NORMENT
Norwegian Centre for
Mental Disorders Research

NORMENT Final Report
2013 - 2023

UNIVERSITY OF OSLO

UNIVERSITY OF BERGEN

Oslo University Hospital

Haukeland University Hospital

Norwegian Centre of Excellence
The Research Council of Norway

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Leader's Comments

It was an exciting moment when we received the news from the Research Council of Norway that we had become a new Centre of Excellence in mental illness, NORMENT. Now, 10 years later, it is time to start planning the next phase, building on the achievements and progress made during this decade of frontline research supported by the NORMENT Centre infrastructure.

After running a large well-organized research centre with over 200 people involved, and with a strong support team and coordination of activities, we recognize the tremendous opportunities the Centre has provided. At the same time, we have invested time and resources in developing NORMENT into an efficient research organization and most importantly, a coherent research environment where people feel they belong and can work together to generate new knowledge and synergy from teamwork.

From day one, NORMENT had ambitious scientific goals, focusing on understanding the underlying mechanisms of severe mental disorders. Our interdisciplinary approach and 10 years' commitment to allow long-term projects have been critical in our highly successful scientific endeavors, with a series of novel discoveries.

Psychotic disorders are a major challenge for the persons affected, their families and society, with large unmet needs and lack of knowledge. The NORMENT Centre has been successful in unleashing the potential by bringing leading Norwegian research groups together in an integrated, collaborative research environment. This has enabled us to identify new causative factors and determinants of clinical outcome in bipolar disorder and schizophrenia, through synergy achieved by tightly linking clinical and basic researchers, clinical studies, health registries and strong international partners. Several of our findings have contributed to better mental health care services, as well as new understanding of disease mechanisms, with large societal impact. The long-term impact will be secured by the establishment of the NORMENT 2050 program, in which our database and biobank material will be stored for future research beyond the Centre period.

An important aspect of a successful research centre is an efficient research infrastructure and support team. We have used a significant amount of the Centre of Excellence funding to develop and maintain Core Resource Units that have supported all aspects of the research activities, from clinical assessments, cognitive testing, and clinical trials, to biobanking, stem cell laboratory, and big data analytics. A good example is our analytical infrastructure on the TSD server, on which we now have 2 petabytes of data. Further, our strong focus on eHealth and digital tools has enabled us to transform into a modern research environment. Our eNORMENT infrastructure has secured our web-based research projects, and the development of digital arenas was critical during the COVID shutdown, where we managed to swiftly move most of our non-clinical activities to the digital space. This approach has also been instrumental in securing strong integration between activities in Oslo and Bergen, and is extensively used to facilitate our international collaborations, where Zoom and Teams have been part of our daily activities.

We are also proud of the development of a strong and active user group, through our User Council and Representatives. They have found their role as consultants in project development, user perspective on ongoing research and involvement in dissemination activities, with impressive results. Another critical factor for our success has been the young researchers with their enthusiasm, new ideas and continuous work to improve our research program.

NORMENT has delivered a series of excellent scientific findings, illustrated by the long list of publications and awards. In addition, building on the infrastructure and new ideas, our scientists have obtained a high number of grants, from international funders (EU, ERC, NIH, Wellcome Trust, NordForsk, Swedish RC, Novo Nordisk Foundation) as well as the Research Council and other Norwegian funding agencies. Thus, we are now in the position to take the next step and use the NORMENT as a foundation for new research projects and programs.

Finally, I will thank all NORMENT staff for their hard work during these 10 years, and I am impressed with your accomplishments. It has been a pleasure and privilege to be the Director of the NORMENT Centre with such outstanding colleagues, and I am looking forward to all the new exciting projects we will conduct in the coming years, building on what we have learned from NORMENT.

Ole A. Andreassen
Centre Director


Proliferation
Migration
Arborization
Myelination
Fertilization
Percentage of maximum
Age (years)
Prefrontal
excitatory synapses
Prefrontal
inhibitory synapses
Stage I: risk
< 12 years
Stage II: prodome
12–18 years
Myelination
Insel, 2010. Nature

Greetings from the NORMENT Partners

NORMENT has served as a genuine melting pot for multidisciplinary research

The Faculty of Medicine at the University of Oslo has been the proud host of the Centre of Excellence, NORMENT, since 2013, in partnership with Oslo University Hospital, University of Bergen, and Haukeland University Hospital. NORMENT has been dedicated to advancing research in the realm of mental disorders, an increasingly crucial area receiving significant attention both nationally and globally. This remarkable research environment has masterfully brought together expertise spanning from fundamental science to clinical research, cutting across various disciplines. It has served as a genuine melting pot for multidisciplinary research.

NORMENT stands as a pivotal and highly productive research center, with a substantial output of more than 1500 scientific publications, many in high-impact journals. Its most notable contribution to the research community lies in the wealth of new knowledge about mental disorders, such as schizophrenia and bipolar disorders. The discovery of numerous genes associated with an increased risk of mental disorders and their links to cognitive function and physical health issues are particularly significant. NORMENT has successfully established a vast database and biobank, encompassing individuals with and without mental illness. This invaluable resource will undoubtedly continue to enhance our understanding of mental disorders in the future.

Over the years, NORMENT has fostered a nurturing environment that has allowed the next generation of outstanding researchers in the field of mental diseases to flourish. The leadership's commitment to sharing experiences with younger generations of researchers is particularly commendable, ensuring a robust foundation for future excellence. To date, NORMENT has seen the completion of more than 60 PhD dissertations and has provided a promising start to the research careers for several postdoctoral researchers and junior scientists.

Since its inception, NORMENT has maintained a clear and strategic focus. The Faculty of Medicine at the University of Oslo is actively engaging in enabling a continuation of this strong and important research area also in the future, NORMENT 2050.

Hanne Harbo
Dean at the Medical Faculty,
University of Oslo

NORMENT has contributed significantly to strengthening of the translational research

The Norwegian Centre for Mental Disorders Research has been an extremely successful Centre of Excellence. Oslo University Hospital has been a partner institution for NORMENT, while University of Oslo has been the main host institution. NORMENT has been very important for our institution and the field of mental disorders research in particular. The Centre has increased the attention and visibility of mental disorders at the hospital. Moreover, it has contributed to increased focus and funding of mental health research.

We are extremely proud of the achievements obtained throughout the 10-year existence of the Centre. The conclusion of the mid-term evaluation was “exceptionally good” confirming the high standard of the milieu. The Centre has performed international top-level translational research, providing important novel insight in the mechanisms involved in severe mental illnesses involving studies on genetic, neurobiological, psychological, and environmental factors. The Centre has provided extensive international collaboration. During the 10 year CoE period, many articles have been published in international top journals and several of these have received “outstanding paper” prizes from Oslo University Hospital. Also, some of the researchers in the Centre, including the Director of the Centre, have received prestigious prizes.

NORMENT has contributed significantly to strengthening of the translational research, which is an important goal for the hospital. Its multidisciplinary nature has contributed to bridging the gap between basic sciences and clinical medicine. In addition, NORMENT has been an important driver for developing research infrastructure at the hospital. The milieu has also received extensive funding from external sources, including EU, and the research will be continued at a very high level. Importantly, a continuation of the established database and biobank is planned for future use (NORMENT 2050). With the high quality of the research milieu, it is our strong belief that the groups will continue to play important roles for the further development of research in severe mental illnesses and for the clinical handling of patients suffering from these disorders.

Erlend Smeland
Director of Research, Education and Innovation,
Oslo University Hospital

NORMENT has indeed paved the way for more excellent research in the future

The Faculty of Medicine at the University of Bergen congratulates all members of NORMENT on their successful completion as a Centre of Excellence. Together with the University of Oslo as host and Oslo University Hospital and Haukeland University Hospital as additional partners, we have been privileged to observe and support the dedicated researchers who have advanced and excelled the research on severe mental disorders, by bridging clinical, biological, and genetic findings into a greater understanding of disease mechanisms and treatment effects.

In my opinion, NORMENT has managed to establish a strong research environment that has facilitated interdisciplinary collaboration between researchers at the partner institutions as well as engagement in international networks. The outstanding achievements of NORMENT are reflected in an impressive number of scientific publications in highly ranked journals and numerous PhD degrees. The Centre has also contributed significantly to the career development of many young and talented researchers. NORMENT has indeed paved the way for more excellent research in the future through the NORMENT 2050 initiative, built on the competence and infrastructure that has been established during ten years of CoE funding.

Most important, NORMENT has significantly lifted the field of mental health research, by focusing on the serious psychotic disorders schizophrenia and bipolar disorder, and by cleverly combining research from many disciplines into novel knowledge. NORMENT has also succeeded in engaging the user groups and disseminating the scientific findings into the public domain. These activities have led to increased awareness of the many challenges associated with severe mental illness.

Well done!

Per Bakke
Dean at the Medical Faculty,
University of Bergen

NORMENT has formed the basis for new clinical studies

Haukeland University Hospital has been a Centre of Excellence partner in NORMENT since 2018. Some of the reason for our participation, was that the field of mental health is an important area with several unmet needs – both to understand aetiology and to improve clinical treatment. Through these years, NORMENT has reached important milestones towards these goals. With a clinical profile, involving investigations of participants with clinical assessments and research technology, NORMENT has formed the basis for new clinical studies. And through this, participated to develop new treatment methods. The long term has provided unique opportunities to build stone on stone.

The work of NORMENT has had a large impact on research areas. The synergy of many researchers with different backgrounds and expertise coming together and using different approaches has been able to clarify complex relationships - "from bench to bedside". NORMENT has worked closely with user representatives. We as a partner, think that to have this expertise close to the projects – is important in order to secure both reliability and actuality.

As one of the proud partners, I thank you all for this impressive work. It is important that the expertise, collaboration, and networking that has been done in NORMENT is continued in new research and new initiatives. In order to secure this, we as partners have to take responsibility.

A great thanks again to user representatives, researchers, staff, leader, centre management, governing board, and scientific advisory committee for the impressive work you have all done at NORMENT. Thank you also to our partners, the University of Bergen, the University of Oslo and Oslo University Hospital for the very good collaboration through these ten years. Together we have all moved ourselves further towards our common goal, which is to find answers to why some people develop severe mental illness.

Randi-Luise Møgster
Vice-Director,
Haukeland University Hospital

The scientific output of NORMENT has been facilitated by a well-organized centre which has used the basic funding by the Norwegian Research Council to gain substantial additional resources awarded to the NORMENT hub

The Institute of Clinical Medicine has been proud host institute within the University of Oslo of CoE NORMENT for a decade, with the Head of Institute as acting chair ex officio of the NORMENT Governing Board. It has been a pleasure to observe the expanding activities of NORMENT; the impressive research infrastructure as well as the outstanding scientific output, both in terms of quantity and quality, pushing the basic understanding of biological psychiatry to the forefront, document the success of this Centre of Excellence.

The scientific output of NORMENT has been facilitated by a well-organized centre which has used the basic funding by the Norwegian Research Council to gain substantial additional resources awarded to the NORMENT hub. This has resulted in an impressive number of sub-projects that has expanded the capacity of young talented researchers in the field and includes many PhDs, postdocs, in part with international recruitment.

Our institute has assisted the formal closure of NORMENT with the intention to secure future activities by keeping key personnel within the organization. Furthermore, the collaborating institutional partners will secure the NORMENT2050 infrastructure further by mutual support. We are grateful to the Norwegian Research Council for its valuable support to NORMENT and can firmly conclude that this investment has been a scientific success in all respects.

Dag Kvale
Leader of NORMENT Board

Vision Statement

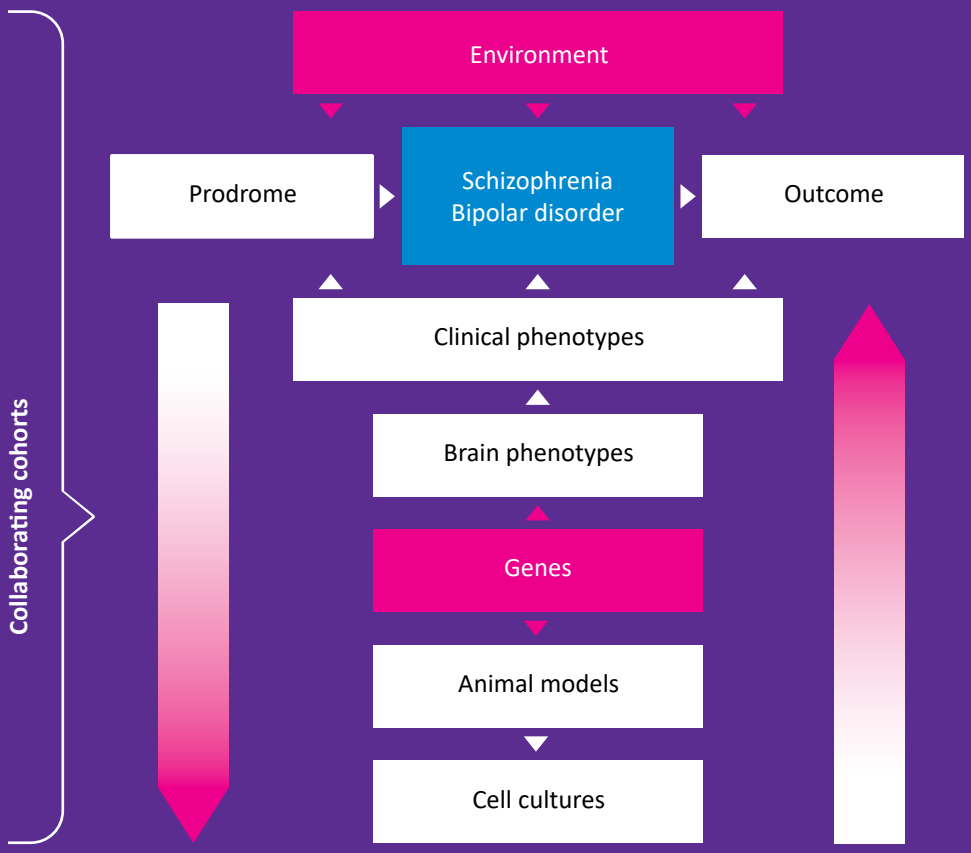
NORMENT's primary objective has been to explore and reveal the underlying pathophysiology of psychotic disorders based on recent discoveries of genetic risk factors, develop tools for stratification and outcome prediction, and translate findings into clinical interventions.

The main research topics at the Centre have been Genetics, Brain Imaging, Outcome Prediction, and Clinical Intervention, which have been reflected in the following subgoals:

1. **Disclose the complete genetic architecture of psychotic disorders and determine their functional impact**
2. **Identify novel brain imaging phenotypes linking genes and clinical phenotypes in a longitudinal setting**
3. **Use genetic, environmental and clinical factors to predict disease progress and outcome**
4. **Translate pathophysiological discoveries into clinical and pharmacological interventions**

We have profited from the homogeneity of the Norwegian population (genetic background, health care system, registries) as the basis for collecting large samples of affected and unaffected people. These individuals have been characterized with the same clinical, cognitive, biochemical, and imaging protocols to identify new disease mechanisms, which have then been studied functionally in animal and cell culture models.

The aim of this "vertical synergy" approach has been to obtain different levels of understanding by bringing together transdisciplinary expertise and methods.



Scientific Aims

GENETICS: Disclose the complete genetic architecture of psychotic disorders and determine their functional impact

- Uncover new rare genetic variants conferring risk of bipolar disorder and schizophrenia
- Leverage new statistical methods to determine the polygenic architecture of bipolar disorder and schizophrenia
- Discover biomarkers and biological mechanisms of psychosis risk genes

OUTCOME PREDICTION: Use genetic, environmental and clinical factors to predict disease progress and outcome

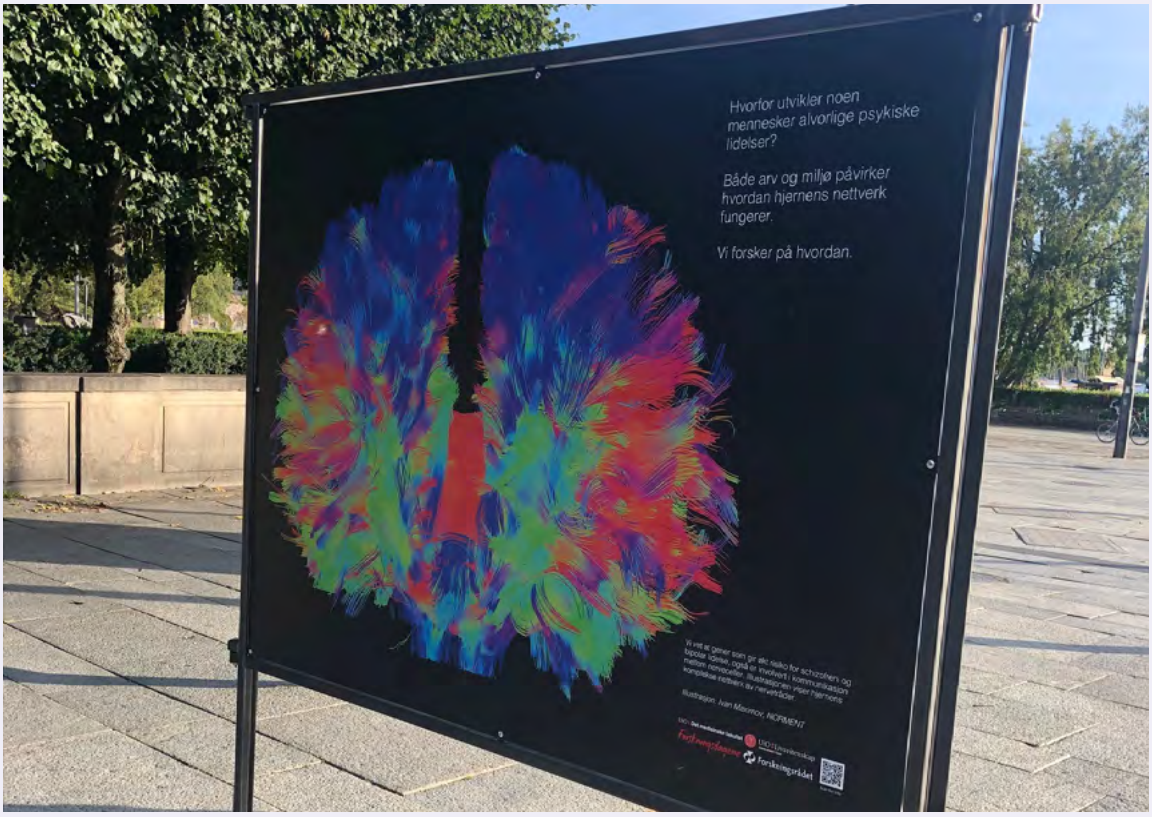
- Define clinical trajectories from premorbid stages and related pathophysiological processes
- Identify gene-environment interactions at critical phases of neurodevelopment with relation to clinical outcome, including mortality
- Develop prediction and stratification tools for disease course and outcome

BRAIN IMAGING: Identify novel brain imaging phenotypes linking genes and clinical phenotypes in a longitudinal setting

- Explore brain network dynamics in psychotic disorders and associated phenotypes
- Identify genetic determinants of brain abnormalities
- Determine brain abnormalities underlying key clinical phenotypes and their genetic architecture

CLINICAL INTERVENTION: Translate pathophysiological discoveries into clinical and pharmacological interventions

- Determine immune and lipid-related mechanisms in psychotic disorders
- Develop a stratification approach based on immune dysfunction profiles
- Perform immune system-related interventions in psychotic disorders



Scientific Highlights

During the years as a Centre of Excellence, NORMENT researchers have been involved in several important discoveries to uncover how genetic, neurobiological, psychological, and environmental factors contribute to the development and outcome of mental disorders. Our findings confirm the importance of a multifactorial understanding of schizophrenia and bipolar disorder, providing a foundation for further research on diagnostics and treatment of severe mental disorders.

Schizophrenia and bipolar disorder are severe mental disorders that pose a major burden on the affected individual, their families and society in general. The clinical characteristics of these disorders have been known since antiquity, and the high heritability is well documented. Despite this, the causes of the diseases have remained largely unknown, although altered brain development seem to play in important role. Furthermore, the context of environmental factors in disease development and outcome is mainly unknown.

When NORMENT received the Centre of Excellence funding, it was an exciting period in psychiatric research. Important new methodologies had recently emerged due to technological developments enabling studies of the human genome and the brain function with ever more sophisticated methods, as well as a growing knowledge about important environmental factors. Thus, there were several opportunities for the Centre to address important knowledge gaps in the field, including the unidentified genetic risk factors contributing to severe mental disorders, the way in which brain regions interact in neural networks, how pharmacological treatment can be improved, understanding the role of immune mechanisms, and characterizing outcome of the disease and develop tools for prediction. Here, we describe some examples of findings from the Centre.

Genetic risk variants for schizophrenia and bipolar disorder

NORMENT has been involved in discoveries of new gene variants associated with severe mental illness. These include large international studies reporting over 100 genetic variants related to schizophrenia (PGC SCZ 2014, Trubetskoy 2022) and more than 60 risk variants associated with bipolar disorder (Stahl 2019, Mullins 2021). Risk genes are related to brain development, neuronal signaling, and the immune system. Many of the genetic variants are shared between schizophrenia and bipolar disorder. NORMENT researchers have also developed novel statistical tools that boost the discovery of genetic variants and improve prediction in mental illness (Frei 2019, van der Meer 2020).

Genetic overlap between mental disorders, personal traits, and other disorders

We have found that genetic variants involved in schizophrenia or bipolar disorder overlap with other mental disorders (PGC 2019, Hindley 2022) and with brain disorders such as ADHD (O'Connell 2021). Further, we have discovered shared genes for mental disorders and personal traits, including cognitive function (Smeland 2017), intelligence (Smeland 2019), personality (Hindley 2022), body mass index (Bahrami 2020), cardiovascular risk factors (Rødevand 2023), and cannabis use (Cheng, Parker 2023).

Brain structure and networks in mental illness, and relation to genes and environment

By using advanced brain imaging technology, NORMENT has contributed with new knowledge about how the brain is affected in mental illness. We have demonstrated cortical brain abnormalities in bipolar disorder (Hibar 2018), reductions (Haukvik 2015) and sex differences (Barth 2023) in hippocampal subfield volumes in schizophrenia, and white matter microstructure alterations in adolescent psychosis (Barth 2023). We have reported that schizophrenia is associated with increased interindividual differences in brain structure (Alnæs 2019) and that cerebellum is among the most affected brain regions in this disorder (Moberget 2018).

Researchers at NORMENT have also identified genetic variants linked to specific brain regions in mental illness, including the brain stem (Elvsåshagen, Bahrami 2020), thalamus (Elvsåshagen 2021), hippocampus (van der Meer 2020), and cortical brain areas (Cheng 2021). We have demonstrated that brain structural measures in mental disorders are associated with factors such as obstetric complications (Wortinger 2022) and use of antipsychotic medication (Jørgensen 2016).

Our research has also shown that alterations of specific nerve fibers in the brain of children and adolescents may increase the risk of mental illness later in life (Alnæs 2018). We have discovered a fingerprint-like pattern in the brain that evolves during development and is associated with mental health challenges (Kaufmann 2017), and we have reported distinct patterns of brain aging in schizophrenia and other disorders (Kaufmann 2019).

The role of the immune system in mental disorders

NORMENT has gained new knowledge about how the immune system is involved in mental illness, both on a genetic level, and in relation to clinical and cognitive symptoms. We have demonstrated abnormalities in a neuroprotective immune pathway in schizophrenia and bipolar disorder (Engh 2022) and dysfunctions of biological pathways associated with the immune system in both disorders (Steen 2020, Torsvik 2023).

Increased immune activity in mental illness has been linked to cognitive impairment (Sæther 2022, Fathian 2018), illness course severity (Elkjær Greenwood Ormerod 2022, Hoprekstad 2023), and childhood trauma (Aas 2017). We have worked to identify new drug treatment targeted at the immune system (Kroken 2019, Nasib 2020) and reported that different antipsychotic drugs impact immune levels differently (Fathian 2022).

