

# Letter from The Directors

Dear Readers,

2023 has been an incredibly productive year for the Norwegian Centre for Headache Research (NorHead). One thousand migraine patients have been included in different clinical trials, and more than 10 new trials have been planned to be initiated in 2024. Clinical trials are resource-intensive, and a long-term centre is therefore required to perform high quality investigator-driven studies. Several innovation projects have been initiated, and one new spin-off company has been established to bring new technology to the society. NorHead register projects have had impact on a European level with data leading to novel guide-

lines from the European Medical Agency, and novel potential candidates for migraine treatment have been identified. Machine-learning and artificial intelligence is being used at several levels to move the research front in headache disorders.

All of this had not been possible without the efforts of motivated researchers and patients. We are therefore extremely thankful to the Norwegian Research Council, to the partner institutions and to other supporters for making this possible.

Sincerely,

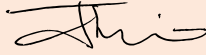


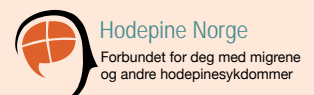
  
**Erling Andreas Tronvik**  
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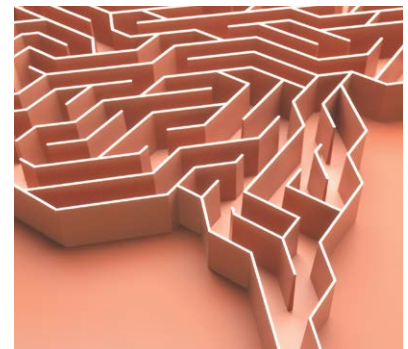


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We found a change in brain function after insufficient sleep immediately following a migraine attack.

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# Executive Summary

The Norwegian Centre for Headache Research – NorHead – brings together leading experts on headache disorders in Norway and around the world. Our partners include research and educational institutions, hospitals, patient organisations and the business sector. Headache patients from across Norway take part in our research studies.

## Our vision is: Improved quality of life for headache sufferers everywhere.

NorHead aspires to be a world-leading and innovative clinical research centre dedicated to enhancing the treatment and management of individuals affected by headache diseases globally. This ambition is pursued through our three main priorities:

1. Performing ground-breaking clinical trials to explore new methods and medical technology.
2. Utilizing health register data and real-world data to develop models for diagnosis and treatment, and to evaluate the societal effect of new treatment options.
3. Developing artificial intelligence and using machine learning to support targeted treatment and clinical decisions.

## Research and innovation

NorHead has had a very busy and productive first period in operation. In 2023 we have achieved significant outcomes in across all three research areas, and we already have notable examples of how our results have been applied in clinical

practice, patient guidance and the development of new innovations.

- Identified a potential preventive effect of cholesterol-lowering medications (statins) in migraines through health register research. The findings were presented at the International Headache Conference (IHC) in Seoul in September and was included in the conference's Highlight Session. This work has prompted the initiation of two randomized controlled trials in 2024, involving 750 migraine patients across Norway.
- Published a study with data from 36,000 individuals, including 4,777 with cluster headaches, in *Annals of Neurology*. The study demonstrated for the first time that smoking is a significant risk factor for developing cluster headaches. As a result, patients who develop cluster headaches are now internationally advised to quit smoking.
- Initiated the Nurse Intervention Trial, including 400 patients with headache disorders in an open, randomized controlled study. The trial aims to evaluate the effect of targeted use of headache nurses instead of neurologist visits. The goal is to find the optimal treatment for individual patients and more efficient follow-up



*The outpatient clinic for image-guided treatment for headache disorders at St. Olavs Hospital is also designed for innovative research. The infrastructure is the first of its kind in Norway dedicated to headache research.*

procedures to contribute to a more sustainable healthcare system.

- Published two articles showing that treatment with migraine preventive medications, topiramate and valproate, is associated with severe developmental disorders in the nervous system of foetuses. These data led to the European Medicinal Agency (EMA) issuing a warning and initiating a pan-European program for the use of topiramate in patients who may become pregnant. These new restrictions completely change the guidelines for preventive medicine for migraines.
- Contributed to two new projects on the safety of migraine preventive medications (CGRP antibodies and paternal use of valproate) using Nordic registry data.
- Completed patient inclusion in the CandMig study (RCT – candesartan for migraines) in November 2023, with 450 patients from 9 centres

in Norway and one in Estonia.

- Acquired 48.5 million NOK in funding for new research projects as well as 5 new research positions.
- Initiated a spin-off company, Keimon Medical AS, focusing on navigation-based cryotherapy for trigeminal neuralgia.
- Developed a plan for innovation and industry collaboration, and held workshops with potential partners from the health industry.

### **Stakeholder involvement**

Our achievements within research and innovation hinge on the crucial involvement of patient organisations and patients participating in clinical studies. A working group led by the Norwegian patient association Hodepine Norge, actively participates in the design of new research projects, plans for recruitment, dissemination, priorities, and addresses non-medical ethical questions.

- The group has worked on a strategy to address gender perspectives and underrepresented groups in study participation.
- The group also developed a checklist for user participation in research and contributed to a checklist for implementation.
- Ten NorHead-studies have been thoroughly reviewed from a patient perspective through conversations with all project leaders. The work continues in 2024 with the review of several more studies.
- A conference for the public was organised in Trondheim with 250 participants, providing the audience with updates on ongoing research and insight about headache disorders, and inviting them to give their input to the researchers.
- A collaboration has been established with other Clinical Research Centers (FKB) for a conference on user involvement in 2024.

### International Collaboration

NorHead has an extensive international network that is continuously expanding:

- NorHead has led the International Consortium for Cluster Headache Genetics with participants from 20 countries.
- Ongoing clinical research studies in Estonia, Germany, England, Spain, and Italy, and collaboration on projects in Switzerland and Denmark.
- Planning a joint project and exchange of researchers with Keio University in Japan, where a delegation from NorHead visited in September.
- Received visits from researchers from several European countries.
- Organised meetings with international guest professors and Scientific Advisory Board.
- Coordinated two EU Applications in 2023: The first was aimed at building a health data platform, with 17 international partners. The second is a project on migraine research and includes 13 international partners. Also partner in an EU-application on migraine subtypes.
- Received funding from Nordic AI to collaborate with Denmark and Sweden on running artificial intelligence on patient data.
- Researchers from NorHead have had a number

of presentations at international conferences, such as the International Headache Congress in Seoul, the European Headache Congress in Barcelona and at MTIS – Migraine Trust International Symposium in London.

### Education and Recruitment

Recruiting talent to headache research and training researchers and health personnel is crucial to strengthen the field and complete our ambitions.

- Hired an Associate Professor in Brain MRS with focus on headache disorders as part of the Onsager Fellowship programme at NTNU.
- Employed 2 PhD candidates and 3 post-doctoral researchers.
- Organised Trondheimskonferansen 2023 with 130 health professionals from the whole of Norway.
- Organised and took part in various courses and seminars for clinicians, general practitioners, nurses and other health personnel.

### Identity and Collaboration

Continuous work to build identity and promote visibility, calling attention to headache research, uniting partners, and strengthening collaboration has been especially important in this initial phase.

- Visit from the Norwegian Parliament's Health Committee in March.
- Organised a stand and was present in debates at Norway's largest political gathering, Arendalsuka 2023
- Presented NorHead and Headache research at Researcher's Night, NTNU's popular science event for high school students and teachers in September.
- Organised partner meetings, board meetings, and participated in a meeting with the other Norwegian Clinical Research Centers (FKB).
- Continuous communication of research activities through extensive media coverage in national and international media, active use of social media and various meetings and events.
- Developed a visual identity that unites the partners under one umbrella across partner institutions.



The Hidden Epidemic:

# Unraveling the Global Burden of Headache Disorders

→ Written by Andreas Kattem Husøy

Through a series of population-based studies, using the same standardized methodology, the Global Campaign against Headache has reported on the prevalence and estimated burden of primary headache disorders from most parts of the world.

**L**ifting The Burden, a UK registered organization in official relations with the World Health Organization, has since 2004 led the Global Campaign against Headache. The campaign's activity can be summarized in three steps:

1. Knowledge for awareness,
2. Awareness for action and
3. Action for change.

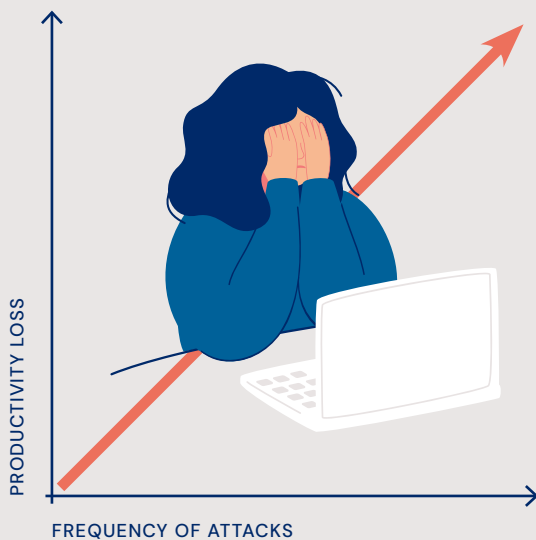
In light of sparse data from the non-western regions, the campaign has especially taken on

the responsibility of providing high-quality data on the size of the headache problem in low and lower-middle income countries. Interestingly, the prevalence and headache-attributed burden seem to vary little across geography and wealth.

Currently the campaign has studies from 6 new countries in the pipeline for publication: Benin, Cameroon, India (Delhi region), Mali, Morocco and Peru. The study from Peru will be the first of its kind from South America. In these countries too, the reported burden of headache is sizable and comparable to that seen in the rest of the world.



Migraine is one of the leading disabling disorders globally: ranked 2nd by the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study.



Frequency of headache attacks is the most important predictor for productivity loss. Improving preventive treatment can be key to regaining productivity.





### A top disabling disorder

Parallel with, and partly as a direct consequence of the campaign's work over the last two decades, migraine has been recognized as one of the absolutely top disabling disorders globally: ranked 2nd in the latest publication from the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study.

As the campaign is nearing its end, the last step has been reached, to inspire action for change. Several publications have been made the last few years focusing on structured headache services as health-care solutions to mitigate headache. Importantly, especially from a governmental and economical perspective, structured headache services have been shown to be not only cost-effective but also cost saving.

Andreas Kattem Husøy is a resident in Neurology and a postdoc at NorHead, Norwegian University of Science and Technology. His main field is headache epidemiology, and he took his PhD on data from the Nord-Trøndelag Health Study. For six months in 2023–2024 he has been working at the Institute for Health Metric and Evaluation in Seattle, to refine the headache models of the Global Burden of Disease, Injuries and Risk Factors study. Utilizing data from the Global Campaign Against Headache has been crucial in this regard.



**Andreas K. Husøy**

Resident in Neurology  
and a postdoc at NorHead,  
NTNU

The duration of a headache attack, on the other hand, has basically no impact on productive days lost. Hence, shortening of headache attacks through acute treatment will barely regain productivity, whereas prevention of attacks will. More studies are pending to further explore the relationship between headache and productivity.

**Structured headache services  
have been shown to be not only cost-  
effective but also cost saving.**

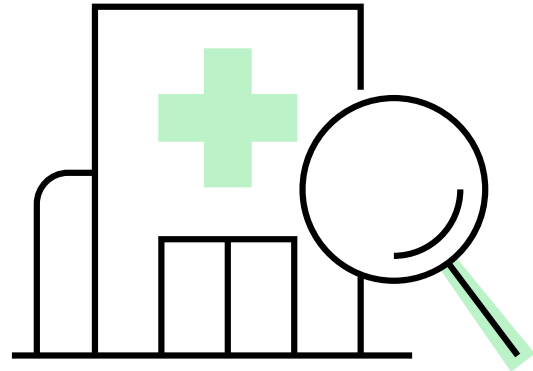
### NorHead Database

Currently all the data from all studies supported by the Global Campaign against Headache are being pooled into one big epidemiological database, hosted at NorHead, NTNU. This database will enable cross-country analyses to establish whether universal truths about headache really exist, or whether factors such as geographical location and wealth have significant impact.

Given the size of the database and the random population-based sampling approach, with samples from all parts of the world, we will also be in a unique position to calculate how much time is spent having headache globally. The data in this database have also been shared with the Institute of Health Metrics and Evaluation (who is leading the GBD study) to further improve their statistical headache models ■

# Research Area 1: Clinical Trials

→ Research area leader: Erling Tronvik



NorHead conducts clinical trials of high international standards, involving participants from all corners of Norway. The aim is to establish evidence-based treatment options for various headache conditions, including migraine, tension-type headache, medication overuse headache, chronic daily headaches, cluster headache, and trigeminal neuralgia.

This initiative serves as a national undertaking, encompassing cutting-edge, innovative, and ambitious trials initiated by publicly funded universities and hospitals, serving as a central hub and infrastructure for industry-funded trials. In 2023, a total

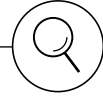
of 12 clinical trials have been in operation, involving a significant number of patients.

