



Annual Report

UiO : NORMENT: Norwegian Centre for Mental Disorders Research



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Welcome from the Leader

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. The team of eight Core Researchers had worked a long time planning the scientific contents and the organization of the new Centre, which we named NORwegian Centre for MENTAL Disorders Research – NORMENT. The Centre has a clear clinical profile, involving investigations of patients with state-of-the art clinical assessments and research technology, and translating findings to experimental studies to identify underlying mechanisms.

We have ambitious scientific goals, focusing on understanding the underlying mechanisms of severe mental disorders. This is a field with large unmet needs and lack of knowledge, which makes the work of our Centre of Excellence very important. We have selected four main areas of activities and will answer the following questions: Why do antipsychotic medications have severe side effects? Where is the 'hidden heritability' of severe mental disorders? How can brain imaging help link genes to clinical characteristics? How can we predict outcome in patients experiencing their first signs of disease?

The Centre was officially opened by The Minister of Education Kristin Halvorsen in April 2013, and the Centre was operational from the July 1, 2013. The first six months of 'excellence' has involved a lot of hard work from the whole organization to establish the infrastructure, communication systems, meetings schedule and budgets. It has also been important to form a coherent Centre.

The total number of people engaged in Centre activities was approximately 80 in 2013. We have been both skilled and "lucky" to attract many young, talented researchers, and are expecting to hire more key experts in the coming years. This will be an essential part of the innovative culture we need to move the field forward. An important aim is to facilitate synergy through interactions between the different research groups and disciplines involved, and we have developed a 'Synergy Program' to ensure we establish a translational research program.

A major advantage of our Centre is the existing long-term collaboration between the Core Researchers on which we are building the Centre and the research projects. This also allows funding for common research infrastructure and platforms for the benefit of all participants. Further, we have already established several research projects, and some have even led to high impact publications in the first year of the Centre. We hope to fulfil even more ambitious goals in the coming year.

Finally, I would like to highlight the collaboration with patient organizations that we have initiated. This will become a fruitful addition to the Centre team.



Ole A. Andreassen, Director NORMENT

A handwritten signature in black ink, appearing to read 'Ole A. Andreassen'.

Centre Opening

Support of about NOK 17,5 million per year from the Research Council of Norway, together with Centre of Excellence (CoE) status, lasts for up to ten years. NORMENT also receives support from the K.G. Jebsen Foundation, as K. G. Jebsen Centre for Psychosis Research. This provides a unique opportunity to make comprehensive and long-term plans, reaching across the country.

NORMENT was established in April 2013, with a formal opening.

Kristin Halvorsen, the former Minister of Education, was present. She emphasized the importance of high quality research on mental disorders - disorders that have major consequences for the patients and for society as a whole. "I have great expectations for NORMENT, and will follow you closely," she said.

Anders Hanneborg, Division Director at the Norwegian Research Council, said the CoE award is a clear recognition of qualifications and ambitions. "CoEs are our flagship and we want to help create lasting change," he said at the opening.

Ole Petter Ottersen, Rector of the University of Oslo, said the research provides a valuable breadth of expertise, and pointed out that success begets success. Quality in one area affects other areas, it becomes like a knowledge spiral that aims ever higher. He praised the Centre for its high aspirations. "NORMENT will be a centre of power in Norwegian psychiatry," he stated.

The causes of severe mental illness are many - and they are complex. Therefore, the research takes time, and the inter-disciplinary approach and long-term commitment are both critical to finding answers. And just the long-term perspective in funding is invaluable. It is important that the road does not suddenly stop when it is difficult to move the final steps.



Centre Leader Ole A. Andreassen and former Minister of Education Kristin Halvorsen.



NORMENT Core Researchers and former Minister of Education Kristin Halvorsen.

Objectives

NORMENT's primary objective is to reveal underlying pathophysiological mechanisms in schizophrenia and bipolar disorder and to develop tools for stratification and outcome prediction, using a vertical synergy approach, with the following sub-goals:

- 1) Identify rare genetic variants or expression variation to reveal 'missing heritability'.
- 2) Define new targets to optimize the ratio of beneficial vs. adverse effects of antipsychotics.
- 3) Determine new brain imaging phenotypes linking genes and core clinical phenotypes.
- 4) Use genetic and environmental factors to predict disease progress and outcome.

