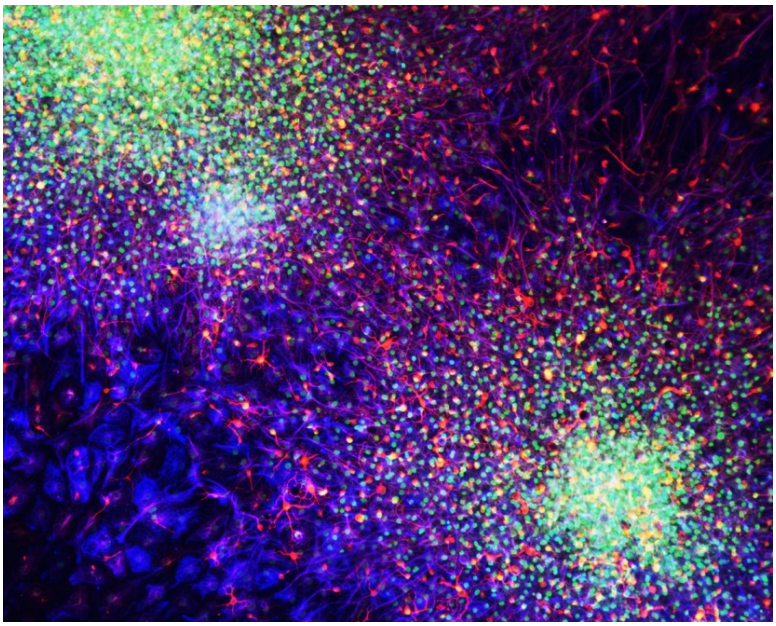
Annual Report

2014

Department of Neuroscience

Uppsala University



Cover Picture:
"Boundary cap neural crest stem cells (GFP-green) are source of neurons (bTUB-red) and glia (GFAP-blue) in vitro"

Photo by Elena Kozlova, Regenerative Neurobiology

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INTRODUCTION

The Department of Neuroscience at Uppsala University Faculty of Medicine covers a broad range of basic and clinical research as well as education about the nervous system. Our Department engages around 300 fellow workers divided in around 160 employees including including PhD students and a large number of postdoctoral fellows. Over one-third of the staff is of non-Swedish origin, enhancing the Department's international profile. The pre-clinical research groups are located at the Uppsala University Biomedical Center while clinical research groups are spread out in different buildings in the main University Hospital campus and engage numerous clinicians. These are employed by the University Hospital, but have part-time teaching and research responsibilities within the Neuroscience Department.

The research focuses on the following areas:

- structure and function of neural networks in the brain and spinal cord
- regulation of appetite and food intake
- biological mechanisms in brain injury, as well as treatment and rehabilitation following these injuries
- genetic mechanisms in neurological, psychiatric and personality disorders.

The year 2014 has continued as a fruitful period due to the work of the qualified and dedicated staff of the Department. Our progressing efforts to increase cross-collaboration in thematic research areas, and to facilitate teaching and administration have been particularly rewarding. We are very pleased to note that the positive appraisal of our scientific performance within the University-wide Quality and Renewal 11 evaluation (KoF11) has continued successfully to guide action in research during 2014 when we received one grant amounting to 1 million Swedish krona and two additional grants of 300 thousand Swedish krona and 150 thousand Swedish krona respectively. The Department has also attracted highly prestigious grants from the Swedish Research Council amounting to 18.5 million Swedish krona. This is a quality marker that makes us proud. However, we act in a dynamic field and with the move of Professor Lars Larsson´s group to the Karolinska Institute in October a fraction of the Research Council grants were also transferred. Joyfully for the Department, Christian Benedict, researcher in Functional Pharmacology got a grant of 5 million Danish krone from Novo Nordisk Excellence Award for Endocrinological Research. The Swedish Brain foundation awarded research grants to the following researchers; Åsa Mackenzie, Functional Neurobiology, Robert Fredriksson, Functional Pharmacology, Christian Benedict, Functional Pharmacology, Kent Nilsson, Child and Adolescent Psychiatry, Klas Kullander, Developmental Genetics, Richardson Leao, Developmental Genetics and Helgi Schiöth, Functional Pharmacology. We are also grateful for all other grants and scholarships that researchers have been awarded, both clinical and pre-clinical, during the year.

Several different awards have been awarded to researchers at the Department during the year. One of the most prestigious, the Martin H:son Holmdahl scholarship, was presented to Abdulbaghi Ahmad, researcher in Child and Adolescent Psychiatry. The Martin H:son Holmdahl scholarship is Uppsala University's foremost award for contributions which promote human rights and liberty.

The visibility of the Department in the scientific community and among the public at large has improved thanks to the restructured website. It supports research groups and individuals, as well as prouding updates of intradepartmental information. The media presence of the Department's researchers has been high during 2013 and 2014. Daily updates regarding the Department's activities are often based on internet searches, mainly in national and international media websites and of material published elsewhere on the activities of the Department's scientists and teachers in the community. This news service has become a popular means for increasing in-house information on the external activities of the Department. The Departmental homepage has also been appreciated as a resource by the media and other institutions within the community as a source of expert advice from researchers within different areas of neuroscience.

Anne-Marie Landtblom was promoted to Professor of Neurology July the 1st 2014 and Pernilla Åsenlöf was appointed Professor of Physiotherapy at the turn of the year.

Members for the Department Board were elected at the end of the spring semester. The newly elected board will serve from July 1st 2014 until June 30th 2017. The number of votes cast was very high and strongly supports the members of the Board in their challenging task to guide the Department through the coming years. The new Board has also begun the search for a new Department Head to succeed Professor Ted Ebendal upon his retirement at the end of September next year. A search committee within the Board has been interviewing several candidates for the post.

The unit of Child and Adolescence Psychiatry has spent the full year of 2014 in new localities at the Biomedical Center. The future localization of this unit has been under discussion and the question is tightly linked to the successor of Professor Frank Lindblad expected to be appointed in 2015. Planning for a relocalization to the House of Psychiatry as initiated at the end of 2014.

The Department agreed to be one of the pioneers of a University-driven survey from an external company, Quick Search, which was carried out during 2014. In order to ascertain perception of the working environment within the Department, this survey addressed questions on leadership, organization, physical environment, goals and strategies, as well as working climate. The nearly 300 persons affiliated to the Department were offered the chance to anonymously rank many parameters of the activities at the Department of Neuroscience. Overall, the results indicate that the staff is highly satisfied with the Department, a situation worth cherishing. A very high rating was given by the staff regarding pride and joy over their work at the Department. Furthermore, the staff´s commendation of their workplace, perception of engaging assignments, as well as good equal opportunities received high scores. There are some aspects of our organization and leadership that require further attention and will be the focus during coming years.

Department Retreat

In August 2014 the Department held a local retreat in Uppsala with focus on undergraduate education for all staff involved in teaching, both teachers and course administrators. The successful meeting was held in the auditorium of the new House of Psychiatry. The main goal of this year´s retreat was to increase competence and ensure teachers´ understanding of

constructive alignment of aims, education and examination. Further visions will be to discuss how to communicate and discuss general teaching issues.

The Department Neuroscience Day was held in March as usual. Again we turned to the House of Psychiatry for this event. The main topic of the day was clinical and non clinical research presentations, which were much appreciated! Four panel lectures and a panel debate about *"Clinical – preclinical collaboration; possibilities and challenges"* were also held by four senior professors. As before, Ph D students took part in the competition for the best poster award. The winner was Linda Solstrand Dahlberg, Ph D student in Helgi Schiöth´s group Functional Pharmacology.

Undergraduate and Graduate Education

The new University honorary title Excellent Teacher has been introduced by our Vice-Chancellor. After a thorough evaluation process our Department is proud that Professor Finn Hallböök was the first of our staff to be awarded this title in 2014.

The teaching responsibilities of the Department have increased substantially over the last few years. The Department of Neuroscience continued to receive the largest budget for teaching within the Disciplinary Domain of Medicine and Pharmacy during 2014, amounting to 16.9 % of the total budget available to the Disciplinary Domin. The Department's courses for medical students in 2014 have been fully adapted to the new medical curriculum. Education in neuroscience is introduced from the start of the new curriculum, largely as case-oriented and student-activating teaching in groups of 8-10 students, with emphasis placed on integrating basic and clinical sciences.

The Department has continued to have extensive responsibilities within the Physiotherapy and Speech Pathology and Therapy programmes during 2014. A new Physiotherapy programme with an updated curriculum began in autumn 2014, with focus on Behavioural Medicine and Physical Activity. We have had considerable commitments within the Biomedicine, Nursing and Pharmacy programmes, and play an active role in the efforts of the faculty to modernize the content and improve the teaching methods of these programmes. In addition, the Department hosts an international Masters Programme in Biomedicine. This Masters programme has been developed by the Department in collaboration with other departments within the medical and pharmaceutical faculties. Furthermore, the Department has also been involved in the Masters programme in Public Health since its inception.
The teaching budget and teaching staff within our complex Department has been intensively reviewed and discussed during year 2014. A critical issue has been the balance between clinical training at the Academic Hospital versus basic teaching at the Biomedical Center.

Finally, we are pleased to announce that 21 students successfully defended a Doctoral Thesis at the Department during 2014. Of these, 12 were males and 9 females, 9 students were from the clinical research areas and 12 students were from the preclinical research area.
Uppsala, February 2nd 2015

Ted Ebendal, PhD
Professor
Head of Department

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Lisa Ekselius

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Karin Nordström, teacher representative
Håkan Askmark, teacher representative (to 140630)
Per Enblad, teacher representative (to 140630)
Lars Hillered, teacher representative (to 140630)
Cecilia Yates, representative for technical/administrative personnel
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Bejan Aresh (from 141001)
Joel Eggert, student representative (to 140930)
Josefina Johannisson, student representative (to 140930)
Camilla Larsson (from 141001)
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Assistant Head of Department for Physiotherapy
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Lena Karlsson

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Lars Hillered (from 140801)

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Nadina Laurent
Sari Thunberg
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Clinical Neurology/ Rehab. medicine: Anja Smits/ Anne-Marie Landtblom
Clinical Neurophysiology: Lars Larsson
Clinical Psychiatry: Lisa Ekselius
Developmental Neuroscience: Finn Hallböök
Experimental Neuroscience: Klas Kullander
Functional Pharmacology: Helgi Schiöth
Neurosurgery: Per Enblad
Ophthalmology: Per Söderberg
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DISSERTATIONS 2014

Andersson, Mikael: Physiotherapy, *"Assessing Physical Activity and Physical Capacity in Subjects with Chronic Obstructive Pulmonary Disease"*.

Arvidsson, Emma: Functional Neurobiology, *"Motion and Emotion - Functional in vivo analyses of the mouse basal ganglia"*.

Burman, Joachim: Neurology, *"Curing Multiple Sclerosis How to do it and how to prove it"*.

Condén, Emelie: Psychiatry, *"Psychometric Properties of the DS14 and Associations with Ill Health and Coronary Heart Disease in General and Clinical Properties"*.

Goergen, Philp: Functional Pharmacology, *"Molecular mechanisms of aggression and feeding behaviour in Drosopilia melanogastere"*.

Holm, Sara: Physiotherapy, *"Children and adolescents with pain in primary care: Biopsychosocial determinants and behavioral medicine treatment in a physical therapy framework"*.

Hägglund, Maria: Functional Pharmacology, *"Characterization of Amino Acid Transporters in the Brain"*.

Isaksson, Johan: Child and Adolescent Psychiatry, *"ADHD and stress. Diurnal cortisol levels, early psychosocial adversity and perceived stress"*.

Klockars, Anica: Functional Pharmacology,*"Non-caloric regulation of food intake"*.

Kronschläger, Martin: Ophthalmology, *"Prevention of experimental cataract induced by UVR"*.

Larhammar, Martin: Developmental genetics, *"Neuronal networks of movement"*.

Lee, Yu-Jen: Physiology, *"Motion vision processing in fly lobula plate tangential cells"*.

Lindqvist, Johan: Clinical Neurophysiology, *"Cellular and molecular mechanisms underlying congentital myopathies-related weakness"*.

Lööv, Camilla: Neurosurgery, *"Cellular and Molecular Responses to Traumatic Brain Injury"*.

Ngamjariyawat, Anongnad: Regenerative Neurobiology, *"The beneficial Effects of Neural Crest Stem Cells om Pancreatic beta cells"*.

Patra, Kalicharan: Developmental genetics, *"Modulation of neuronal functions - the role of SLC10A4"*.

Shirazi Fard, Shahrzad: Developmental Neuroscience, *"The Heterogenic Final Cell Cycle of Retinal Horizontal Cells"*.
Sonnby, Karin: Child and Adolescent Psychiatry, *"Co-occuring symptoms of attention deficit hyperactivity disorder and depression aspects of sex, aetiology, help-seeking and assessment"*.

Swartz, Jackie: Child and Adolescent Psychiatry, *"Allergy, Stress and Sense of Coherence in Families with Children living in accordance with an Anthroposophic Lifestyle"*.

Virhammar, Johan: Neurology, *"Idiopathic Normal Pressure Hydrocephalus Cerebrospinal Fluid Tap Test and Magnetic Resonance Imaging as Preoperative Prognostic Investigations"*.

Xu, Bo: Pharmacology, *"Evolutionary and Pharmacological Studies of NPY and QRFP Receptors"*.

Finance 2014

Total revenues 2014: 157 429 270 Swedish krona

Government grants	103829kkr	
Undergraduate education		59931kkr
Graduate education and research		43197kkr
External grants and fundings	53 600 kkr	
Student fees		701 kkr
Contract education		467 kkr
Research grant and fundings		51459kkr
Contract research		1 674 kkr

Research grants and funds: 51 459 000 Swedish krona

The Swedish Research Council	47,6%
Other private funds	17,8%
Others	6,2%
EU	5,0%
FORMAS	4,1%
Other Nonprofit Organizations, within EU	4,0%
Government grant (co-financing)	4,0%
Swedish Brain Foundation	3,9%
The Foundation of Olle Engström builder	2,7%
Uppsala Akademiförvaltning	2,6%
The National Board of Health and Welfare	2,1%

SCIENTIFIC REPORTS

Klas Kullander, Professor in Developmental Genetics, centre, with Maj-Britt Moser and Edward Moser, Nobel Prize winners in Physiology or Medicine, at The Nobel Lectures at Uppsala University, BMC, december 2014.

Clinical Neurology & Psychiatry

Clinical Neurology

Group leader: Anne-Marie Landtblom, Professor and Anja Smits, Professor

Members of the group during 2014

Amalia Feresiadou, MD
Anja Smits, Professor
Anne-Marie Landtblom, Professor
Atle Melberg, Associate Professor
Birgitta Jakobsson-Larsson, PhD student
Dag Nyholm, Associate Professor
Elisabet Westberg, PhD student
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Peter Grenholm, MD
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Svante Wallmark, PhD student
Torsten Danfors, MD, PhD
Valter Niemelä, M D

Research at the neurology unit of the Dept of Neuroscience is strongly patient-oriented and scientific questions arise from daily clinical practice. Patients with common neurological disorders such as epilepsy, movement disorders, stroke and multiple sclerosis (MS) provide powerful resources for clinical and epidemiological studies. Rare diseases like hereditary neurological disorders and low-grade gliomas are studied in collaboration with other centres. A sleep research group has been established.

Research groups:

Epilepsy

Members of the group: Torsten Danfors, MD, PhD, Imad Halawa, MD, PhD-student, Eva Kumlien, associate professor, Peter Mattsson, associate professor, Athanasios Stavridis, MD, Johan Zelano, associate professor.

Epilepsy is a common and serious disorder of the central nervous system, with a prevalence of approximately 0,5-1 per cent and accounts for 0.5% of the global burden of disease. Epilepsy can have congenital etiologies, often presumed to affect the wiring of the brain with ensuing hyperexcitability of neuronal networks, but also arise after cerebral lesions, such as infections, trauma or stroke. Epilepsy is associated with serious consequences such as premature death, physical problems such as fractures and bruising, as well as higher rates of other diseases or psychosocial issues. Epilepsy has significant economic implications in terms of health-care

needs and lost work productivity. Children of women with epilepsy have increased rates of malformations, lower mean IQ and school grades.

Ongoing Clinical and interventional projects in Epilepsy group:

Role of exposure of antiepileptic drugs in utero in the prevention of later cognitive impairment in children to parents with epilepsy
In this registry-based study we collect data on all children born 1973-2003 (N=2.000.000). We will compare school grades and later socioeconomic achievements of children exposed to anti-epileptic drugs (AEDs) in utero with children unexposed to such drugs.

Role of pharmacological treatment in the prevention of sudden unexpected death in epilepsy (SUDEP)
The study population comprises all persons living in Sweden at the end of 2006, who at some point during 1998-2005 where registered with the diagnosis code for epilepsy in the Swedish National Patient Register. Using death certificates we will identify cases of SUDEP. For these potential cases, medical records including autopsy protocols will be reviewed. For each case we will randomly select three epilepsy controls from the study population. The aim is to analyze the risk of SUDEP in relation to non-adherence to prescribed AEDs, type of prescribed AEDs and comedication with SSRI-type antidepressants. In addition, studies of cardiological problems in persons with epilepsy as a collaboration with the University of Linköping are preformed.

Focal epilepsy – clinical characteristics, prognosis, prevention and search for biomarkers.
We are studying a cohort of patients with newly onset epilepsy after stroke in Uppsala County. Data have been collected with the purpose to characterize the condition, and form the basis of future genetic and imaging studies. A prospective study of patients with newly diagnosed epilepsy is ongoing with the aim to identify biological and clinical biomakers for epileptogenesis with a special focus on inflammation, neuronal antibodies and genetics.

Cortical excitability in epilepsy – studies with navigated Transcranial Magnet Stimulation (nTMS)
We are applying nTMS to measure cortical excitability and risk of seizures in cohorts of patients with a primary cerebral insult, newly onset epilepsy, pharmacoresistant epilepsy and healthy control subjects. We also want to explore the effect of temporal lobe resection on neuronal networks for fear conditioning by means of TMS in relation to fMRI.

Acute symptomatic seizures - a study in patients with dysmetabolic disorders and structural brain damage
Using CFM, cerebral functional monitoring, we will prospectively investigate patient receiving neurointensive care to monitor subclinical acute symptomatic seizures and their influence on outcome.

Economic and psychosocial aspects of epilepsy
Studies of AED use and economy in Sweden in collaboration with the University of Gothenburg. Qualitative studies of persons with epilepsy in collaboration with the University of Linköping.

Clinical Neurogenetics

Authors and co-authors of publications in Clinical Neurogenetics include: Atle Melberg, associate professor, Shala Ghaderi Berntsson, MD, PhD, Amalia Feresiadou, MD, Anja Smits, MD, PhD, Professor, Jimmy Sundblom, MD, PhD.

Clinical Neurogenetics is a rapidly progressing area of research, presently focusing on diagnostics and improved treatments. There is multidisciplinary collaboration between clinical neurology, clinical neurophysiology, neuroradiology, clinical genetics, pathology, molecular biology and biochemistry, within different Departments at Uppsala University, collaboration with other centers in Sweden and internationally.

The focus is on a number of rare neurological disorders affecting the central nervous system, peripheral nervous system or skeletal muscle. These include leukodystrophy, Welander myopathy, rippling muscle disease (RMD), Huntington´s disease, and other diseases.

Neurodegeneration/ Movement disorders

Members of the group: Håkan Askmark, Adjunct Professor, Ingela Nygren, MD PhD, Dag Nyholm, Associate Professor, Birgitta Jakobsson Larsson, PhD student, Valter Nimelä, MD, Paul de Roos, MD, Johan Virhammar, MD, PhD, Marina Senek , PhD student.

In collaboration with the PET-centre the role of PET with the new tracer 11C-PE2I is studied in patients with different types of parkinsonism with the aim to improve the diagnostics. In collaboration with the Human Proteome Resource group at the Rudbeck laboratory and the Department of Physical and Analytical chemistry, Uppsala University screening for potential protein biomarkers is performed in plasma, CSF and muscle from patients with ALS, Parkinson´s disease and atypical parkinsonism. The quality of life and its relation to the disease progression as well as coping strategies in patients with ALS are investigated in a prospective study. Together with a research group at the unit for physiotherapy we are studing pain in ALS-patients. In collaboration with IMBIM, BMC, Uppsala University there is an ongoing genetic study on motorneuron diseases in humans and dogs.
Improved treatments for Parkinson's disease have been developed within the group. The latest development is a dose dispenser for microtablets of levodopa. Pharmacokinetic-dynamic modelling is under development. A new drug designed to prevent gastroparesis in Parkinson´s disease has been tested in an international multicentre trial. Another multicentre trial has been planned and will soon be initiated to compare the efficacy of intestinal levodopa/carbidopa gel infusion versus deep brain stimulation in a randomized design, sponsored from the Swedish Research Council. Ongoing projects are dealing with objective, computerized symptom evaluations in movement disorders and a review of outcome measures has been performed in an international collaboration. A project was initiated in 2014, in collaboration with Acreo Swedish Research Institute, Sahlgrenska University Hospital, Dalarna University, and Department of Information technology at Uppsala University.

Five patients with chronic inflammatory demyelinating polyneuroapthy (CIDP) resistant to conventional treatment have been successfully treated with hematopoietic stem cell transplantation (HSCT). In collaboration with the Karolinska University Hospital,

Sahlgrenska University Hospital and Norrlands University Hospital, clinical data of a total of 11 CIDP patients (the largest published series so far) have been analysed and will shortly be published. In collaboration with the Department of Clinical Neurophysiology the role of vitamin D levels in blood in myasthenia gravis and inflammatory neuropathies are studied.
Clinical and pharmacological studies to optimize the use of botulinum toxin in hyperhidrosis and in cervical dystonia, with direct clinical applications for these groups of patients, have been presented in a recent doctoral thesis (Alma Rystedt, 2012). and the Department participates in a multicenter clinical trial on botulinum toxin in cervical dystonia.

Normal pressure hydrocephalus (NPH) is an increasingly recognized condition among the elderly population and is associated with symptoms of gait impairment, cognitive decline, and urinary incontinence. The symptoms can be reduced by implantation of a shunt system, which leads to improvement in 80% of the patients.
Our clinical studies focus on preoperative prognostic investigations used to diagnose and select patients for shunt surgery. In collaboration with the Department of Radiology at Uppsala University Hospital, advanced MRI methods are evaluated in NPH patients to investigate changes in cerebral perfusion, white matter function and volumetry after shunt surgery.

Neuroinflammation and Multiple sclerosis

Members of the group: Joachim Burman, MD, PhD, Inger Boström, RN, PhD, Jan Fagius, associate professor, Anne-Marie Landtblom,professor.

The Neuro-inflammation group is a collaborative effort by the Departments of Neuroscience and Immunology, Genetics and Pathology. One focus of the group lies on studying clinical effects and mode of action of a novel therapy: hematopoietic stem cell transplantation (HSCT). Since 2004 more than 50 patients with multiple sclerosis and also several patients with chronic idiopathic demyelinating polyneuropathy have been treated in Sweden. The goal of this therapy is to achieve long-term remission through short-lasting ablation of the immune system. This procedure is potentially curative and in a large series of MS patients, progression-free survival was 71 % with a median follow-up time of 48.3 months.

The mode of action is not yet fully understood, and several mechanisms probably contribute to the effect. It has been demonstrated that HSCT causes a profound renewal of the immune system and not just long-lasting immune suppression. At least part of the effect is likely related to removal of auto-reactive cells, but some of these cells probably escape the treatment and remain after HSCT. If so, such auto-reactive cells must be kept in control to maintain remission, which could be due to restoration of tolerance to self-antigens.

Studies of MS epidemiology are performed in the multinational effort EnVIMS (Environmental factors in MS) using questionnaires in order to evaluate the risk contribution of known and suggested risk factors for MS. The study is now ongoing in the county of Värmland.
The sex ratio of MS is now changing in the Western world with an increasing female mortality, which is studied in collaboration with the Swedish Multiple Sclerosis register.

Brain tumours including Low-grade gliomas

Group leader: Anja Smits.
Group members/collaborators within the department: Madelen Braun, MD, Tamador Elsir, PhD, Shala Ghaderi Berntsson, MD, PhD; Anne-Marie Landtblom, professor, Krisztina Szalisznyo, MD, PhD; Maria Zetterling, MD, PhD, Kenney Roodakker, PhD student.

Low-grade gliomas (LGGs) are glial tumours with malignancy grade II according to the WHO classification of brain tumours, constituting an interface between benign (WHO grade I) and malignant gliomas (WHO grade III and IV). LGGs are differentiated tumours characterized by high cellularity and low proliferation, with only few mitoses and no necrosis or vascular proliferation. In spite of their indolent course, LGGs grow continuously with an average diameter increase of 4 mm/year, infiltrating and invading the surrounding brain. In spite of a relatively favourable prognosis (median survival 7 to 10 years), all patients with LGGs will develop malignant gliomas with eventual fatal outcome.
The majority of patients have epileptic seizures at disease presentation without any neurological deficits. The clinical management of LGGs has changed during recent years from a traditional “wait-and-see” policy towards early and more aggressive surgery. There is evidence now to believe that surgery of LGG should aim for “supra-total resections” to improve long-term survival of patients. Thus, maximal tumour resection while retaining neurological function and quality-of-life, is beneficial for patients, delaying malignant tumour transformation and increasing survival. The most effective postoperative treatment, i.e. radiotherapy and/or chemotherapy, as well as the optimal timing of such treatment, is still a matter of debate. This dilemma is strongly related to the variety in natural history and response to therapy between individual patients.
Our clinical studies focus on the role advanced MRI, in combination with11C-methionine PET, for preoperative evaluation, to detect early tumour progression and to monitor response to treatment in patients with LGG. We are also interested in evaluating these parameters to monitor neurological and cognitive functions and epileptic seizures during the course of disease. For this purpose, a computational model has been developed, incorporating two cortical patches and the white matter connections of the uncinate fasciculus. Tumour-induced structural changes were modelled such that different aspects of the connectivity were altered, mimicking the biological heterogeneity of gliomas.
Translational studies to identify proteins that can serve as diagnostic, predictive and prognostic biomarkers for LGGs, are performed in collaboration with the Science Life Lab at Uppsala University. The overall goal of these studies is to develop individualized and biological-based treatment, optimizing the clinical management of this patient group.

In addition, the rare disease neurogenetic tumour disease Von Hippel Lindau syndrome, is studied.

Sleep medicine

Group leader: Anne-Marie Landtblom
Group members: Inger Boström, Md PhD, Atle Melberg Ass professor, Amalia Feresiadou MD, Valter Niemelä MD

This group was established in Upsala during 2014 with internal collaborations with Dept of pediatrics and Dept of lung medicine and allergy. We study diagnoses like narcolepsy, the

Kleine-Levin syndrome and idiopathic hypersomnia from a clinical, epidemiological and imaging perspective. The acitivities are performed in collaboration with Linköping University with input from the group of E Mignot, Stanford. Some acitivities have connections with the national register of narcolepsy, NARK REG.

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Agencies that support the work/ Funding

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Lions Cancerfonden
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Parkinsonfonden
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Swedish Knowledge Foundation
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Ulla-Carin Lindquist stipendium
Uppsala County Council (ALF)
Vinnova

Clinical Neurophysiology

Neuromuscular

Group leaders:
Lars Larsson, Professor, MD, PhD
Stefano Gastaldello, Docent, PhD

Members of the Basic and Clinical Muscle biology group during 2014:

Lars Larsson,(Professor, MD, PhD) Barry Dworkin (Visting Professor, PhD), Stefano Gastaldello (Docent, PhD, Swedish Research Council supported Researcher), Meishan Li (MD, PhD), Niccola Cacciani (MD, PhD), Sara Dahlén (MD), Humberto Gonzales (MD, PhD student), Rebeca Corpeno Kalmagi (PhD student), Johan Lindqvist (PhD student), Hannah Ogilvie (PhD student), Guillaume Renaud (PhD student), Heba Shalah (ERASMUS student), Hazem Akkad (grad student), Johan Peterson (graduate student), Yvette Hedström /Sr. Res. Tech), Ann-Marie Gustafsson (Sr Res Tech), Hazem Aqqad (grad. student).

The aims of our research focusing on neuromuscular muscle wasting disorders in the **Basic and Clinical Muscle biology** are to:
Determine underlying mechanisms
Develop and improve diagnostic methods and monitoring techniques
Implement and evaluate specific therapeutic intervention strategies

The research within *basic and clinical muscle biology* focuses on the mechanisms underlying the muscle wasting and impaired muscle function that is associated with critical illness and aging, at the gene, protein, muscle cell and muscle levels. A significant part of the research efforts are also devoted to detailed studies of regulation of muscle contraction at the motor protein and muscle cell levels in patients with mutations of sarcomeric proteins, such as myosin, myosin associated and regulatory proteins (troponin and tropomyosin). Methods have been developed for detailed studies of:

1. Regulation of muscle contraction at the cell and motor protein levels, i.e., contractile measurements in the short muscle cell segments obtained with the percutaneous muscle biopsy technique and studies of myosin function after extraction of myosin from a short muscle cell segment, i.e. methods to measure catalytic properties (motility speed) and force generation capacity.
2. Quantitative and qualitative analyses of myofibrillar protein expression in single muscle fibre segments, including cell biological, biochemical, structural (mass spectrometry) and biophysical (X-ray diffraction) methods.
3. Imaging techniques for 3D analysis and reconstruction of myonuclei organization in single muscle fibre segments using a novel algorithm
4. Experimental models for detailed mechanistic studies of muscle wasting in critically ill intensive care unit patients, involving large (porcine) and small (rodent) animal

models where animals are mechanically ventilated, pharmacologically ventilated and monitored for long durations (several weeks). These models are used in parallel with clinical studies in intensive care unit patients using methods unique for our group in combination with clinical electrophysiological methods. Different specific intervention strategies are presently being evaluated in the rodent ICU model. Very promising and positive robust effects are observed with a novel chaperone co-inducer. The goal is to transfer this pharmacological intervention to clinical trials during 2014

The different methods for studies of regulation of contraction and myofibrillar protein synthesis/degradation have been developed for studies of small muscle samples and can be used independent of mammalian species. This gives us unique opportunities for combined mechanistic experimental and clinical studies focusing on important clinical problems. Some of these methods are presently being used in routine clinical diagnostics. The combined expertise and methods available in this group for detailed studies skeletal muscle in health and disease from patients and in experimental animal models is unique, second to none and not available in any other research group. The research is conducted in collaboration with excellent research groups at UU, in Europe, Australia, Japan and the US. The research group consists of group leaders Professor/Docent, Adjunct Professor, MDs with a PhD degree, post-docs (PhDs), PhD students, fulltime senior research technicians and graduate/undergraduate students.

The research group was part of a strategic recruitment plan at Karolinska Institutet and research group moved to Karolinska Institutet September 2014, Department of Physiology and Pharmacology, Department of Clinical Neuroscience, Clinical Neurophysiology, Karolinska Institutet.

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International collaborations

18 European groups within a Fp7 EU-project (Myoage), 25 European groups within an EU COST project (CM1001). Prof. Caroline Byron (Copenhagen, Denmark), Profs Lea Sistonen and Leif Eriksson (Turku, Finland), Profs. Vuokko Kovanen, Sarianna Sippilä and Harri Suominen (Jyväskylä, Finland), Profs. Laszlo Vigh and Peter Literti Nagy (Budapest, Hungary), Prof Bertrand Friguet, Dr. Norma Romero and Prof. Mario Pende (Paris, France), Dr. Isabelle Penisson-Besnier (Angers, France), Mathias Gautel, (London, UK), Ass. Prof. Gonzalo Blanco (University of York, UK), Prof. Wolfgang Linke (Munster, Germany), Prof. Bernhard Brenner (Hannover, Germany), Prof. Simone Spuler (Charite University, Germany), Prof. O. Friedrich (Erlangen, Germany), Prof. Antonio Musaro (Rome, Italy), Profs. Marco Sandri, Stefano Schiaffino and Luisa Gorza (Padova, Italy), Profs Naoto Yagi and Hiroyuki Iwamoto (Spring-8, Japan), Prof. Paul Gregorevic (Melbourne, Australia), Prof. Edna Hardeman (Sidney, Australia), Ass. Prof. Kristen Nowak (Perth, Australia), Prof. J.P. Jin (Detroit, USA), Prof. P.O. Hasselgren (Harvard, USA), Prof. A. Goldberg (Harvard, USA), Prof. Rick Moss (Madison, USA), Assoc Prof. Y. Ge (Madison, USA), Prof. Gerald McClearn and Roger McCarter (State College, USA), Prof. Karyn Esser (Lexington, USA), Prof. Velia Fowler (San Diego, USA) , Prof. M. Reid (Florida, USA), Prof. D. Gutridge (Columbus, USA), Prof. J. Kornegay (College Station, USA), Prof. W. Thompson (College Station, USA).

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Karolinska Institutet

Neuromuscular Synapse and Advanced Electrophysiological

Group leaders:
Anna Rostedt Punga, MD, PhD (Neuromuscular synapse and myasthenia gravis)
Erik Stålberg, Professor em. (Development of advanced electrophysiological methods)

Members of the group during 2014:

Anna Rostedt Punga
Johan Widenfalk
Elisabet Westerberg
Arne Sandberg
Erik Stålberg

Collaborators:

Prof Markus Rüegg, Basel, Switzerland, Prof Elisabeth Chroni, Patras, Greece
Prof Sonia Berrih-Aknin, INSERM, Paris, France
Dr Mohammad Alimohammadi, Medical Sciences, Uppsala University
Dr Tanel Punga, IMBIM; Uppsala University
J Navallas, Spain
S Nandedkar, USA
L Puuksa, Estonia
DB Sanders USA
J Kouyoumdjian Brazil
M Sonoo, Japan

The general aims of the neuromuscular group are:

1. Elucidation of the pathogenic mechanisms underlying neuromuscular disorders, and establishment of biomarkers, with focus on myasthenia gravis (MG).