Factors that influence course and outcome of mental illness

NORMENT has identified several environmental, clinical, and genetic factors that are important for clinical outcome and prediction of illness course in mental disorders. We have shown that illness outcome is affected by environmental factors such as early trauma (Aas 2014, Vaskinn 2021, Ottesen 2023), obstetric complications (Wortinger 2020), migration (Berg 2015), and substance use, including tobacco smoking (Icick 2019) and cannabis use (Lagerberg 2014, Helle 2016, Ringen 2016).

Our research has shown that immune markers (as described above), serum lipids (Gjerde 2018), polygenic scores (Engen 2020, Werner 2020), and sleep disturbances (Laskemoen 2021) influence the course of mental illness. Further, we have identified causes and predictors of premature death in first-episode schizophrenia spectrum disorders (Melle 2017).

We have also demonstrated that cognitive deficits in mental disorders do not worsen over time, by showing that cognitive functions in first-episode schizophrenia and bipolar disorder are stable after over 1 year (Haatveit 2015, Demmo 2017) and improve over 10 years (Flaaten 2023).

Medication effects and stem cells

NORMENT has documented significant differences in effectiveness of antipsychotic medication (Johnsen 2020) and sex differences in effects and adverse effects of antipsychotic medication (Hoekstra 2021). We have identified genetic factors that are important for drug treatment response (Athanasiu 2015, Akkouh 2020, Akkouh 2022), and our research on anti-inflammatory drugs has provided promising results for treatment alternatives (Kroken 2019, Nasib 2020).

The long-term Centre funding have also allowed us to develop an advanced stem cells technology lab. We have used this methodology to better understand disease mechanisms in mental disorders, develop better medication, and to study the effect of pharmacological treatment such as Lithium (Osete 2021) and clozapine (Akkouh 2022).

NORMENT researchers have been involved in several important discoveries to uncover how genetic, neurobiological, psychological, and environmental factors contribute to the development and outcome of mental disorders

Research Groups

The research at NORMENT was organized into groups with complementary expertise and a particular focus area of research. There was a close collaboration across research groups and scientific disciplines, as reflected in the "vertical synergy" approach at the Centre. The number and organization of groups changed in 2018, halfway in the Centre period.

In the first phase of the Centre (2013-2018), there were eight research groups, each of them headed by a Core Researcher (CR). In 2018, seven additional groups were included in the Centre. Some of the new groups were already well-established at their institutions and complemented the existing research groups with important expertise such as clinical interventions. Other groups had just recently started and were part of the career development strategy at NORMENT to give early-stage researchers more responsibility and experience. Each of the fifteen research groups were headed by a Group Leader, but had a formal affiliation to one specific Core Researcher in the Scientific Management.

Research Groups 2013 - 2018

Research Groups								
	CR Ingrid Melle **Clinical Psychosis Research**	CR Kjetil Sundet **Neuro-cognition**	CR Kenneth Hugdahl **Brain Imaging**	CR Ingrid Agartz **Structural MRI**	CR Ole A. Andreassen **Translational Psychiatry**	CR Vidar M. Steen **Basic and Clinical Psycho-pharmacology**	CR Stéphanie Le Hellard **Epigenetics and Functional Genomics**	CR Srdjan Djurovic **Psychiatric Molecular Genetics**

Research Groups 2018 - 2023

Research Groups	CR Ingrid Melle	CR Ole A. Andreassen	CR Ingrid Agartz	CR Lars T. Westlye	CR Srdjan Djurovic	CR Vidar M. Steen	CR Stephanie Le Hellard	CR Erik Johnsen
	Illness Trajectories and Outcome Prediction (Ingrid Melle) **Mechanisms of Psychopathology** (Trine Vik Lagerberg) **Cognitive Mechanisms and Outcome** (Torill Ueland)	Precision Psychiatry (Ole A. Andreassen) Biological Psychiatry (Nils Eiel Steen)	Imaging Psychosis (Ingrid Agartz) Forensic Psychiatry (Unn K. Haukvik) Translational Electrophysiology (Erik Jönsson)	Multimodal Imaging (Lars T. Westlye)	Stem Cells and Mechanisms (Srdjan Djurovic)	Molecular Risk Factors (Vidar M. Steen)	Epigenetics of Mental Disorders (Stephanie Le Hellard)	Pharmacology and Intervention (Erik Johnsen) Affective Disorders (Ketil J Ødegaard) Predictive and Pharmacological Imaging (Renate Grüner)* *Replaced Kristiina Kompus in 2021

Illness Trajectories and Outcome Prediction

Group Leader

Ingrid Melle

Research focus

Psychotic disorders show significant variations in course and outcome. Early course parameters, including length of untreated illness and initial treatment response, are among the most important predictors of long-term outcomes. We aim to identify symptom trajectories and significant correlates through prospective longitudinal studies of first-treatment study participants, to address one of the four scientific aims of the Centre: Use genetic, environmental, and clinical factors to predict disease progress and outcome.

The group focuses on establishing an extensively characterized first-treatment cohort of patients with schizophrenia and bipolar spectrum disorders, with personal follow-ups after one- and ten years. The group has also been the base for the ten- and twenty-year follow-ups of the first-episode TIPS study. In phase II, the group split into the Illness trajectories and Outcome Prediction Group and the Mechanisms of Psychopathology group.

Achievements

We first investigated links between environmental risk factors, genetics, and clinical presentations. This includes papers on how different environmental risk factors influence clinical characteristics, including early trauma (Aas et al., 2014, J Psychiatr Res), migration (Berg et al., 2015, Psychol Med), cannabis use (Ringen et al., 2016, Psychol Med), and vitamin D (Nerhus et al., 2017, Schizophr Res). We additionally explored the role of metacognitive beliefs (Østefjells et al., 2017, Psychol Med), self-disturbances (Haug et al., 2016, Front Hum Neurosci), suicidal behaviors (Gohar et al., 2019, Acta Psychiatr Scand), and sleep disturbances (Laskemoen et al., 2021, Psychol Med) for clinical profiles.

We also studied the impact of single genes (Haram et al., 2015, Front Hum Neurosci) and of polygenetic risk (Engen et al., 2020, Transl Psychiatry) on relevant phenotypes. In the first phase, we started a prospective longitudinal study of first-episode psychosis (Barrett et al., 2015, Schizophr Res) and first treatment mania (Aminoff et al., 2013, Bipolar Disord), with reports on baseline and one-year outcome findings. In the second phase, we investigated factors associated with the long-term course and outcome, including the role of self-disturbances (Svendsen et al., 2019, Schizophr Res), negative symptoms (Lyngstad et al., 2020, Eur Arch Psychiatry Clin Neurosci), quality of life (Gardsjord et al., 2018, Schizophr Res), recovery (Åsbø et al., 2022, Schizophr Bull), cannabis use (Ihler et al. 2023, Schizophr Res), diagnostic stability (Widing et al, 2023, Schizophr Bulletin Open), treatment resistance (Wold et al, 2023, Eur Psychiatry), and suicidal behaviors (Gohar et al, 2023, Lancet Psychiatry).

We also worked together with the Mechanisms of psychopathology group to develop the MinDag app (Bjella et al., 2022, Front Med Technol), with the Cognition group to study the long-term course of cognitive dysfunction (Flaaten et al., 2023, Bipolar Disord), and with TIPS Sørøst on studies of service organizations (Romm et al., 2019, Early Interv Psychiatry).

Taken together, the main results from our studies confirm that environmental risk factors for the development of psychotic disorders also have detrimental effects on clinical severity post-onset. The links between polygenetic risk for schizophrenia and clinical symptoms/cognitive functioning are, however, difficult to establish, even in large clinical samples. The main changes in clinical symptoms and cognitive dysfunction occur in the first year of treatment, with most patients displaying stable low levels of symptomatology with a significant chance of recovery.

A smaller group experiences stable high symptom levels, and this group also experiences the highest levels of cognitive and global dysfunction. There are no apparent signs of a “neuroprogressive” course of these disorders at the group level, even if it cannot be completely ruled out for smaller subgroups.

The corona pandemic significantly delayed the data collection for the ten-year follow-up. Some of the main results from the prospective study will be published in the first part of 2024, based on external funding. Several are in press or accepted for presentations at international conferences including papers on long-term trajectories of brain structure (Berthet et al, submitted), psychotic symptom trajectories in schizophrenia spectrum disorders (Kreis et al., in prep), and long-term outcome of bipolar I disorders (Melle et al., in prep).

The primary research questions concerning the predictive power of baseline clinical factors, environmental risk factors, genetic/epigenetic factors, and other biomarkers will be addressed, some together with researchers from the NORMENT environment and/or international collaborators.

In the period 2013-2023, a total of 136 papers originating in the group (based on first and/or last authorships) have been published, in addition to participation in collaborative papers originating in other centre groups. Twelve PhD candidates from the group have defended their thesis during the centre period, and four candidates will complete their PhD in 2024.

Continuation of the group's research

Based on our confirmation of the central role of the first treatment years in shaping the long-term outcome of psychotic disorders, the continuation of the group's research centers on this critical period with a particular focus on early identification to prevent poor outcomes. We have already started projects on clinical factors underlying early suicidal risk and will continue to focus on the early identification of treatment resistance. We also plan to engage in clinical studies addressing adverse outcomes in a collaborative network established during the NORMENT period.

The main results from our studies confirm that environmental risk factors for the development of psychotic disorders also have detrimental effects on clinical severity post-onset

Mechanisms of Psychopathology

Group Leader

Trine Vik Lagerberg

Research focus

The group aims to expand the understanding of mechanisms underlying the significant symptom variation seen in psychotic disorders over time and between individuals. We aim to provide rich clinical characterisations and to investigate the relationship between core affective and psychotic symptoms on one hand, and affective dysregulation, substance use and chronorhythms on the other.

To do so, we have developed and implemented digital tools (MinDag – a smartphone application, actigraphy) designed to prospectively capture a fine-grained picture of several dimensions of symptoms and behaviour. We are also investigating how these digital tools can be used in a clinical setting to boost treatment in bipolar disorder. The group has founded a specialized clinical unit for individuals early in the course of a bipolar disorder at Nydalen District Psychiatric Centre, a catchment area based service where all patients are invited to participate in research.

Achievements

The group was established in 2018. We have investigated the relationship between substance abuse and several clinical aspects of bipolar disorder, demonstrating that tobacco smoking is associated with insomnia (Glastad et al., 2023, J Affect Disord) and recurrent suicide attempts (Icick et al., 2019, J Affect Disord), and that stopping alcohol is related to reduced risk of affective relapse early in the course of illness (Lagerberg et al., 2021, Front Psychiatry).

We have reported that the pharmacological treatment provided to individuals with bipolar disorder both with and without comorbid substance abuse appears to be equally in line with treatment guidelines (Icick et al. 2022, Front Psychiatry). We have demonstrated that the Birchwood Insight Scale, a commonly used scale to assess clinical insight in schizophrenia, has adequate psychometric properties when applied to bipolar disorder (Büchmann et al., 2019, Psychiatry Res), and we are now using the scale to investigate clinical correlates of illness insight in bipolar I and II disorder (Büchmann et al, in prep). Furthermore, with a combination of actigraphy (a wrist-born device) and self-report, we have shown that individuals with bipolar disorder report their sleep with the same accuracy as healthy individuals (Ihler et al., 2020, Int J Bipolar Disord).

The group has also investigated the prevalence and correlates of affective lability across schizophrenia spectrum- and bipolar disorders, and demonstrated that the level of affective lability is higher in individuals with such disorders compared to healthy controls (Høegh et al., 2020, Eur Psychiatry), similar in schizophrenia and bipolar I disorder, and highest in bipolar II disorder (Høegh et al., 2021, Int J Bipolar Disord). Affective lability is also associated with the level of social functioning, particularly in schizophrenia spectrum disorders (Høegh et al., 2022, Eur Arch Psychiatry Clin Neuroschi).

The group has developed and made use of several innovative methods for collection of clinical data. We developed the app MinDag for monitoring of the core symptoms of schizophrenia- and bipolar disorders in parallel with life-style and function-related measures such as sleep, substance use and other relevant behavioural and psychological parameters (Bjella et al., 2022, Frontiers Med Tech).

We were awarded with Oslo University Hospital's Innovation Prize for this development. The app is now being used in several studies both for naturalistic and clinical purposes (Høegh et al., in prep), and for monitoring symptom change in an RCT on Vitamin D supplement in psychotic disorders at Akershus University Hospital, in which the group is involved.

We also use actigraphy to collect objective data on sleep and activity, and have contributed to the development of web-forms for more efficient collection of clinical data. By October 2023, the group has collected data using MinDag and actigraphy from approximately 55 patients, and the

first data analyses have been conducted and will be used in an ongoing PhD and in several post doc/senior projects. A specific area of interest is the temporal relationship between mood, sleep and substance use in bipolar disorder (Glastad et al., in prep).

The group is involved in several international collaborations, the most active as part of an International Partnership for Research and Education (INTPART) grant from the Norwegian Research Council with a research group and expert center on bipolar disorder in Paris, France. This has also yielded grant applications in collaboration with additional European partners led by the group leader, mainly focusing on chronorhythmic disturbances in bipolar disorder.

There is to date one PhD from the group (Margrethe Collier Høegh), and two others ongoing.

Continuation of the group's research

After the CoE-period, the group will continue conducting research investigating drivers of symptom variation between- and within individuals, taking advantage of the fine-grained clinical data collected with digital tools. In collaboration with other reseach groups, we will combine these data with data from cognitive, genetic and biochemical assessments. We are also planning for several clinical trials targeting some of the illness features which the group has identified as major challenges and/or promising avenues in the clinic such as comorbid substance use disorders, affective lability, and chronorhythmic disturbances. We will further test and enhance the clinical value of the digital tools developed by the group in close collaboration with clinical units at Oslo University Hospital. We will continue collaborating with national and international partners and aim for competitive research grants.

The group has developed and made use of several innovative methods for collection of clinical data

Cognitive Mechanisms and Outcome

Group Leader

Torill Ueland

Research focus

The aims of the group have been to study cognitive heterogeneity and its sources, the course of cognitive functioning, mechanisms underlying cognitive dysfunction and the effect of cognitive remediation. Our goal has been to enhance our understanding of cognition in psychotic disorders and identify cognitive subgroups with different treatment needs, allowing more personalized and targeted treatment.

We have collaborated closely with other groups at the Centre and have used clinical, brain imaging, genetic and biochemical data in our studies. We have been responsible for collection of cognitive data at the Centre, including assessment of clinical participants and healthy controls (baseline, 1-, and 10-year follow-ups).

Achievements

Our longitudinal studies of first-episode schizophrenia have shown stability and improvements over 1 (Haatveit et al. 2015, Psychiatry Res) and 10 years (Flaaten et al. 2022, Schizphr Res Cogn) with a similar course to healthy controls, except slight declines in attention and cognitive control at 10 years. In first-treatment bipolar disorder, we found stability at 1 year (Demmo et al. 2017, Psychiatry Res) and stability and improvements over 10 years (Flaaten et al. 2023, Bipolar Disord).

For IQ, we showed declines from premorbid levels to illness onset, with a milder drop in the bipolar group. At 10-year follow-up both clinical groups improved, albeit with maintained impairments relative to healthy controls (Flaaten et al. 2023, Psychol Med). These findings are important because they show that cognitive impairments, though evident, do not progress over time.

Cognitive heterogeneity has been a prime interest of the group. Using cluster analyses, we identified three cognitive subgroups (intact, intermediate and impaired) across schizophrenia and bipolar disorder (Vaskinn et al. 2020, J Int Neuropsychol Soc), and two social cognitive subgroups in schizophrenia (Vaskinn et al. 2022, Schizophr Res Cogn). The groups differed in cognitive profiles, symptom level and functioning. We have found that first-episode psychosis (FEP) participants with sustained negative symptoms are more cognitively impaired than participants with no or mild negative symptoms with stable impairments over 1 (Engen et al. 2019, Psychiatry Res) and 10 years (Engen et al. 2022, Front Psychiatry). Participants with prominent negative symptoms have an inverse brain structure-function relationship, indicating an association between better cognitive function and smaller brain volume in anterior cingulate cortex (Haatveit et al. 2021, Psychiatry Res Neuroimaging).

In the TIPS 10-year follow-up study, FEP participants relapsing within the first year of treatment had weaker verbal learning performance than participants without early relapse (Barder et al. 2013, Front Hum Neurosci). First-treatment bipolar I disorder participants without relapse at one-year follow-up showed larger cognitive improvements and better functioning than those with relapse (Demmo et al. 2018, Bipolar Disord).

We showed that poor cognition was associated with innate immune dysregulation in a subgroup of individuals with schizophrenia or bipolar disorder, indicating that inflammation may also be a source of cognitive heterogeneity (Sæther et al. 2023, Mol Psychiatry).

We have translated several social cognitive tests (Vaskinn et al. 2016, Front Psychol; Frøyhaug et al. 2019, Cogn Neuropsychiatry), showing that social cognition relates to functioning in schizophrenia/bipolar disorder (Engelstad et al. 2017, Scand J Psychol; Vaskinn et al. 2017, Int J Bipolar Disord). Our studies have documented associations between social cognition and insight (Feyer et al. 2020, J Nerv Ment Dis), autism symptoms (Vaskinn & Abu-Akel 2019, Neuropsychology), neural activity (Sæther et al. 2021, Int J Psychophysiol), and childhood trauma (Vaskinn et al. 2020, Schiz Res Cogn).

Impairments are present in offenders with schizophrenia (Engelstad et al. 2019, Psychiatry Res) and sexual offenders (Friestad & Vaskinn 2021, Scand J Psychol), but less in borderline personality disorder (Vaskinn et al. 2015, Front Psychol). We contributed with a state-of-the-art paper on social cognition in schizophrenia (Vaskinn and Horan 2020, Schizophr Bull).

We contributed to a multisite randomized controlled trial of vocational rehabilitation augmented with cognitive remediation or cognitive behaviour therapy, the JMO study. Vocational activity increased from 17% to 77% during the intervention with no differences between groups (Falkum et al. 2017, BMC Psychiatry) but with larger cognitive improvements in the cognitive remediation group (Lystad et al. 2017, Schizophr Res). Significant reductions in inpatient service use were documented after 2 years (Evensen et al. 2019, BMC Psychiatry) and continued positive work outcomes after 5 years (Gjerdalen et al. 2023, Nord J Psychiatry). JMO has since been implemented as a regular vocational program, a breakthrough for a group with poor work rehabilitation options in Norway. A randomized controlled trial of targeted facial emotion perception training in schizophrenia showed improved theory of mind with durable effects after 3 months (Vaskinn et al. 2019, Eur Arch Psychiatry Clin Neurosci). We contributed to an expert group consensus paper identifying core features of cognitive remediation, with recommendations for design and implementation in clinical practice and research (Bowie et al. 2020, Schizophr Res).

Eight PhD candidates have worked in the group since 2013 (six complete, two ongoing).

The group would like to acknowledge Professor Kjetil Sundet's contribution as group leader from 2013 to 2018.

Continuation of the group's research

We will continue our ongoing research projects and apply for funding for new projects. We have received three years of funding by the Wellcome Trust for a collaboration study with Stichting Radbout University and Kings College. We aim to develop cognitive growth charts through normative modelling and investigate subjective cognitive functioning through the view of people with lived experience. We are involved in ongoing applications for vocational rehabilitation studies (Individual Placement and Support) augmented with cognitive remediation and other interventions targeting cognition. We will also continue our collaboration with other groups in the Centre.

These findings are important because they show that cognitive impairments, though evident, do not progress over time

Precision Psychiatry

Group Leader

Ole A. Andreassen

Research focus

What are the causes of mental disorders? And how can we use knowledge of these causes to adapt treatment to the individual? In our research group, we use data from several hundred thousand participants and modern methods for analyzing big data, and our deeply phenotyped clinical samples. Through several Norwegian and international projects, we have worked to collect large amounts of data and develop new analytical and machine learning methods to obtain more knowledge about disease causes and mechanisms of mental disorders, from innate vulnerability (inheritance) to environmental factors, and how these interact.

We use an interdisciplinary research approach, and analyze different types of data such as clinical and cognitive characteristics, brain images, blood markers, genotypes, and data from health registers. The goal is to work together on research that can lay the foundation for personalized treatment of severe mental disorders.

Achievements

The group has made several discoveries that provide new insight into the genetic basis of mental disorders (Smeland et al. 2020, Nat Rev Neurosci; Andreassen et al. 2023, World Psychiatry). We have seen that genetic variants associated with a particular mental disorder are very likely to also affect other mental disorders and traits, such as bipolar disorder and attention-deficit/hyperactivity disorder (O'Connell et al. 2021, Mol Psychiatry), sleep-related phenotypes (O'Connell et al. 2021, Biol Psychiatry), and cannabis use (Cheng, Parker et al. 2023, Lancet Psychiatry).

Interestingly, these genetic variants also affect human characteristics such as cognition (Smeland et al., 2017, JAMA Psychiatry) and personality (Hindley et al. 2022, Am J Psychiatry). This indicates that the majority of "genes for mental disorders" are also "genes for cognition» (Smeland et al. 2020, Mol Psychiatry; Bahrami et al. 2021 Nat Hum Behav) and "genes for personality" (Lo et al. 2017, Nat Genet).

Such findings of genetic overlap have implications for how we interpret genetic results, define mental disorders, and design future tools for precision medicine for mental disorders (Smeland et al. 2020, Nat Rev Neurosci; Andreassen et al. 2023, World Psychiatry). It can also help to improve treatment and prevention of mental disorders in the future. An essential part of this work has been the development of novel analytical tools, which have provided unique opportunities for making new discoveries (Frei et al. 2019, Nat Commun; Smeland et al. 2019, Hum Genet; van der Meer, Frei et al. 2020, Nat Commun; Shadrin et al. 2022, Bioinformatics).

We have also carried out several studies of the link between mental disorders and alterations in brain structure (Cheng et al. 2021, JAMA Psychiatry; Cheng et al. 2022; Mol Psychiatry). Our findings show that the majority of gene variants underlying brain morphology also contribute to schizophrenia, which provides support for a genetic link between schizophrenia and the brain, and specifically genes involved in brain development (Cheng et al. 2021, JAMA Psychiatry).

We have also found a polygenic overlap between severe mental disordes and cardiovascular risk factors (Andreassen et al. 2013, AJHG; Bahrami, Steen et al. 2020, JAMA Psychiatry; Rødevand et al. 2023, Am J Psychiatry), supporting a body-brain link which can help understand the increased cardiovascular comorbidity in severe mental disorders.

The group has been actively involved in several international studies of genetics of mental illness (Stahl et al. 2019, Nat Genet; PGC 2014, Nature; Trubetskoy et al. 2022, Nature), and led the team who identified gene variants that increase the risk of bipolar disorder (Mullins et al. 2021, Nat Genet; O'Connell et al. 2023, medRxiv).

These collaborations have dramatically increased the number of gene variants reported in previous studies. We found that gene variants involved in the communication between brain cells increase the risk of bipolar disorder (Mullins et al. 2021, Nat Genet). Brain cells depend on calcium to communicate, and therefore it was particularly interesting that genes involved in calcium signalling were linked to an increased risk of bipolar disorder. The results of this study may have implications for the prevention and treatment of bipolar disorder in the future. For example, analysis of the genetic findings can help to investigate whether drugs that block calcium in the brain have an effect in the treatment of bipolar disorder.

During the Centre period, nine PhD candidates from the group have defended their thesis.

Continuation of the group's research

We are now working on developing new methods, so that these findings can be translated to clinical applications and used in future treatment of mental illness. A new and exciting approach is the use of digital avatar technology, to develop algorithms to provide personalized norms for individuals to improve prediction of treatment response to personalize treatment and selection of treatment. Thus, we have initiated several projects with this approach, and we intend to use this new technology to transfer knowledge from discoveries of genetic risk factors to help the individual to have a better and more adapted treatment of mental disorders. In addition to new big data analytical tools, we will leverage real-world big data from Norwegian/Nordic biobanks and registers and establish routines for national studies based on clinical operations. We will extend our work in these ciritical infrastructures to enable us to move into the era of precision psychiatry.

