patients in bout were compared with patients in remission using mixed-model analysis. Paired *t*-tests were used for patients who had participated twice. For non-paired analyses standard *t*-test, Mann-Whitney U test and χ^2- tests were used.

Sphenopalatine Ganglion Stimulation (V-VII)

The Pathway CH-1, Long-Term Follow-Up and Registry Studies formed the framework for the multicenter clinical testing and monitoring of a neurostimulator targeting the SPG (Pulsante™, Autonomic Technologies, Inc.) in CH.[5,6,115] The data presented relates to 1) the acute and preventive clinical effect elicited by HF stimulation (V-VII) and 2) experimental studies where LF stimulation is used to provoke CH pathology (X).

In studies V and VI, data was collected at clinic visits for ≥24 months after implantation and via an electronic diary in the remote-control. Reported attack frequency, headache disability and medication use were recorded. Remission periods are defined by the International Classification of Headache Disorders (ICHD) 3 beta as *"The time during which attacks cease to occur spontaneously and cannot be induced with alcohol or nitroglycerine. To be considered a remission, the attack-free period must exceed one month."*[116] Attacks were not attempted provoked, however. The patients in V and VI were the same. In study VII, patients were followed in an open-label design with clinic visits at 3, 6, 9 and 12 months following implant. Patients were monitored according to the same parameters as in V and VI. Patients in V and VI were refractory cCH patients with no remissions for > 1 year. Patients in VII were difficult to treat patients with a high headache burden but not necessarily fulfilling the criteria for refractoriness.[117,118]

In all three studies, the response to SPGS was evaluated according to the following criteria: Frequency responders had ≥50% reduction in attack frequency, acute responders achieved efficacy in ≥50% of attacks, HIT-6 responders experienced an improvement of ≥2.3 units and SF-36 responders ≥ 4 units vs. baseline. Efficacy in an acute attack was defined as pain relief (decrease on the categorical pain scale from 2 or greater to 1 or 0) or pain freedom (decrease from 1 or greater to 0). Frequency was defined as the average number of attacks per week over the prior four weeks. Paired *t*-test was used to compare changes between baseline and different time-points. A generalized estimating equation with least squares means was used to analyse usage for acute attacks. This method accounts for the difference in number of attacks treated per patient.

The Studies of Autonomic Regulation (VIII-X)

Investigations were carried out at The Departments of Clinical Physiology and Nuclear Medicine at Rigshospitalet-Glostrup and Frederiksberg and Bispebjerg Hospitals.

Review of the Literature (VIII)

Despite some interest in the systemic autonomic features of CH the findings had never been reviewed. A PubMed search using specific keywords was conducted and references screened. Studies were included if they contained cardiovascular measurements or data on responses to autonomic tests. Studies exclusively focusing on CAS were excluded. The heterogeneity of the studies did not allow for any form of quantitative metanalysis.

Tilt-Table Testing and Baroreflex Sensitivity (IX)

To study heart rate variability (HRV) and baroreflex sensitivity (BRS) patients underwent head-up-tilt-table testing (HUTT). Intervals between sinus heart beats (RRi) and beat-to-beat blood pressure (BP) were measured using electrocardiogram (ECG) and a Finometer system (Finapres Medical Systems BV, Amsterdam, The Netherlands). After a resting period, baseline readings were recorded after which the subjects were tilted for a total of 15 min. Data was exported using LabChart (AD Instruments Inc., Colorado Springs, CO, USA) and Taskforce (CNSystems Medizintechnik AG, Graz, Austria) and HRV analysed in Kubios (Kubios Oy., Kuopio, Finland) and BRS in Nevrokard (Nevrokard Kiauta d.o.o., Izola, Slovenia).

	Abbreviation	Measure	Reflects
Time domain	meanRR	Mean interval between sinus beats	Heart rate
	SDNN	Standard deviation of intervals	Total variation (Sympathetic and parasympathetic)
	RMSSD	Root mean squared of SD (Numerical difference in intervals)	Fast variation (Parasympathetic, identical to SD1)
Frequency domain	LF	Low frequency power (0.04-0.15 Hz) in spectral analysis. Also presented in normalized units (n.u.)	Slow oscillation (Sympathetic and parasympathetic)
	HF	High frequency power (0.15-0.4 Hz) in spectral analysis. Also presented in normalized units (n.u.)	Fast oscillation (Parasympathetic)
Poincaré plot (Non-linear analysis)	SD1	Standard deviation perpendicular to line of identity	Fast variation (Parasympathetic, identical to RMSSD)
	SD2	Standard deviation along line of identity	Slow variation (Sympathetic)
Baroreflex sensitivity (Sequence method)	"Up" sequences	Change in RR interval in response to an increase in blood pressure.	Fast variation as analysed by the sequence method (Parasympathetic)
	"Down" sequences	Change in RR interval in response to a decrease in blood pressure.	
	Down-Up	Difference in sensitivity to positive and negative changes in blood pressure	

Table 1: Overview of the most commonly used parameters obtained in analysis of heart rate variability and baroreflex sensitivity.[119]

Five-minute periods obtained from the supine and standing periods of the HUTT-recordings were analysed for BRS using the sequence method: Sequences longer than three beats and with an RRi variation >6 ms and BP change greater than 1 mmHg were included. Sequence correlation was >0.8 and the lag between change in blood-pressure and RRi was set to one beat. A high slope means a greater shift in heart rate (HR) in response to a spontaneous fluctuation in BP indicating a high sensitivity of the system. As changes reflect beat-to-beat variation, BRS here is mainly a measure of parasympathetic activity (Table 1). ANOVA was used to compare BRS supine and standing measurements. Other non-parametric data was analysed using Wilcoxon rank sum test and parametric data using *t*-test.

Experimental Stimulation of the Sphenopalatine Ganglion (X)

Theoretically, HF stimulation of the SPG leads to depolarization of presynaptic neurons and depletion of signalling molecules breaking the trigeminal-autonomic reflex or inhibiting parasympathetic outflow from the SSN in an antidromic fashion.[120] LF stimulation is perhaps closer to a physiological firing rate[121] and is proposed to activate the reflex. It has been shown to dilate the middle cerebral artery, small pial arteries, internal carotid artery, anterior carotid artery and to increase cortical blood flow.[121–124] In study X, blinded patients received either

sham (amplitude = 0 mA) or LF stimulation (usual stimulation parameters except a frequency of 20 Hz). Using the E-motion device (Mega Electronics, Kuopio, Finland) two-lead ECG was recorded continuously for 30 min of baseline and sham/LF stimulation. Analysis of HRV was performed on the 5 min preceding the beginning of active stimulation and in 5 min intervals hereafter. Headache details and CAS were recorded at fixed intervals. Patients were their own controls and differences were analysed with paired statistics. Paired *t*-test was used to compare differences between sham and LF stimulation. Changes during attacks were compared using Wilcoxon non-parametric test. Preventive medication and treatment response were analysed using a standard *t*-test.

Results

Clinical Phenotype and Chronobiology (I-IV)

The principal findings were:

- CH attack occurrence can be represented as chronorisk and the resulting chronodistribution described with multimodal Gaussian models and spectral analysis. eCH is characterized by circadian rhythmicity whereas cCH has a more rapid-cycling ultradian rhythmicity.
- Clinical phenotype does not vary between the sexes but the chronobiological manifestation does. cCH is more frequent in women than men.
- fCH is associated with a pronounced increased nocturnal chronorisk. Patients who change phenotype (eCH to cCH or vice versa) have chronobiological "fingerprints" like the phenotype they have changed to. While these fingerprints vary across subgroups, the attacks are stereotypical in presentation.
- Sleep in CH does not normalize outside of the cluster bout. Nocturnal attacks do not seem to be associated with particular phenomena or phases.

I – Chronorisk

A novel tool for analysing the chronobiology of headache attacks is presented. At the time of analysis, data was available for 351 patients. Of these, 82% reported diurnal rhythmicity and were selected for 24-hour chronorisk analysis. The Gaussian models had goodness-of-fit measures between 0.85 and 0.99. A prominent difference emerged between eCH and cCH patients: eCH chronorisk was dominated by circadian oscillation of attack risk whereas cCH had distinct ultradian oscillations (Figure 4).

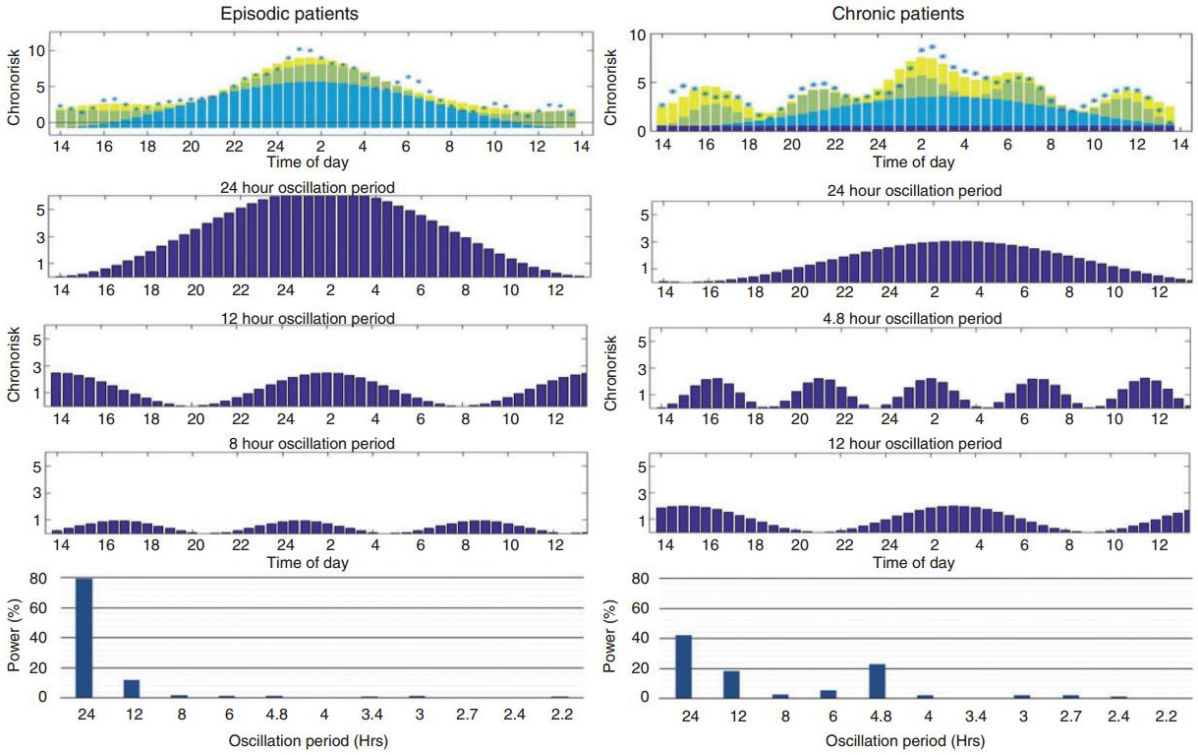

Figure 4: Results from the Fourier analysis of chronorisk for episodic and chronic cluster headache patients. Episodic patients presented a strong 24-hour oscillation whereas chronic patients had a distinct roughly 5-hour oscillation in chronorisk. Reprinted with permission from Sage Journals.

Chronotype influenced the occurrence of the first nocturnal peak with *morning*-types having the earliest peak and *evening*-types the latest, a pattern mirrored in the groups' average time asleep. The few patients who were *good sleepers* (PSQI≤5), had stronger ultradian oscillations in chronorisk than patients who were *poor sleepers* (PSQI>5). Some lifestyle factors seemed to be associated with specific patterns of chronorisk. For example, coffee abstainers had a less prominent circadian oscillation than coffee drinkers.

II –Cluster Headache in Male and Female Sufferers

The dataset for this study was the same as for I. The male:female ratio was 2:1 with cCH being more prevalent in women (44% vs 32%, p=0.034). Peaks in attack prominence occurred 1 hour later for women compared to men (p<0.05, figure 5) with no difference in self-reported bedtime but longer time to fall asleep for women (40 min vs 25 min, p=0.01) and a higher PSQI-score (10.0 vs 8.7, p=0.02).

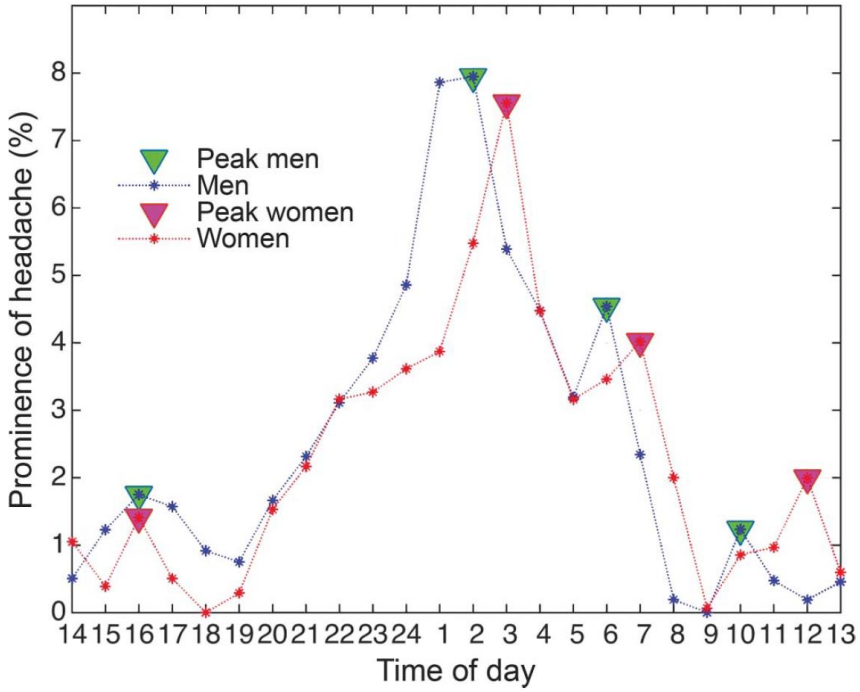

Figure 5: Attack prominence in male and female CH sufferers. Prominence is the increased risk of an attack to occur in a given hour-interval. Women's peaks are delayed by one hour compared to men. Reprinted with permission from Wolters Kluver.