2. Improvement of diagnostic methods/markers in neuromuscular disorders, including loss of motor neurons (ALS, post-polio, SMA) as well as disorders with disturbed neuromuscular transmission.

Project 1) Neuromuscular synapse and myasthenia gravis:

Ny Disorders of disturbed neuromuscular transmission include the autoimmune disorder Myasthenia Gravis (MG), in which antibodies attack the receptors of the neuromuscular synapse. The symptoms manifest as fatigable weakness of skeletal muscles in the face, in the neck, arms and legs and often cause droopy eyelids, difficulty in swallowing and chewing etc. In many patients, there is also a subsequent muscle wasting, in particular in patients with antibodies against the receptor muscle specific tyrosine kinase (MuSK). Our main research interest is to elucidate the pathogenesis of MG and, ultimately, to find new therapeutic

interventions against the muscle wasting following chronic neuromuscular disorders. Additionally, we aim to discover novel biomarkers for improved diagnostics, prognosis and treatment in conditions of disturbed neuromuscular transmission. We work both with the animal model of experimental autoimmune myasthenia gravis (EAMG) and in the clinical setting with MG patients.

During the past year we have found certain circulating microRNAs in the sera of MG patients that correlate with presence of acetylcholine receptor (AChR) antibodies. The most sensitive biomarker, miR150-5p also correlated with clinical improvement after thymectomy. This miR, along with miR21-5p are both important regulators of T cell differentiation, called immuno-miRNAs, and since MG patients have dysregulation of T regulatory cells, these miRNA can prove to be potential biomarkers in the sera of MG patients, where no biomarkers have been available to date. We will now continue to elucidate the role of these immuno-miRNAs in the processes of the autoimmune response more specifically and in the neuromuscular transmission, both in-vivo and in-vitro.
Further, we have established neurophysiological parameters to assess the safety and efficacy upon intramuscular injection of botulinum toxin in the facial muscles.

2) Development of Advanced Electrophysiological Methods

Development of electrophysiological methods for the study of neuromuscular disorders continues. In the past year, our focus has been on new electrodes for jitter analysis. Results have been published, but more reference material is needed. There is also a need to replace conventional reusable and expensive macro-EMG needle with a disposable electrode. The macro EMG technique has a proven value to study and follow reinnervation processes, and is superior to the conventional needle-EMG in these respects.
A study regarding a reusable needle is running and preliminary results are currently being processed. Also, a needle manufacturer has also shown interest in this project.
Over the last few years, criteria and methodological details for the MUNIX method for axonal counting have been developed; and a European and US multicenter study has confirmed its reproducibility. Further, MUNIX has been applied in the follow-up of patients with ALS, providing a good quantitative measure of the dynamic changes in this disease.
Our method of Scanning EMG has resulted in a PhD thesis in Spain for one of the participants (Navallas). The results are now used for simulation studies in muscle.
The method for direct muscle stimulation is being evaluated in critical illness (together with Prof Larssons group). Data have been collected from a large group of critically ill patients to be published as a PhD thesis, Humberto Skott, Huddinge.
Surface EMG is being evaluated as an alternative to invasive needle EMG examinations.
New algorithms for analysis of surface EMG particularly in pediatric praxis are being established, for example in children with spinal muscle atrophy (SMA).
Abnormalities in the neurographic parameters F-waves are studied in relation to various diseases.

International collaborations

Anna Rostedt Punga acted as joint workpackage leader together with Prof Markus Rüegg, Basel, Switzerland, in the “Fight-MG” European research network about Myasthenia Gravis, currently until May 2014 on pathophysiology at the neuromuscular junction.
The group of Prof Sonia Berrih-Aknin, INSERM, Paris, France is working together with “Neuromuscular synapse and myasthenia” in finding new biomarkers in MG.

Prof Amelia Evoli, Catholic University, Rome, is working together with the group on finding biomarkers in MuSK+ MG.
Prof Erik Stålberg is involved in collaborations with J Navallas, Spain, S Nandedkar, USA and M Sonoo, Japan in developing new motor unit analysis techniques.
Both groups are involved in collaboration with DB Sanders USA and J Kouyoumdjian Brazil to improve the method of single-fiber EMG.

Publications 2012-2014

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11. **Sandberg A**. The standard concentric needle cannula cannot replace the Macro EMG electrode. Clin Neurophysiol. 2014 Feb;125(2):406-10.
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Stålberg E. Quantifying needle EMG. In: Adatepe T, editor. Comprehensive Guide and Muscle Atlas for Needle Electromyography. Istanbul: Sep Medikal; 2014. p 15-25

Agents that support the work/ Funding

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Awards

”Eberhardt Pfleiderer Preis” from the German Myasthenia Gravis foundation (ARP)
Honorary member of IFCN (ES).

Central and Somatosensory Nervous System

Members of the group during 2014

Roland Flink, Karin Edebol Eeg-Olofsson, Hans Axelsson, Åsa Amandusson, Kristin Elf, Holger Rothkegel, Roland Schmidt

Research project 1: Focal epilepsy and epilepsy surgery
Project leader: Roland Flink

The aim of the project is to improve the localization of epileptic foci with dipole analysis methods in patients undergoing preoperative evaluation for epilepsy surgery. A new system for dipole analysis and reconstruction of 3D MR scans in order to superimpose dipole location with anatomical structures – Curry 7® - has been implemented.
Another part of the project concerns epidemiological data describing patients subjected to surgical treatment of epilepsy. The National Registry of Surgical Treatment of Epilepsy is administrated at the department of Clinical Neurophysiology, Neuroscience Center, Academic Hospital.

Project 2: Pediatric neurophysiology

Project leader: Karin Edebol Eeg Olofsson

Study of reference values in children in central and peripheral nervous systems performed and manuscript to be written. Author: Karin Edebol Eeg-Olofsson. A manuscript entitled “Low-frequent Repetitive Transcranial Magnetic Stimulation (rTMS) in adolescents with Tourette syndrome and additional psychiatric conditions: results from a pilot study” in progress. Collaborative work between the Departments of Clinical Neurophysiology and Child and Adolescent Psychiatry. Authors: Karin Edebol Eeg-Olofsson and Najah Khalifa.

Project 3: Navigated transcranial magnetic stimulation in the evaluation and treatment of patients with epilepsy

Project leader: Åsa Amandusson

Transcranial magnetic stimulation (TMS) is a well-tolerated technique by which cortical neurons can be activated non-invasively. By using neuronavigation in conjunction with TMS, cortical function can be studied in relation to anatomical structures. Paired-pulse TMS (ppTMS) is a further development of TMS by which it is possible to obtain measurement values of cortical excitability. Recent studies have shown that these values may predict the therapeutic response to antiepileptic drugs and the outcome of epilepsy surgery. We have recently initiated several studies focusing primarily on different aspects of cortical excitability in healthy subjects and patients with epilepsy. We have developed a standardized semi-automatic method for ppTMS measurement and completed a methodological study comparing different ways of performing ppTMS. We have also completed a study in which cortical excitability during trigeminal nerve stimulation (a newly introduced therapeutic neurostimulation for epilepsy) was studied in healthy subjects.

Project 4: Neurophysiologic methods in intraoperativ monitoring (IOM)

Project leader: Hans Axelson

The ION project can be divided in two parts: a) optimize the method for intraoperative neurophysiology (ION) in patients undergoing intraspinal or spine surgery. This also includes analysing data from the last five years of ION to validate used methods. b) preoperative and intraoperative mapping and monitoring of eloquent cortical areas. This part of the project is currently focused on evaluating a method of determining the motor threshold during supratentorial glioma surgery.

Project 5: Continuous EEG during intensive care

Project leader: Kristin Elf, Åsa Amandusson

Continuous EEG has been carried out increasingly in intensive care units for last few years. It has then become evident that subclinical seizures and even status epilepticus is fairly common, especially in patients with a primary brain injury, but also in patients with e g metabolic and infectious diseases.
The interpretation of continuous EEG is very time consuming. The burden of interpretation increases with time recorded and number of electrodes. Reading raw EEG of many channels may lead to reader fatigue when seizures can be missed. Therefore trend analysis of few electrodes is often used. The most commonly used trend is amplitude integrated EEG, aEEG. It is not known how many electrodes are necessary for acceptable sensitivity why we currently perform a study on this.
During 2015 we will start a study regarding stimulus induces rhythmic, periodic and ictal discharges, SIRPIDs. SIRPIDs are pathologic EEG patters and seizures elicited by all kinds of sensory stimuli. Patients with SIRPIDs have an increased risk of seizures and SIRPIDs may cause neuronal injury. We aim at discovering patients with SIRPIDs and also to map what nursing and other medical processes that elicit SIRPIDs with the goal of a better planning of the intensive care to minimize secondary brain injury.
Another study in the pipeline is a prospective study of consecutive patients in the central ICU. The frequency of seizures are probably lower than in patients with a primary brain injury, but some studies have shown that patients with infectious and metabolic disorders also suffer from subclinical seizures which can only be discovered by continuous EEG. The purpose of this study is to describe the incidence of subclinical seizures and other epileptiform patterns in patients without a structural brain injury during intensive care.

Project 6: Pain and Itch in Human Disease

Project leader: Roland Schmidt

Background: About 1.5% of the Swedish population suffers from neuropathic pain. This is difficult to treat and it is estimated that as many as half of all patients receive inadequate pain relief. The mechanisms are largely unknown. No mechanism-based classification system is available. More effective and better tolerated treatments are needed (Swedish Medical Products Agency 2007, Sheets et al. 2008). Extensive experiments on rodent models have been found to be partially misleading since the pain systems in man and rodent are fundamentally different also in the peripheral nerve system.

***Questions, methods and goals**:* The technique of microneurography was initiated in Uppsala by Vallbo and Hagbarth in 1968. For many years we have performed recordings of action potentials from individual nociceptive (pain) C-fibre axons (microneurography) in awake humans who can simultaneously report their sensations. This kind of single fibre recording is technically complex and it is mainly performed only by 2 groups internationally. We are one of these groups (Norway – Sweden – Germany). Since nociceptive axons are extremely thin, they cannot be studied with intracellular electrodes in vivo and also cannot be studied, in a manner relevant for human pain, in vitro, the normal physiology of these axons is largely unknown. But we have revealed parts of their normal physiology that we believe are very relevant for chronic pain.
Pain and central sensitisation in man in experimental conditions is mainly mediated by specific mechanoinsensitive C-nociceptors (CMi) first described by our group (Schmidt et al. 1995). Parts of the sensation of itch is mediated by specific CMi fibres also first described by our group (Schmelz et al 1997).
***Pain mechanisms**:* Now we use our large reference data from recordings in healthy individuals and record from patients with chronic pain or itch. We aim at understanding the contribution of the different ion channels to pathologic axon membrane excitability. (Mutations of NaV1.7 sodium channels can result in pain). Since different classes of human C-nociceptive axons have separate specific and tightly coupled receptive, axonal, central and ion channel properties, it is possible to develop drugs specifically targeting one class of peripheral nociceptive neurons, decreasing high frequency discharges without influencing acute pain and defensive reflexes, and avoiding side effects from the CNS (sedation etc.). Several pharmaceutical companies are now developing drugs targeting voltage gated sodium channels for treatment of neuropahtic pain. (Sheets et al 2008, Dib-Hajj et al 2009) We have the capacity to test such drugs and drug candidates injected in minute amounts near the peripheral axons during microneurography.
***Future**:* We continue to unveil the mechanisms of hyperexitability in patients with neuropathic pain. Recordings include patients with mutations of NaV1.7, NaV1.8 and NaV1.9. As a result of our work a new method to diagnose thin fiber neuropathy by objective laser doppler measurement of the axon reflex is now being implemented in Uppsala.

International collaboration

TH Carr (5) Hermann Handwerker (1) T. Helås (2), E. Jørum (2), IP Kleggetveit (2), MS Kvernebo (2) C. Mørk (2) B- Namer(1), O. Obreja (1), K. Ørstavik (2), H. Quiding (3) H. Saltzer (3) M. Segerdahl (3) M. Schmelz (1), SG Waxman (4), C. Weidner (1).
1: Germany, Erlangen and Mannheim universities
2: Norway, Rikshospitalet and Trondheim University
3: Sweden, Karolinska institutet and Uppsala uni
4: USA, Yale University
5: U.K., AstraZeneca

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Psychiatry

Psychiatry

Group leader: **Lisa Ekselius, Professor**

Members of the group during 2014

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Anders Fredriksson, Associate Professor
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Rickard Färdig, PhD
Robert Bodén, Associate Professor
Tom Lundin, Professor Emeritus
Tommy Lewander, Associate Professor

Within the Department of Neuroscience research related to psychiatry, focuses on investigating factors relevant to psychiatric morbidity. The research group boasts a wide variety of competences, and most members have substantial clinical experience. There is broad expertise in research methods, from pre-clinical and experimental methods to methods used in clinical studies. These include, but are not limited to, methods for evaluation of psychiatric symptomatology and methods used in genetic and proteomic research.

This wide knowledge base facilitates clinically relevant research on many levels. The ultimate goal of our research is to improve psychiatric health. This requires optimal definitions of psychiatric states, optimal diagnostic procedures and subsequently best available, evidence-based care and treatments. All of this must be based on up-to-date knowledge of the enigmas of the nervous system. Individual projects are described below.

Personality and individual differences

I) Vulnerability and resilience; medical, psychological and social adaptation after severe injury

Participants: Lisa Ekselius (PI), Mimmie Willebrand, Caisa Öster, Josefin Sveen, and Josefin Bäckström. From Dept of Surgical Sciences: Professor Bengt Gerdin, Morten Kildal, MD, PhD, Associate professor, Björn Wikehult, RN, PhD, and Andreas Lindahl, MD, PhD.

Collaborators: Professor Elna Marie Larsson, Department of Radiology, Uppsala University, Uppsala, Associate professor Mats Stridsberg, Dept of Medical Sciences, Uppsala University (UU), Professor Elias Eriksson, Institute of Neuroscience and Physiology, Göteborg University, and Professor Folke Sjöberg, Dept of Clinical and Experimental Medicine, Linköping University, Professor Gerhard Andersson, Dept of Behavioural Sciences and Learning, Linköping University.

Our overall aim is to investigate factors that influence outcomes after a severe life threatening physical trauma or stressor, in this case a severe burn injury. According to the working hypothesis, several factors act, and interact, to shape the adaptation process and outcome (see Figure 1 below). Individual factors such as genotype, gender, psychiatric history, cognitive function, personality traits and coping strategies will be related to acute and long-term outcome. Also, physiological stress responses during treatment for the burn injury, with focus on the hypothalamo-pituitary-adrenocortical (HPA)-axis, are studied in relation to individual

factors and to outcome. Another objective is to study signs of neurobiological alterations using neuroimaging techniques. Outcome is broadly defined in medical, psychological and social terms. Some specific outcomes, to which we devote much interest, are cognitive function, e.g. attention and memory, and psychiatric morbidity e.g. delirium, posttraumatic stress disorder and depression.

Patients treated for severe burn injuries and associated family members are assessed prospectively during care and several years after discharge from hospital. Burn injury provides an excellent model for severe trauma with a protracted recovery. Therefore, the results can be generalized and facilitate the development of new treatment strategies that can improve outcome also after other severe conditions with an increased risk for psychiatric morbidity.

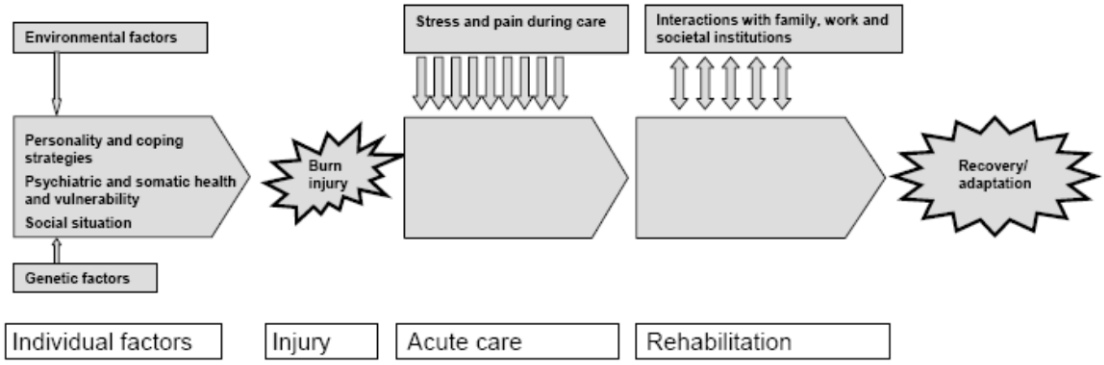

Figure 1. A model of trauma outcome.

II) A number of PhD projects are also performed within the "***Personality and Individual Differences group"***. These include 1) *Long-term outcome after pharmacological treatment in adult ADHD* (Dan Edvinsson); *Effect of CBT in hospital treated patients with depressive or anxiety disorders* (Fredrik Folke), and finally *Personality prediction of outcome after myocardial infarction* (Emelie Condén).

Psychiatric Epidemiology

Participants: Fotios Papadopoulos (PI), Georgios Karamanis, Jan Kask, Georgios Makris, Karin Tillman, Lisa Ekselius.

Collaborators: Dr Helle Kieler's psychopharmacology group at the Centre for Pharmacoepidemiology, KI, Professor Anders Ekbom, Department of Medicine, Karolinska Institute.

Our research focuses on epidemiological aspects of suicide, affective disorders and anorexia nervosa. We investigate predictors of both psychiatric and somatic outcomes.
Various aspects of suicide are studied using descriptive and analytical methods. Seasonality in suicides with a peak incidence during spring/early summer is studied in particular with focus on the theoretical framework and possible clinical implications.
Retrospective register cohorts are utilized to study mortality, comorbidity patterns and somatic outcomes in anorexia nervosa patients, as well as in patients with craniofacial disorders. Anorexia nervosa serves as a model of severe caloric restriction in humans, while

craniofacial disorders may provide neurodevelopmental insights for several psychiatric outcomes.

Emotional instability and impulsivity

Participants: Mia Ramklint (PI), Lisa Ekselius, Adriana Ramirez, Janet Cunningham, Maria Holstad Högberg, Martina Wolf, Dan Edvinsson, Ioannis Kouros, Niklas Hörberg, Charlotta Odelius, Martina Hedman, Cathrine Axfors.

Collaborators: Professor Kent W Nilsson, Center for Clinical Research Västerås, Professor Ulf Högberg, Dept of Women´s and Children´s health, Assoc. professor Alkistis Skalkidou, Dept of Women´s and Children´s health, Assoc. professor Daniel Nowinski, Det of Surgical Sciences, Professor Niklas Dahl, Dept of Immunology, Genetics and Pathology.

Emotions control our behaviors. Difficulty regulating emotions and impulses, therefore, affects our behaviors. Difficulty regulating emotions and impulses is common in various mental disorders. Strong negative emotions can lead to behaviors that are intended to deal with the feeling. However, it may be self-destructive behaviors such as substance abuse, self-starvation, binge-eating, self-harm or suicidal acts.

Difficulty with emotion regulation concerns the ability to handle strong emotions such as being sad or angry, and it is common in patients with psychiatric diagnoses such as borderline personality disorder. The difficulty also concerns the ability to regulate mood states that characterize individual experiences of the world over longer time periods. This difficulty is seen, for example, in bipolar disorder and depression where the patient suffers from longer periods of depression or mania.

The ability to regulate emotions also requires cognitive abilities. Self-control functions such as impulse control are located in the brain's frontal lobes. Patient with neuropsychiatric disabilities such as ADHD and autism spectrum disorders have altered function in their frontal lobes. These patients often have difficulties regulating emotions.

Our research work is based on the stress-vulnerability model. This is an interactive model in which genes and environment interact in the development of mental illness. We study difficulties with emotional and impulse control in psychiatric patients. Is there a common vulnerability in patients with similar symptoms? How do life events affect which symptoms develop? We also work with developing methods in psychiatry, both methods for treatment and assessment. How are problems identified, diagnosed, treated, and how are the treatments evaluated?

Psychosis research

Participants: Bodén Robert (PI), Leif Lindström, Lisa Ekselius, Gabriella Stålberg, Eva Baghdassarian, Eva Lindström, Leif Lindström, Björn Milesson-Fors, Björn Nilsson

Collaborators: Associate professor Johan Sundström, professor Bertil Lindahl, Dept of Medical Sciences; Dr Jakob Hedberg, and associate professor Magnus Sundbom, Surgical Sciences, UU; associate professor Tomas Jernberg at Karolinska Institutet (KI); Associate professor Helle Kieler, biostatistician Lena Brandt, Dr Johan Reutfors, and professor Morten Andersen and Professor Anders Ekbom, at the Centre for Pharmacoepidemiology, Dept of

Medicine, KI. Professor Jari Tiihonen, dpt Neuroscience, KI. Dr Urban Ösby and Professor Claes-Göran Östenson Dept of Molecular Medicine and Surgery, KI; Professor Wolfgang Fleischhacker, Dept of Biological Psychiatry, Medical University Innsbruck, Innsbruck, Austria; Professor René Kahn, Dept of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, Netherlands.

Our projects focus on psychiatric epidemiology in severe mental illness, especially schizophrenia and bipolar disorder. We investigate predictors of both psychiatric and somatic longitudinal outcome. Our research projects encompass both clinical follow-up studies as well as national register-based studies.

Two cohorts of consecutive first-episode psychosis patients in Uppsala County have been followed up in order to study how baseline measurements such as neuropeptide-Y in cerebrospinal fluid, electrocardiographic signs of autonomic balance, and neurocognitive functioning are associated to longitudinal symptomatic remission and psychosocial functioning. Further, an ongoing project evaluates brainstem evoked response audiometry as a diagnostic tool in schizophrenia and ADHD.

Severe mental illness, metabolic syndrome and mortality is another research track. We investigate differences in the care of metabolic syndrome related morbidity in patients with and without schizophrenia or bipolar disorder, from myocardial infarction care to bariatric surgery. We also have several pharmacoepidemiology projects using the Swedish Prescribed Drugs Register, along with other registers such as health care quality registers. In these cohorts we study adherence to drug treatment and outcome in schizophrenia and bipolar disorder and the safety of psychotropic drug use, especially during pregnancy.

Caring sciences

I) A randomized controlled trial comparing auricular acupuncture versus CBT in persons suffering from insomnia

Participants: Lena Bergdahl, Jan-Erik Broman, Lars von Knorring, Kristina Haglund, Agneta Markström.

Collaborators: Anne Berman, Department of Clinical neuroscience, Karolinska Institutet; Jens Sörenssen, Department of Medical Sciences, Clinical Physiology, Uppsala University; Lieuwe Appel, Department of Radiology, Oncology and Radiation Science, Section of Nuclear Medicine and PET, Uppsala University.

In this study we have used actigraphy, sleep-diary and evaluated surveys to measure insomnia, depression/anxiety, daytime sleepiness and quality of life to evaluate improvement in insomnia symptoms during acupuncture- or CBT treatment. Data collection is now ended; analysis is ongoing as well as manuscript writing.
Over the last few years, neuroimaging techniques have contributed greatly to the identification of the structural and functional neuroanatomy of anxiety and mood disorders. An additional aim of our research is to review neuroimaging studies investigating neural correlates during treatment of insomnia with auricular acupuncture.

II) Caring research in psychiatric care and mental health

Participants: Lena Bergdahl, Josefin Bäckström, Kristina Haglund, Christina Nehlin Gordh,

Mia Ramklint, Caisa Öster.

Collaborators: Erebouni Arakelian, Department of Surgical Sciences, Education in Nursing, Uppsala University; Christine Leo Swenne, Department of Public Health and Caring Sciences, Caring Sciences, Uppsala University; Marit Silén, Department of Public Health and Caring Sciences, Centre for Research Ethics & Bioethics, Uppsala University; Mats G Hansson, Department of Public Health and Caring Sciences, Centre for Research Ethics & Bioethics, Uppsala University, Björn Wikehult, Department of Surgical Sciences, Education in Nursing, Uppsala University.

The over all aim is to explore factors of importance for patient care, with respect to patient and close relations unique situation and their wishes. In addition, research aiming to improve education in care.
Ongoing projects investigate:

- experience/perception of psychiatric and mental health
- experience of receiving/giving care and receive support in care
- interaction between personnel, patient, and close persons
- factors of importance for individual quality of life
- factors that improve learning; clinical exams; quality in students' degree projects; and patients' perception of student participation in care.

III) Substance use and psychiatric care

Participants: Christina Nehlin Gordh, Caisa Öster, Johan Dyster-Aas

Collaborators: Fred Nyberg, Department of Pharmaceutical Biosciences, Biological Research on Drug Dependence, Uppsala University, Anders Hammarberg, Department of Clinical neuroscience, Karolinska Institute, Åsa Magnusson, Department of Clinical neuroscience, Karolinska Institute, Kari Jess, Department of Sociology, Uppsala University

The overall aim is to explore the connection between mental health and substance use, in order to develop psychiatric care to better meet the needs of patients with co-occurring problems.

Experimental Psychiatry

Effects on neonatal exposure to drugs/chemicals during brain development

Participants: Anders Fredriksson (PI), Christina Nehlin-Gordh, Tommy Lewander.

Collaborators: Per Eriksson, Professor, and Henrik Viberg, Assoc. Professor, Department of Environmental Toxicology, Uppsala University, Torsten Gordh, Professor, Emma Ponten, Ph student, Dept Surgical Sciences.

Neonatal exposure to drugs/chemicals during brain development might be involved in the induction of psychiatric disorders. In the research we use a "neonatal animal model" where we can study effects induced by low doses of drugs/chemicals during a defined critical stage of neonatal brain development in mice. We can study interacting effects between different agents when co-administered directly to neonatal animals, as well as the interaction between neonatal

and adult exposure, in a controlled manner. Therefore, this animal model allows us to specify certain issues, which can be difficult to solve in traditional neurodevelopmental studies and also in epidemiological studies. In this model we have shown that several drugs and environmental agents, though having differing mechanisms of action, can nevertheless cause the same functional disorder. This shows that functional disorders, measured with behavioural tests, in combination with neurochemical analyses, will provide a suitable endpoint for hazard identification of drugs/chemicals as well as finding safety periods/treatment of drugs in newborn and infants. Compounds currently under investigation are anesthetics (propofol, ketamine), theopylline, caffeine, ethanol, diazepam, paracetamol, donepezil, nicotine and other agents in the environment.

Uppsala Psychiatric patient samples

Uppsala Psychiatric Patient samples (UPP): Prospective Collection of Samples for the Study of Biological Mechanisms in Clinical Psychiatry

Participants: Janet Cunningham, Mia Ramklint, Lisa Ekselius

Collaborators: Uppsala Biobank

Current clinical practice in psychiatry is conducted through subjective evaluation of phenotypes. Diagnostic instruments, such as structured interviews and questionnaires, greatly improve the sorting of patients into valid diagnostic groups where generalizations about etiology and appropriate treatment can be made reliably. Biological markers are, however, absent and an important dimension of diagnostics is missing.

Our major aim is to create an infrastructure for the collection of biological material from patients with well-characterized psychiatric symptoms. The infrastructure would enable systematic collection of material from patients before treatment start and regularly during treatment. This step is essential to:

- identify diagnostic biological markers (including genetic, hormonal, inflammatory markers) for disease
- identify differences between diagnosis groups
- follow biological changes induced by treatment
- conduct case studies on selected patients-validate new diagnostic instruments

UPP has been launched in conjunction with the Carolina project. In summary, the Carolina project entails that all new patients at General Psychiatry undergo the same complete systematic evaluation using a set of established tools for symptom evaluation and diagnostics. The test period has been successful. Samples and data from >370 patients are now included in the project and several studies on the material are underway. A collection of material from healthy individuals is underway and has reached >45 participants. Similar infrastructure is now being implemented in the psychosis department and in the ECT clinic and collection will start in the fall of 2015.

National Centre for Disaster Psychiatry

Participants Mimmie Willebrand, (PI until 140331), Kerstin Bergh Johannesson, (PI from 140401), Filip Arnberg, Cristina Bondjers, Mimmie Willebrand.

The National Center for Disaster Psychiatry (Kunskapscentrum för Katastrofpsykiatri, KcKP) is a centre established and supported by the National Board of Health and Welfare, and located at the Department of Neuroscience at Uppsala University in close collaboration with the Psychiatry department at Uppsala University Hospital. The main aim is to increase knowledge about psychological and psychiatric effects of disasters and psychological trauma – both in a short and long term perspective. A second, related aim is to improve the preparedness for health care and society to meet the needs of those affected by severe accidents and disasters. Important outcomes are the prevalence of psychiatric disorders, primarily posttraumatic stress disorder (PTSD). Factors studied are e.g. exposure to the disaster in terms of geographical proximity, presence of life threat, physical injury, and traumatic loss of family members, and potentially contributing factors such as social support, personality traits and socio-demographic characteristics. Specific projects are listed briefly below.

Project 1: Systematic follow-up and identification of persons at risk after a natural disaster
Project leaders and researchers: Kerstin Bergh Johannesson, Filip Arnberg.

Collaborators: Professor Christina Hultman and Professor Paul Lichtenstein, Deprtment of Medical Epidemiology and Biostatistics, Karolinska institutet, and MD PhD Abbe Schulman, CeFAM, Karolinska Institutet Huddinge.

This project concerns a longitudinal follow-up of Swedish survivors and home-staying relatives after the tsunami in South-East Asia in 2004. The large group of affected individuals creates a unique opportunity to study effects of different exposure to a natural disaster, patterns of recovery and risk factors for chronic symptoms. Potentially contributing factors such as social support, personality traits and socio-demographic characteristics are studied with respect to the risk for maintenance of symptoms. The project involves the study of long term trajectories of recovery, and psychiatric morbidity as compared to the general population.

Project 2. Systematic review and meta-analysis of PTSD in survivors from disasters and major accidents
Project leader: Filip Arnberg.

There is a large variation in the prevalence rates of psychiatric disorders in populations afflicted by a transient yet extreme stressor, with rates of posttraumatic stress disorder (PTSD) ranging from 2 to 95% across samples that were highly exposed to potentially traumatic stimuli. This project aims to explicate whether the variation in the prevalence rates of psychiatric disorders after disasters can be explained. The study focuses on disasters worldwide during the period 1980 to 2013. Differences in the rates of PTSD in survivors from these large-scale traumatic events are assessed by multi-level meta-regression analytic strategies, in order to quantify the impact of characteristics pertaining to the event, the surviving population, and the study methods. This project is underway and will potentially provide quantitative data that will inform future research as well as preparation and implementation of psychosocial services after disasters.

Project 3. TRACES, trauma and stress in a longitudinal survey.
Project leader: Filip Arnberg. Researcher: Mimmie Willebrand. Project assistant: Kristina Bondjers.

This project concerns psychological aspects of psychiatric morbididty related to highly stressful events. Research on how humans respond to stressful and potentially traumatic life events have flourished, yet there is still a lack of consensus about how PTSD should be conceptualized and diagnosed, as well as a scarcity of prospective studies on the impact of PTSD on functional impairment and health costs.

This project aims to advance our understanding of posttraumatic stress by investigating the prevalence, course and correlations among stress reactions and related psychopathology, functional disability and health-economic aspects. It will also examine patterns of distress related to core symptoms and more peripheral symptoms, and their predictive validity for the course and severity of the disorder. To accomplish this task, a longitudinal study is prepared in which we will follow a cohort of adults with a recent experience of a traumatic event recruited among patients in primary and outpatient psychiatric care as well as among individuals not seeking out healthcare services .

The significant changes to the diagnostis of PTSD in the new editions of the diagnostic manuals bring about new sets of criteria that need to be evaluated. A second aim of the project is therefore to evaluate current and novel methods of assessing PTSD. This project will thus provide valuable data on psychometric properties of several assessment methods commonly used in research and clinical settings.

Project 4. Evaluation of support for children following the loss of a family member
Project leader: Kerstin Bergh Johannesson. Researcher: Filip Arnberg. Project assistant: Cristina Bondjers.

Collaborators: Associate professor Doris Nilsson and PhD Teresia Ängarne-Lindberg, Department of Psychology, University of Linköping. Associate professor Mikael Rostila, Centre for Health Equity Studies (CHESS), Stockholms Universitet/Karolinska Institutet.

This project aimed to evaluate the experiences of support services offered to children after the sudden loss of a close family member and to assess the children's present psychological health. A second part of the project aimed to further our knowledge regarding how young people have been able to move on in life after a substantial loss. A third part aimed to map and compare the affected municipalities in a national perspective.

Project 5. Validation and standardization of a Swedish version of the Trauma Symptom Inventory 2 (TSI-2), a self evaluation scale for adults for symtoms of complex traumatic experiences.
Project leader: PhD Kerstin Bergh Johannesson. Researcher Mimmie Willebrand. Project assistant: Sofia Egerlid.

Collaborators: Associate professor Doris Nilsson and associate professor Marie Wadsby, Department of Psychology, University of Linköping.

Complex psychological trauma can be defined as resulting from severe stressors that are either repetitive or prolonged; involve harm or abandonment by caregivers and occur at

vulnerable times in a victim's life. The result can be a complexity of symptoms that include posttraumatic stress disorder (PTSD) as well as symptoms that highlight self-regulatory disturbances like dissociation, somatic distress, relational alienation and impulsiveness.
The assessments instruments that are most common today are mainly developed to assess consequences of single or limited traumatic events or specific time points. These instruments are insufficient for this group of clients and have not focused on interpersonal affect regulation. Consequently, there is a need for the development of reliable and valid assessment methods that can discriminate between PTSD and more complex PTSD conditions.
The aim of the present study was to examine, in a Swedish setting, the psychometric properties such as reliability and validity of the TSI-2 (Briere, 2011), a self evaluation scale for symtoms of complex traumatic experiences. The validation was based on 781 individuals recruited from Linköping University, patients from the psychiatric outpatient clinics of Akademiska sjukhuset in Uppsala and Tranås outpatient clinic and from homecoming Swedish soldiers.