Such findings of genetic overlap have great significance for how we interpret genetic results, define mental disorders and design future tools for precision medicine for mental disorders

Biological Psychiatry

Group Leader

Nils Eiel Steen

Research focus

The group investigates biological mechanisms in schizophrenia and bipolar disorder by integrating genetic, biological, environmental, and clinical data in a translational approach. We use the richly characterized TOP/NORMENT sample in combination with data from international genetic consortia and health registries. Several biological processes related to severe mental disorders and their treatment are investigated with a special focus on inflammation, candidate metabolism pathways and cardiovascular comorbidity.

The overall goal is to increase the knowledge of the underlying biological mechanisms of severe mental disorders with potential implications for prevention, treatment, course prediction and diagnostics. Our aims include gaining knowledge of underlying immune mechanisms, identifying pathophysiological pathways, and identifying mechanisms of the increased cardiovascular risk.

Achievements

Basic mechanisms: Our studies indicate that most of the low-grade inflammation in severe mental disorders is explained by other factors than the illness genetics, autoimmunity and infection rates (Werner et al., 2022, Transl Psychiatry; Werner et al., 2022, Prog Neuropsychopharmacol Biol Psychiatry). We have demonstrated dysregulation in a potentially neuroprotective immune pathway in both bipolar disorder and schizophrenia spectrum disorders (Engh et al., 2022, Schizophr Bull), and the group was among the first to investigate the interplay of immune pathways and the relationship to illness course characteristics in severe mental disorders, indicating involvement of pro-inflammatory processes associated with dysregulated neuroprotective mechanisms in illness course severity (Elkjær Greenwood Ormerod et al., 2022, Brain Behav Immun Health). Genetic overlap between schizophrenia and various white blood cell counts with a mixture of effect directions has been shown (Steen et al., 2023, Schizophr Bull).

We have linked childhood trauma with cortisol dysregulation, showing elevated long-term, cumulative cortisol levels (Aas et al., 2019, Schizophr Res) and increased cortisol clearance (Aas et al., 2020, Front Psychiatry), and reduced telomere length (Aas et al. 2019, Transl Psychiatry), as well as demonstrated an association between shorter telomere length and suicide attempts (Birkenæs et al., 2021, J Affect Disord), linking exposure to stressors with cortisol dysregulation and accelerated aging in severe mental disorders. A history of multiple types of childhood trauma was associated with a more severe illness course (Aas et al., 2023, Psychiatry Res), and shorter telomere length was associated with poorer verbal learning in bipolar disorder (Mlakar et al., 2023, J Affect Disord). By applying the emerging metabolomics technology, we found dysfunctions of the kynurenine pathway and the noradrenergic and purinergic systems in both schizophrenia spectrum and bipolar disorders (Steen et al., 2020, Psychol Med).

Cardiovascular risk: We showed modest improvements in the level of cardiovascular disease risk factors in bipolar disorder but no improvements in individuals with schizophrenia during the last decade (Rødevand et al., 2019, Acta Psychiatr Scand). Tobacco smoking behavior and central obesity in patients with experiences of childhood trauma was found to be mediated by impusiveness and reduced cognitive control, suggesting impaired inhibitory abilities as a sequela of early trauma affecting the regulation of health behavior (Lunding et al., 2021, Eur Psychiatry; Lunding et al., 2023, Schizophr Res). Physical activity seemed to have beneficial effects on depression and memory in these patients (Aas et al., 2021, World J Biol Psychiatry).

Moreover, we indicated a link between low-grade inflammation and abnormal neutrophil activation and atherogenic lipid ratios (Reponen et al., 2020, Front

Psychiatry), and dysregulation of metabolic hormones such as insulin, adipokines and thyroid stimulating hormone, both related and not related to psychopharmacological treatment including sex-differences, in severe mental disorders (Reponen et al., 2021, Front Psychiatry; Johansen et al., 2022, Psychoneuroendocrinology; Johansen et al., 2022, Schizophr Res). By analyzing genome-wide association study summary statistics, extensive polygenic overlap between severe mental disorders and body mass index was demonstrated with a mixture of association directions; however, with a preponderance of discordant ones in schizophrenia, suggesting environmental factors as main drivers of weight gain in these patients (Bahrami & Steen et al., 2020, JAMA Psychiatry).

Treatment: We indicated a link between treatment-resistance to antipsychotic medication and higher polygenetic risk of schizophrenia (Werner et al., 2020, Schizophrenia Research), suggesting that treatment-resistance is related to genetic factors that also drive core pathophysiological processes in schizophrenia. Moreover, we showed higher serum levels of second-generation antipsychotics to be associated with slightly improved attention, but worsened memory and executive performance, suggesting the need for careful antipsychotic dosing in patients with severe memory and executive problems (Steen et al., 2017, World J Biol Psychiatry).

Two candidates have defended their thesis for the degree of PhD during the second phase of the centre period.

Continuation of the group's research

We will continue to develop the research profile by integrating biological measurements at different levels of regulation, including metabolomics, proteomics and genetics, with clinically focused studies in severe mental disorders. Collaborations with labs and relevant expertise are established as well as with the clinics.

The collaboration with other groups and researchers from NORMENT continues; specifically, we will be actively involved in the Youth-TOP project, an established project within NORMENT investigating clinical and biological aspects of psychosis among young people. Moreover, new collaborations with European groups on cardiovascular risk, proteomics, infections and inflammation in severe mental disorders have recently been initiated.

Our studies indicate that most of the low-grade inflammation in severe mental disorders is explained by other factors than the illness genetics, autoimmunity and infection rates

Imaging Psychosis

Group Leader

Ingrid Agartz

Research focus

The focus of the group's research is to characterize brain morphology and function in severe mental disorders (schizophrenia and bipolar disorders) in a longitudinal perspective, and study the relationship with disease etiology (genes and environmental factors) and early life risk factors (e.g. obstetric complications, infections) and with the clinical phenotype and medication. The project uses magnetic resonance imaging (MRI) methodology (structural, diffusion-weighted, and functional MRI). MR brain phenotypes (e.g. cortex thickness, volume, area and folding, myelin mapping, contrast, white matter tracts, functional network dynamics) are measured. We follow brain trajectories over 13 years.

One subproject (Youth-TOP) focuses on early-onset psychosis (EOP) disorders and bipolar disorders in adolescents, their brain development over time, biomarkers, and early risk factors. We participate in international consortia and coordinate multi-site studies on adolescent psychosis. The goal is to find the biological mechanisms, brain correlates, and important antecedents to severe mental illness to improve knowledge, clinical diagnosis, and treatment.

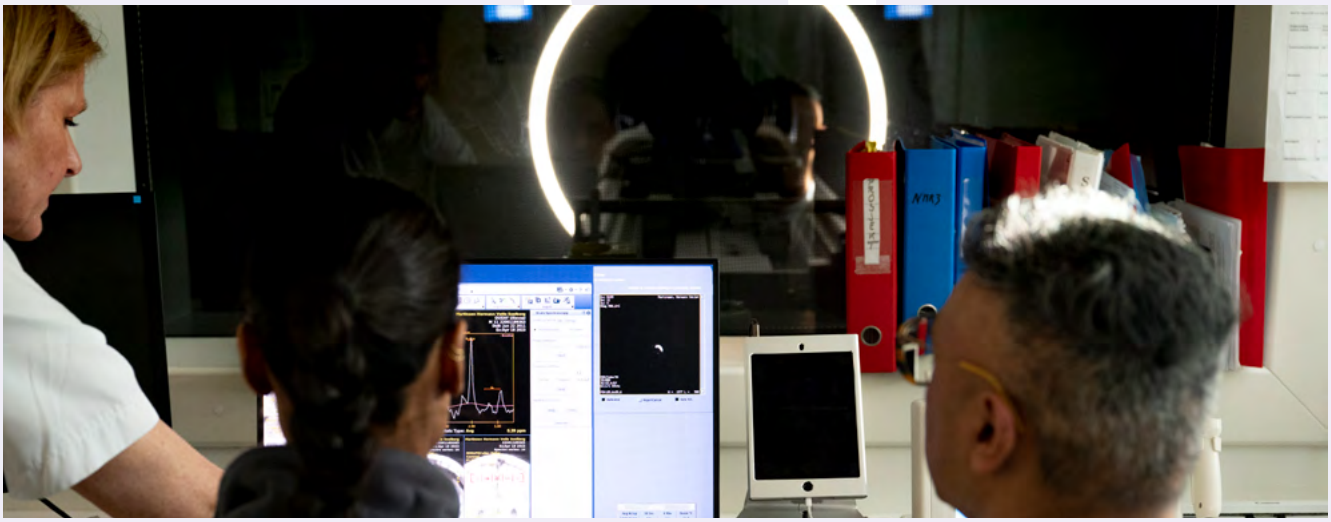
Achievements

The group contributed data to the TOP-project, Youth-TOP study, and Karolinska Institutet psychosis cohorts. Youth-TOP comprises the largest adolescent EOP-cohort investigated with MRI, cognitive testing, blood markers, national registry data and clinical follow-up. We lead the multisite Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Early Onset Psychosis (EOP) Working Group. We also developed new MRI protocols for myelin mapping in white and gray matter and assessed measurements reliability (Nerland et al, 2021, Neuroimage; 2022, Hum Brain Mapp). Standardized normative scoring tables of cognitive performance data from 502 healthy adolescents (Smelror et al, 2019, Schizophr Bull) were developed. Among numerous brain imaging findings, we find specificity of volumetric differences in individual nuclei of the amygdala, thalamus, hypothalamus and hippocampal subfields (Barth et al, 2021, Schizophr Bull; Haukvik et al, 2022, Hum Brain Mapp; Mørch-Johnsen et al, 2023, Schizophr Bull; Ruggeri et al, 2023, Schizophr Bull.). Cortical gray/white matter intensity contrast is altered in primary sensory and motor regions (Jørgensen et al, 2016, Psychol Med) suggestive of altered cortex myelination.

In a 13-year follow-up of schizophrenia, cortical measures were not reduced at a faster rate than in healthy individuals but minor reduction from antipsychotic treatment was noted (Barth et al, 2020, Schizophr Res). Psychotropic medication use is associated with altered brain structure (Barth et al., 2020; PLoS One; Di Sero et al, 2019, Schizophr Res; Jørgensen et al, 2017, Acta Psychiatr Scand).

Antipsychotic medication use is associated with a regional pattern consisting of larger basal ganglia volumes and thinner cortices. We demonstrate relationships to clinical symptoms (Mørch-Johnsen et al, 2017 Schizophr Bull) and observe brain effects from alcohol use, BMI, cigarette smoking and vitamin D (references not shown) and importance of sex differences (Barth et al, 2022, Front Psychiatry; Barth et al, 2023, Schizophr Bull). In a pioneer study using cardiac-MRI, ventricular ejection fraction was pathologically reduced in antipsychotic-treated men with schizophrenia (Andreou et al, 2020, Schizophr Res).

Among patients with severe mental disorders but not healthy controls, cytomegalovirus infection was associated with smaller cortical surface area (Andreou et al, 2022, Schizophr Bull) and smaller hippocampal dentate gyrus in males (Andreou et al, 2021, Brain Behav Immun), and Herpes Simplex virus 1 infection with smaller total grey matter and cortical volumes (Andreou et al, 2022, Transl Psychiatry).



Prospectively reported obstetric complications on brain function and structure revealed lower IQ and smaller intracranial volume in patients with schizophrenia or bipolar disorder and healthy controls (Wortinger et al, 2020, 2021, 2022 Psychol Med, 2023 Transl Psychiatry), suggesting obstetric complications' impact early structural and functional brain development in all groups.

Adolescents with early-onset psychosis are impaired on all cognitive domains demonstrating age effects and minor sex effects (Smelror et al, 2021, Neuropsychol). Cognitive test scores show association with psychosis symptoms and impaired functional outcome (Mørch-Johnsen et al, 2022, Front Psychiatry). Default functional connectivity network is weaker in cortical regions (Hilland et al, 2021, Neuroimage Clin). We demonstrate altered biomarkers (Andreou et al, 2021, Psychol Med) and lower tau protein (Andreou et al, 2022, J Psychiatr Res) in early-onset psychosis.

Cytomegalovirus-exposed patients have lower cognitive performance and lower verbal IQ relative to non-exposed patients, and indicate that adolescent patients might be susceptible to a negative impact of this infection (Calkova et al, 2022, J Psychiatr Res). Inflammatory cytokine interleukin (IL)-18 is elevated (Wedervang-Resell et al, 2020, Psychoneuroendocrinology). Activation of inflammatory pathways in psychosis disorders may thus occur in early-onset psychosis.

A mega-analysis from 11 adolescent EOP cohorts showed smaller intracranial volume and hippocampus and larger caudate and ventricles in EOP (Gurholt et al, 2022, Human Brain Mapp). We find a similar profile of volumetric structures as in adult-onset psychosis disorders except for low intracranial volume and large caudate volumes. In a multi-site diffusion-weighted imaging study using the largest EOP sample to date, we report widespread white matter microstructure alterations, most prominently in boys with schizophrenia and in individuals with shorter illness duration (Barth et al, 2023, Mol Psychiatry).

Seven PhD students from the group completed their thesis during the Centre period.

Continuation of the group's research

In 2023, the Adolescent psychosis project received a grant from the National Research Council of Norway to develop new MR brain phenotypes, study the longitudinal trajectories, and determine the essential risk factors for psychosis and brain development in adolescence, and to continue data collection and the ENIGMA-EOP working group. A PhD project on immune marker and childhood trauma began in 2023.

The postdoc and researchers in 2023 secured their own funding for continued and new projects. The three-pronged projects all study vulnerability to mental disease and heterogeneous brain neurodevelopment by investigating the importance of 1) biological sex differences, 2) early pre- and postnatal events and placental genomic risk, and 3) pathogens and immune markers. Diakonhjemmet Hospital is acknowledged for generous support throughout the entire study process.

Among numerous brain imaging findings, we find specificity of volumetric differences in individual nuclei of the amygdala, thalamus, hypothalamus and hippocampal subfields

Forensic Psychiatry

Group Leader

Unn Kristin H. Haukvik

Research focus

Violence committed by persons suffering from severe mental disorders is a tragedy for the people involved, the treating health services, and the society at large. A key to prevent such events is to understand the complex biopsychosocial underpinnings of violence associated with severe mental disorders.

Since 2018, research group's main aim has been to study violent behaviour in severe mental disorders by combining frontline MRI-methodology with social-, psychological-, and clinical characteristics and registry data in the search for mechanistic underpinnings and targets for treatment and prevention. We have also explored legal aspects of violence commited by persons with psychosis through interdisciplinary collaboration with scholars in law and philosophy.

Achievements

Using advanced MRI methods and modelling, we have reported novel association between brain morphology and violent behaviour. We have shown brain cortical abnormalities related to neurodevelopment, in areas involved in sensory processing, emotion recognition, and reward (Storvestre et al., 2019, Psych Res Neuroimaging), and widespread reductions in white matter integrity (Tesli et al., 2019, Eur Arch Clin Psych), and also affected by psychopathy traits (Tesli et al., 2021, Schiz Bull Open).

Hippocampal subfield volume reductions are associated with schizophrenia and bipolar disorder with (Tesli et al., 2020, Eur Arch Clin Psych) or without (Haukvik et al, 2018, J Clin Psych, 2022, Hum Brain Mapp) a history of violence. The amygdala which is key to affect regulation and fight-or-flight responses show reduced nuclei volumes associated with violence and psychosis (Bell et al., 2022, Psych Res Neuroimaging).

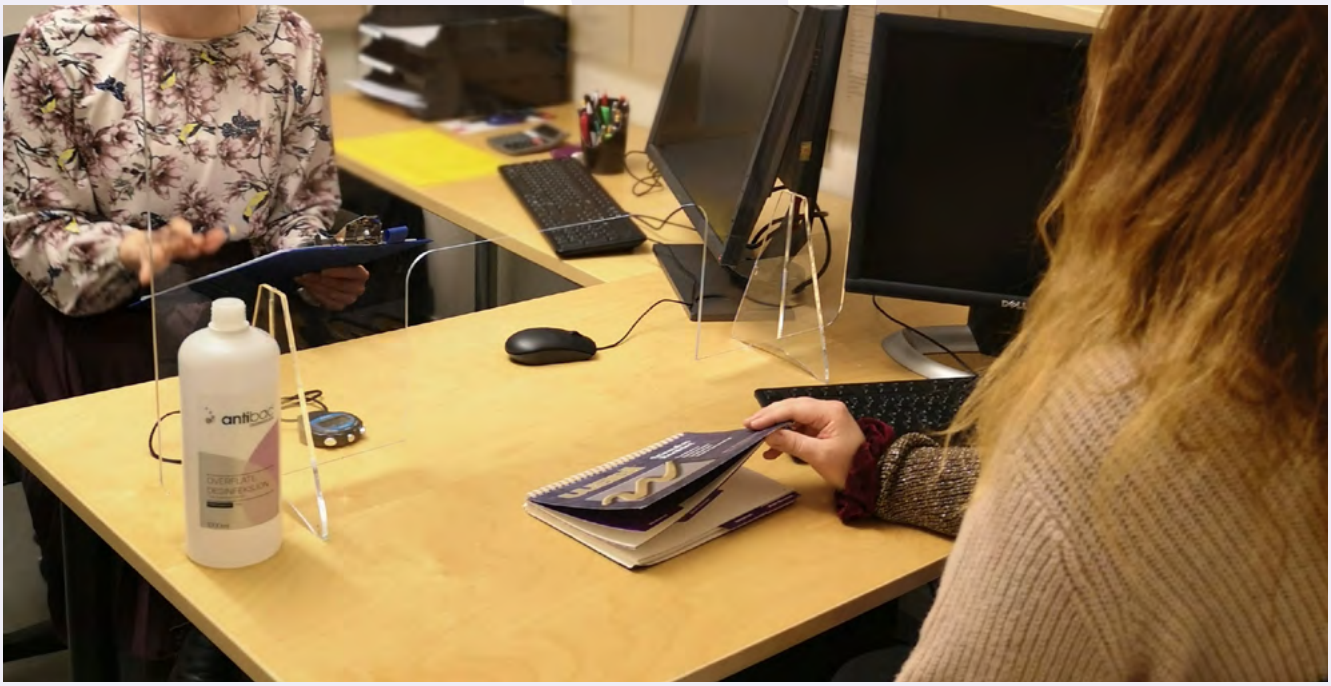
The brain age gap (i.e., the discrepancy between real age and MRI-based brain age) of persons with psychosis with or without a history of violence is higher than in controls, but not altered in non-psychotic persons with a history of violence (Tesli et al., 2022, Neuroimage Clinical).

By applying novel normative modelling of brain heterogeneity in forensic psychiatry, we found extreme deviations associated with violence and psychosis on an individual level within the subcallosal and insular cortices, and the cerebellum (Haukvik et al, submitted). By analyzing gene expression data in human post-mortem brain samples, we demonstrated the involvement of oxytocin signaling in mental disorders (Rokicki et al., 2022, Neuropsychopharmacology).

Our clinical studies span biological, psychologcial, and social domains. We found no support for an association between cholesterol and aggression as a state marker (Hjell et al., 2021, Brain Behav). The inflammation marker Il18b was associated with agitation (Hjell et al., 2022, Psychoneuroendocrinology), whereas impulsivity traits were not linked to inflammation markers but lithium use (Hjell et al., 2023, BMC Psychiatry). Psychosis patients with a history of violence show reduced insight (Fischer-Vieler et al., Schiz Bull Open). They show lower levels of core psychopathy traits such as shallow effect, lack of remorse and empathy, which could suggest they would be more responsive to treatment (Bell et al., 2023, Nord J Psych).

Patients with a history of violence have experienced more severe childhood trauma and neglect than non-violent schizophrenia patients (Storvestre et al., 2020, Front Psychiatry). Violent offenders with and without psychosis show social cognitive impairments, related to theory of mind (Vaskinn et al., 2023, Schiz Bull).

A multilevel and inter-disciplinary analysis of different rules of legal insanity, show that the Norwegian model has advantages and limitations compared to other mixed models (Gröning et al., 2020, New J Europ Crim Law).



The Norwegian model can be utilised to systematize and reconsider the central philosophical, legal, and medical premises involved in the insanity debate (Gröning et al., 2022, Int J Law Psych), which constitute a key scientific method development within this field.

The clinical sTOP study comprises a unique cohort of persons from security forensic psychiatry wards and prisoners serving a preventive detention sentence, where we have collected MRI scans, EEG recordings and thorough clinical characteristics including blood samples. As a thematic research group we have collaborated closely with the other groups within the centre and pioneered the use of advanced statistical modelling and novel MRI-segmetation algorithms in forensic psychiatry.

We have established and developed an inter-disciplinary national collaboration between NORMENT and the SIFER network of forensic psychiatry research, the correctional services, clinical forensic psychiatry wards, and strengthened this research area within Norway.

Thus far, one PhD candidate has defended her thesis, and five other PhD candidates will hand in their thesis during 2023-24.

Continuation of the group's research

We will continue working with researchers from the centre, with the sTOP-study as part of NORMENT2050. We will expand the sTOP study by including a cohort from South Africa with University of Cape Town, and through a newly established Scandinavian forensic psychiatry collaboration. We will explore the develoment and comorbidity of anti-social behaviour in psychosis through molecular and imaging genetic methods and registry data (HSØ-funded).

In the PreVio project, we will collaborate with hospitals, correctional services and the police in a multilevel study of trajectories and prevention of violence in severe mental disorders. The legal perspectives will be further explored as part of a RCN-funded project at the University of Bergen. With this inter-disciplinary approach, we seek to bridge the gap between the law, clinical forensic psychiatry, and neuroscience, and continue the search for mechanistic underpinnings and targets for treatment and prevention of violence in severe mental disorders.

Using advanced MRI methods and modelling, we have reported novel association between brain morphology and violent behaviour

Translational Electrophysiology

Group Leader

Erik Gunnar Jönsson

Research focus

The group studies nerve cell function in patients with psychosis and other psychiatric disorders using electroencephalography (EEG) and related electrophysiological methods.

The electrophysiological indices are also analyzed in connection with clinical symptoms, genetic variation, morphological variation in the brain, computerized models of nerve cells, and stem cell-based methods.

The group aims to examine whether EEG-based indices of synaptic function and neuronal excitability regulation are altered in schizophrenia and bipolar disorder.

We assess effects of novel schizophrenia and bipolar disorder genetic risk loci on the EEG-based indices and to examine whether the EEG-based indices can be used to predict illness severity in schizophrenia and bipolar disorder.

Achievements

The group started up in 2015 and an EEG lab was established in 2016. The first participant was investigated the same year and during the years EEG data including three evoked response potential paradigms (visual evoked potential (VEP), mismatch negativity (MMN), pre-pulse inhibition (PPI)) as well as resting state recording with open and closed eyes have been obtained from about 850 participants.

We participate in the ENIGMA world-wide collaboration of EEG-research groups, where data from 10,000s of participants will be available to obtain robust results (Smit et al., 2021).

We found that modulation of the VEP, especially its N1b component, is a robust non-invasive index of cortical plasticity (Valstad et al., 2020, Neuroimage). Further VEP analyses showed decreased cortical plasticity in patients with schizophrenia and bipolar disorder (Valstad et al., 2021, Schizophr Bull).

