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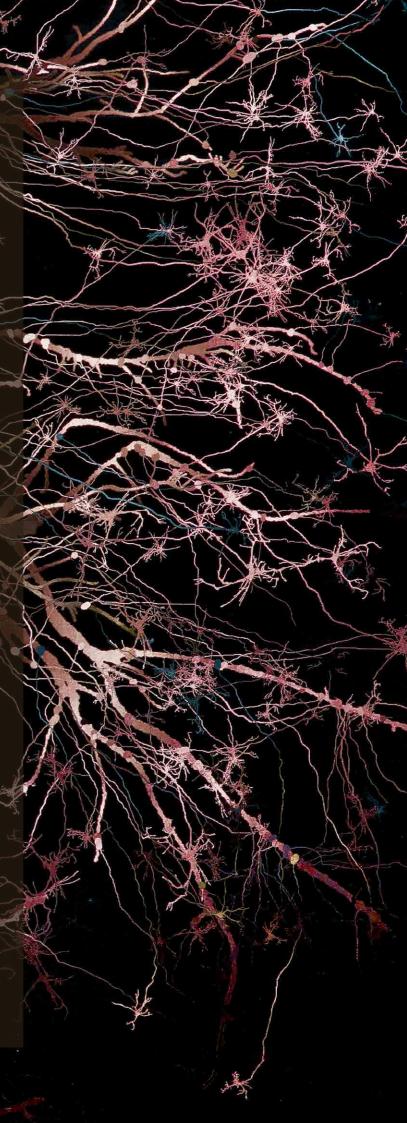
Annual Report 2022

NORWEGIAN CENTRE FOR HEADACHE RESEARCH

National centre for clinical treatment-research and innovation



Centre for Clinical Treatment Research



Letter From The Directors

Dear Readers,

The Norwegian Centre for Headache Research (NorHEAD) officially celebrated its opening on September 1st, 2022. Together with stakeholders, headache researchers and clinicians, along with the presence of international guests, government and university leaders, a unified theme was conveyed: we need to raise awareness on headache disorders and find new treatments. NorHEAD, a national research centre combining Norway's leading headache research communities - is a long-sought after initiative. Expectations are high for NorHEAD's success.

Headache disorders are remarkably common and constitute a major public health issue around the globe. In less than a year, NorHEAD has already begun to respond to this call-to-action, and make some waves in the scientific community of international headache researchers.

The centre and its partners have received significant media attention throughout the fall and winter of 2022. Furthermore, having presented a number of publications and findings at international headache research arenas. In 2022 NorHEAD onboarded new researchers, students and staff and implemented activities for all three main research areas. Within six months after opening NorHEAD secured additional funding in the amount of approximately 30 million NOK for the procurement of new personnel and equipment, along with launching new research studies.

We are thankful for the support of the Norwegian Government and The Research Council of Norway, who align with our vision to combine the efforts of all leading headache institutes in Norway. In collaboration with some of the world's leading experts in headache research and our patient organisations, we will continue to improve understanding, treatment methods and techniques in headache management.

NorHEAD is pleased to share our earliest results in this annual report for 2022.

Sincerely,

Erling Andreas Tronvik Scientific Director

Jaya Syltern Thomlison

Administrative Director

Jake Helone Bjørt

Marte-Helene Bjørk Deputy Director





Minister of Health

Photo: Esten Borgos

"There is no doubt that we need more knowledge and research on headache and brain-health. The Norwegian Centre for Headache Research is the new research centre for clinical treatments, financed by The Research Council of Norway."



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"I want headache sufferers to feel seen, heard, understood, and taken seriously."





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Executive Summary

Headache disorders are among the most common and disabling diseases worldwide. Nonetheless, they have been poorly understood and under-emphasised in government policies. Finding new treatments have not always historically been prioritised, yet now there is new hope for headache patients.

n pursuit of our vision **"Improved quality of life for headache sufferers everywhere"**, NorHEAD will carry out world-leading research and innovation.

The centre brings together the foremost experts across countries and disciplines. In collaboration with our stakeholders and the business community, we generate and disseminate new knowledge to achieve optimal management and treatment for headache disorders.

- NorHEAD performs ground-breaking clinical trials to investigate new methods and medical technology.
- We use health registries and real-world data to develop models for diagnosis and treatment, and to evaluate the societal impact of new treatment options.
- We develop artificial intelligence and machine learning for supporting targeted treatment and clinical practice.

Within the first five months of its existence NorHEAD has already paved the way for realising its mission, and bringing forth new results:

Identity and collaboration

As a national centre covering the whole of Norway, it is our responsibility to build and foster a common identity among participants and partners, and to furthermore strengthen collaboration between different organisations.

- Grand opening ceremony on September 1st, 2022 with prominent international guests, the Research Council of Norway, University top leadership, partners and stakeholders.
- Inclusive partner meetings and presentations from August 30th to September 2nd.
- Launch of brand, and start of strategic visioning process including partners.
- Presence and visibility at Arendalsuka, Norway's largest political gathering.
- Extensive media coverage of our activities and expertise on headache disorders.
- Visit from the Norwegian Minister of Health and Care Services, Ingvild Kjerkol.

Research and innovation

Our research is moving forward at full speed. During our first five months we have received funding for 15 new applications, including the prestigious *Onsager Fellowship Award*. The centre has acquired financing for an additional five positions in 2022, and increased our budget by 50 million NOK from 2023.

- Commenced inclusion of patients within three clinical research studies, and four new clinical studies are planned for 2023.
- Identified a new drug with a probable antimigraine effect through data analysis from the pharmaceutical registry. We will examine the drug in two randomised trials.

- Established our health data space on HUNTcloud and identified over 10,000 variables, linking data from health registries and data sources across Norway.
- Built multidisciplinary research teams spanning several fields, including computer science and AI experts, both in Norway and internationally.
- Received funding for an innovation-PhD focussing on developing prediction models for migraine with advanced machinelearning techniques.
- Developed a plan for innovation and industry collaboration, while identifying 1-2 new business cases.
- Granted funding for the purchase of advanced navigation equipment (1.6 mill NOK) for the development of new treatment methods, as well as funds for a new 7-T MR coil (value approximately 3 mill NOK) for the development of new, innovative protocols for spectroscopy.

Education and recruitment

NorHEAD aims to be a hub for introducing clinicians and students to headache research and attracting new talent to neurology.

- In December 2022, together with NTNU and Norwegian Advisory Unit on Headache, we organised Trondheimskonferansen. 100 health professionals from across Norway were gathered to hear and discuss the latest on headache treatments and research.
- Involved four Masters students in research projects.
- Received applications for International Onsager Fellow.
- Two Post-Doctoral positions commenced.

Stakeholder involvement

A core value for NorHEAD and key to ensuring we are on the right track, is our approach of actively involving stakeholders in our planning, research studies and commercialisation efforts.