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Child & Adolescent Psychiatry

Introduction

Research within the unit is closely connected with the clinical child and adolescent psychiatry at Uppsala University Hospital, where many of the researchers are employed. Five senior researchers have reached associate professor level and another eleven have reached PhD. Two doctoral students are registered at the unit in December 2014. The research is performed within six groups/themes: Affective disorders; Foetal and childhood developmental aberrations; Childhood Trauma; Clinical intervention; Psychophysiology and mental health; Child psychiatric epidemiology.

Affective Disorders

Group leader: Anne-Liis von Knorring, Professor emerita

Members of the group during 2014

Hans Arinell, Statistician
Hannes Bohman MD, PhD
Ulf Jonsson, PhD
Gunilla Olsson MD, PhD

Aivar Päären MD, doctoral student
Anne-Liis von Knorring, Professor emerita
Lars von Knorring, Professor emeritus

Collaboration

Tord Næssén, Professor, Department of Women's & Children's Health, Uppsala University;
Agneta Siegbahn, Professor, Department of Medical Sciences, Uppsala University

Publications 2012-2014

1. Jonsson U, Goodman A, von Knorring AL, von Knorring L, Koupil I. School performance and hospital admission due to unipolar depression: a three-generational study of social causation and social selection. Soc Psychiatry Psychiatr Epidemiol, 2012:47:1695-1706.

2. Päären A, Bohman H, Jonsson U, von Knorring L, Olsson IG, von Knorring A-L. Long term follow up of adolescent depression. Prescription drug use. Pharmacoepidemiol Drug Saf, 2012:21:130-136.

3. Päären A, von Knorring A-L, Olsson G, von Knorring L, Bohman H, Jonsson U. Hypomania spectrum disorders from adolescence to adulthood: A 15-year follow-up of a community sample. Journal of Affective Disorders, 2012,

4. Bohman H, Jonsson U, Päären A, von Knorring L, Olsson G, von Knorring, A-L. The prognostic significance of functional somatic symptoms in adolescence. A 15 years community based follow-up study of adolescents with depression compared with healthy peers. BMC Psychiatry. 2012 Jul 27;12(1):90.

5. Päären A, von Knorring A-L, Olsson G, von Knorring L, Bohman H, Jonsson U. Hypomania spectrum disorders from adolescence to adulthood: A 15-year follow-up of a community sample. Journal of Affective Disorders, 2013:145:190-9.

Other publications from the research network of Anne-Liis von Knorring 2012-2014

1. Bahmanyar S, Sundström A, Kaijser M, von Knorring A-L, Kieler H. Pharmacological treatment and demographic characteristics of pediatric patients with Attention Deficit Hyperactivity Disorder, Sweden. European Neuropsychopharmacology 2013, http://dx.doi.org/10.1016/j.euroneuro.2013.07.009

2. Andersson G, Waara J, Jonsson U, Malmaeus F, Carlbring P, Ost LG. Internet-based exposure treatment versus one-session exposure treatment of snake phobia: a randomized controlled trial. Cogn Behav Ther. 2013;42(4):284-91.

Books and reviews

1. von Knorring A-L. Barnpsykiatri. In Olsson L (ed.). En bok om hjärnan. Karolinska Institute Press. Stockholm, 2012:239-69.

2. von Knorring A-L. Psykisk ohälsa hos barn och ungdomar. Studentlitteratur AB. Lund, 2012.

3. Hultcrantz E, von Knorring A-L. Apatiska barn finns – och de har rätt till vård. Läkartidningen 2012; Oct 24-Nov 6;109(43-44):1932-3.

von Knorring A-L, von Knorring L, Wærn M. Depression från vaggan till graven. Läkartidningen 2013;110(9-10):480

Fetal and Childhood Developmental Abberations

Group leader: Viveka Sundelin Wahlsten, Associate professor

Members of the group during 2014

Birgitta Johansson Niemelä, Psychologist, PhD
Viveka Sundelin Wahlsten, Psychologist, PhD

Collaboration

Gunilla Hallberg, MD PhD, Dept of Women's and Children's Health, Uppsala University; Anders Helander, professor, Dept of Clinical Neuroscience, Lars Oreland, professor, Dept of Neuroscience, Uppsala University; Ihsan Sarman, Associate professor, Dept of Women and Children´s Health, KI.

Project II:1. Alcohol Consumption among Pregnant Women in a Swedish sample and its Effects on the Newborn Outcomes
Viveka Sundelin Wahlsten, Gunilla Hallberg, Lars Oreland, Anders Helander

This project is a broad interdisciplinary study, involving several departments at the University of Uppsala and the Karolinska Institute of Stockholm, with the purpose of investigating the role of prenatal alcohol, genetic inheritance and psychosocial environment for neuropsychological development in children. Regular Fetal Alcohol Syndrome (FAS) with distinct physical and mental defects is relatively rare and little is known about the effect of maternal alcohol use for neuropsychological development, which is not necessarily being recognized by showing pathological dimensions (Fetal Alchol Spectrum Disorders;FASD). This study originated from the work of the National guidelines of The National Board of Health and Welfare.
“Alcohol Consumption among Women in a Swedish Sample and Children's Health and Development at One and a Half Years of Age.” The extensive work to review and merge the contents of multiple databases into one has now been completed. Compilation and evaluation of data is underway and some of the main findings will be compiled for a second publication.

Publication

Comasco E, Hallberg G, Helander A, Oreland L, Sundelin-Wahlsten V. Alcohol consumption among pregnant women in a Swedish sample and its effects on the newborn outcomes. Alcohol Clin Exp Res. 2012;36:1779-86.

Project II:2. Neurobehavioral developmental profile at preschool age in children exposed for Buprenorphine
Viveka Sundelin Wahlsten, Ihsan Sarman

Buprenorphine maintenance treatment (BMT) was introduced in Sweden 1999, first in the Stockholm region, and the number of pregnant heroin dependent women who have been treated with methadone has successively decreased, while treatment with buprenorphine has become more frequent. All children of pre-school age, born to opiate dependent women from Stockholm County treated with buprenorphine maintenance during pregnancy,in 2001, 2002 and 2003 at the Karolinska University Hospital, Huddinge were invited for investigation by neuropsychological tests at 4.5-5.5 years of age. The aim of the present study is to examine the neuropsychological development of infants exposed to buprenorphine during foetal life in the era of BMT in Sweden.

Publication

Sundelin Wahlsten, V., Sarman, I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy.Acta Paediatrica Volume 102, Issue 5, pages 544–549, May 2013.

Childhood Trauma

Contact person: Abdoulbaghi Ahmad, MD, PhD, Associate Professor

Members of the group during 2014

Abdoulbaghi Ahmad, MD, PhD, Assoc. Professor
Nezar Ismet Taib, MD, doctoral student
Frank Lindblad, professor

Collaboration with the University of Duhok in the Kurdistan Region of Iraq has been in place since 1991, producing child mental health professionals at three levels since 2001. The sixth Master thesis was successfully defended on 5th April 2012 concerning *Autism among children in Duhok*. One PhD student is struggling in the third year of his research plan about *Street children in Duhok.*
Further PhD research plans are ready for application, mostly concerning the psychosocial situation for the displaced and refugee children in Kurdistan from the ISIS war in Iraq and Syria. Following research projects have been discussed: 1- Development of a Preventive Crisis Intervention Program for Posttraumatic Psychopathology among Children and Adolescents (CPCA). First article on the CIPCA has obtained a preliminary acceptance for publication, and a manuscript is submitted. 2- Comparing CBT/EMDR and SSRI in treatment of childhood PTSD (4 local research students in Kurdistan have showed interest to plan own financially supported PhD projects). 3- CIPCA and Posttraumatic Brain Changes (3 research

students in Sweden are waiting for financial support). A Training of Trainers course has been provided to several professionals in Sweden, Iraq and Turkey, to deliver the CIPCA for the displaced and refugee children from ISIS war. The World Health Organization (WHO) has approved financial support to a CIPCA project delivering crisis intervention to 67500 displaced school children through training of 300 displaced teachers in Duhok region.
Collaboration continues with the maternal and child care centre in Duhok (Metin Health House) and the Duhok Polytechnic University regarding research, training, and education programs concerning child mental health in the region. First article on a new method for early treatment of Autism, which has been developed at the MHH, has been published now (publication list nr 3).
Requests are still coming from national and international researchers to include our RCT on EMDR for children with PTSD and the child specific EMDR protocol in meta-analysis studies. Other researchers have requested permission to use our trauma instruments (Genogram, HUTQ-C and PTSS-C) in their studies.
Frank Lindblad has been involved in a study of data from the Swedish National Public Health Survey 2004–2009 (23,394 women, 18,274 men, aged 16–29 years). Effects of potential health-related factors on scores of the 12-item General Health Questionnaire (GHQ-12) were investigated (see publication 14 under "Psychophysiology and Mental Health"). One question was whether GHQ reflects two mental health dimensions (positive and negative) or not. A factor analysis gave some support for such a conclusion but the wording of the items may be an alternate explanation. There was a strong association between humiliation and negative mental health.
In an experimental study Katrin Lainpelto, Johan Isaksson and Frank Lindblad have investigated how information that a specific child has a neuropsychiatric disorder influences law students´ evaluations of allegations concerning sexual abuse from this child (manuscript submitted). Students who were informed about the neuropsychiatric disorder found the child less credible and rated the narrations as less detailed.

Publications

1. Ahmad A. Psychosocial and biological risk factors in childhood. In Ekman R & Arnetz B (red.), Stress, molecules, individuals, organisations and society (in Swedish language) (pp. 252-266), Stockholm:Liber AB,2013.
2. Ahmad A. Child mental health in Iraqi Kurdistan, setbacks and sustained recovery. IACAPAP Bulletin 2013;36:29-31.
3. Ahmad A. Autism-specific Pedagogic Intervention (ASP); Case Report. Duhok Med J 2013;7(2):41-46.
4. Taib NI & Ahmad A. Psychiatric Comorbidity among Street Children in Duhok. Clinical Medicine; Pediatrics 2014;10(8):6-11.

Award

Abdoulbaghi Ahmad*; "The Martin H:son Holmdahl Scholarship for the promotion of human rights and liberty 2014"*

Clinical Intervention

Projects related to the Child and Adolescent Psychiatry at Uppsala University Hospital

Project IV:1 Follow-up of patients treated for eating disorder

Members of the group

Agneta Rosling
Helena Salonen Ros

Collaboration

Assoc. professor Ingemar Swenne, department of women & children's heath, Uppsala University; Professor Helgi Schiött, Section of Functional Pharmacology at our department; Samantha Brooks, PhD, postdoc, Section of Functional Pharmacology at our department.

The Eating Disorder unit in the Dept of Child and Adolescent Psychiatry, Uppsala University Hospital, provides the only specialised treatment facility for Eating Disorders in the county. A treatment program, based on cognitive behavioural therapy, was introduced in January 2002. The treatment is in an out-patient and day-care setting with a multidisciplinary team including adolescent psychiatrist, paediatrician, family therapist and specialised nursing staff. Treatment includes motivational sessions, mealtime support followed by bed rest, and scheduled sessions with the nursing staff for problem solving as well as parental support and training. Follow-ups are continuously performed including analyses of biological markers. In an on-going project – directed by Samanta Brooks and Helgi Schiött - adolescents with eating disorders are recruited for functional neuroimaging.

Publications

Swenne I, Rosling A. Omega-3 essential fatty acid status is improved during nutritional rehabilitation of adolescent girls with eating disorders and weight loss. Acta Paediatr. 2012 Aug;101(8):858-61.

Project IV:2. Psychosomatic and somato-psychic processes

Members of the group

Birgitta Johansson Niemelä, licensed psychologist, PhD
Barbro Thurfjell, MD, PhD

Collaboration

Professor Agneta Nordenskjöld, Department of Women's and Children's Health, Karolinska Institutet; Anna Nordenström, Department of Molecular Medicine and Surgery, Karolinska Institutet; Louise Frisén, Department of Clinical Neuroscience, Karolinska Institutet; Anna Bengtsson Strandqvist, Department of Molecular Medicine and Surgery,

Karolinska Institutet; Magdalena Fossum, Department of Women's and Children's Health, Karolinska Institutet; Angelica Linden-Hirschberg, Department of Women's and Children's Health, Karolinska Institutet; Professor Anna Wedell, Department of Molecular Medicine and

Surgery, Karolinska Institutet; Chief physician Maria Halldin Stenlid, Department of Women's and Children's Health, Uppsala University; Professor Jan Gustafsson, Department of Women's and Children's Health, Uppsala University; Chief physician Gillian Barker, Department of Women's and Children's Health, Uppsala University; Professor Göran Läckgren, Department of Women's and Children's Health, Uppsala University.

In this research we study the interplay between psychological and somatic factors. On one side, psychological factors may contribute strongly to the development of somatic symptoms, psychosomatics. On the other side, somatic conditions and symptoms may evoke psychological reactions. Both procedures, which may be intertwined, may call for professional intervention.

Disorder of sex development patients (DSD) *(Birgitta Johansson Niemelä)*
A multicenter study (Stockholm, Uppsala, Göteborg and Lund) initiated by professor Agneta Nordenskjöld at KI. Children with DSD will be followed in a prospective study with an interdisciplinary perspective: surgical; endocrinological; genetic and psychological/psychiatric.

Mental Health in Children Undergoing Reconstructive Surgery: Studies on Self-Esteem and Social Interaction*. (Birgitta Johansson Niemelä, Valdemar Skoog, Tor-Göran Henriksson, Björn Tjernström, Viveka Sundelin Wahlsten)*
Studies on orthopaedic and other surgical treatments demonstrate that psychological problems are associated with lengthy procedures, lack of information and support to parents, lack of counselling to patients and parents, maladaptive coping behaviour, and child surgery at an inappropriate developmental level. Lower levels of reported parental stress were also related to better social skills in a child. Children´s reactions to reconstructive surgery in general have not been studied to any great extent.

A follow up study of patients with leg length inequality who have undergone leg lengthening has been completed, see below.

Publication
Johansson Niemelä B, & Tjernström B. Somatic and mental health after leg lengthening with Ilizarov procedure- a clinical report of a prospective study with a 10 years follow-up. J Depression &Anxiety2014,3:2.

Project IV:3 Neuropsychiatric disorders

Members of the group

Najah Khalifa

Collaboration

Professor Niklas Dahl, department of genetics & pathology, Uppsala University; Associated professor Karin Edebol, department of neuroscience, clinical neurophysiology, Uppsala University; Robert Bodén Md, Phd. department of neuroscience, psychiatry, Uppsala University.

Tourette syndrome
Tourette syndrome (TS) is common (about 1%) among primary school children. Most affected children also suffer from other neuropsychiatric disorders and poor self-esteem, and school failures are common. Diagnosis is important for early intervention. Several studies are in progress:

1. We want to map the potential genetic significance for the development of neuropsychiatric disorders in children, with a focus on Tourette syndrome. Genetic and environmental factors play a role in the aetiology of TS, but the exact causes are unknown. This study is designed to learn more about why TS, and related tic disorders, may occur more commonly in some families than others.

2. Treatment with repetitive transcranial magnetic stimulation (rTMS) for adolescents (15-25 years of age) with severe TS with the aim of reducing the intensity of the tics.

3. About 80% of children with TS have learning difficulties that require some type of support at school. We want to determine the frequency and describe the learning disabilities (LD) of children with TS with and without attention deficit hyperactivity disorder (ADHD). We aim at studying psychosocial, psychoeducational, and neuropsychological data from children 7-15 years of age. Two groups: TS only and TS plus ADHD.

4. Treatment with repetitive transcranial magnetic stimulation (rTMS) for adolescents and adults with depression with the aim of reducing the intensity of the depressive symptoms.

Psychophysiology and Mental Health

Contact person: Frank Lindblad, Professor

Members of the group during 2014

Åsa Hogmark, Master of Public Health, research assistant
Johan Isaksson, licensed psychologist, doctoral student
Malena Ivarsson, doctoral student (registered at Stockholm University)
Frank Lindblad, MD, PhD
Jackie Swartz, MD, doctoral student
Residents (Child and adolescent psychiatry): Eva Berntsson, Gävle; Hilke Sievers, Falun
Medical student: Malin Eickhoff

Collaboration

Professor Marie Allen, Department of Immunology, Genetics and Pathology, Genomics, Uppsala University; Johan Alm, Researcher, M.D., Department of Clinical Science and Education, Södersjukhuset, KI; Professor Jan Gustafsson, Department of Women's and Children's Health, Uppsala University; Professor Ulf Högberg, Department of Women's and Children's Health, Uppsala University; Katrin Lainpelto, PhD, Faculty of Law, Stockholm University; Ass. Professor Lene Lindberg, Department of Public Health Sciences, KI; Professor Kent Nilsson, Centre for Clinical Research, County of Västmanland; Professor Fred Nyberg, Faculty of Pharmacy, Uppsala university; Professor Göran Pershagen, Institute of Environmental Medicine, KI; Professor Annika Scheynius, Department of Medicine, KI;

Professor emer. Töres Theorell, Stress Research Institute, Stockholm University; Professor Torbjörn Åkerstedt, Stress Research Institute, Stockholm University.

This research forms part of a programme established in April 2008 with a grant from the Swedish Council for Working Life and Social Research. The aim of the programme is to investigate the ***interplay between genetic and environmental vulnerability in the development of psychological symptoms/psychiatric disorders***. Various methods are applied: psycho-physiological methods (saliva cortisol, heart rate variability and activity/motion), epidemiological methods; genetic analyses (SNP – Single Nucleotide Polymorphism); qualitative methods (for interview data and legal documents). Three doctoral students with psycho-physiological approaches have presented their theses during 2014 (Johan Isaksson: ADHD and cortisol; Jackie Swartz: Life style, cortisol and allergy; Malena Ivarsson: violent gaming and heart rate variability.

ADHD. The thesis of Johan Isaksson had four substudies: The first demonstrated substantially lower saliva cortisol levels than in comparisons, at waking-up and 30 minutes later and also in the evening.[4] These low levels were found only for children above 10 years of age. Children with ADHD scored higher than comparisons on perceived stress, but no associations were found between stress scores and cortisol levels, indicating the complexity of the stress regulating system.[12] Children in the ADHD group had to a higher degree also been exposed to foetal and childhood psychosocial adversity than comparisons but no relation was found between such exposures and diurnal cortisol levels.[6] Neither did continuous medication with stimulants or atomoxetine explain the low cortisol levels; medication rather increased the levels, a finding that opens up for complementary hypotheses about the mechanisms behind the treatment effects with these drugs.[9] Hypothetically, the low diurnal cortisol levels may be related to the hypothesized under-arousal possibly underlying several of the core symptoms of ADHD.

Given the well established heritability of ADHD we have also looked for genetic contributions to the low cortisol levels. One potential candidate for such genetic contribution would be FK506 binding protein 5 (*FKBP5*). This protein regulates the sensitivity of the glucocorticoid receptor to cortisol. In one study, we investigated *Single Nucleotide Polymorphisms* (SNPs) in *FKBP5* in relation to ADHD and in relation to diurnal cortisol levels. Two genotypes that were significantly associated with ADHD were also associated with lower cortisol levels (submitted manuscript). We have also performed SNP-analyses suggesting that the mineralocorticoid receptor gene may be involved in the low cortisol levels associated with ADHD and we will try to replicate these findings in an American GWAS database (analyses on-going).

We have also studied metabolic effects of the low cortisol levels. In a study performed over the last two years fasting blood glucose and HbA1c were investigated in 10 children (10-15 years) with ADHD and 22 comparisons (Lindblad et al, 2015). Fasting blood glucose was similar in both groups but HbA1c (a measure that reflects blood glucose levels during the preceding 6 –8 weeks) was higher in the ADHD-group. The results suggest an association between ADHD and an altered blood glucose homeostasis but the findings need replication with a larger study group and a more elaborated design with standardized conditions.

Lifestyle, cortisol and allergy. An anthroposophic lifestyle protects against developing allergy during childhood. This finding has been the starting point for a research program directed at finding the components that mediate this preventive capacity. In the thesis by Jackie Swartz stress related issues are investigated. His fourth substudy has been finalised during 2014 (Swartz et al, accepted Jan 2015): Children from families with an anthroposophic

lifestyle had lower risk than comparisons of developing sensitization up to 5 years of age. This risk was partially explained by low cortisol levels during infancy. High cortisol levels at 6 months predicted sensitization up to 24 months. We speculate that hyperactivity of the HPA-axis may influence the immunological system in several ways, thereby stimulating allergy-promoting processes.

Violent gaming and heart rate variability. In the thesis of Malena Ivarsson, another psycho-physiological approach has been applied, Heart Rate Variability. The regulating systems of the heart differ in time between activation and inhibition (i.e. cycle time). These cycle times can be extracted into different frequency bands, which have been found to correspond to different parts of the Autonomous Nervous System. One of these parts is anatomically and neurophysiologically linked to social communication via regulation of the striated muscles of the face and head, which underlie, for example, eye gaze, facial expression, listening and prosody. It also has the capacity to dampen the HPA-axis. We have studied reactions to violent and non-violent TV-gaming in naïve versus experienced gamers (boys, 13–15 years of age).[7] The boys were invited to play two different games (violent and non violent game) on two different occasions in their homes. Different combinations of extent of previous gaming experiences and experimental violent/non-violent gaming exposure were related to different reactions patterns – physiologically, emotionally and sleep related. Desensitising effects stood out as one possible explanation.

Foetal and recent exposure/s to maternal stress (Nicaragua). This project is directed by Professor Ulf Högberg, Department of Women's and Children's Health, Uppsala University. The overall purpose is to answer the question of the importance of perinatal exposure for children´s cognitive and emotional development in relation to adaptive and supportive environment during childhood. Our group is primarily involved in the branch addressing HPA-axis regulation of the children in relation to foetal and recent exposure/s to psychosocial environmental challenges, particularly maternal exposure to intimate partner violence. Data have been collected and the first manuscript is under preparation..

Publications, 2012-2014

1 Jablonska B, Lindblad F, Ostberg V, Lindberg L, Rasmussen F, Hjern A. A national cohort study of parental socioeconomic status and non-fatal suicidal behaviour--the mediating role of school performance. BMC Public Health. 2012;12:17.

2. Hjern A, Ekeus C, Rasmussen F, Lindblad F. Educational achievement and vocational career in twins - a Swedish national cohort study. Acta Paediatr. 2012;101:591-596.

3. Swartz J, Stenius F, Alm J, Theorell T, Lindblad F. Life style and salivary cortisol at the age of 12 and 24 months. Acta Paediatr. 2012;101:979-84.

4. Isaksson J, Nilsson KW, Nyberg F, Hogmark A, Lindblad F. Cortisol levels in children with Attention-Deficit/Hyperactivity Disorder. Journal of Psychiatry Research 2012;46:1398-1405.

5. Taghavi Bayat J, Hallberg U, Lindblad F, Huggare J, Mohlin B. Daily life impact of malocclusion in Swedish adolescents: A grounded theory study. Acta Odontol Scand.

2013;71(3-4):792-8. (results described under ”Psychosomatic and somato-psychic processes”).

6. Isaksson J, Nilsson K, Lindblad F. Early psychosocial adversity and cortisol levels in children with Attention-Deficit/Hyperactivity Disorder. European Child & Adolescent Psychiatry. Eur Child Adolesc Psychiatry. 2013 ;22:425-32.

7. Ivarsson M, Anderson M, Åkerstedt T, Lindblad F The effect of violent and non violent video games on Heart Rate Variability, sleep and emotions in adolescents with different violent gaming habits. Psychosomatic Medicine. 2013;75:390-6.

8. Swartz J, Alm J, Theorell T, Lindblad F. Parental Sense of Coherence is neither related to parental and child cortisol rhythm nor proxies of anthroposophic life style. Acta Paediatrica. 2013;102:920-4.

9. Isaksson J, Hogmark A, Nilsson KW, Lindblad F. Effects of stimulants and atomoxetine on cortisol levels in children with ADHD. Psychiatry Res. 2013;209:740-1

10. Otterman G, Lainpelto K, Lindblad F. Factors influencing the prosecution of child physical abuse cases in a Swedish metropolitan area. Acta Paediatrica. 2013;102:1199-203.

11. Karlsson E, Lindblad F, Ruchkin V. Risk and protective factors for peer victimization: A one-year follow up study of urban American students. European Child & Adolescent Psychiatry. 2014;23:773-81.

12. Isaksson J, Nilsson KW, Lindblad F. The Pressure-Activation-Stress scale in relation to ADHD and cortisol. Eur Child Adolesc Psychiatry. 2014 Apr 16. [Epub ahead of print]

13. Löfving-Gupta S, Lindblad F, Stickley A, Schwab-Stone M, Ruchkin V. Community violence exposure and severe posttraumatic stress in suburban American youth: risk and protective factors. Soc Psychiatry Psychiatr Epidemiol. 2014 Oct 10.

14. Winzer R, Lindblad F, Sorjonen K, Lindberg L. Positive versus negative mental health in emerging adulthood: a national cross-sectional survey. BMC Public Health. 2014 Dec 1;14:1238.

Swartz J, Lindblad F, Arinell H, Theorell T, Alm J. Anthroposophic lifestyle and salivary cortisol are associated with a lower risk of sensitization during childhood. Pediatric Allergy and Immunology, accepted Jan 2015

Lindblad F, Eickhoff M, Forslund AH, Isaksson J, Gustafsson J. Fasting blood glucose and HbA1c in children with ADHD. Psychiatry Research, accepted Jan 2015

Reviews 2012-2014

Lindblad F (2012) Samspelet mellan sociala förhållanden och livsförutsättningar - ett barnperspektiv (*The interplay between social conditions and prerequisites for life – a child perspective*). Ed. Theorell, T. In: Psykosocial miljö och stress (*Psychosocial environment and stress*). Studentlitteratur AB, Lund. Upplaga 2:1, ISBN 978-91-44-07023-0, sid 225-245.-

P2978.

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Swedish Council for Working Life and Social Research
Swedish Brain Foundation

Child Psychiatric Epidemiology

Contact person: Vladislav Ruchkin, Associated Research Scientist

Members of the group during 2014

Sandra Löfving–Gupta
Vladislav Ruchkin, MD, PhD
Medical students: Olga Tingstedt, Linnea Zachrison

Collaboration

Elena Grigorenko, Child Study Center, Yale Medical School, USA; Roman Koposov, Child Psychiatric Unit, Tromsö University, Norway; Denis Sukhodolsky, Child Study Center, Yale Medical School, USA; Andrew Stickley, Tokyo University, Japan; Marek Blatný, National Academy och Science, Brno, Czech Republic; Michal Hrdlička, Dept of Child Psychiatry, Charles University, Prague, Czech Republic; Britt af Klinteberg, Stockholm University;

This research program aims at assessing epidemiological aspects of an adverse environment and its impact on social competence and adjustment in children. The collaborative studies that conducted in the framework of the program are described below based on the types of populations involved in the studies (juvenile delinquents, pre-school children, adolescents from the general population, high-risk children (e.g. children of the street, children from isolate populations).

Several large studies address the prevalence of psychopathology and recidivism in juvenile offenders. To date, the database on the prevalence of psychiatric disorders in Russian juvenile delinquents is one of the largest in the world, with over 400 youth assessed by means of semi-structured psychiatric interview (K-SADS), as well as by use self-reports and teacher reports. Another research project related to antisocial behavior in youth includes a collaborative study of effectiveness of social problem solving training in detained juvenile delinquents State of Connecticut, USA (in collaboration with Dr. Elena Grigorenko, Yale University).

Two large epidemiological studies with younger children were conducted. The first study has focused on the developmental precursors of behavior problems in Russian preschool children (1.5-4 years old, N=800), based on extensive self-reports from mothers. The second study assessed the role of institutional environment for attachment and social-emotional development in children from Russian orphanages (1-3 years old, N=150) that included a detailed developmental assessment of children, including the data on attachment, socio-emotional and cognitive development and behavior problems. Information was collected from multiple informants. The long-term outcomes of early placement in an institutional environment has been further investigated in a collaborative study of ‘Risk and protective

factors for the development of learning disorders in children adopted from Russia: a multi-group comparison' (with Dr. Elena Grigorenko, Yale University).

A large epidemiological survey of students from the general population (13-17 years old), the Social and Health Assessment (SAHA) was conducted in several countries (Belgium, Czech Republic, Gambia, Germany, Iran, Japan, Korea, Lithuania, Mexico, Netherlands, Russia, Surinam and the US). The study focuses on the prevalence of problem behaviors, both internalizing and externalizing, as well as family and school environment, and involved 1,000-3,000 students at each site (the data are being analyzed).

Other collaborative research projects included an assessment of effectiveness of cognitive-behavioral therapy for posttraumatic stress in street children in Mexico city (in collaboration with Dr Janet Szydlo), and epidemiological study of the phenotypic and etiological overlap between disorders of spoken and written language in an isolate population in Northern Russia (in collaboration with Dr. Elena Grigorenko, Yale University).

Under the supervision of Dr Ruchkin (co-supervisor Prof LÅ Persson, Department of Women's and Children's Health) Sandra Löfving–Gupta has successfully defended her Master's thesis at the Department of Women's and Children's Health entitled "Community violence exposure and severe posttraumatic stress: risk and protective factors: A cross-sectional study of suburban American youth". An article with the same title has been published in a peer-reviewed journal.

Publications, 2012-2014

1. Ruchkin, V., Koposov, R., Vermeiren, R., Schwab-Stone, M. The Strength and Difficulties Questionnaire: Russian validation of the teacher version and comparison of teacher and student reports. Journal of Adolescence 2012, 35:87-96.
2. Schwab-Stone, M., Koposov, R., Vermeiren, R., Ruchkin V. Cross-Cultural Findings on Community Violence Exposure and Internalizing Psychopathology: Comparing Adolescents in the United States, Russia, and Belgium. Child Psychiatry & Human Development 2013, 44:516-524.
3. Stickley A., Koyanagi, A., Koposov, R., McKee, M., Roberts, B., Murphy, A., Ruchkin, V. Binge drinking among adolescents in Russia: prevalence, risk and protective factors. Addictive Behaviors 2013, 38:1988-1995.
4. Stickley, A., Koyanagi, A., Koposov, R., McKee, M., Roberts, B., Ruchkin, V. Peer victimization and its association with psychological and somatic health problems among adolescents in northern Russia. Child and Adolescent Psychiatry and Mental Health 2013, 14;7(1):15.
5. Ruchkin, V., Schwab-Stone, M. A longitudinal study of somatic symptoms in adolescents: The role of internalizing psychopathology and somatic anxiety. Journal of Youth and Adolescence 2013, Jun 7 [Epub ahead of print], 2014 43:834–845.
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Experimental Neuroscience

Developmental Genetics

Formation and Function of Neuronal Circuits

Group leader: Klas Kullander, Professor

Members of the group during 2014

Amilcar Reis, Post doc
Arthur Franca, PhD student
Atieh Tafreshiha, PhD student
Chetan Nagaraja, PhD student
Christiane Peuckert, Post doc
David J. Lyons, Post doc
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Fabio Caixeta, Post doc
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Henrik Boije, Post doc
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Martin Larhammar, PhD student
Martina Blunder, Post doc
Samer Siwani, Master student
Sharn Perry, PhD student
Siv Strömberg, Technician

Neuronal circuits are essential components of the nervous system and determine various body functions. We are interested in the function of neuronal circuits in the central nervous system. Our goals are to increase the knowledge in how neuronal networks develop into functional units and what the roles are for specified sets of neuronal populations in their circuitries.

In 2012, we discovered that DMRT3 is expressed in a previously unknown type of neurons in the spinal cord of mice. The characteristics of these neurons, including their location, suggested that they could take part in neuronal circuits coordinating movements. In collaboration with Leif Anderssons group, we could show that a mutation in dmrt3 is critical for the ability to perform ambling gaits, for pacing and that has a major effect on performance in harness racing. Experiments with this gene in mice have led to new fundamental knowledge about the neural circuits that control leg movements. The study is a breakthrough for our understanding of spinal cord neuronal circuitry and its control of locomotion in vertebrates. The study was published in Nature. The same year, we discovered a new group of nerve cells that regulate processes of learning and memory. These cells act as gatekeepers and carry a receptor for nicotine, which can explain our ability to remember and sort information. The discovery of the gatekeeper cells, which are part of a memory network together with several other nerve cells in the hippocampus, reveal new fundamental knowledge about learning and memory. The study was published in Nature Neuroscience.

We have recently discovered that a novel member of the solute carrier co-transporter family is exclusively expressed in the presynaptic vesicles of cholinergic and monoaminergic neurons. We have named this transporter vesicular aminergic-associated transporter, VAAT, to reflect its location in presynaptic vesicles and its exclusive expression in aminergic neurons of the brain. Most people have heard of and understand the aminergic systems of the brain through common drugs such as Prozac, nicotine, cocaine and amphetamine and through Parkinson’s and Alzheimer’s disease, two of the disorders of the brain related to dopamine and acetylcholine. As a surprising twist to this story, the other members belonging to the same family as VAAT are bile acid transporters found in the gut. Thus, functions shared by the bile system and the brain, has the capacity to modulate our behavior. The discovery of the VAAT transporter also raises the possible presence of a so far undiscovered neurotransmitter. To explore its function and its transporter substrate, we investigate VAAT knock-out mice. Using this and other tools we have generated behavioral, immunohistochemical and electron microscopy data that has been of considerable value to answer our questions regarding its function in the nervous system. Several papers are being prepared for publication, the first one was published in Experimental Neurology in 2013.