Both men and women CH patients experienced the same association between number of daylight hours and cluster worsening through the year (R^2=0.72, p=0.0005, R^2=0.52, p=0.008, respectively) with this being more pronounced in eCH than cCH. Despite a similar attack presentation, previous misdiagnosis was more common in women compared to men (61% vs 46%, p<0.01) but the diagnostic delay was similar in the sexes (p=0.21).

III – Cluster Headache in Episodic and Chronic Sufferers

When the analysis of this data was conducted The Danish Cluster Headache Survey had expanded to 400 patients. Apart from an increased attack frequency (4.1 vs. 3.3 attacks/day, p=0.005) and longer treated attack duration (47 vs. 34 min, p=0.024) cCH presented no differences in phenotype or triggers when compared to eCH. However, a positive family history (23% vs 13%, p=0.008) and THI (53% vs 37%, p=0.004) was more common in cCH than eCH.

Using the new chronorisk analysis tool, remarkable differences emerged in the subgroup analysis. fCH patients had a nocturnal chronorisk which was twice as high as sporadic CH (sCH) patients. In accordance with the cCH association, these patients also had strong ultradian oscillations despite the very strong 2 a.m. circadian signal (Figure 6).

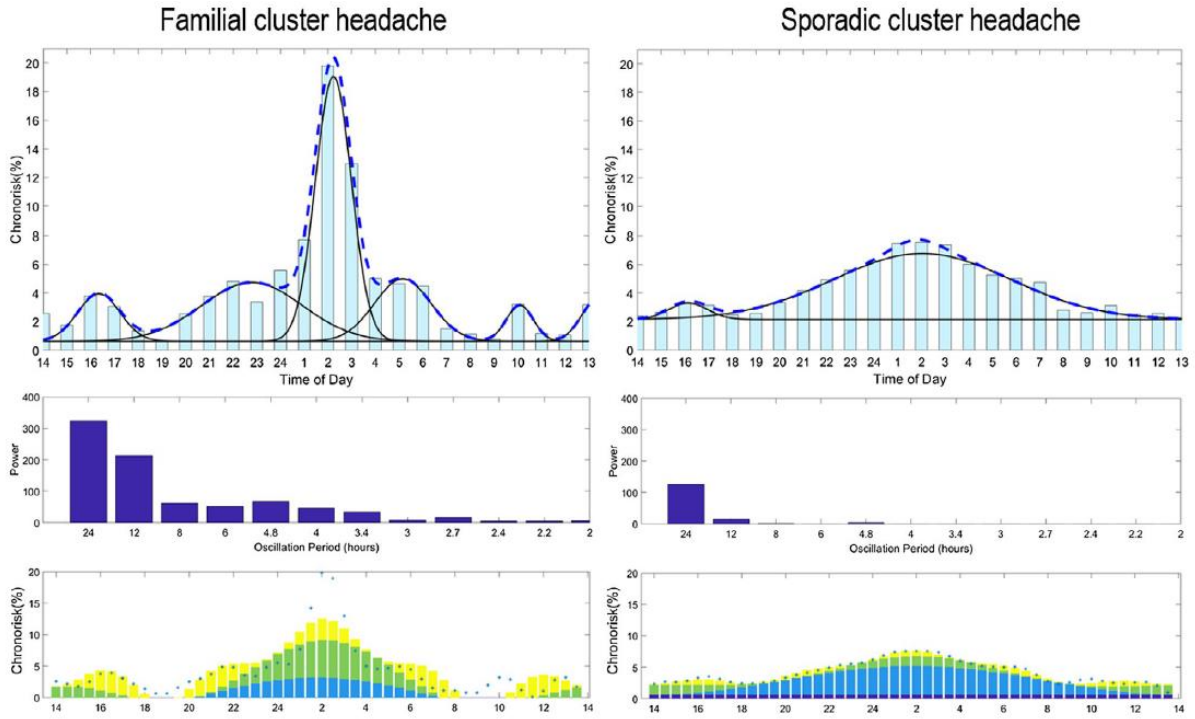

Figure 6: Chronorisk analysis for patients with familial and sporadic cluster headache. The very prominent peak for familial cluster headache at 2 a.m. stands out. These patients maintained strong ultradian oscillations (middle and bottom panels) confirming the association with chronic cluster headache. Reprinted with permission from Wiley.

In an analysis of the patients who had changed subdiagnosis, i.e. gone from eCH to cCH or vice versa, and those who had not undergone such phenotype changes, it was found that associated features were unchanged but the chronobiological fingerprint was similar to the subtype they had morphed into (Figure 7).

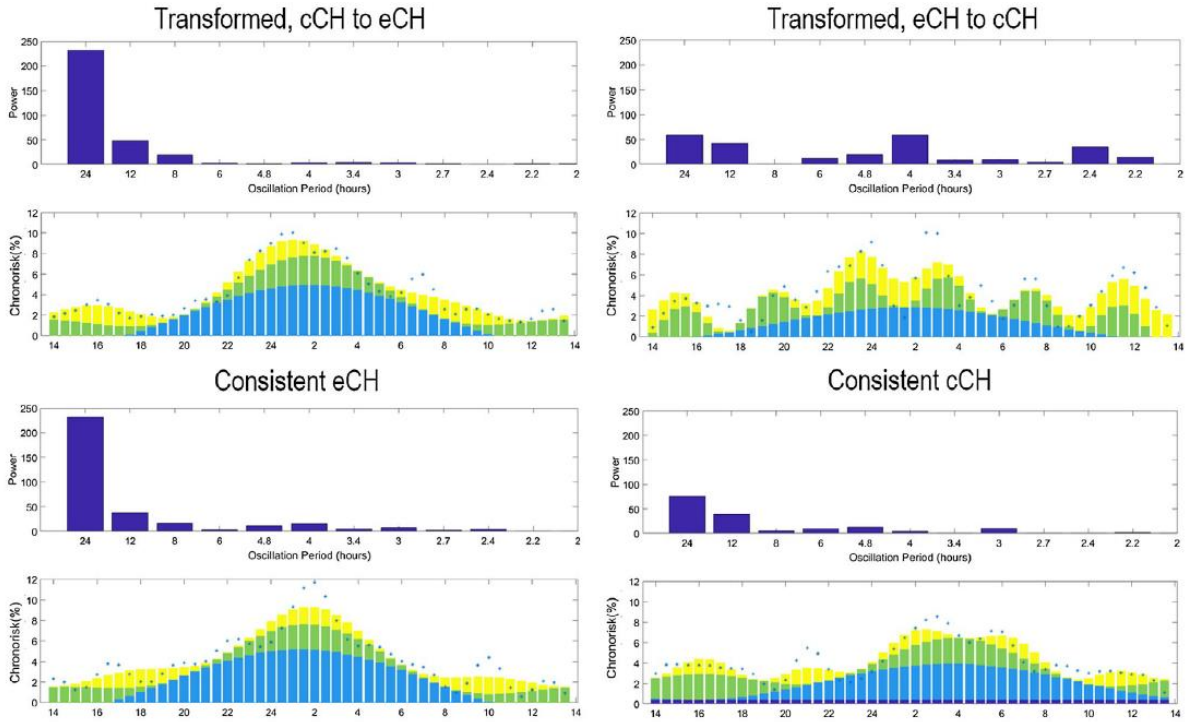

Figure 7: Chronorisk analysis for patients who had changed subdiagnosis vs. patients who had not. Patients who had changed from chronic to episodic were similar in chronorisk pattern to those who had always been episodic. Patients who had changed from episodic to chronic were similar to patients who had always been chronic. Reprinted with permission from Wiley.

IV – Sleep in Cluster Headache

Forty-one patients with eCH and 25 controls participated. Sleep in bout did not differ from sleep in remission in the analysed parameters. Compared to controls, patients in bout had longer sleep and REM sleep latency ($p<0.05$). In remission, patients only had longer sleep latency ($p<0.01$). Attacks occurring during recording did not approximate apnoeas, limb movements or arousals. They were, however, preceded by unstable sleep and arousals (Figure 8).

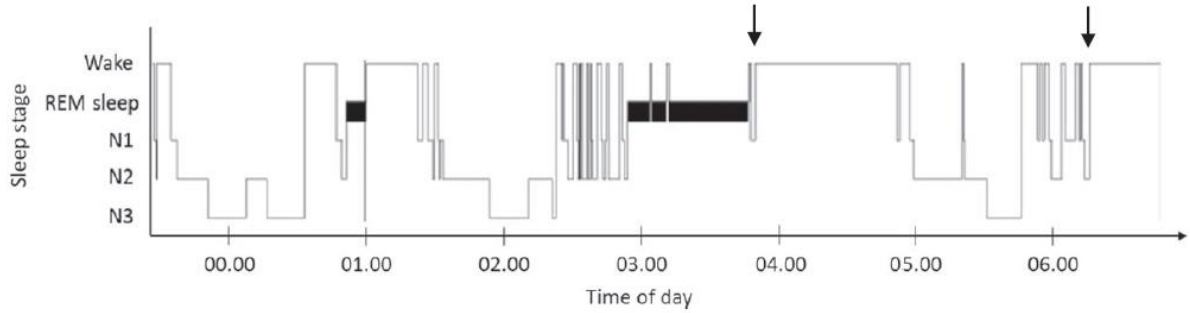

Figure 8: Hypnogram showing unstable sleep preceding attacks (arrows). The first attack occurred after a period of rapid eye movement sleep, the second following a period of wake and non-rapid eye movement sleep. Overall, the hypnogram shows a highly fragmented sleep pattern but otherwise normal progression through the sleep stages.

There was no statistical difference in the apnoea-hypapnoea index between the bout and remission phases. Nor was there any difference between patients and controls. This was also true when stratifying according to apnoea severity.

Sphenopalatine Ganglion Stimulation (V-VII)

The CH-1 study included 33 medically refractory cCH patients with established, unchanging diagnoses of cCH (ICHD-2/3-beta)[115] who were followed for ≥24 months recording just under 6000 attacks (V, VI). The registry study (VII) followed 85 eCH and cCH patients for 12 months. All patients had a high disease burden.

The principal findings were:

- In varying populations, SPGS is safe and induces acute-, frequency- or combined responses in roughly 2/3 patients. This response is stable across time and accompanied by improvements in use of preventive medication and headache disability.
- Roughly 1/3 of patients treated with SPGS experience attack free periods ≥1 month following initiation of stimulation.

V – Effects of Sphenopalatine Ganglion Stimulation

In this study, 61% of the patients were responders with either an acute, frequency or combined response pattern. In frequency responders, the average reduction in the number of attacks/week was 83% versus baseline and in acute responders 78% of 4340 evaluated attacks could be treated effectively using SPGS. The majority of responders were stable at 12 months, 18 months and 24 months (Figure 9).

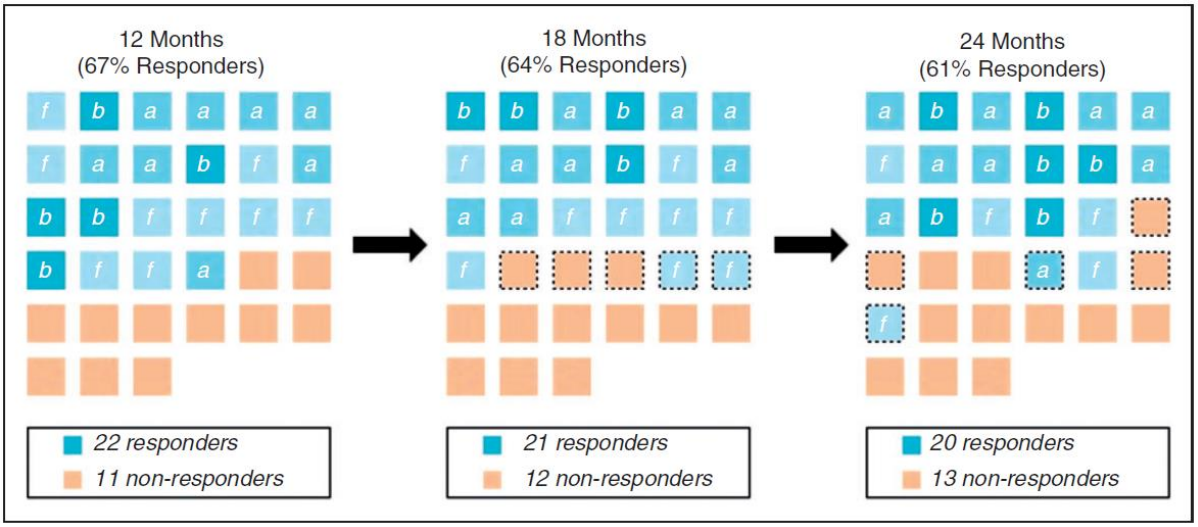

Figure 9: Response consistency analysis. Overall, only few patients change category over time which may both reflect the natural fluctuation of CH as well as treatment response. "a" – acute responder, "f" – frequency responder, "b" – both frequency and acute responder. Reprinted with permission from SAGE.