- **The CandMig-trial**, exploring Candesartan's effectiveness in treating migraines, successfully completed its inclusion phase with over 450 patients across 9 hospitals in Norway and one in Estonia.
- **The BioCer-trial**, focused on drug-free preventive treatment using biofeedback, has enrolled 319 patients, and ended recruitment in January 2024.
- **The Migrinor-trial**, targeting preventive migraine treatment, reached a milestone with the inclusion of 240 participants.
- **The CovaxHEAD-trial**, addressing post-COVID-vaccine headaches, has included all its 50 participants.

**12 clinical trials in 2023**



*Ongoing trials are currently investigating the efficacy of a specialized injection technique aimed at safely paralyzing a cluster of nerves central to various headache conditions.*



# Headache Nurses: A Key to Better Patient Care?

**The substantial demand for care and treatment of headache patients is an issue in countries all over the world. A solution that has been proposed many places is increasing the number of nurses specializing in headache.**

**R**esource scarcity and long waiting lists at neurological outpatient clinics has set limitations for the follow-up of headache patients in Norway. Can clinic capacity be improved by increasing the involvement of headache nurses? The Nurse intervention trial seeks to answer this question.

“Very few studies have evaluated the benefits of headache nurses in specialized healthcare. Furthermore, many neurological departments in Norway lack dedicated headache nurses. This clinical trial could provide evidence for the inclusion of headache nurses in more hospitals”, says Knut Hagen, Professor and Neurologist at NTNU and St. Olav’s University Hospital.

Together with his research team Knut Hagen will investigate patients initiating preventive treatment for headaches, where the treating physician identifies a need for follow-up visits in specialized healthcare.

“This study will clarify the effectiveness of two different follow-up strategies. We seek to determine whether the implementation (compliance) and overall satisfaction of patients are enhanced when follow-up is conducted by a headache nurse, compared to standard follow-up procedures with a neurologist”, Knut explains.

**The goal is to provide better treatment for each headache patient and more efficient follow-up procedures, and thereby contributing to a more sustainable healthcare system.**



**Knut Hagen**

Professor and Neurologist  
at NTNU and St. Olav’s  
University Hospital

Photo: Jarle Hvidsten

The study will involve the participation of three hospitals, namely St. Olav’s University Hospital, Haukeland University Hospital, and Oslo University Hospital, with a focus on including patients from these institutions.



Good collaboration with the patients is key to efficient collection and documentation of research data. Participation in clinical trials should feel both safe and meaningful, and the research nurse plays a crucial role in ensuring this.



Photo: Kim L'Orange Sørensen

## Meet Headache Nurse Marit Fjærli

Marit Fjærli serves as a headache nurse at St. Olavs Hospital and contributes as a research nurse in clinical trials at NorHead. Through her experiences in the clinic, she has gained valuable insights into the challenges faced by headache patients. "My interest in headache care sparked when I began administering Botox injections to patients with chronic migraines. I have recognized the need for closer and more attentive follow-up within this patient group, and I am eager to make a meaningful contribution", Marit says.

In the clinic, Marit often stands as the health-care professional closest to the patient, and can ask relevant questions. This also enables her to inform them about clinical trials they may be interested to take part in. "This allows research

to seamlessly integrate into the daily operations of the clinic," she explains.

The expertise Marit has acquired as a headache nurse proves advantageous in her role as a research nurse, where she actively participates in the planning and execution of clinical trials.

"Good collaboration with the patients is key to efficient collection and documentation of research data. Participation in clinical trials should feel both safe and meaningful, and the research nurse plays a crucial role in ensuring this", Marit says. She finds her work deeply motivating, highlighting the potential of high-quality research to lead to improved, tailored treatments for individual patients in the future ■

## Research Area 2: Exploitation of Health Registries and Real-World Data

→ Research area leader: Marte-Helene Bjørk

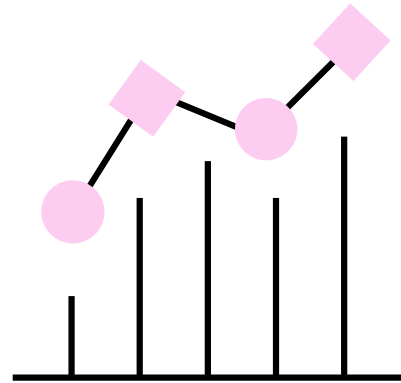
NorHead utilises health registries and real-world data to develop diagnostic and therapeutic models and assessing the epidemiological impact. The goal is to leverage real-world data for monitoring the usage and impact of prophylactic medications, acute medications, opioids, and more for headache disorders.

Additionally, NorHead aims to identify demographic, symptomatic, or genetic markers that delineate the classification of headache diagnoses and responses to different treatments. The project also seeks to repurpose medications for headache treatment through the screening of concomitant drug usage.

In 2023, NorHead conducted the largest population survey in Norway to date on headaches, known as the PopHEAD study. 8,559 adults residing in Vestfold and Telemark participated in the survey.

Population-based studies form the foundation of our knowledge when it comes to understanding a disorder. These studies often provide a comprehensive overview of the information needed to identify the challenges. They can serve as the basis for new research studies, priorities and resource allocation, as well as addressing health economic questions.

**8,559 adults  
participated in the  
PopHEAD study**





# Health Registry Insights for Better Drug Choices

Nationwide health registers serve as invaluable sources of information for headache researchers, holding data with great potential to enhance treatment strategies when explored. This article highlights two recent registry studies, both serving as important contributions to efficient and safe migraine treatment.

## Comparing migraine preventive medications in Norway

For many migraine sufferers, it takes years to find a medication that works. "Today, a variety of drugs are prescribed to prevent migraine, but patients often report that they have to try many types before finding one that works for them without causing side effects", says Marte-Helene Bjørk, Professor at the University of Bergen and a Consultant Neurologist at Haukeland University Hospital. She also holds the position of Deputy Director at NorHead.

Using data from the Norwegian Prescription Database, Marte and her colleagues aimed to investigate how effective and well tolerated migraine preventive drugs are, by looking at all persons in Norway using migraine medication. "Most preventive migraine drugs are never tested against each other, so no one really knows which

one works best, especially when considering the entire population. Most research studies tend to only include relatively healthy and resourceful migraine patients", Marte says.

## Three drugs stood out

Among the 100,000 migraine patients included in the study, the researchers identified three medications which had particularly good effect. "Our most important finding was that especially amitriptyline, simvastatin and CGRP inhibitors seemed to work well for the patients", says Marte. CGRP inhibitors are specifically developed for episodic and chronic migraine. Amitriptyline is a drug initially developed for depression and chronic pain, while simvastatin is a statin, a group of drugs used to reduce cholesterol.

The aim is to investigate how effective and well tolerated migraine preventive drugs are, by looking at all persons in Norway using migraine medication.



**Marte-Helene**

**Bjørk**

Deputy Director  
at NorHead

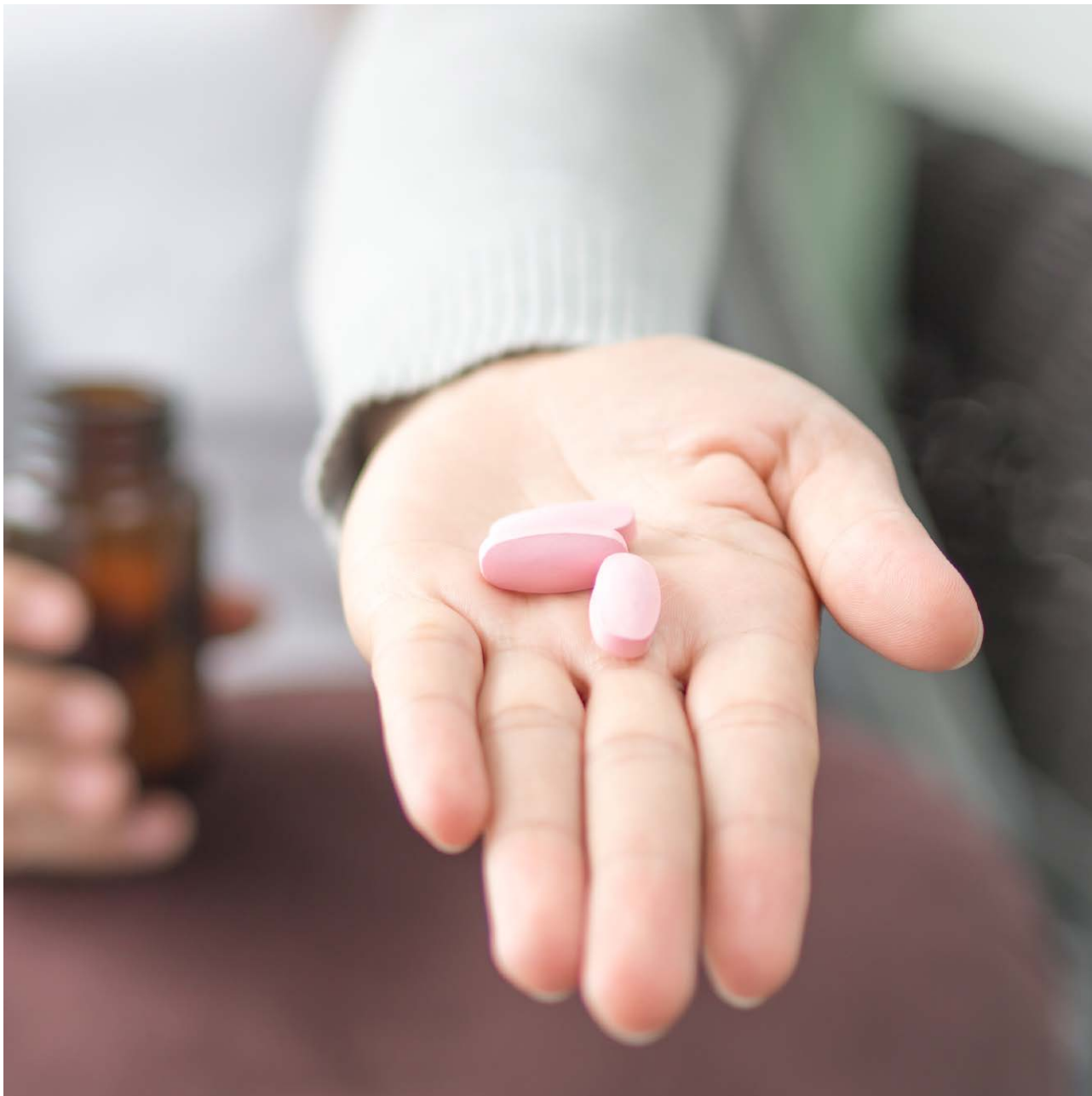
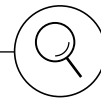


Photo: Gettyimages

"We were surprised that simvastatin seemed to reduce migraine because it is not a well-known migraine preventive. Most of the people included in our analysis used simvastatin to lower blood cholesterol or prevent cardiovascular diseases, not to treat migraine", says Marte.

Both statins and amitriptyline have a long history of use and are known for being safe. They are also inexpensive, which means that they can be made

accessible for many more migraine patients and make them better. However, before statins can be widely recommended for migraines, it is necessary to test the effect in migraine patients through clinical trials. "We used the results from the register study to ask for financial support to properly test atorvastatin against migraine in Norway, and we got funded!", says Marte, excited about the new NorHead trial starting in 2024.





## The study aimed to identify the safest antiseizure medication for women in childbearing age.

### Revealing pregnancy risks

Marte-Helene Bjørk's research team has recently published two other papers with very important consequences for drug recommendations. The Nordic registry-based study on antiepileptic drugs in pregnancy: SCAN AED collected nationwide registry data from 30 health and socioeconomic registries in Norway, Denmark, Sweden, Finland, and Iceland.

The study aimed to identify the safest antiseizure medication for women in childbearing age. Antiseizure medications are used to prevent epilepsy, and some are also indicated for migraine and cluster headache. The study found that the two drugs used for headache disorders are associated with serious developmental abnormalities in the nervous system in fetuses.

"We identified women that picked up prescriptions for antiseizure medications during pregnancy. After birth, we looked for diagnoses of neurodevelopmental disorders such as autism and intellectual disability in the child. We discovered that women that used topiramate and valproate in pregnancy were 2-4 times more likely to have a child with these disorders", Marte says. Both topiramate and valproate are frequently used to treat migraine and chronic cluster headache. Many people must try these drugs before they become eligible for reimbursement of CGRP antibodies or Botulinum toxin treatment for migraine.