We will take advantage of 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 will be characterized with the same clinical, cognitive, biochemical and imaging protocols to identify new mechanisms which will be studied functionally in animal and cell culture models.

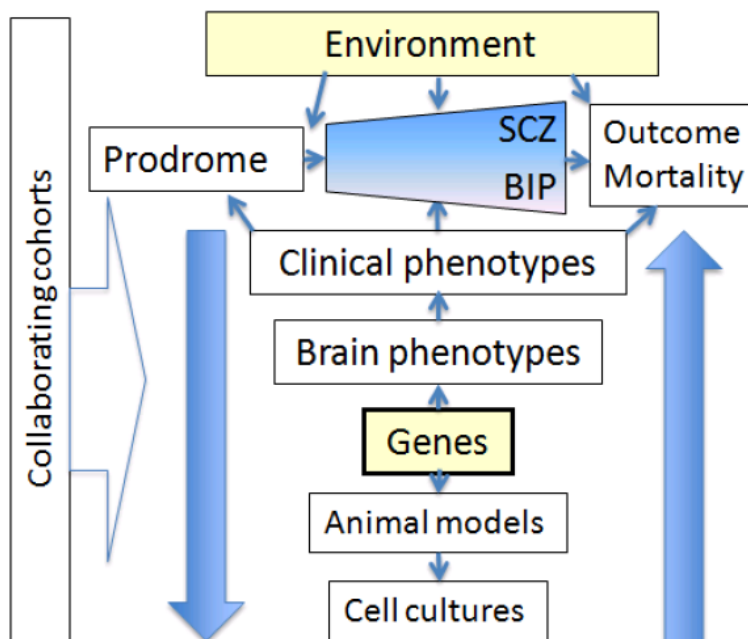
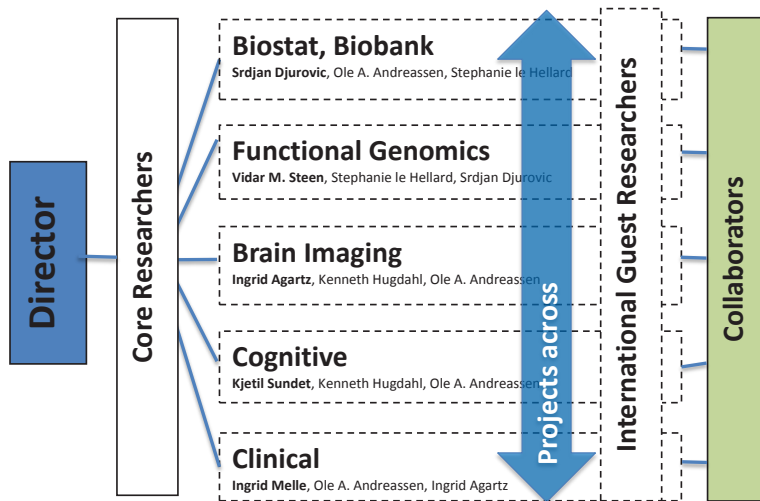


Fig. 1 The research strategy, with a vertical synergy approach. SCZ; Schizophrenia, BIP; Bipolar disorder

Organization and Research Areas

Translational Team/Senior Researchers

NORMENT has organized the research into interdisciplinary research groups with complementary expertise. Each research group is led by a senior researcher. NORMENT has eight Core Researchers.