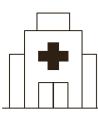
- The patient association, Hodepine Norge, has a 50% position in NorHEAD and is involved in and consulted on new research projects, patient recruitment, dissemination, priorities, and ethics.
- Started plans for a Patient Conference to be held in September 2023.

International collaboration

NorHEAD has a large and continually growing international network. Throughout 2022 partners have attended several international conferences, delegation tours and received visiting from leading headache experts.

- Ongoing clinical studies in Estonia, Germany, England, Spain and Italy.
- Research collaborations with Switzerland, Denmark and USA.
- Researchers from NorHEAD gave presentations at two international headache congresses, MTIS in London, and the European Headache Congress EHF in Venna. As well as several presentations at Nordic headache meetings held in Sweden and Denmark.
- Began working on an EU application for the call "HORIZON-HLTH-2023-TOOL-05-04: Better integration and use of health-related real-world and research data, including genomics, for improved clinical outcomes".
- Organised delegation visits from our international guest professors and scientific advisory board.

Goals and Activities



Research area 1 Clinical trials

NorHEAD will conduct clinical trials of high international standard that include participants from all corners of Norway, leading to evidence-based treatment options for migraine, tension-type headache, medication overuse headache, chronic daily headaches, cluster headache, and trigeminal neuralgia.

This will be a national initiative for high-end, novel, innovative, and ambitious publicly funded university and hospital-initiated trials, and a hub and infrastructure for industry-funded trials.



Research area 2 Exploitation of health registries and real-world data

NorHEAD will use health registry and real-world data in the development of diagnostic and therapeutic models and evaluation of the epidemiological impact.

The aim is to use real-world data to monitor the use and impact of prophylactic medications, acute medications, opioids, etc., for headache disorders. In addition, we aim to identify demographic, symptomatic, or genetic markers delineating the classification of headache diagnoses and responses to different treatments and repurpose medications for headache treatment by screening concomitant use of drugs.



Research area 3

Artificial intelligence and machine learning

NorHEAD will develop and apply artificial intelligence and machine learning methods to increase the understanding and accuracy of diagnosis, the prediction of disease progression, and prediction of effective treatments for primary headaches. This will be a basis for developing e-health tools that support GPs and specialists in treating headache disorders.

Headache: A Public Health Issue



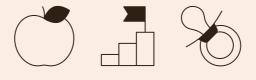
globally

Each day there are one in six persons around the globe who suffer from headaches. Half of these experience migraines



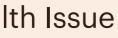
leading cause

Migraines are the leading cause of reduced health in patients under 50



life quality

Headache disorders reduce quality of life and effects education, career path and family life







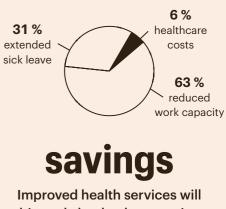


One of 20 will experience a headache ever other day, on average





and society 11 billion NOK annually



ultimately lead to large savings

The Global Campaign Against Headache

Written by Lars Jacob Stovner

The Global Campaign Against Headache was launched in 2004. This initiative, spearheaded by Director Tim Steiner at Imperial College in London, acting on behalf of the International Headache Society, resulted after several years of consultations with the World Health Organisation (WHO) in Geneva.

ars Jacob Stovner, Professor of Neurology at the Norwegian University of Science and Technology in Trondheim was engaged to lead the work on adducing all available evidence about headache prevalence (migraine and tension-type headache in particular) and its subsequent burden. In 2009 Steiner was appointed Adjunct Professor at NTNU, which has since been the academic base of the Campaign.

Lifting the Burden

In order to formalise relations with strategic partners, particularly with the WHO, an organisation, independent of funding from commercial partners, was needed to run the Global Campaign. This was achieved in 2009 by founding Lifting The Burden (LTB), a non-governmental organisation registered in the UK. LTB received official recognition and ties with WHO in 2011. Another important partner has, since 2009, been the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, in Seattle, US. IHME has been running the Global Burden of Disease (GBD) project, in understanding with the WHO.



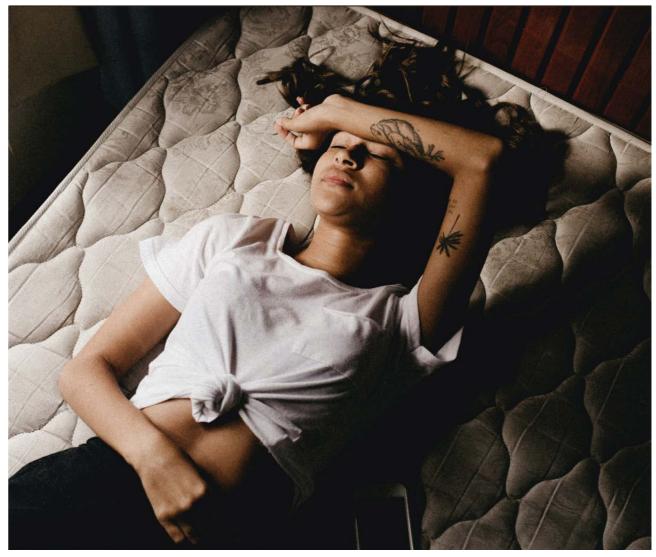
Lars Jacob Stovner Professor Emeritus in Neurology

Through his engagement in international projects and organisations over many years, Professor Lars Jacob Stovner has been central in documenting the prevalence headache disorders globally. His work is an important contribution to the fact that headache disorders now have received much greater attention in public health policy debates in many countries.

There have been three stages in the Global Campaign's activities:

Knowledge for Awareness

Stage 1 focussed on documenting the scope and scale of headache as a problem, globally. This work indicated that Western Europe and North America had far better representation of data than elsewhere. Additionally, no studies had been conducted in countries containing more than half of the world's population. To fill this knowledge gap, the campaign has since been running headache epidemiological studies in many low and middle-income countries all over the world. A standardised methodology and an instrument – the HARDSHIP questionnaire was developed for this purpose in 2011 during an international expert conference held in Trondheim.



• Awareness for Action

In stage 2 the knowledge gathered from the first stage was used to raise awareness - particularly among people experiencing headache, health-care providers and health-policy makers. One key finding and message: headache is not a problem only in industrialised high-income countries - this was an historical misperception. The Atlas of Headache Disorders and Resources in the World 2011 collated data from more than 100 countries and was jointly published by WHO and LTB. Carrying the WHO logo on the cover, the Atlas has become an important tool for advocates of improved headache care towards governments, particularly in poorer countries.

Action for Change

Stage 3 focussed on health-care solutions to mitigate headache. This essentially consisted of a template for structured headache services, primarily based in accessible primary care, and emphasising the need for education on all levels, being adaptable to local needs and resources. This template was supported with scientific, political and economic arguments.