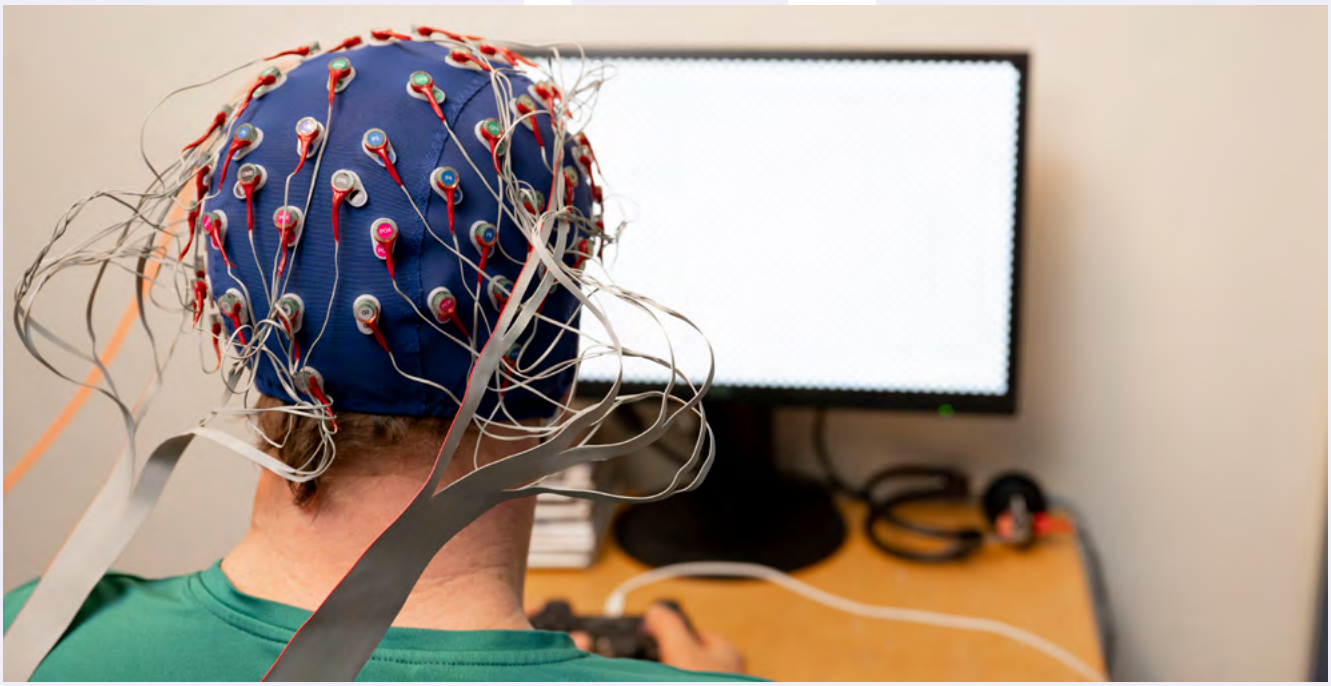
We replicated an association between the P100 component of the VEP and area of the visual cortex in healthy controls but not among patients with schizophrenia and bipolar disorder (Slapø et al., 2023, Psychiatry Res Neuroimaging).

We found that heart rate variability was reduced and associated with symptom severity in psychosis spectrum disorders (Benjamin et al., 2021, Prog Neuropsychopharmacol Biol Psychiatry).

We also found that it was possible to reduce the investigation time in a specific visual perspective task, making it better suited for clinical populations (Saether et al., 2021, Int J Psychophysiol).

We found that MMN was attenuated in schizophrenia and correlated with greater severity of psychotic symptoms and lower level of functioning (Pentz et al., 2023, Schizophr Res). N100, a negative component of the evoked response potential which we measured with the auditory PPI paradigm, was associated with thickness of the auditory cortex in patients with schizophrenia (Slapø et al., 2023, Schizophr Bull Open).

So far one PhD student has defended his thesis (Valstad, 2023). Eight master students have delivered their theses within the group.



Continuation of the group's research

We plan to continue with the research in collaboration with the other NORMENT research groups and the ENIGMA EEG consortium, with continued EEG investigations of new patients and controls.

One EEG assistant has funding for another year. Three PhD students in the group are anticipated to defend their theses within the next two years, related to 1) EEG VEP, PPI, and structural MRI data, 2) patients with autism spectrum disorders and controls, and 3) the MMN paradigm.

Two postdocs work with data in the intersection point of EEG and structural MRI and have funding for up to 2 years. One postdoc works in the intersection between electrophysiology in stem cells and humans. We anticipate interesting reports to emerge from these research efforts in the future.

We found that MMN was attenuated in schizophrenia and correlated with greater severity of psychotic symptoms and lower level of functioning

Multimodal Imaging

Group Leader

Lars Tjelta Westlye

Research focus

Structural and functional brain characteristics are highly heritable, and our research aims at increasing our understanding of how genes, environments and gene-environment interactions influence mood, cognition and risk of mental disorders during sensitive periods in life, in particular childhood and adolescence.

We use brain imaging to identify neurodevelopmental trajectories associated with genetic and environmental risk and apply machine learning to assess the clinical sensitivity and specificity on an individual level. We combine data from patients with different brain disorders and various clinical conditions, which allows us to zero in on patterns and mechanisms that are specific to each disorder.

Achievements

The group has made several contributions to the field, both in terms of methods development and empirical findings. With respect to methods, the group has developed and applied powerful multivariate and machine learning approaches, enabling estimation of individual participants' "brain age" and charting normative trajectories of brain development, opening new perspectives on the brain and its involvement in mental disorders.

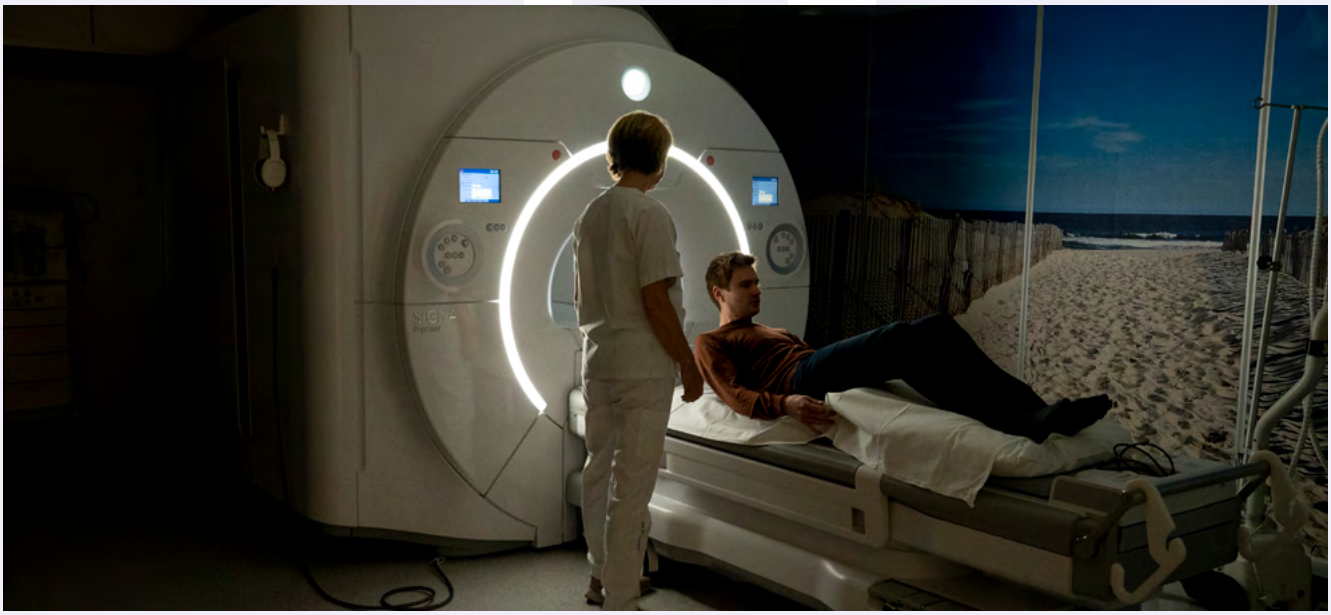
With such methods, we have increased our knowledge on the complex associations between brain structure, genetics, and environmental factors. We have reported that brain age is increased in several clinical conditions and is genetically influenced (Kaufmann et al., 2019, Nat Neurosci; Hogestol et al., 2019, Front Neurol), that parous women show less evidence of brain aging compared to their nulliparous peers (de Lange et al., 2019, PNAS), and that cardiometabolic risk factors (e.g. smoking, high blood pressure) are associated with brain age and accelerated brain ageing (Beck et al., 2021, Hum Brain Mapp).

We have identified genetic loci that influence brain age, and investigated their implications for biological processes (Leonardsen et al., 2023, Mol Psychiatry). Using normative modeling, we reported that deviations from age-expected brain white and gray matter trajectories were associated with cognitive performance, psychopathology, and early symptoms of psychosis in youth (Kjelkenes et al., 2022, Dev Cog Neurosci).

We have contributed with novel insight on gene variants linked to subcortical structures such as midbrain, pons, and medulla oblongata (Elvsåshagen and Bahrami et al., 2020, Nat Commun), basal ganglia (Sønderby et al., 2020, Mol Psychiatry) and thalamus (Elvsåshagen et al., 2021, Nat Commun). We have also shown shared genetic underpinnings between independent mental health profiles, suggesting a shared biology (Roelfs et al., 2021, Transl Psychiatry).

Combining state-of-the art tools for neuroimaging and genetic data, we discovered 351 loci associated with cerebellar morphology (Moberget et al., 2023, medrxiv). In addition to mean-level associations, we have adapted an alternative framework to identify variance-controlling loci, i.e. genetic markers associated with higher or lower individual differences among the carriers (Córdova-Palomera et al., 2021,. Mol Psychiatry).

We reported genetic loci associated with phenotypic variability in thalamus volume and cortical thickness. The variance-controlling loci implicated genes involved in brain and mental health and were not associated with the mean anatomical volumes. This proof-of-principle of the hypothesis of a genetic regulation of brain volume variability contributes to establishing the genetic basis of phenotypic variance (i.e., heritability), provides a window into the study of brain robustness, and opens new research avenues in the search for mechanisms controlling brain and mental health, including brain heterogeneity among patients with schizophrenia and population based samples with genetic risk (Alnæs et al., 2019, JAMA Psychiatry).



The group has also reported novel findings of individual (e.g., birth weight) and societal (e.g., socioeconomic status) determinants of child and adolescent brain development (Alnæs et al., 2020, PNAS). In a sample of youth where the majority had at least one psychiatric disorder, we reported cross-diagnostic patterns of impaired social skills and cognitive ability in brain structure (Voldsbekk et al., 2023, Dev Cog Neurosci).

Using a finger-printing approach on functional MRI data we demonstrated that the brain connectome develops into a more stable, individual wiring pattern during adolescence and that a delay in this tuning process is associated with reduced mental health in adolescence (Kaufmann et al., 2017, Nat Neurosci) and in patients with severe mental disorders (Kaufmann et al., 2018, JAMA Psychiatry).

We have also generated new knowledge on the role of the neuropeptide oxytocin in cognition and mental disorders, and reported enriched expression of oxytocin pathway genes in central, temporal, and olfactory regions of the human brain (Quintana et al., 2019, Nat Commun).
The group's high research activity is also reflected in major data collection efforts and involvement in a range of ongoing studies involving both patients groups and population based samples. The group's focus on early career researchers and high quality research is evident by 17 PhD candidates who have already completed their doctoral thesis and several ongoing candidates. Members of the group have been awarded various prestigious prizes and grants. Since 2018 members of the group have received a total of seven early career researcher awards, and the group alumni have successfully taken up professional positions both within academia, the public sector and the private industry.

Continuation of the group's research

The multimodal imaging group will continue its mission beyond the CoE period through well-rooted research projects investigating how dynamic changes in the brain, combined with genetic and environmental factors, impact mental health.

These projects increased both in workforce and collaborations towards the end of the CoE period, and has strengthened data collection across multiple labs, resulting in a rich, diverse and growing database. Going forward, these data will be key to understanding why some people develop mental health issues in relation to sensitive periods of life. The group is determined, and well-positioned, to continue this work well into the future.

The group has developed and applied powerful multivariate and machine learning approaches, enabling estimation of individual participants' "brain age" and charting normative trajectories of brain development, opening new perspectives on the brain and its involvement in mental disorders

Stem Cells and Mechanisms

Group Leader

Srdjan Djurovic

Research focus

The group's current research aims are to perform molecular genetic analysis to increase the knowledge and expertise in psychiatric genomics and to identify the cellular molecular networks underlying psychiatric disease. Induced pluripotent stem cells (iPSCs) are well suited for study of in vitro aspects of patients' neuronal function and thus may aid to unravel the core pathological processes behind neurodevelopmental symptoms.

We have established the required competence and facilities for human iPSC reprogramming and differentiation, enabling investigation of neuronal cells and cortical spheroids from patients and healthy controls.

Achievements

Our efforts in identifying the polygenic basis of the human brain and neurodevelopmental disorders have resulted in several translational studies focusing on links between genotypes, clinical phenotypes, and RNA expression. For example projects aimed at the ANK3 gene, for which there is strong genomic evidence of an association with bipolar disorder, analyses of genetic variation have enabled us to identify a specific variant of this gene in bipolar disorder and evaluate further which molecular and cellular functions of ANK3 are disrupted in bipolar disorder (Wirgenes et al. 2014, Br J Psychiatry; Hughes et al. 2016, Biol Psychiatry; Hughes et al. 2018, Transl Psychiatry; Hughes et al. 2020, Sci Rep).

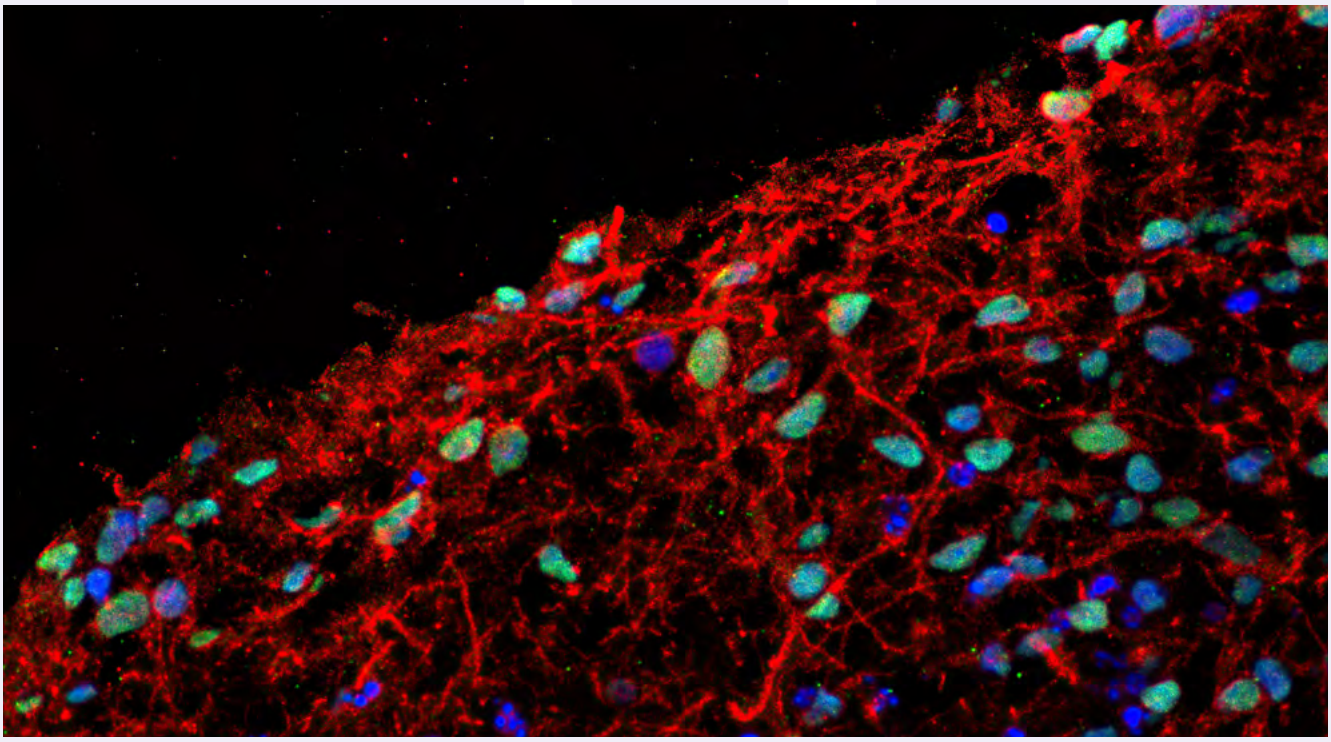
We have also examined genetic data using methods where large amounts of data can be analyzed simultaneously (microarray and RNA sequencing), to map the genetic variation with a particular focus on identifying genetic factors that are important for drug treatment response (Athanasiu et al. 2015, J Psychopharmacol; Holmgren et al. 2022, Transl Psychiatry; Akkouh et al. 2018, Sci Rep; Akkouh et al. 2020, Neuropsychopharmacology). The research group is also involved in studies that combine genetics and brain imaging. One of these projects deals with neurodevelopmental disorders where we investigate rare genetic variants, in particular copy number variants (CNVs), and how these affect the course of the disease, as well as the structure and function of the brain (Sønderby et al. 2020, 2021, Mol Psychiatry).

We have also completed the inclusion of samples for stem cells projects and building up of stem cells infrastructure including production and characterization of induced pluripotent stem cells. Validated iPSCs have been differentiated to neural progenitor cells, and regionalized neuronal subtypes, astrocytes and other glial populations, as well as cortical spheroids.

Functional phenotyping including RNA-Seq., scRNA Seq., fluorescent microscopy, and various functional assays including multidisciplinary platform combining cell electrophysiology, calcium imaging as well as voltage imaging and mitochondrial assays have been established. We have also developed a psychopharmacological screening platform for psychiatric disorders using iPSC-derived neurons and cortical spheorids.

For the reason of the complex interactions of the brain and immune system and their implications for pathophysiology and treatment, studies on the neuroinflammatory aspects of psychiatric disorders has been an emerging topic (Szabo et al. 2020, Front Psychiatry; Szabo et al. 2022, Brain Behav Immun; O'Connell et al. 2021, Psychol Med).

We published studies on the potential involvement of astrocyte-related dysfunctions in schizophrenia. These results implicate novel transcriptional dynamics in astrocyte differentiation in schizophrenia together with functional changes that are potentially important biological components of schizophrenia pathology (Szabo et al. 2021, Transl Psychiatry; Akkouh et al. 2020, 2021, Brain Behav Immun).



The stem cells are also used to study the effect of pharmacological treatment. We studied the transcriptional and functional effects of lithium, valproate and lamotrigine in neuronal progenitor cells, as well as lithium in 3-dimensional (3D) cortical spheroids models from bipolar disorder patients (Osete et al. 2021, Transl Psychiatry; Osete et al. 2021, 2023, Mol Psychiatry). Using this approach, we are currently making further attempts to use this psychopharmacological screening platform to investigate the molecular effects of other drugs such as clozapine, which is used in the clinic treatment-resistant schizophrenia patients.

In our recent study, we assessed organoid maturation at several time points, which enabled us to establish the persistent nature of the disturbances throughout neurodevelopment as an early contribution to disease risk (Akkouh et al. 2023, Biol Psychiatry).

Our research group has been responsible for the management and operation of the biobank and stem cell facilities at NORMENT. This CRU includes sampling, treatment of samples (storage, tracking, retrieval) and shipment between different partners, as well as data processing/coordination to ensure quality of associated data for the collected biobank samples. New national and international collaborations have also been established.

During the Centre period, 3 PhD fellows defended their thesis, and 2 more are in the finalizing phase.

Continuation of the group's research

We will continue with the projects including (i) human iPSC technologies in psychiatric molecular genetics, (ii) establishment of pipeline for functional characterization of new gene loci identified for psychiatric diseases, as well as (iii) continue with further studies on neuro-immune interactions and (iv) genetics of neuropsychopharmaceutics. We also want to extend to develop and maintain infrastructure/platform activities on biobanking, database, sample preparation and quality control, including cooperation and biobanking with the national cohorts and further collaboration with other large-scale studies. Further attempts in advancing transdisciplinary culture of change and adaptability in the rapidly evolving field of genomics and novel technologies are also in progress.

The stem cells are also used to study the effect of pharmacological treatment

Molecular Risk Factors

Group Leader

Vidar M. Steen

Research focus

The group aims at identifying and understanding genetic and biological factors that are involved in illness mechanisms and therapeutic response during pharmacological treatment of schizophrenia and bipolar disorder. We have used a combination of clinical data, biomarker screening and functional studies in patient samples and various experimental models.

A major hypothesis has been that lipid biosynthesis-promoting actions of antipsychotic drugs may be relevant for the metabolic adverse effects but also their therapeutic effects in patients with psychotic disorders.

We have also focused on the complex interplay between metabolic factors and inflammation processes in development of psychosis and during antipsychotic treatment. The research group is also responsible for running the Genomics Core Facility at the University of Bergen, to provide guidance and service on large-scale genomic analyses, such as whole genome-, exome- and RNA sequencing.

Achievements

Before and during the NORMENT period, we used in vitro cell culture experiments and rat studies to demonstrate that several antipsychotic drugs induce lipid-production in cells through activation of the SREBP transcription factors that control many lipid biosynthesis enzymes, and that genetic variantion in this system is associated with risk for schizophrenia (Steen VM et al., 2017, Eur Neuropsychopharmacol).

We developed the rat model to include long-acting formulations of antipsychotics, to monitor weight gain and other metabolic effects during one year of drug exposure (Ersland et al., 2019, Int J Neuropsychopharmacol).

Of relevance for a possible link between the lipogenic effects of antipsychotics and their therapeutic effects, we found that subchronic exposure with olanzapine lead to increased expression of myelination-related genes in the fronto-medial cortex of rat brain (Ersland et al., 2017, Transl Psychiatry).

These experimental data were translated into the clinical setting, to further explore the potential connections between metabolic effects and immune-related changes in serum versus the clinical outcome in antipsychotic-treated patients with psychotic disorders.

In a sample of patients with schizophrenia, we examined genetic variation in more than 100 myelination-related genes and confirmed the genetic association between the SREBP system and risk for schizophrenia (Stokowy et al., 2018, Sci Rep).

We also found that an increase in serum HDL level is associated with less negative symptoms (Gjerde et al., 2018, Schiz Res) and improvement in verbal learning (Gjerde et al., 2020, Eur Arch Psychiatry Clin Neurosci) after one year of antipsychotic treatment in first-episode psychosis.

We have also contributed to document differential effectiveness between three antipsychotic medications and different patterns of response in patients with schizophrenia-spectrum disorder (Johnsen et al., 2020, Lancet Psychiatry). Interestingly, we have found that patients with schizophrenia and bipolar disorder display a similar global gene expression signature in whole blood that reflects elevated proportion of immature neutrophil cells with association to lipid changes (Torsvik et al., 2023, Transl Psychiatry).

Post-hoc analysis has demonstrated a positive correlation with triglyceride and a negative correlation with HDL-cholesterol. These findings of neutrophil granulocyte-associated transcriptome signatures in both SCZ and BD point at altered innate immunity pathways with association to lipid changes and potential for clinical translation that will be further examined in the post-NORMENT period.

Finally, we have contributed with clinical, cognitive and genetic data to several GWAS papers, including both NORMENT-headed projects and international consortia. These studies have demonstrated how common genetic variants influence human subcortical brain structures (Hibar et al., 2015, Nature 2015), subcortical brain volumes and risk for schizophrenia (Franke et al., 2016, Nat Neurosci), shared heritability in common disorders

of the brain (Brainstorm Consortium, 2018, Science), cognitive functions (Savage et al., 2018, Nat Genet), heritable patterns of apparent aging of the brain (Kaufmann et al., 2019, Nat Neurosci 2019), human brainstem structures and their involvement in common brain disorders (Elvsåshagen et al., 2020, Nat Commun), and longitudinal changes in brain structure across the lifespan (Brouwer et al., 2022, Nat Neurosci).

During the Centre period, one PhD fellow defended her thesis.

Continuation of the group's research

The research projects, competence, collaborations, networks and infrastructure that have been established during the NORMENT period will be the basis for continued research in our group.

We have generated rich transcriptomic and lipidomic data sets for several clinical samples (TOP, BeStInTro) of patients with psychotic disorders, and will pursue the studies of connections between metabolic effects and immune-related changes versus the clinical outcome in antipsychotic-treated patients with psychotic disorders. We intend to continue the existing CoE collaborations through the NORMENT 2050 network, and several of the NORMENT group leaders are planning to establish a research center for clinical psychosis research.