### New regulations

After the publication of the results of this Nordic study, the Pharmacovigilance Risk Assessment Committee of the European Medicines agency started an investigation into the pregnancy safety of topiramate. The investigation led to a launch of a pregnancy prevention program during the fall of 2023. A similar pregnancy prevention program was already in place for valproate since 2018. "According to these regulations, topiramate and valproate should only be prescribed by specialists within epilepsy or headache, and only to women of childbearing age if other treatment options are not suitable", Marte says. They must not be used for migraine in pregnancy. Women must also take a pregnancy test before starting the drug. "We expect that treatment guidelines for headaches will be changed all over Europe consequently", Marte adds ■

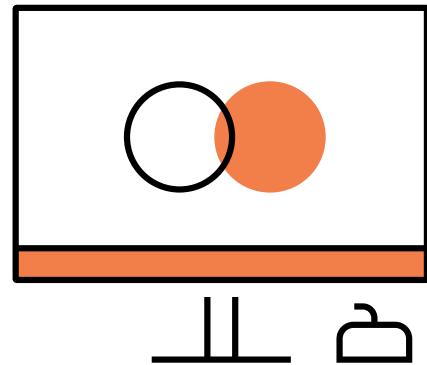
### References:

Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. Dreier et al. in *JAMA Neurology* 2023

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. Bjørk et al. in *JAMA Neurology* 2022

Comparative retention and effectiveness of migraine preventive treatments: A nationwide registry-based cohort study. Bjørk et al. in *European Journal of Neurology* 2024

## Research Area 3: Artificial Intelligence and Machine Learning



→ Research area leader: Heri Ramampiaro

NorHead will pioneer the development and application of artificial intelligence and machine learning methods to enhance the understanding and accuracy of headache diagnosis, predict disease progression, and forecast effective treatments for primary headaches. This innovative approach lays the foundation for creating e-health tools that support general practitioners and specialists in treating headache disorders.

In 2023, NorHead started preparations for collecting substantial amounts of data, enabling the integration of genetic data with clinical data. The question of whether specific genetic traits can predict specific

clinical features is investigated. In addition, machine learning is used to investigate whether our genes can predict if an individual will have effect of a migraine medication or not.

We have developed machine-learning algorithms to predict which order migraine preventive drugs should be given to patients at an individual level. A clinical trial has also been planned where we will investigate the use of such algorithms in clinical practice. The ultimate goal is to develop an algorithm that can be used by clinicians as decision-support when treating patients.

Machine learning will be extremely important in research on headache disorders. As these conditions have so many potential factors contributing to the pathophysiology, the ability to look for patterns in large amounts of data is highly needed.



# Forecasting Migraine With Machine Learning

→ Q&A with Anker Stubberud

Mobile health apps and wearables are becoming increasingly popular for monitoring health, energy, and stress. Can data from these remedies also be used to predict migraine attacks?





The MI-HEAD study aims to develop models that can:

Help  
diagnosing

**A**nker Stubberud is a doctor at Ålesund Hospital and a researcher at NTNU and NorHead. He is the project leader of MI-HEAD, a large-scale interdisciplinary research project combining clinical headache research, artificial intelligence, and machine learning. Recently, he published a pilot study investigating the possibility of employing machine learning to forecast migraine attacks.

#### Why is it useful to be able to predict migraine?

The background for studying the possibility of predicting, or forecasting, headaches is patients' desire for better control over their own headache disease. Migraine is an unpredictable condition that often interferes with both patients' day-to-day life and worsens their quality of life. Predicting migraine has several benefits: It can empower patients and aid in self-management of migraine; it allows the patient to take precautionary measures and administer treatment at the correct time; and it may increase our understanding of migraine.

#### How do you use machine learning in your research?

In NorHead and MI-HEAD we use machine learning to address many challenges in headache research. We aim to develop models that can help

diagnosing headache disorders, choose optimal therapy and, as presented in the pilot study, forecast migraine attacks.

#### What were the most important findings in this pilot study? And what will be the next steps?

The most important finding of this study is demonstrating the feasibility of using machine learning for forecasting headaches. We will follow up the pilot study with conducting machine learning studies on large datasets of headache diary data. We will use self-reported headache diary data combined with physiological data from headache apps to improve the machine learning models and increase their accuracy.

#### How do you expect your research to improve the lives of migraine sufferers?

Accurate forecasting models can be a valuable tool in the management of headache. It can be used alongside electronic headache diaries to help patients better understand the patterns of their individual disease, and it may also enable clinicians to better tailor treatments for each individual ■

Choose  
therapy

#### Reference:

Forecasting migraine with machine learning based on mobile phone diary and wearable data. Stubberud et al. *Cephalalgia* 2023



Photo: Amanda Schröder/NTNU

*The Norwegian Open AI Lab at NTNU and RA3 leader Heri Ramampiaro hosted a visit from Prime Minister Jonas Gahr Støre before the kick-off for a new national digitization strategy in June. Together with the lab's excellent AI-researchers, NorHead is well underway exploring the promising potential in Machine Learning to address challenges within treatment of headache disorders.*

## Forecast attacks

Accurate forecasting models can be a valuable tool in the management of headache.

Anker Stubberud is in the starting pit of examining how data from mobile health apps and wearables can be combined with machine learning to create valuable tools for forecasting headache and migraine.



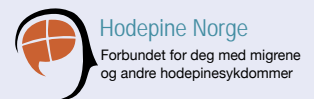
### Anker Stubberud

Doctor at Ålesund Hospital and a researcher at NTNU and NorHead

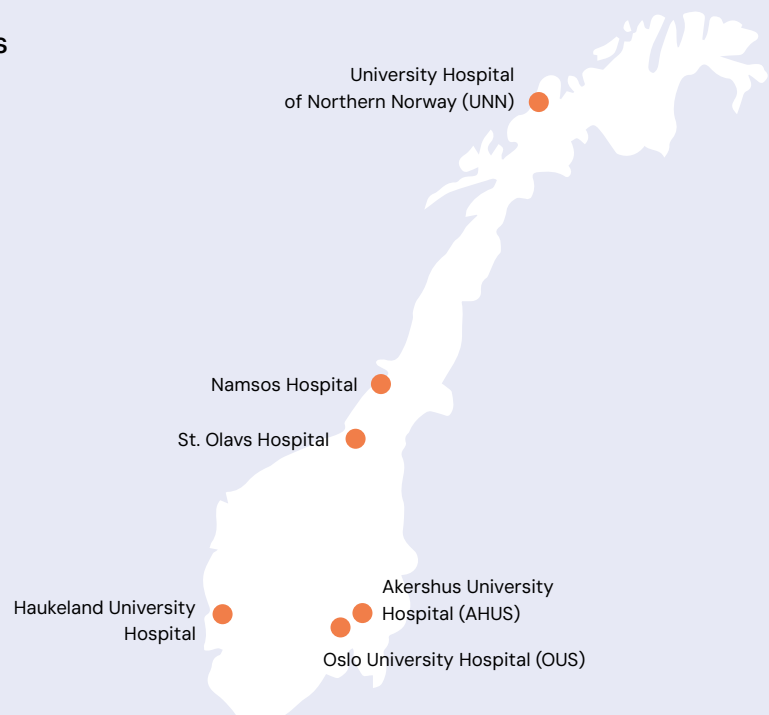
# Organisation

NorHead brings together leading experts on headache disorders in Norway and from around the world. Our partners include research and educational institutions, hospitals, patient organisations and the business sector. Headache patients from all over Norway participate in our research studies.

## Partners

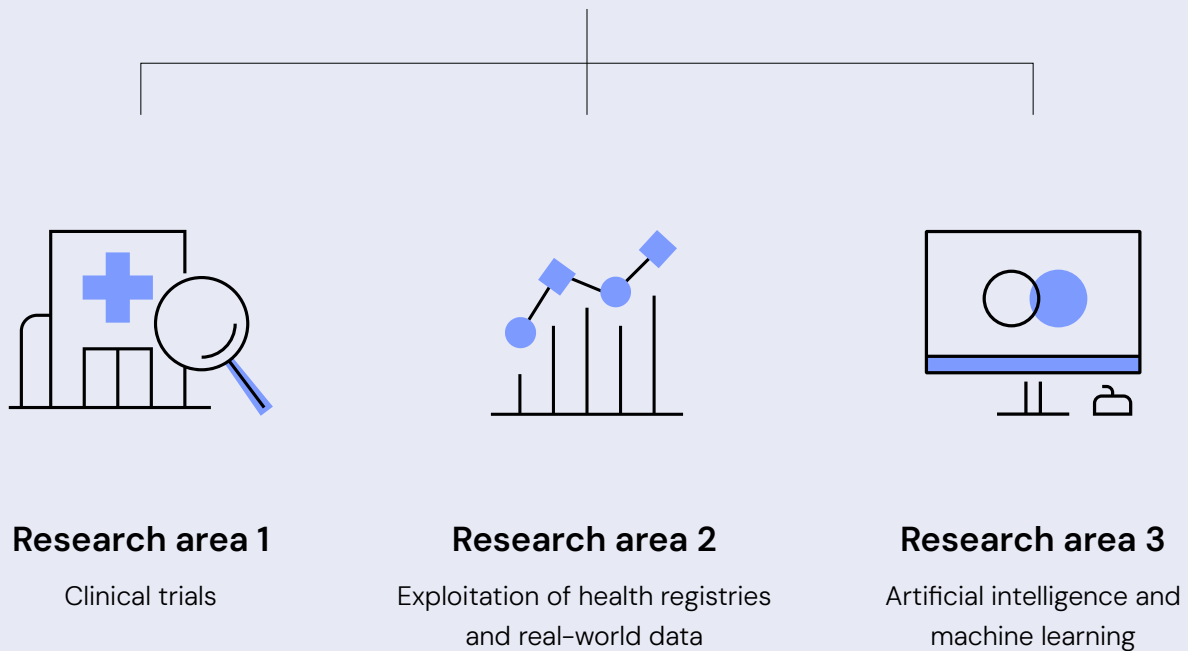


NorHead includes hospitals from all four Norwegian health regions



Overall objective for NorHead

Gain and distribute new knowledge to optimise management and care for patients with headache disorders



- Operational units**
- ou1 Data collection and management
  - ou2 Clinical care implementation
  - ou3 Innovation
  - ou4 Industry collaboration
  - ou5 Stakeholders, ethics and sustainability
  - ou6 Centre growth
  - ou7 Communication and dissemination
  - ou8 Centre management

# Profiles

## Centre Management



**Jaya Syltern Thomlison**  
*Administrative Director*  
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**Erling Andreas Tronvik**  
*Scientific Director*  
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**Marte-Helene Bjørk**  
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**Gunnar Bovim**  
*Executive Advisor*  
NTNU



**Tom Christian Martinsen**  
*Vice Managing Director*  
St. Olavs University Hospital



### Scientific Advisory Board



**Anne Hege Aamodt**  
*Senior Researcher /  
 Senior Consultant Neurologist*  
 Oslo University Hospital



**Simona Sacco**  
*Professor of Neurology*  
 University of L'Aquila



**Hans-Christoph Diener**  
*Professor of Neurology*  
 University of Duisburg-Essen



**Peter Goadsby**  
*Professor of Neurology*  
 King's College London



**Messoud Ashina**  
*Professor of Neurology*  
 Danish Headache Centre



**Hedvig Nordeng**  
*Professor of Pharmacoepidemiology*  
 University of Oslo

### International Guest Professors



**David Dodick**  
*Professor of Neurology*  
 Mayo Clinic Arizona



**Manjit Matharu**  
*Professor of Neurology*  
 University College London



**Arne May**  
*Professor of Neurology*  
 University of Hamburg

# International Collaboration

In 2023, NorHead has solidified and strengthened its position as a prominent international partner in headache research.

Through partnerships with renowned research institutions and medical centers across the world, we are creating a dynamic network for the exchange of ideas, methodologies, and research findings, that will advance global research and ensure large-scale international dissemination and clinical implementation.

## Global Research Partnerships – Coordination of international research consortiums

Our commitment to collaborative research is exemplified by our role as coordinator of two large international and multidisciplinary consortiums applying for funding by the EU Horizon program: The first submitted in April 2023 (19 partners, achieving a score of 14 out of 15 possible points) and the second (first stage application, 13 partner, awaiting evaluation) submitted in September 2023. By different means, both projects include the use of international health data and cross-border collaboration that will allow us to pool resources and expertise – accelerating progress and leading to breakthroughs that have the potential to reshape our understanding of headache disorders, diagnosis, and treatment.

## International guest professors and advisory board

As initiated during 2022, in 2023 NorHead arranged seminars with our International Guest professors and Scientific Advisory Board. During these meetings, ongoing and prospective studies were discussed and both new and established researchers at NorHead were given the opportunity to present their projects and ideas to receive feedback from our excellent and experienced advisors. Guest professors include Professors David Dodick (US), Manjit Matharu (UK), and Arne May (affiliations), while the scientific board include Professors Peter Goadsby (UK), Simona Sacco (IT), Messoud Ashina (DK), Hans-Christoph Diener (DE), Hedvig Nordeng (NO) and Anne-Hege Aamodt (lead, NorHead partner).