Publications 2012-2014

Rogoz K, Andersen HH, Lagerström MC, Kullander K. Multimodal use of calcitonin gene-related peptide and substance P in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily V member 1 neurons. J Neurosci. 2014, 34:14055-68.

Najet Serradj1, Sónia Paixão2, Tomasz Sobocki1, Mitchell Feinberg1, Rüdiger Klein2, Klas Kullander3, John H. Martin1. EphA4-mediated ipsilateral CST misprojections establish bilateral voluntary movements but not bilateral stereotypic locomotion J Neuroscience 2014, 34:5211-21

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Agencies that support the work/ Funding

Swedish Medical Research Council (SMRC) 2011-2015
Quality and Renewal UU
Swedish Brain Foundation
STINT

Neurodynamics

Group leader: Richardson N Leão, MD, PhD

Members of the group during 2014

Sanja Mikulovic, PhD student
Stefano Pupe Johann, visiting PhD student
Ernesto Restrepo, Postdoc, Klas Kullander's group
Helton Maia, visiting PhD student

Project 1: How brain oscillations are generated

Participants: Sanja Mikulovic, Ernesto Restrepo & Richardson N. Leão

We have shown that brain oscillations at theta band (4-12Hz) can be generated by the modulation of a single cell type. For these experiments, we have used optogenetic stimulation of a single inhibitory cell type in the hippocampus to artificially induce theta rhythm in the hippocampus to answer a question that for long has intrigued neuroscientists: Are brain oscillations relevant to brain function? These results have a great impact on the behavior of animals. We found that when theta oscillations in the hippocampus are inhibited, the animal moves and explores less. Meanwhile, when we induce theta artificially, the animals display a 'courageous' behavior, exploring the new environment fearlessly. These results indicate that oscillations in the brain may not be an epiphenomenon (as it is believed by several research groups) but rather serve as form for neuronal communication.

Project 2. Development of new neural recording technologies adapted to optogenetics

Participants: Stefano Pupe Johann, Sanja Mikulovic, Helton Maia, Richardson N. Leão

Optogenetics has taken all neuroscience fields as a storm. The penetration of the technique in all fields has happened at such a speed that scientists had no time to properly evaluate the 'side effects' of optogenetic control of neurons. One important unwanted effect of light stimulation (one of the main requirements for excitation or inhibition of neurons expressing optogenetics proteins) onto recording electrodes. This effect is known as optoelectric or Becquerel effect (as the phenomenon was first observed by the French physicist Alexandre Edmond Becquerel). In collaboration with two Brazilian universities and a Swedish company, we are developing new electrodes that minimise the strong effect of the light in recording electrodes. Currents and potentials produced by neurons are tiny and the light interference is orders of magnitude higher. The worse part is that, depending on the configuration and position of recording electrodes in relation to the light source, currents produced by Becquerel effect can resemble real neural activity. This issue is rather serious as it can make the interpretation of data difficult and even produce whole theories based on fake results. We are systematically exploring the effect of different light stimulation patterns and wavelengths on different types of electrodes. We are also working with new materials that seem to be less pervious the Becquerel effect. These results will surely lead to a 'healthier' use of optogenetics and electrophysiology.

Publications 2012-2014

Peixoto HM, Munguba H, Cruz RM, Guerreiro AM, Leao RN. (2014) Automatic tracking of cells for video microscopy in patch clamp experiments. Biomed Eng Online. 13:78.

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Agencies that support the work/ Funding

Kjell och Märta Beijers Foundation
The Swedish Research Council
Brain Foundation

Sensory Circuits

Group leader: Malin Lagerström, Associate Professor

Members of the group during 2014

Marina Franck, postdoctoral fellow
Katarzyna Rogoz, postdoctoral fellow
Bejan Aresh, PhD student
Fabio Freitag, PhD student
Elín Magnusdottír, PhD student
Jon Jakobsson, Master student
Nynke Moelijker, Master student
Jennifer Westblom, Bachelor and SOFOSKO student
Edda Blumel, project student
Linn Larsson Ingwall, project student
Siv Strömberg, technician

Project description

The neuronal circuit that resides in the spinal cord dorsal horn is responsible for accurately relaying and modulating sensory information. This neuronal network consists of primary afferent neurons, that respond to sensory stimuli e.g. heat, touch, pressure and tissue injury, and transmits stimuli information to the spinal cord, descending neurons from higher brain areas that modulate the sensory signal and dorsal horn interneurons and projection neurons that receive and relay the input from the periphery and the brain. Through these neuronal populations, pain and itch perception can be modulated and regulated both from the periphery and higher brain areas. In states of chronic pain or itch, this system is imbalanced. Current

treatments of chronic sensory conditions are most often experienced as inadequate and display severe side effects. To restore the balance in the dorsal horn in a more targeted manner, we need to understand how this circuit is organized in detail. Project 1 is therefore focused on finding the neuronal populations that transmit, fine-tune and regulate different kinds of sensory information in the dorsal horn of the spinal cord. The goal is to increase our understanding of the "gate" of sensory signaling and central processing of especially itch and pain signals. We also aim to find small populations of interneurons with restricted and relevant functions, which can be useful in therapeutic intervention of chronic sensory diseases. We are using techniques such as in vivo two-photon microscopy, in situ hybridization, immunohistochemistry and optogenetics to reach our goals. Project 2 is focused on finding the primary afferent populations and neurotransmitters that mediate and fine-tune the sensations of itch and of heat, cold, chemical, inflammatory and neuropathic pain from the periphery to the spinal cord. One of the projects are focused on the TRPV1 expressing population. TRPV1 is a ligand gated ion channel that is associated with thermosensation, including infrared detection (Gracheva et al, 2011, Neuron; Caterina et al, 1997; Nature). Studies using TRPV1 null mice have also revealed a central function for TRPV1 in inflammation-induced heat hyperalgesia (Caterina et al, 2000, Science; Davis et al, 2000, Nature). We have previously shown that the transmission of heat pain to the spinal cord depends mainly on VGLUT2-mediated glutamatergic transmission (Lagerström et al, 2010, Neuron) and we are now focused on identifying which neurotransmitters mediate the other actions of the TRPV1 population.
Our data show that the Trpv1-Cre population express substance P (SP) and calcitonin gene-related peptide (CGRP) besides VGLUT2 and that removal of the entire population, using the diphtheria toxin line (R26DTA) (Ivanova et al, 2005, Genesis) together with Trpv1-Cre, renders mice that are resistant to the development of heat hyperalgesia associated with peripheral inflammation whereas mechanical hyperalgesia was unaffected. We can also show that removal of VGLUT2-mediated glutamatergic transmission from the Trpv1-Cre expressing neurons does not prevent heat hyperalgesia which suggests that this glutamatergic pathway is not important for mediating this sensation. However, when we treated our VGLUT2-deficient mice with SP or CGRP antagonists, the VGLUT2-deficient mice and not littermate controls, proved to be resistant to the development of heat hyperalgesia, suggesting that glutamate together with SP and CGRP mediates inflammation-induced heat hyperalgesia and that glutamate could compensate for the loss of either SP or CGRP and vice versa. Our data shows that neurotransmitters work co-operatively to mediate painful sensations from the periphery (Rogoz et al, 2013, Mol Pharm) and we are now continuing the analysis, focusing on acute pain and itch transmission on the above mentioned transgenic lines.

Publications 2012-2014

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2. Rogoz K, Stjärne L, Kullander K, Lagerström MC. VGUT2 controls heat and punctuate hyperalgesia associated with nerve injury via TRPV1-Cre primary afferents.
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3. Rogoz K, Andersen HH, Lagerström MC# and Kullander K#. Multimodal use of calcitonin gene-related Peptide and substance p in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily v member 1 neurons.

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4. Caruso V, Lagerström MC, Olszewski PK, Fredriksson R, Schiöth HB.
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5. Rogoz K, Andersen HH, Kullander K# and Lagerström MC#.
Glutamate, substance P, and calcitonin gene-related peptide cooperate in inflammation-induced heat hyperalgesia.
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7. Rogoz K, Lagerström MC, Dufour S, Kullander K. VGLUT2-dependent glutamatergic transmission in primary afferents is required for intact nociception in both acute and persistent pain modalities. Pain. 2012 May 25.

Prizes and awards

Malin Lagerström received “Jeanssons stiftelsers pris till framgångsrik ung forskare och gruppledare” from the Jeansson Foundation in 2014.

Malin Lagerström was appointed Ragnar Söderberg Fellow in Medicine 2013.

Katarzyna Rogoz thesis “Signaling Mechanisms in the Neuronal Networks of Pain and Itch”, 2012-12-07. Co-supervised was awarded best pre-clinical thesis from Uppsala University, Medical faculty in 2012 by the Uppsala Society of Physicians.

Agencies that support the work/ Funding

Ragnar Söderberg Foundation
Swedish research council
The Åke Wiberg foundation
The Jeansson foundation

Ophthalmology & Retina Biology

Ophthalmology

Ophthalmic Biophysics

Group leader: Per Söderberg, MD, PhD, Professor Ophthalmology

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Yu, Zhaohua, MD, MSc, PhD student, full time

External collaboration 2014

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Skarman, Eva, BSc, PhD, matematics, Melerit Medical AB, Sweden
Steinvall, Ove, BS, Docent, physics, FoI, Linköping

Varma, Shambu, BSc , Professor, Biochemistry, University of Maryland, School of Medicine, MD, USA
Wählby, Carolina, BSc , Professor, information technology, Division of Visual Information and Interaction, Dept. of Information Technology, UU

Overall aim main project
Prevent or delay visual impairment due to disease in the optics of the eye and glaucoma, and improve diagnostic procedures for diseases, and contribute to safer cataract surgery, using biophysical strategies.

Clinical significance
Cataract is the most common cause of bilateral blindness in the world and glaucoma is the third most common cause of visual impairment. Both diseases present a rapidly increasing financial burden on society due to an increasing and aging world population and lack of efficient objective diagnostic procedures.

Project 1: Improvement of guidelines for avoidance of cataract after exposure to ultraviolet and near infrared radiation

Participants: Konstantin Galichanin, Martin Kronschläger, Nooshin Talibizadeh, Jing Wang, Zhaohua Yu, Joakim Ekström, Fabrice Manns, Jean-Marie Parel, Karl Schulmeister.

Aim
To improve safety guidelines for exposure of the eye to ultraviolet and infrared radiation (UVR and IRR).

Methods
Mathematical derivation of methods for estimates of precision of Maximum Tolerable Dose (MTD2.3:16), experimental single and repeated exposure of lenses in vitro and in vivo in experimental animals to spectrally and radiometrically defined optical radiation, macroscopic imaging of damage, quantitative measurement of intensity of forward light scattering.

Significance
Optical radiation has been identified as the most important changeable risk factor for cataract development. Current safety guidelines for optical radiation are partly based on theoretical assumptions and interpolations that need to be experimentally verified, or rejected, to improve the safety guidelines.

Project 2: Molecular mechanisms in ultraviolet radiation cataract formation and possibilities for pharmacological intervention

Participants: Konstantin Galichanin, Martin Kronschläger, Nooshin Talibizadeh, Jing Wang, Zhaohua Yu, Jonas Bergquist, Marjorie Lou, Stefan, Löfgren, Jan Bergmanson, Peyman Björklund, Marjorie Lou, Roy Quinlan, Shambhu Varma, Carolina Wählby

Aim
To elucidate molecular mechanisms in cataract formation caused by exposure to UVR. To use in vivo UVR-induced cataract as a model for identification of potential pharmaceutical agents for prevention or delay of cataract.

Methods
Morphologic events during UVR cataract formation are studied with light- and electron microscopy. Genetically modified mice lacking important genes for protection against UVR-induced cataract, are studied. The kinetics of the apoptosis pathway after experimental exposure to UVR is studied with immunohistochemistry, and qPCR. Immunohistochemical images are analyzed with morphometry using automated image analysis. Oxidation defense systems in the lens are studied biochemically. The antioxidant α-tocopherol is analyzed quantitatively with HPLC coupled with mass spectrometry. The antioxidant caffeine is investigated as a potential anti-cataract agent. Caffeine is detected with UVR-detection after HPLC separation.

Significance
Better understanding of the pathophysiology of UVR induced cataract is anticipated to provide tools for improvement of safety guidelines. Considering the increasing problem of cataract disease in a world perspective, it would be of substantial value to identify cheap pharmaceuticals for intervention against cataract.

Project 3: Safe cataract surgery

Participants: Carl-Gustav Laurell Eva Skarman, Gunnar Zoega

Aims
1) To develop an instrument that allows fully automatic clinical measurement of corneal endothelial cell density and to study the importance of corneal endothelial cell density for prediction of outcome of cataract surgery. 2) To develop a simulator that enables training in phacoemulsification cataract surgery in a virtual reality learning environment.

Methods
1) Imaging of the corneal endothelium in the Fourier plane of the imaging optics with video detection and subsequent computerized image analyses. Clinical investigation of the predictive power of endothelial cell density. 2) Virtual reality phacoemulsification cataract surgery: 2.1 Add more functions to developed simulator. 2.2 Develop a strategy for optimal training sessions with the instrument. 2.3 Compare learning with the simulator to current clinical learning of cataract surgery. The software development is done by engineers specialized in medical simulators.

Significance
1) Pre-operatively not detected relative insufficiency of the corneal endothelium is one of the most significant remaining problems in modern cataract surgery. Current technology for evaluation of the corneal endothelium is too complex to be used in clinical routine. We have developed a fast method that can be used clinically. This now requires clinical evaluation. 2) Modern cataract surgery is performed under local anesthesia making teacher-trainee communication very difficult. Coordination has to be learnt operating a large number of patients under supervision of a teacher. We have developed a virtual reality simulator that aims to reduce acquisition of surgical skill on patients.

Project 4: Contrast sensitivity measurement, Uppsala Contrast Sensitivity Test

Aim
To develop a tool for clinical routine measurement of contrast sensitivity.

Participants: Lars Malmqvist

Methods
Presentation of a target image that contains spatial frequency and contrast simultaneously that allows interactive indication of perceived contrast sensitivity.

Significance
All problems in the optics of the eye are associated with decreased contrast sensitivity. However, current contrast sensitivity tests are too slow to be used routinely in the clinic. It is anticipated that with a clinically useful method for contrast sensitivity measurement, indications for procedures such as cataract surgery and Yag laser capsulotomy for secondary cataract can be judged on a sound basis. The method also has the potential to replace visual acuity measurement with a visual acuity chart.

Project 5: Interactive digital visual acuity charts, AxAnIvIs-Acuity

Aim
To develop a tool for clinical routine measurement of contrast sensitivity.

Participants: Lidija Tomic, Julia Henriksson

Methods
Software that allows interactive visual acuity chart measurement on a digital visual acuity chart was developed. The strategy is beeing evaluated clinically and compared to the gold standard for visual acuity measurement, the ETDRS-chart.

Significance
Currently used visual acuity charts were developed in the 19th century and are static. The simultaneous presentation of a large number of letters creates confusion in children and elderly people and makes currently available refraction and estimation of visual acuity slow. Examiner guided interactive presentation of optotypes has the potential to make both refraction and estimation of visual acuity faster and more accurate.

Project 6: Detection of glaucoma progress, morphometric analysis of the optic nerve head

Aim
To develop a measurement procedure that allows evaluation of glaucoma progression on the basis of the topography of the optic nerve head.

Participants: Camilla Sandberg-Melin, Curt Eriksson, Albert Alm, Filip Malmberg.

Methods
1) Statistical analysis of the sources of variability in estimates of the 3-D topography of the optic nerve head recorded with confocal microscopy (HRT). Statistical modelling of optimal clinical strategies for follow up of glaucoma progression. 2) Development of strategies for estimating the 3-D topography of the optic nerve head with optical coherence tomography (OCT). Automatic detection of glaucoma progress with image analysis of OCT images of the optic nerve head.

Significance: Glaucoma is the 3rd most significant of loss of vision and quickly increasing. The current gold standard for follow up of glaucoma progression, computerized estimation of the visual field, is time consuming and associated with substantial variation, making follow up expensive, inefficient and questionable as a support for pharmacological control of the disease. Imaging of the topographical changes in the optic nerve head has recently become available and is an attractive alternative for follow up of glaucoma progression but the resolution in the images is unknown. Clinically significant morphometric variables have to be identified and an efficient clinical measurement strategy has to be established and validated.

Project 7: Epidemiology of the corneal endothelium

Aim
Estimate risk factors for loss of corneal endothelial cells.

Participants: Gunnar Zoega

Methods
In vivo specular microscopy images of the corneal endothelium in an age defined, randomly selected cohort of the Islandic population is analyzed epidemiologically.

Significance
Corneal transparency depends on a minimum number of corneal endothelial cells and corneal endothelial cells lost after birth due to trauma and environmental factors are not replaced. To minimize the number of patients suffering from loss of corneal transparency a better understanding of factors that are associated with loss of corneal endothelial cells is required.

Additional projects/ collaborations

Investigation of effects to the eye and vision at exposure to green when laser driving

Aim
To determine the hazardous effects of exposure to green laser when driving.

Participants: Ove Steinvall, Zhaohua Yu, Per Söderberg

Methods
Drivers are exposed to green laser light while driving on a test track. The eyes are examined before and after exposure. The driving behavior during exposure is measured. The psychological reaction to the laser exposure while driving is evaluated.

Significance
Better knowledge of effects of blinding drivers with green laser light provide a basis for improved legislation and advice to drivers exposed while driving.

Clinical evaluation of steroids in treatment of intraocular inflammation

Aim
To evaluate the clinical significance of intraocular slow release administration of steroids in intraocular inflammation.

Participants: Nikos Merkoudis, Eva Landgren, Elisabet Granstam, Per Söderberg

Methods
Subconjuctival injection of slow release steroid is compared to topical application of steroids after cataract surgery and for prevention of macular edema in patients with diabetic retinopathy. Intraocular administration of steroid slow release device for treatment of macular edema in after retinal vein occlusion is clinically evaluated. Macular edema is measured with OCT. Intraocular inflammatory proteins are measured.

Significance
Subconjuctival injection of slow release steroids has the potential to increase compliance and therefore decrease postoperative intraocular inflammation after cataract surgery and to prevent macular edema in patients with diabetic retinopathy undergoing cataract surgery. Intraocular administration of a slow steroid release device has the potential to improve vision in patients with macular edema associated with retinal vein occlusion.

Ultrastructural changes in keratoconus

Aim
Elucidate the mechanism for development of keratoconus.

Participants: Jessica Matthews, Jan Bergmanson, John Goosey, Per Söderberg

Methods
Morphometry in transmission electron micrographs of cornea from normal eye bank eyes and from keratoconus eyes.

Significance
Keratoconus is a progressive non inflammatory destruction of the cornea that induces abnormal corneal curvature and in serious cases perforation of the eye that requires corneal transplantation. The mechanism is unknown. It is anticipated that knowledge on ultrastructural changes associated with keratoconus will provide guidance to prevention and treatment.

Administrative Commissions

Chair Subcommittee IV, Optical Radiation, International Commission for Non-Ionizing Radiation Protection (ICNIRP). ICNIRP develops guidelines for safe exposure of the human body to non-ionizing radiation, adopted by most national radiation protection boards.
Co-chair Ophthalmic Technologies, SPIE. International conference for technological development in ophthalmology.
Chair Pascal Rol Foundation for support of new developments in ophthalmic technologies.

Publications 2012-2014

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Manns F, Söderberg PG, Ho A Ophthalmic Technologies XXIV. SPIE Proc 2014;8930:
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Manns F, Ho A, Söderberg PG Ophthalmic Technologies XXII. SPIE Proc 2012;8209:

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Paediatric Ophthalmology

Group leader: Gerd Holmström, MD, PhD, Professor

Members of the group during 2014

Eva Larssson, MD, PhD, Assoc Prof, Ophthalmologist
Dordi Austeng, MD, PhD, Ophthalmologist
Hanna Åkerblom, MD, PhD Student, Ophthalmologist
Anna Molnar, MD, PhD Student, Ophthalmologist
Jonina Hreinsdottir, Orthoptist
Eva Nuija, research nurse

Collaborators

Uwe Ewald, MD, PhD, Professor, Neonatology
Bo Strömberg, MD, PhD, Assoc Prof Paediatric Neurology
Lena Westas, Professor, Neonatology
Katarina Strand-Brodd, MD, PhD (2011-GH partly supervisor), Neonatologist
Marie-Louise Bondesson, PhD, Professor, Dep Genetics, Uppsala University Hospital
Claes von Hofsten, Prof, Dept of psychology
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Sten Andreasson, MD, PhD, Professor in ophthalmology, University of Lund
Prof Karel Marsal, Dep of Gynecology and obstetrics, Lund University
Assoc Prof Karin Källen, statistician and epidemiologist, Tornbladsinstitutet, Lund University

Our group collaborates with other paediatric ophthalmologists and paediatricians at Uppsala University Hospital, other University Hospitals and other hospitals in Sweden, as well as with international paediatric ophthalmologists, geneticists (Prof G Anneren, Marie-Louise Bondesson and their team, Uppsala) and neurophysiologists. Since 2009 - 2010 we have established collaboration with Prof Sten Andreasson, University of Lund.

Our major field of research concerns ophthalmologic findings and visual functions in prematurely-born children. Over the last two decades population-based studies on the incidence and risk factors of ROP have been performed, and extensive prospective follow-up studies on various visual functions have been undertaken. Various other paediatric ophthalmology studies have been performed on children with, amongst other conditions, haemangioma, x-linked retinoschisis, Down's syndrome, incontinentia pigmentii, neurofibromatosis type II, albinism, aniridia etc. In recent years we have focused on imaging of the retina and optic nerve; during 2009 we set up equipment for ERG and in 2011 for multifocal ERG, and this equipment is now used in our research.

Project 1: A prospective, population-based, multidisciplinary study on the development of visual perception in infants born very preterm and the relation to cerebral injury (the LOVIS study).

Commencing in January 2004, with the aim of developing predictive methods for the early detection of deficiencies, the study followed one hundred infants in the County of Uppsala for four years, up to the age of five. In this project we collaborate with neonatologists, paediatric neurologist and psychologists K Strand-Brodd, PhD 2011. A two and a half year follow-up

was completed in 2009. The first preliminary results were presented at ARVO (Association for Research in Vision and Ophthalmology) in Florida during May 2006 and a Paediatric Research Congress in San Francisco, also in May 2006. In 2011 two papers on Development of Smooth Pursuit Eye Movements in very preterm born infants were published in Acta Paediatric. The 2.5-year ophthalmological outcome together with a test of visual perception was presented by J Hreinsdottir et al at the European Paediatric Ophthalmologica Assoc (EPOS) held in Uppsala in June 2012 and in Sept 2013 in Marseille at the European Strabismological Assoc (E) meeting. A paper was published in Acta Paediatrica Aug 2013. We are now analysing results from a 6.5-year follow-up of theses children.
The LOVIS study will hopefully lead to early detection, possibly prevention and we hope early intervention of future visual perceptual difficulties.

Project 2: National study on extremely preterm infants born before the 27th week of gestation (the EXPRESS study).

In collaboration with neonatologists and obstetricians, a national study was undertaken on all preterm infants in Sweden born before the 27th week of gestation over three years (2004-2007). Our aim was to evaluate neonatal mortality and morbidity and also outcome at 2.5 and 6.5 years. GH was responsible for the organization and logistics of the ophthalmologic part of this national project, including eye screening in the neonatal period. Dordi Austeng was a PhD student working on the project - dissertation 12 June 2010. Five papers have been published on the neonatal part of the study, of which one on regional aspects on ROP 2013. Further, an ophthalmological follow-up at 2.5 years was recently published in JAMAOphthalmology. G Holmström has been a coauthor of one paper on Survival of this extreme population of prematurely-born infants (JAMA 2009), on Incidence and risk factors for neonatal morbidity (Acta Paediatrica 2010) and on one paper on the general follow-up at 2,5 years (JAMA2013). Data on a national 6.5 year follow-up are now being analyzed, an abstract has been accepted at an American paediatric ophthalmology meeting in USA April 2015. Several papers are to be published on this cohort. A national follow-up at 11 years of age has been designed and prepared during 2014 and is about to start in the autumn of 2015.

Project 3: Longterm follow-up at 10 years of prematurely-born children.

This is an epidemiological, population-based study of prematurely born and full-term children born in the County of Stockholm. Various functions of these children have been studied and compared to children born at term. The results have been published continuously since 2004. During 2011, analysis of data on accommodation of preterm and fullterm children was completed and the resultant paper published in "Strabismus" 2012. A review paper on the longterm outcome and follow-up of prematurely-born children was published in 2013 (Holmström & Larsson; Clinal perinatology). A population-based study on various ophthalmological findings on healthy10 year old children have been finalized and published during 2014 (Rydberg Acta Ophthalmol).

Project 4 : The SWEDROP register

A national register for retinal disease (ROP) in prematurely born infants with GH as register holder, has been established. The register (SWEDROP) has a national steering group, it is web based and started collecting national data in Sept 2006 with the aim of covering the whole country. We have a close collaboration with a perinatal register (PNQ), which will enable us to relate ROP data to neonatal findings. This is the first national register for ROP worldwide

and will provide unique data on the incidence, natural history and risk factors of ROP, as well as indications and methods of treatment for ROP.

The coverage of the population is increasing and during 2008-9 96% of infants were registered. Analyses on data from 2008 to 2009 and 2010-1011, respectively, have been analysed and published in Arch Ophthalmology (Nov 2012) and Acta Ophth (July 2014).

Project 5: Retinal morphology and function in school-aged children born at term and preterm.

This study is an evaluation of retinal function in children born at term and preterm. Our previous studies have revealed subnormal visual function in prematurely-born children. With the help of imaging techniques such as OCT (Optical coherence tomography) and HRT (Heidelberg tomography), we evaluate the retinal morphology and nerve fibre layer. Our group has previously reported on OCT findings in children with X-linked retinoschizis (Eriksson et al, Acta Ophtalmol 2004) and foveal hypoplasia (Holmström et al – 09). Results on children born at term, regarding both macular thickness and retinal nerve fibre layer, have been published 2009. In 2010 we reported on increased macular thickness in prematurely-born children (Åkerblom et al) and 2012 on reduced retinal nerve fibre layer (Åkerblom et al). Investigations of the retinal function in prematurely-born children 6 – 16 years with the help of ERG have been performed in collaboration with Prof Sten Andreasson, the university of Lund, and the results have been accepted for publication in an American journal, TSV 2014 (Åkerblom et al). Studies on Multifocal ERG (MfERG) are undergoing.

Project 6: Macular morphology and function in children born at term and preterm.

This study aims to create a normal material in healthy children, regarding OCT and MfERG, to study the macular development during childhood. We also aim to study the macular and retinal morphology and function in 6.5 years old extremely preterm infants, belonging to the EXPRESS Study, i.e. born before 27 weeks in Sweden 2004 – 2007, and to compare them with children born at term. In January 2015 a study on OCT in healthy children was accepted for publication (Acta Ophthalmologica) and a paper on MfERG is soon to be submitted.

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Book chapter

Holmström G and Larsson E. Kapitel Ögonsjukdomar s526-535. Pediatrik 2011. Liber AB, Stockholm.

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Ögonfonden

Prices/ awards

G Holmström was awarded to give the Rendals presentation by the Swdish Ophthalmological Society, at the yearly meeting, held in Malmö 2013.

Glaucoma

Group leader: Curt Ekström, MD, PhD

Members of the group during 2014

Albert Alm, MD, Professor emeritus
Amelie Botling Taube, MD, PhD student
Curt Ekström, MD, PhD
Inger Fällman Hedberg, Orthoptist
Börje Nordh, Research engineer
Eva Nuija, Research nurse
Camilla Sandberg-Melin, MD, PhD student

Project 1: Incidence of advanced visual field defects in newly diagnosed open-angle glaucoma

Participants: Curt Ekström, Inger Fällman Hedberg.

Background: By contrast with numerous reports on the prevalence of glaucoma blindness, information on its incidence in affected patients is sparse.

Purpose: Long-term incident rate of glaucoma blindness in open-angle glaucoma is studied.

Methods: In 1978-2007, patients examined at the Eye Department in Tierp with a diagnosis of glaucoma were registered in glaucoma case records. The incidence of glaucoma blindness in newly diagnosed open-angle glaucoma is estimated. Blindness is defined as the occurrence of advanced visual field defects. While masked to clinical information, a nurse practised in perimetry evaluates the visual fields.

Project 2: Risk factors for blindness in incident open-angle glaucoma

Participants: Curt Ekström, Inger Fällman Hedberg.

Background: Open-angle glaucoma is an optic neuropathy characterized by progressive loss of optic nerve fibres and reduction of the visual field. Blindness in affected eyes is a possible outcome of the disease.

Purpose: Long-term prognosis is studied in a population-based cohort of newly diagnosed cases. The effects of age, comorbid conditions, presence of pseudoexfoliation, stage of visual field defect, and intraocular pressure on the risk of developing glaucoma blindness are tested.

Methods: The cohort is composed of patients examined at the Eye Department in Tierp. In the eye under study, blindness is defined as the occurrence of advanced visual field defects. While masked to clinical information, a nurse practised in perimetry evaluates the visual fields. Cox proportional hazards models are used to assess the relationship between potential risk factors and glaucoma blindness.

Project 3: Open-angle glaucoma and Alzheimer´s disease

Participants: Curt Ekström, Lena Kilander

Background: Open-angle glaucoma is an optic neuropathy characterized by progressive loss of optic nerve fibres and reduction of the visual field. Alzheimer´s disease is a slow, chronic neurodegenerative disorder leading to cognitive deterioration and changes in personality. Similarities between the two diseases have raised the question if subjects with open-angle glaucoma run an increased risk of Alzheimer´s disease.

Purpose: Associations between open-angle glaucoma and the development of dementia are studied in a cohort of people 65-74 years of age.

Methods: The cohort is based on the glaucoma survey undertaken in Tierp in 1984-86. To expand the sample size, patients examined at the Eye Department in 1978-2007 were enrolled. By this mean, the cohort comprises more than 1,500 people. Information about incident cases of dementia is obtained by searching medical records. As a rule, diagnoses are based on clinical judgement by general practitioners. A specialist in geriatrics accomplishes classification of cases. Standardized morbidity ratios are calculated.

Project 4: The role of imaging in the follow up of eyes with glaucoma

Participants: Camilla Sandberg-Melin, Per Söderberg, Albert Alm, Börje Nordh, Eva Nuija.

Background: Glaucoma progression is due to loss of optic nerve axons, which results in structural changes in the optic disc and nerve fibre layer and visual field defects. The rate of progression is important for determining the effects of treatment. Automatic perimetry is the main tool for follow-up, but it requires several fields and a long follow-up. New instruments for imaging the optic nerve head and the retinal nerve fibre layer are now used in clinical work. However, there is little data on their use in follow-up of the disease.

Purpose: The potential of imaging in the follow-up of glaucoma is evaluated.

Methods: Thirty normal individuals were examined with repeated measurements over 4 weeks in order to determine different types of variance components. A total of 80-100 patients will be followed every 4 months for 2-5 years with imaging and visual field examination. Multiple linear regression is used to analyse study results.

Preliminary results: Studies in normal eyes demonstrate that using the mean of three measurements instead of one single measurement with imaging instruments improves the power to detect a clinically meaningful rate of loss of nerve tissue by about 50%. Scanning laser tomography may signal disease progression earlier than visual field examination.

Project 5: Proteomic studies on aqueous humor in eyes with pseudoexfoliation

Participants: Amelie Botling Taube, Albert Alm, Jonas Bergquist, Emilia Hardenborg, Magnus Wetterhall, Jörg Hanrieder, Marit Andersson**.**

Background: Pseudoexfoliation is an inherited, age-related condition. The presence of pseudoexfoliation in the anterior eye segment increases the risk for capsular glaucoma, a form

of open-angle glaucoma. The pathogenesis of pseudoexfoliation is not fully understood. Studies on the chemical composition of exfoliation material have been restricted due to small sample volumes and problems in dissolving the substance.

Purpose: Methods for proteomic studies are developed. The protein content in aqueous humor from normal eyes and eyes with pseudoexfoliation is compared, and the chemical composition of exfoliation material is analysed.

Methods: Proteomics are applied to identify proteins in pooled samples of aqueous humor from eyes with and without pseudoexfoliation. Aqueous humor is obtained at cataract surgery. Proteomic imaging techniques are used in studies on exfoliation material adhered to the lens capsule.

Preliminary results: It is possible to analyse very small samples of aqueous humor. The protein content differs between eyes with and without pseudoexfoliation. Osteopontin, angiotensinogen and crystallines B2 have altered concentrations in eyes with pseudo-exfoliation.

Publications 2012-2014

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Uppsala University, grants for PhD students

Retinal Stem and Progenitor Cell Development

Group leader: Finn Hallböök, PhD professor

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Henrik Ring, Med Mag PhD Adjunct
Shahrzad Shirazi-Fard, MSc, PhD, post doc
Caridad Galindo-Romero, MSc, PhD, post-doc
Maria Blixt, MSc, PhD student
Rashid Harun, MSc, PhD student
Minas Al-Baghdadi, Msc, PhD student
Marta Diaz-DelCastillo, Master student

One overall aim of our research is to be able to direct the in vitro development of human stem- or progenitor cells to more mature cells as disease models that can be used for understanding pathogenesis or eye disease. Such cells may also be used for cell therapy in the eye and we have focused on the early phase of photoreceptor and horizontal cell fate establishment. We also study activation of retinal endogenous stem cells after injuries. This includes aspects of Müller cell activation, their gliotic responses after injuries and their potential capacities to generate new cells. Species differences, where cool-blooded non-mammlian vertebrates are able to differentiate these cells into neurons while mammals are not are studied. The role of differentiated Müller cells in the injured retina for protection of retinal neurons is one aspect that is studied and another aim is to understanding how the cancer retinoblastoma is formed.