Ole A. Andreassen, Professor, Centre Leader, Translational Psychiatry (OUS/UiO)



Ingrid Melle, Professor, Clinical Psychosis Research (OUS/UiO)



Vidar M. Steen, Professor, Functional Genomics (UiB)



Kjetil Sundet, Professor, Neurocognition (UiO)



Srdjan Djurovic, Research Professor, Psychiatric Molecular Genetics (OUS/UiO/UiB)



Ingrid Agartz, Professor, Structural MRI (UiO)



Stéphanie le Hellard, Professor, Molecular Genetics (UiB)



Kenneth Hugdahl, Professor, Brain Imaging, Cognition (UiB)

NORMENT Scientific Aims

Define New Targets for Antipsychotic Medication

Antipsychotic medications are the cornerstone in the treatment of schizophrenia, and have in recent years also been used for bipolar disorder. The medications are not equally effective for all patients, and have a limited effect on the core symptoms for approximately 20 % of those treated. Adverse effects are problematic and in some cases serious, such as cardiovascular risk factors (weight gain, abnormal fat levels in the blood, diabetes etc).

Research at NORMENT has a particular focus on the immune and lipid (fat) metabolism systems. We use animal and other experimental models to enhance our knowledge about the mechanisms of action of antipsychotic medication. We aim to optimize antipsychotic treatment by increasing the desired effect of medication and reducing adverse effects.

Brain Imaging: Identify Brain MRI Phenotypes Linking Genes to Core Clinical Phenotypes

Advanced neuroimaging techniques including structural and functional MRI have revolutionized the understanding of the structural and functional makeup of the human brain. NORMENT researchers have contributed to the identification of structural brain abnormalities in schizophrenia, including volumetric alterations in frontotemporal cortical areas and subcortical structures. Partly

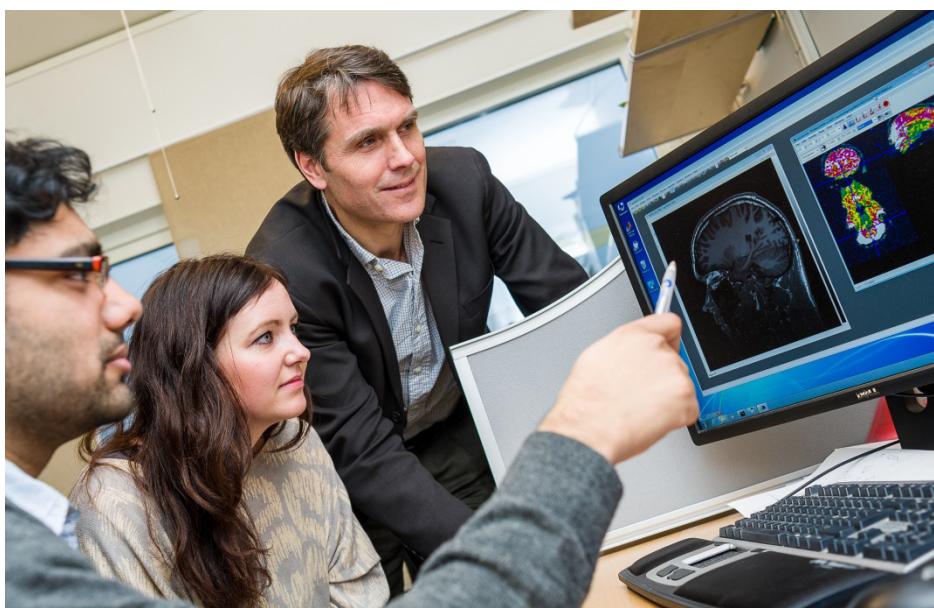
overlapping and partly diverging patterns have been found in bipolar disorder.

Structural and functional brain phenotypes are highly heritable, and current research at NORMENT aims to identify the genetic underpinnings of individual differences in the structural and functional organization of the human brain, and to disentangle the genetic and phenotypic associations with severe neuropsychiatric disorders.

Identify Genetic Factors for Psychiatric Disorders – Common and Rare Variants

Family and twin studies have shown that schizophrenia and bipolar disorder have high heritability. Researchers at NORMENT have contributed to major international GWAS (“genome-wide association studies”). We have found evidence for new vulnerability genes for these disorders. Preliminary results show that inherited changes in many genes (i.e. gene variants) are involved, but each variant contributes to a relatively modest degree. The identified gene variants explain only a small portion of susceptibility to psychotic disorders. Heritability is therefore still far from fully explained.