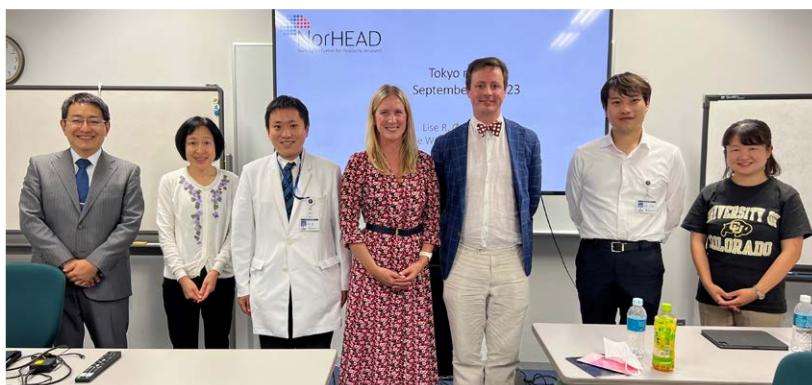


Photo: XXXX

*The Headache Clinic at Keio University is one of four clinics in Tokyo specializing in headaches. Researchers Lise Øie and Tore Meisingset from NorHead visited the clinic in September 2023 to exchange knowledge and lay the groundwork for potential research collaboration in the future.*

















### Active Participation in Global Events

NorHead has also actively participated on several international conferences and symposiums throughout the year, sharing our research, ideas, and methodologies— paving the way for future collaborations. Of special mention is the International Headache conference in Seoul, South Korea, and the European Headache Conference in Barcelona. At both venues, NorHead researchers headlined and lectured at influential symposiums/ thematic sessions.

### At the board of the European Headache Federation

On the 9th of December 2023, NorHead's Scientific Director, Erling Tronvik, was elected as one of four new board members at the European Headache Federation Council. The position will enable NorHead to influence the direction of the headache research agenda in Europe, increase our outreach and reputation as a attractive collaborative partner, and work for more European funding of headache-related science and industry.

### International partners

 Belgium	 Italy	 Estonia	 Argentina
 Germany	 Denmark	 Japan	 Taiwan
 Spain	 Sweden	 USA	 Iceland
 Switzerland	 Finland	 Netherlands	 Greece

# Patient Involvement

Throughout 2023, patient participation has been a key component in NorHead's work. Through various initiatives, patients have significantly contributed to research and development in the field of headache disorders.



→ **Research Studies:** A group of patients took an active step to familiarize themselves with ongoing studies. They invited project leaders of existing studies for a thorough review, where they provided valuable feedback and expanded their own knowledge.

→ **Board Participation:** A patient representative has been an integral part of NorHead's board, participating as a full board member.

→ **Development of Tools:** Patients have also been involved in developing a checklist for implementation, a project led by OU2.

→ **Patient Conference:** In collaboration with the patient organization Hodepine Norge, NorHead organized a large patient conference. The participants, mainly patients, contributed with written evaluations and provided insights into their desires for future headache research.

→ **Steering Group:** A patient representative is a member of the professional steering group and actively participates in decision-making processes in steering group meetings.

→ **Research after Covid Vaccine:** With the initiation of a study to explore persistent headaches after Covid vaccination, there emerged a strong need for information among patients. In response,

the patient organization established a special group for information sharing, where the user representative from the study shared insights after the participants' study period was over.

→ **Contributions to Applications for Research Funding:** Patients contributed to the application for EU funds from the Horizon program for the development of the analysis platform CoHeads. They also contributed to the application for women's health funds from the Research Council.

→ **Assessment of National Service:** Patients contributed to an assessment of the need for a national third-line service for headache patients, a task from the Directorate of Health.

→ **Evaluation of New Study:** There has been an evaluation of the initiation of a new study on vestibular migraine in collaboration with otorhinolaryngologi specialists in Bergen. The patient organisations special group for members with vestibular migraine has participated and contributed with valuable patient experiences right from the start.

→ **Development of Courses in User Participation:** Patients have also participated in the design of courses in user participation, where they have contributed to the agenda, acquiring lecturers, and users for the course.

Highlight – Headache Evening:

# A Successful Meeting between Researchers and the Public

On September 28th 2023, NorHead and the patient organization Hodepine Norge hosted an engaging public meeting in Trondheim, titled “Headache Evening – Hope for Better Treatment”.

→ Written by Laila Mathisen, Hodepine Norge



Photo: Nor-Head

All 250 seats in the hall were booked, and the event was highly successful. Participants had the opportunity to meet experts involved in research and clinical work, learning more about headache disorders, research, treatments, and the needs of those affected by headache disorders.

## Meaningful Dialogue on Research and Treatment

The event served as a platform for dialogue between healthcare professionals, researchers, and patients. Several lectures were presented, covering topics from new research to how to make the most of your doctor’s appointment. The aim was to provide insights into the research being conducted at NorHead and to gather feedback for the research work from the public.

## Hope for Better Treatment

“Headache Evening – Hope for Better Treatment?” became an important meeting point for everyone affected by headache disorders. It fostered hope that better treatments are on the horizon.

→ In the evaluation, 90% of the audience responded that they received information that could be useful as a patient or caregiver.

→ 90% also said that the conference lived up to their expectations.

The headache evening was educational and rewarding. I got lots of new knowledge to share with my doctor.

I really liked that I could talk to the researchers during the breaks.

# Strategy for Diversity and Inclusion in NorHead Studies

At NorHead, we recognize that headache disorders can have different expressions and directions depending on age, gender, and cultural background. To ensure that our research is as relevant as possible for the entire population, we therefore strive to include all groups in our studies.



## The best possible research utility

Gender-sensitive research will reach a broader group of end-users in a more relevant way. Research that does not concern a human research population might still have human end-users. Again, this population consists of men and women, with their different needs and aspirations. And these gender differences might very well influence the use of the research outcome. Taking gender into account and asking from the start who will use the results, when and how, can avoid an unintentional gender bias in the outcome.

The goal of including all groups does not necessarily apply to every individual research project. In cases where this cannot be fulfilled, a valid justification must be provided. Such reasons may include research where it is not relevant to include all groups. An example might be studies of menstrual-related migraine.

## We ensure inclusion of underrepresented groups by:

- All studies use a checklist for assessing studies from a patient perspective, which addresses this issue in Item 7: Description of how patients are selected -> Underrepresented groups.
- If the group working on a study notices a lack of underrepresented groups, ways to include the underrepresented group should be considered.
- We use broad recruitment strategies to reach as many people as possible. Targeted information campaigns for individual studies. General overview on [norhead.no](http://norhead.no) of studies accepting participants.
- We ensure that the informational materials are in plain language so that they can be understood by as many people as possible.
- We regularly evaluate the gender balance and diversity in the study population and adjust recruitment strategies as needed.

# Industry Partnerships and Innovation

NorHead has a dedicated work group led by Bjarte Reve at the Nansen Neuroscience Network, that is developing and employing an active strategy for innovation and industry collaboration.

In March 2023, a workshop was conducted with several pharmaceutical companies and a SME in collaboration with Melanor – a trade association for MedTech and lab in Norway. A follow-up workshop was held in November 2023, with new companies also participating. One aim was to investigate how NorHead best may help startup companies that wish to enter the headache treatment market.

Further, in 2023 four NorHead researchers initiated a spin-off company, Keimon Medical AS, that develops navigation-based cryotherapy for trigeminal neuralgia. A patent application has been submitted via the Technology Transfer Office (TTO). The company secured external professional investors in the first round, and a FORNY

grant has been applied for as a collaboration between Keimon Medical AS and NorHead. We have also received internal funds from the health region and national funds from DAM to conduct clinical trials using the guided device.

Additionally, the research group behind NorHead has previously started two spin-off companies (Nordic Brain Tech and Palion Medical—now part of Man&Science). There is a strong emphasis on innovation and business activity linked to our research.

In 2023, the Norway Health Tech cluster was a collaborative partner on an EU application coordinated by NorHead.

There is a strong emphasis on innovation and business activity linked to our research.



Photo: NorHead

# Highlights 2023

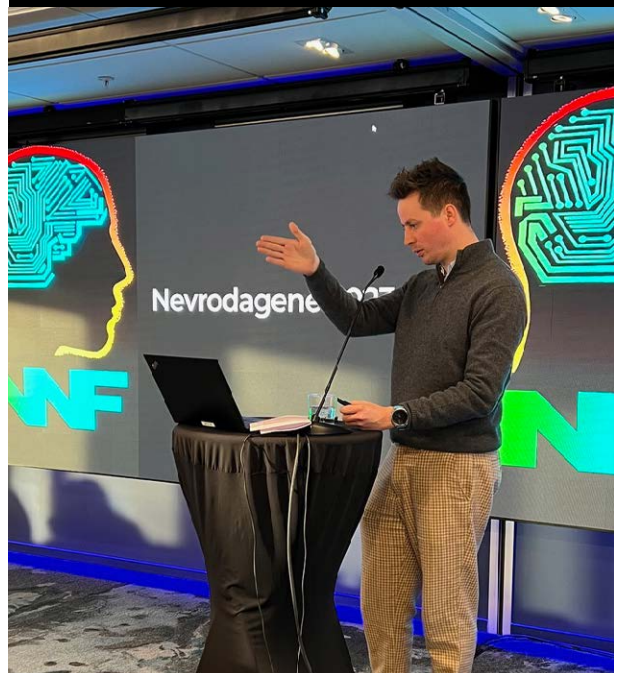
**02.03**

Visit from the Norwegian Parliament's Health Committee



**14.03**

NorHead satellite symposium in connection with Nevrodagene 2023



**14.08–19.08**

Participation at Arendalsuka – Norway's largest political gathering



**23.09**

Hjernesnakk: Søvnens kraft – Hyfer Science festival in Trondheim

**14.09–17.09**

International Headache Congress in Seoul





# 28.09

Hodepinekveld – Håp om bedre behandling?



# 29.09

Researchers' Night – Ungdommens forskernatt på NTNU

# 13.11–14.11

National Headache Conference – Trondheimskonferansen 2023



# 06.12–09.12

European Headache Congress in Barcelona



# Decoding the Genetics of Cluster Headache

Probably no pain surpasses the intensity of cluster headaches. Affecting one in a thousand individuals, this condition causes extreme, one-sided headaches, often with pain behind the eye. Sufferers from cluster headaches are in dire need of new treatment options, but experience that there is still a long way to go in terms of research. An international research team, led by scientists from NorHead, have now uncovered insights that shed light on this mysterious disease.

**T**hey have conducted the largest genetic study of cluster headaches ever, analyzing genomic data from over 36,000 people, of which 4,777 had cluster headaches. The data has been collected in ten European and one East Asian country. In 2023, the results were published in *Annals of Neurology*.

## Smoking as a risk factor

Cluster headaches are four times more prevalent in men than in women, but why some people get cluster headaches has largely been unknown. Uncovering the biological mechanisms of cluster headache is an important step towards enhanced treatment.

The study provides, for the first time, research-based evidence that smoking may play a role in the development of cluster headaches. "Most people with cluster headaches smoke, but it has so far been unclear whether smoking actually

The study provides, for the first time, research-based evidence that smoking may play a role in the development of cluster headaches.



## Bendik Winsvold

Senior Researcher at  
Oslo University Hospital  
and NorHead

causes cluster headaches or if people with cluster headaches are more prone to smoking," says Bendik Winsvold, a Senior Researcher at Oslo University Hospital and NorHead, who has led the international consortium of researchers.



## Three world-leading headache researchers about the study:



→ Manjit Matharu, Professor in Neurology, University College London (UCL):

Understanding that smoking may be a modifiable risk factor brings vital insights for patients and healthcare providers. It reinforces the message that efforts to quit smoking are essential in the management of patients with cluster headache.



→ Arn van den Maagdenberg, Professor in Molecular and Functional Neurogenetics, Leiden University:

Migraine is the only other headache disorder that has been properly explored genetically. It is fascinating that some genetic risk factors for cluster headache are shared with migraine, while others are not. Follow-up research from this study may give us insights into why they sometimes have similar symptoms and even respond to the same medications.



→ Andrea Carmine Belin, Group Leader, Centre for Cluster Headache, Karolinska Institutet:

This study was made possible by international collaborations across many countries, in the International Consortium for Cluster Headache Genetics. The study not only sets the groundwork for even more in-depth investigations into the causes of cluster headache by this consortium, but also emphasizes the importance of future studies to include cluster headache patients from a broader range of populations globally.

The researchers have also found genetic links between cluster headaches and migraines. Among the nine genes they investigated with significance for cluster headaches, they identified three that also were significant for migraines.