We have established a system to study early human neuroretinal development based on *in vitro*-differentiation of human embryonic stemcells. Furthermore, by using the chicken embryo we have a versatile *in vivo* experimental system that complements the human in vitro system. The chicken is also a representative for a species with an elevated regenerative capacity of injured retinal cells compared to that seen in mammals.

The experimental model based on the chick embryo has led to several collaborations with developmental biologists and animal geneticists aiming at gene discovery that contribute to specific selection traits.

Project 1: Terminal cell cycle during generation of retinal neurons

Participants: Blixt, Ring, Shirazi-Fard, Al-Baghdadi, Hallböök

One aim of our work is to understand how “early” retinal neurons (ganglion cells, cones and horizontal cells) are generated. The knowledge may be used to instruct progenitor cell development for exploration of possibilities to counteract death of retinal ganglion cells and production of retinal cells for cell therapy. Ganglion cells and cones are relevant from a clinical perspective due to their loss in glaucoma and photoreceptor degenerations.

The transcription factors FoxN4 and Ptf1a have been identified to play a pivotal role in the generation of horizontal and amacrine cells; two types of interneurons in the retina. We have

characterized their expression in the chick retina and analyse both over-expressing and shRNA knock-down of their expression to elucidate their role in the generation of these cell types. During the work regarding analysis of the terminal mitosis of horizontal cells we discovered that the horizontal cells arrest in their last cell cycle during the G2-phase, followed by ectopic mitoses.

One important approach is to establish a method for cell-specific lineage tracing during embryonic development in the chicken retina. In ovo electroporation of expression vectors is used to study gene function and a minimal TATA box promoter in combination with hyperconserved non protein-coding DNA elements are used to drive cell specific gene expression. The Cre-lox piggyBac system is used to achieve constitutive GFP expression in the daughter cells of retinal progenitor cells.

Project 2: Regulation of the final cell division in retinal progenitor cells and their relation to development of childhood Retinoblastoma

Participants: Shirazi-Fard, AlBaghdadi, Hallböök

The most common intraocular cancer is retinoblastoma. It represents approximately 4% of all pediatric malignancies. Recent results from animal studies imply that the cancer retinoblastoma originates from specific retinal celltype – the retinal horizontal cell (Hc) or from their immediate progenitors. It has been shown that the Hcs have properties that separate them from other retinal cells and even among nervous system cells in general.
The aim of this project is to investigate the retinoblastoma cell-of-origin in regard to its special characters using animal models and human retinoblastoma material collected at St Eriks children's eye clinic. The identification of the retinoblastoma cell-of-origin and molecular mechanism behind retinoblastoma will provide novel targets for retinoblastoma therapy.
Cells with aberrations in chromosomal ploidy are normally removed by apoptosis. However, aneuploid neurons have been shown to remain functional and active both in the cortex and in the retina. Lim1 horizontal progenitor cells in the chicken retina have a heterogenic final cell cycle, producing cells that enter S phase without proceeding into M phase. The cells become heteroploid but do not undergo developmental cell death. This prompted us to investigate if the final cell cycle of these cells is under the regulation of an active DNA damage response. Our results show that the DNA damage response pathway, including γ-H2AX and Rad51 foci, is not triggered during any phase of the heterogenic final cell cycle of horizontal progenitor cells. However, chemically inducing DNA adducts or double-strand breaks in Lim1 horizontal progenitor cells activated the DNA damage response pathway, showing that the cells are capable of a functional response to DNA damage. Moreover, manipulation of the DNA damage response pathway during the final cell cycle using inhibitors of ATM/ATR, Chk1/2, and p38-MAPK, neither induced apoptosis nor mitosis in the Lim1 horizontal progenitor cells. We conclude that the DNA damage response pathway is functional in the Lim1 horizontal progenitor cells, but that it is not directly involved in the regulation of the final cell cycle that gives rise to the heteroploid horizontal cell population.

Project 3: Retinal progenitors and Müller cells in the perinatal and adult retina and their capacities to generate and protect retinal neurons.

Participants: Harun-Or-Rashid, Galindo-Romero, Diaz-DelCastillo, Hallböök

Retinal ganglion cells play a crucial role in the relay of visual signals from the eye to the brain. This cell type is affected and eventually lost in the eye disease glaucoma, resulting in progressive and irreversible loss of vision. This project is directed to understand what determines the fate of the Müller cells after injuries that trigger their proliferation and how this response may be modulated to contribute to restoration of neural functions in the eye. A main question is whether a regenerative response that produce new neurons is only positive for the retinal ganglion cells in the injured retina.
α2-Adrenergic receptor agonists are used in glaucoma treatment and have been shown to have some neuroprotective effects. We performed this study to test the
hypothesis that epidermal growth factor receptors on chicken Müller cells are
transactivated by α2-adrenergic receptors and we focused on the extracellular signal activated kinases 1/2 (ERK) pathway. Embryonic chicken retina and cultures of primary Müller cells were stimulated by α2-adrenergic receptor agonist brimonidine. Immunostaining, qRT PCR and western blot techniques in combination with Src- and matrix metalloproteinase inhibitors were used for analysis of the cellular responses. Our results showed that Müller cells express α2A-adrenergic receptors in vivo and in vitro and that brimonidine triggered a robust and transient phosphorylation of ERK1/2. This ERK-response was Src-kinase dependent, associated with tyrosine phosphorylation of epidermal growth factor receptors (phospho-Y1068, Y1173) and was mediated by matrix metalloproteinase-activity on the Müller cells. Conclusion. Müller cells express the α2A-adrenergic receptor and brimonidine triggers both Src-kinase- and matrix metalloproteinase-mediated autocrine ligand dependent activation of epidermal growth factor receptors on Müller cell. This response is consistent with transactivation of epidermal growth factor receptors by stimulation of α2-adrenergic receptors.

Project 4: Functional genetics using domestic animal
Participants: Ring**,** ShirazFard, Hallböök and Leif Andersson and co-workers

These projects are part of collaborative efforts to utilize the domestic chicken as a tool for gene discovery in relation to feeding behaviours, results of domestication and morphological development. Performed in collaboration with Leif Andersson's group and other collaborators.
1. Analysis of the function and importance of differentially expressed genes in hypothalamus in two selected lines for high and low body weights. Analysis of regions and comparison of location of differentially expressed genes with QTLs and regions that have been under selection. We investigate the importance of the SH3RF2 gene for the metabolism and cognitive functions in the two chicken lines.
2. Identification and analysis of genes and mutations and their regulatory consequences for morphological growth of soft tissue development. Comb modifiers in Pea-comb (Sox5), Rose-comb, double comb and single-comb.
3. One of the most striking differences between wild and domesticated rabbits is that the tamed animals can live and breed in captivity, even when they living among potential predators as dogs. In collaboration with Leif Andersson (IMBIM, Uppsala) and Miguel Carneiro (CIBIO, Portugal) we seek to find the genetics behind the differences. Based on the results of total brain RNA sequencing qRT PCR, immunohistochemistry and *in situ* hybridization techniques are used to visualize the quantitative expression and locations of genes that could explain why this species have such diverse characteristics.

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Physiology and Pharmacology

Physiology

Gastrointestinal Physiology

Group leaders: Olof Nylander, Professor and Markus Sjöblom, Assistant Professor

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Professor Dr Gerolf Gros, Hannover Medical School, Germany.
Professor Per Hellström, Dept. of Medical Sciences, Uppsala University, Sweden

The duodenum, which is the first segment of the small intestine, has a number of important physiological functions. Beside its important task to absorb nutrients, vitamins, electrolytes and water, it also has to neutralize the acidic juice discharged from the stomach, adjust luminal osmolality and prevent absorption of potentially injurious agents and microbes that may be present in water and food. To perform these functions the duodenum must be able to recognize various constituents in the lumen and respond appropriately to the changes in the luminal environment by regulating motility, fluid absorption and secretion, mucosal permeability and the secretion of antibacterial agents and immunoglobulins. The endocrine cells of the gut, the enteric nervous system and the mucosal immune system possibly cooperate in an extremely complicated manner to maintain gut homeostasis. The overall aim of research is to identify, in the living animal, how different luminal constituents are "sensed" by the duodenal mucosa and to reveal those mechanisms that participate in the response to different provocations such as luminal hypo- and hypertonicity, gastric juice, ethanol, microbes and systemic hypoxia.

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Neurophysiology of Motion Vision

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Paloma Gonzalez-Bellido, University of Cambridge, UK

Motion vision

Animals successfully navigate in a natural world full of highly complex information. Many animals have evolved sensory systems that are optimized for rapidly extracting vital information from a continuous, noisy flow constantly approaching the senses. What mechanisms allow the extraction of salient features extracted from a noisy surround? This broadly interesting question has received a reignited interest in recent years, as it is interesting not just for vision scientists, but the findings additionally have many potential applications, for example in the development of unmanned vehicles, and for information processing of large data sets (so called Big data).

Visual motion can be crudely sub-divided in two types: Wide-field optic flow, which is generated by the animal's own motion through the world, and the motion of objects that move independently of the rest of the surround. For humans, such focal motion may represent an

approaching ball during a game of tennis, or a flying bird. Many animals are quite good at rapidly detecting focal object motion, even though the mechanisms are complex, and still difficult to solve reliably in silico. In our lab we investigate both these types of motion vision.
Natural scenes
We recently described a novel neuron in the fly lobula plate that clearly does not derive its input from classic EMDs (De Haan et al., J Neurosci, 2013). Centrifugal stationary inhibited flicker excited (cSIFE) is strongly excited by flicker, up to very high temporal frequencies. The non-EMD driven flicker sensitivity leads to strong, non-directional responses to high-speed, wide-field motion. Furthermore, cSIFE is strongly inhibited by stationary patterns, within a narrow wavelength band. cSIFE's outputs overlap with the inputs of well-described optic flow sensitive lobula plate tangential cells (LPTCs). Driving cSIFE affects the active dendrites of LPTCs, and cSIFE may therefore play a large role in motion vision.
We are currently investigating the spatial characteristics of scenes that inhibit the neuron. Natural scenes may appear random, but they are not. Instead they contain feature distributions that are surprisingly predictable. Such redundancy has led to animal eyes and brains that are adapted to the spatial characteristics of natural scenes, and the human visual cortex, for example, is strongly tuned to their second-order statistics. However, very little has been known about how the fly brain responds to similar images. We redress this striking omission and show that cSIFE is strongly tuned to the spatial statistics in natural scenes, thus, in strong analogy with the vertebrate visual cortex.

Fly behavior

We are using several techniques for measuring fly behavior. Malin Thyselius and Frank Lee developed a free flight arena, which was big and bright enough for hoverflies to display conspecific interactions. By filming the flies from below or above, we can reconstruct the 3D flight trajectories of flies in the arena. We are currently developing the arena further, to make it as naturalistic as possible, while still maintaining experimental control of stimuli.

During last year Olga Dyakova and Kristian Johansson developed a trackball set-up where we record the behavioral responses of hoverflies to many different stimuli for which we know the neurophysiological responses. Olga is particularly interested in natural images, so this will be a major component of the planned experiments.

Malin Thyselius is also working on measuring the diurnal activity of hoverflies, and comparing this to what is known about *Drosophila*.

Pollination project

The world's bee and bumblebee populations are declining, though an estimated 80% of European crops are directly dependent on insects for pollination. Preserving and promoting wild pollinators is therefore crucial for sustainable agriculture. In addition to maintaining natural habitats and reducing pesticide use, an increased understanding of why and how wild pollinators utilize certain sources will allow us to propose efficient planting and maintenance strategies that maximize crop pollination. Hoverflies are ecologically important alternative pollinators and provide an extremely valuable alternative to the world's wavering bee populations.

In this project Josefin Dahlbom utilizes a multimodal and multivariate approach to determine the cues that attract hoverflies to specific pollination sites. We have a unique ability to measure multimodal parameters on a very local scale. Our pilot data suggests that a combination of visual, chemical, and abiotic cues create an optimal hoverfly signature for increased attraction to certain sites.

After quantitatively characterizing this signature in several sites, we will test our hypotheses using artificial and/or natural lures to increase wild pollination in unattractive sites. Finally, in conjunction with local, national, and international garden and agricultural organizations, this data will ultimately allow us to publically offer specific ecologically-based strategies to maximize the attractiveness of crops to wild pollinators.

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Prices and awards

Best paper award, ICUMT6, 2014: Hidayat, E, Medvedev, M and Nordström, K (2014) *"Identification of a Layer of Spatially Distributed Motion Detectors in Insect Vision"*

Molecular Physiology and Neuroscience

Group leader: Bryndis Birnir, Professor

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Frida Lindberg, project student
Mårten Nilsson, Project student
Krzysztof Nowak, Master student
Xiaolin Huang, Exchange student
Karin Nygren, Technical engineer
Hanna Taylor, Administrator

Project 1: Regulation of neuronal inhibition by metabolic hormones

A major focus of the lab has been on GABA-generated neuronal inhibition in the hippocampus. We are particularly interested in the so-called tonic inhibition. Tonic GABA-generated currents are a relatively new discovery and we were the first to describe the underlying extrasynaptic GABA-A receptors (Birnir *et al.*, 1994). Tonic currents have been shown to significantly alter neuronal excitability and neuronal survival. The extrasynaptic GABA-A receptors, unlike their synaptic counterparts, are activated by very low extracellular ambient GABA concentrations and are probably also the main targets of drugs such as benzodiazepines and other medicines that target the inhibitory system.

We have discovered that insulin and GLP-1 at physiological concentrations induce tonic GABA-activated currents in hippocampal neurons (Jin *et al.*, 2011, Korol *et al.*, 2014). This has important implications as the hippocampus is the centre for memory and learning plus has a vital role in metabolic homeostasis. Our results are relevant for diseases like diabetes, dementia and Alzheimer´s disease but also epilepsy, multiple sclerosis (MS) and a number of psychiatric diseases. We are continuing these studies with the aim of understanding metabolic hormones, and their mimetics, like exendin-4 and liraglutide, modulation of GABAergic inhibition in the hippocampus in health and disease.

Project 2: GABA signalling in the pancreatic islets

GABA is produced by the insulin-releasing beta cells and in humans, both the beta cells and the glucagon-producing alpha cells plus the delta cells have GABA-A receptors . In rats and mice only the alpha cells have GABA-A receptors (Jin *et al.*, 2013). Our studies are, therefore, exclusively carried out in human pancreatic islets as no good animal models are available for pancreatic islet GABA signalling. Based on our experience of working on brain slices, we have now been able to use the patch-clamp technique to record from cells in intact human islets. Our results show that the ambient GABA concentration in the islets affects the electrical activity of both the alpha and beta cells thus affecting hormone secretion and the balance of insulin and glucagon release. If this balance is disturbed, it may be a part of the underlying cause of type 2 diabetes (Taneera *et al.*, 2012). In addition, our qPCR data shows that in islets from type 2 diabetic patients specific GABA-A subunits are down-regulated as compared to healthy controls. The results very clearly identify GABA-generated tonic currents and thus GABA-A receptors as central parts of the normal physiology of healthy islets as well as the pathophysiology in type 2 diabetes. We are continuing these studies in

order to establish the role played by GABA signalling in determining insulin and glucagon secretion, as well as looking at how it can be modulated by medicines like exendin-4, liraglutide as well as GABA-A receptors specific drugs some the benzodiazepines. We focus on human tissue from the Uppsala Human Tissue Lab within the strategic research initiative EXODIAB.

Project 3: GABA is a natural immunomodulatory molecule

Extrasynaptic GABA-A receptors have affinity for GABA in the pM - nM range or more than million times higher affinity than synaptic channels (Lindquist and Birnir, 2006, Jin *et al*, 2011). After making this discovery we decided to examine if lymphocytes expressed GABA-A receptors as there are low concentrations of GABA present in the blood. And yes, lymphocytes have GABA-A receptors and activation of these channels decreased the T cell proliferation. We have proposed that the GABA-activated brake on immune cell proliferation is an important mechanism in keeping toxic lymphocytes in check and if this "brake" is malfunctioning, diseases like MS and type 1 diabetes may arise or progress more rapidly (Bjurström *et al.*, 2008, Mendu *et al.*, 2011). We are further characterizing by what mechanism GABA is able to decrease lymphocyte proliferation and what subtypes of the receptors are expressed. Recently, we examined, in human peripheral blood mononuclear cells, if the GABA receptors varied between men and women and if pregnancy or depression influenced their mRNA expression. It turned out that gender, pregnancy and depression modulated the expression of the receptors in the cells! The results imply that in humans the GABA signalling system in immune cells is finely tuned to physiology (Bhandage *et al.*, 2014). These results may open up interesting treatment and diagnostic possibilities in a number of diseases.

Project 4: GABA-A receptors in cancer

In collaboration with professors A. Smits (Uppsala University) and E. Aronica (Neuropathologist, Netherlands) we have characterized expression of GABA-A receptors subunits in human gliomas of various malignancy. Our results show that GABA-A subunit expression in human glioma correlates with tumor histology and clinical outcome (Smits *et al*., 2012). The results indicate that if we can boost the GABA system we may be able to decrease tumor malignancy/proliferation. In a cell-line derived from human glioblastoma, in collaboration with professors K. Forsberg-Nilsson, B. Westermark and L. Uhrbom, we demonstrated that the GABA-A receptors were functional and modulated by drugs and in particular by the anaesthetic etomidate (Babateen *et al*., 2014).

Project 5: In brains of human alcoholics there are selective brain areas that have specific changes in GABA-A and Glutamate receptors subunits

In a series of papers (Jin *et al*., 2011, 2014a, b; Bhandage *et al.*, 2014) we have shown in samples from postmortem human brains that a decrease or an increase in the inhibitory GABAergic signalling system is mirrored by changes in the glutamate excitatory signalling system. Moreover, changes in the brains of alcoholics take place in specific brain areas with the greatest alterations in areas where new memories are formed, like the hippocampus and amygdala. Our results further indicate that there is an altered balance between caudate-mediated voluntarily controlled and automatic behaviors in alcoholics, including diminished executive control on goal-directed alcohol-seeking behavior. This conclusion has important implications for relapse and potentially ways of inhibiting relapse.

It is not known why some brain areas are vulnerable to alcohol exposure when other areas are not. Whether the changes in one neurotransmitter system drives changes in the other or if they change independently but change in order to maintain neuronal networks functional integrity, is currently not known.

Project 6: ENABLE: European Gram-negative Antibacterial Engine

Antimicrobial resistance is a major public health threat. Infections caused by resistant bacteria are increasing. Despite the strong need for new antimicrobials, very few new, effective antibiotics have been brought to the market in the last decades. The ENABLE project is a collaboration between many Universities and pharmacautical companies, working to advance the development of potential antibiotics against Gram-negative bacteria, such as *Escherichia coli*. The ultimate goal of the project is to develop attractive antimicrobial candidates for testing in the clinic, bringing the possibility of new antibiotics to treat Gram-negative infections one step closer to patients. Our laboratory participates in the project by testing compounds on specific voltage-gated ion channels

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Novo Nordisk project grant
The Swedish Diabetes Foundation
ENABLE
Fredrik and Ingrid Thurings Foundation
Åke Wibergs Stiftelse
Ernfors Foundation
Uppsala University

Honours

Bryndis Birnir is the Secretary General of the Scandinavian Physiological Society and Treasurer of the Federation of the European Physiological Societies.

Behavioural Neuroendocrinology

Group leader: Svante Winberg, Professor

Members of the group during 2014

Arianna Cocco, PhD-student
Dean Basic, PhD-student (supervised together with Dr E. Höglund, DTU)
Josefin Sundin, postdoc
Laura Vossen, PhD-student
Maria Moltesen, PhD-student (supervised together with Dr E. Höglund, DTU)
Per-Ove Thörnqvist, Research Associate
Abdul Alim, project student
Johan Rudin, project student

External collaboration

Evolutionary Biology Centre, Uppsala University
Dept. of Zoology, Göteborg University
Sahlgrenska Academy at Göteborg University
Swedish University of Agricultural Sciences, Umeå, Sweden
Danish Technical University, Hirtshals, Denmark
Norwegian University of Life Sciences, Aas, Norway
Norwegian School of Veterinary Science, Oslo, Norway
University of West Scotland, UK
University of Exeter, UK
University of Oslo, Norway
Linköping University
Göteborg University

Our research is focused on neuroethology and comparative neuroendocrinology, and we are especially interested in the adaptive value of variable individualized stress responses and possible behavioural correlates of various neuroendocrine stress response profiles. A role of

social experience in modifying the behavioural output of an individual seems to be well established, but the physiological background of differing life histories and behavioural tactics is largely unknown.

Project 1: Personality traits in zebrafish (Danio rerio): Behaviour and neuroendocrine mechanisms

Participats: Per-Ove Thörnqvist, Abdul Alim, Svante Winberg

The aim of this project is to use zebrafish as a model to study personality traits and neuroendocrine and molecular mechanisms controlling these traits. As well as being a major model organism in terms of developmental anatomy, the zebrafish is also an excellent, if under-used, model for studies on behavioral genetics. The short generation time (about 3 months) is a clear advantage when creating divergent strains by selective breeding. In the present project we will create two strains of zebrafish differing in personality traits. These strains will be used to study correlations between behavioral and physiological traits.

Project 2: Mechanisms of improved stress tolerance and welfare of farmed fish

Participants: Chinmaya Sadangi, Per-Ove Thörnqvist, Svante Winberg

We have found that divergent inherent stress coping strategies akin to those described as proactive and reactive coping strategies in mammals exists also in fish. However, recent studies suggest that stress coping strategies are modulated by the epigenetic effects of social interaction. Previous studies show that the behavior and physiology of fish is dramatically affected by social interactions, and that the brain serotonergic system plays a key for these effects. The serotonergic (5-HT) system is also known to be important for the expression of coping strategies. We will now explore to what extent behavior and neuroendocrine stress responses of reactive and proactive rainbow trout is affected by social interaction. Moreover we will study the effects of stimulation on the 5-HT system on behavioral profiles and stress responses in a non-selected hatchery population as well as in rainbow trout strains selectively bread for high (HR) and low (LR) post-stress plasma cortisol, respectively. There is a large interest in generating stress tolerant fish strain that could cope with the unavoidable stress in aquaculture. This task is complicated by the fact that traits like stress tolerance and boldness is linked to aggressiveness. Moreover, environmental enrichment is often discussed, and is believed to have positive effects on fish welfare and performance. Still our knowledge on the effects of environmental enrichment on fish performance is very limited.

Project 3: Improved production efficiency and animal welfare in aquaculture through elevated dietary tryptophan (TRP) levels

Participants: Dean Basic, Svante Winberg (collaboration with BioMar AS, Norway, and Norwegian School of Veterinary Science, University of Bergen and Danish Technical University)

The aim of this project is to develop a cost effective method for using TRP supplemented feed to enhance production efficiency and welfare of fish in aquaculture. TRP, a naturally occurring amino acid and precursor of serotonin, has been shown to reduce stress responsiveness in all vertebrates. This effect has a wide variety of implications as elevated levels of TRP have proven to increase appetite after stressful situations as well as reducing

aggression. Moreover, TRP also contributes to increased circulating levels of melatonin. In addition to reducing aggression, melatonin affects sexual maturation and seasonal cycles in growth and fat deposition.

Project 4: Sustainable smolt production - an integrated approach (SMOLTPRO)

Participants: Per-Ove Thörnqvist, Svante Winberg

The main aim of SMOLTPRO is to develop ecologically and ethically sound methods for supplementary rearing of salmonids. To achieve these goals SMOLTPRO integrates the competences and resources in this field of research using a multidisciplinary approach, where experiments will be conducted in a series of full-scale hatchery model systems. The results will be evaluated together with novel meta-analyses of existing data, and new hatchery guidelines will be developed in close dialogue with stakeholders.

Partners: University of Gothenburg (Prof. Jörgen Johnsson, coordinator), Uppsala University, Swedish University of Agricultural Sciences and Umeå University, Norwegian Institute for Nature Research and Norwegian University of Science and Technology, Technical University of Denmark and the National Institute for Aquatic Resources, Ocean Science Centre, Memorial University of Newfoundland.

SMOLTPRO started in January 2010, and is a four-year strategic project funded by the Swedish Research Council Formas.

Project 5: Effects of increasing ocean CO2 on fish neurophysiology and behaviour

Participants: Svante Winberg, Bryndis Birnir, Arianna Cocco, Laura Vossen, Josefin Sundin (collaboration with Fredrik Jutfelt, Göteborg University, Göran Nilsson, Oslo University).

Ocean CO2 concentration increases in line with atmospheric CO2 resulting in ocean acidification. In addition, rising ocean CO2 concentrations may by itself have severe disturbing effects on fish behaviour. Recent studies have shown that near future CO2 levels, can cause a behavioural reversal in larval fish, significantly reducing settling success. In fish, high pCO2 could lead to a shift in the gradients of Cl- and/or HCO3- across neural membranes, resulting in a reversal of the GABA-A receptor action, i.e. making it excitatory instead of inhibitory. This hypothesis is supported by a recent report that treatment with a GABA-A receptor antagonist counteracts the behavioural effects of elevated pCO2. The effect could be widespread among marine fish species since GABA-A receptor mechanisms appear conserved. However, the time-course of the behavioural effects of elevated pCO2 suggests that effects on gene expression may be involved. Moreover, it is likely that fresh water fish living shallow eutrophic environments, where pCO2 may fluctuate, display adaptations to high pCO2. The current proposal will apply a comparative approach, comparing marine fish to zebrafish in order to assess behavioural effects of GABA-A receptor ion permeability and subunit composition. This will provide information on the mechanisms behind the behavioural changes, which can subsequently be used to predict the sensitivity of different species to rising ocean CO2 concentrations.

The project started 2013 and is financed for 4 years by VR.

Project 6: A new integrative framework for the study of fish welfare based on the concepts of allostasis, appraisal and coping styles (COPEWELL)(http://www.imr.no/copewell)

The aim of COPEWELL is to establish, evaluate, and further develop, a new scientific framework for the understanding and application of the concept of animal welfare in farmed fish derived from the evolutionary based concepts of allostasis, allostasic load and overload. The project will propose and implement, as a whole and at the particular Tasks, an innovative hypothesis-driven multidisciplinary approach, where a range of hypotheses will be tested. The COPEWELL project will through four scientific work packages focus on underpinning mechanisms in four essential welfare relevant concepts: COPING STYLES, APPRAISAL, ALLOSTASIS and ONTOGENY. The consortium consists of 17 groups from all over Europe.

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Agencies that support the work/ Funding

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Pharmacology

Pharmacology

Group leader: Dan Larhammar, PhD, Professor

Members of the group during 2014

Bo Xu, PhD student
Christina Bergqvist, research engineer
Daniel Ocampo Daza, PhD
David Lagman, PhD student
Ingrid Lundell, PhD, reader (lecturer) em.
Jasna Pruner, PhD student
Kateryna Shebanits, PhD student
Lars G. Lundin, docent, reader (lecturer) em.
Xesús Abalo, PhD, researcher
Xiao Zhang, PhD, researcher

Project students:
Andreas Torell, SOFOSKO student
Christos Gkolfos, project student
Ella Franzén, project student
Enrico Konrad, ERASMUS student
Hanaz Jumaa, project student
Helen Haines, project student
Joel Eggert, SOFOSKO student
Karin Hedin, project student
Oscar Klockars, project student
Rebecca Faresjö, SOFOSKO student
Sofia Kaneberg, SOFOSKO student
Tong Zhang, project student

Our research has two primary aims:
1) To deduce the evolution of important gene families in vertebrates, particularly gene families expressed in the nervous system and in the endocrine system. We wish to find out when new genes and functions have arisen and how functions have changed during evolution. We are primarily investigating gene families for G-protein-coupled receptors and genes involved in vision.

2) To characterize the NPY (neuropeptide Y) system of peptides and receptors of importance in appetite regulation.

Thousands of vertebrate gene families are now known to have expanded in the two genome doublings (tetraploidizations) that took place approximately 500 million years ago. A third genome doubling occurred in the ancestor of teleost fishes. These dramatic events explain a great deal of the complexity of presently living vertebrates, and also explain functional overlap for genes belonging to the same family. We combine phylogenetic sequence analyses and chromosome comparisons across species to determine gene duplication time points. This allows identification of corresponding genes (orthologues) in different species for comparisons of functions. The results help explain how functions arise, change, and even disappear during evolution. Among the gene families that we have studied, or are presently studying, are the opioid peptides (enkephalins etc.) and their receptors, growth hormone and prolactin and their receptors, oxytocin-vasopressin receptors, sodium and calcium channels, and the gene families involved in signal transduction in the rods and cones of the eye.

NPY is an abundant neuropeptide in the brains of all mammals including humans. NPY and its two related peptides PYY and PP regulate appetite, metabolism and numerous other physiological functions. We investigate how these peptides bind to their 4-7 receptors in different vertebrate species, primarily the four human receptors. We are especially exploring the opposing roles of NPY and PYY/PP in appetite regulation. The methods used include molecular biology, functional expression and in vitro pharmacology. We also investigate how genetic variation in one of the human receptor genes correlates with body weight and obesity.

Project 1: Evolution of vertebrate neuronal and endocrine gene families

Participants: Daniel Ocampo Daza, Bo Xu, Christina Bergqvist, Lars G. Lundin

Our studies have shown that many neuronal and endocrine gene families gained new gene copies in the two ancient vertebrate tetraploidizations. These ancestral duplications have allowed evolution of many new functions and more highly specialized functions in the vertebrates. Examples include NPY receptors, oxytocin-vasopressin receptors and ion channels. We are presently investigating several families of neuropeptides, G protein-coupled receptors and ion channels.

Project 2: Functional and genetic studies of the NPY system

Participants: Bo Xu, Jasna Pruner, Kateryna Shebanits

In mammals, NPY stimulates appetite primarily via receptor subtypes Y1 and Y5, whereas the related gut endocrine peptide PYY reduces appetite via receptor Y2 and pancreatic polypeptide (PP) inhibits appetite via Y4. We investigate the ligand-binding properties of the human Y2 receptor by making mutants and expressing them in cultured cells for binding studies with ligands. We have identified important interaction points between peptides and receptors and are now exploring the unique ligand preferences for each receptor subtype. The results will facilitate drug development to reduce appetite. We are also investigating NPY receptors relatives to see how these have become distinct after duplication from a common ancestral receptor gene.

Recent studies have shown that the PP receptor Y4 is associated with childhood obesity and adult body weight. Our functional studies in vitro revealed that one receptor variant

(allele) displayed reduced functional coupling to signal transduction pathways. We are now resolving the complicated inheritance of this gene which displays both copy number variation (CNV) and single nucleotide polymorphisms (SNPs). We have recently confirmed that the copy number correlates with obesity.

Project 3: Evolution of colour vision in vertebrates

Participants: Xesús Abalo, David Lagman, Daniel Ocampo Daza

Numerous gene families are involved in vertebrate vision. We have found that the genome doublings in early vertebrate evolution generated gene duplicates that became specialized on expression in cones or rods, i.e., for color vision and dim-light vision, respectively. A surprising conclusion from these comparisons is that colour vision arose before dim-light vision. We are investigating gene families in the phototransduction signalling cascade, starting with the light receptors themselves, the opsins, via transducins and beyond. We use the zebrafish as experimental model because it has retained more of the ancestral vertebrate colour vision genes than mammals. Furthermore, the zebrafish shares with other teleost fishes the third tetraploidization that has resulted in additional gene duplicates. We have found that duplicated genes have become specialized by being expressed differentially during development, in distinct anatomical parts of the retina, or in the pineal gland. Furthermore, the duplicates differ in the circadian cycle. Thus, the genome doublings have facilitated elaboration of vertebrate vision by supplying additional gene copies that have evolve new functions (neofunctionalization) as well as more specialized functions (subfunctionalization).

Project 4: Zebrafish eyes: a colourful model to study human visual disorders

Participants: Xesús M. Abalo, David Lagman

The aim of the project is to shed light on photoreceptor dysfunctions related to mutations of phototransduction proteins. The project merges genetics and epigenetics in a combination of loss-of-function and gain-of-function experiments to reveal the molecular mechanisms that trigger apoptosis in certain types of blindness using a well established model of human visual disorders: zebrafish. Three transgenic lines of zebrafish have been established in order to identify the photoreceptor types in the retina with a fluorescent marker. The project involves studies of genetics, electrophysiology, histology and visual behaviour. Epigenetic experiments are in progress to silence the expression of a gene that we have demonstrated is expressed in a specific subset of cones (*gngt2b*).

Project 5: Involvment of heparan sulfate in reward and Alzheimer's disease

Participants: Xiao Zhang

Heparan sulfate (HS) proteoglycans have numerous roles and influence a range of physiological functions, for instance by binding to peptides and proteins. It has been found that HS and degradation of HS by heparanase affect feeding and that HS binds to the appetite-stimulating peptide AgRP. This will be investigated further by exploring the role of HS and AgRP in the reward circuitry of dopamine neurons in genetically modified mice. In Alzheimer's diesease, HS seems necessary for macrophage-mediated clearance of the Aβ peptide. The mechanisms for this are explored further in mouse models. Also, changes in heparanase during aging will be investigated.

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Honours

Dan Larhammar is president of the European Society for Comparative Endocrinology (ESCE) 2010-2014.

Dan Larhammar was awarded the "Pedagogical Rose" teaching award in May 2013 by the Medical Student Association at Uppsala University.
Dan Larhammar was awarded the "Pedagogical Rose" teaching award in May 2013 by the Medical Student Association at Uppsala University.