In our research, we use combined approaches that include new genotyping methods to identify rare genetic variants. We also use new statistical methods for mapping multiple gene variants, each of which has a small effect on its own.



Predict Course and Outcome – Including Mortality

Currently, we can only make general assumptions about the most likely prognosis for someone who develops a severe mental illness. We are unable to predict the outcome for individual patients. We know variability is large with regard to how these disorders develop – some patients recover completely while others become chronically affected.

NORMENT investigates whether genetic and environmental risk factors, combined with clinical assessment and brain imaging, can improve our understanding of illness course and outcome. Ultimately, the goal is to improve the prediction for those afflicted at the individual level.



Staff

Senior scientists, Professors and Associate Professors

Bjarte Håvik, Senior Scientist
Jan Ivar Røssberg, Professor II
Lars Ersland, Scientist, MR-physicist
Lars Westlye Tjelta, Associate Professor
Renate Grüner, Associate professor, MR physicist
Rene Westerhausen, Senior Scientist,
Thomas Espeseth, Associate Professor
Torill Ueland, Senior Scientist

Research Fellows

Beathe Haatveit, MSc
Carla Fernandes, MSc
Christine Demmo, Cand.psychol.
Christine Lycke Brandt, MSc
Elisabeth Lange, Cand.med.
Eva Høseth, Cand.med.
Helene Barder, Cand.psychol.
Ingeborg Bolstad, MSc
Kjetil Nordbø Jørgensen, Cand.psychol.
Kristina Skåtun, MSc
Levi Kvitland, Cand.psychol.
Liv Falkenberg, MSc
Luiz Goulart, Cand.med.
Lynn Mørk Johnsen, Cand.med.
Maiken Brix, Cand.med.
Mari Nerhus, Cand.med.
Marit Haram, Cand.med.
Morten Mattingsdal, MSc
Saurabh Srinivasan, MSc
Siren Tønnessen, Cand.psychol.
Thorny Olafsdottir, Cand.med.
Tiril Østefjells, Cand.psychol.
Vera Lonning, Cand.med.

Post docs

Akiah Ottesen Berg, PhD in Psychology
Andrew Brown, PhD in Biostatistics
Anja Vaskinn, PhD in Psychology
Carmen Simonsen, PhD in Psychology
Cecilie Bhandari Hartberg, PhD in Medicine
Daniel Quintana, PhD in Psychology

Francesco Bettella, PhD in Biostatistics
Ida Sønderby, PhD in Molecular Genetics
Kari M. Ersland, PhD in Biomedicine
Karolina Kauppi, PhD Medicine
Kristina Kompus, PhD in Psychology
Lavinia Athanasiu, PhD in Molecular Genetics
Martin Tesli, PhD in Medicine
Monica Aas, PhD in Psychology
Nhat Trung Doan, PhD in Medical Imaging
Silje Skrede, PhD in Biomedicine
Sudheer Giddaluru, PhD in Biostatistics
Tatiana Polushina, PhD in Biostatistics
Tobias Kaufmann, PhD in Psychology
Trine Vik Lagerberg, PhD in Psychology
Unn Haukvik, PhD in Medicine
Verena Zuber, PhD in Biostatistics
Yunpeng Wang, PhD in Biostatistics

Other Research Personell

Camilla Büchmann, Cand.psychol.
Erlend Gardsjord, Cand.med.
Galyna Kovalchuk, MA, Research Assistant
Hilde Therese Juvodden, Cand.med.
Jorid Aas, Cand.med.
Kristoffer Grimstad, Cand.psychol.
Vilja Bidtnes, Cand.psychol.