### Variations between population groups

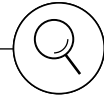
A third observation is that the manifestation of cluster headaches may vary in different population groups. Bendik underscores the genetic distinctions between individuals in Europe and Asia experiencing cluster headaches, stating, "Cluster headaches do not behave the same in all population groups. For example, it seems circadian features of cluster headache, with the headache attacks occurring at the same time every night,

are more prominent in European than in Asian patients". Bendik suggests further investigation into the degree to which the biological mechanisms of cluster headaches differ among various populations, and whether this divergence has implications in the selection of treatment approaches ■

*The study is a collaborative effort between research groups from the Netherlands, the United Kingdom, Sweden, Germany, Denmark, Norway, Greece, Spain, Italy, and Taiwan.*

### Reference:

Cluster Headache Genomewide Association Study and Meta-Analysis Identifies Eight Loci and Implicates Smoking as Causal Risk Factor Winsvold, Bendik S et al., in *Annals of Neurology*



# Severe Headaches: Four Clinical Trials

Individuals grappling with immensely painful and recurrent headaches without an underlying disease being the cause, often find themselves with limited treatment alternatives.

Here, we present four different clinical trials exploring innovative approaches to managing various primary severe headache diagnosis.

## Non-invasive vagus stimulation for cluster headache

Together with NorHead researchers, colleagues at UCL in London have explored the effectiveness of non-invasive vagus nerve stimulation in chronic cluster headache. With many patients not responding well to existing treatments, the study aimed to assess the impact of neuromodulation home devices used to simulate nerves. Participants, instructed to use the device preventively for at least 3 months, experienced a notable reduction in monthly attack frequency. Additionally, the average severity of attacks decreased in the same period. The findings suggest a potential benefit of non-invasive vagus nerve stimulation in managing cluster headaches.

## Treating cluster headache and migraine by blocking the SPG nerve

This open-label, real-world study investigates the efficacy and safety of repeated Botox injections

toward the nerve sphenopalatine ganglion (SPG) in patients with chronic cluster headache and chronic migraine. The injection technique demonstrated promising results, with an 81% response rate in migraine patients and a 69% response rate in cluster headache patients after one single injection. Over four consecutive injections, response rates remained high, and both groups experienced a significant reduction in headache days and attack frequency. The study concludes that injections towards the SPG-nerve is an effective and safe treatment method, likely to last for at least three months. The study was not placebo-controlled and included a relatively small number of patients, but a multi-center trial is underway to provide more robust evidence for this treatment.

## CPAP treatment for cluster headache

A study was conducted to assess the effect of continuous positive airway pressure (CPAP) as a treatment for chronic cluster headaches. CPAP involves the use of an individually fitted mask, providing air pressure to keep the airways open, ensuring a more stable oxygen supply in the blood during sleep. Among the 25 patients who



### National Registry for Severe Headaches

The Norwegian Quality Registry for Severe Primary Headaches was established by the Norwegian Directorate of Health in 2022 and started its activity in full in 2023. Its main objective is to ensure equal and high-quality diagnosis without delay for patients with severe primary headaches, as well as high-quality treatment and follow-up. Additionally, the registry aims to facilitate research.

In 2023, a total of 205 headache patients were included across 14 different neurological departments in Norway. Among them were 76% with cluster headache, 10% with hemicranias continua, 7% with paroxysmal hemicranias and 4% with SUNCT/SUNA. The remaining were probable TACS.

### Primary headache diagnosis included in the registry:

- Cluster headache
- Paroxysmal hemicranias
- Hemicranias continua
- SUNCT/SUNA

The registry is based on signed consent and includes patients aged 18 or over.

→ [hodepineregisteret.no](https://hodepineregisteret.no)



completed CPAP treatment, the researchers did not find a reduction in the frequency of cluster headache attacks when they compared them to patients receiving sham treatment.

### Cryotherapy for trigeminal neuralgia

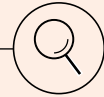
In 2023, NorHead secured funding for the Cryo-Gem Trial, focusing on a novel treatment for

trigeminal neuralgia, a condition characterized by intense facial pain. The trial aims to explore the effectiveness and safety of a freezing technique applied to nerves to alleviate pain in adults suffering from trigeminal neuralgia. The trial will enroll 24 adults with trigeminal neuralgia, who will be randomly allocated to either a treatment group or a sham therapy group ■

# Key Researchers and Staff

Name	Institution	Research Area / Role
Erling Tronvik	NTNU / St. Olavs Hospital	Scientific Director. (All research areas)
Marte-Helene Bjørk	Univ. of Bergen / Haukeland Univ. Hospital	Register research. Deputy Director, NorHead
Heri Ramampiaro	NTNU	Computer sciences, artificial intelligence
Jaya Thomlison	NTNU	Centre leadership, innovation and business development
Guglielmo Genovese	NTNU	MR physics
Anker Stubberud	NTNU	Machine learning
Lars Jacob Stovner	NTNU	Public health
Helge Langseth	NTNU	Machine learning
Martin Syvertsen Mykland	NTNU / St. Olavs Hospital	Basal science and neuophysiology
Alexander Olsen	NTNU / St. Olavs Hospital	Post traumatic headache
Torill Skandsen	NTNU	Post traumatic headache
Sasha Gulati	NTNU / St. Olavs Hospital	Neurosurgery/ trigeminal neuralgia
Tore Meisingset	NTNU / St. Olavs Hospital	Clinical trials
Lise Øie	NTNU / St. Olavs Hospital	Clinical trials
Hanne Smevik	NTNU	Psychology, Neuroscience
Edona Zilkiqi	NTNU	Psychology, cognitive rehabilitation after aquired brain injury
Amalie Poole	NTNU	Clinical trials
Antonios Danelakis	NTNU	Machine learning
Andreas Husøy	NTNU	Register research
Joakim Østhus	NTNU / St. Olavs Hospital	Clinical trials
Gøril Storvig	NTNU	Clinical trials
Fahim Fasal	NTNU	Machine learning
Johanne Rauwenhoff	NTNU	Innovation
Timothy Steiner	NTNU / Imperial College London	Public health
Kristina Devik	NTNU / Namsos Hospital	Clinical trials
Johan Crespi	NTNU / St. Olavs Hospital	Clinical trials
Tjasa Kumelj	NTNU	Database Officer
Kristina Jones	NTNU	Communication
Yngvild Gagnat	NTNU	Research coordinator
Karoline Nordvik	NTNU	Administration and research coordination
Hanne Snerting	NTNU	Financial officer
Jan Sigurd Blackstad	NTNU	Special advisor / Scientific writer
Vikram Singh Parmar	NTNU	Innovasjon
Nina Bäcklund	NTNU / St. Olavs Hospital	Research nurse

Marit Fjærli	NTNU / St. Olavs Hospital	Research nurse
Irina Aschehoug	NTNU / St. Olavs Hospital	Research nurse
Gøril Bruvik Gravdahl	NTNU / St. Olavs Hospital	Research nurse, patient facilitation
Avneesh Jain	NTNU / St. Olavs Hospital	MRI research assistant
Knut Hagen	St. Olavs Hospital	Clinical Trials
Eiliv Brenner	St. Olavs Hospital	Clinical Trials
Trond Sand	St. Olavs Hospital	Neurophysiology
Petter Omland	St. Olavs Hospital	Neurophysiology
Martin Uglem	St. Olavs Hospital	Neurophysiology
Sozaburo Hara	St. Olavs Hospital	Neurosurgery
Jon Gunnar Skogås	St. Olavs Hospital	Industry collaboration and test lab
Bendik Winswold	Oslo Univ. Hospital / University of Oslo	Health data and genetics
Anne Hege Aamodt	Oslo University Hospital	Clinical trials
John Anker Zwart	Oslo University Hospital	Clinical trials
Helene Engstrand	Oslo University Hospital	Clinical trials
Maria Argren	Oslo University Hospital	Clinical trials and register research
Elisabeth Gjefsen	Oslo University Hospital	Clinical trials
Sigrid Børte	Oslo University Hospital	Genetics
Tone Rønning	Oslo University Hospital	Research nurse
Janicke Igland	University of Bergen	Register research
Andrej Khanevski	Haukeland University Hospital	Clinical trials
Ane Bakke Øvrevik	Haukeland University Hospital	Clinical trials
Mari Nordtveit	Haukeland University Hospital	Research nurse
Marianne Blomdal Karlsen	Haukeland University Hospital	Research nurse
Kjersti Grøtta Vetvik	Akershus University Hospital	Women and migraine, multidisciplinary headache treatment
Espen S. Kristoffersen	Akershus University Hospital	Migraine and vascular diseases, MOH, multidiscip. treatment
Oda V Lunder	Akershus University Hospital	Non-pharmacological treatment, multidiscip. treatment
Christofer Lundqvist	Akershus University Hospital	MOH, chronic headache
Kjersti Aaseth	Akershus University Hospital	Migraine and vascular d., multidiscip. trt., secondary chr headache
Eva Lillian Kolstad	Akershus University Hospital	Research nurse
Linda Hagen Aasbakken	Akershus University Hospital	Research nurse
Linn-Marie Wølneberg	Akershus University Hospital	Research nurse
Aina Kristin Paulsen	Akershus University Hospital	Multidisciplinary headache treatment
Iben Larsen	University Hospital of Northern Norway	Clinical trials
Kine Dalby	University Hospital of Northern Norway	Research nurse
Parashkev Nachev	University College London	Machine learning
Laila Mathisen	Hodepine Norge	Patient collaboration, ethics
Bjarte Reve	Nansen Neuroscience Network	Business collaboration, business modelling
David Dodick	Mayo Clinic, USA	Headache research, clinical trials
Arne May	University of Hamburg	Headache research, imaging and diagnostics
Manjit Matharu	University College London	Headache research, clinical trials and machine learning
Mathias Linde	Salgrenska University Hospital	Headache Research



# Unveiling the Link between Migraine and Sleep

→ Written by Martin Syvertsen Mykland

Despite an estimated 12% of the world's adult population experiencing disability due to migraine, the cause of the condition remains unknown. Consequently, there is no diagnostic test which can confirm the migraine diagnosis or separate potential subgroups of migraine. The lacking understanding of pathophysiological mechanisms also limit the development of targeted and effective migraine treatments.

**T**here is a well-known connection between migraine and sleep. In the recent years, it has been discovered that there also is a likely connection between the brain systems controlling sleep and circadian rhythm, and migraine mechanisms. My colleagues and I have investigated this relationship further to uncover new mechanisms that may lead to new treatment targets and become diagnostic markers. We did this by examining facilitatory and inhibitory mechanisms of the brain after varying amounts of sleep. We compared these mechanisms between people with migraine and healthy controls.

We found interesting differences between the two groups, even outside migraine attacks. Insufficient sleep led to reduced function of inhibitory mechanisms in migraine patients. This change in inhibitory function was also related to the degree of symptoms individuals typically experience before and during attacks. This finding was also specific to those who usually experience attacks during daytime, suggesting different causes for the migraine disease between those who typically have attacks during sleep compared to daytime.

We also made another interesting observation in

the migraine patients: In the period before a migraine attack, reduced sleep gradually increased the effectiveness of another inhibitory system. This system is believed to be partially controlled by deep brain centers that also regulate sleep function and stress response. This finding provides new insights into the relationship between previous findings of altered function in deep brain centers and the cerebral cortex before migraine attacks.

Finally, we found a change in brain function after insufficient sleep immediately following a migraine attack. This change was similar to what can be observed in healthy individuals who go a whole night without sleep. This finding suggests that individuals with migraines may be more vulnerable to insufficient sleep during and immediately after an attack.

Our findings suggest advising people with migraine to obtain regular and sufficient sleep, especially during attacks. This research also adds important pieces to the puzzle that makes up our knowledge about migraine pathophysiology and lays a foundation for new research projects which may lead to new diagnostics and treatments ■



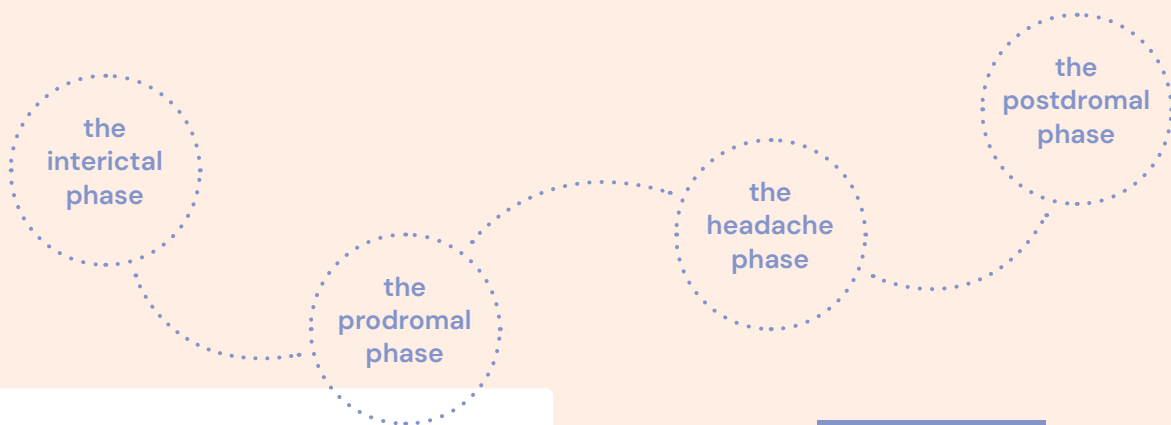


Photo: Kim Sørensen / NTNU



Martin Mykland used the methodologies of electroencephalography (EEG) and transcranial magnetic stimulation (TMS) to investigate brain function.