The therapeutic benefits also manifested as headache disability improvement, with a HIT-6 reduction of 4.8 points at 24 months (p=0.005 compared to baseline), and clinical improvements in preventive medication in 64% of patients. Side effects were predominantly associated with the surgery in 81% of patients, were mild-moderate and resolved within an average of 68 days.[115]

VI – Attack Remission During Sphenopalatine Ganglion Stimulation

The study population was the same as in V. Of these 33 patients, ten experienced remissions, the earliest occurring 21 days after implantation but none before the initiation of regular, titrated stimulation (Figure 10). One patient experienced a 4-week remission but was not counted as the ICHD-2-criteria state "1 month". Each patient's longest remission lasted 149 days on average

(range 62-322). Several patients experienced more than one attack-free period during the observational period but there was no apparent pattern in when these remissions occurred, neither in relation to months of the year nor time passed since implantation. HIT-6 scores improved during remission periods (67.7 vs 55.2, p=0.012) as did preventive medication in six of the ten patients.

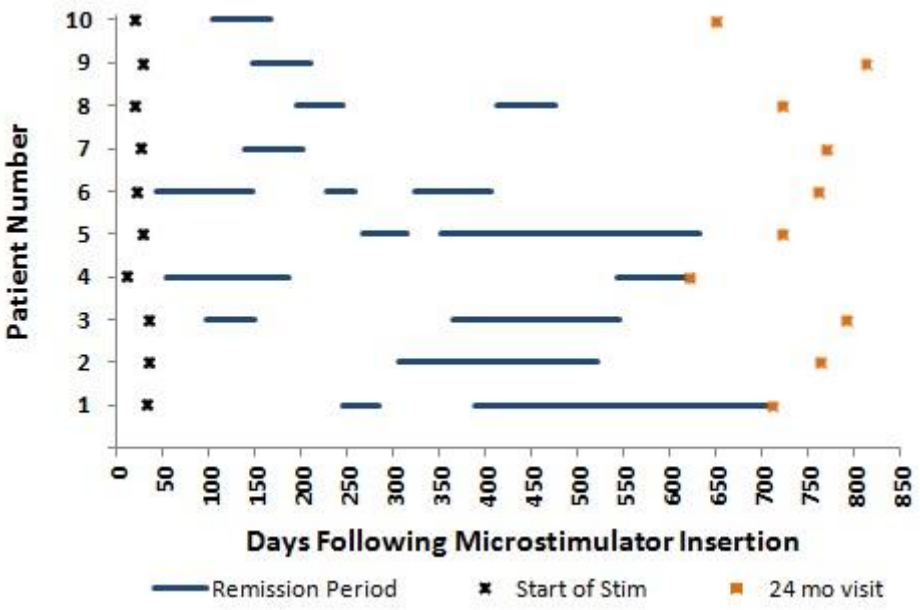

Figure 10: Remission periods (blue lines) experienced by the 10/33 patients enrolled in the long-term follow-up study. Reproduced under the terms of the Creative Commons Attribution 4.0.

VII – Sphenopalatine Ganglion Stimulation in the Clinical Setting

The analysis of treatment effectiveness included 85 patients (7 eCH, 78 cCH) followed for 12 months. Ninety-seven patients were included in the safety analysis. In this clinically more diverse and heterogenous population including both subdiagnoses results from previous studies were reproduced.

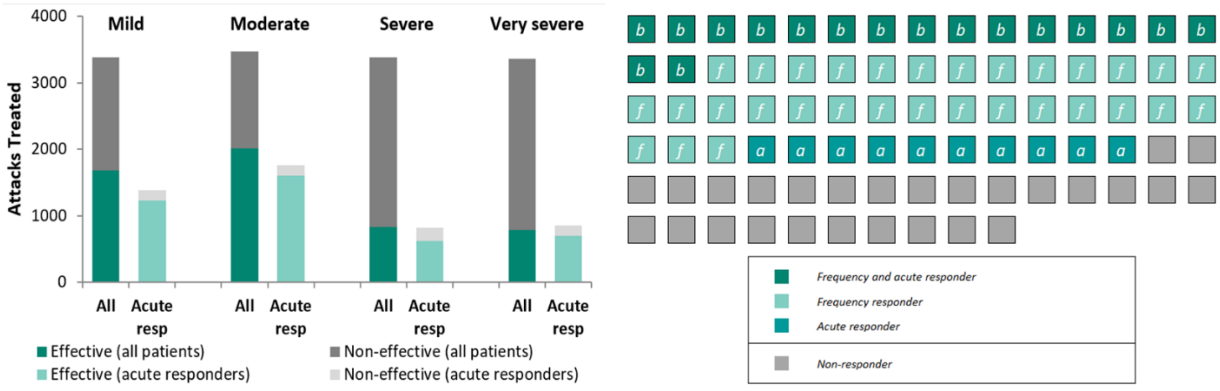

Figure 11: Acute response in all patients and acute responders (left panel). 13,000 attacks were treated over the 12 months of which 39% achieved effective therapy. In the combined acute and frequency responder analysis (right panel), of all patients (n=85), 68% achieved at least a 50% response. Partially reproduced under the terms of the Creative Commons CC BY license.

Sixty-eight percent of patients were responders per protocol (Figure 11) and 55% of the chronic patients had a frequency reduction greater than 50% with 29% experiencing complete attack remission 12 months post-implant. 13,000 attacks were treated in this period and in 39% pain relief or freedom was achieved giving an acute responder rate of 32%. Dramatic reductions in medication usage followed implantation: Use of acute medication and oxygen fell by 52% and in the chronic patients, 74% experienced a clinical improvement in preventive medication. It was also noteworthy that of the chronic patients, 47% experienced a therapeutic response at the 75%-level, and 74% of patients experienced a response at the 30%-level. Similar to V, 73% of patients experienced postoperative side-effects, mostly in the mild to moderate category and which resolved within 2-3 months.

Autonomic Regulation (VIII-X)

The principal findings were:

- There is a dearth of literature on the topic of systemic autonomic regulation in CH and what is available is heterogenous. However, overall, it supports the notion that cardiac autonomic control is altered in CH with ictal parasympathetic hyperfunction and sympathetic hypofunction. Interictally there is reduced reactivity of the ANS.
- CH patients have decreased BRS at rest. This is more pronounced in patients who have recently suffered an attack.
- LF SPGS increases sympathetic tone which precedes CAS-induction. In contrast, cluster pain is associated with increased parasympathetic activity.
- During possible SPGS-provoked cluster-like attacks systemic parasympathetic tone is increased.

VIII – Review of the literature

Out of 380 identified studies, 22 were eligible. These fell into the categories of studies investigating heart rate, blood pressure and ECG changes; studies employing varying batteries of autonomic challenges; and studies using spectral and nonlinear analysis of HRV. Overall, methodology and findings were heterogenous to some extent although the consensus suggests borderline clinical autonomic dysregulation which is most pronounced just before and during attacks. Studies were mostly exploratory in nature and involvement of the trigeminal-cardiac reflex has been briefly considered but this notion has never been substantiated. Possible mechanisms, including involvement of this reflex is presented.

IX – Baroreflex Sensitivity

Recordings from 26 patients and controls were analysed. While at rest patients exhibited a decreased HR responsiveness to spontaneous drops in BP. In the tilted position, patients and controls responded similarly (Table 2).

		Supine				**60° tilt**			
	N	**Up**	**Down**	**Down-Up**	**All**	**Up**	**Down**	**Down-Up**	**All**
Patients	26	16.2	14.3*	-2.4*	14.9	7.6	8.3	0.7	8.0
Controls	26	17.6	22.3*	4.9*	19.4	8.4	9.0	0.6	8.7

*Table 2: Results from the sequence analysis reported as ms/mmHg. In the resting position patients exhibit a decreased responsiveness to spontaneous drops in blood pressure compared to controls. In the standing position there is no difference between patients and controls indicating that in a state of parasympathetic withdrawal responses are normal. *p<0.05. After VII.*[9]

Additionally, patients who had recently suffered an attack had a greater drop in systolic BP (at the level of the carotid sinuses) than patients who had not recently suffered an attack and controls. Despite this greater drop in pressure the HR response was similar. This patient group also had lower BRS at rest and a smaller change in BRS when changing position compared to controls.

X – Low frequency SPGS and changes in heart rate variability

Paired data was available for analysis from 16 patients (10/16 therapeutic responders). Analysis of 5 min epochs during baseline and provocation revealed a greater increase in HR and LFnu and a greater decrease in SDNN, HFnu during sham stimulation compared to LF stimulation (Figure 12). These changes occurred prior to the observed autonomic symptoms.

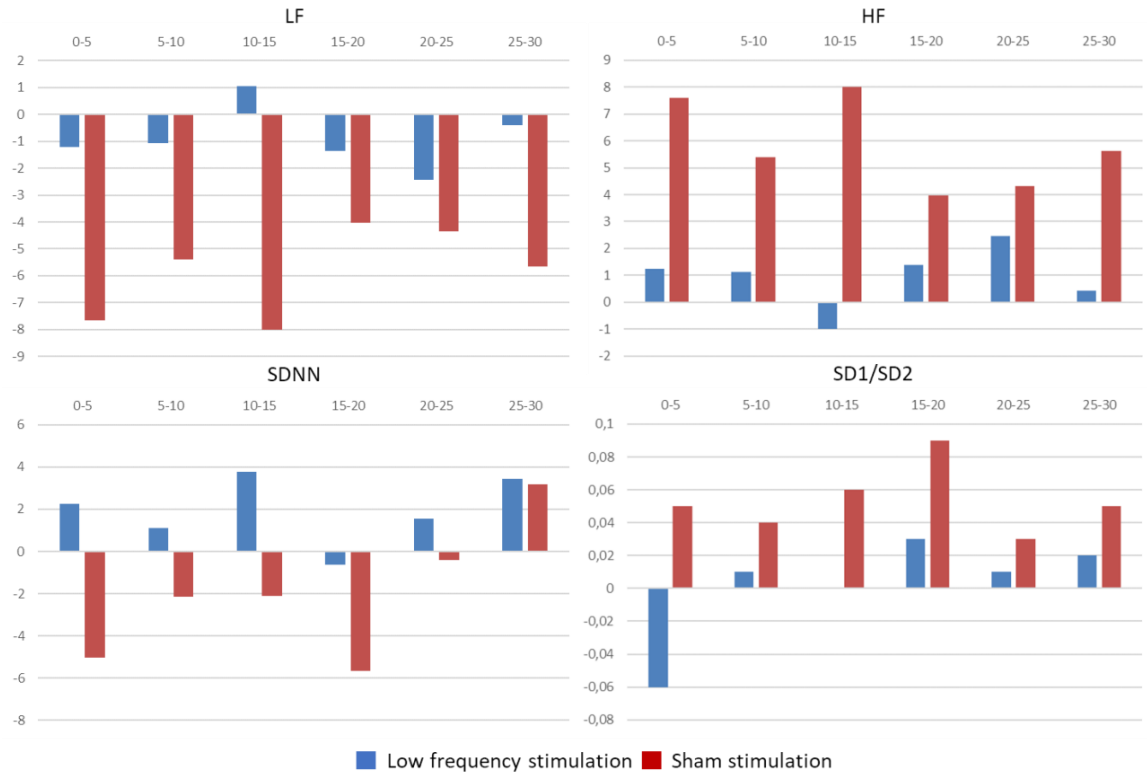

Figure 12: Change from baseline (%) in the low frequency (LF) and high frequency (HF) spectrum, standard deviation of sinus beats (SDNN) and ratio between SD1 and SD2 (Poincaré plot) during active stimulation and sham stimulation. After X.[10]

Cluster-like attacks did not arise more frequently during LF stimulation than sham (6 vs. 4 respectively, $p>0.05$). Regardless, during attacks there was an increase in HFnu ($p<0.05$), a decrease in LFnu ($p<0.05$) as well as slowing of the HR ($p<0.05$).

Discussion

Central mechanisms under chronobiological influence determine the timewise manifestation of stereotypical CH attacks as a consequence of pathological interaction between trigeminal nociceptive processing and oscillating, homeostatic mechanisms. Previously proposed CH models include the trigeminal model,[91] the vascular model[125] and the cavernous sinus model.[126] The best supported of these, the trigeminal model, is not specific for CH[91,127,128] and does not encompass the pathophysiological implications of several ictal and interictal features including predictable attack occurrence, systemic autonomic alterations and the dissociation between pain and autonomic features. Generally, the implicated areas must include those involved in central pain processing, the hypothalamus as well as peripheral structures. Here follows a proposal, inspired by the tripartite model,[32] for a theoretical framework for understanding CH from a homeostatic, chronobiological perspective with an oscillator and a mediator/threshold component (Figure 13). While exact physiological and neurophysiological and -anatomical mechanisms lie beyond the scope of the presented works, it is possible to superimpose this model on anatomic structures based on both human and animal studies.