Technical and Administrative Positions

Bilal Safdar, Economist
Cecilie Evjen, Lab Assistant
Eivind Bakken, Head Nurse
Elin Inderhaug, Bioengineer
Gerard Dwyer, Research Technician
Kate Eli Frøland, Senior Excecutive Officer
Kristin Myklebust, Centre Coordinator
Kristine Kjeldal, MSc
Lars Johan Hansson, MSc
Lena Stabell, Psychiatric Nurse
Line Gundersen, Nurse
Marianne Navdal, Engineer
Øyvind Rustan, Scientific Assistant
Ragnhild Bettina Storli, Executive Officer
Rita Holdhus, Chief Engineer
Runar Kristiansen, Database Assistant
Tanzeela Parveen, Medical Secretary
Thomas Bjella, Database Consultant

International Cooperation

The research requires close cooperation with leading research environments, both national and international. In addition to this, the Centre will work actively to attract excellent researchers, both national and international. The Centre will facilitate the exchange of staff between the participants and international collaborators.

Scientific Advisory Committee

NORMENT has established an Advisory Committee of external scientific researchers. Their tasks are as follows:

1. Contribute to NORMENT's research activity by evaluating and advising on the activities within each of the research groups of the Centre and by acting as scientific advisors to the Centre Director.
2. Contribute by giving an annual lecture at postgraduate level.
3. Take an active part in NORMENT's annual meetings.
4. Participate in preparing an annual written evaluation with SWOT analysis.

The following researchers participate in the Committee:



Marcella Rietschel, Professor, University of Mannheim, Department of Genetic Epidemiology in Psychiatry.



Terry Jernigan, Professor, University of California, San Diego, Department of Psychiatry.



Michael Green, Professor, University of California, Los Angeles, Department of Psychiatry and Biobehavioral Sciences and the Semel Institute for Neuroscience and Human Behavior at the Geffen School of Medicine.

Visits Abroad

Professor Ingrid Agartz makes regular visits to the Department of Clinical Neuroscience, Karolinska Institute, Sweden.

Senior Researcher Bjarte Håvik made a research visit in July (10 days) to the Department of Psychiatry, Nara Medical University, Japan.

Post doc Sudheer Giddaluru made three research visits (each of 2 days) to the Umeå Center for Functional Brain Imaging at Umeå University, Sweden.

Professor Ole A. Andreassen made a research visit to the Multi-Modal Imaging Laboratory, San Diego, USA, for 10 days (July, October).

Post doc Yunpeng Wang participates in an exchange program, working in the Multi-Modal Imaging Laboratory, San Diego, USA, from August.

Post doc Verena Zuber made a research visit to the Multi-Modal Imaging Laboratory, San Diego, USA, for 1 month (July)

Post docs Lavinia Athanasiu and Ida Sønderby made a research visit for 3 months to deCODE Genetics (a biopharmaceutical company), Iceland.

Post doc Andrew Brown holds a 50 % position at the Sanger Institute (a genomics and genetics research institute), UK.

Professor Ole A. Andreassen and Srdjan Djurovic visited the Broad Institute (a biomedical research institution), USA, in October.

Research Professor Srdjan Djurovic visited the RUCDR Stem Cells Laboratory, Rutgers University, NJ, USA, in November.

Visits from Abroad

NORMENT Scientific Advisory Committee: Terry Jernigan (San Diego, USA) and Marcella Rietschel (Mannheim, Germany) visited NORMENT in September for NORMENT's first annual gathering.

MSc Eva Janousova (Czech Republic) visited NORMENT from August 22 – September 4.

Professor Anders Dale (San Diego, USA) and Professor Wes Thompson (San Diego, USA) visited NORMENT in August for a workshop.

Further International Cooperation

With the International Consortium on Hallucination Research at the University of Liege, Belgium, (Professor Frank Laroi).

With the University of Oxford, UK (Professor Steve Smith, Dr. Eugene Duff and colleagues).

With King's College London, UK (Dr. Michel Thiebaut de Schotten).

With the University of Copenhagen, Denmark (Dr. Randi Starrfelt).

With the Psychosis Research team at the UCLA Department of Psychiatry and Biobehavioral Science, Los Angeles, CA, US.

With the Early Psychosis Research team at Yale University School of Medicine, New Haven, CT, US.

With the University of California, San Diego, US (Professor Anders M. Dale and colleagues).

With the University of Southern California, US (Dr. Derrek P Hibar, Professor Paul M Thompson).

With the Bipolar Disorder research team at INSERM, Creteil, France.