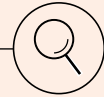
Mykland works as a neurology resident at St. Olavs Hospital and is a researcher at NTNU. In 2023, he completed his PhD on the relationship between sleep and migraine.



### Migraine

Migraine is a primary headache disorder, believed to cycle through different migraine phases; the interictal phase, the prodromal phase, the headache phase and the postdromal phase. Various symptoms can be experienced in the different phases.

We found a change in brain function after insufficient sleep immediately following a migraine attack.



# Concussion – A “Mild” Traumatic Brain Injury with a Severe Impact

→ Written by Gøril Storvig and Johanne Rauwenhoff

The Clinical Neuroscience Laboratory at NorHead studies the consequences of mild traumatic brain injury, commonly referred to as concussion. You might have experienced it yourself, taking a hit to your head after falling or while playing sports. Subsequently, you might have felt dizzy or nauseous.

**C**oncussions are very common with at least 302 per 100,000 people seeking medical care for concussions annually in Norway. The incidence is likely higher as many do not consult a doctor following a concussion. Concussions can cause a range of different post-concussion symptoms, including headache, fatigue, and cognitive complaints. Post-traumatic headaches often have migraine-like features, but people can also experience other headache phenotypes.

At least 302 per 100,000 people seek medical care for concussions annually in Norway.

While most people recover spontaneously within a few days or weeks, a considerable subgroup of people experience persistent symptoms. We don't exactly know why this is. It is likely that biological, psychological, as well as social factors play a role. We do know that persistent post-concussion symptoms, PPCS for short, have a big impact on daily functioning and quality of life.

Ongoing research at the Clinical Neuroscience Laboratory includes an innovation project developing a mobile app for PPCS symptom mapping. The app is similar to a digital headache diary, as previously developed at NorHead, but also lets you map other post-concussion symptoms as well as factors known to be important for symptom burden such as sleep, physical activity, and alcohol intake. This will help us understand symptom variability, explore patient sub-groups, and gain a better understanding of why some people keep experiencing symptoms after a concussion.

We also study treatments for PPCS. We are investigating if Metacognitive Therapy, a psychological treatment, can help people with persistent symptoms following a concussion. The study is not yet published, but the results are promising, also for post-traumatic headache. Other projects explore neural correlates of cognitive control function, sleep, and fatigue across various neurological and psychiatric conditions. In an ongoing experimental study, we investigate the importance of sleep in people with PPCS.

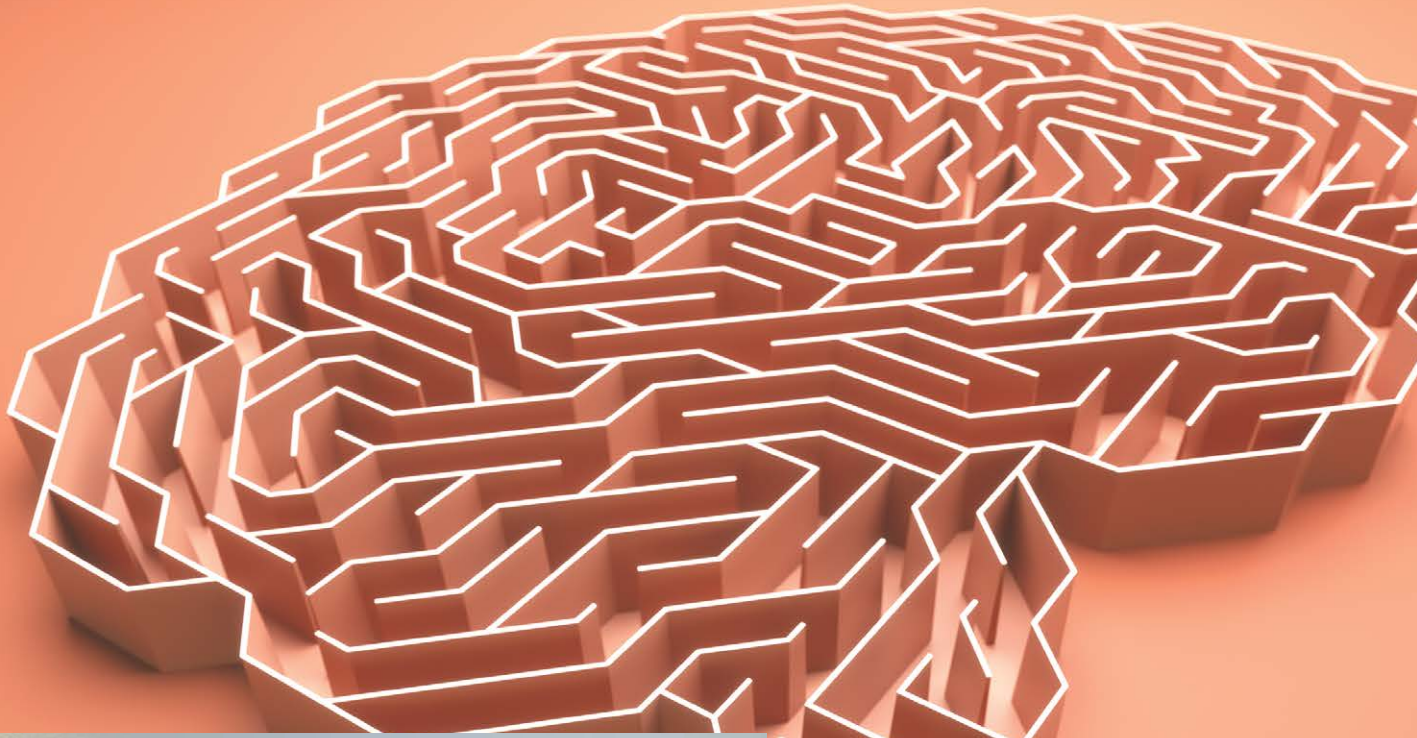


Photo: Kim L'Orange Sørenssen

*Johanne Rauwenhoff is a psychologist and postdoctoral researcher. Gøril Storvig is a nurse and PhD candidate. They both work at the Department of Psychology, NTNU, and are part of the Clinical Neuroscience Laboratory and NorHead.*

There is an enormous need for better treatment options for people experiencing PPCS. Understanding why people develop persistent symptoms is an important part of developing effective and personalized interventions. We hope to enhance the care offered to people with concussion, which will ultimately improve their quality of life. This is what motivates us at the Clinical Neuroscience Laboratory to work with and conduct research for individuals experiencing persistent symptoms after a concussion ■

### **Persistent symptoms after a concussion**

Symptoms not resolving weeks or months after a concussion are referred to as persistent postconcussion symptoms (PPCS). They may include a diverse array of somatic, cognitive, and emotional manifestations, varying greatly between individuals.

Photo: Gettyimages

## Funding and Growth

NorHead has an ambitious strategy for center growth. We aim to be a leading international research center that is also relevant in all Norway's health regions. Our ambition is to have a continuous growth—including acquiring increased and new sources of funding for existing research, developing new projects and innovation, and increasing the geographical area where we recruit study participants. This will be essential to maintain and increase our productivity and excellent science.

In 2023, NorHead researchers have submitted more than 30 applications, including two proposals as coordinator for international consortiums targeting collaborative RIA health calls in the Horizon Europe program. While we unfortunately did not secure funding from the EU calls, the feedback we received was exceptionally positive. In the first call, we achieved a score of 14 out of 15 points, reflecting the high quality of our proposal. In the second call, the competition was fierce with 118 applications for 4 grants. Although we did not receive funding, our proposal surpassed the threshold and got a very good review. Despite the outcome, these results underscore the strength of our submissions and position us favorably for future opportunities.

In total, NorHead was awarded more than 48 million NOK and funding for 5 new research positions in 2023. Of special mention is project funding from KlinBeForsk for conducting ambitious multicenter clinical trials testing the efficacy of candidate preventive medications for chronic and episodic migraine (13.4 million NOK) and cluster headache (19.9 million NOK). This is the first time that KlinBeForsk has supported two research projects from the same research group in the same calendar year.

Additionally, testing and developing our innovative solution for navigated cryotherapy for trigeminal neuralgia was awarded with funding both from DAM Foundation (2.9 million NOK) and the Liaison

Committee between the Central Norway Regional Health Authority and NTNU (4.5 million NOK).

During 2023, NorHead-partners hired 2 PhD candidates and 3 Postdocs. We also hired an associate professor in Brain MRS, Guglielmo Genovese, PhD, former postdoctoral researcher at the Center for Magnetic Resonance Research at the University of Minnesota. His research will focus on using ultra-high field magnetic resonance imaging to understand GABAergic and glutamatergic metabolisms in migraine.

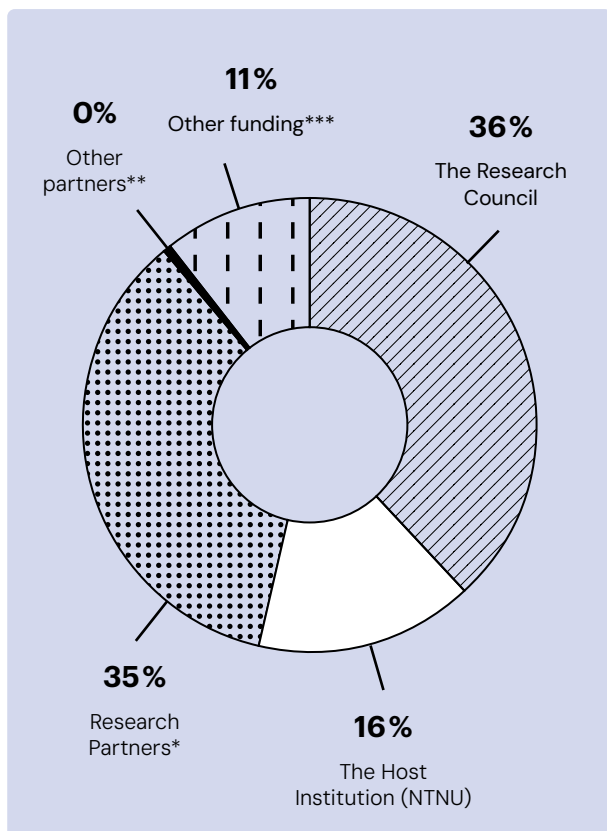
In the upcoming year, NorHead aims for a 6% annual increase in funding and financing of a minimum of 10% of our proposals.

The center will invest much time in securing funding from the European Research Council and both through Horizon Europe collaborative health calls, but also funding through other initiatives. Finally, we will invest time and resources to support our young and ambitious researchers developing their own project ideas, international networks, and support their efforts to apply for externally funded projects.