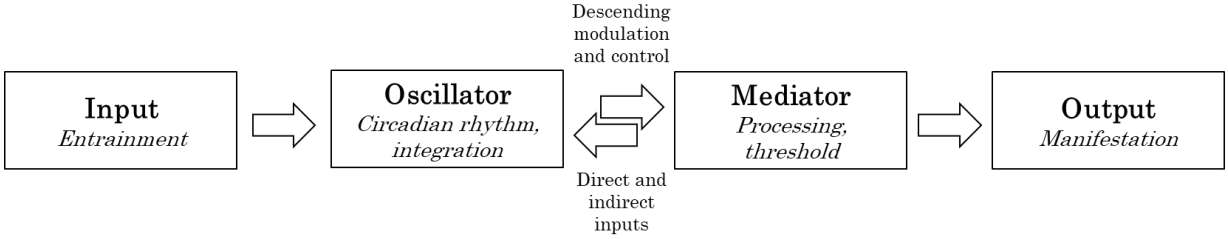

Figure 13: Schematic representation of involved circuits visualizing the bidirectional nature of oscillator-mediator interaction at the center of cluster headache pathology. From left to right: ***Input*** *includes time cues from the environment as well as levels of activity, meals etc. Therapeutic interventions could be included here as well. These inputs entrain the central* ***oscillator*** *in the hypothalamus which integrates these with viscero- and somatosensory information and dictates circadian rhythm and orchestrates responses to maintain homeostasis. The most relevant nuclei include the suprachiasmatic nucleus, the lateral hypothalamus (hypocretin) and the paraventricular nucleus. With bidirectional connections to diencephalic and brainstem nuclei the hypothalamus is in close connection with the* ***mediator*** *component of the model. This includes numerous nuclei and cell groups most central of which are the nucleus raphe magne, the locus coeruleus, the rostral ventrolateral medulla, the periacqueductal grey, the parabrachial nucleus, the nucleus of the solitary tract, the superior salivatory nucleus and the trigeminocervical complex. In both the oscillator and mediator component there is an extensive overlap between areas involved in pain processing, autonomic regulation and sleep, all under chronobiological influence. The final pathway is the* ***output*** *which includes perturbation of autonomic regulation, sleep disturbances as well as a decreased threshold for activation of the trigeminal autonomic reflex the result of which is the complex symptomatology of cluster headache.*

The concept of threshold revolves around the multifactorial nature of most headache disorders and theorizes that seemingly unconnected exposures and vulnerabilities can induce a state of attack vulnerability. While pain perception may vary through the day,[129] and the sensitization phenomenon may bear similarities and has been discussed for years in headache[130] there is a conceptual dissimilarity between a lower pain threshold in the absence of attacks and a mechanism facilitating paroxysmal all-or-nothing crises. The multifactorial aetiology, in an oscillation-threshold interaction as depicted above, likely includes both intrinsic and/or extrinsic protective and aggravating factors and fundamentally the chronobiological

manifestation of the attacks may result from the (regularly) fluctuating presence of these. As trigeminal pain processing, autonomic functioning and sleep converge at several levels there is ample grounds for suspecting involvement of disperse circuits and integration of multiple influencing factors.

Input and Oscillation

In some diseases with fluctuating symptom intensity there are apparent mechanisms. This is seen in nighttime flaring of arthritic disease during low cortisol levels or morning cardiac events coinciding with increased cardiovascular demand.[131–134] Neuro-chronobiological symptomatologies are complex without easily detectable physiological correlates. Epilepsy, for example, has various lobe seizures occurring at specific times of the day without apparent causative mechanisms.[32] In headache, migraine is loosely associated with the morning,[63] tension type-headache with the afternoon[135] and CH, is strongly associated with the early hours of the night.

There is reasonable congruency between reports of CH chronobiology,[51,136–138] the main difference being a mid-day peak in the Manzoni study.[136] This has been attributed to cultural differences (*riposo/pisolino ~ siesta*) and would be in agreement with studies showing attacks occurring 1-2 hours after bed-time. However, with the exception of a case report by Jürgens and colleagues, no previous studies have approached the issue from an oscillation point of view.[139] In I and III a novel tool specifically designed to explore such oscillations and the chronobiology of CH was tested. Diurnal oscillations can be ultradian (<24 hours), circadian (24 hours) and infradian (>24 hours) and the finding of different patterns in eCH and cCH alludes to possible fundamental pathophysiological differences. Further, in II, the attack prominence pattern in men and women sufferers is similarly configured, but phase shifted. Fundamentally, this indicates that variables include both timing or phase, and oscillation. A recent metanalysis of family history and CH discovered that females have a higher preponderance of fCH.[140] Although we did not identify such a pattern in II or III it does fit with the identification of a distinct chronobiology in both women and fCH-patients.

The two sleep studies from the Danish Headache Centre (IV and reference 54) gave indications that nocturnal attacks may occur at the end of a sleep cycle (not necessarily REM). Women also report worse sleep quality (II) and a more fragmented first sleep cycle, together with longer time to fall asleep, could theoretically explain part of the observed phase shift. Part of the observed difference may be driven by a higher proportion of cCH patients in women as self-reported sleep quality is worse in cCH.[51] Several nuclei of the hypothalamus are sexually dimorphic (including the paraventricular nucleus which integrates homeostatic and pain control[141]) perhaps also lending part of the explanation for these differences.

Study I-III demonstrates that chronorisk varies according to factors including, but probably not limited to, sex, medication, smoking and alcohol- and coffee consumption. Further, THI may influence manifestation in the diagnostic eCH/cCH spectrum which again is associated with different chronobiological fingerprints. It could be speculated that THI influences a threshold mechanic rather than affecting chronobiology but the number of systems influenced by verapamil, smoking, alcohol and coffee does not allow for speculation with regards to their effect on threshold or oscillation. Curiously though, response to melatonin (influences 24-hour oscillations) is stronger in eCH and cCH responds better to lithium (influences faster oscillations).[70,71,142,143] Considering their documented influence on the sleep-wake cycle[37] and the fact that verapamil has some effect in bipolar disorder, theoretically, these three CH-medications may elicit their effects through influence on oscillating circuits. However, there is

also evidence that melatonin and verapamil changes pain thresholds so no firm conclusion can be drawn.[144,145]

Figure 14 illustrates possible scenarios for such oscillation-threshold interaction in the two subdiagnoses. Importantly, study I-III also showed that while chronorisk may vary, and severity notwithstanding, the attacks themselves only differ minimally,[146] if at all, across subgroups. Thus, the label "stereotypical" is apt and the frequent misdiagnosis in women (II) may be due to coexisting migraine or lack of awareness of CH rather than a more migrainous phenotype per se.

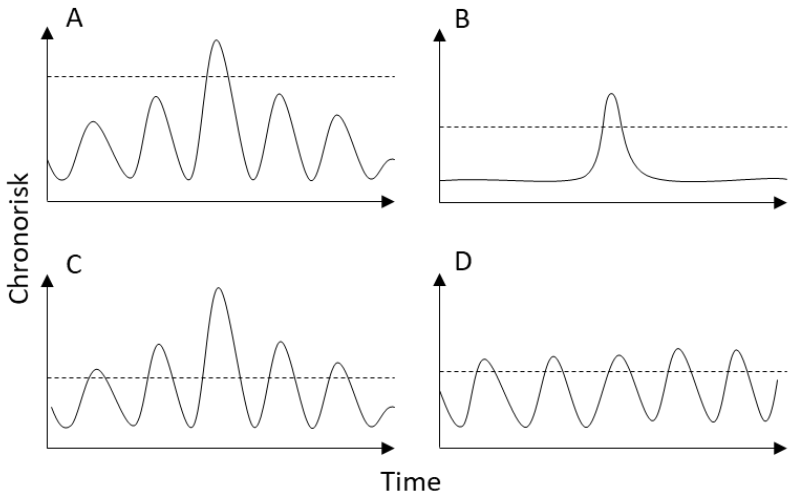

Figure 14: Possible scenarios for oscillation-threshold interaction in CH. The dashed line indicates a theoretical threshold for attack penetrance. The solid lines indicate chronorisk. Panel A and B could thus represent the episodic phenotype – A with ultradian oscillating chronorisk but a high threshold and B with circadian oscillation where threshold plays a lesser role. Panel C and D could represent the chronic phenotype. C has ultradian oscillation and low threshold and D a low threshold and less variation in the ultradian oscillation amplitude.

Chronotherapy

Other fields of medicine have benefitted from adjusting the timing of administration of various treatments[32,64,147–153] and a reevaluation of how therapy is administered in CH may be in order. A complete understanding of the significance of proper timing and dosage of a drug must consider chronopharmacokinetics and -dynamics as well as rhythmic differences in effects of drugs on the organism as a whole (chronergy).[154] Very high doses of verapamil are occasionally necessary[155] and lead to side-effects and decreased treatment adherence. It is entirely unlikely that a 200 mg morning dose has the same effect as an equal evening dose. For example, constant-rate administration of valproic acid produces dramatic, rhythmic fluctuations in plasma concentration throughout the 24 hours of the day.[156]

Verapamil is the drug of choice for preventive treatment of CH (reviewed by Petersen and colleagues[157]). The drug is metabolized by CYP3A4[158] and although this hepatic enzyme exhibits minimal diurnal variation in activity[159] other fluctuating factors including smoking, diet and gastric motility influence plasma concentrations.[160–162] The varying chronopharmacokinetics of different verapamil formulations are known,[148,163] however, the use of extended-release formulations in eCH patients with clear peaks in chronorisk and varying plasma concentrations may not be optimal. Trials are needed to map verapamil metabolism throughout the day and determine if a constant concentration or maximum serum verapamil during increased chronorisk is desirable. It may also be that fCH patients respond particularly well to

medications which modulate circadian oscillators such as melatonin. Varying administration of verapamil according to chronorisk has been tried tentatively with promising results[61] but results need to be verified.

In II, cCH was more common in women than men and these women also had a higher attack frequency possibly due to a poorer treatment response. In a recent study it was also found that complete response to acute therapy was most common in men.[164] However, in this study no association was found between subdiagnosis or sex and effect of verapamil. If women suffer their attacks at different times, with chronotherapy in mind, theoretically, the phase-shifted attack pattern may affect treatment response due to the influence of chronopharmacokinetics, -dynamics and chronergy. New studies focusing on these issues are warranted.

The Mediator and Output

Compared to the oscillating circuits, the trigeminal-autonomic reflex is well understood and can be manipulated in animal models.[165] It has also been targeted in various ways in humans[81] and SPGS is the latest iteration. Theoretically, at least part of the effect of SPGS is due to modification of brainstem mediator circuits.

Sphenopalatine Ganglion Stimulation

Studies V-VII showed that the clinical effect of SPGS is maintained over time and is reproducible. The acute effect is most likely due to a mechanism breaking the trigeminal-autonomic reflex directly, as a form of block depolarizing neurons in the SPG, in an antidromic manner working on mediator-structures in the brainstem or as a combination of the two.[166] The frequency effect is likely due to modulation of processing in oscillating or mediating circuits.

The remission periods (VI) and frequency reductions (V, VII) observed following SPGS in otherwise refractory chronic CH patients demonstrate that chronicity is not a permanent state. This could theoretically be due to changes in the relative influences of diencephalic and brainstem circuits on trigeminal pain processing. Panel D and C in figure 14 would thus come to be more like A. Interestingly, the response pattern is not locked – ie. a patient may be acute responder, become a combined responder and then return to the former. This is suggestive of two separate mechanisms. Concrete neurophysiological evidence is sparse, but not completely lacking. In an animal model, electrical stimulation of the greater petrosal nerve induced firing in two groups of neurons in the trigeminal cervical complex (TCC): some with short (3-20 ms) and others with longer latency (9-40 ms).[166] The firing of the short-latency neurons can be explained by antidromic stimulation which could also contribute to central neuromoculation.[83] Alternatively, an effect similar to that of ONS could be postulated, ie. convergence of trigeminal afferents in the TCC. Continuing along these lines, analogous predictors of response might be present for SPGS.[167]

The preventive effect of SPGS seems attenuated compared to DBS and ONS.[168,169] If a central neuromodulatory process is behind the preventive effect in all three, it is plausible that direct, central modulation of key structures would have a stronger effect than peripheral. However, this cannot explain the difference between ONS and SPGS. Here, it could be theorized that the difference in preventive effect could be due to targeting of sensory fibers[170–172] as opposed to primarily autonomic fibers.

The Role of the Autonomic Nervous System

Changes in systemic autonomic functioning in CH are well-documented and detectable by a variety of methods including very simple and accessible ones such as ECG (VIII). They are not subtle and include attack-related junctional rhythm, bradycardia, asystole, atrial fibrillation,

sinoatrial block (reversed with atropine), as well as pathological or near-pathological responses to a number of provocations. Some of these observations can be explained by parasympathetic transients[103,105,173] giving rise to the label "parasympathetic paroxysm"[102] or "autonomic storm".[100] From a pathophysiological point-of-view they implicate dispersed mediator circuitry in CH. The network of nuclei regulating autonomic function include several areas of the hypothalamus, the insular and anterior cingulate cortices, the central nucleus of the amygdala, the periaqueductal grey (PAG), the parabrachial nucleus, the nucleus of the solitary tract (NTS), the ventrolateral reticular formation and the raphe nuclei.[174] Fibres conveying visceral and nociceptive information converge on these areas where it is integrated and responses orchestrated via projections to preganglionic sympathetic and parasympathetic neurons.[175] The findings of reduced BRS (IX) and HRV[86] in CH show autonomic reactivity to be blunted and is evidence of autonomic dysfunction possibly influenced by the attacks themselves (IX). This state may be reversible as a study by Cortelli and colleagues,[87] showed that DBS in cCH patients corrected a diminished sympathoexcitatory drive, perhaps mediated through increased hypothalamic stimulus to the lateral PAG and from here to the rostral ventrolateral medulla, also part of the endogenous pain processing pathway. These findings suggest that a sympathetic deficit is associated with the cluster state and that increased sympathetic tone may have a warding effect on the attacks. This may be substantiated by the findings of stimulant consumption possibly reducing daytime chronorisk (I) and attacks predominantly arising from states of increased parasympathetic tone (VIII).[101,176]

LF SPGS, administered without regard to patient chronorisk, induces CAS[95] and changes in autonomic regulation but not actual attacks.[97,177,178] HF SPGS has also previously been shown to induce changes in HR (not a prespecified outcome measure).[177] In X, the changes in autonomic regulation which were observed prior to the CAS (increased sympathetic activity) were different from those observed during attacks (parasympathetic discharges). Antidromic activation of brainstem circuits[166] or the trigeminal cardiac reflex are possible explanations. In the latter, the changes may be similar to those described during maxillofacial procedures[179] where parasympathetic discharges result in bradycardia, asystole, apnea and gastric hypermobility.[180–183] It can be provoked by electrical, chemical or physical manipulation of the trigeminal branches, the ganglion or trigeminal brainstem centers and is a phylogenetic oxygen-preserving reflex akin to the diving reflex.[183] Involvement of this brainstem reflex in headache pathology has not received much attention but could explain the systemic parasympathetic phenomena and may provide a coupling between peripheral stimulation of the ANS and systemic changes.[184,185] It is likely not the only factor, however, as trigeminal pain alone does not induce similar responses.[105,186] The changes occurring during CH-crises are also different from those elicited by experimental pain (Reviewed by Koenig et al.[187]) which is associated with a decrease in parasympathetic activity and an increase in sympathetic leading to tachycardia[184] dissimilar to the paradoxical increase in parasympathetic tone and bradycardia seen in CH crises (X).[184,185] Further elaborating on this point, the study by Cortelli and colleagues[87] showing increased sympathoexcitatory drive following DBS, as well as a study showing altered autonomic functioning as well as aspects of the CH phenotype following stimulation and intentional lesioning of the posterior hypothalamus,[188] substantiates the notion that higher centers are involved in the systemic autonomic manifestations.