These experimental data were translated into the clinical setting, to further explore the potential connections between metabolic effects and immune-related changes in serum versus the clinical outcome in antipsychotic-treated patients with psychotic disorders

Epigenetics of Mental Disorders

Group Leader

Stephanie Le Hellard

Research focus

In the first Centre of Excellence years, we were involved in the identification of genetic factors implicated in psychiatric disorders, cognitive and brain imaging with other NORMENT groups and international consortia. In the second phase, our original contribution to the research field and to NORMENT has been a focus on epigenetic mechanisms. Epigenetic mechanisms can explain molecular risk factors beyond genetic effects. Epigenetic factors can be modified with age, with sex development, with environmental influences, and with treatments.

We have investigated disease specific DNA methylation differences in schizophrenia and the effect of specific environmental risk factors. We also focus on the dynamic changes of DNA methylation that could be associated with treatment and response to treatment, and which could identify potential responders or non responders before treatment (e.g. antipsychotics, behavioural therapy or electroconvulsive therapy).

Achievements

Identification of genetic variants associated with mental disorders and across disorders: In the first years of our research we looked at genetic factors implicated in mental disorders and related traits.

We have been involved in the identification of many genetic variants associated with brain morphological traits (Kaufmann et al. 2019, Nat Neurosci; Sonderby et al. 2021, Transl Psychiatry), with cognitive traits (Le Hellard et al. 2017, Schizophr Bull; Christoforou et al. 2014, Genes Brain Behav), and genetic variants associated with mental disorders (Havik et al. 2011, Biol Psychiatry; Havik et al. 2012, PLoS One). We also show that at the gene levels many risk variants are associated across traits (Polushina et al. 2017, Transl Psychiatry; Polushina et al. 2021, Transl Psychiatry).

The implication of recent human evolution in the genetic risk for schizophrenia: The persistence of a disease like schizophrenia despite burden on patients has been hypothesised to be associated with recent evolution of the human genome. Using recent large genetic studies, we show that indeed regions that have been recently selected in the human evolution have more effects in the genetic risk for schizophrenia than the rest of the genome (Banerjee et al. 2018, BMC Evol Biol; Banerjee et al. 2019, Schizophr Res).

A major focus of our research has been to generate large datasets with DNA methylation in individuals with schizophrenia and bipolar disorder and healthy controls. Using this dataset we could perform several studies to identify DNA methylation changes associated with disease and with environmental exposure.

Identification of DNA methylation changes associated with psychosis: We have obtained DNA methylation data on a large number of cases with psychosis and controls. In this dataset, we examined differences in cell blood counts between cases and controls (Villar et al. 2023, Transl Psychiatry). We reported significant differences between cases and controls for several cell types and showed that these differences were also observed in untreated patients. Using our samples and samples publicly available, we reported differences in DNA methylation between individuals with schizophrenia and controls. Furthermore, we showed that these differences are largely influenced by the individual sex, with females showing larger differences. Finally, we showed that in samples of a few thousand individuals, a poly-methylation score could explain up to 2.5% liability in schizophrenia (Tesfaye et al. in review).

Identification of DNA methylation changes associated with environmental factors: We have also examined the influence of different environmental factors on DNA methylation. We have shown differences associated with current use of cannabis and shown that these differences are not significant anymore in individuals that have stopped using cannabis (Stavrum et al. submitted).

We have identified DNA methylation differences in individuals that have been exposed to trauma in childhood, and some of these differences were in genes that have been implicated in trauma related mental disorder (Løkhammer et al. 2022, Transl Psychiatry). We also identified DNA methylation differences in individuals that had been exposed to asphyxia at birth and that these effects interacted with the risk for a psychosis diagnosis in adults (Wortinger et al. preprint).

Identification of DNA methylation differences associated with response to electro convulsive therapy: We have also performed the comparison of DNA methylation in patients that have undergone treatment by electric convulsive therapy and have identified differences between responders and non responders.

During the Centre period, two candidates defended their thesis for the degree of PhD.

Continuation of the group's research

We are financed for different projects which we will continue in the near future: Identification of differences in DNA methylation during treatment with electroconvulsive therapy for major depression, and concentrated exposure therapy for patients with anxiety disorders. We are also looking at genetic variants associated with resilience to exposure to trauma. We are leading a large meta-analysis for the identification of DNA methylation differences between cases with bipolar disorder and controls.
In the long term we will continue our research on the epigenetic mechanisms of treatment of mental disorders and especially will move towards combining epigenetic biomarkers with other markers in order to develop predictive scores for diagnosis and treatment response.

We have investigated disease specific DNA methylation differences in schizophrenia and the effect of specific environmental risk factors

Pharmacology and Intervention

Group Leader

Erik Johnsen

Research focus

The group became part of NORMENT in the second 5 years of the Centre period, and overlaps with the Bergen Psychosis Research Group at Haukeland University Hospital and University of Bergen. We study schizophrenia spectrum disorders at several levels in an integrated fashion, including clinical symptoms and signs, treatment effects and side effects, brain imaging measures, as well as molecular vulnerability and disease mechanisms. The research group has 20 years of experience in conducting researcher initiated drug trials independently of pharmaceutical industry.

Our specific aims in NORMENT have been to identify differential effectiveness among antipsychotic drugs; identify predictors of treatment effects and side effects at the individual level to facilitate personalized medicine; unravel disease mechanisms and potential new treatment targets; investigate the value of immune-modulating treatment in psychosis; and investigate the protective value of omega-3 fatty acids to avoid conversion to psychotic disorder in persons with ultra-high risk of psychosis.

Achievements

Clinical outcomes: We have documented differential effectiveness between antipsychotic medications and different patterns of response in patients with schizophrenia-spectrum disorder (Johnsen et al. 2020, Lancet Psychiatry; Sinkeviciute et al. 2021, J Clin Psychopharmacol; Sinkeviciute et al. 2018, Neuropsychiatry; Bjarke et al. 2020, Nord J Psychiatry; Drosos et al. 2022, World J Psychiatry; Kjelby et al. 2023, Schizophr Res; Kjelby et al. 2018, J Psychiatr Res), and that men and women respond differently to particular antipsychotics, both in terms of efficacy and side effects (Hoekstra et al. 2021, NPJ Schizophr).

We have found that childhood trauma may be associated with cognitive performance (Mørkved et al. 2020, Schizophr Res Cogn), and influence antipsychotic effectiveness, as the treatment effects seem to be delayed in those with childhood trauma compared to those without (Mørkved et al. 2022, Schizophrenia Res), but substance use does not, contrary to common beliefs, influence efficacy or side effects of antipsychotic drugs (Alisauskiene et al. 2021, Subst Use Misuse; Alisauskiene et al. 2019, Nord J Psychiatry).

Moreover, cognitive performance increased significantly during antipsychotic drug use, with no differences between the comparator drugs (Anda et al. 2021, Schizophr Res Cogn), and atypical antipsychotics improve insight (Stabell et al. 2023, BMC Psychiatry). As part of the European Long-acting Antipsychotics in Schizophrenia Trial (EULAST), we have demonstrated non-superiority of long-acting antipsychotics compared to the oral variants of the same drugs, for treatment discontinuation (Winter-van Rossum et al. 2023, Lancet Psychiatry).

These findings are important for the choice of treatment and can be directly used in clinical settings to improve pharmacological treatment outcomes. Another venue of research in the group has addressed the controversial issue of how use versus non-use of psychotropic drugs impact outcomes related to premature mortality in persons with schizophrenia.

Use of antipsychotics compared to periods with non-use seems to strongly reduce risk of all-cause mortality (Strømme et al. 2021, Schizophr Res), and the risk reduction might at least in part be related to the documented reduced risks of readmission (as a proxy for disease severity) (Strømme et al. 2022, Schizophr Res), and readmission associated with agitation and aggression in periods with use of antipsychotics (Strømme et al. 2022, J Psychopharmacol). On the other hand, use of benzodiazepines was found to increase the risk of readmission (Strømme et al. 2022, J Psychopharmacol). This finding has direct relevance to clinical decision making in psychosis treatment.

Basic mechanisms outcomes: The group has had particular interest in inflammation and immunology in the search for critical biology in the pathogenesis of schizophrenia, and underlying different symptom domains, with the aim of identifying new drugable treatment targets (Kroken et al. 2019, Front Psychiatry). We have identified inverse associations between the inflammatory marker CRP and cognitive performance (Fathian et al. 2018, Acta Neuropsychiatr), relations between proinflammatory cytokines and different courses of depression in schizophrenia-spectrum disorder (Hoprekstad et al. 2023, Schizophr Res), and inverse association between the proinflammatory cytokine IFN-γ and psychomotor speed (Larsen et al. 2021, Brain Behav Immun Health).

Finally, different antipsychotic drugs were found to impact CRP levels differently, some being pro-inflammatory, other antiinflammatory in different phases of psychosis (Fathian et al. 2022, Schizophr Res). Taken together the findings suggest that the proinflammatory state may be related to some of the symptoms in schizophrenia left untargeted by other treatments, and that anti-inflammatory treatment may potentially have beneficial effects particularly on cognitive dysfunctions.

Accordingly, we started a double-blind, randomized, controlled trial, with add-on prednisolone, a potent anti-inflammatory drug, or placebo in early schizophrenia (the NorPEPS-trial) (Nasib et al. 2020, Trials), to investigate whether six weeks of anti-inflammatory treatment could reduce symptoms and improve cognition. NorPEPS had to be prematurely terminated because of the COVID-19 pandemic, but have collected clinical data that will be associated with data from repeated MRI's (Free Water Imaging) and inflammatory markers in serum in search of relevant associations..

During the NORMENT centre period a total of 6 PhD-candidates have had their doctoral dissertations.

Continuation of the group's research

The group will continue its research and collaborations with the NORMENT partners through among others the NORSMI network (clinical multi-centre studies and shared biobank), NORMENT 2050 (shared database), and Mohn Research Centre for Regenerative Medicine (stem cell models in schizophrenia).

The group continues to be organized as the Bergen Psychosis Research Group, and will still focus on clinical intervention studies, such as the semaglutide add-on treatment for metabolic control in antipsychotic-using patients (STABIL-NOR) study and the exercise therapy in mental disorders-study that aims to investigate different types of exercise in severe mental disorders.

We have documented differential effectiveness between antipsychotic medications and different patterns of response in patients with schizophrenia-spectrum disorder

Affective Disorders

Group Leader

Ketil Ødegaard

Research focus

The group became part of NORMENT in the last 5 years of the centre period, and overlaps with the Bergen Bipolar and Depression Research Group at Haukeland University Hospital and University of Bergen. We study bipolar disorders and other illnesses of depression using different methods and approaches.

Our studies focus on psychopharmacology, neurostimulation treatments, sensor technology, registry research, cognitive function, genetics and other biological biomarkers, as well as brain imaging.

The research group has a translational focus with the aim of contributing to increased etiological knowledge of pathophysiological processes in affective disorders, mainly through clinical intervention studies. This report sums up findings from research published by our group the last 5 years.

Achievements

We have made significant contributions to the understanding of ECT treatment, drawing from local, national, and global studies. These studies, including the Global ECT-MRI Research Collaboration (GEMRIC) led by Leif Oltedal in Bergen and studies based on data from the regional ECT registry in Western Norway led by Ute Kessler, have revealed several novel findings.

For example, a randomized controlled trial follow-up study showed that right unilateral electroconvulsive therapy does not result in more cognitive impairment than pharmacologic treatment for treatment-resistant bipolar depression (Bjoerke-Bertheussen 2018, Bipolar Disord).

Another study has demonstrated the failure of remifentanil to confer long-term benefits as an adjunct to anesthesia for ECT (Kessler 2018, Br J Anaesth). In MR based studies, we have assessed the relationship between the volume of the human hippocampus and clinical response following ECT (Oltedal 2018, Biol Psychiatry), the distribution of brain changes induced by ECT (Ousdal 2020, Biol Psychiatry), the association between structural changes and clinical outcome (Mulders 2020, Brain Stimul), and the impact of body weight on subcortical volume change and associated clinical response following ECT (Opel 2021, J Psychiatry Neurosci) as well as the short and long-term effects of single and multiple ECT sessions on brain gray matter volumes (Brancati 2021, Brain Stimul).

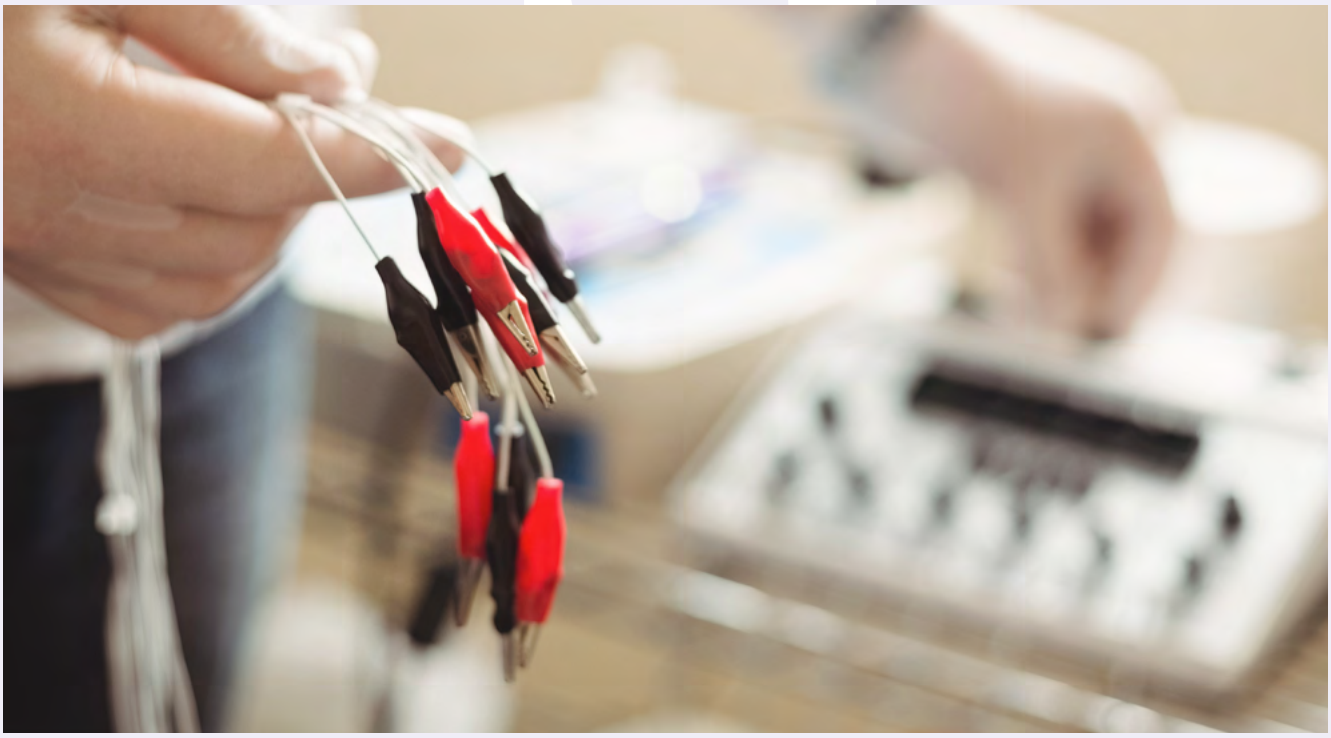
Further, we investigated concentrations of the neurotransmitter gamma-aminobutyric acid (Erchinger 2020, Brain Behav) and other metabolites that can be assessed with Magnetic Resonance Spectroscopy in depressed subjects treated with ECT (Erchinger 2021, Front Psychiatry).

Additional studies have examined the electrical field in relation to the effect of ECT on the brain volume (Argyelan 2019, Elife). Further, we have investigated the impact of ECT on blood tryptophan metabolites (Aarsland 2019, Brain Stimul), and explored the effects of ECT on memory functions (Blomberg 2020, Prim Care Companion CNS Disord).

Based on our clinical experience, study findings and literature review (Ousdal 2022, Biol Psychiatry), we have proposed that ECT works by disrupting aberrant neuronal network activity, stimulating neuroplasticity (potentiation) to facilitating the formation of new neuronal connections (rewiring); the DPR-model.

Our research group has also contributed to new knowledge about the response to lithium treatment in patients with bipolar disorder through our participation in two international research collaborations, the Pharmacogenomics of Bipolar Disorder Study (PGBD) and the R-Link initiative (Nudell 2019, Mol Neuropsychiatry; Scott 2019, Int J Bipolar Disord; Burdick 2020, Neuropsychopharmacology; Mishra 2021, Mol Psychiatry; Lin 2021, Bipolar Disord; Federoff 2022, Bipolar Disord).

We have three PhD candidates (theses to be submitted in 2023/2024) working on analyzing data collected with various sensor technology devices from patients with affective disorders, partly in collaboration with the Intromat study (INtroducing personalized TReatment



Of Mental health problems using Adaptive Technology) and machine-learning experts from the Institute of Informatics at the University of Oslo. This has led to numerous publications with interesting novel findings (Garcia-Ceja 2018, Pervasive Mobile Computing; Fasmer 2018, PLoS One; Jakobsen 2020, PLoS One; Jakobsen 2022, PloS One; Syrstad 2022, BMC Psychiatry).

The group leader of the Bergen Mood and Cognitive Function Group, Professor Åsa Hammar and her PhD candidates, are members of the Affective Research group and have led the cognition research in various sub-projects, including above mentioned ECT related findings and findings in the INTROMAT study (Myklebost 2022, Front Psychiatry).

In addition, several other papers have provided novel clinical findings of importance (Ronold 2020, Appl Neuropsychol Adult; Hammar 2022, Appl Neuropsychol Adult; Ronold 2020, Front Psychiatry).

In addition, members of our group have published several papers from other dataset and studies the last 5 years.

The research group has also been a center, recruiting patients, in a Pharmaceutical industry sponsored trial of nasal ketamine (Spravato).

During the second phase of the Centre, one candidate defended her thesis for the degree of PhD.

Continuation of the group's research

The group will continue its research and collaborations with the NORMENT partners through among others the NORSMI network (clinical multi-centre studies and shared biobank), NORMENT 2050 (shared database), and Mohn Research Centre for Regenerative Medicine (stem cell models in schizophrenia).

The group continues to be organized as the Bergen Bipolar and Depression Research Group, and will still focus on clinical intervention studies, such as a newly funded ECT-TMS study: The Neurobiological Fundaments of Depression and Its Relief Through Neurostimulation Treatments (FundECT).

We have made significant contributions to the understanding of ECT treatment, drawing from local, national, and global studies

Predictive and Pharmacological Imaging

Group Leader

Renate Grüner*

Research focus

Our research focus over the years has been on exploring and developing novel neuroimaging biomarkers, across scales and in time, to better understand underlying disease mechanisms and monitor the course of illness and treatment effects in mental health and disorders.

The group has taken on a broad range of challenges, from more technical and methodological approaches in data acquisition, analysis, and visualization to linking neuroimaging data to other relevant clinical and non-clinical factors expressing individuals' responses and reports on cognitive tasks, psychiatric symptoms, external markers on inflammation or hormone levels and more.

Achievements

Excitatory and inhibitory neurotransmission and their relations to hallucinations and pharmacological aspects, as well as identifying potential predictive factors, has been the main target of our investigations throughout the years.

Major research achievements include novel approaching of mapping dynamic brain networks and connectivity and their interplay (Beresniewicz et al. 2023, Front Hum Neurosci), such as the extrinsic mode network (EMN) and the default mode network (DMN) (Riemer et al. 2020, Sci Rep). Methodologically, these findings have been underpinned by the development of novel functional neuroimaging paradigms (fMRI) to best map the EMN and DMN networks (Hugdahl et al. 2019, PLOS One) and their relation to structural connectivity (diffusion-based mapping, DTI) (Riemer et al. 2023, Commun Med; Beresniewicz et al. 2021, Diagnostics).

The group has for many years focused on specific symptoms in schizophrenia, with a particular emphasis on auditory verbal hallucinations and auditory perception (e.g. Kusztrits et al. 2022, Psychol Psychother; Laloyaux et al. 2022, Cogn Neuropsychiatry; Næss et al. 2022, Schizophr Res). Through former Core Researcher at NORMENT, Professor Kenneth Hugdahl, several longstanding international collaborations were established that still continue to inspire and nurish our research activities in combining imaging and symptom aspects.

These include in particular our longstanding collaborations with the universities in Utrecht and Groningen, as well as Plovdiv, which have also given rise to data mining across multiple sites (e.g. Hugdahl et al. 2023, Schizophr Bull). Other international collaborations include the Padua collaboration (Spironelli et al. 2023, Schizophr; Marino et al. 2022, J Psychiatr Res).

A prerequisite in this line of reasearch is that the functional neuroimaging strongly reflects the underlying neurochemical balance between exhitatory and inhibatory neurotransmitters (Hjelmervik et al. 2022, Brain Behav; Weber et al. 2020, Front Psychiatry; Hjelmervik et al. 2020, Schizophr Bull). The group has therefore had a strong focus on developing novel methodological advances in measuring brain neurotransmitter concentrations (MRS) with an emphasis on GABA, glutamate and glutamine and also their temporal dynamics in response to cognitive tasks (fMRS) (Craven et al. 2023, NMR Biomed; Dwyer et al. 2021, Front Hum Neurosci).

Again, the work has found strong international collaborations (e.g. Bell et al. 2023, eNeuro). The group has also explored the feasibility of multinuclear magnetic resonance spectroscopy, such as phosphorus and sodium spectroscopy.

Too often are research findings reported from unimodal data, i.e. structural MRI alone. The group has taken on the challenge of exploring approaches for multimodal acquisition and analysis, by combining magnetic resonance spectroscopy with functional and structural neuroimaging, PET and more.

Both hypothesis driven and data driven approaches have been explored, including machine learning and potential prognostic features thereof. Studies have been performed examining temporal aspects, for instance in the process of repeated application of Transcranial Direct Current Stimulation (tDCS) to ease symptoms (Marquardt et al. 2022, Brain Sci; Dwyer et al. 2019, Front Neurol).

The group has estabilised collaborations to other scientific disciplines such as medical visualization and computer science. Through common collaborative efforts this has resulted in novel methodological developments in visualizing functional magnetic resonance imaging data, e.g. through time warping, integration of multimodal information, and interactive exploration of biomarkers from imaging (Garrison et al. 2020, Computers & Graphics; Solteszova et al. 2019, Computer Graphics Forum).

During the second phase of the Centre, three PhD fellows defended their thesis.

Continuation of the group's research

Over the years, the majority of the members in the research group have hold research positions at various academic levels at the Haukeland University Hospital (HUH) in Bergen and the University of Bergen (UIB). Due to the highly interdiciplinary research focus, all members in the NORMENT research group on predictive and pharmacological imaging have also been part of the two largest imaging research groups in Bergen, such as the Bergen fMRI group and /or the Mohn Medical Imaging and Visualization Centre. The research has been funded through external grants to several individual group members and will continued through these existing and hopefully new grants.

The group has for many years focused on specific symptoms in schizophrenia, with a particular emphasis on auditory verbal hallucinations and auditory perception

*Replaced Kristiina Kompus in 2021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er det håp!
NORMENT
Norsk senter for forskning
på mentale lidelser

User Involvement

During the years as a Centre of Excellence, NORMENT developed a strong and active user group, to bring the user perspective into our research activities. The users have provided valuable input and complemented the Centre in its effort to carry out research that is relevant for society.

User Council

NORMENT's User Council was established in 2016 and has consisted of individuals with lived experience, competency, and expertise related to mental health. The User Council has provided input to research strategy, practical research protocols and grant applications, and has been consulted on matters that affect participants in the studies. The User Council has also contributed to dissemination activities and helped strengthen the communication between NORMENT, the user organizations, and the community at large.

Members of the User Council have been Lena-Maria Haugerud, Fabian Stang, Fred Gerkum, Inger Hagen, Karoline Fløystad Thorsen, and Halvor Stokke Devor.

User Representatives

The Centre also employed part-time User Representatives in Oslo and Bergen. The User Representative in Oslo coordinated the User Council and brought the user perspective into research activities, including group meetings, project planning, grant applications and dissemination (Facebook, user-directed events), and acted as a link to user organizations such as the Norwegian Bipolar Association. The User Representative in Bergen coordinated the stakeholder forum "PEK", consisting of people with lived psychotic experience and next of kin.