# Financial Overview

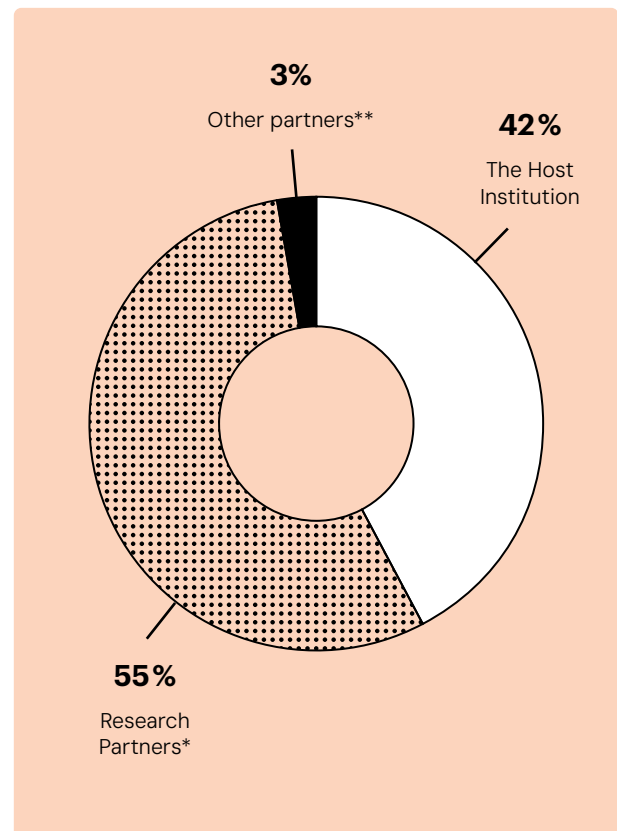
## Funding in 1000 NOK

The Research Council	9 071
The Host Institution (NTNU)	3 679
Research Partners*	8 402
Other partners**	99
Other funding***	2 500
<b>Total funding</b>	<b>23 751</b>



## Costs in 1000 NOK

The Host Institution (NTNU)	10 059
Research Partners*	13 086
Other partners**	606
<b>Total costs</b>	<b>23 751</b>



\* Research Partners: University of Bergen, St. Olavs Hospital, Oslo University Hospital, Akershus University Hospital, University Hospital of North Norway, Haukeland University Hospital, Nord-Trøndelag Hospital Trust

\*\* Other partners: Hodepine Norge, Nansen Neuroscience Network

\*\*\* Other funding: Cash contribution from The Liaison Committee for Education, Research and Innovation in Central Norway and The joint research committee (FFU) between St. Olavs Hospital HF and the Faculty of Medicine and Health Sciences, NTNU

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*JAMA Neurology*

### **Global epidemiology of migraine and its implications for public health and health policy**

Timothy J. Steiner and Lars Jacob Stovner *Nature Reviews Neurology*

### **The relationship between headache-attributed disability and lost productivity: 3 Attack frequency is the dominating variable**

Andreas Katterem Husøy, Zaza Katsarava and Timothy J. Steiner *The Journal of Headache and Pain*

### **Randomized controlled studies evaluating Topiramate, Botulinum toxin type A, and mABs targeting CGRP in patients with chronic migraine and medication overuse headache: A systematic review and meta-analysis**

Samita Giri, Erling Andreas Tronvik, Anders Mattias Linde, Sindre Andre Pedersen and Knut Hagen *Cephalalgia*

### **Insufficient sleep may alter cortical excitability near the migraine attack: A blinded TMS crossover study**

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### **Effects of insufficient sleep on sensorimotor processing in migraine. A randomised, blinded crossover study of event related beta oscillations**

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### **Associations between intelligence, everyday executive functions, and symptoms of mental health problems in children and adolescents with mild intellectual disability**

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*International Journal of Developmental Disabilities (IJDD)*

### **The HARDSHIP databases: a forthcoming free good from the Global Campaign against Headache**

Timothy J. Steiner, Andreas Katterem Husøy, Hallie Thomas and Lars Jacob Stovner *The Journal of Headache and Pain*

### **Phenotype of new daily persistent headache: subtypes and comparison to transformed chronic daily headache**

Sanjay Cheema, Anker Stubberud, Khadija Rantell, Parashkev Nachev, Erling Andreas Tronvik and Manjit Matharu  
*The Journal of Headache and Pain*

### **A protocol for the development and validation of a virtual reality-based clinical test of social cognition**

Martin Matre, Truls Sveløkken Johansen, Alexander Olsen, Sveinung Tornås, Anne Cathrine Trægde Martinsen, Anne Lund et al.  
*BMC Digital Health*

### **Poorer sleep health is associated with altered brain activation during cognitive control processing in healthy adults**

Hanne Smevik, Sarah Habli, Simen Berg Saksvik, Elisabeth Kliem, Hallvard Røe Evensmoen, Virginia Conde et al. *Cerebral Cortex*

### **Comparative retention and effectiveness of migraine preventive treatments: A nationwide registry-based cohort study**

Marte-Helene Bjørk, Solveig Borkenhagen, Francisco Oteiza, Aud N. Dueland, Frank E. Sørsgaard, Erik Magnus Sæther, et al. *European Journal of Neurology*

### **An open-label observational study and meta-analysis of non-invasive vagus nerve stimulation in medically refractory chronic cluster headache**

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### **Forecasting migraine with machine learning based on mobile phone diary and wearable data**

Anker Stubberud, Sigrid Hegna Ingvaldsen, Eiliv Brenner, Ingunn Grøntveit Winnberg, Alexander Olsen, Gøril Bruvik Gravdahl et al. *Cephalalgia*

### **Multimodal Analysis of Secondary Cerebellar Alterations**

**After Pediatric Traumatic Brain Injury** Finian Keleher, Hannah Lindsey, Rebecca Kerestes, Houshang Amiri, Robert Asarnow, Talin Babikian et al. *JAMA Network Open*

### **Continuous positive airway pressure in cluster headache:**

**A randomized, placebo-controlled, triple-blind, crossover study** Gøril Bruvik Gravdahl, Lars Aakerøy, Lars Jacob Stovner, Morten Engstrøm, Kai Ivar Müller, Marte-Helene Bjørk et al. *Cephalalgia*

**Onabotulinum toxin A block of the sphenopalatine ganglion in patients with persistent idiopathic facial pain: a randomized, triple-blind, placebo-controlled, exploratory, cross-over study** Kent Are Jamtøy, Wenche Moe Thorstensen, Lars Jacob Stovner, Annika Rosén, Stine Maarbjerg, Daniel Fossum Bratbak, et al. *Cephalalgia*

**Current treatment options for cluster headache: limitations and the unmet need for better and specific treatments—a consensus article** Nunu Laura Timotheussen Lund, Anja Sofie Petersen, Rolf Fronczek, Jacob Tfelt-Hansen, Andrea Carmine Belin, Tore Wergeland Meisingset et al. *The Journal of Headache and Pain*

**Transient ischemic attack or migraine with aura?** Karl Bjørnar Alstadhaug, Erling Andreas Tronvik og Anne Hege Aamodt *Tidsskrift for Den norske legeforening*

**Moderate and Severe Traumatic Brain Injury** Alexander Olsen, Andrew Cwiek, Emily Dennis og Frank G. Hillary *The SAGE Handbook of Clinical Neuropsychology*

**Cluster Headache Genomewide Association Study and Meta-Analysis Identifies Eight Loci and Implicates Smoking as Causal Risk Factor** Bendik Kristoffer Slagsvold Winsvold, Aster V. E. Harder, Caroline Ran, Mona A. Chalmer, Maria Carolina Dalmaso, Egil Ferkingstad et al. *Annals of Neurology*

## Doctoral Thesis 2023

**Migraine and sleep: The effects of insufficient sleep on brain function in migraine** Martin Syvertsen Mykland, NTNU

## Academic Presentations

**Lecture: The burden of Headache. An outline and discussion of the findings of The Global Campaign against headache.** Presenter: Gøril Bruvik Gravdahl. IHC 2023 Rising Sun over Headaches, Seoul, 14.09.2023. Organiser: International Headache Society

**Lecture: NorHEAD – Hodepine, by Gøril Bruvik Gravdahl.** Nevrokongressen 2023, Trondheim, 08.–09.06.2023  
Organiser: NSFs faggruppe for nevrosykepleiere (Norwegian Association of Neuroscience Nurses)

**Lecture: Population-based approaches to determining risk of neurodevelopmental diagnoses with antiseizure medications: in females and males.** Presenter: Marte-Helene Bjørk. 35th International Epilepsy Congress, Dublin, 02.–06.09.2023.  
Organiser: International League Against Epilepsy

**Lecture: Behandling av hodepine under graviditet.** Presenter: Marte-Helene Bjørk, Trondheimskonferansen 2023, Trondheim, 13.–14.11.2023. Organiser: NorHead

**Lecture: Comparative retention and effectiveness of migraine preventive treatments – A nationwide registry-based cohort study.** Presenter: Marte-Helene Bjørk. International Headache Conference, Seoul, 14.–17.09.2023. Organiser: International Headache Society

**Lecture: Challenges and opportunities when Nordic drug prescription registries inform antiseizure medication label-**

**ling.** Presenter: Marte-Helene Bjørk. The 15th Annual NorPEN Meeting–Strengthening our Nordic network for preparedness and impact, Oslo, 23.11.2023. Organiser: Nordic Pharmacoepidemiological Network (NorPEN) and Norwegian Institute of Public Health

**Lecture: Behandling av migrene hos kvinner i fruktbar alder.** Presenter: Marte-Helene Bjørk. Nevrodagene 2023, Oslo, 14.–16.02.2023. Organiser: Norsk Nevrologisk Forening

**Lecture: Hodepineomsorgen på norske sykehus: Resultater fra spørreundersøkelse sendt ut til nevrologiske avdelinger.** Presenter: Gøril Bruvik Gravdahl and Lars Jacob Stovner. Trondheimskonferansen 2023, Trondheim, 13.–14.11.2023. Organiser: NorHead

**Lecture: Ikke-medikamentell behandling, monitorering og oppfølging.** Presenter: Gøril Bruvik Gravdahl. Digitalt emnekurs i hodepine. 15.–16.11.2023. Organiser: Nordland Medical Association / The Norwegian Medical Association

**Lecture: Tverrfaglig hodepinebehandling – Helse i Arbeid.** Presenter: Kjersti Vetvik. Trondheimskonferansen 2023, Trondheim. 13.–14.11.2023. Organiser: NorHead

**Lecture: Migrene og søvn.** Presenter: Martin Syvertsen Mykland. Trondheimskonferansen 2023, Trondheim, 3.–14.11.2023

**Lecture: The prevalence of headache disorders among**

*epilepsy patients in the Trøndelag Health Study (HUNT).*

Presenter: Helene Engstrand. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Lecture:** *What do headache-attributed burden and disability actually mean?* Presenter: Timothy J. Steiner. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Poster presentation:** *Migraine patients need increased amounts of sleep during attacks to maintain neurological functioning.* Presenter: Martin Syvertsen Mykland. 9th Congress of the European Academy of Neurology. Budapest, 01.–04.07.2023

**Poster presentation:** *New-onset severe headache after Covid-19 vaccine in Norway (CovaxHEAD).* Presenter: Maria Bengtson Argren. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Poster presentation:** *The burden of headache disorders in Norway: a population-based cross-sectional study in adults using the HARDSHIP questionnaire (PopHEAD).* Presenter: Maria Bengtson Argren. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Poster presentation:** *Randomized controlled studies evaluating Topiramate, Botulinum toxin type A, and mABs targeting CGRP in patients with chronic migraine and medication overuse headache: a systematic review and meta-analysis.* Presenter: Samita Giri. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Poster presentation:** *Migraine and risk of atrial fibrillation. A 9-year follow-up based on the Trøndelag health study.* Presenter: Samita Giri. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Poster presentation:** *Is there a link between migraine and stroke? A population-based register-linked cohort study?* Presenter: Samita Giri. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

**Poster presentation:** *BACT – Botulinum toxin A in frequent and chronic tension-type headache with the FollowThe-Sutures paradigm. A triple blind, randomized, placebo-controlled cross-over trial.* Presenter: Kristina Devik. 17th European Headache Congress (EHC). Barcelona 06.–09.12.2023

## Presentations for Stakeholders and The Public

02.03.2023: *Presentasjon for Stortingets helse- og omsorgskomiteé*, by Lars Jacob Stovner and Erling Andreas Tronvik. NorHead, St. Olavs hospital. Organiser: Helse Midt-Norge

14.03.2023: *NorHEAD satellite symposium* held in connection with Nevrodagene 2023, Legenes hus, Oslo. Presentations by Tore Wergeland Meisingset, Daniel Fossum Bratbak, Irina Aschehoug, Kjersti Vetvik, Maria Argren and Bendik Kristoffer Slagsvold Winsvold. Organisers: NorHead – Norsk senter for hodepineforskning and Man&Science

21.04.2023: *NorHead: Hvorfor har forskningsrådet gitt en kvart milliard til hodepineforskning?* Friday Lecture at St. Olavs Hospital and NTNU, by Lars Jacob Stovner

11.05.2023: *Deeptech – from fundamental research to business*, meeting organized by NTNU Discovery. Presentation by Erling Tronvik

31.05.2023: *Norsk senter for hodepineforskning inviterer til samarbeidsmøte med næringslivet.* Industry meeting with presentations by Erling Tronvik, Tore Wergeland Meisingset, Lise Rystad Øie, Bjarte Reve, Jon Gunnar Skogås

14.08.2023–18.08.2023: *Stand at Arendalsuka 2023.* Contributors: Tore Meisingset, Lise Rystad Øie, Gøril Bruvik Gravdahl, Yngvild Gagnat and Kristina Jones

16.08.2023: *Migrene og samfunnsmessige gevinster av bedre hodepineomsorg.* Political debate at Arendalsuka 2023, where Tore Meisingset took part in the panel.

23.09.2023 *Hjernesnakk: Søvnens kraft.* Presentations from Alexander Olsen, Gøril Storvig, Edona Zilkiqi, Sarah Habli, Håvard Kallestad and Johanne Rauwenhoff. Organised by Hyfer festival, NTNU.

28.09.2023: *Hodepinekveld: Håp om bedre behandling?* Conference for the public organised by NorHead. Presentations from Erling Tronvik, Martin Mykland, Tore Wergeland Meisingset, Gøril Bruvik Gravdahl, Lise Rystad Øie, Knut Hagen, Marit Fjærli, Eiliv Brenner, Toril Skandsen. Laila Mathisen chaired the event.