That attacks cannot be reliably provoked by peripheral stimulation of the afferent[97] or efferent[178] arc alone indicates that higher structures are necessary for attack initiation. These structures could play the role of a "cluster generator" or perhaps more likely, put the patient in a permissive state under chronobiological influence. Interestingly, as almost a reverse design, nVNS modulates the trigeminal-autonomic reflex, theoretically through connections via the NTS to the TCC and the SSN or through mechanisms involving higher brain centers including the

hypothalamus.[88] Lastly, these results encourage the notion that CH pain and CAS are not inseparable and can manifest independently.[94,96–98,178,189] The question remains, however, whether the results had been different if patient chronorisk had been taken into consideration. Provoking attacks may not be as simple as subjecting a patient to a noxious factor as this would disregard the concept of chronorisk.

Oscillator-mediator interaction

Connections between nuclei in the diencephalon and brainstem involved in autonomic control, sleep/arousal and pain modulation are both direct and indirect. The indirect connections allow for integration of several signals. This is seen, for example, in the connections from the SCN to arousal centres via the dorsomedial hypothalamus and supraventricular zone where information on thermoregulation and corticosteroid release is processed.[190] It is likely because of these indirect connections and such integration that we see many factors influencing attack timing perhaps through a form of summation. Apart from receiving descending pain modulatory signals, the TNC has direct connections to hypothalamic nuclei via the trigeminal-hypothalamic tract.[191] Consequently, trigeminal pain processing is subject to top-down modulation, but also exerts influence on homeostatic regulation.

Nociceptive inputs, cranial or somatic, can elicit autonomic responses via the viscerotopically organized NTS, parabrachial nucleus (PBN), amygdala, hypothalamus and ventrolateral medulla but can also stimulate autonomic preganglionic neurons directly.[192] This is the case on the level of the spinal cord, but also on a brainstem level through direct and indirect connections from the TNC to the preganglionic parasympathetic neurons of the SSN.[175] A recent functional magnetic resonance study demonstrated decreased hypothalamus-salience network coactivation interpreted as defective central pain and ANS integration.[28] Together with the hypothalamus, the salience network plays a pivotal role in pain perception and -control[193–197] and the decreased coactivation could indicate both dysfunctional descending pain control and altered autonomic functioning.[28] The salience network is anchored in the anterior cingulate cortex in which hypometabolism following ONS is associated with a positive treatment response.[29] This region and the insula are involved in both sympathetic and parasympathetic regulation.[198] In summary, the altered ANS functioning in CH could be a consequence of involvement of both connections on the same level but also altered functioning of higher centres.

Sleep and Hypocretin

Sleep is intricately a part of CH pathophysiology with extensive anatomical and physiological overlap[36] but knowledge about these systems' integration with autonomic function is sparse. The HCRT-system, which is known to exert top-down influence on trigeminal pain processing, sleep-regulation and autonomic function,[199–201] is known to have integrative functions in regulation of autonomic control and corresponding areas receive hypocretinergic innervation.[202–204] These neurons directly or indirectly process chemo-, viscero- and somato-sensory information (including trigeminal pain[205–208]) to orchestrate cognitive and autonomic-, breathing-, blood-pressure-, locomotor- (including the hyperlocomotive "flight" response[209]), energy flux- and risk-taking responses.[210] As specific examples, HCRT-1 signalling facilitates inhibitory and diminishes excitatory inputs to cardiac vagal neurons in the nucleus ambiguus[211] and hypothalamic pain processing[205–207] involves hypocretinergic connections from the lateral area directly to the SSN.[212]

HCRT levels fluctuate subtly with the seasons with a summer surge.[213] This is noteworthy, considering the inverse pattern of CH chronorisk.[51] Further speculation could suggest that the decreases in autonomic dynamics in CH patients may be linked to the lower HCRT-levels,[214] as

can be seen in HCRT-deficient narcoleptics who have a decreased sympathetic drive.[215] CH is partly familial[216] and, as demonstrated, fCH patients have a distinctly increased nocturnal chronorisk (III). These observations have directed efforts in CH genetics and several target genes have been investigated, the most relevant of which include *CLOCK*[217] and those encoding the HCRT-2-receptor,[58] but reproducibility is lacking in both cases.[59,218–220] The possibility of association with a specific single nucleotide polymorphism in the HCRT2-receptor gene, accentuated when stratifying according to presence of circadian rhythmicity also needs confirmation.[220] CH patients have decreased HCRT-1 in their CSF[57] which could be explained by general suppression of hypothalamic function and concomitant conditions.[221–223] It could also be part of a dysregulated descending, anti-nociceptive influence on the brainstem but mechanisms are complex and likely state-dependent as HCRT-neurons control their targets also via co-transmitters with compound effects.[210] Thus, drawing on these findings from multiple fields, HCRT represents a research target as a point of coalescence for CH pain, chronobiological integration and homeostatic functions.

Previous sleep studies have suggested that eCH attacks are associated with REM-sleep,[42–45,48,49,224] and data from the Danish Headache Centre (IV)[4,49] does show a numerical overrepresentation of attacks in this phase. A point could be made that the theory is corroborated by chronorisk results (I, III) – i.e. the peak 1-2 hours after falling asleep coinciding with the usual timing of the first REM-cycle. However, an association with a specific sleep phase may be simplistic and it is more likely that the initiation or termination of the greater REM-NREM cycle is central.[49] In IV, no difference was found between bout-sleep and remission-sleep confirming results from epidemiological research[51] and also research applying the Ewing test battery inside and outside of the bout without difference in results.[225] Together these results indicate a state of permanent or long-lived perturbation of homeostatic regulation, including sleep and autonomic control, and changes are likely not attributable to the direct effect of (nocturnal) CH attacks.[49] Furthermore, a theory associating nocturnal CH attacks with the first REM-phase would find it problematic that attacks would not occur during subsequent REM-phases. With the same caveats, another common ground between attacks arising from sleep and wake are the changes in arousal and shifts in autonomic tone.[226–228] Thus, barring the existence of a form of refractory period, no theory can currently completely explain the vulnerability exclusively associated with the first hours of sleep although fluctuating autonomic tone does occur in both sleep and wake whereas REM sleep obviously does not.

The topic of OSA and its possible association with CH is becoming controversial. Sleep apnoea or hypopneas occur when breathing is partially or completely interrupted during sleep due to upper airway collapse. It is the result of anatomical factors and insufficient neuromuscular compensation.[229] A possible physiological correlate between CH and OSA does exist, namely that of possible decreased autonomic innervation of upper airway muscles, partially regulated from the hypothalamus and possibly involving hypocretinergic signaling.[223] Uncontrolled studies have found a high prevalence in CH patients,[43,45–47,230,231] which was reproduced in a recent controlled study also showing association with the bout-periods.[50] Here, like in our sleep study, controls were matched for age, BMI and sex. In IV, as well as in the precursor study from our group,[49] a moderate numerical difference in AHI between patients and controls did not reach statistical significance nor was there any difference between patients in cluster and outside. CH patients are heavy smokers[112] and the relationship between OSA and smoking has been investigated to some degree (Reviewed by Krishnan et al.[232]) showing that smoking worsens pre-existing apnoea tendencies. In the general population OSA is common with a prevalence of 2-14% and 21-90% in patients undergoing sleep evaluation.[233] Smoking is the third-best predictor for sleep apnoea after age and daytime sleepiness and current smokers have an odds-ratio for moderate or severe OSA of 4.4 (95% CI 1.3-13) compared to nonsmokers.[234] Smoking

worsens sleep apnea by changing sleep architecture, relaxing airway muscles and neural reflexes, increasing arousal threshold and causing airway inflammation.[232] Additionally, an association between CH and OSA might also manifest as a lack of difference in breathing parameters between the sexes, yet this is not the case. In data from the Danish Headache Center male patients have an average AHI of 13.3 and female 2.7 ($p<0.01$) in the first study[49] and 12.0 and 4.5 ($p<0.05$) in IV (post hoc analysis). Of course, this vast difference could also be attributed to other factors. Thus, as it stands now, the issue cannot be resolved without additional studies with careful consideration of possible confounding factors.

Reflections on Methodology

Questionnaires and diaries remain the most efficient way to obtain information about fluctuating symptoms and is widely used[148] in the same context as here – i.e. reporting per clock-hour interval. By doing so coinciding patterns are aggregated whereas individual patterns, not following the trend will appear as noise. In study I-III, it is quite remarkable that such prominent patterns were found but due caution in their interpretation must be exercised and application to individuals carries with it the same caveats as all epidemiological research does where another major limitation is that the observational nature prevents causality from being ascertained.

Sleep studies are notoriously difficult to conduct. A particular issue with regards to CH arises when investigations demand that patients be admitted. Are results obtained during hospitalization representative of the real world? In the sleep studies, patients were contacted and the ongoing presence of daily attacks, in most cases also nocturnal, was confirmed. However, in some, upon admission, attacks would cease or become significantly reduced in frequency and severity. The presented studies were not directly dependent on attack observations and PSG and BRS-data most likely *does* represent the cluster state. Still, the mechanism behind this unanticipated attack frequency reduction is interesting and represents a scientific conundrum.

There are no guidelines on neuromodulation trial design and result reporting in headache.[235] Consequently, there is an unequivocal heterogeneity across and within the modalities making comparison problematic. Also, the fluctuation of disease intensity and the tendency for patients to seek treatment during exacerbations lead to increased recruitment at this time. A subsequent spontaneous return to the average symptom intensity can be interpreted as treatment effect. A longer baseline could provide a better reference but ethical considerations, referral bias and regression towards the mean would still contribute to increasing the risk of a type 1 error.

BRS and HRV analysis are sensitive and affected by many factors difficult to control for. However, the influence is attenuated when conducting measurements in close temporal proximity and using patients as their own controls. Analysis of HRV and BRS represent modalities which are accessible and non-invasive but the presented results need to be corroborated using other modalities. Previous studies using microneurographic recordings of muscle nerve sympathetic activity[236] or lipolysis analysis[237] are such examples and should be expanded upon.

Future Research Opportunities

This dissertation sets the stage for two lines of research: Mechanistic studies and studies on therapeutic improvements. Functional neuroimaging can advance our understanding of brain disorders. However, a recent study has illustrated the importance of timing these investigations in relation to attack occurrence or chronorisk[238] and the different phases of attacks should also be kept in mind.[93] Detailed diaries and establishing individual participants' attack cyclicity will

help in this regard. Chronotherapy is a concept with direct patient benefit which deserves further development in CH. The ability to test serum levels of verapamil and other prophylactics should be exploited to identify possible 24-hour fluctuations in blood concentrations and their influence on attack prevention. Future studies should compare administration of preventive drugs at fixed times and anticipatory administration before increased chronorisk.

Conclusion

The triad of pain, predictability in attack occurrence and altered autonomic functioning encompassing the CH phenotype stem from altered hypothalamic-diencephalic interaction with brainstem circuits involved in trigeminal nociception and homeostasis. The enclosed works have provided new insight into and provided new tools to investigate the elusive mechanisms behind the most painful disorder known to man. For the first time an integrated model, which incorporates both local, cranial and systemic aspects of CH pathology, has been proposed and individually the studies have advanced our knowledge of CH.