The last years of the Centre, User Representatives were Cecilie Busch (2020-2023) and Marthe Hagen (2017-2020) in Oslo, and Anne Blindheim (2019-2023) in Bergen.

Collaboration with the Norwegian Bipolar Association

For many years, NORMENT has had a close collaboration with the Norwegian Bipolar Association. Researchers from the Centre have contributed with presentations at several seminars, webinars, and courses organized by the Association, and a volunteer in the Bipolar Association has been a member of the NORMENT User Council.

Presentation by the NORMENT User Representatives at the Final Centre of Excellence Meeting (2023).

User-directed seminar about NORMENTs research on genetic and environmental factors (2019).

International Collaboration

The research at NORMENT has been conducted in close cooperation with leading research environments, both in Norway and abroad.

International consortia and networks

Researchers at the Centre have had a central role in several international consortia and networks, such as the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium and the Psychiatric Genomics Consortium (PGC). Core Researcher Ingrid Agartz has been the chair of the ENIGMA Early Onset Psychosis Working Group, while Centre leader Ole A. Andreassen has chaired the Bipolar Disorder and CNV Working Groups. Early-career researchers Claudia Barth, Ida Sønderby, and Tiril Gurholt have been co-chairs of these working groups. Ole A. Andreassen has also chaired the PGC Bipolar Disorder Working Group, as well as the European College of Neuropsychopharmacology (ECNP) Bipolar Disorders Network.

Our international collaborations have resulted in numerous important scientific findings in high-ranked journals such as Nature and Molecular Psychiatry, particularly within the fields of psychiatric genetics and brain imaging. Large collaborative studies have been crucial to discover new risk genes for mental illness and detect alterations in brain structure and networks.

International Researchers and Guest Researchers

NORMENT has also actively recruited excellent researchers from other countries through international advertisements and networking. As a result, the Centre staff has consisted of people of 43 different nationalities. We have also emphasized the mobility of PhD students, postdoctoral fellows and senior scientists encouraging both short- and long-term research stays abroad.

Further, we have hosted students from European countries for internships, and received regular visits from international researchers coming for project meetings, collaborative discussions and to give guest lectures.

During the years, we have also had several guest researchers with part-time positions at NORMENT. All our guest researchers have collaborated closely with researchers at the Centre, contributing with knowledge and analyses, participated in project discussions, and been involved in planning of future studies.

We would like to thank the following people for their contributions to NORMENT as guest researchers:

- Professor Anders M. Dale, University of California San Diego, USA (2013-2023)
- Professor Tyler Seibert, University of California San Diego, USA (2021-2022)
- Professor Wesley Thompson, University of California San Diego, USA (2013 - 2021)
- Professor Anna Devor University of California San Diego, USA (2016 - 2018)
- Professor Tom McGlashan, Yale University, USA (2016 - 2017)
- Professor Hreinn Stefansson, deCODE Genetics, Iceland (2016 - 2017)
- Professor Sven Cichon, University of Basel, Switzerland (2014 - 2016)
- Professor Frank Larøi, University of Liège, Belgium (2014 - 2016)

EU projects

NORMENT researchers have been involved in several projects funded by the European Union, of which two have been coordinated by the Centre.

CoMorMent: Investigating comorbid mental illness and cardiovascular disease

The CoMorMent project (2020-2024, EU Horizon 2020) investigates how and why mental illness interacts with cardiovascular disease. The project takes on a big data approach, using information from 1.8 million volunteers from across Northern Europe, with the aim to identify the genetic, brain and body markers that are common in both cardiovascular and mental health conditions, thus uncovering the mechanisms underlying the higher incidence of cardiovascular disease in people with mental disorders.

Partners in the project are from Iceland (Islensk Erfda -greining EHF), Denmark (Region Hovedstaden), Sweden (Karolinska Institutet, Amra Medical AB), UK (University of Edinburgh), Estonia (Tartu Ulikool), and the USA (Multimodal Imaging Services Corporation, dba HealthLytix).

REALMENT: Using real-world big data from eHealth, biobanks and national registries, integrated with clinical trial data to improve outcome of severe mental disorders

The REALMENT project (2021-2025, EU Horizon 2020) investigates how real-world data can be used to improve treatment. The main aim of the project is to optimize the treatment of mental disorders through novel precision

medicine strategies based on current pharmaceutical options. Project partners are from Sweden (Karolinska Institutet), Denmark (Region Hovedstaden), Iceland (deCODE Genetics), Finland (University of Helsinki), Estonia (University of Tartu), Italy (University of Bari), UK (Cardiff University), the Netherlands (Vrije Universiteit, Stichting Buro ECNP), the USA (CorTechs Labs), Belgium (Janssen Pharmaceuticals), and Norway (Smerud Medical Research Int AS, DNV-GL).

INTPART projects

Researchers at NORMENT have also received funding from the Research Council of Norway for several projects in the INTPART programme (International Partnerships for Excellent Education, Research, and Innovation).

INTPART South Africa: Integrating global mental health with brain imaging and genetics in mental illness research and education

The South Africa project (2018-2022) included NORMENT and the University of Cape Town. The main purpose of the project was to combine and integrate mental health research across sites and to educate researchers in modern neuroimaging and genetic tools, and share transcultural clinical expertise. Principal investigators were Professor Ole A. Andreassen at NORMENT and Professor Dan Stein, Head of the Brain Behaviour Unit at the University of Cape Town.

INTPART France: Improving clinical services in bipolar disorder through education and research on illness mechanisms

The France project (2019-2023) was built on a long-term collaboration with researchers at INSERM and University of Paris. The project focused on clinical aspects of bipolar disorder.

The main aims were to provide better integration of research and clinical services, investigate early illness phases while providing front-line treatment, using new digital tools in data collection and clinical intervention, and to investigate underlying illness mechanisms including circadian rhythms and lithium response. Principal investigators were Senior researcher Trine Vik Lagerberg at NORMENT and Professor Bruno Etain from INSERM and the University of Paris.

INTPART USA: Simulating the multi-scale pathophysiology of mental illness

The USA project (2019-2023) was an extension of a long collaborative effort with researchers at the University of California, San Diego, now focusing on multidisciplinary neuroscience. The primary objective was to enhance the existing interdisciplinary synergy between sites, improve tools and approaches for understanding mental disease, and educate translational researchers to address questions that require integration of big data (genomics) with clinical measurements of function.

The project was headed by the Simula Research Laboratory in Oslo and also included the Centre for Integrative Neuroplasticity (CINPLA) at the University of Oslo.

CoMorMent Kick-off meeting in 2020. Oslo, Norway.


INTPART France meeting in 2019. Paris, France.

Infrastructure

The 10-year Centre of Excellence grant from the Research Council of Norway has been of high importance for building up and maintaining a well-functioning research infrastructure at NORMENT. The CoE funding has given us a unique opportunity for long-term investment in a robust and extensive system for data collection and storage, but also an organizational structure for meetings and communication supported by technical and administrative personnel.

Core Resource Units

About half of the Centre of Excellence grant was allocated to support functions at the Centre. The daily infrastructure for collection, storage, and processing of scientific data at NORMENT was divided into different units, called Core Resource Units (CRU) (Working Units in the first phase of the Centre). These sections were responsible for and had expertise in different methodological aspects of the data collection, reflecting the Centre's focus on "vertical synergy" and thereby the integration of various research methods and approaches. Most scientific projects at the Centre included several Core Resource Units, since they were based on data collected from different groups and involved both clinical and other information about the participants.

The main responsibilities of the CRUs are listed on these two pages.

Clinical CRU

- Recruitment and standardized clinical assessments of participants with psychotic disorders
- Development, maintenance and quality assurance of clinical assessments and protocols

Cognitive CRU

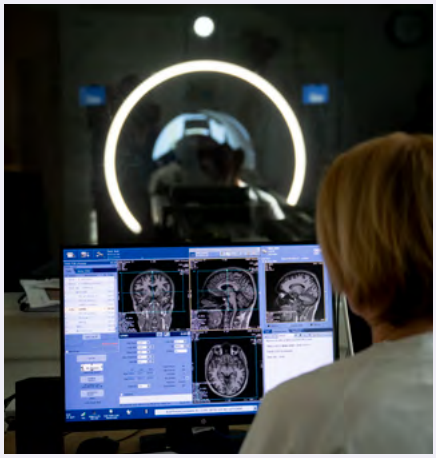
- Neuropsychological assessments of patients with psychotic disorders and healthy control individuals, including neuropsychological reports for clinical participants
- Development, maintenance and quality assurance of cognitive assessments and protocols

Database and Biostatistics CRU

- Development and maintenance of secure and accessible storage structures, analytical tools, and communication platforms to facilitate the process between data collection and data distribution
- Procedures for data formatting, transfer, and storage across all units; solutions for electronic data collection and ethical approvals

Neuroimaging CRU

- Infrastructure for magnetic resonance imaging (MRI) and electroencephalography (EEG) in the study of severe mental illness
- Implementation of standard protocols for MRI and EEG, and procedures for brain imaging data collection, quality control, storage, and processing



Functional Genomics CRU

- Infrastructure for large-scale analysis of the genome, focusing on global gene expression and epigenomics
- Validation experiments in cell cultures and animal models, including RNA sequencing and DNA methylation assays of clinical samples
- Implementation and development of bioinformatic tools for data analysis, including multiomic methods for integration of corresponding genomic, transcriptomic and epigenomic data.

Biobank and Stem Cells CRU

- Coordination of biobank activities, including biological sampling (blood, urine, saliva etc.), storage of samples, quality control, and shipment between partners
- Facilities for human induced pluripotent stem cell (hiPSC) technology allowing investigation of neuronal cells from participants

Pharma and Intervention CRU

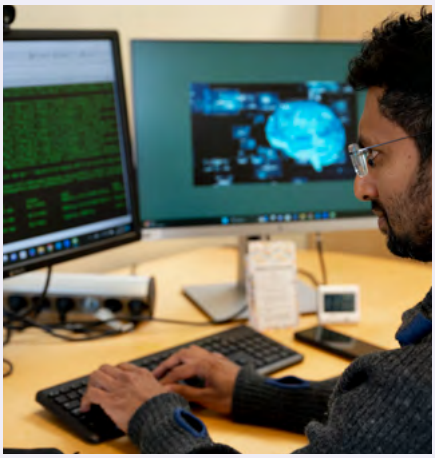
- Infrastructure for intervention studies (RCTs) with medicinal products and other treatments for mental disorders

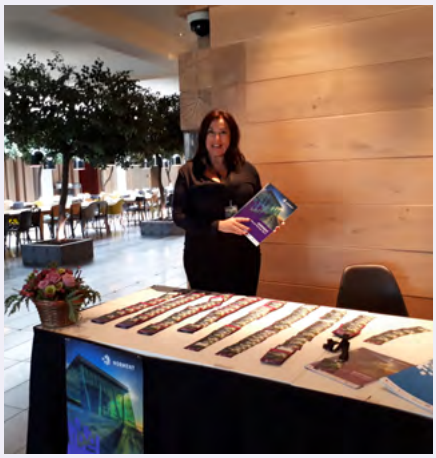
Technical and Administrative Support

Well-organized support functions have been crucial to ensure a stable and efficient infrastructure for excellent research. The Centre has been lucky to have a great team of technical and administrative personnel who continuously have worked to fulfil these functions in a good way. These support functions have ranged from IT assistance and project economy to communication, meeting organization, a project coordination.

Both the size and organization of NORMENT has required well-working systems for internal communication and information flow, including digital platforms for meetings that became increasingly important during the Covid pandemic in 2020-2021. Our intranet, Wiki and Slack were also increasingly used for exchange of both formal and informal information across the Centre.

Technical support for data storage and computational platforms has also been essential. Database staff have cleaned and prepared data for analysis and ensured data security and adherence to national and international regulations. Support personnel has also kept track of project budgets and yearly reports required by funding agencies, and have worked to improve central administrative systems, procedures, and protocols that that are essential for an efficient research organization.





Centre Meetings

Annual Retreat

The Annual Retreat has been the main social and scientific event for everyone at NORMENT. It has been organized as a two-day meeting at a conference hotel in Oslo or Bergen, except during the Covid pandemic when the meeting was digital.

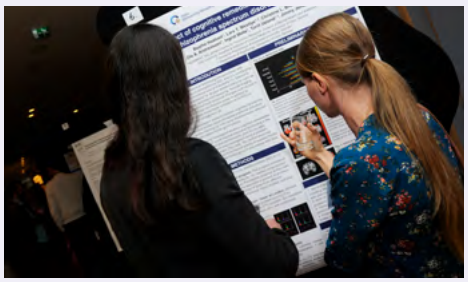
The retreat covered keynote lectures on selected topics, updates from researchers at the Centre, an interactive and social session, as well as a poster session.

The best poster was awarded a main prize of NOK 10.000 from the Dr. Einar Martens Foundation to be used on research. About 120-150 participants have attended the retreat every year.

Synergy Meetings

The Synergy Meetings have been monthly meetings alternating between Oslo and Bergen, where researchers at all levels have presented ideas and preliminary data to facilitate interactions and discussions. These meetings reflect NORMENT's overall focus on “vertical synergy”, in which the aim is to obtain different levels of understanding by bringing together transdisciplinary expertise and methods.

An important part of the meetings has been to initiate new collaborative projects and discuss ongoing projects across the Centre. During the CoE years, there have been about 6-8 meetings a year, on topics such as Pharma and interventions, Epigenetics and environment, Biological models, Developmental factors, Population cohorts, Cardiovascular comorbidity, Advanced Neuroimaging and Longitudinal studies.



Researcher Training

NORMENT has offered a range of training and development opportunities for our PhD students, postgraduate researchers, and other research staff. During the years, we have organized various meetings with the aim of providing the best possible researcher training. Scientific sharing and synergy across domains have been important topics at these events and have been underlying principles for all research activities at the Centre.

PhD Education and Training of Researchers

The PhD students at NORMENT have enrolled at the mandatory PhD education programme at the University of Oslo and University of Bergen. In addition, several PhD students have been members of the Norwegian Research School in Neuroscience (NRSN) which organizes courses, training, and a conference for PhD candidates in neuroscience nationwide. NORMENT has also been involved in the National Research School in Bioinformatics, Biostatistics and Systems Biology (NORBIS), where PhD students and postdocs may attend courses in genetic analyses and statistics.

Regular research meetings have been an important arena for PhD students and postdocs across research groups and scientific disciplines to present their projects, results, and future plans. The Centre has also organized regular workshops in academic writing and clinical supervision, as well as group meetings for the different research groups at the Centre where PhD students and postdocs have presented their research.

The yearly TOP Day has also been an important arena for PhD students to get training in dissemination of their research. The term "TOP" comes from the name of the main study at the Centre, the "Thematically Organized Psychosis" Study. PhD students from various groups and scientific backgrounds have presented their research projects, to share ideas and give each other feedback on topics ranging from genes to clinical symptoms.

Career Development

Another important aspect of the researcher training at the Centre has been to focus on career development of early career investigators. A Career Development Task Force was established at the Centre in 2019, and focused on better integration of new employees, including a “buddy” program and a checklist for group leaders, making information about career development courses and workshops available on the NORMENT intranet, and put a mentor program in place for early stage researchers. The last Centre years, a group of early career researchers also have organized several workshops on career development, focusing on careers of former NORMENT scientists, transferrable skills, and career opportunities inside academia.

NORMENT has also emphasized guiding of early stage researchers by involving them in grant writing and encouraging them to participate in the postdoctoral and mentor programme at the Universities of Oslo and Bergen. These programmes include courses in career planning, research management, and external funding. Early stage scientists have also participated in international research education and training at the University of California San Diego (UCSD) in the USA, funded in part by the Research Council of Norway (INTPART grant).

Early Career Researchers Meeting

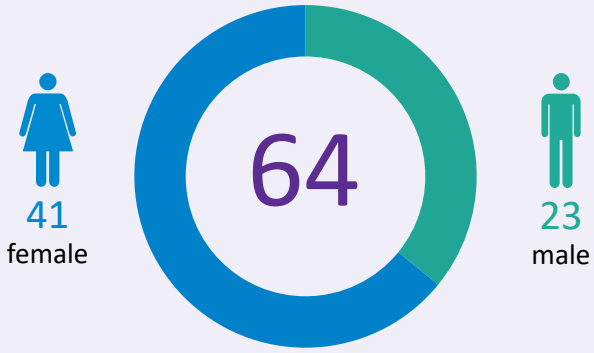
The Early Career Researchers Meeting, first termed the Young Researchers Meetings, was established in 2015 as a yearly one-day meeting for PhD students, postdocs and other researchers who are at an early stage in their career. The meeting has been fully planned by the early career researchers themselves and has been an arena to discuss topics that they have considered important to their scientific development and career. External speakers have been invited to give inspiring keynote lectures, and the meeting has also included presentations by NORMENT affiliates, interactive sessions, and time for mingling and social interaction.

Except for the pandemic years, the meetings took place at the Norwegian Academy of Science and Letters in Oslo, and about 50 people attended each time. The topics of the meetings have ranged from research communication and open science to transferrable skills and the future diagnostic system.

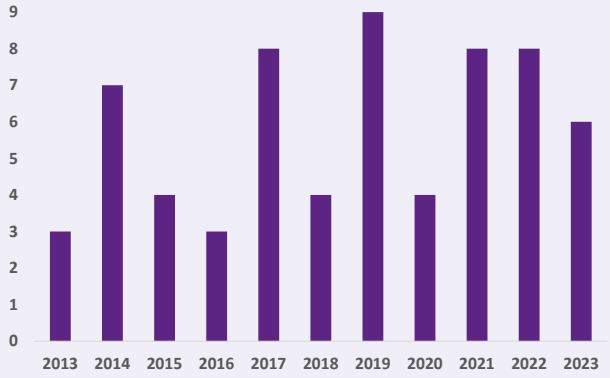
PhD Dissertations 2013 - 2023

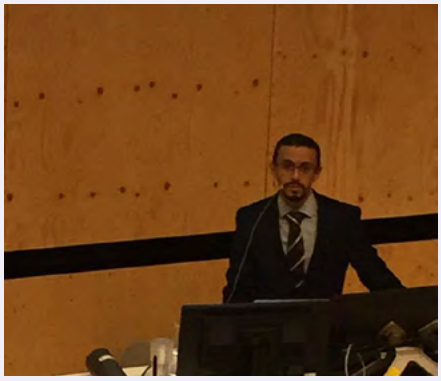
Over the course of ten years, NORMENT has steadily educated and helped employees complete their PhD. As of December 2023, 64 affiliates have completed their philosophiae doctor at NORMENT. Several more are expected to defend their thesis within a year.

64 students completed their PhDs at the Centre



PhD Dissertations - year by year





2013

Ingrid Dieset: Endothelial and inflammaiton markers in schizophrenia and bipolar disorder. Supervisor: Ole A. Andreassen, 28.11.2013

Greg Reckless: A functional MRI investigation of the relationship between extrinsic motivation and descicion-making: normal characteristics and possible dysfunction in schizophrenia. Supervisor: Jimmy Jensen, 20.12.2013

Katrine Wirgenes: Genetic factors in schizophrenia associated with endophenotypes. Supervisor: Ole A. Andreassen, 04.12.2013

2014

Helene Barder: Longitudinal neurocognitive trajectories in first-episode psychosis: Relationships between illness severity and cognitive course. Supervisor: Kjetil Sundet, 23.06.2014

Unni Bratlien: The relevance of premorbid and prodromal phases in psychotic disorders. Supervisor: Merete Glenne Øie, 28.05.2014

Torbjørn Elvsåshagen: A study of cortical structure and plasticity in bipolar II disorder. Supervisor: Ulrik Fredrik Malt, 19.05.2014

Liv Eggset Falkenberg: Neuronal underpinnings of healthy and dysfuntional cognitive control. Supervisor: Kenneth Hugdahl, 05.12.2014

Aina Holmen: Neurocognition in early-onset schizophrenia with a particular focus on executive function. Supervisor: Bjørn Rishovd Rund, 23.01.2014

Morten Mattingsdal: Functional profiling of single-nucleotide polymorphisms associated with bipolar disorder. Supervisor: Ole A. Andreassen, 02.09.2014

Erlend Mork: Self-harm in patients with schizophrenia; risk factors and clinical characteristics. Supervisor: Lars Mehlum, 04.09.2014

2015

Josef Bless: The smartphone as a research tool in psychology. Assessment of language lateralization and training of auditory attention. Supervisor: Kenneth Hugdahl, 15.10.2015

Carla P. D. Fernandes: A genetic study of schizophrenia and bipolar disorder - a cognitive endophenotype approach. Supervisor: Stephanie Le Hellard, 05.03.2015

Elen Gjevik: Psychiatric comorbidity in children with autism spectrum disorder - from genes to clinical characteristics. Supervisor: Ole A. Andreassen, 27.05.2015

Nasrettin Sönmez: Depresseive symptoms and cognitive behavior therapy in first episode psychosis. Supervisor: Jan Ivar Røssberg, 29.05.2015

2016

Ingeborg Bolstad: Effects of aripipralzole vs haloperidol on brain activity in healthy volunteers. Supervisor: Jimmy Jensen, 08.03.2016

Christine Lycke Brandt: Brain networks in psychotic disorders: A neuroimaging study of working memory related activation, connectivity and anatomy. Supervisor: Lars Tjelta Westlye, 13.06.2016

June Ullevoldsæter Lystad: Neurocognition, cognitive remediation and functional outcome in schizophrenia spectrum disorders. Supervisor: Torill Ueland, 09.12.2016

2017

Kristina Skåtun: Abnormal brain connectivity in schizophrenia and bipolar disorder – a resting state functional MRI study. Supervisor: Lars T. Westlye, 19.01.2017

Mari Nerhus: Migration and Vitamin D in psychotic disorders – A cross sectional study of clinical and cognitive correlates. Supervisor: Ingrid Melle, 03.03.2017

Marit Haram: The relationship between oxytocin pathway genes and personality traits and psychosis characteristics. Supervisor: Martin Tesli, 01.06.2017

Kjetil Nordbø Jørgensen: Understanding brain structure alterations in severe mental disorders: The influence of cigarette smoking, antipsychotic medication and weight gain. Supervisor: Ingrid Agartz, 20.06.2017

Beathe Haatveit: Executive functioning in schizophrenia spectrum disorders: Methods of measurement and longitudinal course. Supervisor: Torill Ueland, 22.08.2017

Lynn Mørch-Johnsen: Brain structure imaging of apathy and auditory hallucinations in psychotic disorders. Supervisor: Ingrid Agartz, 01.12.2017

Tiril Østefjells: Metacognition in severe mental disorders. Supervisor: Jan Ivar Røssberg, 07.12.2017

Levi Kvitland: Cannabis use in the early phase of bipolar disorder. A naturalistic longitudinal study of a first treatment sample. Supervisor: Petter Andreas Ringen, 08.12.2017

2018

Ragni Mørch: Inflammatory pathways in severe mental disorder – a transdiagnostic approach. Supervisor: Ole A. Andreassen, 15.05.2018

Erlend Strand Gardsjord: Subjective quality of life in first episode psychosis - A 10-year follow-up study. Supervisor: Jan Ivar Røssberg, 20.09.2018

Niladri Banerjee: An evolutionary epigenetics approach to schizophrenia. Supervisor: Stephanie Le Hellard, 28.09.2018

Christine Demmo: Neurocognitive functioning, clinical course and functional outcome in the early phase of bipolar I disorder: A prospective longitudinal study. Supervisor: Torill Ueland, 25.10.2018

2019

Nathalia Zak: A longitudinal investigation of cortical plasticity and structure in bipolar disorder type II. Supervisor: Torbjørn Elvsåshagen, 13.05.2019

Trude Jahr Vedal: The side effect burden of antipsychotic drugs - A naturalistic study with focus on metabolic disturbance. Supervisor: Erik G. Jönsson, 31.05.2019

Saurabh Srinivasan: A Polygenic Enrichment Approach to Human Evolution in Schizophrenia and Cognitive Function. Supervisor: Ole A. Andreassen, 13.06.2019

Gerard Dwyer: New approaches to the use of magnetic resonance spectroscopy for investigating the pathophysiol ogy of auditory -verbal hallucinations. Supervisor: Renate Grüner, 09.10.2019