With the research team at the Department of Molecular and Translational Medicine, Università degli Studi di Brescia, Brescia, Italy and the Department of Pharmacological Sciences, University of Milan, Milan, Italy.

NORMENT in the Media

“Nevrovitenskap på gyngende grunn”, Tidsskrift for den norske legeforening, nr 15 – August 20, 2013: <http://tidsskriftet.no/article/3042183>. Associate professor **Lars Westlye** explains how the statistical strength of neuroscientific studies is often low. (Journal of the Norwegian Medical Association.)

“App mot stemmer i hodet”, PåHøyden, Internal Newspaper, University of Bergen, September 3, 2013: <http://pahoyden.no/2013/08/app-mot-stemmer-i-hodet> Professor **Kenneth Hugdahl** talks about the development of an iPhone app which might help schizophrenia patients ignore voices in the head.

“Nye brikker i psykosepuslespillet”, Bladet Forskning, September 2013: http://www.forskningsradet.no/prognett-bladetforskning/Nyheter/Nye_brikker_i_psykosepuslespillet/1253989192884 Professor **Ole A. Andreassen** explains the complexity of the schizophrenia and bipolar disorder puzzles.

“Risikogener kan utvikle schizofreni”, Aftenposten, September 12, 2013: <http://www.aftenposten.no/fakta/innsikt/Risikogener-kan-utvikle-schizofreni-7308632.html#Ux3B83bKzIU> Professor **Ole A. Andreassen** explains how risk genes can lead to schizophrenia.

“De unge er faktisk eldst”, Aftenposten, September 17, 2013: <http://www.aftenposten.no/meninger/De-unge-er-faktisk-eldst-7312902.html#Ux3Cbn-bKzIU> Post doc **Akiah Berg** contributes to public debate about the present role and responsibilities taken by young people today. She considers young adults in their specific context and possible consequences for both the individual and society as a whole.

“Knytter 100 nye gener til schizofreni og bipolar lidelse”, Apollon, September 19, 2013: http://www.apollon.uio.no/artikler/2013/3_dna_schizofreni.html Professor **Ole A. Andreassen** explains how NORMENT researchers have identified risk genes which increase vulnerability.

“Schizofrene får hjelp med app-mobil”, NFR/Nevronor/Nyheter, December 13, 2013: http://www.forskningsradet.no/no/Nyheter/Schizofrene_far_hjelp_med_mobilapp/1253991020366?lang=no Professor **Kenneth Hugdahl** talks about the development of an iPhone app which might help schizophrenia patients ignore voices in the head.

“More links found between schizophrenia and cardiovascular disease” <http://www.sciencedaily.com/releases/2013/01/130131144116.htm> Professor **Ole A. Andreassen** comments on a study about the biological and genetic links between cardiovascular disease and schizophrenia.

“Genetikk og atferd”, NRK TV – Schrødingers Katt, October 10, 2013
A popular scientific TV programme about the interaction between genes and environment.

“Childhood trauma link to bipolar symptoms strengthened”, Journal of Clinical Psychiatry, March 2, 2013: http://www.medwirenews.com/47/105114/Psychiatry/Childhood_trauma_link_to_bipolar_symptoms_strengthened.html Post doc **Monica Aas** and colleagues show that there are consistent associations between childhood trauma and more severe clinical characteristics in bipolar disorder.

“Emotional abuse in childhood is a risk factor for bipolar disorder”, Bipolar Network News, November 11, 2013: <http://bipolarnews.org/?p=2220> Post doc **Monica Aas** and colleagues have found that emotional abuse in childhood, especially before age five, also increases risk of bipolar disorder.

“ICOSR 2013—Creating vulnerability via epigenetics”, Schizophrenia research forum: <http://www.schizophreniaforum.org/new/detail.asp?id=1879> Post doc **Monica Aas** reports from the 2013 International Congress on Schizophrenia Research (ICOSR), held on April 21-25 in Colorado Springs, Colorado, US.