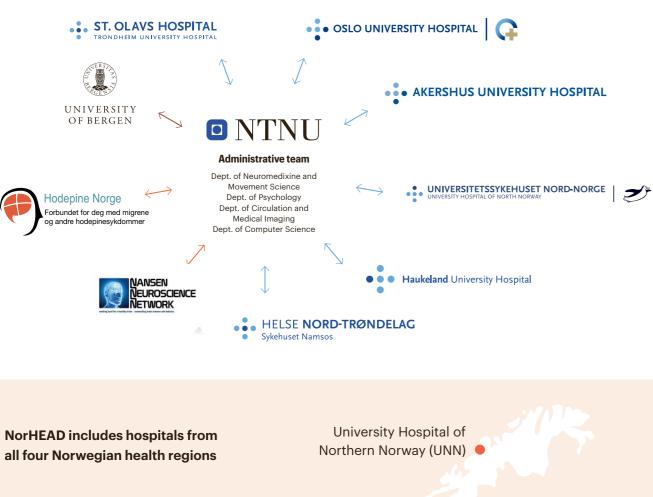
The Global Campaign Against Headache has now been ongoing for nearly two decades. Headache has now been identified as the second most disabling disorder worldwide, and its importance for public health is widely recognized. As a result, more resources have been directed to headache research and to improvement of healthcare systems for headache patients in many countries across the globe.

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Organisation

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 clinical research studies.

Partners





Research Areas and Operations

Overall objective for NorHEAD

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



Operational units

- **OU1**
- **OU2 OU3** Innovation
- Industry collaboration 0U4
- 006 Centre growth
- **OU7**
- **OU8** Centre management

Data colletion and management Clinical care implementation

OU5 Stakeholders, ethics and sustainability

Communication and dissemination

Mitigating Migraine

Highlighting the latest NorHEAD studies to help combat episodic migraines

Written by Emma Steer

ttacks can strike up to 14 days a month. Extreme headaches, nausea, vomiting, and an intolerance to light and sound are common. Migraine affects 800,000 people in Norway and is the leading cause of disability in people under

50. "These headaches affect people in the most productive times of their lives and the impact to individuals and society is huge" explains Erling Tronvik, Senior Consultant, Professor, and Scientific Director of NorHEAD and the National Advisory Unit on Headaches (NKH). "Several times a month, people are unable to care for their family, continue their education, or contribute to their workplace."

For some people, migraines begin in childhood or adolescence, for others they start in adult life. "Some may have a genetic predisposition, meaning that due to their genetics, they are more likely to develop episodic headaches if they are triggered by events in their environment," explains Erling. This could be stress, hormonal changes, sleep deprivation, or even alcohol. But in most cases, an attack comes without an

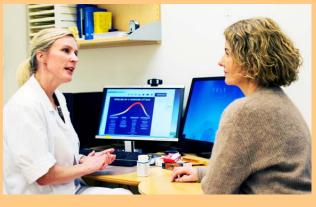


obvious trigger. Despite this complexity, there is support for headache sufferers (see box: Seeking help for headaches?) and research coordinated by NorHEAD aims to expand available treatment options.

BioCer: Trialling a drug-free approach

One headache trigger is stress. BioCer is a drug-free treatment study that tests if episodic migraines can be improved by stress-relieving exercises and self-monitoring of a patient's pulse, blood pressure, temperature, and muscle tension. Wireless biosensors, co-developed by NorHEAD and spin out company Nordic Brain Tech, coupled to the patient's phone allow them to visualise their stress levels. If they sense their stress is increasing, patients are encouraged to do exercises to relax. "By visualising how their body reacts to these exercises through the app in a term we call biofeedback - patients can see their progress in real time," says Erling. An effective drug-free approach can be highly beneficial. Some patients may not respond to available drugs, while others experience intolerable side effects or simply do not wish to use medication for extended periods. "Drug-free treatments have very little chance of side effects," explains Erling, "and if successful, the study could be tested in children and adolescents".

"Drug-free treatments have very little chance of side effects, and if successful, the study could be tested in children and adolescents." "If candesartan is recommended as a first-line treatment, this would be a global game changer for headache sufferers."



CandMig: Repurposing drugs to combat migraines

CandMig tests the ability of candesartan - a drug taken by patients with high blood pressure - to reduce episodic migraines. The idea for the CandMig study was first seeded in Trondheim when a local neurologist was prescribed a candesartan-like drug and discovered a beneficial but unintended side effect: fewer headaches. Smaller studies have shown promising results, but now CandMig takes the research to the next level. The study involves more than 400 patients from nine hospitals in Norway and another in Estonia. "The results from this study could rewrite national and international guidelines, if candesartan is found to be effective against episodic migraines," explains neurologist and researcher Lise Rystad Øie, the study's principal investigator. Candesartan is safe to use, has few side effects, is readily available, and inexpensive. "If candesartan is recommended as a first-line treatment, this would be a global game changer for headache sufferers," says Lise.

MigriNor: Mapping the relationship between drug concentrations and effects

MigriNor is a study that includes patients with migraine that are planning to start or change type of prophylactic drug. By measuring the concentration of the drug in the patient's blood and correlating it with their headache diary, it is hoped that the study will begin to unpick the varied effects and side effects that drugs have on different people. "In this study we hope to clarify which drugs and doses are best for treating migraine in different people," explains Lise.

Empowering patients

Due to their rigorous scientific design, it is difficult to know the studies' success until they are finalised. Until then, those involved want to educate and increase people's awareness of migraines (see box: Seeking help for headaches?). In her role as a senior research nurse at NorHEAD and NKH, Gøril Bruvik Gravdahl, aims to empower people to take control of their headache and do something about their situation. "At NKH, I talk to doctors, guidance counsellors, headache sufferers, and their families on a daily basis," says Gøril. "I want headache sufferers to feel seen, heard, understood, and taken seriously."

"I want headache sufferers to feel seen, heard, understood, and taken seriously."



SEEKING HELP FOR HEADACHES?

Gøril Bruvik Gravdahl is the Senior Research Nurse at NorHEAD and the National Advisory Unit on Headaches (NKH). She encourages all patients who are seeking help to participate in a headache research study. It is an opportunity to meet experts on headaches and educate yourself on your diagnosis. If you don't fulfil the criteria for any of the current studies:

- 1. Start a headache diary on your **mobile phone**. For one month, record the severity and duration of every headache and all of your medication.
- 2. Bring your headache diary to a GP **appointment**. Use the diary to explain your headaches to your doctor. Tell them how many days it interferes with your life.
- 3. Ask your doctor what can improve your symptoms. Acute and preventative treatment options are available. Finding the medication with the biggest impact and most tolerable side effects is important.
- 4. Continue or restart your headache **diary**. This can help you and your doctor see if your treatment is helping. It can also be an alert, in case symptoms get worse.
- 5. Remember, you are not alone. You can get more information from the patient organisation Hodepine Norge, one of the partners in NorHEAD.