Runar Elle Smelror: Cognitive and clinical characteristics in adolescent non-affective early-onset psychosis and healthy controls. Supervisor: Ingrid Agartz, 08.11.2019

Geneviève Richard: Identifying markers of brain health and plasticity: A neuroimaging and behavioral study of cognitive aging and cognitive training following stroke. Supervisor: Lars T. Westlye, 11.11.2019

Linn Norbom: The illumination of the developing brain, Using MRI signal intensity contrasts to probe microstructural brain maturation, and associations with psychopathology and cognition. Supervisor: Christian K. Tamnes, 28.11.2019

Farivar Fathian: C-reactive protein in schizophrenia-spectrum disorders; relationship to cognitive functions and medications. Supervisor: Erik Johnsen, 05.12.2019

Luigi Maglanoc: Elucidating depression heterogeneity using clinical, neuroimaging and genetic data. Supervisor: Lars T. Westlye, 06.12.2019

2020

Priyanthi Borgen Gjerde: Lipid effects during antipsychotic drug treatment and their relevance for clinical outcomes. Supervisor: Vidar M. Steen, 29.01.2020

Ibrahim Akkouh: Transcriptional Modeling of Severe Mental Illnesses. Supervisor: Srdjan Djurovic, 06.05.2020

Eirik Kjelby: Depressive symptoms in psychotic disorders: Trajectories of depression and antidepressive effectiveness of antipsychotic medication. Supervisor: Erik Johnsen, 16.10.2020

Tone Elise Gjøtterud Henriksen: Blue-blocking glasses as adjunctive treatment for bipolar mania - and exploration of motor activity patterns in serious mental disorders. Supervisor: Anders Lund. 23.10.2020

2021

Ingrid Hartveit Svendsen: Basic self-disturbances in first treated psychosis – A seven-year follow-up study. An exploration of stability, impact on recovery and sense of coherence. Supervisor: Ingrid Melle. 18.01.2021

Jannicke Fjæra Laskemoen: Sleep disturbances in schizophrenia spectrum and bipolar disorders. Supervisor: Carmen Simonsen. 22.01.2021

Lynn Marquardt: tDCS as treatment in neuro-psychiatric disorders. The underlying neuronal mechanisms of tDCS treatment of auditory verbal hallucinations. Supervisor: Marco Hirnstein. 04.02.2021

Isabella Kusztrits: About psychotic-like experiences and auditory verbal hallucinations. Transdiagnostic investigations of neurobiological, cognitive, and emotional aspects of a continuous phenomenon. Supervisor: Marco Hirnstein. 19.03.2021

Kirsten Wedervang-Resell: Immune and metabolic markers in early-onset psychosis. Supervisor: Anne Margrethe Myhre. 07.05.2021

Dani Beck: Cardiometabolic health and the ageing brain: Using brain and body MRI to elucidate the body-brain axis in healthy adults. Supervisor: Lars Tjelta Westlye. 05.10.2021

Linn Rødevand: Cardiovascular disease risk across psychosocial and genetic factors in severe mental disorders. Supervisor: Ole Andreassen. 03.12.2021

Kristine Moe Ulrichsen: Dissecting and alleviating post-stroke fatigue: Cognitive phenotype, brain disconnectome mapping and non-invasive brain stimulation. Supervisor: Lars Tjelta Westlye, 17.12.2021

2022

Siv Hege Lyngstad: A 10-year perspective on apathy development in psychotic disorders: Genetic risk and early predictors, associations with depression, and functional outcome. Supervisor: Ann Færden, 28.03.2022

Adriano Winterton: The Oxytocin Genetic Pathway Links Severe Mental Illness and Metabolic Syndrome. Supervisor: Daniel S. Quintana, 01.04.2022

Natalia Tesli: Imaging violence in psychosis: Using MRI to investigate neurobiological correlates of violence in psychotic disorders. Supervisor: Unn Kristin H. Haukvik, 05.05.2022

Martina Jonette Lund: The brain functional connectome across the lifespan. Investigating associations of resting-state functional connectivity with age, sex, cognitive abilities and psychopathology. Supervisor: Tobias Kaufmann, 05.09.2022

Nina Mørkved: Childhood Trauma in Schizophrenia Spectrum Disorders: A comparison to substance abuse disorders, and relation to cognitive performance and antipsychotic treatment outcomes. Supervisor: Else-Marie Løberg, 15.09.2022

Tor Gunnar Værnes: Anomalous self-experiences in subjects with increased risk of developing psychosis. Supervisor: Paul Møller, 27.09.2022

Margrethe Collier Høegh: Affective lability in psychosis spectrum disorders: characteristics and correlates. Supervisor: Trine Vik Lagerberg, 13.10.2022

Maren Caroline Frogner Werner: Immune abnormalities and treatment resistance in severe mental disorders: the role of polygenic risk, infections and autoimmunity. Supervisor: Nils Eiel Steen, 29.11.2022

2023

Mathias Valstad: Examining schizophrenia and bipolar disorder pathophysiology with an EEG-based assay of cortical synaptic plasticity. Supervisor: Torbjørn Elvsåshagen, 20.01.2023

Magnus Johan Engen: Cognitive Heterogeneity in Schizophrenia Spectrum Disorders: Genetic Variation and Negative Symptom Groups. Supervisor: Torill Ueland, 29.03.2023

Rikka Kjelkenes: Disentangling cognitive and brain structural correlates of mental health symptoms in youth. Supervisor: Lars Tjelta Westlye, 09.06.2023

Knut Kolskår: Stroke and cognitive control: functional MRI, lesion characteristics, and treatment response. Supervisor: Lars Tjelta Westlye, 21.06.2023

Guy Frederick Lanyon Hindley: Polygenicity and pleiotropy in mental disorders and related traits: insights from cross-trait genome-wide association studies. Supervisor: Ole A. Andreassen, 05.09.2023

Stener Nerland: Probing the dysmyelination hypothesis in schizophrenia spectrum and bipolar disorders: Methodological appraisal and clinical investigations of cerebral grey and white matter myelination. Supervisor: Ingrid Agartz, 01.11.2023

Societal Impact

NORMENT has contributed to a series of scientific discoveries providing new insight into underlying mechanisms and treatments of severe mental illness. Our research also has the potential for a significant impact on society when it comes to clinical application, reducing stigma, and the development of innovative tools.

Clinical utility and application

Several scientific findings from the Centre are of clinical relevance and may be applied in the clinic in the short term, particularly related to treatment of mental illness.

Researchers at the Centre have documented differences in effectiveness of antipsychotic medication (e.g., Johnsen 2020, Lancet Psychiatry), and sex differences in effects and adverse effects (Hoekstra 2021, NPJ Schizophr). These findings are important for choice of treatment and can be translated to the clinic in the near future, to improve pharmacological treatment and reduce adverse effects.

Further, our research on the immune system and anti-inflammatory medication has provided promising results for treatment alternatives (Kroken, 2019, Front Psychiatry).

In addition, supporting eHealth and developing and testing digital tools have been prioritized research areas for the Centre. Our projects related to apps for clinical monitoring of patients has the potential for improving illness management and early intervention, since patients are followed over time. These research tools can be further developed and integrated in the clinic to monitor variations in symptoms and behaviour. eHealth can in general improve health care, reduce costs, and increase the focus on user needs and preferences.

NORMENT researchers have also worked to develop and test treatment for cognitive difficulties in people with severe mental disorders. We have shown that cognitive training can improve cognitive function and work function (Lystad 2017, Schizophr Res) and that social cognitive training can help patients drawing better conclusions about others' feelings and thoughts (Vaskinn 2019, Eur Arch Psychiatry Clin Neurosci). There is also a large potential for improving quality of life with these interventions.

Further, our research has important implications for clinicians regarding diagnosis and treatment, and in providing information to patients.

For instance, we have characterized several factors that affect clinical outcome and prediction of illness course, including traumatic experiences (Ottesen 2023, Psychol Med), drug use (Lagerberg 2021, Front Psychiatry), and sleep disturbances (Laskemoen 2021, Psychol Med).

Another example is our focus on cardiovascular disease in relation to mental disorders. Here, our research has documented a high prevalence of comorbid cardiovascular disease in patients, which has not been reduced during the last decade as in the rest of the population (Rødevand 2019, Acta Psychiatr Scand). This knowledge is important both for clinicians regarding focus on somatic aspects, as well as motivation for exercise and healthy diet.

Lastly, the Centre has been involved in a number of important discoveries related to genes and brain function, that have provided increased insight into disease mechanisms. These findings can serve as a platform for new research to develop better early intervention and more targeted treatment in the long term. Knowledge about variation of individual patients within diagnostic categories is the basis for the development of more individualized treatment (precision medicine).

Dissemination

Mental disorders still have large knowledge gaps in society, and there is misinformation and stigma. Dissemination is an important part of research, and through the years, we have focused on sharing our findings both with the larger science community and with the lay audience.

In addition to publishing our research in scientific journals, we have participated with posters and oral presentations at important international conferences, such as the World Congress of Psychiatric Genetics (WCPG), the Organization of Human Brain Mapping Conference (OHBM), the European Congress of Psychiatry (EPA), the Society of Biological Psychiatry (SOBP), the Schizophrenia International Research Society Conference (SIRS), and the European College of Neuropsychopharmacology (ECNP).

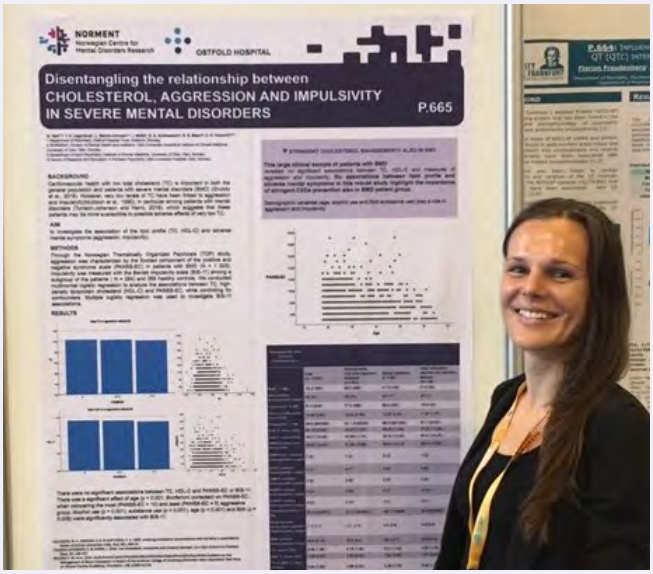
To make the new knowledge generated from our research available to the lay audience and counteract stigma, we have actively used our website, social media, newsletter and public events. Altogether, our dissemination activities reflect our aim to be a provider of knowledge about severe mental disorders that can help break down stigma in society.

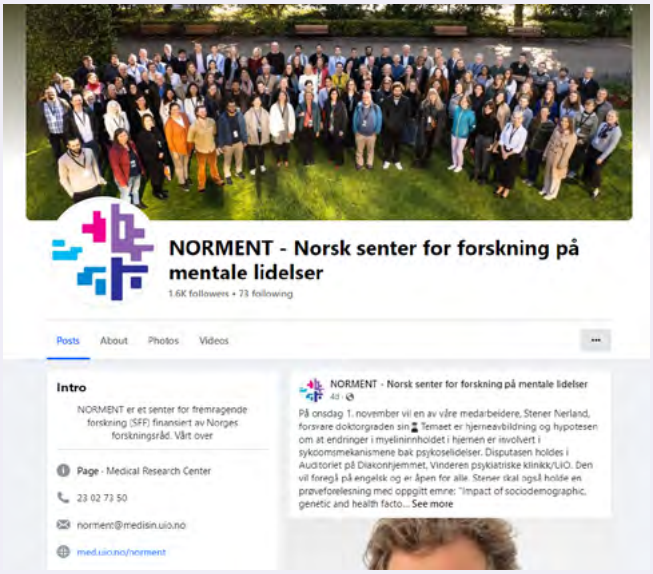
Web, social media and newsletter

On the NORMENT website, we have shared news and events, and our researchers have contributed with popular science texts about their research to reach out to a broader audience. Twitter has been used since 2016 to share news about publi- cations, meetings, thesis defences, and other information related to science and mental disorders. As of December 2023, NORMENT had about 1200 followers on Twitter.

The Centre has also been on Facebook since March 2019. Our Facebook page has mainly been targeted towards people with lived experience, health personnel and the general public, and has been administrated by our User Representative. Facebook has been used to share new research and events from the Centre. As of December 2023, about 1600 people were following us on Facebook.

The NORMENT newsletter was launched in 2020, and has been distributed quarterly to health personnel, research participants, and the general public. Our last newsletter was published in June 2023 and was distributed to about 300 subscribers, with information about research news, events, and activities at the Centre, focusing on the applicability of our research. The newsletter has also included presentations of each research group, a summary of their findings, and in what way the research may be of importance for people with severe mental disorders.





Public events

In collaboration with our User Council, User Representatives and the Bipolar Association, we have organized several public events, including open seminars and webinars. The aim has been to reach out with our ongoing research and findings to people with lived experience, family members, health personnel, and other user groups.

We have received a lot of positive feedback on these events, which shows the need for updated knowledge in society and the importance of being present and visible to get in contact with the users of our research.

Arendalsuka

- Mentale lidelser koster: Forsker vi nok? (panel debate, 2018)
- Ensomhet: Den glemte faktor i psykisk helsearbeid? (panel debate, 2019)

Forskningsdagene

- Kan hjerneforskning være en nøkkel til å forstå psykiske lidelser? (webinar, 2020)
- Den fantastiske hjernen (photo exhibition in Oslo, 2020)

Events by NORMENT

- Sinnssyk forskning: Arv og miljø (seminar, 2019)
- Psykiske lidelser i vårt teknologiske samfunn (OUS symposium, 2019)
- Schizofreni: Hvilken betydning har miljøfaktorer? (webinar, 2021)
- Hvordan kan forskning bidra til bedre behandling av alvorlige psykiske lidelser? (webinar, 2021)
- Hvordan kan alvorlige psykiske lidelser oppdages tidligere? (webinar, 2022)
- Hva er sammenhengen mellom betennelser og alvorlige psykiske lidelser? (webinar, 2022)
- Der det er forskning, er det håp! (seminar, 2023)

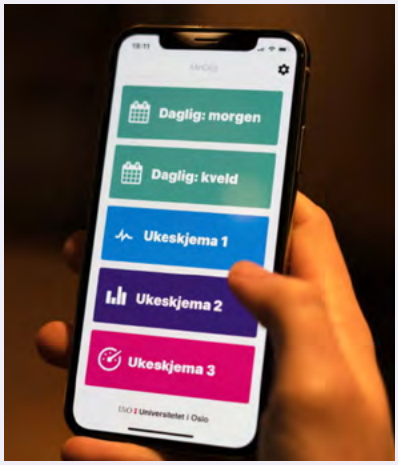
Events in collaboration with the Bipolar Association

- Bipolar lidelse, arbeid, og recovery (seminar, 2018)
- Skam (seminar, 2019)
- Selvmord (seminar, 2020)
- Familierelasjoner og bipolar lidelse (seminar, 2020)
- Bipolar Webinars (six different topics, 2021)

Media coverage

Innovation

NORMENT has also provided added value by developing tools for prediction and stratification (genetics, imaging) which can lead to new knowledge to improve clinical treatment. These include novel statistical tools developed in collaboration with researchers at the University of California San Diego, such as “MOSTest” (van der Meer et al. 2021, Science Advances). Gaining more knowledge about mechanisms and developing diagnostic tools for stratification and outcome prediction will lead to better treatment planning for psychotic disorders and will thus be directly and indirectly of large value to society.



As part of our eNORMENT strategy, we have had several projects based on new promising eHealth technology. A good example is the smartphone app called "MinDag" ("My Day"), which has been developed at NORMENT and is now applied in research projects (Bjella et al. 2022, Front Med Technol). The app enables self-reports on sleep, daily activities, mood and psychotic symptoms, and substance use over time. Participants also use an activity tracker (actigraph) that passively measures physical movement and exposure to light. The project will improve the understanding of interplay between lifestyle and environment, and symptoms levels. The MinDag app may give new insights into the variations in the course of severe mental illness and contribute to detect early signs of relapse and thereby improve treatment. We have also been involved in the development of an app for assessing hallucinations in adolescent psychosis (Smelror et al. 2019, JMIR Form Res).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Future Perspectives

The years as a Centre of Excellence have laid the foundation for continued research on mental illness in the future. Our scientific findings, extensive research infrastructure, and large-scale collection of clinical and biological data will form the basis for studies in the coming years.

Excellent research in the future

After the Centre of Excellence period, NORMENT's research will continue with several projects that were initiated during the Centre years. Researchers at the Centre have also received funding for new projects, of which several are leaded by our young scientists. The continued research activities will be supported by the partner institutions and reorganized at the universities and university hospitals in Oslo and Bergen. The NORMENT Centre has built the foundations for an extensive research agenda in the future, driven to a large degree by young scientists trained at the Centre.

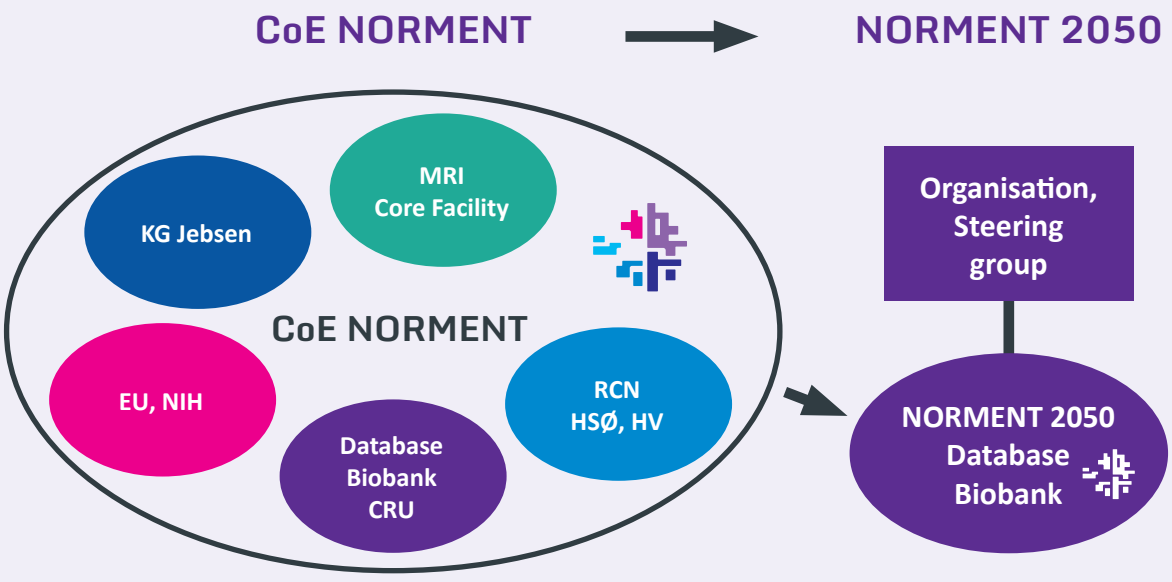
Continuation of database and biobank

During the years as a Centre of Excellence, NORMENT has collected clinical and biological data from several thousand participants who have generously volunteered to take part in our research. These valuable and unique data are stored in a large database and biobank that will be available for future studies after the Centre of Excellence period. The initiative to preserve and make data available post-NORMENT is called "NORMENT 2050", since the original ethics approval for data storage lasts until 2050.

The four NORMENT partner institutions will contribute with joint funding for the maintenance and management of the accumulated database and biobank. This will enable us to maintain infrastructure and personnel for organization and data management, and thereby securing access to the rich database for new projects in the field.

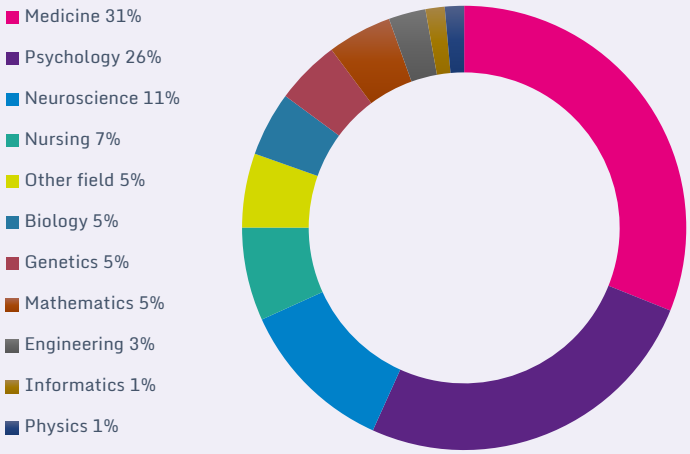
The database and biobank will increase in value due to continuous collection of new data and biomaterial from projects connected to the NORMENT 2050 initiative. Access to data will require approvals from ethics and data protection agencies and will be made available to researchers following regulations overseen by the steering group.

This new infrastructure is well aligned with the transformation to electronic data capture solutions developed during the NORMENT period. Further, new technological solutions are being developed for accessing data from electronic Health Records (eHR) to obtain relevant information about participants' disease history, treatment, clinical characteristics, somatic comorbidities as well as treatment.

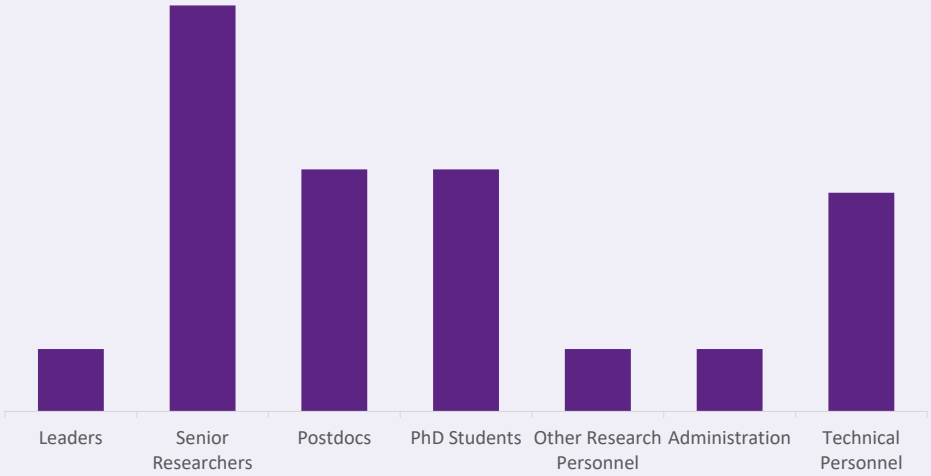


Facts about NORMENT

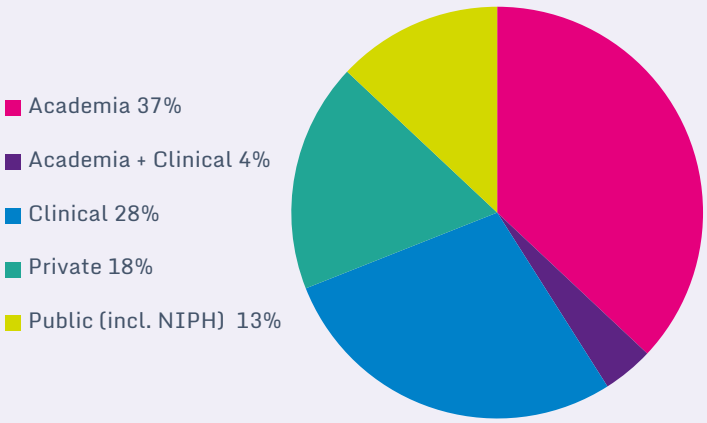
Professional backgrounds of staff



Staff positions



Where do PhDs and postdocs work after NORMENT?