Functional Pharmacology

Group leaders: Helgi B. Schiöth, Professor and Robert Fredriksson, Assoc. Professor

Members of the team during 2014

Anders Eriksson, PhD student
Andreas Johansson, PhD student, part-time
Anica Klockars, PhD student (defended)
Arunkumar Krishnan, PhD student
Björn Sundberg, PhD student, part-time
Christian Benedict, researcher, associate professor
Colin Chapman, PhD student
Emil Nilsson, PhD student
Emilie Perland, PhD student
Frida Rångtell, PhD student
Jessica Mwinyi, post doc
Jonathan Cedernaes, post doc
Linda Solstrand Dahlberg, PhD student
Lyle Wiemerslage, post doc
Madeleine Le Grevés, lecturer, course leader
Marcus Bandstein, PhD student
Maria Hägglund, PhD student (defended)
Maria Ling, PhD student, part-time
Mathias Rask-Andersen, post doc
Michael Williams, researcher, associate professor
Nathalie Bringeland, PhD student
Olga Titova, PhD student
Philip Goergen, PhD student (defended)
Pleunie Högenkamp, post doc
Sahar Roshanbin, PhD student
Samantha Brooks, affiliated researcher
Sarah Voisin, PhD student
Sofia Kanders, PhD student
Sofie Hellsten, PhD student
Sonchita Bagchi, post doc
Vanni Caruso, post doc
Wei Zhou, PhD student

General: The team studies pharmacological, genetic and behavioural aspects of functions related to central regulation of food intake, sleep, neurotransmission, transporters, reward and psychology using both human and animal models. We perform molecular biology and neuroanatomical studies in a fully equipped molecular biology lab as well as transgenic mouse and transgenic fly work linked with behavioural characterisation. We have human sleep laboratories and perform human experimentation on both patients and healthy volunteers. We use bioinformatics studies with focus on evolution of membrane proteins and perform several types of genetic, epigenetic and biostatic studies. The research group was

ranked in 2011 at the highest category of "*top international class*" by external international panel evaluation of Uppsala University (KoF2011) stating that the "*research output of this group is exceptional*" with projects "*highly relevant for society*".

Progress 2014: We have been very productive in 2014 with more than 30 papers published. We continued to publish papers in high impact journals during year 2014. This includes papers in *Diabetes* (IP; 8.474) (Benedict et al.,), *PLoS Genet.* (IP; 8.167)(Williams et al.*), Alzheimers Dement. (IP; 17.472) (*Benedict et al.*), Annu Rev Pharmacol Toxicol*. (IP; 21.543) (Rask-Andersen et al.,), *Nature Reviews Neuroscience* (IP; 31.673) (Caruso et al.), *Brain Behav Immun*. (IP 6.128) (Christoffersson et al.,), *Trends Pharmacol Sci.* (IP; 9.988) (Rask-Andersen et al.) and an accepted paper in *Pharmacol Rev*. (Hamann et al.,) (IP 18.551). The unit of functional pharmacology is currently the most productive unit at the department of neuroscience considering the total impact of the published papers during the last four years. The unit contributes with papers of total impact of above 100 (total impact of papers) in average per year in recent years. Recent papers have continued to receive high number of citations during 2013 and the total number of citations received by Schiöth HB (Google Scholar) was above 1800 during 2014, Fredriksson R more than 900 citations and Benedict C, more than 600. Papers that were generated entirely at this department, contribute to a very important part of this high rate of citations, including papers such as (Fredriksson et al., *Mol. Pharmacol*. 2003, that has received in total more than 1400 citations. This paper is one of the most cited papers that has been entirely produced at Uppsala University published 2003 or later. Schiöth has published 27 papers (22 original papers and 5 reviews) that have received more than 100 citations. Schiöth is on Thomson Reuters 2014 list of the worlds "*most influential researchers*" based on citations.

Grants: The unit for functional pharmacology has been very successful during year 2014 in receiving external grants. The unit has currently three VR-project grants. Schiöth has two grants at VR-M, a main grant of 1.3 mSEK/year for 3 years "Central regulation of food intake and reward" and another grant, 3R, "Development of a replacement model to determine short and long term effects of environmental toxin mixtures using Drosophila" of 0.68 mSEK per year in 3 years. Fredriksson has also a VR-NT project grant for 0.4 mSEK/year on "Functional characterization of novel amino acid transporters". This plan aims to understand how novel amino acid transporters function regarding substrate specificity, intracellular partner proteins, cell type specificity and physiology. We are using histological methods (immunohistochemistry and in situ hybridization), uptake assays in oocytes and biochemical and molecular biology methods to ultimately identify the substrate specificity and physiological role for each neuronal amino acid transporter. Fredriksson has also a VR-NT senior researcher grant for salaries of 1.2 mSEK/year, 3 + 3 years. Schiöth has also grant at Hjärnfonden 0.5 mSEK/year for studies on novel transporter using conditional knockout mice and Benedict another for 0.5 mSEK/year for sleep research. Fredriksson has grant from NOVO Nordisk of 0.4 mDDK/year for endocrinology and molecular biology of novel transporters involved in food intake and several other smaller grants and Benedict a another NOVO Nordisk grant of 1 mDDK/year on sleep research for 6 years. AFA has granted Benedict 0.6 mSEK per year for three years for sleep research.

Development of the laboratory and techniques: The group has a strong molecular biology laboratory, creating conditional knock-outs, neuroimaging using fMRI, immunohistochemisty, human genetics, animal behaviour, pharmacology on cellular expression systems and bioinformatics. While the group has had strong focus on molecular biology of food intake with emphasis on key functional nodes such as GPCRs and

transporters for many years, we are now focusing increasingly on genetics and pathology. We have a fly (drosophilia) lab which studies the genetics of obesity and molecular mechanisms of aggression under the leadership of researchers Michael Williams. This has enabled us to study gene knock outs in large number of genes involved in behaviour. We have a fully equipped sleep lab and several studies on the effect of sleep deprivation on cognitive and molecular endocrinological functions. We are performing functional magnetic resonance imaging (fMRI) studies in humans, performed in collaboration with professor Elna-Marie Larsson, head of radiology at the University Hospital in Uppsala on several studies including anorexia, bariatric surgery and genetics. We collaborate with professor Lars Lind, Acute and Internal Medicine, related to the PIVUS, ULSAM, EpiHealth cohort studies. We are collaborating with Prof. Dr. Bernd Schultes, Head of the Interdisciplinary Obesity Center, St. Gallen, Switzerland. Through him, we have access to unique cohort data (very detailed phenotypes and follow up) with over 1000 individuals that have undergone bariatric surgery resulting in large weight loss over short period of time. The molecular biology lab has well working oocyte injection facility allowing functional characterization of novel transporters in terms of substrate and drug specificity. This will allow us to clarify the role of each individual transporter in neurons and to identify transporters with unique as well as redundant functions in specific neuronal cell types. We have several new conditional knock out mice lines that are being characterized.

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AFA

Functional Neurobiology (Motions and Emotions Lab)

Group leader: Åsa Mackenzie, Associate Professor

Members of the group during 2014

Emma Arvidsson, PhD student to October/ Post doc
Nadine Schweizer, PhD student
Stéfano Pupe Johann, PhD student
Thomas Viereckel, PhD student
Julia Pedersen, PhD student
Ernesto Restrepo Leidefors, Post doc (until February)
Camille Ridde, Exam project student (Fall 2014)
Tomas Westergren, Exam project student (Fall 2014)

Our Unit of Functional Neurobiology was formed in June 2014 from our previous group Neuronal Circuits of the Basal Ganglia, which was part of the Developmental Genetics Unit. Our research interest around brain functions that are important for regulating *motions and emotions* has been kept intact and we study these functions using *transgenics, optogenetics, behavior, pharmacology, electrophysiology, amperometry/chronoamperometry, histology and molecular biology*. Our two main research areas are focused around *i*) the Ventral Tegmental Area (VTA), and, *ii*) the subthalamic nucleus (STN). In the *VTA project*, we study how neuronal circuits regulate responses to various situations involving reward and aversion, and how these are important for mediating motivated and goal-directed behaviour. We study dopaminergic and glutamatergic neurons primarily but also those co-releasing both glutamate and dopamine. In the *STN project*, we study how voluntary movement, including initiation of an intended movment, and also how reward-responses, are correlated to glutamatergic function of the STN and its target areas. In both the VTA and STN projects, we have a specific interest in identifying subpopulations within these regions; subpopulations that we can define by specific gene expression patterns, for the purpose of enhancing the selectivity in targeting a restricted set of neurons. In both projects, we identified a series of such molecular markers during the year that we now implement in transgenics and optogenetics and study physiological and behavioral outputs. Our research is intended to increase the knowledge of how motion and emotion circuits function, not least as these are important in several human disorders, including *Parkinson's disease, addictions and substance dependence as well as aspects of depression.*

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Series: Methods in Molecular Biology: Springer protocols, Series Editor JM Walker, Book Editor RM Hnasko. In press.

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Uppsala University

Neuropsychopharmacology

Group leader: Erika Comasco, Ph.D.

Members of the group during 2014

Lars Oreland, Prof. em.
Jarmila Hallman, Prof.
Aniruddha Todkar, PhD student
Samra Syyada Yafri, guest PhD student
Simone Toffoletto, MD
Megha Bendre Nankumar, M.Sc.
Sofia Bergman, Master Student
Maria Sapounidou, Master student
Maria Vrettou, Master student
Mujtaba Aljumah, MD student
Samet Albayrak, Erasmus student
Shana Verschuere, Erasmus student

Focusing on genetics of psychiatric disorders, activities of the group include:

- clinical research on gonadal hormone changes and women's mental health, using a complementary approach including genetics, endocrinology, psychiatry and neuroimaging in collaboration with prof. I. Sundström-Poromaa, doc. A. Skalkidou and prof. R. Lanzenberger;

- translational research on (epi)gene-by-environment interaction mechanisms and effects related to alcohol use disorder using animal experiments with rats and human population-based and clinical samples, with a special focus on the period of the adolescence in collaboration with prof. K.W.Nilsson, I. Nylander, S. Hodgins, C.-G.Svedin, and E. Roman.

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2. Drogernas historia by Oreland L. In: "Mot en ny drogpolitik". Eds Almqvist K, Gröning L. Publisher: Axel & Margaret Ax:son Johnson stiftelse (2014). ISBN 978-91-89672-57-4
3. Läkarutbildningen i Sverige 400 år - tillkomst och de första åren by Oreland L. In: Medicin och Farmaci 400 år vid Uppsala universitet. Eds Hulter-Åsberg K, Östlund K. Publisher: Uppsala universitet (2014). ISBN 978-91-554-8972-4.

Popular science article

1. Förlossningsdepression. Comasco E, Poromaa-Sundström I, Skalkidou A. Magasinet BestPractice, Psykiatri/Neurologi. 2013

Agencies that supported the work/ funding

Fredrik and Ingrid Thuring Foundation
Kempe-Carlgrenska Foundation
Swedish Brain Foundation

Prizes and Awards

Best poster prize to Aniruddha Todkar at the congress "Alcoholism and Stress: A Framework for Future Treatment Strategies" sponsored by the NIAAA (NIH).

Neurotrauma & Restorative Neuroscience

Neurosurgery

The Neurosurgical research comprises two major research programs:

Clinical Brain Injury Program – Neurocritical care

Group leader: Per Enblad, Professor

Traumatic Brain Injury and Subarachnoid Haemorrhage are the major patient groups treated in the Uppsala Neurointensive care unit (NICU). The continual refinement of neurointensive care and improved knowledge of secondary brain injury mechanisms are the corner stones of this program. With a translational approach combining basic research in animal models with clinical research in the NICU, we strive to find novel therapeutical interventions to minimise secondary brain damage and improve patient outcomes.

Experimental Brain Injury Programme – Neurotrauma

Group leader: Lars Hillered, Professor

The basic goal of this program is to provide new knowledge on important brain injury mechanisms in animal models, to be translated for exploration in the NICU. Several group members are active in both neurosurgical programs, which is instrumental for achieving the translational goals of the research. Our neurotrauma research is organized in a translational network named the Uppsala Brain Injury Center – UBIC (http://www.neuro.uu.se/collaboration/uppsala-brain-injury-center-ubic/) with the overall goal of conducting multidisciplinary research to combat Traumatic Brain Injury – a major global public health problem - from molecule to man. The ultimate goal of the research is to find new targets for therapeutic intervention to restore brain function following TBI.
Both neurosurgical programs are integral parts of the Centre of Excellence Neurotrauma at the Uppsala University Hospital (http://www.akademiska.se/neurotrauma/). A close interaction between these centers and the Uppsala Berzelii Technology Centre for Neurodiagnostics (www.berzelii.uu.se) is currently in action.

Members of the group during 2014

Per Enblad, MD, PhD, Professor of Neurosurgery
Lars Hillered, MD, PhD, Professor of Neurochemistry
Fredrik Clausen, PhD, Research Engineer, Animal modelling
Andeas Dahlin, Researcher, Materials science and proteomics
Philip Dyhrfort, Neurosurgery Resident
Sara Ekmark Lewén, BSc, PhD student
Johanna Flygt, PhD student
Sami Abu Hamdeh, Neurosurgery Resident, PhD Student
Anders Hånell, BSc, PhD, post doc at Medical College of Virginia, USA
Tim Howells, PhD, Researcher, Computer science
Charlotte Israelsson, PhD, Post-Doc
Ulf Johnson, MD, Radiology Resident, PhD Student
Anders Lewén, MD, PhD, Neurosurgeon, Associate professor (50% research time)
Camilla Lööv, BSc, PhD, currently post-doc at MIND, Boston, USA
Sara Magnéli, Neurosurgery resident
Niklas Marklund, MD, PhD, Neurosurgeon, Associate professor(30% research time)
Pelle Nilsson, MD, PhD, Neurosurgeon, Pediatric neurosurgery chief
Christoffer Nyberg, MD, Neuroradiology Resident, PhD Student
Lena Nyholm, NICU Nurse, PhD Student
Elisabeth Ronne, MD, PhD, Adjunct professor, Neurosurgeon (20% research time)
Elham Rostami, MD, PhD, Neurosurgery resident (Forskar-ST block)
Mats Ryttlefors, MD, PhD, Neurosurgeon
nger Ståhl-Myllyaho, NICU Technician
Parmenion Titsopoulos, Neurosurgeon, PhD Student
Maria Zetterling, MD, PhD, Neurosurgeon

Undergraduate students and project researchers

Nina Farrokhnia (30 hp MD program)
Gudrun Andrea Fridgeirsdottir (30 hp Master thesis + 15 hp Project)

Project 1: Clinical brain injury program – Neurocritical care

Participants: Per Enblad (Group leader), Lars Hillered, Philip Dyhrfort, Tim Howells, Ulf Johnson, Anders Lewén, Sara Magnéli, Niklas Marklund, Pelle Nilsson, Christoffer Nyberg, Lena Nyholm, Karlis Purins, Elisabeth Ronne, Elham Rostami, Mats Ryttlefors, Inger Ståhl, Parmenion Titsopoulos, Maria Zetterling.

Background

Traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) are common and critical medical conditions. The development of modern neurointensive care has markedly reduced mortality and improved patient outcomes, while clinical trials of neuroprotective drug candidates have to date been unsuccessful. Basic research has identified a number of secondary injury mechanisms following TBI and SAH. The challenge ahead is to translate this knowledge into the clinical setting, in order to find new treatment strategies to hinder secondary injuries and improve patient outcomes even further. The neurointensive care unit (NICU) with highly standardised health care, a multitude of monitoring methods and powerful computerised data collection systems provides an excellent platform for this translational research.

Overall goal

To study secondary brain injury mechanisms in patients with TBI and SAH in the NICU, utilising the available multimodality monitoring and computerised data collection systems.
To specifically study secondary injury mechanisms caused by intracranial secondary insults/complications (e.g. intracranial hypertension owing to brain swelling) and secondary systemic insults (e.g. hypotension with a reduced cerebral blood perfusion).

Methods and Networks

Multimodality monitoring – The technical equipment available in our NICU allows for continuous monitoring of intracranial pressure, systemic blood pressure, cerebral perfusion pressure, intracerebral neurochemistry changes (e.g. energy metabolic perturbations and biomarkers), neurophysiology (e.g. post traumatic seizure activity), brain temperature, brain tissue oxygen pressure, jugular venous oxygen saturation, cerebral blood flow velocity, intracranial compliance. Neuroimaging (CT, CT/PET and MRI) are important complimentary methods for monitoring the brain injury process. The recently acquired mobile CT scanner with a xenon CBF device provides a powerful additional monitoring tool for the future.
Computerised data collection systems – A computer system has been developed and implemented in the NICU allowing for collection, analysis and illustration of clinical data (e.g. type of brain injury, CT findings), physiological data (e.g. intracranial pressure, brain tissue oxygen pressure), treatment data (e.g. ventricular CSF drainage to lower the intracranial pressure). A TBI database has been established in the NICU in collaboration with the Uppsala Clinical Research Centre (UCR) to facilitate patient follow up and outcome assessment (www.ucr.uu.se/tbi). All TBI patients treated in our NICU during the last 5 years are included in the database to date.

Biobanking facilities

Approved systems for biobanking of body fluid samples, brain biopsies and resected brain tissue have been established.
The NICU as a "clinical laboratory" – A standardised clinical protocol corresponding to the concept of "good laboratory practice" has been developed and implemented in the NICU. The clinical protocol, the multimodality monitoring system and the computer data collection

system together enable extensive control and monitoring of the clinical condition, resembling a basic science laboratory environment. The facilities thus create an excellent platform for neurointensive care and clinical research of top international quality.
Brain IT group – We have, in collaboration with distinguished colleagues in the field established an international research network comprising over 20 centers in Europe, with focus on neurointensive care of TBI patients (www.brainit.org). Information technology (IT) is used to collect patient data for a common web-based database for TBI research. This will provide a powerful research tool for international multi-center trials on e.g. novel treatment strategies and neurosurgical methods.
Uppsala Brain Injury Center (UBIC) – This is a translational research network with focus on TBI research that was established in 2004. The basic objective of this multidisciplinary endeavour is to combat TBI with a broad spectrum of competencies ranging from molecule to man, i.e. from molecular genetics, cell-culture systems, animals models, TBI patients in the NICU to rehabilitation and follow-up (http://www.neuro.uu.se/collaboration/uppsala-brain-injury-center-ubic/). The Uppsala NICU is of top international standard, providing one of the major research platforms within the UBIC. The UBIC concept received top marks regarding research quality, research environment and future potential by the external international review board in the recent evaluations "Quality and Renewal 2007 and 2011" of the research at Uppsala University.
The Centre of Excellence Neurotrauma (http://www.akademiska.se/neurotrauma/) is a joint effort between Uppsala University Hospital and Uppsala University, launched in 2008. The purpose of this venture is to stimulate the synergies between highly specialised neurointensive care and research, in order to further improve patient outcomes. The effort involves financial support for dedicated research time (50%) for one neurosurgeon, one NICU technician (50%), one researcher in Computer science (50%) and one PhD student nurse (50%).
Another multidisciplinary project was launched in 2007 in a collaborative effort between UBIC and the Uppsala Berzelii Technology Center for Neurodiagnostics (www.berzelii.uu.se) combining clinical microdialysis technology with modern proteomic methodology and Materials Science. The main goal is to find clinically useful diagnostic and prognostic biomarkers for point-of-care use in the NICU. The basic working hypothesis is that harvesting of biomarkers directly in the injured brain by microdialysis will be instrumental in the translation and validation of brain-derived biomarkers of secondary injury mechanisms (e.g. neuroinflammation) shown to be of importance in our pre-clinical brain injury models. Modern proteomics methodology is a powerful tool to screen for entirely novel biomarkers of TBI. Materials Science technology is instrumental in optimising protein biomarker sampling performance and combined biosensor technology.

Main results in 2014
For main results in 2014 the reader is referred to the list of publications below.

Significance
The organisation of neurointensive care into a "laboratory-like" environment with powerful multimodality monitoring, and computerised data collection provides a unique opportunity to monitor the acute brain injury process and the effect of treatment strategies, enabling the study of pathophysiological and neurochemical mechanisms of acute brain injury directly in the human brain. We hypothesise that this opportunity will be instrumental in the translation of promising basic science results to the NICU setting, a development that is likely to improve the outcome of patients with acute brain injury.

Project 2: Experimental brain injury program – Neurotrauma

Participants: Lars Hillered (Group leader), Per Enblad, Fredrik Clausen, Andreas Dahlin, Johanna Flygt, Sami Abu Hamdeh, Anders Lewén, Camilla Lööv, Niklas Marklund, Inger Ståhl, Nina Farrokhnia, Gudrun Andrea Fridgeirsdottir.

Overall goal

Uppsala Brain Injury Center (UBIC) – Experimental neurotrauma research is organised as a translational research network with focus on Traumatic Brain Injury (TBI) research. The basic objective of this multidisciplinary endeavour is to combat TBI with a broad spectrum of competencies ranging from molecule to man, i.e. from molecular genetics, animals models, TBI patients in the Neuro-ICU to rehabilitation and follow-up (http://www.akademiska.se/neurotrauma/). The ultimate goal of the research is to find new targets for therapeutic intervention to restore brain function following TBI that can be translated to the NICU setting.

Methods

The Division of Neurosurgery provides a well-established animal modelling facility, one of the major research platforms within the UBIC. To model the high degree of complexity of human TBI pathophysiology (e.g. focal contusions, epidural, subdural and intraparechymal hemorrhages, diffuse axonal injury and mixed forms) a battery of animal models with different mechanical impact properties is required. We have established two focal contusion models of TBI (the Controlled Cortical Contusion Model and the Controlled Cortical Impact Model) and one mixed model (the lateral Fluid Percussion Injury Model) and lately a new model of diffuse axonal injury (the central Fluid Percussion Injury Model) for rats and mice. These models are widely used internationally, thus facilitating comparison of data between research groups.

In recent years, a long term strategy was adopted in close collaboration with Prof Bengt Meyerson, BMC to establish a battery of methods for evaluation of the functional outcome of animals following TBI. Behavioural outcome measures are considered increasingly important in studies of neuroprotective drug effects, other therapeutic interventions and neurorepair strategies. The following methods have thus far been set up: the Morris Water Maze, the Rotarod, the Cylinder test, a four-grade Neuroscore testing neurological function and the Concentric Square Field Method testing a number of features of spontaneous behaviour of mice in a complex environment.
Other in-house methodology comprises cerebral microdialysis and biomarker analysis methods in our NICU lab, as well as basic molecular biology and morphology methods.
A number of additional methods including contemporary proteomics methodology, genetics and neuroimaging, are available to us in our collaborative network activities (see above).

Main lines of research

The main conceptual lines of research within the UBIC comprise molecular studies of secondary brain injury mechanisms in animal models of TBI with focus on oxidative stress, neuroinflammation, diffuse traumatic axonal injury, endogenous brain repair and plasticity, as well as neuroprotection.
Interventional studies are ongoing in the following directions:
Neuroprotection: studies on neuroprotective drug candidates (e.g. anti-IL1β antibody, VEGF antibody) to block important secondary injury mechanisms such as injurious components of the inflammatory response (e.g. immune cell trafficking, blood-brain barrier perturbation) to

reduce the total amount of brain damage and brain edema or targeting specific components (e.g. traumatic axonal injury).
Endogenous repair: studies on strategies to enhance axonal regeneration and plasticity following TBI.

Main results in 2014
For results in 2014 the reader is referred to the below list of publications. The main achievements are: i) continued characterization of our novel rodent model of diffuse axonal injury, including molecular and biomarker studies of early neuroinflammation after TBI to be translated to human TBI patients; ii) continued studies on changes in acute changes in interstitial levels of amyloid species in human TBI patients, exploring the demonstarated link between TBI and Alzheimers disease; iii) the development of a refined microdialysis method allowing for improved sampling performance for protein biomarkers and proteomic studies in animal models and acute human brain injury in the NICU setting.

The group actively participated in the following international scientific meetings in 2014:

1. Hillered L, Dahlin A, Purins K, Wetterhall M, Bergquist J, Hjort K, Enblad P, Lewén A (2014) New microdialysis method for protein biomarker sampling in the neurointensive care setting. *11th Symposium of The International Neurotrauma Society*, Budapest, Hugary, March 19-23, 2014. *J Neurotrauma* Volume: 31, Issue: 5, Pages: A22-A22, Meeting Abstract: 72.
2. Clausen F, Dahlin A, Chu J, Käller B, Düring E, Marklund N, Hillered L (2014) Novel microdialysis method to study the acute cytokine response to diffuse traumatic brain injury in the rat. *11th Symposium of The International Neurotrauma Society*, Budapest, Hugary, March 19-23, 2014. *J Neurotrauma* Volume: 31, Issue: 5, Pages: A19-A19, Meeting Abstract: 62.
3. Enblad P, Hillered L, Marklund N, Ronne-Engstrom E (2014) Active participation in the International Microdialysis Forum, Cambridge university, resulting in an International Consensus Statement with guidelines on the use of microdialysis in Neurointensive Care Patients.

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Agencies that support the work/ Funding

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Tore Nilsson Foundation

Developmental Neuroscience

Molecular and Genetic Analysis of Experimental Traumatic Brain Injury

Group leader: Ted Ebendal, Professor

Members of the group during 2014

Ted Ebendal, Ph.D., Professor
Nestor G. Carri, M.D., Ph.D., Visiting Scientist
Charlotte Israelsson, Dr. Med. Sci., Researcher
Annika Kylberg, Research Engineer

When a traumatic brain injury (TBI) afflicts a person, e.g. caused by a traffic accident or fall, many severely impairing processes are initiated. At present, there is no effective pharmacological treatment available for the patients suffering from these disabling conditions. One main issue is the lack of detailed molecular understanding involved in the brain response to trauma. The research has identified a variety of functional groups emerging at different time points after trauma. Our strategy is to further identify key players involved in cell interactions and activation of various genes especially in the immunological cascade after TBI, as a basis for development of novel neuroprotective therapies reducing the damaging effects in the brain. Findings are likely to be applicable also to other major neurological problems, such as stroke and degenerative diseases, based on our observations of reactions in the brain that are similar in several models of brain injuries and pathological conditions.

The gene regulations occurring after a trauma cover mainly inflammation and immunity, tissue remodeling, and cell signaling. After an injury, using an experimental TBI model in mice, different immune cells invade the brain already in the first hour but continuing up to several months. When this cell invasion occurs, it results in a strong and diverse inflammatory response which may worsen the tissue damage. Inflammation utilizes both beneficial as well as detrimental effects and results in a complex pattern of effects in the brain. Our research has detected particulary strong expression levels among various chemokines and their receptors linked to specific cells in the immune system and exhibiting both inhibitory and promoting effects. Thus, an induced trauma shows differences in temporal expression levels which differ both in time and regarding the strength and effect of the response but also among the interacting pathways. Moreover, we have observed similar effects in comparative studies using other neurodegenerative conditions such as in mouse models of Alzheimer's disease, ALS and multiple sclerosis.

Theurapeutic approaches have so far been unsuccessful in patients suffering from truma. We have investigated several compounds already in therapeutic use in other pathological conditions and have found two substances of special interest. Both of them are in different ways affecting leucocytes with effects on the network of chemokines and other factors involved in the inflammatory cascade.

The methods we used to analyze the effect on cells and transcripts in the brain after trauma are cell sorting (flow cytometry, magnetic beads and cell depletion), microarray analysis and quantitative RT-PCR from neocortex in mice subjected to focal injury (controlled cortical impact injury) and behavioural studies.

The research group is located at the Biomedical Center and collaborates closely with the Neurosurgery Unit of our Department, located at the University Hospital, in a Neurotrauma research consortium. Additionally, the research group is also part of the Uppsala University Brain Injury Center (UBIC).

Project 1: Outcome of treatment strategies in TBI

Participants: Ted Ebendal, Annika Kylberg, Charlotte Israelsson

At different time-points postinjury, we performed a large survey of transcriptional alterations in the neocortex and hippocampus. Many of the upregulated genes encode proteins that serve functions in inflammatory responses and tissue remodeling. The chemokine family belonging to the group of cellular growth factors, gave the strongest responses to injury. In particular, we identified activation of *Ccl3* (macrophage inflammatory protein–1 alpha) and its receptors *Ccr1* and *Ccr5*, as well as strong up-regulation of *Ccl2* (monocyte chemoattracting protein-1) and *Ccl12* (monocyte chemoattracting protein-5) and their shared receptor *Ccr2*. A marked upregulation of *Cxcl10* (interferon induced protein-10) in clustered cells, partly dependent of the two pathways mentioned above, was also detected and likely represent inflammatory monocyte-derived cells invading the injured brain.

Project 2: Transcriptional responses after inflicting injury to the mouse brain

Participants: Charlotte Israelsson, Annika Kylberg, Anders Hedin, Ted Ebendal

At different time-points postinjury, we performed a large survey of transcriptional alterations in the neocortex and hippocampus. Many of the upregulated genes encode proteins that serve functions in inflammatory responses and tissue remodeling. The chemokine family belonging to the group of cellular growth factors, gave the strongest responses to injury. In particular, we identified activation of *Ccl3* (macrophage inflammatory protein–1 alpha) and its receptors *Ccr1* and *Ccr5*, as well as strong up-regulation of *Ccl2* (monocyte chemoattracting protein-1) and *Ccl12* (monocyte chemoattracting protein-5) and their shared receptor *Ccr2*. A marked upregulation of *Cxcl10* (interferon induced protein-10) in clustered cells, partly dependent of the two pathways mentioned above, was also detected and likely to represent plasmacytoid dendritic cells invading the injured brain.

Publications 2012-2014

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Agencies that support the work/ Funding

The Swedish Research Council
The Swedish Brain Foundation

Honours

Ted Ebendal was selected to present the Karl-Johan Öbrink Lecture at Uppsala University Biomedical Center, December 2012.

Regenerative Neurobiology

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International: Dr Christian Berens, Dept Microbiology, Univ Erlangen-Nuremberg, Germany; Prof Vladimir Berezin, Panum Institute, Copenhagen Univ, Denmark; Prof Thomas Knöpfel, Imperial Coll, London, UK; Prof Harry Heimberg, Diabetes Research Center, Brussels, Belgium; Drs Arsen Mikaelyan and Ekaterina Vorotelyak, Inst Dev Biol, Russian Acad Sci, Moscow, Russia; Prof Alexej Tomilin, Inst Cytology, Russian Acad Sci, St Petersburg, Russia.

Our research has two long-term objectives:

- Promote functional recovery after dorsal root and spinal cord injury.
- Exploit the beneficial potential of stem cells for renewal and repair of insulin producing beta-cells.

Injured peripheral nerve fibres are able to regenerate, and thereby restore, lost nervous system functions. Nerve fibres in the brain and spinal cord are, however, unable to regenerate, and functional loss after injuries to these parts of the nervous system is often permanent. Furthermore, injury or disease of the nervous system can result in longstanding even chronic, pain conditions, so-called neuropathic pain. Our objective is to restore those functions that are lost following spinal cord injury, by:
– promoting regeneration of injured nerve fibres in the spinal cord,
– promoting functionally useful reorganization of neural connections (plasticity), and
– repairing lost connections by transplantation of stem cells, which are guided to become desired type of neurons.

In recent studies we have also shown that growth, survival and function of insulin producing cells in the pancreas are promoted if the cells are cultured or transplanted together with so-called boundary cap neural crest stem cells, a transient cell population residing at the junction between dorsal roots and spinal cord during embryonic development. These observations can offer novel opportunities to treat patients with type 1 diabetes who have lost large amounts of their insulin producing cells.
Our objective is:
– to identify the mechanisms underlying these stimulating effects, and
– to contribute to their exploration for the treatment of patients with diabetes type 1.

Embryonic stem cells can be differentiated to specific neurons in vitro and in vivo using a novel nanodelivery system

Stem cells are attractive as a source for replacement of lost nerve cells in the injured or diseased nervous system by transplantation. A major problem with this approach is to improve survival of transplanted stem cells (which first have to be immature in order to survive) and to differentiate them later to the desired type of nerve cells. Our research aims at developing novel tools to regulate long-term survival and specific differentiation of transplanted stem cells. We have now developed a novel nanodelivery system for release of small peptide mimetics of neurotrophic factors, i.e. molecules which promote survival and specify neuronal differentiation (Stem Cells Transl Med, 2013; Nanomedicine, 2014. The results of these studies can contribute to improved survival and differentiation of stem cells for cell replacement therapy in neurological disorders, and also to develop novel biocompatible delivery systems for directional guidance axonal growth.

Transplantation of neural stem cells restores lost sensory functions after injury to dorsal roots

Sensory information from peripheral tissues is conveyed to the spinal cord via sensory neurons located in paired segmental dorsal root ganglia just outside the spinal cord. These neurons send their information via dorsal roots into the spinal cord. After injury to these roots, often referred to as plexus avulsion injury, sensory nerve fibres are unable to regenerate into the spinal cord. As a result, avulsion injuries result in permanent loss of sensation from the affected part of the body, most often the hand and arm, and often also intractable chronic pain. Our research aims to restore the sensory functions lost following these injuries.

We implant stem cells at the junction between the dorsal root and spinal cord with two different aims: i) To provide the injured dorsal root nerve fibres with a cellular environment supportive for growth into the spinal cord, or ii) To generate neurons which can serve as functional relay at the dorsal root-spinal cord interface by receiving contacts from injured dorsal root nerve fibers and, thereafter, transmit this information into the spinal cord. Our main results show that i) boundary cap neural crest stem cells implanted at the site of re-attached dorsal root form longitudinal tubes that appear to support growth of sensory axons, and ii) similarly implanted embryonic stem cell-derived human neural stem cells support functional repair of avulsed dorsal roots. In a long term perspective, these findings can help to develop novel treatment for patients who have suffered plexus avulsion injury, and possibly, also other injured to the spinal cord.