STAKEHOLDERS, SUSTAINABILITY AND PATIENT-CENTRED RESEARCH

Written by Laila Bratterud Mathisen, General Secretary, Hodepine Norge

Hodepine Norge is a national, independent, non-profit organisation aiming to ensure that all headache patients receive the right diagnosis, treatment, and support they require.



The organisation works to influence policy on behalf of headache patients' rights and interests in their encounters with Norwegian health services and welfare systems, educational institutions, and in their working life. In order to provide expert counsel, Hodepine Norge employs a Medical Council ensuring that their information about diagnostics and treatment is rooted in evidence-based medicine.

Headache disorders have historically been under-prioritised, underdiagnosed and lacked funding. Hodepine Norge's members will likely find great value in the establishment of NorHEAD and its imminent results. Many members also

PARTICIPATION IN RESEARCH

Henriette Robertsen from the Norwegian city of Tromsø, experiences migraines with aura. Migraine with Aura is a recurring migraine that is affects a patient following, or concurrent to sensory disturbances that include flashes of light, blind spots or altered vision. Henriette participated in the Migraine Aura-app Study, which will provide new insight into how migraine auras are experienced and they various ways they develop and express themselves in different migraine patients.

wish to participate in ongoing research projects. We take great interest in news about headache research studies where results are mentioned.

NorHEAD's Operational Unit 5: Stakeholders, Ethics and Sustainability is led by Hodepine Norge. In 2022 we established a working group including patient representatives, commencing a number of activities including mapping stakeholders, devising plans for patient-recruitment in research, establishing ethical guidelines and advising NorHEAD as a centre. The working group is also planning a patient conference open for the general public, to be held in September, 2023.

"I want to contribute to improved treatments and a better understanding of headaches, and I would recommend anyone who has the opportunity to contribute to the headache cause by taking part in headache studies to do so."

Profiles

Centre Management



Jaya Thomlison Administrative Director NTNU



Erling Tronvik Scientific Director NTNU and St. Olavs Hospital



Marte-Helene Bjørk Deputy Director UiB and Haukeland 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





Board of Directors



Jorunn Helbostad (Chairman) Head of Department NTNU



Torstein Baade Rø Vice Dean of Research NTNU Faculty of Medicine and Health Science



Laila Mathisen Secretary General Hodepine Norge



Gunnar Bovim Executive Advisor NTNU



Eli Renate Grüner Associate Professor University of Bergen



Tom Christian Martinsen Vice Managing Director St. Olavs University Hospital







Peter Goadsby





International Guest Professors



David Dodick Professor of Neurology Mayo Clinic Arizona



Manjit Matharu Professor of Neurology University College London

David Dodick is Professor of Neurology at the Mayo Clinic College of Medicine and a consultant in neurology at the Mayo Clinic, in Scottsdale, Arizona. Here he is the Director of the Headache Program and the Sports Neurology and Concussion Program.

Professor Dodick is a member of the scientific committee of the International Migraine Trust and Chair of the International Headache Academy.

Manjit Matharu is Professor at UCL Queen Square Institute of Neurology in London, where he Academic Lead of the Headache and Facial Pain Group. He is an Honorary Consultant Neurologist and Clinical lead of the Headache group at the National Hospital for Neurology and Neurosurgery, London.

Professor Matharu is a member of the education subcommittee of the International Headache Society.



Arne May Professor of Neurology University of Hamburg

Arne May is Professor of Neurology in the Department of Systems Neuroscience at the University of Hamburg and Head of the Headache Outpatient Clinic and the Facial Outpatient Clinic of the University clinic of Hamburg.

Professor May is currently the Editor of Cephalalgia and a member of the Board of trustees of the International Headache Society.

International Collaboration

NorHEAD has multiple international connections and several ongoing research collaborations across the globe, with continued growth.

W e currently have ongoing clinical research studies with patient inclusions in Estonia, England, Spain, Italy, and Germany. Additionally, we have active research projects with partners in Switzerland, Denmark and the USA.

Awareness-building

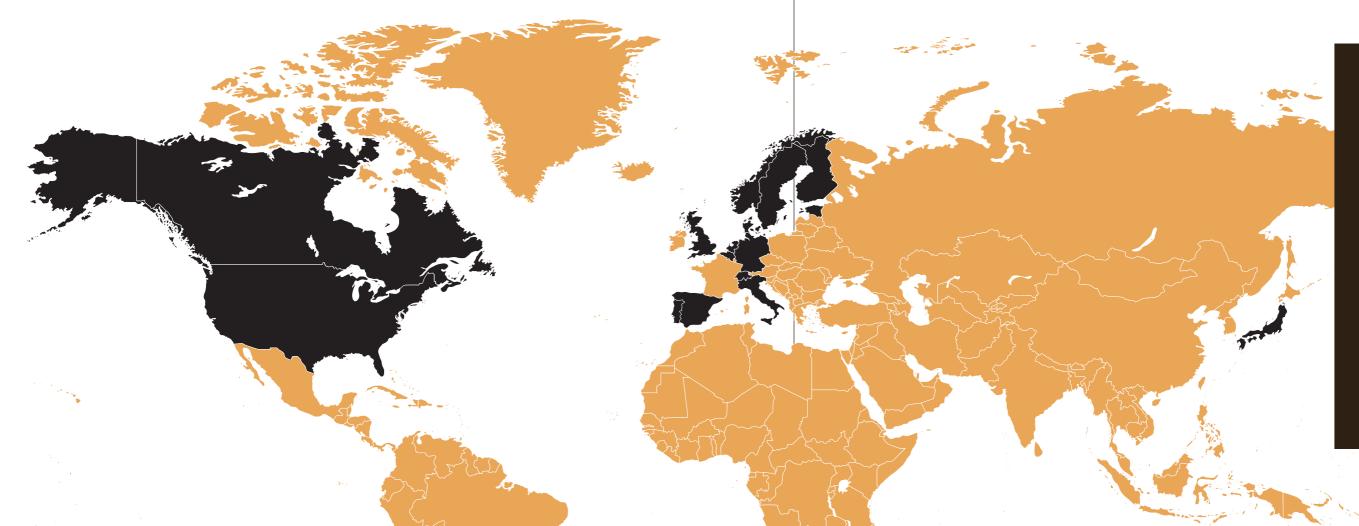
Since its opening NorHEAD researchers have been invited to present at a number of international conferences. Notably, NorHEAD had two keynote presentations at the international migraine conference MTIS in London last September, as well to keynote presentations at the European Headache Congress EHF in Vienna last December. We have also been active in at Nordic meeting spaces and presented NorHEAD at regional headache meetings in Sweden and Denmark.