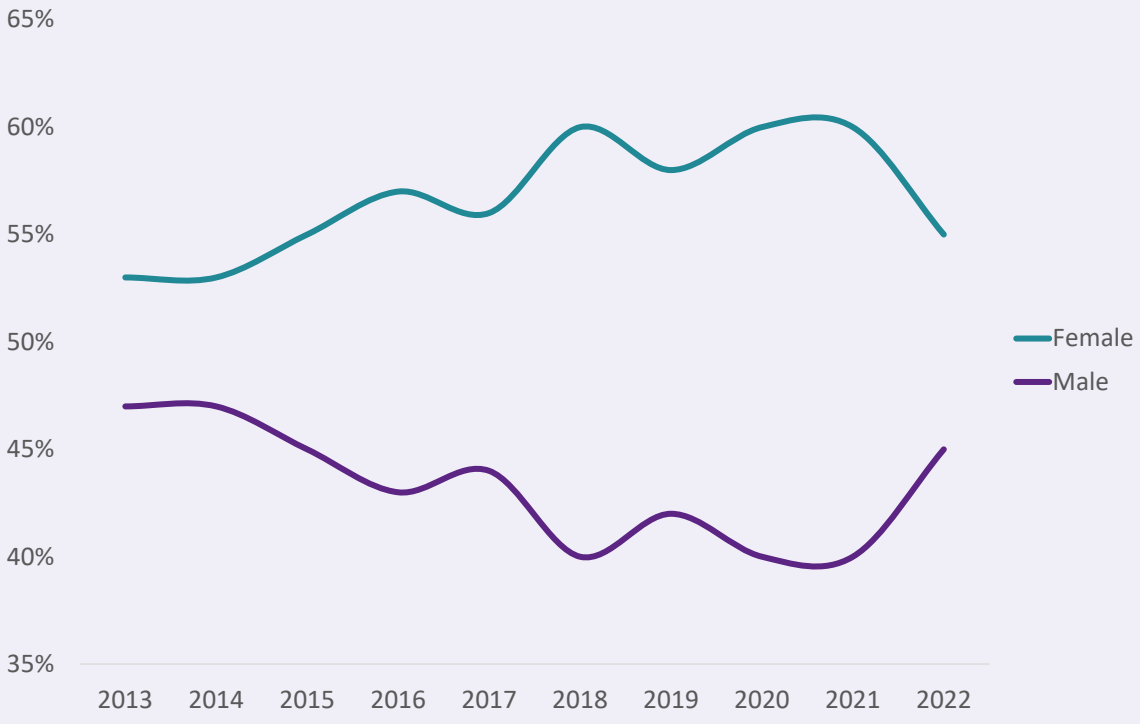


* Numbers from 2022

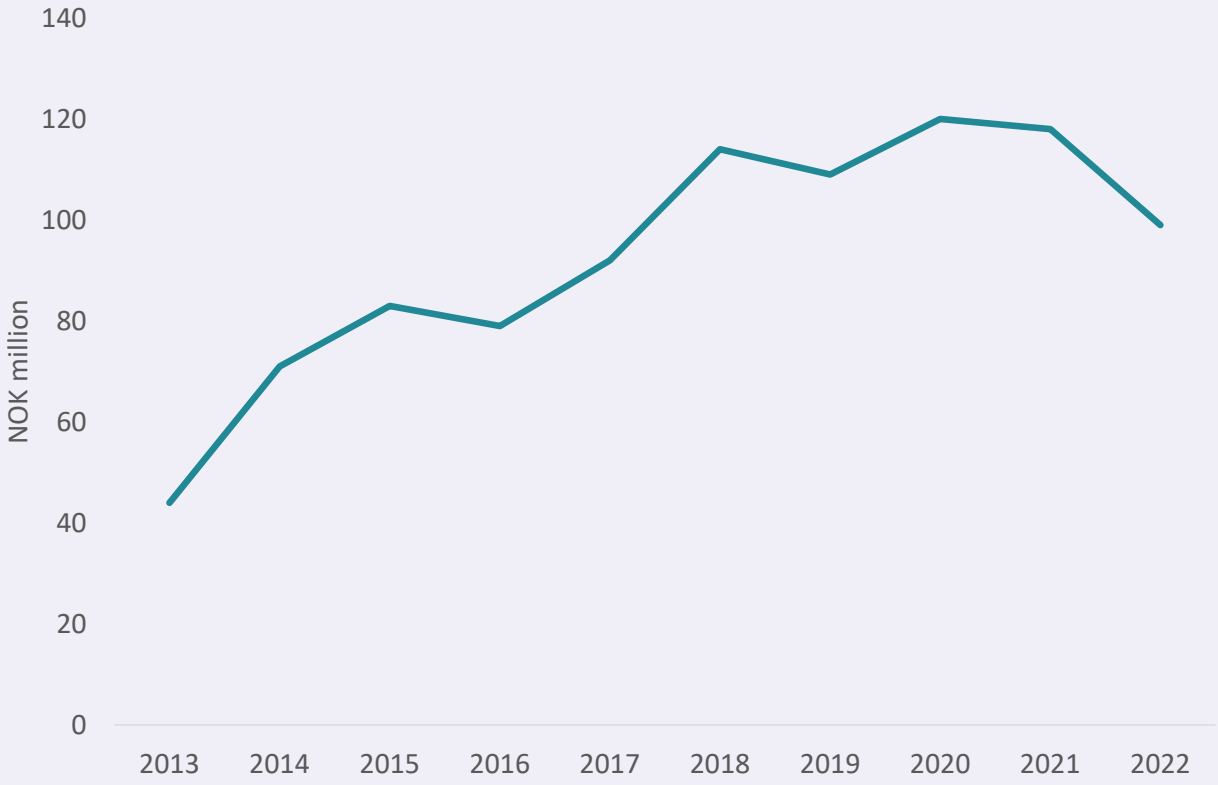
43 different nationalities

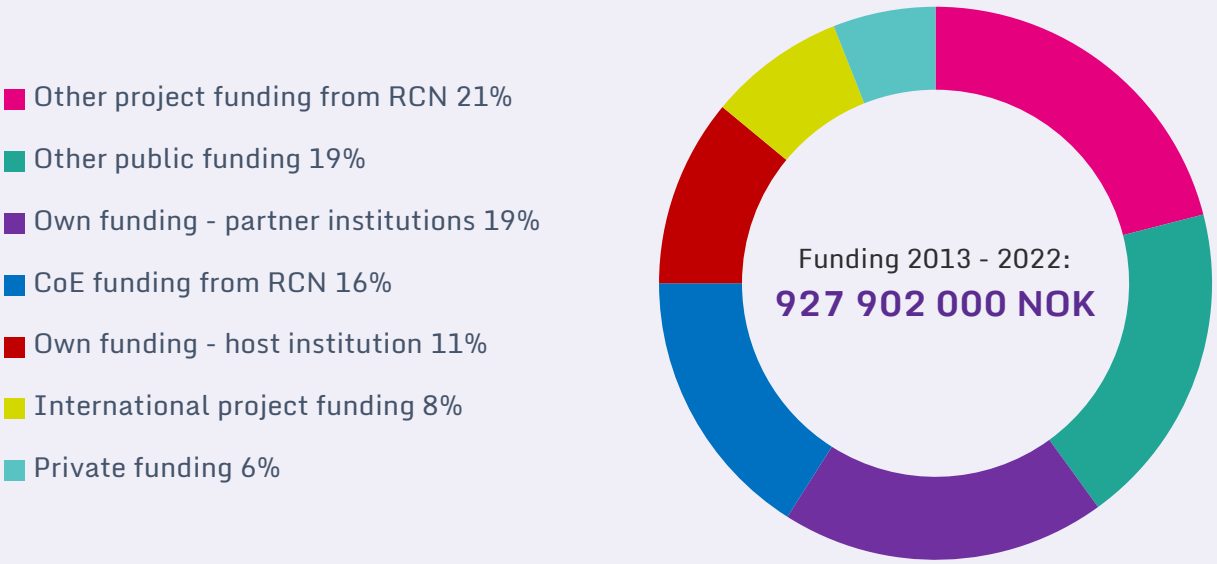
From 2013 to 2023, NORMENT employed excellent staff from 43 countries, including people from Africa, Asia, Europe, North- and South America and Oceania. The diverse international research environment has contributed to a great exchange of knowledge and fresh perspectives on research.

Gender distribution



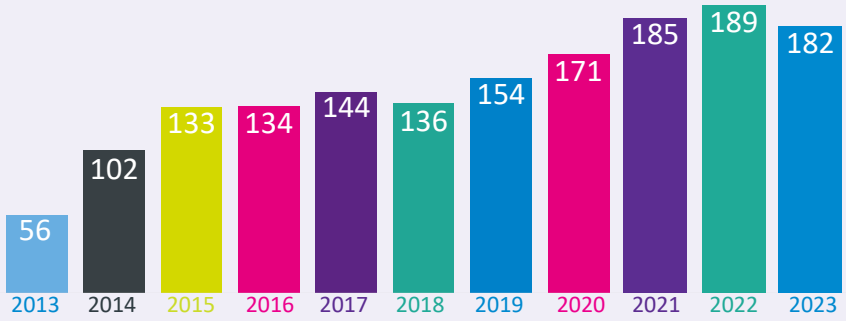
Funding 2013 - 2022*





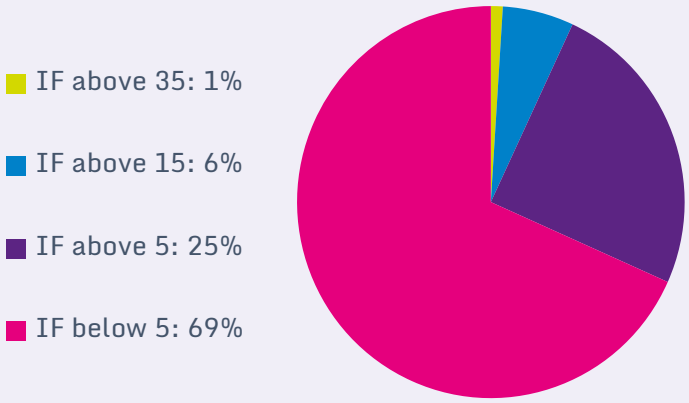
* Funding does not include numbers for 2023, as these are not available until 2024.

Publications 2013 - 2023

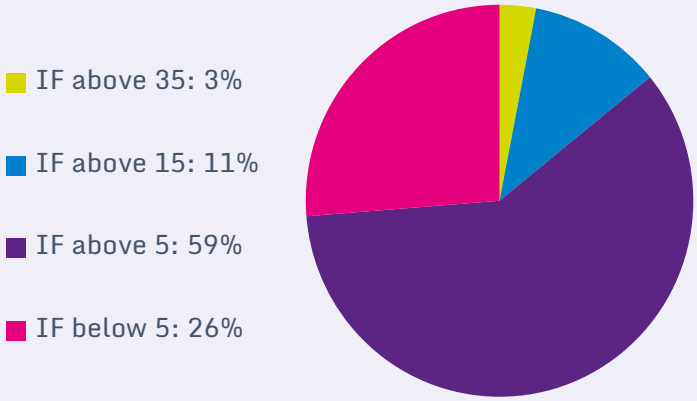


As of December 2023, NORMENT researchers have published 1586 scientific papers, of which many have been published in scientific journals with a high impact factor. These include Science, Nature Genetics, Nature Human Behaviour, Nature Communications, JAMA Psychiatry, Lancet Psychiatry, and Molecular Psychiatry.

Impact factor 2014



Impact factor 2022



Prizes and Awards

A selection of prizes and awards given to NORMENT affiliates.

2013

2014

- Professor **Kenneth Hugdahl** was awarded the Møbius Prize from the Research Council of Norway for his outstanding research on the brain and contribution to increased knowledge of schizophrenia.
- Professor **Kenneth Hugdahl** received the Meltzer Honorary Award for Excellence in Research from the University of Bergen.

2015


- Postdoc **Monica Aas** received the Young Scientist Award from the Scandinavian College of Neuropsychopharmacology.
- Postdoc **Tobias Kaufmann** was awarded the Prize for Outstanding Paper from Oslo University Hospital for his paper on sensorimotor brain networks in schizophrenia.

2016

- Researcher **Silje Skrede** received the Annual Research Price from the Norwegian Psychiatric Association for her paper on olanzapine treatment and lipid genes.
- Postdoc **Akiah Ottesen Berg** was awarded the Prize for Outstanding Paper from Oslo University Hospital for her paper on childhood trauma in psychotic disorders.


2017


- Researcher **Petter Andreas Ringen** was awarded the Prize for Outstanding Paper from Oslo University Hospital for his paper on premorbid cannabis use in schizophrenia spectrum disorders.
- Postdoc **Julien Laloyaux** received the Young Investigator Travel Award from the International Congress of Schizophrenia Research for his work on hallucinations in the general population.
- Postdoc **Tobias Kaufmann** was awarded the Prize for Outstanding Paper from Oslo University Hospital for his paper on connectome development and mental illness.

2018

- Professor **Ole A. Andrea** the Honorary Award fro Foundation for his outst research in psychiatry.
- Associate professor **Lars** received the Early Caree Oslo University Hospital ments as researcher wit ing and mental illness.
- Postdoc **Torgeir Moberg** the Young Researcher A Fulbright Foundation fo the role of the cerebellu schizophrenia.

- Associate professor **Lars T. Westlye** received the Anders Jahre's Medical Prize for Younger Researchers, for his research on how innate characteristics can explain predisposition to mental illness.
- Professor **Ole A. Andreassen** received the Excellent Researcher Award from Oslo University Hospital for his outstanding research in molecular psychiatry.
- Associate professor **Leif Oltedal** received the Fulbright Article of the Year Prize for his paper on clinical and brain response of electroconvulsive therapy.

2019

- Senior researcher **Trine Vik Lagerberg** and Database manager **Thomas Bjella** were awarded Oslo University Hospital's Innovation Prize for developing the "MinDag" app.
- Researcher **Jordi Requena Osete** received the Prize for Outstanding Paper from Oslo University Hospital for his paper on stem cell technology and effect of Lithium treatment.
- Professor **Erik Johnsen** and Associate professor **Rune Kroken** received the Prize for Best Publication from Haukeland University Hospital for their paper on the effectiveness of anti-psychotic medication.

2021

- Postdocs **Weiqiu Cheng** and **Nadine Parker** were awarded the Prize for Outstanding Paper by Oslo University Hospital for their paper on cannabis use, genetics and mental illness.
- Professor **Ole A. Andreassen** received the Fridtjof Nansen Award for Excellent Research, for his research in psychiatric molecular genetics.

2023

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2020

- Professor **Ole A. Andreassen** received the Research Prize from the University of Oslo for developing new analytical tools to reveal the genetic architecture of mental disorders and contributing to enhance the status of mental health research in Norway.
- Postdocs **Claudia Barth** and **Ann-Marie De Lange** received the Young Investigator Award at the Women's Brain Health Conference for their work on brain aging in women.
- PhD candidate **Petter Jakobsen** received the Best Poster Award from the International Society of Bipolar Disorders, for his study on motor activity in depression.

2022

- PhD candidate **Maria Fagerbakke Strømme** received This Year's Poster Award from Haukeland University Hospital for her work on agitated behavior and psychotropic medication in schizophrenia.
- Senior researcher **Daniel Quintana** was awarded the Prize for Young Researchers from the University of Oslo for his research on oxytocin and its importance for physical and mental health.

Centre Organization

Partners

NORMENT was based on a collaboration between four partners: The University of Oslo (host institution), the University of Bergen, Oslo University Hospital, and Haukeland University Hospital.

Centre Management

Head of the Centre was Ole A. Andreassen (Oslo). Deputy Directors were Ingrid Melle (Oslo) and Vidar M, Steen (Bergen). Administrative Manager of NORMENT were Christine Lycke Brandt (2019-2023), Åshild M. Eftevåg (2015-2019), and Kristin Myklebust (2013-2015).

Scientific Management

Eight Core Researchers (CR) with complementary expertise from different disciplines constituted the scientific management of NORMENT.

As of 2023, the scientific management consisted of Ole A. Andreassen (University of Oslo), Ingrid Melle (Oslo University Hospital), Vidar M. Steen (University of Bergen), Ingrid Agartz (University of Oslo), Srdjan Djurovic (Oslo University Hospital), Stephanie Le Hellard (University of Bergen), Lars T. Westlye (University of Oslo), and Erik Johnsen (Haukeland University Hospital).

Kenneth Hugdahl and Kjetil Sundet were part of the scientific management from 2013-2018 and were replaced by Lars T. Westlye and Erik Johnsen.

Governing Board

The NORMENT Centre Board was headed by Dag Kvale (2019-2023), Ivar Prydz Gladhaug (2017-2019), and Hilde Irene Nebb (2013-2017) from the Medical Faculty, University of Oslo.

As of 2023, the partner institutions were represented by Petter Andreas Ringen, Oslo University Hospital (replaced Marit Bjartveit in 2022); Trine Waaktaar, University of Oslo (Faculty of Social Sciences); Marit Bakke, University of Bergen and Hans Olav Instefjord, Haukeland University Hospital.

Scientific Advisory Committee

A group of internationally renowned scientists have continously evaluated the research activities at NORMENT and given valuable advice to the Centre.

Terry Jernigan (2013-2023): Professor in Cognitive Science, Psychiatry, and Radiology, and Director of the Center for Human Development, University of California, San Diego (UCSD), USA, as well as Co-Director of the Coordinating Center for the ABCD Study.

Michael Foster Green (2013-2023): Professor-in-Residence at the Department of Psychiatry and Biobehavioral Sciences and the Semel Institute for Neuroscience and Human Behavior at the Geffen School of Medicine at the University of California Los Angeles (UCLA), USA.

Peter Falkai (2018-2023): Professor of Psychiatry and Psychotherapy and Chairman of the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilian University in Munich, Germany.

Marcella Rietschel (2013-2018): Professor and Scientific Director of the Department of Genetic Epidemiology in Psychiatry at the Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany.

User Council

NORMENT's User Council consisted of individuals with lived experience and competency who provided input to research activities and matters affecting research participants. Members were Lena-Maria Haugerud, Fabian Stang, Fred Gerkum, Inger Hagen, Karoline Fløystad Thorsen, and Halvor Stokke Devor.

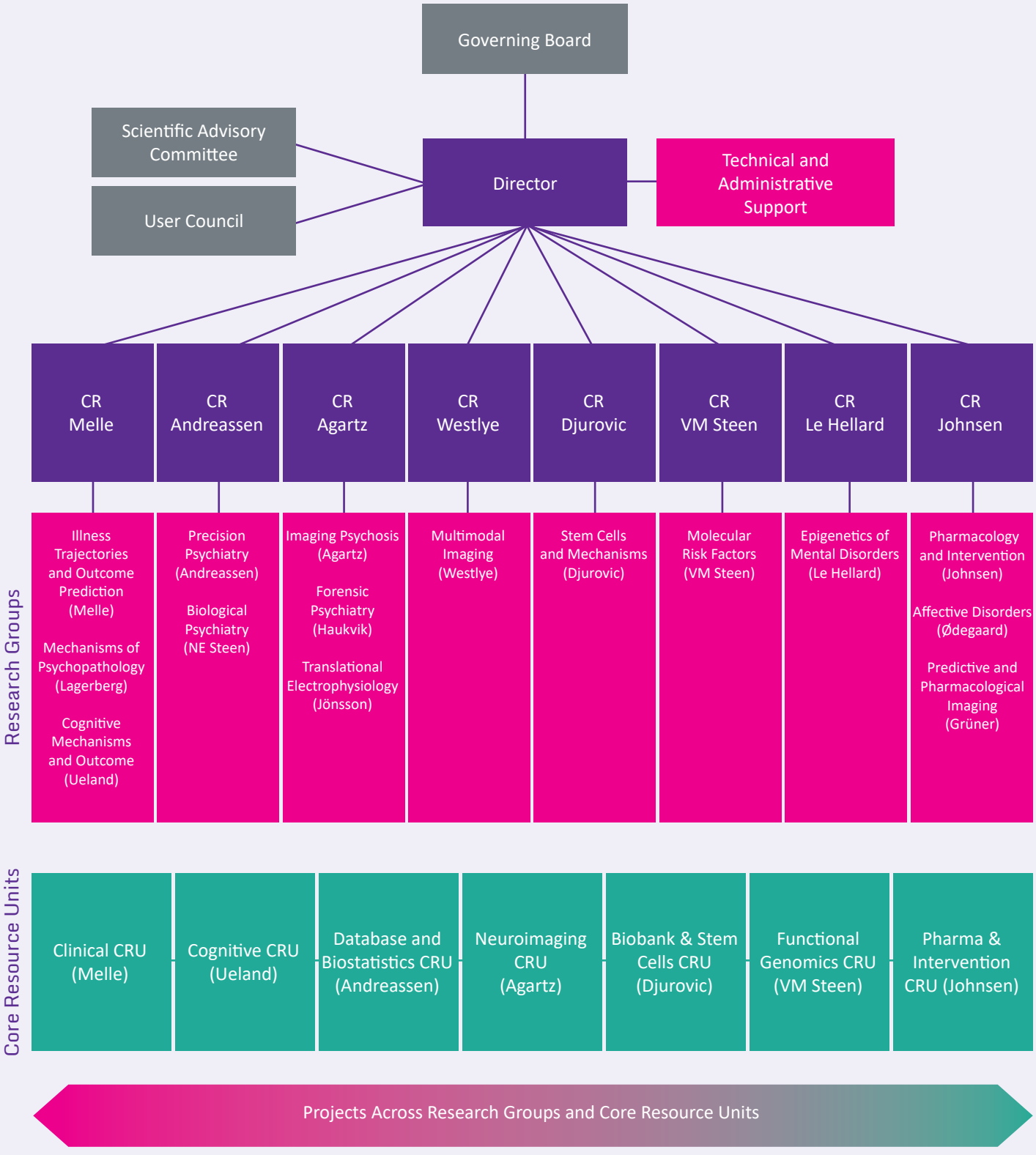
Core Researchers from 2013 - 2018. Left to right: Srdjan Djurovic, Ingrid Melle, Kjetil Sundet, Stéphanie Le Hellard, Ole A. Andreassen, Kenneth Hugdahl, Ingrid Agartz, Vidar M. Steen

Core Researchers from 2018 - 2023. Left to right: Stéphanie Le Hellard, Ole A. Andreassen, Ingrid Agartz, Vidar M. Steen, Ingrid Melle, Erik Johnsen, Lars T. Westlye, Srdjan Djurovic

Centre Management 2023. Left to right: Vidar M. Steen, Ingrid Melle, Christine Lycke Brandt, Ole A. Andreassen

Scientific Advisory Committee 2018-2023. Left to right: Peter Falkai, Terry Jernigan, Michael Foster Green.

Centre Organization as of 2023



CR: Core Researcher, CRU: Core Resource Unit

Acknowledgements

The research at NORMENT is the result of contributions from a large number of people and institutions during many years. We would like to express our great appreciation and thank you to:

The participants of our research for generously taking part in extensive assessments and contributing with valuable data also for future studies of mental illness.

The Research Council of Norway for providing long-term funding of our research.

Our partner institutions – University of Oslo, University of Bergen, Oslo University Hospital, and Haukeland University Hospital – for support and infrastructure during all these years.

The members of our Scientific Advisory Committee for valuable advice and discussions.

Our collaborators in Norway and abroad for great team effort and new perspectives.

The NORMENT Governing Board for constructive feedback and support.

Our Centre administration for ensuring an efficient and stable research infrastructure.

All NORMENT affiliates – scientific, technical, and administrative staff – for your enthusiasm, creativity, and great effort, including during the Covid-19 pandemic.

Photo Credits

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Erlend Smeland (p8): OUS
Per Bakke (p. 9): Kim Andreassen, UiB
Randi-Luise Møgster (p. 10): Katrine Sunde, HUS
Dag Kvale (p. 11): Bård Gudim, UiO
Ingrid Melle (p. 18): UiO
Trine Vik Lagerberg (p. 20): Kirsten Sjøwall
Torill Ueland (p. 22): Kirsten Sjøwall
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Monica Aas (p. 70): Kirsten Sjøwall
Tobias Kaufmann (p. 70): Kirsten Sjøwall
Julien Laloyaux (p. 70): Kirsten Sjøwall
Petter Andreas Ringen (p. 70) Kirsten Sjøwall
Silje Skrede (p. 70): Eivind Senneset, UiB
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