References

1. Barloese, M., Haddock, B., Lund, N. T., Petersen, A. & Jensen, R. Chronorisk in cluster headache: A tool for individualised therapy? *Cephalalgia* ePub (2018).
2. Lund, N., Barloese, M., Petersen, A., Haddock, B. & Jensen, R. Chronobiology differs between men and women with cluster headache, clinical phenotype does not. *Neurology* **88**, 1069–1076 (2017).
3. Barloese, M. C. J. *et al.* Episodic and Chronic Cluster Headache: Differences in Family History, Traumatic Head Injury, and Chronorisk. *Headache J. Head Face Pain* head.13730 (2019). doi:10.1111/head.13730
4. Lund, N. *et al.* Disturbed sleep in cluster headache is not the result of transient processes associated with the cluster period [submitted]. *Eur. J. Neurol.* (2018).
5. Jürgens, T. P. *et al.* Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia* **37**, 423–434 (2017).
6. Barloese, M. *et al.* Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. *J. Headache Pain* **17**, 67 (2016).
7. Barloese, M. *et al.* Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry. *J. Headache Pain* **19**, 6 (2018).
8. Barloese, M. A Review of Cardiovascular Autonomic Control in Cluster Headache. *Headache* **56**, 225–239 (2016).
9. Barloese, M. C. J. *et al.* Reduced Baroreflex Sensitivity in Cluster Headache Patients. *Headache J. Head Face Pain* **55**, 815–824 (2015).
10. Barloese, M. *et al.* Sphenopalatine ganglion stimulation induces changes in cardiac autonomic regulation in cluster headache. *Clin. Physiol. Funct. Imaging* ePub (2017).
11. Vos, T. *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1545–1602 (2016).
12. Katsarava, Z., Mania, M., Lampl, C., Herberhold, J. & Steiner, T. J. Poor medical care for people with migraine in Europe – evidence from the Eurolight study. *J. Headache Pain* **19**, 10 (2018).
13. Jensen, R. M., Lyngberg, A. & Jensen, R. H. Burden of cluster headache. *Cephalalgia* **27**, 535–41 (2007).
14. Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U. & Jönsson, B. The economic cost of brain disorders in Europe. *Eur. J. Neurol.* **19**, 155–62 (2012).
15. World Health Organization. *Lifting the Burden*. *Atlas of headache disorders and resources in the world* (WHO, 2011).
16. Abu Bakar, N. *et al.* Quality of life in primary headache disorders: A review. *Cephalalgia* **36**, 67–91 (2016).
17. Fischera, M., Marziniak, M., Gralow, I. & Evers, S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia* **28**, 614–8 (2008).
18. Evers, S., Fischera, M., May, A. & Berger, K. Prevalence of cluster headache in Germany: Results of the epidemiological DMKG study [7]. *J. Neurol. Neurosurg. Psychiatry* **78**, 1289 (2007).
19. Goadsby, P. J. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. *Lancet Neurol.* **1**, 251–7 (2002).
20. Ji Lee, M. *et al.* Increased suicidality in patients with cluster headache. *Cephalalgia* 333102419845660 (2019).
21. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* **38**, 1–211 (2018).
22. Sjaastad, O. *Cluster headache syndrome*. (W.B. Saunders, 1992).
23. Barloese, M. C. J. The pathophysiology of the trigeminal autonomic cephalalgias, with clinical implications. *Clin. Auton. Res.* (2017).

24. May, A. *et al.* Cluster headache. *Nat. Rev. Dis. Prim.* **4**, 18006 (2018).
25. May, A. *et al.* Hypothalamic activation in cluster headache attacks. *Lancet* **352**, 275–8 (1998).
26. Lodi, R. *et al.* Study of hypothalamic metabolism in cluster headache by proton MR spectroscopy. *Neurology* **66**, 1264–6 (2006).
27. Wang, S.-J., Lirng, J.-F., Fuh, J.-L. & Chen, J.-J. Reduction in hypothalamic 1H-MRS metabolite ratios in patients with cluster headache. *J. Neurol. Neurosurg. Psychiatry* **77**, 622–5 (2006).
28. Qiu, E., Tian, L., Wang, Y., Ma, L. & Yu, S. Abnormal coactivation of the hypothalamus and salience network in patients with cluster headache. *Neurology* **84**, 1402–8 (2015).
29. Magis, D. *et al.* Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study. *BMC Neurol.* **11**, 25 (2011).
30. Akram, H. *et al.* Optimal deep brain stimulation site and target connectivity for chronic cluster headache. *Neurology* **89**, 2083–2091 (2017).
31. Jean-Jacques de Mairan. Observation botanique. *Hist. l'Académie R. des Sci. avec les mémoires mathématique Phys. tirés des Regist. cette Académie* 35 (1729).
32. Loddenkemper, T., Lockley, S. W., Kaleyias, J. & Kothare, S. V. Chronobiology of epilepsy: diagnostic and therapeutic implications of chrono-epileptology. *J. Clin. Neurophysiol.* **28**, 146–53 (2011).
33. Provencio, I., Jiang, G., De Grip, W. J., Hayes, W. P. & Rollag, M. D. Melanopsin: An opsin in melanophores, brain, and eye. *Proc. Natl. Acad. Sci. U. S. A.* **95**, 340–5 (1998).
34. Panda, S. *et al.* Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. *Science* **298**, 2213–6 (2002).
35. Dijk, D.-J. & Lockley, S. W. Integration of human sleep-wake regulation and circadian rhythmicity. *J. Appl. Physiol.* **92**, 852–62 (2002).
36. Brennan, K. C. & Charles, A. Sleep and headache. *Semin. Neurol.* **29**, 406–18 (2009).
37. Nesbitt, A. D., Leschziner, G. D. & Peatfield, R. C. Headache, drugs and sleep. *Cephalalgia* **34**, 756–66 (2014).
38. Holland, P. R. Headache and sleep: Shared pathophysiological mechanisms. *Cephalalgia* **34**, 725–744 (2014).
39. Evers, S. Special issue on headache and sleep. *Cephalalgia* **34**, 723–724 (2014).
40. Evers, S. Sleep and headache: The biological basis. *Headache* **50**, 1246–1251 (2010).
41. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. (American Academy of Sleep Medicine, 2005).
42. Dexter, J. D. & Weitzman, E. D. The relationship of nocturnal headaches to sleep stage patterns. *Neurology* **20**, 513–8 (1970).
43. Kudrow, L., McGinty, D. J., Phillips, E. R. & Stevenson, M. Sleep apnea in cluster headache. *Cephalalgia* **4**, 33–8 (1984).
44. Pfaffenrath, V., Pöllmann, W., Rüther, E., Lund, R. & Hajak, G. Onset of nocturnal attacks of chronic cluster headache in relation to sleep stages. *Acta Neurol. Scand.* **73**, 403–7 (1986).
45. Nobre, M. E., Leal, A. J. & Filho, P. M. Investigation into sleep disturbance of patients suffering from cluster headache. *Cephalalgia* **25**, 488–492 (2005).
46. Nobre, M. E., Filho, P. F. M. & Dominici, M. Cluster headache associated with sleep apnoea. *Cephalalgia* **23**, 276–9 (2003).
47. Chervin, R. D. *et al.* Timing patterns of cluster headaches and association with symptoms of obstructive sleep apnea. *Sleep Res. online SRO* **3**, 107–12 (2000).
48. Della Marca, G. *et al.* A sleep study in cluster headache. *Cephalalgia* **26**, 290–4 (2006).
49. Barloese, M., Jennum, P. J., Lund, N. T. & Jensen, R. H. Sleep in cluster headache - beyond a temporal rapid eye movement relationship? *Eur. J. Neurol.* **22**, 656-e40 (2015).
50. Evers, S., Barth, B., Frese, A., Husstedt, I.-W. & Happe, S. Sleep apnea in patients with cluster headache: A case-control study. *Cephalalgia* **34**, 828–32 (2014).
51. Barloese, M. *et al.* Sleep and chronobiology in cluster headache. *Cephalalgia* **35**, 969–78 (2015).

52. Chiou, L.-C. *et al.* Orexins/hypocretins: pain regulation and cellular actions. *Curr. Pharm. Des.* **16**, 3089–100 (2010).
53. Mignot, E. *et al.* The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch. Neurol.* **59**, 1553–62 (2002).
54. Bartsch, T., Levy, M. J., Knight, Y. E. & Goadsby, P. J. Inhibition of nociceptive dural input in the trigeminal nucleus caudalis by somatostatin receptor blockade in the posterior hypothalamus. *Pain* **117**, 30–9 (2005).
55. Millan, M. J. Descending control of pain. *Prog. Neurobiol.* **66**, 355–474 (2002).
56. Holland, P. R. Biology of Neuropeptides: Orexinergic Involvement in Primary Headache Disorders. *Headache J. Head Face Pain* **57**, 76–88 (2017).
57. Barloese, M. *et al.* Reduced CSF hypocretin-1 levels are associated with cluster headache. *Cephalalgia* **35**, 869–876 (2015).
58. Schürks, M. *et al.* Cluster headache is associated with the G1246A polymorphism in the hypocretin receptor 2 gene. *Neurology* **66**, 1917–9 (2006).
59. Weller, C. M. *et al.* Cluster headache and the hypocretin receptor 2 reconsidered: A genetic association study and meta-analysis. *Cephalalgia* (2014). doi:10.1177/0333102414557839
60. Ohdo, S. Chronotherapeutic strategy: Rhythm monitoring, manipulation and disruption. *Adv. Drug Deliv. Rev.* **62**, 859–75 (2010).
61. Blau, J. N. & Engel, H. O. Individualizing treatment with verapamil for cluster headache patients. *Headache* **44**, 1013–8 (2004).
62. Hofstra, W. A., Gordijn, M. C. M., van Hemert-van der Poel, J. C., van der Palen, J. & De Weerd, A. W. Chronotypes and subjective sleep parameters in epilepsy patients: a large questionnaire study. *Chronobiol. Int.* **27**, 1271–86 (2010).
63. Fox, A. W. & Davis, R. L. Migraine chronobiology. *Headache* **38**, 436–41 (1998).
64. Manfredini, R. *et al.* Chronobiology of Takotsubo Syndrome and Myocardial Infarction. *Heart Fail. Clin.* **12**, 531–542 (2016).
65. Ferraz, E., Borges, M. C. & Vianna, E. O. Influence of Nocturnal Asthma on Chronotype. *J. Asthma* **45**, 911–915 (2008).
66. Truong, K. K., Lam, M. T., Grandner, M. A., Sassoon, C. S. & Malhotra, A. Timing Matters: Circadian Rhythm in Sepsis, Obstructive Lung Disease, Obstructive Sleep Apnea, and Cancer. *Ann. Am. Thorac. Soc.* **13**, 1144–1154 (2016).
67. Glasser, S. P. Circadian variations and chronotherapeutic implications for cardiovascular management: a focus on COER verapamil. *Heart Dis.* **1**, 226–32
68. Yin, L., Wang, J., Klein, P. S. & Lazar, M. A. Nuclear receptor Rev-erbalpha is a critical lithium-sensitive component of the circadian clock. *Science* **311**, 1002–5 (2006).
69. Johansson, A.-S., Brask, J., Owe-Larsson, B., Hetta, J. & Lundkvist, G. B. S. Valproic acid phase shifts the rhythmic expression of Period2::Luciferase. *J. Biol. Rhythms* **26**, 541–51 (2011).
70. Leone, M., D'Amico, D., Moschiano, F., Fraschini, F. & Bussone, G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* **16**, 494–6 (1996).
71. Li, J., Lu, W.-Q., Beesley, S., Loudon, A. S. I. & Meng, Q.-J. Lithium Impacts on the Amplitude and Period of the Molecular Circadian Clockwork. *PLoS One* **7**, e33292 (2012).
72. Cambiaghi, M. & Sconocchia, S. Scribonius Largus (probably before 1CE–after 48CE). *J. Neurol.* **265**, 2466–2468 (2018).
73. Goadsby, P. J. Sphenopalatine (pterygopalatine) ganglion stimulation and cluster headache: new hope for ye who enter here. *Cephalalgia* **33**, 813–5 (2013).
74. Pedersen, J. L., Barloese, M. & Jensen, R. H. Neurostimulation in cluster headache: a review of current progress. *Cephalalgia* **33**, 1179–93 (2013).
75. Leone, M., Franzini, A. & Bussone, G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. *N. Engl. J. Med.* **345**, 1428–9 (2001).
76. Leone, M. *et al.* Lessons from 8 years' experience of hypothalamic stimulation in cluster

headache. *Cephalalgia* **28**, 787–97; discussion 798 (2008).
77. Burns, B., Watkins, L. & Goadsby, P. J. Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. *Lancet* **369**, 1099–106 (2007).
78. Schwedt, T. J., Dodick, D. W., Trentman, T. L. & Zimmerman, R. S. Occipital nerve stimulation for chronic cluster headache and hemicrania continua: pain relief and persistence of autonomic features. *Cephalalgia* **26**, 1025–7 (2006).
79. Miller, S., Watkins, L. & Matharu, M. Treatment of intractable chronic cluster headache by occipital nerve stimulation: a cohort of 51 patients. *Eur. J. Neurol.* **24**, 381–390 (2017).
80. Silberstein, S. D. *et al.* Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study. *Headache* **56**, 1317–32 (2016).
81. Sluder, G. The role of the sphenopalatine (or Meckle's) ganglion in nasal headaches. *New York Med J* 989–990 (1908).
82. Rosso, C., Felisati, G., Bulfamante, A. & Pipolo, C. Cluster headache: crosspoint between otologists and neurologists—treatment of the sphenopalatine ganglion and systematic review. *Neurol. Sci.* **40**, 137–146 (2019).
83. Ansarinia, M. *et al.* Electrical Stimulation of Sphenopalatine Ganglion for Acute Treatment of Cluster Headaches. *Headache* **50**, 1164–74 (2010).
84. Tepper, S. J. *et al.* Acute Treatment of Intractable Migraine With Sphenopalatine Ganglion Electrical Stimulation. *Headache J. Head Face Pain* **49**, 983–989 (2009).
85. Assaf, A. T. *et al.* Technical and surgical aspects of the sphenopalatine ganglion (SPG) microstimulator insertion procedure. *Int. J. Oral Maxillofac. Surg.* **45**, 245–254 (2016).
86. Barloese, M. *et al.* Blunted autonomic response in cluster headache patients. *Cephalalgia* **35**, 1269–1277 (2015).
87. Cortelli, P. *et al.* Effect of deep brain stimulation of the posterior hypothalamic area on the cardiovascular system in chronic cluster headache patients. *Eur. J. Neurol.* **14**, 1008–15 (2007).
88. Möller, M., Schroeder, C. F. & May, A. Vagus nerve stimulation modulates the cranial trigeminal autonomic reflex. *Ann. Neurol.* **84**, 886–892 (2018).
89. Mathias, C. J. & Bannister, R. *Autonomic failure : a textbook of clinical disorders of the autonomic nervous system*.
90. Lai, T.-H., Fuh, J.-L. & Wang, S.-J. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. *J. Neurol. Neurosurg. Psychiatry* **80**, 1116–1119 (2009).
91. Goadsby, P. J. & Edvinsson, L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. *Brain* 427–34 (1994).
92. Gaul, C. *et al.* Differences in clinical characteristics and frequency of accompanying migraine features in episodic and chronic cluster headache. *Cephalalgia* **32**, 571–7 (2012).
93. Snoer, A. *et al.* Cluster headache beyond the pain phase. *Neurology* **91**, e822–e831 (2018).
94. Schytz, H. W. *et al.* Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* **33**, 831–41 (2013).
95. Guo, S. *et al.* Cranial parasympathetic activation induces autonomic symptoms but no cluster headache attacks. *Cephalalgia* ePub (2017).
96. Matharu, M. S. & Goadsby, P. J. Persistence of attacks of cluster headache after trigeminal nerve root section. *Brain* **125**, 976–84 (2002).
97. Möller, M., Haji, A. A., Hoffmann, J. & May, A. Peripheral provocation of cranial autonomic symptoms is not sufficient to trigger cluster headache attacks. *Cephalalgia* 033310241773824 (2017).
98. Martins, I. P., Gouveia, R. G. & Antunes, J. L. Double dissociation between autonomic symptoms and pain in cluster headache. *Cephalalgia* **25**, 398–400 (2005).