Boundary cap neural crest stem cells promote survival and function of insulin producing beta-cells

Transplantation of pancreatic islets is en established treatment for patients with diabetes type 1. Islet survival after transplantation to these patients is, however, insufficient and new strategies to enhance transplant viability need to be developed. We previously showed that cultures or transplants of boundary cap neural crest stem cells together with insulin producing β-cells are able to stimulate their proliferation and promote their survival and function (Diabetologia, 2009; Pancreas, 2012). Using culture systems combining boundary cap neural crest stem cells and β-cells we have determined that these cells need to be in direct contact with each other in order for neural stem cells to exert their beneficial effects (Diabetologia, 2012), that these connections are necessary to protect β-cells from cytokine induced apoptosis (Pancreas, 2013), and that this protection requires the establishment of specific cell interactions, which appear to be based on cadherin-β-catenin connections (PLoS One, 2013). Interestingly, these effects may be specific for neural crest stem cells from the boundary cap, since corresponding cells derived from hair follicles were unable to influence co-cultured β-cells. These findings provide a basis for the development of stem cell-based strategies to improve outcome of islet or β-cell transplantation, and for increasing the endogenous β-cell mass in patients with diabetes type 1.

Publications 2012-2014

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Agencies that support the work/ Funding

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Physiotherapy

Rehabilitation and Physical Activity in Patients with Chronic Diseases and in Geriatric Patients

Group leaders: Margareta Emtner, PhD, PT, Associate Professor
Karin Hellström, PhD, PT, Associate Professor

Members of the group during 2014

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Elisabeth Westerdahl, PhD, PT, Associate Professor, Örebro University
Mats Arne, PhD, PT, Medical Sciences, Uppsala University
Lena Kallings, PhD, Exercise physiologist, Stockholm University
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Kjell Alving, Professor, Uppsala University
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Evidence links higher levels of physical activity to improved health. Increased physical activity improves quality of life, and individuals reaching recommended physical activity levels are more likely to have a better overall health-related quality of life and perceived health status than those who do not. Regular physical activity is widely accepted as behaviour that is likely to improve a number of health outcomes and reduce all-cause mortality.
In subjects with chronic diseases, neurologic diseases, and geriatric subjects the level of physical activity is markedly reduced compared to healthy individuals. It has also been recommended that physical activity should be one of the highest priorities for preventing and treating disease.

Our group and collaborators include researchers from the fields of physiotherapy, clinical physiology, pulmonary medicine, cardiology, neurology, epidemiology, gerontology, nutrition, and surgical sciences.

Our main focus is on clinical research with the aims of identifying physical activity and physical capacity in subjects with chronic diseases, neurologic diseases and in geriatric subjects; investigating reasons for physical inactivity and physical limitations, investigating fall prevention interventions, identifying simple tests to measure physical capacity; and, evaluating rehabilitation interventions.

Our current research includes studies in subjects with chronic obstructive pulmonary disease (COPD), asthma, sleep apnoea, heart diseases, dysfunctional breathing, subjects with exercised induced breathing problems, subjects with stroke, Parkinson' disease, Multiple sclerosis, Charcot-Marie-Tooth disease, Cervical dystonia, patients with amyotrophic lateral sclerosis (ALS) and elderly people with increased fall risk.

Our ongoing research during 2014

Ambulatory oxygen in patients with COPD – A multicenter study (AMBOX-study).

Maintenance of physical activity after pulmonary rehabilitation in patients with COPD – a multicenter study.

Muscle function in patients with COPD – a multicenter study.

Identification, description and treatment of subjects with dysfunctional breathing problems.

Exercise-induced breathing problems in 13-14 year old subjects.

Pulmonary rehabilitation for patients with COPD in Sweden: a national survey.

Five-year follow-up of patients with COPD who participated in pulmonary rehabilitation.

Breathing exercises after heart surgery - a multicenter study.

Physical activity in a population of COPD patients in northern Sweden (Olin study).

Physical activity, capacity and exercise testing in patients with Cystic Fibrosis
Methods to increase physical activity and capacity in patients with hip or knee osteoarthritis that are treated in primary care.

Physical and psychological problems and the effect of an intensified physical activity intervention for patients with stroke.

Effects of individually-tailored physical and daily activities for residents in nursing home settings – A Nordic multi-centre study.

A comparison of Dysport (100 U/ml) and Botox (100 U/ml) using dose conversion factor 3:1 and 1.7:1 in the treatment of cervical dystonia.

Physical activity in subjects with neurological diseases.

Effects of fall-prevention intervention in community dwelling elderly people over 75 years – a CRT.

The ability of the Functional Balance Test for Geriatric patients to predict fall.

Predicting fall risk in subjects with stroke treated in primary care.

Validation of outcome measures in canine physical rehabilitation and physiotherapy.

End of Life care in Oxygen-Dependent Chronic Obstructive Pulmonary Disease and Cancer patients.

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Jerning C*, Martinander E*, Bjerg A, Ekerljung L, Franklin K, Järvholm B, Larsson K, Malinovschi A, Middelveld R, Emtner M*, Janson C*. Asthma and physical activity – a population based study. Results from the GA2LEN survey. Respiratory Medicine 2013;107;1651 * contributed equally to the manuscript

Andersson M, Slinde F, Grönberg AM, Svantesson U, Janson C,

Emtner M. Physical activity level and its clinical correlates in chronic obstructive pulmonary disease. Respir Res. 2013;14:128

Bohlen S, Ekwall C, Hellström K, Vesterlin H, Björnefur M, Wiklund L, Reilmann R. Physical therapy in Huntington's disease – towards objective assessments? European Journal of Neurology 2013 Feb;20(2):389-93

Grönstedt H, Frändin K, Bergland A, Helbostad JL, Granbo R, Puggaard L, Andresen M, Hellström K. Effects of individually tailored physical and daily activities in nursing home residents on activities of daily living, physical performance and physical activity level: A randomized controlled trial. Gerontology 2013;59(3):220-9.

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Farkhooy A, Janson C, Arnardottir RH, Emtner M, Hedenström H, Malinovschi A. Impaired carbon monoxide diffusing capacity is the strongest lung function predictor of changes in 12 minute-walking distance in COPD over a five-year follow-up. COPD. 2014 Sep 10. [Epub ahead of print]

Anens E, Emtner M, Hellström K. An exploratory study on physical activity in persons with Charcot-Marie-Tooth disease. Arch Phys Med Rehabil. 2014 Oct 3. pii: S0003-9993(14)01119-8. doi: 10.1016/j.apmr.2014.09.013. [Epub ahead of print]

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Essner A, Sjöström R, Ahlgren E, Gustås P, Edge Hughes L, Zetterberg L, Hellström K.
Comparison of Polar RS800CX heart rate monitor and electrocardiogram for measuring inter-beat intervals in healthy dogs. Accepted Physiology & Behavior 2014 10 31

Reviews and books

Emtner M. Fysisk aktivitet och träning vid Kroniskt Obstruktiv Lungsjukdom, KOL. I Äldres Hälsa ur ett Sjukgymnastiskt perspektiv. Red E Rydwik. Studentlitteratur, 2012, page 59-76. ISBN: 978-91-44-06874-9. Upplaga 2:1.

Emtner M, Wadell K. Sjukgymnastik vid KOL. I KOL-Kroniskt Obstruktiv Lungsjukdom. Red K Larsson, Studentlitteratur, 2012, page 301-318. ISBN: 91-44-01932-7

Agencies that support the work/ Funding

The Faculty of Medicine, Uppsala University
Heart and Lung Foundation, Sweden

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Uppsala County Council
ALF
Uppsala Community
Uppsala-Örebro Research Fund
Stroke Research Fund

Behavioural Medicine and Physiotherapy

Group leader: **Pernilla Åsenlöf, Associate Professor**

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Christina Emilson, PhD student
Sara Holm, PhD student/PhD
Helena Igelström, PhD
Per Lindberg, Professor (Psychology, Uppsala University)
Susanne Pettersson, Post doc
Åsa Revenas, PhD student (Karolinska Institutet)
Maria Sandborgh, PhD (Mälardalen University)
Sören Spörndly-Nees, PhD student
Ylva Åkerblom, PhD-student

The Behavioural Medicine and Physiotherapy group is an interdisciplinary research group with a strong focus on clinical behavioural medicine intervention research. Current members include physiotherapists, nurses and psychologists associated with the Faculties of Medicine and Social Sciences. The group does ground-breaking work in behavioural medicine interventions within the physiotherapy context, showing that physiotherapy interventions benefit from including health behaviour change strategies that are theoretically based and tailored to the individual patient.

Research activities focus on issues related to adoption and maintenance of health-related behaviours (e.g. physical activity and sedentary behaviours, eating behaviours, and self-management behaviours) within a bio-psycho-social framework. The understanding of how biological, psychological and social variables interact during development of chronic conditions as well as recovery is the basis for research. Theoretical principles from social cognitive theory and learning psychology are integrated with empirical evidence on prognostic factors of each particular condition studied to create and evaluate tailored behavioural medicine interventions targeting relevant health behaviours.

A comprehensive future goal is to find optimal matches of assessment strategies, treatments, self-management procedures and individual patient profiles/characteristics. The comprehensive research question is “Who benefits from which dose and content of behavioural medicine treatment at which time?”Aspects unifying and differentiating conditions as well as patient profiles regarding prerequisites and effects of health behavior interventions are expected.

Ongoing research targets acute and chronic musculoskeletal conditions in adults and children respectively, rheumatoid arthritis, obstructive sleep apnea and overweight, schizophrenia, and ALS/Motor Neuron Diseases. Methods applied are guided by the research questions and as a consequence the group has its main expertise in clinical trials which is combined with competencies in qualitative methods and participatory designs for implementation. An important branch of our research is on how to cost-effectively implement the new and effective treatments developed in health and well care respectively.

Ongoing main projects are entitled:

1. A Behavioural Medicine Perspective on Acute Whiplash Associated Disorders

2. Development, evaluation and cost effectiveness of a treatment program with a behavioral medicine approach for adolescents with persistent pain

3. Stepped care and tailored pain management. A randomised controlled trial for the study of a stepped-care model of tailored behavioral medicine pain in treatments in primary care.

4. Health related behaviour change in obstructive sleep apnea syndrome and overweight

5. Effects of physical activity on snoring and insomnia in women

6. Integration of patients' innovations in a web-based intervention targeting physical activity. A case study among individuals with rheumatoid arthritis.

7. ALS/MNS and pain.

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2. Demmelmaier I, Åsenlöf P, Opava C. Supporting stepwise change. Improving health behaviors in rheumatoid arthritis with physical activity as the example. International Journal of Rheumatology 2013;8:89-94.

Agencies that support the work/ Funding

The Swedish Rheumatism Association; The Pain Initiative
Uppsala University Medical Faculty Caring Sciences Funding
ALF 1 (PhD-student 50%)
ALF 2 (PhD-student 100%)
KID-funding, Karolinska Institutet

Prices/ awards

Spörndly-Nees S, Åsenlöf P, Theorell-Haglöw J, Svensson M, Igelström H, & Lindberg, E. *Leisure-time physical activity predicts snoring in women: a prospective population-based cohort study over 10 years.* The 16th Nordic Sleep Conference, Copenhagen, Denmark, 2013. Awarded best poster presentation.

Speech and Language Pathology

Group leader: Monica Blom Johansson, PhD

Members of the group during 2014

Per Alm, PhD, senior lecturer
Monica Blom Johansson, PhD, senior lecturer
Martina Hedenius, PhD, lecturer
Margareta Gonzalez Lind, PhD student
Margareta Jennische, PhD, assistant professor
Cecilia Nakeva Von Mentzer, PhD

The research of the group focuses on normal and pathological speech, language and swallowing, and its neural correlates across the life span. It aims to understand the neurological bases of language development, to explore language development and communication practices in and around individuals who use graphic systems as alternative communication forms, to understand the causal mechanisms of stuttering from a neuroscience perspective, and to study psychosocial consequences of acquired language disorders.

Project 1: REMEMBR (Reading, Memory, and Brain)

Participants: Martina Hedenius (PI), Juha Kere, Martin Ingvar, Lars Nyberg, Jonas Persson. Research assistants: Maria Hällgren and Zeinab Shareef.

Developmental dyslexia (DD) is characterized by unexpected reading difficulties, in the context of otherwise apparently typical development and educational oppurtunities. The disorder, which has a strong genetic component, affects 5-8% of all children. Children with DD have characteristic difficulties with phonological aspects of both language and reading.

Although current pedagogical intervention programs for DD have been shown to enhance reading accuracy in affected individuals, they do not appear to be effective for promoting reading fluency. Slow and effortful reading typically remains a persistent trait of dyslexic readers despite considerable pedagogical efforts.

It has been proposed that the persisting reading fluency problems in DD may be partly explained in terms of abnormalities of the fronto-striatal procedural memory brain system. This brain system is involved in the implicit acquisition, consolidation and use of knowledge. Although previously considered to be important mainly for motor functions (such as learning how to ride a bicycle), it is becoming increasingly clear that this system also underlies a range of perceptual, cognitive and linguistic skills. Importantly, previous studies indicate that impairments of procedural memory may be compensated for by medial temporal lobe dependent memory functions (declarative memory). Project 1 examines learning and memory functions in children with DD in one behavioral study and one follow-up neuro-imaging study. The specific aims are as follows:

- To specify the nature of a potential procedural memory deficit in children with dyslexia (i.e. is the impairment related to initial learning, memory consolidation or automatization of procedural knowledge?).
- To clarify the relationship between procedural memory, phonological processing ability, and reading skill/fluency in children with dyslexia.
- To investigate a potentially compensatory role of declarative memory in children with dyslexia,
- To test the procedural deficit hypothesis at the level of brain function by including brain imaging technology.
- To examine the effects of genetic variation on memory and reading related skills in children with dyslexia and in typically developing children.

Project 2: Aided language skills in children aged 5-15 years - a multi-site and cross-cultural investigation

Participants: A multinational project involving about 20 countries. Margareta Jennische, and Annika Dahlgren Sandberg, Maria Larsson, Britt Amberntson (Göteborg), Stephen von Tetzchner (University of Oslo, Norway).

Augmentative and alternative communication (AAC) systems have gradually become more important as a supplement to, or a substitute for, spoken language, supporting the development of language and communication in children with little or no functional speech. Aided language development is the acquisition of aided language forms, that is, graphic systems used with communication boards or technological aids. Children's development of aided communication forms does not only suggest deficits (in spoken language), but also achievements. The children's functioning abilities are reflected both in the failure to acquire spoken language and the ability to learn aided communication modes.

The acquisition of aided communication may also provide insights into the nature of the underlying processes of language development in general. The use of aided communication is not simply a non-vocal expression of spoken language but has its own characteristics. The developmental path, from the use of pictograms and photographs via Blissymbols to orthographic script implies discontinuities in form not present in the acquisition of spoken language, and thus can help to elucidate the interaction between language meaning, language structure and language form.

The lack of crucial knowledge within the field of aided communication is the motivation for the present project. It is a joint international effort. The goal is to obtain a large corpus of utterances produced with communication aids by children aged 5-15 years, covering a large range of topics and produced in a variety of situations for different purposes, as well as

systematic knowledge of how the children interpret utterances produced by others in their own communication form. By providing this information, the present study will be a much needed reference study for research on aided communication development.

Project 3: The neurobiological basis of fluency disorders (stuttering and cluttering)

Participant: Per Alm

The causal background of speech fluency disorders such as stuttering and cluttering has long been poorly understood. This project aims to clarify the underlying causal mechanisms, to enable development of more effective methods of treatment. The work proceeds through two types of activities: (a) critical review and theoretical integration of published research data, and (b) empirical studies of stuttering and cluttering, especially focusing on neurophysiological aspects. The previous studies in this project have focused on biochemical variables, sensory gating, auditory feedback mechanisms, neuromuscular reactivity, and morphological analysis of relevant brain structures. The main focus of ongoing studies is detailed analysis of the symptomatology of stuttering, with EMG recordings and high speed video, in combination with motor threshold measurement using TMS (transcranial magnetic stimulation).
The current working hypothesis is that stuttering and cluttering are speech motor sequencing disorders, on the premotor level, affecting the ability to correctly initiate speech motor activity. The functional impairment is suggested to be related to the automatization of speech sequencing, involving the circuits from the basal ganglia to the SMA (the supplementary motor area). A possible mechanism in stuttering is that hypofunction of the left frontal lobe speech network results in compensatory right hemisphere activity. As a result, the basal ganglia contribution to speech sequencing may become bilateral, with a risk for asynchronous and dysfunctional bilateral signaling from the basal ganglia to the SMA.

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Project 4: Aphasia and communication in everyday life

Participants: Monica Blom Johansson, Karin Sonnander

This project focuses the communicative rights of persons with aphasia and their ability to be active participants in their social environment and in community. In particular the significant others of persons with aphasia are focused; how they could contribute to increase autonomy and social participation of persons with aphasia and what support they may need themselves. The aim of the project is to obtain more knowledge about how persons with aphasia, significant others and speech-language pathologists perceive the altered communication between the significant other and the person with aphasia. A second aim is to study how aphasia affects everyday life of persons with aphasia and in particular their significant others. This project also includes evaluation of an intervention in early rehabilitation phase aimed at

supplying individualised information, emotional support and communication partner training to the significant other of the person with aphasia.

Project 5: Language impairment or typical language development? Developing methods for linguistic assessment of bilingual children in Sweden

Participants: Ute Bonnacker (Professor of general linguistics, Department of Linguistics and Philology, Uppsala University), Margareta Jennische, Eva-Kristina Salameh (PhD**,** Skåne University Hospital, Malmö)

Many children in Sweden grow up in a multilingual setting. Some of these children are slow in their language development and are referred to a speech-language pathologist (SLP) for assessment and intervention. The SLP´s task is to decide whether slowness is due to language impairment (LI) or reflects typical language development in a multilingual setting. This assessment is vital for the child´s future, as untreated LI often leads to impaired reading and writing development, and other learning difficulties in school. LI implies that the child´s language development is much slower compared to non-verbal intelligence, motor skills and socio-emotional abilities. Bilinguals with LI display deficits in both languages, so both languages must be assessed, yet the tools available today are inappropriate for bilinguals as they are based on results from monolingual Swedish children. This newly started project aims to develop methods for the assessment of bilingual children for reliable diagnosis in both languages. Arabic and Turkish are in focus, as these languages are well represented in Sweden and belong to two different language groups.
Linguists and SLPs collaborate in studying the core linguistic features of typically developing bilingual children at age 4-7, with a focus on narratives. These data are then compared to samples from children with alleged LI, in order to identify clinical markers of LI in Arabic, Turkish and Swedish. The research group closely cooperates with the EU COST Action on bilingualism and LI.

Project 6: Assessing Children's Speech Processing Ability, The Listen-Say Test

Participants: Cecilia Nakeva von Mentzer, PhD

Impaired speech perception occurs in several groups of children enrolled at Speech Language Pathology and Audiological clinics. These may be children with Language Impairment (LI), attentional difficulties (ADHD), Hearing Impairment (HI) and children with (Central) Auditory Processing Disorders (CAPD). At present no standardized speech perception test in Swedish provides information about how children discriminate, identify and produce consonantal contrasts in words. It is therefore of great importance to develop diagnostic tools to obtain a reliable test procedure and enable differential diagnostics. The first data collection with the Listen-Say test indicate that the test appear to be sensitive for predicted perceptual difficulties of different consonant contrasts.

Publications 2012-2014

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12. Nakeva Von Mentzer, C., Lyxell, B., Sahlen, B., Dahlstrom, O., Lindgren, M., Ors, M., Kallioinen, P., Engstrom, E., & Uhlen, I. (2014). Segmental and suprasegmental properties in nonword repetition - An explorative study of the associations with nonword decoding in children with normal hearing and children with bilateral cochlear implants. Clinical Linguistics & Phonetics, 1-20

Reviews 2012-2014

1. Alm PA, 2014. Stuttering in relation to anxiety, temperament, and personality: Review and analysis with focus on causality. Journal of Fluency Disorders, 40, 5-21.

Agencies that support the work/ Funding

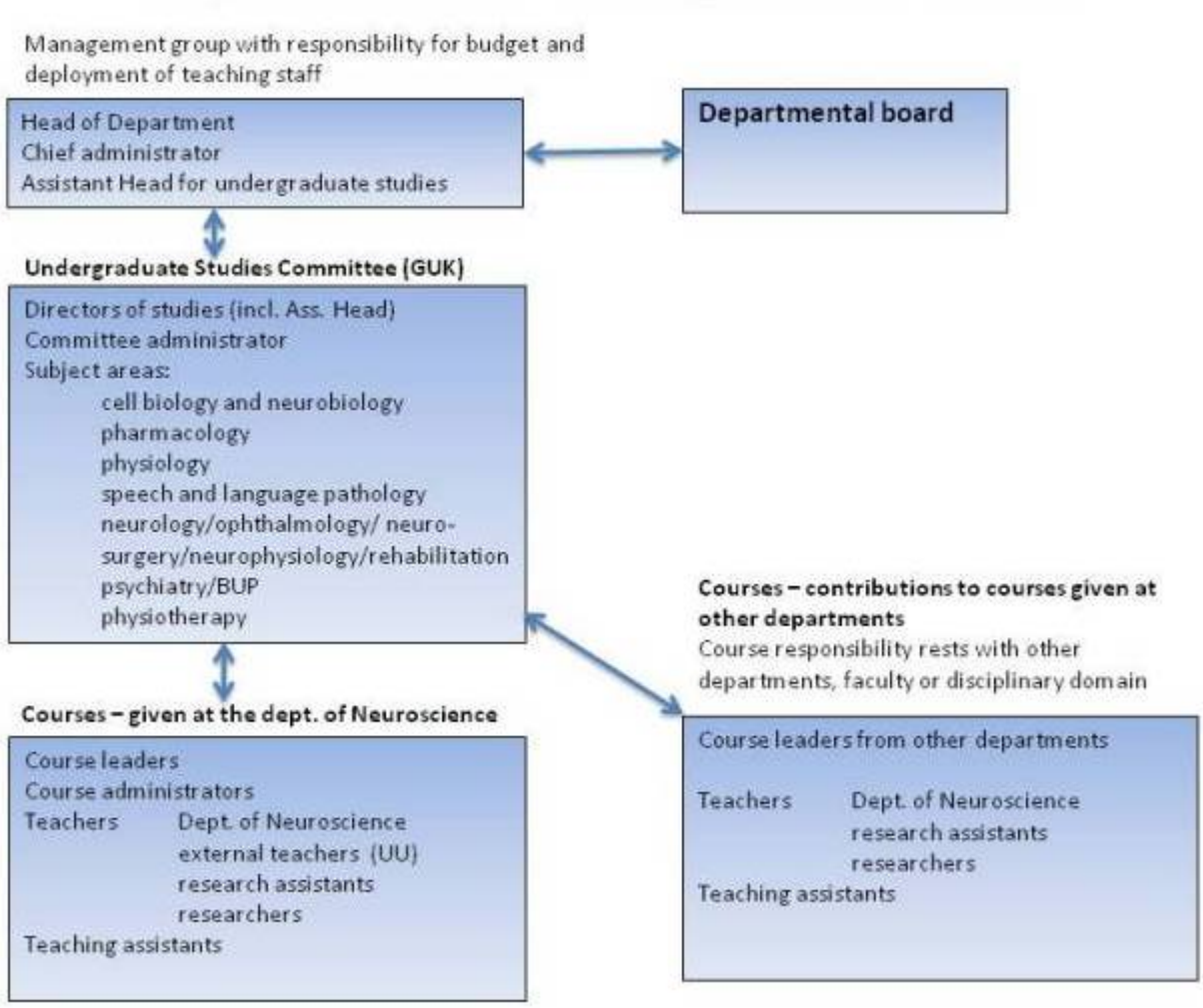
Stiftelsen Sunnerdahls Handikappfond (Project 1)
Jerringfonden (Project 1)
Stiftelsen Promobilia (Project 1)
Strokefonden (Project 4)
The Swedish Research Council, Humanities and social science (Project 5)
Faculty of Medicine at Uppsala University (Project 3)
Morins donation (Project 4)
Kungliga Vetenskapsakademien (Project 1)

UNDERGRADUATE STUDIES 2014

Markus Sjöblom, senior lecturer and researcher in Gastrointestinal Physiology, teaching physiology, for students of Pharmacy at Bachelor of Science Programme in Pharmacy.

Organization of Undergraduate studies at the Department

The organisational structure of the Department's educational efforts at basic and advanced levels was revised in 2011/12. The tasks of the directors of studies (studierektorer), course leaders, teachers and course administrators were more clearly defined in order to promote a more efficient pedagogical leadership within all levels of undergraduate teaching at the department. This revision was initiated and performed by the committee for undergraduate studies (Grundutbildnings kommitteen, GU). During 2014 this new organisation gained in strength as the role of the assistant head of department for undergraduate studies (Finn Hallböök) in drawing up the department's budget for teaching became firmly established.



Our leadership organisation for undergraduate studies is described in the figure above. The main organ for pedagogical leadership is the committee for undergraduate studies (grundutbildningskommittéen, GUK). The membership of the committee consists in the directors of studies and one administrator. The directors of studies represent seven major subject areas, as shown in the illustration above. Each sector covers several courses, and a course may fall under more than one director of studies depending on the content of its syllabus.

Members of the undergraduate studies committee in 2014:

Seven major subject areas with director of studies
- Cell biology and neurobiology (C&N)
  Finn Hallböök (convenor)
- Pharmacology (FA)
  Robert Fredriksson
- Physiology (FY)
  Olle Nylander
  Markus Sjöblom – courses at the Pharmaceutical faculty
- Speech and language pathology (LOG)
  Monica Blom-Johansson
- Neurology/opthalm./n-surgery/n-physiol./rehab. (NEUR)
  Ann-Marie Landtblom
- Psychiatry/Child and adolescent psychiatry/ nursing pr. (PSYK)
  Mia Ramklint
  (Lisa Ekselius - Nursing and medium-length healthcare pr.)
- Physiotherapy (PT)
  Lena Zetterberg

Neil Ormerod (administrator)

The committee meets regularly, on at least two occasions per semester. In addition, in 2014 a half-day teaching conference was held at the Psychiatry building on 22nd August for all involved in teaching at the department. The conference focussed on forms for examination with guest speakers from KUUP, the unit for Quality Enhancement and Academic Teaching and Learning (Geir Gunnlaugsson) on examination in general and IMBIM, the Department of Medical Biochemistry and Microbiology (Catharina Svensson) on computer-based written examinations, as well as the Department's own Olof Nylander on innovative forms of examination.
A general information meeting with all members at the Department of Neuroscience was held in Decemper 2014. Information about challenges in the budgets for 2015 and 2016 was discussed and a new pedagogic award at the department *"Neuroscience award for better teaching 2015"* was announced that will be given out at the Neuroscience Day 2015.

Director of studies, course leader and course administrator

- Director of studies:
  Long-term development and planning of the educational offering, cases of cheating and resolution of disputes, introduction of new teachers.
- Course leader (block co-ordinator):
  Scheduling, planning and implementation of courses, course information, student contact, examination and grading.
- Course administrator:
  Study documentation, educational and course information (Selma, student portal), administration of current and prospective courses.

The table above presents a brief summary of the tasks for director of studies, course leader and course administrator.

List of Courses given by the Dept of Neuroscience

Programme/ Course	Course code/ course part	Course Leader	Course administrator
Within the faculty of medicine			
Medicine			
KNEP Communication and the Nervous System	3NR113	Klas Kullander	Stefan Petersson
NHoI, Neurobiology, Homeostas and Intervention	3NR137	Madeleine Le Grevès	Neil Ormerod
Clinical Medicine V	3NR008	Mia Ramklint	Gunneli Ekberg
	Neurology	Ann-Marie Landtblom	Sari Thunberg
	Psychiatry	Mia Ramklint	A.-C. Fält
	Ophthalmology	Gerd Holmström	Gunneli Ekberg
Communication and verbal communicative skills	*3FV259*	Maria Holstad/ Mimmie Willebrand	A.-C. Fält
Biomedicine			
CMB - Cell and Molecular Biology	3MU123	Finn Hallböök	Karin Nygren
VBE - Tissue Biology with Embryology	3MU122	Finn Hallböök	Karin Nygren
Neurobiology	3MU132	Klas Kullander	Neil Ormerod
Comparative medicine	3MU142/3MU143	Madeleine Le Grevès	Neil Ormerod
Master's programme in biomedicine			
Advanced Neurobiology	3NR600,	Bryndis Birnir / Zhe Jin	Karin Nygren
Nya mål för läkemedel - identifiering och utvärdering	3NR380	Helgi Schiöth	Karin Nygren
Masterprojekt i biomedicin	3MU215	Henrik Ring	Karin Nygren
Research training in biomedicine and laboratory animal science	3NR730	Madeleine Le Grevès	Neil Ormerod
Nursing			
Omvårdnad och medicinsk vetenskap inom psykiatrisk vård	3PS040	Josefin Bäckström	A-C Fält
Specialist nursing			
Psykiatri	3PS300	Kristina Haglund	A-C Fält
Omvårdnad I	3PS301	Kristina Haglund	A-C Fält
Omvårdnad II	3PS302	Kristina Haglund	A-C Fält
Fördjupning	3PS303	Kristina Haglund	A-C Fält
Examnsarbete spec ssk	3PS304	Kristina Haglund	A-C Fält
Speech and language pathology			
Anatomi, fysiologi, patofysiologi	3LG020	Elena Kozlova	Anki Gustafsson
Logopedens yrkesroll I	3LG110	Nadina Laurent	Anki Gustafsson
Logopedens yrkesroll II. Rösten. Terapeutiskt förhållningssätt.	3LG111	Sofia Ögefeldt	Anki Gustafsson
Barnlogopedi I, Störningar i tal-, språk- och kommunikationsutveckling.	3LG210	Maria Krüger-Vahlquist	Anki Gustafsson
Klinisk barnlogopedi I. Avvikande tal- och språkutveckling,	3LG610	Maria Krüger-Vahlquist	Anki Gustafsson
Logopedi vid störningar i språk-, läs- och skrivutveckling hos barn i skolåldern.	3LG217	Martina Hedenius	Anki Gustafsson
Klinisk logopedi vid störningar i språk-, läs- och skrivutveckling.	3LG621	Maria Krüger-Vahlquist	Anki Gustafsson
Logopedi vid medfödda sjukdomar och skador i nervsystemet.	3LG214	Monica Blom Johansson	Anki Gustafsson
Klinisk logopedi vid medfödda sjukdomar och skador i nersystemet.	3LG619	Maria Krüger-Vahlquist	Anki Gustafsson
Logopedi vid röststörningar.	3LG215	Sofia Ögefeldt	Anki Gustafsson
Klinisk röstlogopedi. Funktionella och organiska röststörningar,	3LG613	Maria Krüger-Vahlquist	Anki Gustafsson
Nervsystemets sjukdomar och skador hos vuxna	3LG024	Per Alm	Anki Gustafsson
Talavvikelser. Stamning. Huvud/halscancer. Dövas och hörselskadades tal.	3LG403	Per Alm, Sofia Ögefeldt, Cecilia Nakeva von Mentzer	Anki Gustafsson
Logopedi vid förvärvade sjukdomar och skador i nervsystemet.	3LG216	Monica Blom Johansson	Anki Gustafsson
Klinisk logopedi vid förvärvade sjukdomar och skador i nervsystemet.	3LG620	Maria Krüger-Vahlquist	Anki Gustafsson
Logopedens yrkesroll III. Muntlig presentation. Terapeutiskt	3LG112	Nadina Laurent	Anki Gustafsson

förhållningssätt

Forskningsmetodik	3LG501	*Viktor Granvald (Psychology)*	Anki Gustafsson
Klinisk kurs, talavvikelser. Stamning	3LG615	Maria Krüger-Vahlquist	Anki Gustafsson
Logopedens yrkesroll IV. Logopedens roll i vården. Juridik	3LG113	Nadina Laurent	Anki Gustafsson
Examensarbete i logopedi - magisternivå	3LG503	Per Alm, Monica Blom Johansson	Nadina Laurent
Valbar kurs, klinisk fördjupning	3LG616	Monica Blom Johansson	Anki Gustafsson
Valbar kurs, teoretisk fördjupning	3LG617	Monica Blom Johansson	Anki Gustafsson
Physiotherapy			
Fysiologi	3SG098	Svante Winberg	Stefan Petersson
Grundläggande anatomi	3SG038	Ann Månsson	Stefan Petersson
N motorik	3SG075	Ewa Wenngren	Stefan Petersson
Fys akt/inakt	3SG076	Johanna Holmbäck	Stefan Petersson
Teoretisk ämnesfördjupning	3SG085	Cathrin Martin	Stefan Petersson
VFU neurologiska funktionsstörningar	3SG036	Camilla Ekwall	Stefan Petersson
VFU vid smärta	3SG096	Christina Emilsson	Stefan Petersson
Beteendemedicin 2	3SG097	Pernilla Åsenlöf	Stefan Petersson
Biomek/funk	3SG039	Jonas Olsén	Stefan Petersson
Smärta	3SG037	Cecilia Norrbrink	Stefan Petersson
Neurologi	3SG069	Dag Nyholm	Sari Thunberg
Sjukgymnastik inkl vfu neurologiska funktionsstörningar	3SG036	Camilla Ekwall	Stefan Petersson
Pediatrik	3SG086	Eva Gåve	Stefan Petersson
Somatisk (med vfu)	3SG027	Johanna Holmbäck	Stefan Petersson
Profession, kunskap och lärande	3SG028	Ann Sundbom	Stefan Petersson
Vet met I	3SG087	Sara Holm	Stefan Petersson
Rehabilitering	3SG081	Margareta Emtner	Stefan Petersson
Vet met II	3SG091	Mikael Andersson	Stefan Petersson
Hälsa	3SG072	Ann Månsson	Stefan Petersson
Äldrevård	3SG068	Marie Sandström	Stefan Petersson
Uppsats	3SG090	Karin Hellström	Stefan Petersson
Valbar VFU	3SG029	Helena Ekbrink	Stefan Petersson
Rehabilitering av äldre	3SG024	Karin Hellström	Stefan Petersson

Within the faculty of pharmacy

Pharmacy (bachelor's programme)			
Fysiologi	3FF112	Olof Nylander	Stefan Petersson

Within the disciplinary domain of science and technology

Bioloyi/Molecular biology			
Neurobiology	1BG207	Malin Lagerström	Neil Ormerod
Civil engineer chemistry/technology			
Fysioi&mol. cellbiol	3FF158	Olof Nylander	Stefan Petersson

Elective courses

Within the faculty of medicine

Psykotraumatologi	3PS038	Per-Olof Michel	A-C Fält
Medicinens historia	3NR501	Eva Ahlsten	Stefan Petersson
Laboratory Animal Science	3FD130	Madeleine Le Grevès	Neil Ormerod
Hjärnan - funktioner, sjukdomar och mysterier I	3NR201	Klas Kullander	Stefan Petersson
Hjärnan - funktioner, sjukdomar och mysterier II	3NR202	Klas Kullander	Stefan Petersson
Psykiatri	3PS050	Caisa Öster	A-C Fält

Barn, unga och trauma	3PS051	Per-Olof Michel	A-C Fält
Fördjupningskurs inom neurosjukvård	3NR009	Karin Skoglund	Sari Thunberg
Projektarbete i logopedi	3LG511	Per Alm	Nadina Laurent
Examensarbete i logopedi - magisternivå	3LG512	Per Alm	Nadina Laurent
Examensarbete i logopedi - masternivå	3LG513	Per Alm	Nadina Laurent
Fördjupningsprojekt i logopedi	3LG515	Per Alm	Nadina Laurent
Fördjupningsprojekt i logopedi	3LG514	Per Alm	Nadina Laurent
Evaluation of Scientific Reports, Methods and Statistics	3LG516	Per Alm	Nadina Laurent
Klinisk handledning	3LG927	Maria Krüger-Vahlquist	Anki Gustafsson
Blissymbolics 7,5	3LG944	Maria Krüger-Vahlquist	Anki Gustafsson
Blissymbolics 3	3LG943	Maria Krüger-Vahlquist	Anki Gustafsson
Beteendemedicin	3SG048	Pernilla Åsenlöf	Stefan Petersson
Idrottsmed	3SG007	Charlotte de Belder Tesséus	Stefan Petersson
VFU		Ann Sundbom	Stefan Petersson
Rehabiliteringsmedicin	3NR401	Staffan Stenson, psykolog	Sari Thunberg

Within the faculty of pharmacy

Humanfysiologi	3FF117	Markus Sjöblom	Stefan Petersson

Laboratory courses

Fördjupningskurs i genetisk utvecklingsbiologi	Several		Karin Nygren
Fördjupningskurs i neurofarmakolog	Several		Karin Nygren
Fördjupningskurs i neurovetenskap	Several		Karin Nygren

Programmes at the Dept of Neuroscience

Programme in Biomedicine

The bachelor's programme in Biomedicine (Kandidatprogrammet i Biomedicin) has approximately 43 students per year with a total of 128 over its three years.