Events

Regular Internal Meetings NORMENT

NORMENT has worked hard to establish regular, internal meetings for different purposes. This is an essential part of the communication structure within the Centre, and is particularly important because NORMENT staff members are located in several different places.

The Core Researchers have Telephone Conferences every second week.

The Core Researchers arrange Synergy Meetings once a month.

The different research groups meet weekly.

All NORMENT staff meet annually for a 2-day seminar.

Presentations

“Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders”
Post doc **Monica Aas** and colleagues. Poster presentation.
Scandinavian College of Neuropsychopharmacology (SCNP) Congress, May 2013, Copenhagen, Denmark.

“Childhood trauma is associated with antipsychotic medication, higher PANSS scores and lower GAF scores.”
Cand.psychol. **Christine Demmo** and colleagues.
Poster presentation,
Scandinavian College of Neuropsychopharmacology (SCNP) Congress, May 2013, Copenhagen, Denmark.

“A large-scale meta-analysis of subcortical brain volume abnormalities in schizophrenia via the enigma consortium”
Professor **Ole A. Andreassen** and colleagues.
The ENIGMA-Schizophrenia Working Group. Biological Psychiatry, September 2013, San Francisco, US.

“The impact of immigration and ethnic minority status on psychosis symptom profile.”

Post doc **Akiah Berg**.

4th European Conference on Schizophrenia Research, September 2013, Berlin, Germany.

“Bipolar lidelse og rusmidler.”

Post doc **Trine Vik Lagerberg**.

Open seminar for Patient and Relatives Education, November 2013, Oslo University Hospital.

“Association analysis between bipolar disorder risk genes and brain structural phenotypes.”

Post doc **Martin Tesli** and colleagues.

The 4th National PhD Conference in Medical Imaging, October 2013, Norwegian University of Science and Technology, Trondheim, Norway

“Genome wide significant associations between variants in Aurora Kinase A gene and Regulator of Calcineurin 3 gene and monoamine metabolite cerebrospinal fluid concentrations in a mixed group of psychiatric patients and controls”.

Professor **Ingrid Agartz** and colleagues.

The XXIst World Congress of Psychiatric Genetics, October 2013, Boston, US.

“Shared gene loci between schizophrenia and comorbid diseases suggest polygenic pleiotropy”.

Professor **Ole A. Andreassen**.

Molecular Psychiatry Association Meeting, November 2013, San Francisco, US.



Disputations

Ingrid Dieset, Cand.med.
(November 28)



“Endothelial and inflammation markers in schizophrenia and bipolar disorder.”

The results from Dieset’s thesis indicate that the mechanisms involved in immune and endothelium-related activity could potentially be part of the mechanisms that underlie schizophrenia and bipolar disorder. These findings will hopefully contribute to the development of new and better medication for this patient group.

Katrine Verena Wirgenes, Cand.med.
(December 4)



“Genetic factors in schizophrenia associated with endophenotypes.”

Through this PhD work, certain gene variants were identified that are associated with clinical features of psychotic disorders (particularly symptoms of delusion and thought disorders) and with changes in brain anatomy assessed with brain imaging.

Wirgenes’ work has contributed to increased knowledge of genetic risk factors for schizophrenia and bipolar disorder, and increased understanding of how genetics play a role in the disease mechanisms underlying these disorders.

Gregory Reckless, M.Phil.
(December 20)



“A functional MRI investigation of the relationship between extrinsic motivation and decision-making: normal characteristics and possible dysfunction in schizophrenia.”

Doctoral Candidate Greg Reckless and colleagues have investigated how motivation affects how we make decisions, both behavioral and brain activity associated with this.

Reckless and colleagues believe that this relationship may suggest that patients with schizophrenia have an altered relation between brain areas responsible for motivation and decision making. This may therefore be the mechanism leading to persistent negative symptoms in patients with schizophrenia even after successful treatment with antipsychotic medications.

Publications

1. Aas, M., Etain, B., Bellivier, F., Henry, C., Lagerberg, T., Ringen, A., . . . Melle, I. Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders. *Psychol Med*, 1-10 (2013). <http://www.ncbi.nlm.nih.gov/pubmed/24028906>
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