99. Eulenburg, A. *Lehrbuch der Nervenkrankheiten*. (Hirschwald, 1878).
100. Kunkle, E. C. & Anderson, W. B. Dual mechanisms of eye signs of headache in cluster pattern. *Trans. Am. Neurol. Assoc.* **85**, 75–9 (1960).
101. Russell, D. Cluster headache: severity and temporal profiles of attacks and patient activity prior to and during attacks. *Cephalalgia* **1**, 209–16 (1981).
102. Bruyn, G. W., Bootsma, B. K. & Klawans, H. L. Cluster headache and bradycardia. *Headache* **16**, 11–5 (1976).
103. Erdinler, I., Afsar, N., Sanli, A. & Okmen, E. Asystole associated with cluster headache. *Can. J. Cardiol.* **20**, 1369–70 (2004).
104. Manzoni, G. C., Terzano, M. G., Moretti, G. & Cocchi, M. Clinical observations on 76 cluster headache cases. *Eur. Neurol.* **20**, 88–94 (1981).
105. Russell, D. & Storstein, L. Cluster headache: a computerized analysis of 24 h Holter ECG recordings and description of ECG rhythm disturbances. *Cephalalgia* **3**, 83–107 (1983).
106. Kruszewski, P., Bordini, C., Brubakk, A. O. & Sjaastad, O. Cluster headache: cardiovascular responses to head-up tilt. *Headache* **35**, 465–9 (1995).
107. Kruszewski, P. Respiratory sinus arrhythmia in cluster headache syndrome. *Headache* **33**, 98–104 (1993).
108. Tassorelli, C. *et al.* Combined evaluation of pupillary and cardiovascular responses to cold pressor test in cluster headache patients. *Cephalalgia* **18**, 668–74 (1998).
109. Leone, M. & Bussone, G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. *Cephalalgia* **13**, 309–17 (1993).
110. Perrotta, A. *et al.* Facilitated temporal processing of pain and defective supraspinal control of pain in cluster headache. *Pain* **154**, 1325–32 (2013).
111. Matharu, M. & May, A. Functional and structural neuroimaging in trigeminal autonomic cephalalgias. *Curr. Pain Headache Rep.* **12**, 132–7 (2008).
112. Lund, N., Petersen, A., Snoer, A., Jensen, R. H. & Barloese, M. Cluster headache is associated with unhealthy lifestyle and lifestyle-related comorbid diseases: Results from the Danish Cluster Headache Survey. *Cephalalgia* (2018).
113. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* **28**, 193–213 (1989).
114. Horne, J. A. & Ostberg, O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int. J. Chronobiol.* **4**, 97–110 (1976).
115. Schoenen, J. *et al.* Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study. *Cephalalgia* **33**, 816–830 (2013).
116. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* **33**, 629–808 (2013).
117. Goadsby, P. J., Schoenen, J., Ferrari, M. D., Silberstein, S. D. & Dodick, D. Towards a definition of intractable headache for use in clinical practice and trials. *Cephalalgia* **26**, 1168–70 (2006).
118. Jürgens, T. P. *et al.* Stimulation of the sphenopalatine ganglion in intractable cluster headache: Expert consensus on patient selection and standards of care. *Cephalalgia* **34**, 1100–10 (2014).
119. Merrick, J., Grippo, A. J., Bartlett, G., Shaffer, F. & Ginsberg, J. P. An Overview of Heart Rate variability Metrics and Norms. *Front. Public Heal.* **5**, 2583389–258 (2017).
120. Ansarinia, M. *et al.* Electrical stimulation of sphenopalatine ganglion for acute treatment of cluster headaches. *Headache* **50**, 1164–74 (2010).
121. Goadsby, P. J. Characteristics of facial nerve-elicited cerebral vasodilatation determined using laser Doppler flowmetry. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* **260**, (1991).
122. Takahashi, M., Zhang, Z.-D. & Macdonald, R. L. Sphenopalatine ganglion stimulation for vasospasm after experimental subarachnoid hemorrhage. *J. Neurosurg.* **114**, 1104–1109 (2011).

123. Suzuki, N., Gotoh, F., Gotoh, J. & Koto, A. Evidence for in vivo cerebrovascular neurogenic vasodilatation in the rat. *Clin. Auton. Res.* **1**, 23–26 (1991).
124. Suzuki, N., Hardebo, J. E., Kahrstrom, J. & Owman, C. Selective electrical stimulation of postganglionic cerebrovascular parasympathetic nerve fibers originating from the sphenopalatine ganglion enhances cortical blood flow in the rat. *J. Cereb. Blood Flow Metab.* **10**, 383–391 (1990).
125. Markowitz, S., Saito, K. & Moskowitz, M. A. Neurogenically Mediated Plasma Extravasation in Dura Mater: Effect of Ergot Alkaloids: A Possible Mechanism of Action in Vascular Headache. *Cephalalgia* **8**, 83–91 (1988).
126. Moskowitz, M. A. Cluster headache: evidence for a pathophysiologic focus in the superior pericarotid cavernous sinus plexus. *Headache* **28**, 584–6 (1988).
127. Fanciullacci, M., Alessandri, M., Figini, M., Geppetti, P. & Michelacci, S. Increase in plasma calcitonin gene-related peptide from the extracerebral circulation during nitroglycerin-induced cluster headache attack. *Pain* **60**, 119–23 (1995).
128. Goadsby, P. J., Edvinsson, L. & Ekman, R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann. Neurol.* **28**, 183–7 (1990).
129. Labrecque, G. & Vanier, M. C. Biological rhythms in pain and in the effects of opioid analgesics. *Pharmacology and Therapeutics* **68**, 129–147 (1995).
130. Gómez-Mayordomo, V. *et al.* Widespread Hypersensitivity to Pressure Pain in Men With Cluster Headache During Prolonged Remission Is Not Related to the Levels of Depression and Anxiety. *Pain Pract.* **20**, 147–153 (2019).
131. Földes, K., Bálint, P., Gaál, M., Buchanan, W. W. & Bálint, G. P. Nocturnal pain correlates with effusions in diseased hips. *J. Rheumatol.* **19**, 1756–8 (1992).
132. Shutty, B. G. *et al.* Sleep disturbances in psoriasis. *Dermatol. Online J.* **19**, 1 (2013).
133. Muller, J. E. *et al.* Circadian Variation in the Frequency of Onset of Acute Myocardial Infarction. *N. Engl. J. Med.* **313**, 1315–1322 (1985).
134. Millar-Craig, M. W., Bishop, C. N. & Raftery, E. B. Circadian variation of blood-pressure. *Lancet (London, England)* **1**, 795–7 (1978).
135. Kikuchi, H., Yoshiuchi, K., Yamamoto, Y., Komaki, G. & Akabayashi, A. Diurnal variation of tension-type headache intensity and exacerbation: An investigation using computerized ecological momentary assessment. *Biopsychosoc. Med.* **6**, 18 (2012).
136. Manzoni, G. C. *et al.* Cluster headache--clinical findings in 180 patients. *Cephalalgia* **3**, 21–30 (1983).
137. Ofte, H. K., Berg, D. H., Bekkelund, S. I. & Alstadhaug, K. B. Insomnia and periodicity of headache in an arctic cluster headache population. *Headache* **53**, 1602–12 (2013).
138. Rozen, T. D. & Fishman, R. S. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden*. *Headache* **52**, 99–113 (2011).
139. Jürgens, T. P., Koch, H. J. & May, A. Ten years of chronic cluster--attacks still cluster. *Cephalalgia* **30**, 1123–6 (2010).
140. Waung, M. W., Taylor, A., Qualmann, K. J. & Burish, M. J. Family History of Cluster Headache. *JAMA Neurol.* (2020). doi:10.1001/jamaneurol.2020.0682
141. Loewen, S. P. *et al.* Sex-specific differences in cardiovascular and metabolic hormones with integrated signalling in the paraventricular nucleus of the hypothalamus. *Exp. Physiol.* **102**, 1373–1379 (2017).
142. Bussone, G. *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* **30**, 411–7 (1990).
143. Steiner, T. J., Hering, R., Couturier, E. G., Davies, P. T. & Whitmarsh, T. E. Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* **17**, 673–5 (1997).
144. Stefani, L. C. *et al.* A Phase II, Randomized, Double-Blind, Placebo Controlled, Dose-Response Trial of the Melatonin Effect on the Pain Threshold of Healthy Subjects. *PLoS One* **8**, e74107 (2013).
145. Tamaddonfard, E., Erfanparast, A., Taati, M. & Dabbaghi, M. Role of opioid system in

verapamil-induced antinociception in a rat model of orofacial pain. *Vet. Res. forum an Int. Q. J.* **5**, 49–54 (2014).
146. Rozen, T. D. & Fishman, R. S. Female cluster headache in the United States of America: what are the gender differences? Results from the United States Cluster Headache Survey. *J. Neurol. Sci.* **317**, 17–28 (2012).
147. Manfredini, R. *et al.* Twenty-Four-Hour Patterns in Occurrence and Pathophysiology of Acute Cardiovascular Events and Ischemic Heart Disease. *Chronobiol. Int.* **30**, 6–16 (2013).
148. Smolensky, M. H. *et al.* Diurnal and twenty-four hour patterning of human diseases: Cardiac, vascular, and respiratory diseases, conditions, and syndromes. *Sleep Med. Rev.* **21**, 3–11 (2015).
149. Smolensky, M. H. *et al.* Diurnal and twenty-four hour patterning of human diseases: acute and chronic common and uncommon medical conditions. *Sleep Med. Rev.* **21**, 12–22 (2015).
150. Burioka, N. *et al.* Asthma: Chronopharmacotherapy and the molecular clock. *Adv. Drug Deliv. Rev.* **62**, 946–955 (2010).
151. Hermida, R. C. *et al.* Circadian Rhythms in Blood Pressure Regulation and Optimization of Hypertension Treatment With ACE Inhibitor and ARB Medications. *Am. J. Hypertens.* **24**, 383–391 (2011).
152. Hermida, R. C. *et al.* Chronotherapy with conventional blood pressure medications improves management of hypertension and reduces cardiovascular and stroke risks. *Hypertens. Res.* **39**, 277–292 (2016).
153. Yegnanarayan, R., Mahesh, S. D. & Sangle, S. Chronotherapeutic Dose Schedule of Phenytoin and Carbamazepine in Epileptic Patients. *Chronobiol. Int.* **23**, 1035–1046 (2006).
154. Reinberg, A. E. Concepts in Chronopharmacology. *Annu. Rev. Pharmacol. Toxicol.* **32**, 51–66 (1992).
155. Cohen, A. S., Matharu, M. S. & Goadsby, P. J. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. *Neurology* **69**, 668–75 (2007).
156. Song, J. G., Ohdo, S. & Ogawa, N. Chronopharmacokinetics of valproic acid following constant-rate administration in mice and influence of feeding schedule. *Zhongguo Yao Li Xue Bao* **16**, 113–7 (1995).
157. Petersen, A. S., Barloese, M. C. J., Snoer, A., Soerensen, A. M. S. & Jensen, R. H. Verapamil and Cluster Headache: Still a Mystery. A Narrative Review of Efficacy, Mechanisms and Perspectives. *Headache* head.13603 (2019).
158. Lemma, G. L. *et al.* The effect of short- and long-term administration of verapamil on the disposition of cytochrome P450 3A and P-glycoprotein substrates. *Clin. Pharmacol. Ther.* **79**, 218–30 (2006).
159. Tomalik-Scharte, D. *et al.* Population pharmacokinetic analysis of circadian rhythms in hepatic CYP3A activity using midazolam. *J. Clin. Pharmacol.* **54**, 1162–1169 (2014).
160. Fuhr, U. *et al.* Effects of grapefruit juice and smoking on verapamil concentrations in steady state. *Eur. J. Clin. Pharmacol.* **58**, 45–53 (2002).
161. Tfelt-Hansen, P. & Tfelt-Hansen, J. Verapamil for cluster headache. Clinical pharmacology and possible mode of action. *Headache* **49**, 117–25 (2009).
162. Bailey, D. G. & Dresser, G. K. Interactions between grapefruit juice and cardiovascular drugs. *Am. J. Cardiovasc. Drugs* **4**, 281–97 (2004).
163. Black, H. R. *et al.* Principal Results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial. *JAMA* **289**, 2073 (2003).
164. Petersen, A. S., Lund, N., Jensen, R. H. & Barloese, M. Acute therapy is more effective in episodic than in chronic cluster headache [submitted]. (2020).
165. Akerman, S. & Goadsby, P. J. A Novel Translational Animal Model of Trigeminal Autonomic Cephalalgias. *Headache J. Head Face Pain* **55**, 197–203 (2015).
166. Akerman, S., Holland, P. R., Lasalandra, M. P. & Goadsby, P. J. Oxygen inhibits neuronal activation in the trigeminocervical complex after stimulation of trigeminal autonomic