Guest Professors and Scientific Advisory Board 2022 provided a year of formalising longterm commitments and collaborations from world-renowned headache researchers, professors and advisors. NorHEAD has now signed contracts with three leading actors in headache research as guest professors until 2027: Professor David Dodick from USA – Canada, Dr. Manjit Matharu from England, and Professor Arne May from Germany. These actors contribute with a large international network, knowledge of local business networks and international academic perspectives.

Additionally, NorHEAD organised its first scientific advisory committee meeting comprised of by world-leading researchers and clinicians, for a two-day seminar held in Trondheim, Norway. Scientific advisory board members include Peter Goadsby from Austalia, Simona Sacco from Italy, Messoud Ashina from Demark, and Hans-Chrisoph Diener from Germany. The group is lead by Anne Hege Aamodt from Norway.

Delegation Tours

NorHEAD has participated in a small-scale local application for research funding in Japan. Our spin-off and collaborator Nordic Brain Tech



participated in a Nordic Innovation organised delegation tour to Japan, focussing on emerging health technology. The centre has strategical plans to increase activities in Japan, planning to collaborate on systematic data collection of clinical data.

EU application

NorHEAD submitted a letter of intent for applying for the EU project: "HORIZON-HLTH-2023-TOOL-05-04: Better integration and use of health-related real-world and research data, including genomics, for improved clinical outcomes". The application work and consolidation of partners continues in 2023. 19 partners from 9 different countries are participating in this consortium.

INTERNATIONAL PARTNERS

- USA / Canada
- England
- Netherlands
- Belgium
- Germany
- Spain
- Portugal
- Switzerland
- Italy
- Denmark
- Sweden
- Finland
- Estonia
- Norway
- Japan

Al & Machine Learning in Life Sciences

Artificial intelligence & machine learning have become increasingly relevant tools in all sectors of society, and almost omniscient in their presence. Over the last 46 years, development of new technologies incorporating these methodologies has moved at an incredible pace. Today, Al generators are popping up everywhere online, with a lot of them being free to demo and providing prospects of saving time. Applications can be used for instance, to make intricate art, to analyse a problem, or even automate a letter in your own voice. Their applicability in life sciences and health technology has indeed raised some questions connecting to clinical-care, however the offer of support for diagnosis and treatment is promising.

The Department of Computer and Information Science at NTNU has been an active partner in NorHEAD prior to, and since its opening on September 1st, 2022.



The Gartner report forecasts that 50 % of all future medicines will be developed based on AI.



Written by David O. Skarbø





Heri Ramampiaro Research Leader and Head of Department

Helge Langseth Professor and Project Leader

Can you tell us about yourselves, and your connection to NorHEAD?

Heri: I am Director of the Norwegian Open AI Lab (NAIL) and Head of the Department and Professor in the Department of Computer Science at NTNU. I have been associated with NorHEAD since we first delivered our application. Initially through our common project MiHEAD Machine Learning in Headache Research, and then later NorHEAD, as a National research centre.

Helge: I am a Professor in the Group of Data and Artificial Intelligence at the Department of Computer and Information Science at NTNU. Currently I am affiliated with the Norwegian Research Center for AI Innovation (NorwAI) and the Norwegian Open AI Lab. I work with machine learning. I am a Researcher in NorHEAD and mentor for the Post-doc positions within Computer Science. They wanted to expand our collaboration, so I joined.

What significance does the growing interest in AI & machine learning applied in the health sector have for you as researchers?

Heri: There is great significance; I am very passionate about technology gaining ground in

with Heri Ramampiaro and Helge Langseth

society. Research on headache disorders is very valuable in itself. The negative effects from headache disorders are a huge cost to society, and a huge public health problem. Being able to contribute with research and technology that can help with this problem - through implementing treatments and journal systems that work for bigger groups - is great. For those of us that work with AI & machine learning, it is important to be able to apply the technology on real issues, and further develop the process. It feels very meaningful.

Helge: For me, it is exciting to be part of serious cases using the technology, in an area where it means something if you succeed, or not. This is an area where it is important that things work as they should. You have to know what you are doing and make systems that let you know when things are not as they should. It provides different types of challenges, as opposed to a lot of the 'play' stuff with AI & Machine learning. Like for instance, teaching it to recognise cats, or producing pictures of underwater astronauts.

What are your thoughts on cross-disciplinary collaboration between departments?

Helge & Heri: We think that the health-people are an impressive bunch. They are very competent, show great interest in explaining how things work to us and they are also interested in understanding what we are doing. It's only positive. Some previous projects between different departments have had some struggles.

NorHEAD has some people who are amazing within the field of computer sciences, who already have ideas about how they want to utilise us.

MiHEAD's Project Leader, Anker Stubberud, is a genius. He is a bridge-builder – doctor and computer-guy. We need more people like him who are interested and knowledgeable. He acts like a connector and can communicate across the disciplines.

Why should we use AI & machine learning in research and development on headache disorders?

Heri: Machine learning has shown us that it can be used in many different ways, fields and areas. Gartner recently published a report forecasting that 50% of all future development of medicine will be based on AI.

For NorHEAD, learnings from previous experiences together with the sheer amount of available health data, will make it easier to provide treatments. For example, people react differently to different medications – and through machine learning we can better determine what works for them personally, while considering all their variables. We can use it to determine diagnosis and offer customised treatments.

Helge: We are good at collecting data from the healthcare sector in Norway. There are a lot of things here that can be analysed using machine learning techniques, which can help us to better understand the issues at hand. NorHEAD's Anker Stubberud has been working on how to design treatments for patients with headache disorders. If you can implement machine learning to provide a better treatment plan in a shorter time than what doctors are able to, this is a good thing. We are also currently working to understand the genetics behind migraines. Doctors have questions related to this, which they may be able to answer through data analysis.

How is AI & machine learning applied in NorHEAD?

Heri: We are trying to standardise the collection, identification and analysis of data and figure out which machine learning procedure will work on this type of data. This data may originate from patients directly, or a headache journal, but this is still a bit in the future.

Helge: One of the things we are working on is using the data from the longevity study Health Survey of Nord Trøndelag to try to and understand what the triggers are for headache disorders, genetically. We also have another idea about personalised suggestions for treatment. More ideas are being considered, but I think that these two are going to be the first projects.

What is the future for AI & machine learning in the healthcare sector?

Heri: The development of medication. An article was published not too long ago about an AI that could identify and generate 3D representations of proteins. It could be the scientific break-through or invention of the century. This can be used to develop new vaccines much faster, and identify illnesses faster.

The Norwegian health sector is generally concerned about its dwindling workforce, and when that's the case, you need to make better use of your available resources. Here, AI can support decision-making. I know that AI has been used to optimise staff schedules; better tools for the employees to optimise resource allocation.