29.09.2023: *Stand at the popular science event Researchers' Night – Ungdommens forskernatt ved NTNU.* Contributors: Marit Fjærli, Yngvild Gagnat and Kristina Jones



06.11.2023: *Migrene, en kvinnesykdom eller et folkehelseproblem?* Lecture by Lise Rystad Øie at a public meeting organised by "For kvinners helse"

## Media Coverage

04.01.2023: *Kristin har hatt migrene hele livet, men ble nesten 40 før hun søkte hjelp.* Interview in Bergens Tidene with Marte-Helene Bjørk

06.01.2023: *Småbarnsmoren Carolina er slått ut av hodepine over 20 dager i måneden.* Interview on NRK Distriksnyheter for Vestfold og Telemark and nrk.no with Maria Argren

06.01.2023: *Vil kartlegge hovudpineplager.* Interview in Vest-Telemark blad with Maria Argren

04.01.2023: *Legeprat #24 Hjernehelse, podcast from the Norwegian Medical Association.* Podcast interview with Anne Hege Aamodt

16.01.2023: *Women and chronic migraine pain, BBC World Service, The Conversation.* Podcast interview with Lise Rystad Øie

05.02.2023: *Denne kirurgen opererer migrenepasienter.* Interview in Bergens Tidende Marte-Helene Bjørk

10.02.2023: *Vil Botox virke mot Idas spenningshodepine?* Interview in Namdalsavisa with Kristina Devik

11.02.2023: *Hodepine i overgangsalder: – Definitivt et problem.* Interview on vi.no with Kjersti Vetvik

18.02.2023: *Nå forteller den kjente senjapolitikeren Line Miriam Haugan (53) for første gang om hvordan sykdommen terroriserer henne.* Interview in Nordlys with Erling Tronvik

02.03.2023: *Orientering om Norsk senter for hodepineforskning og migrene som folkehelseutfordring.* Visit from the Norwegian Parliament's Health Committee. Presentation by Lars Jacob Stovner and Erling Tronvik

10.03.2023: *Nevrologer: Behandlingen mot migrene som hjelper.* Interview on Lommelegen.no with Tore Meisingset og Lise Rystad Øie

11.03.2023: *900.000 er rammet: – Det er en evig kamp.* Interview on TV2 and TV2.no with Erling Tronvik

04.04.2023: *Overlege mener det trengs hodepineteam ved alle nevrologiske avdelinger.* Interview in Dagens medisin with Anne Hege Aamodt

05.04.2023: *Cathrine ble labrotte og fikk livet tilbake.*

Interview on NRK Midt-Nytt and nrk.no with Martin Mykland

07.05.2023: *Advarer om vanlig diagnose: – Altfor lite kontroll.* Interview on TV2.no with Christofer Lundqvist

21.06.2023: *Norsk nevrolog om ny studie: Tror migrene-tablett vil brukes mer i fremtiden.* Interview on HealthTalk.no with Anne Hege Aamodt

30.06.2023: *Nevrolog frykter strenge krav kan gjøre pasienter med migrene enda sykere.* Interview on HealthTalk.no with Anne Hege Aamodt

20.07.2023: *Brukte kunstig intelligens for å lage «værvarsel» for migrene.* Interview on Gemini.no with Anker Stubberud

21.07.2023: *Forskere varsler migrene ved hjelp av kunstig intelligens.* Interview in Dagens medisin with Anker Stubberud

18.08.2023: *Migrene-forsker: – Pasienter har gått flere tiår uten diagnose og behandling.* Interview in Dagens medisin with Tore Meisingset

01.10.2023: *Migreneskolen Podcast, Episode 6: Forskning på migrene.* Podcast interview with Martin Mykland and Tore Meisingset

08.10.2023: *Nye funn om "verdens verste hodepine".* Interview in VG and VG.no (10.10.2023: *Ny forskning på klasehodepine: – En hinsides smerte*) with Bendik Winsvold and Laila Mathisen.

20.10.2023: *Maria fant migrene-behandling som virket: – Man blir jo desperat.* Interview on vg.no with Andrej Netland Khanevski and Erling Tronvik

09.11.2023: *Smertestillende har ingen effekt på Nora-Anastasia: – Migrene set meg ut av spel i dagar av gangen.* Interview on NRK Dagsrevyen and nrk.no with Marte Bjørk

28.11.2023: *Billige migrenemedisiner fungerte like bra som dyre.* Interview on Forskning.no with Marte Bjørk

18.12.2023: *Ny forskning: Dette kan forklare hodepine.* Interview on Nettavisen.no with Erling Tronvik

29.12.2023: *Cheap migraine medications worked just as well as more expensive ones.* Interview on Sciencenorway.no with Marte Bjørk

## **Editors**

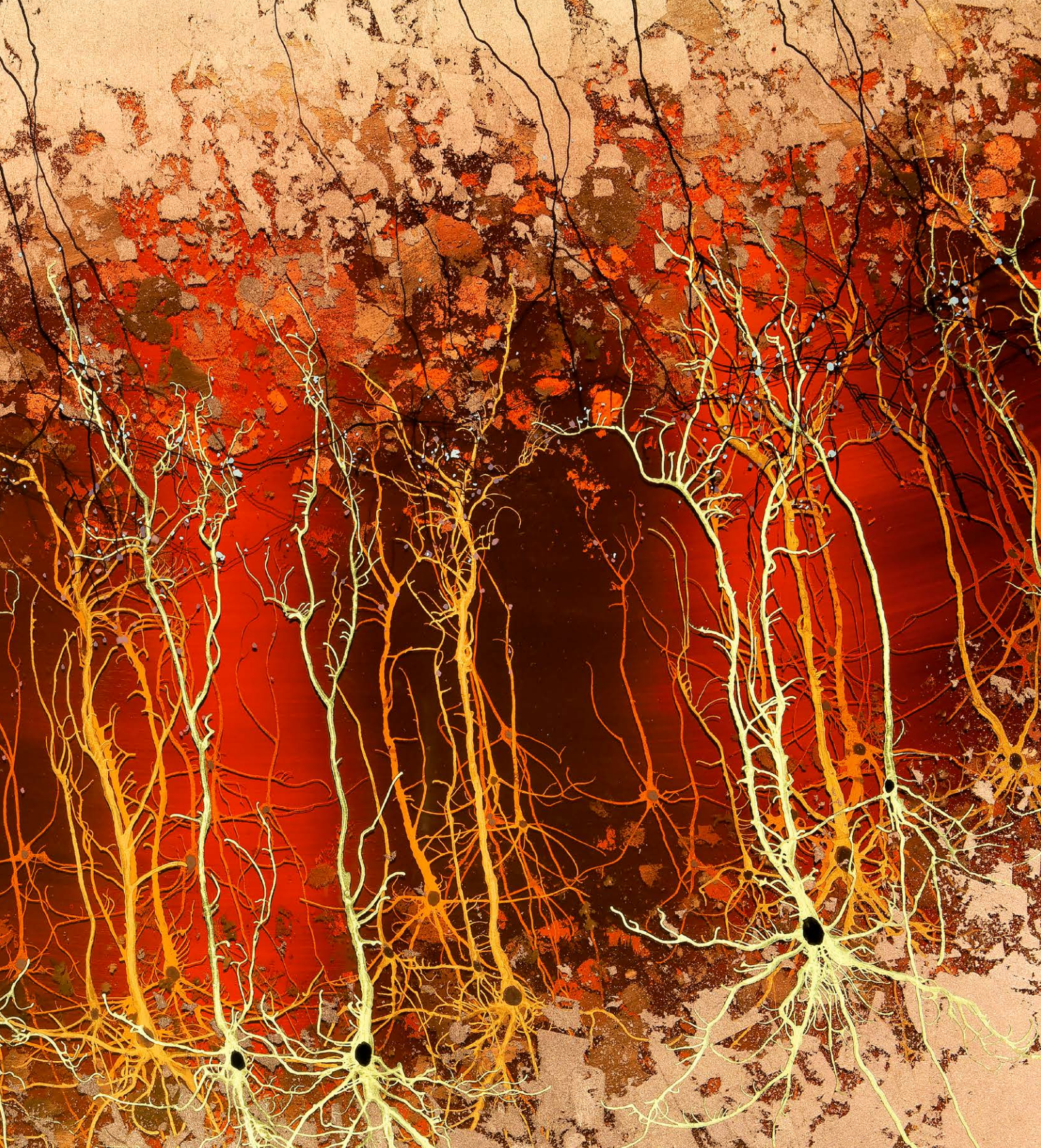
NorHead Management  
and Communication

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## **Cover art**

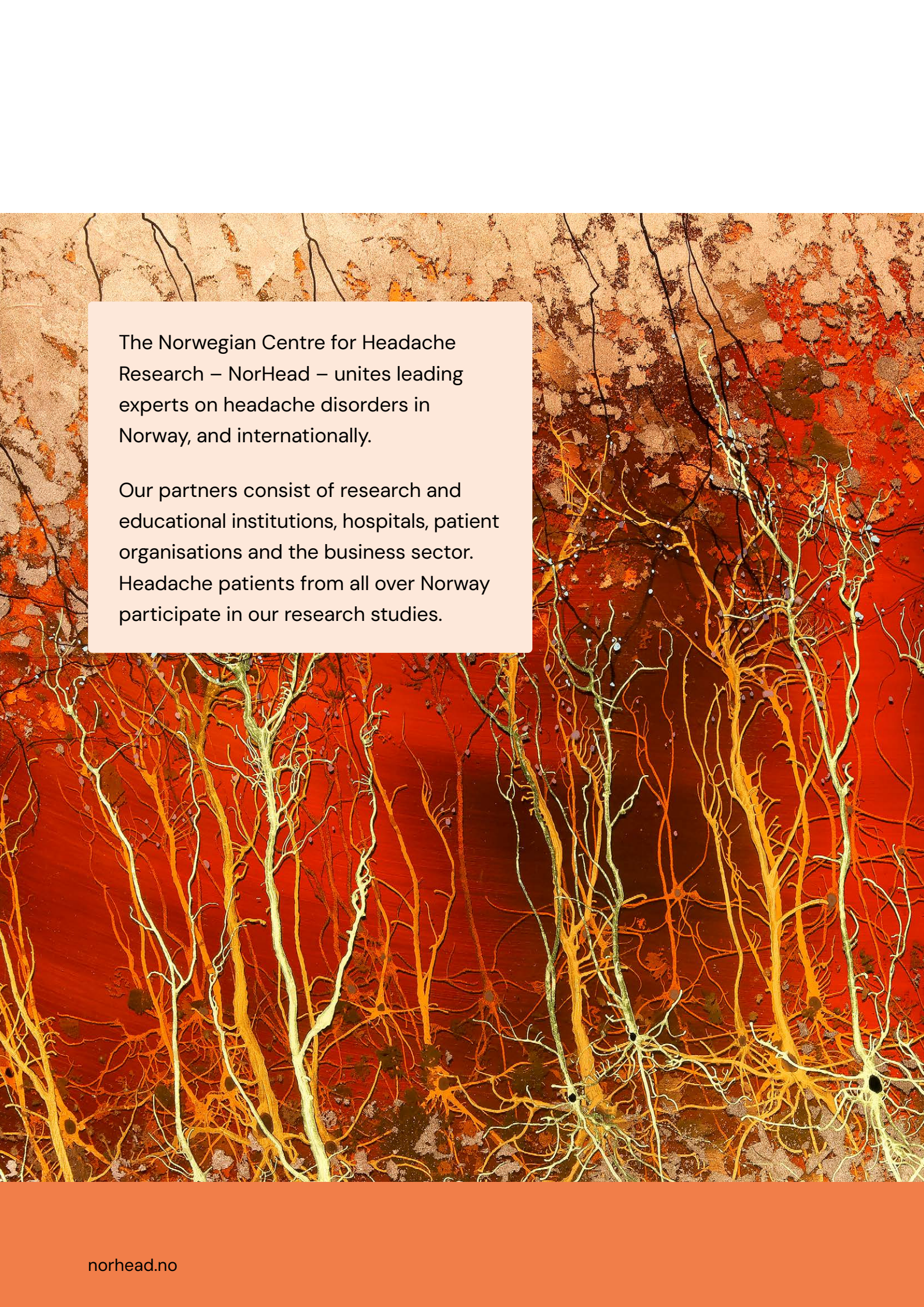
Greg Dunn



**Red and Gold Cortex by Greg A. Dunn**

Dr. Greg Dunn uses his knowledge of neuroscience to create works of fine art that celebrate the brain. His works are dedicated to the neuroscientists, psychologists, psychiatrists, neurologists, and neurosurgeons who explore the brain's beauty, mystery, and anatomy.

→ [gregadunn.com](http://gregadunn.com)



The Norwegian Centre for Headache Research – NorHead – unites leading experts on headache disorders in Norway, and internationally.

Our partners consist of research and educational institutions, hospitals, patient organisations and the business sector. Headache patients from all over Norway participate in our research studies.