reflex, but not during direct dural activation of trigeminal afferents. *Headache* **49**, 1131–43 (2009).
167. Miller, S., Watkins, L. & Matharu, M. Predictors of response to occipital nerve stimulation in refractory chronic headache. *Cephalalgia* 333102417728747 (2017).
168. Vukovic Cvetkovic, V. & Jensen, R. H. Neurostimulation for the treatment of chronic migraine and cluster headache. *Acta Neurol. Scand.* **139**, 4–17 (2019).
169. Vyas, D. B. *et al.* Deep Brain Stimulation for Chronic Cluster Headache: A Review. *Neuromodulation Technol. Neural Interface* **22**, 388–397 (2019).
170. Piovesan, E. J., Kowacs, P. A. & Oshinsky, M. L. Convergence of cervical and trigeminal sensory afferents. *Curr. Pain Headache Rep.* **7**, 377–83 (2003).
171. Goadsby, P. J. & Hoskin, K. L. The distribution of trigeminovascular afferents in the nonhuman primate brain Macaca nemestrina: a c-fos immunocytochemical study. *J. Anat.* **190 (Pt 3**, 367–75 (1997).
172. Goadsby, P. J. & Zagami, A. S. Stimulation of the superior sagittal sinus increases metabolic activity and blood flow in certain regions of the brainstem and upper cervical spinal cord of the cat. *Brain* **114 (Pt 2**, 1001–11 (1991).
173. Attanasio, A. *et al.* Sinus bradycardia, junctional rhythm and blood pressure increase during repeated cluster headache attacks. *Headache* **30**, 509–10 (1990).
174. Benarroch, E. E. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin. Proc.* **68**, 988–1001 (1993).
175. Benarroch, E. E. Pain-autonomic interactions. *Neurol. Sci.* **27**, s130–s133 (2006).
176. Barloese, M., Jennum, P., Knudsen, S. & Jensen, R. Cluster headache and sleep, is there a connection? A review. *Cephalalgia* **32**, 481–91 (2012).
177. Schytz, H. W. *et al.* Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* **33**, (2013).
178. Guo, S. *et al.* Cranial parasympathetic activation induces autonomic symptoms but no cluster headache attacks. *Cephalalgia* **38**, ePub (2017).
179. Bohluli, B. *et al.* Trigeminocardiac reflex, bilateral sagittal split ramus osteotomy, Gow-Gates block: a randomized controlled clinical trial. *J. Oral Maxillofac. Surg.* **69**, 2316–20 (2011).
180. Lai, Y.-H., Hsu, H.-T., Wang, H.-Z., Cheng, K.-I. & Wu, K.-Y. The oculocardiac reflex during strabismus surgery: its relationship to preoperative clinical eye findings and subsequent postoperative emesis. *J. AAPOS* **18**, 151–5 (2014).
181. Loewinger, J., Cohen, M. & Levi, E. Bradycardia during elevation of a zygomatic arch fracture. *J. Oral Maxillofac. Surg.* **45**, 710–1 (1987).
182. Meuwly, C. *et al.* Definition and Diagnosis of the Trigeminocardiac Reflex: A Grounded Theory Approach for an Update. *Front. Neurol.* **8**, 533 (2017).
183. Meuwly, C., Golanov, E., Chowdhury, T., Erne, P. & Schaller, B. Trigeminal Cardiac Reflex. *Medicine (Baltimore).* **94**, e484 (2015).
184. De Marinis, M. *et al.* Sympathetic-parasympathetic activation during spontaneous attacks of cluster headache: evaluation by spectral analysis of heart-rate fluctuations. *Cephalalgia* **15**, 504–10 (1995).
185. Tubani, L. *et al.* Heart rate variability in cluster headache. *Ann. Ital. di Med. interna organo Uff. della Soc. Ital. di Med. interna* **18**, 42–6 (2003).
186. Russell, D. & von der Lippe, A. Cluster headache: heart rate and blood pressure changes during spontaneous attacks. *Cephalalgia* **2**, 61–70 (1982).
187. Koenig, J., Jarczok, M. N., Ellis, R. J., Hillecke, T. K. & Thayer, J. F. Heart rate variability and experimentally induced pain in healthy adults: a systematic review. *Eur. J. Pain* **18**, 301–14 (2014).
188. Sano, K., Mayanagi, Y., Sekino, H., Ogashiwa, M. & Ishijima, B. Results of stimulation and destruction of the posterior hypothalamus in man. *J. Neurosurg.* **33**, 689–707 (1970).
189. Ekbom, K. Evaluation of Clinical Criteria for Cluster Headache With Special Reference to The Classification of The International Headache Society. *Cephalalgia* **10**, 195–197 (1990).

190. Fuller, P. M., Gooley, J. J. & Saper, C. B. Neurobiology of the Sleep-Wake Cycle: Sleep Architecture, Circadian Regulation, and Regulatory Feedback. *J. Biol. Rhythms* **21**, 482–493 (2006).
191. Malick, A., Strassman, R. M. & Burstein, R. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J. Neurophysiol.* **84**, 2078–112 (2000).
192. Saper, C. B. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* **25**, 433–69 (2002).
193. Ikeda, H., Takasu, S. & Murase, K. Contribution of Anterior Cingulate Cortex and Descending Pain Inhibitory System to Analgesic Effect of Lemon Odor in Mice. *Mol. Pain* **10**, 1744-8069-10–14 (2014).
194. Tracey, I. & Mantyh, P. W. The Cerebral Signature for Pain Perception and Its Modulation. *Neuron* **55**, 377–391 (2007).
195. Seeley, W. W. *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* **27**, 2349–56 (2007).
196. Ossipov, M. H., Dussor, G. O. & Porreca, F. Central modulation of pain. *J. Clin. Invest.* **120**, 3779–87 (2010).
197. Derbyshire, S. W. G. *et al.* Cerebral Responses to Noxious Thermal Stimulation in Chronic Low Back Pain Patients and Normal Controls. *Neuroimage* **16**, 158–168 (2002).
198. Beissner, F., Meissner, K., Bär, K.-J. & Napadow, V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J. Neurosci.* **33**, 10503–11 (2013).
199. Fujiki, N. *et al.* Changes in CSF hypocretin-1 (orexin A) levels in rats across 24 hours and in response to food deprivation. *Neuroreport* **12**, 993–7 (2001).
200. Estabrooke, I. V *et al.* Fos expression in orexin neurons varies with behavioral state. *J. Neurosci.* **21**, 1656–62 (2001).
201. Chieffi, S. *et al.* Orexin System: The Key for a Healthy Life. *Front. Physiol.* **8**, 357 (2017).
202. Dun, N. J. *et al.* Orexins: a role in medullary sympathetic outflow. *Regul. Pept.* **96**, 65–70 (2000).
203. Ferguson, A. V & Samson, W. K. The orexin/hypocretin system: a critical regulator of neuroendocrine and autonomic function. *Front. Neuroendocrinol.* **24**, 141–50 (2003).
204. Plazzi, G. *et al.* Autonomic disturbances in narcolepsy. *Sleep Med. Rev.* **15**, 187–96 (2011).
205. Bartsch, T., Levy, M. J., Knight, Y. E. & Goadsby, P. J. Differential modulation of nociceptive dural input to [hypocretin] orexin A and B receptor activation in the posterior hypothalamic area. *Pain* **109**, 367–78 (2004).
206. Holland, P. R., Akerman, S. & Goadsby, P. J. Modulation of nociceptive dural input to the trigeminal nucleus caudalis via activation of the orexin 1 receptor in the rat. *Eur.J.Neurosci.* **24**, 2825–2833 (2006).
207. Holland, P. R., Akerman, S. & Goadsby, P. J. Orexin 1 receptor activation attenuates neurogenic dural vasodilation in an animal model of trigeminovascular nociception. *J.Pharmacol.Exp.Ther.* **315**, 1380–1385 (2005).
208. Benjamin, L. *et al.* Hypothalamic activation after stimulation of the superior sagittal sinus in the cat: a Fos study. *Neurobiol. Dis.* **16**, 500–5 (2004).
209. Kuwaki, T. Orexin links emotional stress to autonomic functions. *Auton. Neurosci.* **161**, 20–27 (2011).
210. Burdakov, D. Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons. *Neuropharmacology* (2018). doi:10.1016/j.neuropharm.2018.10.024
211. Dergacheva, O. *et al.* Hypocretin-1 (Orexin-A) Facilitates Inhibitory and Diminishes Excitatory Synaptic Pathways to Cardiac Vagal Neurons in the Nucleus Ambiguus. *J. Pharmacol. Exp. Ther.* **314**, 1322–1327 (2005).
212. Spencer, S. E., Sawyer, W. B., Wada, H., Platt, K. B. & Loewy, A. D. CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. *Brain Res.* **534**, 149–69 (1990).
213. Boddum, K., Hansen, M. H., Jennum, P. J. & Kornum, B. R. Cerebrospinal Fluid Hypocretin-

1 (Orexin-A) Level Fluctuates with Season and Correlates with Day Length. *PLoS One* **11**, e0151288 (2016).
214. Barloese, M., Lund, N. & Jensen, R. Sleep in trigeminal autonomic cephalagias: a review. *Cephalalgia* **34**, 813–22 (2014).
215. Donadio, V. *et al.* Lower wake resting sympathetic and cardiovascular activities in narcolepsy with cataplexy. *Neurology* **83**, 1080–6 (2014).
216. Russell, M. B. Epidemiology and genetics of cluster headache. *Lancet Neurol.* **3**, 279–83 (2004).
217. Fourier, C. *et al.* A genetic CLOCK variant associated with cluster headache causing increased mRNA levels. *Cephalalgia* **38**, 496–502 (2018).
218. Rainero, I. *et al.* Haplotype analysis confirms the association between the HCRTR2 gene and cluster headache. *Headache* **48**, 1108–14 (2008).
219. Rainero, I. *et al.* Association between the G1246A polymorphism of the hypocretin receptor 2 gene and cluster headache: a meta-analysis. *J. Headache Pain* **8**, 152–6 (2007).
220. Fourier, C. *et al.* Analysis of *HCRTR2* Gene Variants and Cluster Headache in Sweden. *Headache J. Head Face Pain* **59**, 410–417 (2019).
221. Salomon, R. M. *et al.* Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects. *Biol. Psychiatry* **54**, 96–104 (2003).
222. Appelbaum, L. *et al.* Circadian and homeostatic regulation of structural synaptic plasticity in hypocretin neurons. *Neuron* **68**, 87–98 (2010).
223. Wang, W., Pan, Y., Li, Q. & Wang, L. Orexin: A potential role in the process of obstructive sleep apnea. *Peptides* **42**, 48–54 (2013).
224. Terzaghi, M. *et al.* Episodic cluster headache: NREM prevalence of nocturnal attacks. Time to look beyond macrostructural analysis? *Headache* **50**, 1050–4 (2010).
225. van Vliet, J. A., Vein, A. A., Ferrari, M. D. & van Dijk, J. G. Cardiovascular autonomic function tests in cluster headache. *Cephalalgia* **26**, 329–31 (2006).
226. Okada, H., Iwase, S., Mano, T., Sugiyama, Y. & Watanabe, T. Changes in muscle sympathetic nerve activity during sleep in humans. *Neurology* **41**, 1961–6 (1991).
227. Hornyak, M., Cejnar, M., Elam, M., Matousek, M. & Wallin, B. G. Sympathetic muscle nerve activity during sleep in man. *Brain* **114 (Pt 3)**, 1281–95 (1991).
228. Noll, G., Elam, M., Kunimoto, M., Karlsson, T. & Wallin, B. G. Skin sympathetic nerve activity and effector function during sleep in humans. *Acta Physiol. Scand.* **151**, 319–29 (1994).
229. Lin, J. & Suurna, M. Sleep Apnea and Sleep-Disordered Breathing. *Otolaryngol. Clin. North Am.* (2018).
230. Graff-Radford, S. B. & Newman, A. Obstructive sleep apnea and cluster headache. *Headache* **44**, 607–10 (2004).
231. Chervin, R. D. *et al.* Sleep disordered breathing in patients with cluster headache. *Neurology* **54**, 2302–2306 (2000).
232. Krishnan, V., Dixon-Williams, S. & Thornton, J. D. Where there is smoke…there is sleep apnea: exploring the relationship between smoking and sleep apnea. *Chest* **146**, 1673–1680 (2014).
233. Myers, K. A., Mrkobrada, M. & Simel, D. L. Does This Patient Have Obstructive Sleep Apnea? *JAMA* **310**, 731 (2013).
234. Wetter, D. W., Young, T. B., Bidwell, T. R., Badr, M. S. & Palta, M. Smoking as a risk factor for sleep-disordered breathing. *Arch. Intern. Med.* **154**, 2219–24 (1994).
235. Barloese, M. & Lambru, G. Methodological Difficulties in Clinical Trials Assessing Neuromodulation Devices in the Headache Field. in 227–239 (Springer, Cham, 2020). doi:10.1007/978-3-030-14121-9_17
236. Nordin, M., Fagius, J. & Waldenlind, E. Sympathetic vasoconstrictor outflow to extremity muscles in cluster headache. Recordings during spontaneous and nitroglycerin-induced attacks. *Headache* **37**, 358–67 (1997).
237. Meyer, E. L., Waldenlind, E. & Marcus, C. Diminished nocturnal lipolysis in cluster headache: a sign of central sympathetic dysregulation? *Neurology* **61**, 1250–4 (2003).

238. Schulte, L. H. & May, A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* **139**, 1987–1993 (2016).