Al is going to impact everything from treatments and rota systems, to the development of new medication and vaccines. Al was used for "We are good at collecting data from the healthcare sector in Norway. There are a lot of things here that can be analysed using machine learning techniques, which can help us to better understand the issues at hand.

development of the vaccines during the pandemic. AI will have a huge significance in the health sector moving forward.

Helge: I think that AI systems are already capable of doing picture analysis on a level that is superior to what doctors can do. With that, you can reduce the burden on doctors, without a loss in quality. The sky's the limit. Though realistically, it is about making systems that can assist in doing routine work. Limited input and limited output. Here's the x-ray – is there a problem here? AI can assist with things that are easy to automate so you don't have to do it yourself. There is real interest for this type of stuff, that is doable and solvable, without much risk to the patient.

An underlying problem in this field is that doctors are educated to do what they do and the risk of something going wrong is a part of the business. It's a different scenario of 'who is to blame?' if it is a computer that makes the mistake. The AI train is running at break-neck speed (and then some), while the authorities are still standing at the station. There are going to be some challenges. It is solvable, but not solved yet.



MIHEAD

MI-HEAD (Machine Intelligence in Headaches) is a large-scale interdisciplinary research project with an overall aim to use machine learning to improve our understanding of, and optimise the treatment of primary headache disorders. Using various large, and rich data sources such as registry data, data from clinical trials, genomic data and prospective self-reported mHealth data, we aim to develop data-driven models to guide diagnostics, disease trajectories and prediction of treatment effects. We wish to develop models that can serve as a basis for clinical decision support tools and precision medicine. MI-HEAD is a part of RA3, one of the main research areas of NorHEAD and will constitute an important methodological framework for many of the research activities within the Centre, as well as collaboration with our international partners.

Diversity & Inclusion

Diversity and inclusion are two interconnected concepts that we integrate through set values and practices in both our scientific work, and as part of our organisation in NorHEAD.

n one respect, we actively reflect upon the representation of lived experience, through gender, ethic and cultural backgrounds, age, and other defining factors. Meanwhile, we actively work to ensure that these representations and perspectives are thoroughly integrated and intentional in our attitudes and work, and present in our plans and activities.

This is not only important for our culture, but to guide our approach and interaction with patients, stakeholders and broader society.

NorHEAD has a diverse working group, with researchers, doctors and staff originating from approximately twenty different countries over four continents. Our employees and collaborators represent perspectives from four generations, ranging from 20 to 75 years of age. NorHEAD combined, has an above-average representation of women in decision-making positions, through leadership roles and as leading researchers.

Gender perspectives, and the awareness of how various types of headaches affect men and women differently, are important considerations in both research and dissemination. In addition to working on highly international projects and global collaborations, NorHEAD has identified a number of initiatives to increase diversity and inclusion in our effort.

Together with our Ethics and Sustainability working group, our Clinical Care working group and our Communication and Centre Management working group, we are creating a framework for diversity and inclusion in strategic plans, and research activities.

Recruiting patients, researchers, students, and partners across gender, ethnicity, orientation and background, is an important aim for NorHEAD. In 2022 we:

- Started a funding application for a large research project focussing on women and migraine.
- Commenced activities around the Women in Migraine Task Force.
- Began a written plan to secure that inclusion of ethnicity and gender perspectives are present in our scientific activities.
- Executed international hiring for new Post-docs and Onsager Fellowship.

There is a good gender balance in the centre management, Executive Board and Scientific Advisory Board. Four out of five top leadership positions are held by women. In our work packages, four out of seven Operational Unit Managers (OUs) are women and two men and one woman are Research Area Leaders. Leadership positions are of both Norwegian and Non-Norwegian heritage. There are six women and four men in the Centre's administration.

NorHEAD includes many foreign employees who contribute to diversity and internationalisation. We have personnel with backgrounds from Serbia, Slovenia, Lithuania, Estonia, Germany, Spain, Italy, Madagascar, Kenya, India, Pakistan, Nepal, Japan, Great Britain, Canada and USA. Both Norwegian and English are used as working languages.

Industry Partnerships and Innovation

NorHEAD has a responsibility to harness the innovative potential of research projects and facilitate collaboration with Norwegian Technology Transfer Offices and industry partners to secure intellectual property generation of NorHEAD. Systematic IP assessments will be performed every second year.

A dditionally, NorHEAD works with national programs including NorTrials and Innovation Norway-funded business clusters, arenas and events to stimulate research and development avenues.

Every research project will be analysed for innovation potentials and identifiable intellectual assets. An example of this could be whether new sensors or e-health tools should be further developed to give added-value to the project, and whether there are opportunities for patenting and establishing spin-off companies.

NorHEAD and industry partners will be actively linked through a series of business meeting



and idea competitions, in the form of a living lab model. The goal is to create a one-stop-shop for industry and med-tech companies/partners to access potential partners for clinical trials and experiment with new pre-seed and seed ideas. Additionally ensuring that findings, results and potential business models are viewed through a multidisciplinary lens including innovation and business partners, early in the process.

This model will work in partnership with existing networks including Nansen Neuroscience Network, as well as political channels, with an aim to promote the development of new diagnostic tools and treatments for brain diseases.

hoto: Alexander Jocc

New and Innovative Treatments

Deep in our facial structures there is a tiny bundle of nerves, the *ganglion sphenopalatinum*. For many sufferers of extreme headaches, getting help to give these nerves a break may be key to a better life.

Written by Kristina Jones

he sphenopalatine ganglion – SPG for short – is central to different headache conditions, such as the extremely painful cluster headache and the highly prevalent migraine. Paralyzing SPG with a neuro toxin can reduce attacks and

make these conditions easier to bear. The challenge is, however, to get the toxin injected in this nerve bundle, which is located

A new medical innovation sees the light of day

4-5 centimeters within the facial skeleton.

In the intersection between clinical treatment and research at St. Olav's Hospital and NTNU in Trondheim, a solution to the problem came to life. A new medical instrument was developed in a joint effort between neurologists, neurosurgeons, engineers and entrepreneurs.

"Through years of prototyping, we came up with the Multiguide", says Neurosurgeon and Associate Professor Daniel Fossum Bratbak. He is one of the innovators behind the instrument, together with Professor in Neurology, Erling Tronvik.

"With the Multiguide, and the help of an advanced surgical navigation system, we can make injections with tremendous precision", Bratbak explains.

Efficient treatment

The Multiguide makes it possible to give safe and regular treatments, where SPG is blocked with botulinum toxin. The toxin works for about 3 months after injection.

"The injections are minimally invasive, and do not require long preparations, so they can be conducted in an outpatient office. The patient is awake during the procedure, only given local anesthetics", says Associate Professor in Neurology, Tore Wergeland Meisingset.

"With the Multiguide, and the help of an advanced surgical navigation system, we can make injections with tremendous precision."



An image gudied navigation system maps the patient's anatomy for precise injections.

Current Research on SPG Block

Meisingset is currently leading two clinical trials on SPG block; BASIC and MiBlock. "In the BASIC-study we are investigating how blocking SPG can prevent attacks in patients with chronic cluster headache. In MiBlock we are examining the same for patients with chronic migraine," Meisingset says.

"There is an enormous need for better treatment options for patients facing so much intense pain due to their headache disorders. This makes it immensely motivating working to help this group of patients", he adds.



Tore Wergeland Meisingset Associate Professor in Neurology Photo: Jarle Hvidsten

EXTREME HEADACHE CONDITIONS

Cluster headache is considered one of the most painful conditions known to humans, with an intensity rated stronger than any other pain conditions examined, such as labor pain or kidney stones.

It is characterized by an extreme pain around the eye and forehead.

Attacks last between 15 minutes and 3 hours, up to 8 times a day.

The attacks often come in periods, or clusters – thereby the name. Symptomfree periods in between are common before the headaches start again.

Chronic migraine is defined as having at least 15 headache days a month, with at least 8 days of migraine, for more than 3 months.

Migraine symptoms include pulsating head pain on one or both sides, nausea and vomiting, and sensitivity for light and sounds.

Most people with chronic migraine have had a gradual worsening from a less frequent headache pattern.



ARENDALSUKA 2022

NorHEAD's management and central researchers were fully present at Arendalsuka 2022, the largest annual political gathering in Norway. At our stand and participating at various events, we spoke about headache as a public health issue, research and treatment, and presented considerations and needs to politicians and journalists, university leadership, partners, and the general public.





01.09





GRAND OPENING CEREMONY

NTNU's Rector Anne Borg opened NorHEAD together with the Executive Director of the Research Council of Norway, Anne Kjersti Fahlvik. "We have now received the largest grant ever for headache research. It offers wonderful opportunities, but also commitments. Headaches have great societal and personal consequences. Both Society at large and NTNU expect high-quality research, with results that benefit the patients", said Anne Borg in her opening speech.

VISIT FROM INGVILD KJERKOL

Norwegian Minister of Health Ingvild Kjerkol visited our clinical treatment research and innovation lab at St. Olav's Hospital, for a presentation of NorHEAD. The Minister was provided a demonstration of Multiguide, a medical instrument developed at NTNU and St. Olav's that treats cluster headaches.



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TRONDHEIMSKONFERANSEN 2022

Together with NTNU and Norwegian Advisory Unit on Headache, we organised Trondheimskonferansen. 100 health professionals from across Norway were gathered to hear and discuss the latest on headache treatments and research.

The Role of Citizen Response in Research and Trends

Surveys have always been an integral tool in research, furthering scientific knowledge. With increased means of initiating direct dialogue with the general public, it opens up possibilities for incredible crowdsourcing of information.

Written by Már Másson Maack

ne recent example of this is PopHEAD, the first fully digital research to the general population in Norway — and the country's biggest population survey on headaches to date. In January this year, 31,500 people living in Vestfold and Telemark received an invitation to take part in the survey through HelseNorge.

"We wanted to know how common headache disorders are in the general population, especially migraine and tension-type headache, and the burden of it." "We wanted to know how common headache disorders are in the general population, especially migraine and tension-type headache, and the burden of it," says Bendik Winswold a Senior Researcher at Oslo University Hospital. People were asked how often they experienced headaches and how it affected their work and social lives. This was later followed up with 500 interviews conducted by consultant neurologists. The specialists provided the participants with diagnoses which in turn informed the study that the data sources from the responses were indeed reliable.



Bendik Winswold Senior Researcher Photo: Jarle Hvidsten

"I'm very proud we actually put in a week of proper PR work right before the survey went out."

"This method was especially enlightening for tension-type headaches, which often go under the radar. They are so common that it's hard to map the true impact they have, which has resulted in less research on them," says Winswold.

A key part of getting this incredible 'crowdsourced' overview was getting the public's attention beforehand. "I'm very proud we actually put in a week of proper PR work right before the survey went out," says Maria Argren, neurologist and researcher working on PopHEAD. Argren appeared in local newspapers, on the news, and on TV to promote the importance of the research. "It's hard to provide an incentive for a 'cold call' survey, especially when we're also looking for people that do not suffer from headaches at all, so you have to make people proud to have contributed," Argren explains. And it appears the public was engaged by this. Participation was more than expected and many of the phone interviewees mentioned they had heard about it through the media.

Having the public take a more active role in research can be insightful, as it can provide more unbiased data. However, it will of course continue to respond to trends the general public might not notice. For example, Argren is part of a study looking into headaches following COVID-19 vaccinations called CovaxHEAD which is led by senior researcher and neurologist Anne Hege Aamodt. "The idea came during the winter of 2021, as we received a lot of cases in the clinic describing severe new-onset headaches following vaccinations," Aamodt explains. "We had to provide them with advanced treatment



Researcher Maria Argren and the PopHEAD survey was featured in a number news channels. Here in Vest-Telemark blad.

and report on it, which eventually turned into this prospective observational study where we will primarily describe the phenotype of these headaches and the treatment responses." Over 70 patients around Norway are a part of the study and the hope is to shed light on the pathophysiology of these headaches.

> "The idea came during the winter of 2021, as we received a lot of cases in the clinic describing severe new-onset headaches following vaccinations."



Anne Hege Amodt Senior Researcher and Neurologist

Key Researchers and Staff

Trond Sand

Morten Engstrøm

Associate Professor /

Professor / Consultant Neurologist

NTNU Department of Neuromedicine and St. Olavs Hospital

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Senior Consultant / Senior Researacher **Elisabeth Gjefsen**

Consultant Neurologist Tone Hakvåg Rønning **Research Nurse**

Helle Skalleberg **Research Nurse Helene Engstrand**

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Namsos Hospital

Kristina Devik Consultant Neurologist / PhD Candidate (NTNU)

Hodepine Norge

Laila Mathisen General Secretary

Nansen Neuroscience Network

Bjarte Reve General Manager

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Passing the Torch

To ensure the future of studies on headaches and migraines, it is incredibly important we keep attracting new people. We want the world's brightest minds to work on finding solutions within this vast and exciting field of research. To NorHEAD, this means encouraging healthcare professionals who are faced with a varied job market, to dig deeper into headache research. We need to help engaged nurses and young neurologists get involved. We also need to convince people with technical skills and expertise in fields like data and computer science to explore further research avenues and build dynamic cross-disciplinary environments where people can pitch fresh ideas, and approach the problem from different angles.

Written by Már Másson Maack



eet PhD Candiate Kristina Devik, a senior neurologist at Namsos Hospital and a researcher at NorHEAD. Before beginning her

current research, Devik worked for over a decade as a full-time clinical neurologist after completing her specialisation. She was looking to explore new perspectives in her clinical work, so she turned to new attaining new knowledge and now divides her time evenly between patient care and research. Devik is exploring new opportunities for headache treatments. Her first study is called BACT – exploring the possibility of using Botulinum toxin to treat tension-type headaches. This study is conducted in Namsos, where one group of patients is injected with botulinum toxin using the 'sutures protocol' developed for migraine treatment, while the control group receives a saline solution. For Devik, it is interesting to focus on tension-type headaches as they are somewhat



"I'm a practical researcher who wants to help people directly, so I hope we find a way to do so through BACT."

underrepresented in the field, compared to migraine research, despite how many people suffer from them. Devik always found it difficult when she met patients with tension-type headaches before beginning the study as there was no good medication or treatment to offer them. "I'm a practical researcher who wants to help people directly, so I hope we find a way to do so through BACT" says Devik. For her next study, Devik will look into app-based biofeedback treatment techniques.

Financial Overview

Funding	Amount
The Research Council	2 232
The Host Institution (NTNU)	881
Research Partners*	1 927
Other Partners**	21
Other public funding***	1 167
Total funding	6 228

ADDITIONAL FUNDING SINCE START UP

NorHEAD has currently secured 30 MNOK in additional funding from other external and internal sources such as The Liaison Comittee for Education, Research and Innovation in Central Norway, The joint research committee (FFU) between St. Olavs Hospital HF and the Faculty of Medicine and Health Sciences, Eurostars, Onsager fellowship NTNU, internal Phd fellowship, investments funds, donations to research.

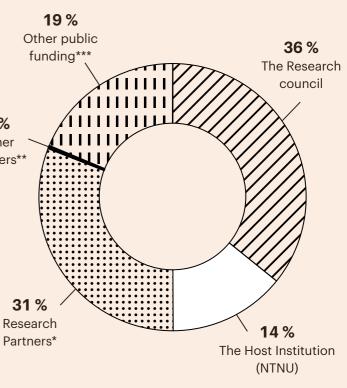
0% Other Partners**

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

** Other Partners: Hodepine Norge, Nansen Neuroscience Network

*** Cash contribution from The Liaison Comittee 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

Costs	Amount
The Host Institution (NTNU)	3 112
Research Partners*	2 913
Other Partners**	203
Total funding	6 228



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Sleep restriction alters cortical inhibition in migraine: A transcranial magnetic stimulation study

Martin Syvertsen Mykland, Martin Uglem, Jan Petter Neverdahl, Lise Rystad Øie, Tore Wergeland Meisingset, David W. Dodick c, Erling Tronvik, Morten Engstrøm, Trond Sand and Petter Moe Omland *Clinical Neurophysiology*

The bidirectional temporal relationship between headache and affective disorders: longitudinal data from the HUNT studies Samita Giri, Erling Andreas Tronvik and Knut

Hagen The Journal if Headache and Pain

The impact of topiramate, botulinum toxin type A, and CGRP-antibodies on medication overuse headache in patients with chronic migraine: A protocol for systematic review and meta-analysis Samita Giri, Erling Andreas Tronvik, Mattias Linde

and Knut Hagen Cephalalgia Reports

FollowTheSutures: Piloting a new way to administer onabotulinumtoxinA for chronic migraine Lars Jacob Stovner, Knut Hagen, Erling Andreas Tronvik, Gøril Bruvik Gravdahl, Rami Burstein and David W. Dodick

Cephalalgia

Epidemiology of diagnosed cluster headache in Norway

Joan Crespi Vidal, Sasha Gulati, Øyvind Salvesen, Daniel Fossum Bratbak, David W Dodick, Manjit Singh Matharu and Erling Andras Tronvik **Cephalalgia Reports** Machine prescription for chronic migraine Anker Stubberud, Robert Gray, Erling Andreas Tronvik, Manjit Singh Matharu and Parashkev Nachev Brain Communications

Surgery for degenerative cervical myelopathy

in patients with rheumatoid arthritis and ankylosing spondylitis: a nationwide registrybased study with patient-reported outcomes Siril Therese Holmberg, Agnete Malm Gulati, Tonje Okkenhaug Johansen, Øyvind Salvesen-Vetle Vangen-Lønne, Tore Solberg, Erling A. Tronvik, Øystein P. Nygaard and Sasha Gulati Acta Neurochirurgica

Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial Sozaburo Hara, Hege Andresen, Ole Solheim, Sven Magnus Carlsen, Terje Sundstrøm, Greger Lønne, Vetle Vangen Lønne, Kristin Taraldsen, Erling Andreas Tronvik, Lise Rystad Øie, Agnete Malm Gulati, Lisa Millgård Sagberg, Asgeir Store Jakola, Tore Solberg, Øystein Petter Nygaard, Øyvind Olav Salvesen and Sasha Gulati Journal of the American Medical Association (JAMA)

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01.11.2022: NorHEAD – En nasjonal satsing på hodepinesykdommer. A set of interviews with reserachers and management at NorHEAD, in the magazine "Migrene". Contributors: Erling Andreas Tronvik, Lise Rystad Øie, Tore Wergeland Meisingset, Gøril Bruvik Gravdahl and Jaya Syltern Thomlison

12.10.2022: Hele familien har samme lidelse

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24.09.2022: Hjernehelse: Seaside chat NorHEAD and Kavli. Popular science presentation, discussions and public interactions at Hyfer – NTNUs knowledge festival. Contributors: Erling Andreas Tronvik, Alexander Olsen, Cathrine Ro Heuch and Jaya Syltern Thomlison 07.09.2022: Et alvorlig hodebry for hele

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Lecture: Boosting Research: New Norwegian Headache Research Center. Neuroscience Expert Meeting, Stockholm, September 16-17, 2022 Organiser: Abbvie Contributor: Erling Andreas Tronvik Academic lecture: Injecting botulinum toxin towards the sphenopalatine ganglion in persistent idiopathic facial pain. Migraine Trust International Symposium (MTIS), London, September 8-11, 2022

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Academic lecture: Machine prescription in chronic migraine. Migraine Trust International Symposium (MTIS), London, September 8-11, 2022 Organiser: International Headache Society (IHS) Contributors: Anker Stubberud, Erling Andreas Tronvik, Manjit Matharu and Parashkev Nachev Lecture: NorHEAD - a new headache research center. Summary Meeting - MTIS 2022, London, September 10, 2022.

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Design and Layout Tank Design Cover art description

ACTION POTENTIAL BY GREG DUNN AND BRIAN EDWARDS

The triggering of an action potential is one of the foundational principles on which the brain operates. Action Potential is an animated microetching that simulates how a neuron receives and integrates incoming signals from connected neurons to trigger an action potential. Incoming action potentials from the small neurons hit the dendrites of the large neuron while their collective input builds through the large neuron's dendrites. When these signals simultaneously reach the cell body, they trigger the large neuron to fire its own action potential.

www.gregadunn.com