The Biomedicine Programme teaches the biology of the human body from the smallest molecule to the functions of the whole organism, and the complex brain in heath and in disease. The curriculum of the Biomedicine programme underwent substantial revision during 2013 and as a result several new or updated courses were given by the department in 2014. Four courses in the Bachelor’s programme were given from our department and a fifth course is boing planned for: Cell and Molecular Biology (new 2015) (course leader Finn Hallböök/Henrik Ring, 15 hp), Tissue Biology with Embryology (revised) (course leader Finn Hallböök, 15 hp), Neurobiology (new 2014) (course leader Klas Kullander/Jörgen Jonsson/Malin Lagerström 10 hp) and the course on Experimental animal welfare. This last course in laboratory animal science was given twice, once in the spring term following the old programme (course leader Madeleine Legreves, 3 hp) and once in the autumn term as part of the revised programme (5 hp). The department has also a major participation in the physiology course (Olle Nylander/Markus Sjökvist, 16,5 hp). A new course in Pharmacology and medicinal chemistry is being planned for the fall of 2015 (Robert Fredriksson/Dan LArhammar). The courses in Neurobiology and Experimental animal welfare will be given in English 2015 and will be open for external applicants.

Assurance of quality

The educational quality of the programme is continuously assessed: Course- and programme syllabus, course evaluations, communication skills, mentor support, professional identity and exam project reports are regularly reviewed. Course evaluations are used as a basis for revising courses. These course evaluations are summarised by two student representatives. Good points, bad points and suggestions for improvements are presented, and a discussion with the course leader follows. The results of evaluation are further discussed in the programme committee. In the mentor system senior students may act as mentors and are reimbursed for tutoring students studying for re-exams. To strengthen their professional identity and employability, students pay visits to different companies. The form of examination for the degree project was revised, following advice from the Pedagogic Unit, in order to ensure that it meets the criteria for the Swedish Higher Education Authority's evaluation. The program is headed by the programme committee for Biomedicine (PKB). Department of Neuroscience has representatives in the committee including Finn Hallböök, Malin Lagerström, Madeleine Legrevés, and Henrik Ring.

Development of teaching and learning

“Professional training” with practice in oral presentation, discussion techniques, giving feed-back, writing short reports as well as scientific papers. These training progresses throughout the different courses during subjects covered in the curriculum. The seminars are given by invited experts and cover extra-curricular topics. The overall aim of the project is to increase the employability and general proficiency of the students.

Internationalization

The programme has exchange agreements with universities in several countries, for instance Denmark, Portugal and UK as well as a pharmaceutical company in England for exam projects. America and Australia are the most popular countries and most students choose universities in English-speaking countries.

Broader recruitment

Students are very much engaged in activities related to PR for the programme, such as recruiting new students and making the programme known among future employers and students. There is an “Ambassador” project in which biomedical students visit different schools to give a presentation of the program. They also participate in educational fairs.

The Master Programme in Biomedicine

The Department hosts the international Master Programme in Biomedicine, which started in 2010. The programme is intended as an extension of the Bachelors Programme in Biomedicine and was conceived and planned by the Programme Committee of the Biomedicine Programme. Lina Thorvaldson, from the Department of Medical Cell Biology, is programme coordinator and Karin Nygren is the administrator for the programme. The courses in the first year are given by several different departments in the medical and pharmaceutical faculties. During the second year students can choose freely from other courses, and are able to specialize in their field of interest. They also complete a master's project in their chosen specialty. The most popular option for the second year is the Clinical Drug Development course. It is also common for students to do independent laboratory projects during this period.

There is also an option of ending the programme after a year, when students may take a one-year master's degree that fulfils the requirements for Swedish post-graduate studies.

The Master in Biomedicine is dimensioned for 30 students. The number of admitted students has varied slightly, but the most variation has been in the number of fee-paying students (between one and seven). Twenty-nine non-paying students were accepted each year in 2012, 2013 and 2014. Between two and five students each year choose to finish with a one-year master. Among the students who study two years, almost all finish the programme on time and we have very few students who drop out (one or two each year).
Of the students that have graduated from the programme so far, many have begun post-graduate studies or have been employed within life science or drug development.

The courses in the programme are also listed as independent courses taught in English; and students that are not enrolled in the master programme may be registered for these courses. Our department contributes two courses; Advanced Neuroscience (15 credits) given by the Physiology unit and Drug Target Identification and Evaluation (15 credits) given by the Functional Pharmacology unit. Other courses in the first year are Major Diseases – homeostasis and endocrine diseases (15 credits) from the Department of Medical Cell Biology, Drug Discovery and Development (7.5 credits) and Computational Medicinal Chemistry (7.5 credits) from the Department of Medicinal Chemistry. The students also have the option to study Immunology (15 credits), given by the Biology Education Centre, instead of the two 7,5 credit courses. Department of Neuroscience also coordinates the Master Theses projects.

The programme provides in-depth knowledge of some of our major diseases, as well as concerning the brain; in health and in disease. Students follow the process of developing new drugs, from finding new targets to developing the final product. The theme of the programme is: “From the ailing body and the ailing brain to the discovery and development of new drugs”. The focus of the programme is placed on research-oriented questions for application in academic research and in pharmaceutical and biotechnological industry. The curriculum includes scheduled lectures, laboratory practicals, seminars, problem-oriented group assignments, demonstrations and study visits.

Assurance of quality
During 2013 and 2014, the master programme was evaluated by the Swedish Higher Education Authority. Both the one-year master (magister) and the two-year master got criticized on several points, and a substantial work has been done under 2014 to meet the remarks and improve the programme. A programme council, with a responsibility for the continuous quality control of the programme, has been formed. Several changes have been made in the courses of the programme in the form of new lectures, seminars, laboratory practicals and assignments, and all course syllabi have been revised. There has been new lectures added to the common seminar series for all the master programme at the Medical Faculty. The organization of examination of the Master thesis projects has been revised so that there now are three subject experts examining the student theses. The instructions and criteria for the projects have been revised so that no reports should be passed unless they fulfil the stricter criteria. The importance of ethical aspects and considerations and the Society benefits of each project must be discussed as separate subjects.
Continuous quality work will proceed with meetings with the programme council and regular meetings with students in the programme, as well as course evaluations. The master programs are coordinated by the central master program committee at the faculty and our program is

represented by Lina Thorvaldsson.

Development of teaching and learning

Our teachers are recruited from amongst the teaching staff and specialists at each participating department. They are expected to follow the university policy on professional development and participate in relevant pedagogical training. Lectures in project planning and leadership, design methods, presentation techniques and research ethics are integrated in the courses during the first semester.

Over the course of the programme, some measures have been made to counteract the tendency for students to leave the programme during the second semester to pursue other studies. First of all, laboratory project courses within the programme were instigated so that students wishing to get more experimental experience did not have to take a study break, but had the opportunity to gain this experience so within the framework of the programme. These courses are also popular options during the elective period in the third semester.
Another measure was to introduce the option to study immunology during the first part of the second semester. Since many students came from a pharmaceutical background, they found that the course content of the programme during the second semester tended to overlap with courses they had already taken. The immunology course became a popular alternative and between five and eleven students take the course each year.
Students from other universities had often not taken any course in laboratory animal science, which caused problems for those wishing to complete master projects that include animal research. The university has a 4,5 credit course in Laboratory Animal Science, but that is difficult to combine with other courses - especially for the fee-paying students who are forced to pay extra, if room could not be found in the 30 credits for which they have already paid. The solution was to establish a 15 credit course, in which the Laboratory Animal Science elements are combined with a laboratory project that can be taken during the elective period of the third semester.

Internationalization

The proportion of students with an international background decreased with the introduction of the tuition fees in 2011, but remains significant. Two thirds of students registered in 2010 came from an international background. With the introduction of tuition fees in 2011, this dropped to one third, but has now recovered to between 33 and 50%. Four tuition-fee paying students were accepted in 2014. Among the 33 new students admitted in the autumn 2014, eleven had an international background (they came from Bangladesh, Germany, Great Britain, France, Greece, Romania, Sudan and China).

The Speech and Language Pathology Programme

The sixth class (LK10) of speech and language pathologist (SLP) (28 students) graduated in January and 41 new students were admitted to the program in the spring semester (37 females and 4 males).

In addition to regular courses, two courses at advanced level in ‘Sign as Alternative Augmentative Communication’ and ‘Dyscalculia, Assessment of Numeracy Skills’ were given during 2014. The diversity in background and experience among participants contributed to fruitful discussions.

Development of teaching and learning

The National meeting for education in speech and language pathology in 2014 was hosted in Stockholm with participants, teachers and students from all Speech and language pathology programmes in Sweden. The meeting discussed common problems and possible collaborations. The self-teaching course in law for SLP students, which had earlier been developed in this collaboration, was given for the sixth year in 2014.

Regarding general and subject-based professional development in teaching and learning, our teachers have attended courses in accordance with their individual development plans.

Clinical training is an important and significant part of the programme. One of our teachers is responsible for the recruitment of a sufficient number of high-quality supervisors. The high quality of the students' internships is maintained by close contact between these supervisors and university teachers. A meeting is held every year for clinical supervisors. The theme for this year was "Assessment of students during clinical placements". In addition, senior lecturer Per Alm gave an appreciated talk about "The human brain: Novel insights related to speech motor control, attention, and executive functions". About 65 clinical teachers attended the meeting.

Internationalization

The program participates in STUREN, the Stuttering Research and Education Network, involving representatives from all Nordic countries, also including Belgium. Martina Hedenius is external sensor at the SLP program at Bergen University, Norway.

Some collaboration has been undertaken with the SLP program at Turku University, Finland, with one of their students participating in our courses on different levels during the year.

In addition, four students have been doing their elective course on advanced level, 7.5 hp or part of their master thesis abroad (USA).

Broadened recruitment

Two students participated at the SACO educational fair in Stockholm. Speech and language pathology is a relatively unknown to the general public.

The Medicine Programme

A new medical curriculum was introduced in spring 2006 and a revision was introduced during 2013 - 12014 that mainly deals with the clinical semesters (7-11). The Department played a major role in the discussions and preparations for the new and revised curriculi and continues to contribute to the development of the programme through two representatives in the Program commitee. The curriculum is divided into three stages, each of them run by a study council of teachers and students, and headed by two teachers - one from a basic science department and the other from a clinical science department.

Stage 1 encompasses semesters 1-4 and has its emphasis on basic sciences in an integrative perspective with the relevant clinical sciences. Teachers from the clinical science departments regularly participate as lecturers and in classes. Stage II encompasses semesters 5 – ca 2/3 of semester 8 and has its emphasis on integrated teaching between clinical medicine and surgery. Throughout this period periods of two to several weeks are scheduled for integrated

preclinical-clinical teaching. Stage III encompasses the final part of the curriculum, i.e. semesters 8 through 11. This stage includes a 30 ECTS independent project work in accordance with the Bologna process and the rest is dedicated to clinical courses alternating with short periods of preclinical-clinical integration.

The Department's specific educational activities and teaching within the curriculum is described below in more detail. In brief, the Department is responsible for an introductory neuroscience course *(Communication, Nerves and Psyche)*, has major roles in the courses *Energy and Metabolism, Circulation and respiration* in semester 1, *Growth and Development, Homeostasis and Endocrinology*, semester 2, is responsible for *Neurobiology, Homeostasis and Intervention*, semester 3, and has an overall administrative responsibility for *Clinical Medicine V*, semester 8-9. The Department's teaching commitments in *Clinical Medicine* V include integrated preclinical-clinical neuroscience, neurology, neurosurgery, clinical neurophysiology, rehabilitation medicine, psychiatry and ophtalmology.

The Department has distinct activities also in *Clinical Medicine VI* as being responsible for an integration period with focuses on reproduction endocrinology and neuroendocrine mechanisms in gender biology, as well as a clinical course in child and adolescent psychiatry. The Department also make significant contributions to excercises in group dynamics and discussion skills, several other courses through lectures and as tutors in problem based learning sessions, laboratory classes, and the independent thesis projects.

The Physiotherapy Programme

In the fall semester of 2014 the Physiotherapy programme with curriculum 2014 (UP 14) started. Years of preparation were over and 47 students were admitted to the programme. Forty-one students graduated in the spring and 40 students in the autumn of 2014.
Twenty-eight students were registered to write the thesis of 15 credits at the one-year Master Programme.

Development of teaching and learning

During the spring semester in 2014 the process of creating a new curriculum for the whole programme continued with the aim of implementing and integrating a behavioural medicine profile in the physiotherapy courses starting in the fall 2014.
The working process of the development of UP 14 was, as earlier described and based on "co-participation" between academic staff and clinical representatives in the implementation phase. A project manager together with a project team and a steering group, selected from the teachers and staff at the unit, guaranteed the progress of the work in three phases.
Phase 1 matched a period of "planning and professional development"; phase 2 "development of curriculum"; and, phase 3 "implementation of the curriculum".
During 2014 phase 2 was completed and phase 3 started in the autumn with the first semester of the programme.
The first course in the fall semester of 2014 was totally new. The behavioural medicine concept was integrated in the physiotherapy course where the study of behaviour and movement was incorporated. A closer corporation with the Department of Psychology resulted in a new course in Psychology also with a clear behavioural approach.
The teachers in the first semester implemented new pedagogical moments in their course with increased activity-promoting forms of teaching, to encourage the students to take increased responsibility for their own learning.

In parallel with the start of UP 14 in the first semester of the program, preparations for the second semester, with start in the spring 2015, continued.

All teachers participated in an internal education course at our program about the pedagogical teaching tool “Case methodology”, arranged by Division for Development of Teaching and Learning. Two teachers also attended an additional five-day course in “How to write a Case” arranged by the Division for Development of Teaching and Learning.
All teachers in the programme were also invited to attend the educational courses, seminars and workshops offered by the Division for Development of Teaching and Learning e.g. “Students as change agents in learning and teaching”

Four teachers attended the “Teachers´ National Learning Days” in Lund for two days. The days are a national meeting for all teachers at the physiotherapy programs in Sweden, this year with the theme “Examinations”. Majority of the teachers at the program also attended the yearly “Teachers´ Learning Day” at the Department of Neuroscience with the theme “Examination: How, Why and When”?

In order to expand the competence in manual physiotherapy at the programme, one teacher attended a course in orthopedic manual therapy (OMT) with the aim to later on conquer an exam in the field of OMT.

Assurance of quality
Continued efforts towards the assurance of quality in the physiotherapy programme have proceeded during 2014. The work to assure quality in the programme included theoretical and clinical activities among the staff, evaluation of clinical training and course evaluations in every course as well as self-evaluations. The results were compiled so strengths, weaknesses and need for change in the programme emerged. However, during the year it was a great difficulty in getting response rates above 60 % in the courses on course evaluations. Regular discussions with the student groups have improved the response rates to some extent.

Clinical training
Finding trainee posts for clinical practice for our students was accomplised.
Efforts and fundings in regard to find trainee posts for a new course in semester three of UP14, coming up in the fall of 2015, had a high priority during 2014. Teachers and staff travelled to different regions (Gävleborg, Dalarna, and Gotland) as well as visited trainee posts in Uppsala, to motivate and inspire clinical physiotherapists, as well as inform about supervising, with the objective of securing trainee posts for the new course in the third semester of UP14.
Annual meetings for clinical supervisors formed part of our ongoing efforts to maintain a high level of quality in the trainee posts during 2014.
We feel that the general teaching quality in the clinics has been guaranteed during the year.

Internationalisation
The programme committee for the physiotherapy programme had stated to reduce the internationalisation efforts during 2014 due to the implementation work with the new curriculum. However, a visit to the University of Liverpool was conducted by the director of the program and the international coordinator during the year. The purpose of the visit was to create opportunities for student and staff exchanges. Seven students at the program did their elective clinical practice abroad; six students in Spain and one on Iceland.

Broader recruitment
The programme has about 40% male students. The recruitment should be extended to students with immigrant backgrounds to reflect the patient base physiotherapists meet in clinic. Our study adviser and director of studies are continuously engaged in information activities, such as those directed to high-school students.

Grants and awards
Nina Wallnor from Uppsala University Hospital and Josefin Wennberg from Habilitation Centre in Uppsala, Uppsala County, were awarded with the programme's annual award for excellent clinical teaching.

The Specialist Nursing Programme

The Specialist Nursing programme admits a total of 150 students per year, of which 15 students were in the Programme in Psychiatric Care, based at the Dept. of Neuroscience, in the spring of 2014 and, 18 students were admitted in the autumn semester. In the one-year programme in Psychiatric Care efforts have been made over several years to attract a greater number of students. The application rate is somewhat dependent on the labour market, for example as regards the opportunities for nurses to take paid leave.

The programme provides in-depth knowledge of psychiatry and mental health as a medical science, but is primarily concerned with psychiatry and mental health as caring sciences. The focus of the programme is placed on the diversified knowledge base necessary for a specialized nurse in a modern health-care environment, with incorporation of the international research field.

Assurance of quality
The evaluation of the programme is on-going with course evaluations, evaluations of clinical training and evaluation of different parts of education. Changes to the programme are made in collaboration with teachers, students and staff at the unit. The results of evaluation are further discussed in the programme committee. In 2013 the programme have been evaluated according to the parameters laid down by Swedish Higher Education Authority (the Swedish National Agency for Higher Education). During 2014 work has been done in order to adjust criteria for examination procedures according to recommendations from the Higher Education Authority.

Development of teaching and learning
Clinical examinations (OSCE’s) of professional competence in nursing, at an advanced level, have been used in the programme for several years. Since 2013 we have developed a more standardized approach in the station-based examination. Main focus is on assessment of communication skills, as this is one of the most central competences in psychiatric nursing. Assessment measures and checklists were re-designed in order to facilitate and get a more reliable assessment of the learning outcomes. In addition, the group remodelled and developed scenarios with the intention to create pedagogical models with two different levels and different complexities in the examination (semester I and II).

Clinical training
Trainee posts for clinical practice for the students have been arranged, with a preference for placements in the region of Uppsala and Stockholm. Students perform 10 weeks of clinical

practice during the programme. The teachers' work together with five clinical psychiatric specialist nurses employed as head clinical supervisors at the University Hospital, Department of Psychiatric Care. They are responsible for the quality of clinical practice, and they make practical arrangements in order to help students to attain their learning objectives. Information, education and motivation for the clinical supervisors are a recurrent part of quality assurance in clinical practice. We arrange meetings for the supervisors in Uppsala every semester, presenting information on the curriculum, syllabus and learning outcomes for the students and arranging different lecturers. One of our aims is to only have clinical specialist nurses at an advanced level as supervisors.

Broader recruitment

All teachers are continuously engaged in information activities directed to nurses at a basic level in clinical practice.

The Nursing Programme

The Nursing programme admits a total of 230 students per year of which the course *"Omvårdnad och medicinsk vetenskap inom psykiatrisk vård 7.5 hp"*.

The programme provides knowledge of psychiatry and mental health in medical as well as caring sciences. The focus of the programme is placed on the knowledge base necessary for a nurse at a basic level in a modern health-care environment, with incorporation of the international research field.

Assurance of quality

During 2014 lecturers and seminars were arranged for the teachers at the unit and clinicians in the hospital involved with, and teaching in, the programmes at the unit. Focus has been on curriculum, course syllabus, learning outcomes, examinations, assessments and pedagogical discussions. The evaluation of the programme is on-going with course evaluations, evaluations of clinical training and evaluation of different parts of education. Changes to the programme are made in collaboration with teachers, students and staff at the unit. The results of evaluation are further discussed in the programme committee. The course has, over several years, been one of the highest rated in the Nursing Programme. The course leader works together with the teachers in the nursing programme in order to develop pedagogical strategies and to adjust the course to the overall design of the nursing programme.

Development of teaching and learning

It is a challenge to acquaint students with psychiatry and psychiatric care in the short time available. There are two examinations relating to the theoretical education and one of them, an oral individual examination has been further improved during 2014. A more stringent assessment guide for teachers, and a detailed reading guide for students are now in use.

Clinical training

Students undertake two weeks of clinical practice during the course. The teachers' work together with five clinical psychiatric specialist nurses employed as head clinical supervisors at the University Hospital Department of Psychiatric Care. They are responsible for the quality of clinical practice, and they make practical arrangements in order to help students to attain their learning objectives. Information, education and motivation for the clinical supervisors are a recurrent part of quality assurance in clinical practice. We arrange meetings

for the supervisors in Uppsala every semester, presenting information on the curriculum, syllabus and learning outcomes for the students and arranging different lecturers. One of our aims is to only have clinical specialist nurses at an advanced level as supervisors.

Broader recruitment
Teachers are engaged in information activities arranged by the Nursing Programme.

Elective courses

The department offered a wide range of elective courses in 2014, touching on topics ranging from Laboratory animal science to Medical history as well as Neuroscience, Drug targeting and development and Physiology. English was the language of instruction for some of these courses, including Laboratory animal science and the advanced level courses in neuroscience and drug targeting.

Both the physiotherapy and speech and language pathology units gave a number of elective courses aimed at students wishing to further their professional development. The most popular of these was offered by the unit for physiotherapy in Sports Medicine and Sports Rehabilitation.

In 2014 the department also offered courses in psychiatry aimed at professionals working in related disciplines, such as social work. These courses are greatly valued by professionals working in the field.

The department also offered individually-tailored laboratory-based courses. These courses are valuable for students who wish to develop expertise in scientific research and laboratory techniques.

Teaching by Units in the Department

Developmental Genetics

During the past year the following lecturers and PhD students have participated in the teaching of neurobiology for biomedical, biology and pharmacy students:

***Lecturers*:** Klas Kullander, Malin Lagerström, Sharn Perry, Katarina Leao, Richardson Leao, Christiane Peuckert, Atieh Tafreshiha, Samer Simwani
Supervisors of practicals and seminars: Bejan Aresh, Henrik Boije, Samer Simwani and Sharn Perry.

Staff at the Unit have course leader responsibility for the following courses:

Communication and the Nervous System (KNEP), 5 hp, the Medicine Programme: Klas Kullander took on responsibility for this course in the Medicine programme's first term from Håkan Aldskogius. Approximately 120 students each term .learn about the fundamental organisation of the nervous system. The course consists of lectures, demonstrations, lab practicals, and case-based seminars, with a written examination at the end.

Neurobiology, 10 hp, the Biomedicine Programme: New for 2014 the course is given once per year (second period of fall semester) as an integrated part of the Biomedicine programme. 35-45 students attend the course on each occasion. The course is given in Swedish. Klas Kullander is course leader, with assistance from Jörgen Jonsson. The course consists of lectures, demonstrations, lab practicals, oral and written exams, and seminars.

Neurobiology, 15 hp, Biology Programme of the Faculty of Science and Technology: The course is given once per year (first period of the spring semester) and attracts 20-30 students. The course is given in English and approximately one third of the students are usually exchange students. Malin Lagerström is the main organizer of the course. The course consists of lectures, demonstrations, practicals, oral and written exams and seminars.

Elective course: Exploring the brain I and II, 7.5 hp
Klas Kullander, with assistance from Sharn Perry, is responsible for these popular evening courses, which offer an introduction to issues in neuroscience to interested members of the general public.

Several lectures are given in other courses such as, Cell and Molecular Biology (Biomedicine programme) and Physiology for Pharmacy students (neurobiology).

Lectures are also given at the Advanced Neurobiology master's course.

Developmental Neuroscience

The undergraduate teaching by staff at the unit for Developmental Neuroscience for 2014 took place mainly within the courses: Growth and degeneration (ToD, T2) Medicine programme 2nd semester, medical embryology section (2,5 weeks 100% 115 students); Cell and Molecular Biology in the Biomedicine programme, 2nd semester; Tissue biology with Embryology in the Biomedicine programme, 3rd semester.

Finn Hallböök was course leader for the two courses in the Biomedicine bachelor's programme, as well as the human embryology block within the ToD-course in the Medicine programme.

Bachelor programme in Biomedicine:
Cell and Molecular Biology 15 hp
During 2014 a new version of the course in Cell and Molecular Biology was launched. The curriculum was revised and problem based learning and case-based methodology was introduced. An examination of practical skills in laboratort technique was used to asses the skills of the students. The new course worked well and got overall good evaluation but several parts may be improved during 2015.

Tissue biology with embryology 15 hp
The Tissue biology with Embryology biomedicine course is given in collaboration with Departments at BMC: IMBIM and Med Cell Biology. Within this course, embryonic development is used as a primer for understanding the establishment of specialized tissues in the vertebrate embryo.

Medicine programme:

Growth and degeneration (ToD) 16,5 hp

The embryology block within the ToD-course in the Medicine programme spans 2.5 weeks and covers human embryology and basic mechanisms of developmental biology. The course is given twice a year with approximately 90 students per semester. The course is part of the revised medicine programme and hosts one case-based seminar. In addition to the lectures in embryology, we exercise supervision responsibility for 3 seminars and six case-based seminar groups per semester.

Other courses:

Several lectures are given in other courses such as Experimental Animal research, Neurobiology for both the biomedicine programme and the medicine program, and the Masters course in Neurobiology.

Assurance of quality:

Biomedicine programme courses are subject to a web-based student course evaluation. In addition to the formal and anonymous evaluations we have scheduled an informal discussion at the end of the course where the structural and pedagogic organization is brought up. These discussions are very useful and informative.

Functional Pharmacology

Medicine Programme: In the Medicine Programme we are responsible for the course Neurobiology, Homeostasis and Intervention (T3, 20.5 hp). Here Madeleine Le Grevès is course responsible and Robert Fredriksson is director of undergraduate studies in pharmacology. This course is given twice a year with around 90 students each time. Personal at the unit have lectures in pain and analgesia as well as vascular pharmacology, PBL cases, seminars, and we organize exams.

We are also responsible for a 3 hp integrative course in the medical program which integrates clinical and preclinical aspects of neuropharmacology and related subjects. Here Robert Fredriksson is responsible for the course and this course is given once per semester.

In the Medicine Program we are also participating in the courses Homeostasis and Endocrine Regulation (T2, 8.5 hp) where we have PBL cases and seminars. We also teach in the course Integration VII (4.5 hp, T8) where we are responsible for the preclinical parts.

Biomedicine: In the Master's programme in Biomedicine we are responsible for the course Drug Target Identification and Evaluation in Neuroscience (15hp) with Helgi Schiöth as the responsible person. This course runs entirely within the unit with a few invited lecturers.

In the Biomedicine programme, we are responsible for the course Comparative Medicine (3,5hp), with Madeleine Le Grevès acting as course leader. The course is given yearly for approximately 40 students and provides theoretical knowledge and practical skills in laboratory animal science. The course teaches legislation concerning the use of laboratory animals, laboratory animal ethics, biology and welfare of laboratory animals, experimental techniques, planning, execution and publication of animal experiments and alternatives. Handling and common invasive techniques of rats and mice is mandatory.

In the Biomedicine programme we are also share the responsibility with the department of medical chemistry for the course “pharmacology with medicinal chemistry”, 12 hp, with Robert Fredriksson as course leader. This is a new course which will be held for the first time in autumn 2015.

We also participate with lectures on G Protein Coupled Receptors, transporters, synaptic transmission, neurotransmitters and cardio vascular pharmacology in other courses in the program.

Medical History

The aim is to introduce knowledge about medical history within the Faculty of Medicine and Pharmacy by lectures and seminars for medical students, by initiating research projects within medical history, and by offering elective courses in medical history. Eva Ahlsten and Lars Oreland teach, every half year, medical and pharmacological history to medical students, term three. Besides that, every half year all medical students, during their term three are shown the exhibitions at a free guided tour at the Medical History Museum. The guides are Henry Johansson, Bertil Karlmark, Lars Oreland and Mats Westman. Every half year, nurse students, during their term one, are invited to a free guided tour at the museum. The guides are Eva Ahlsten, Urban Josefsson and Bertil Karlmark. Pharmacist students visit the museum twice a year to learn *ex tempore*-making by a pharmacist, Anders Uppfeldt.

Elective course in Medical history, 7,5 p
The fifth course in Medical History was performed during spring 2014. Like 2013 Eva Ahlsten was the leader of this course. The teachers were doctors, a pharmacist, senior researchers and academic teachers (listed above). The lectures were given at the Medical History Museum in Uppsala. Every lecture was followed by a short visit to the exhibition rooms where the students were shown those exhibition cases and apparatuses that are connected to the subject of the lecture. The subjects of the course, besides an introduction of common medical history, were psychiatric history and psychopharmacological drugs, epidemics and vaccinations, the increasing importance of genetics, the history of surgery, midwifery, the history of alleviation of one´s pain and the history of resuscitation, the history of childhood leukaemia, the history of insulin, the portraits of the world famous doctors Olof Rudbeck and Carl von Linné and their great importance in the history of medicine. Twenty students attended the course.

Pharmacology

The unit for Pharmacology's major teaching commitments are in the programmes of Medicine and Biomedicine, and primarily concern pharmacology, neurobiology and endocrinology.

In the *Medicine Programme*, our main teaching is in the courses Homeostasis and Endocrinology (T2, 8.5 hp) and Neurobiology, Homeostasis and Intervention (T3, 20.5 hp). Our teaching includes lectures, seminars, laboratory practicals, and examinations. The unit is responsible for an integration course on T9 (1.5 hp), spanning the fields of endocrinology, neurobiology, and gender aspects. All of these courses are run once every semester.

Numerous lectures are given in other courses (including other faculties) at undergraduate and graduate level, particularly lectures concerning the distinction between science and pseudoscience but also various aspects of neurobiology.

Exam and degree projects and advanced level courses are supervised for students in biomedicine, medicine, biology, pharmacy and engineering as well as international exchange students.

Physiology

During the past year the following lecturers and Ph.D. students have participated in the teaching of physiology for medical, biomedical, civil engineering and pharmacy students:
Lecturers: Bryndis Birnir, Zhe Jin, Karin Nordström, Olof Nylander, Markus Sjöblom and Svante Winberg, Sergiy Korol
Ph.D. Students: Amol Bhandage, and Omar Babateen.

In the ***Medicine Programme*** we teach biophysics, cardiovascular, endocrine, gastrointestinal and neural physiology. We also participate as case supervisors in different courses. Ph.D. students participate as supervisors in the laboratory course for medical students. We have responsibility for the following subjects: Membrain potential (T1), ergometry test on bicycle (T1), refraction (T3), nystagmus (T3), neurological examination (T3), temperature regulation (T3), and electrophysiology (T3).

In the ***Biomedicine Programme*** we teach cardiovascular and gastrointestinal physiology. We have responsibility for the following student laboratory subject: Ergometry test on bicycle and temperature regulation.

In the ***Physiotherapy Programme*** Svante Winberg is the course leader responsible for teaching a course in physiology, in which both Olof Nylander and Markus Sjöblom participate extensively.
For ***Pharmacy students***, 180 + 130 per year, Master of Science programme in pharmacy (12 hp): We teach sensory and basic neural physiology, respiratory, endocrine and gastrointestinal physiology. We have responsibility for the laboratory classes: Spirometry. Bachelor of Science program in pharmacy (7.5 hp): We teach sensory and basic neural physiology, cardiovascular, respiratory and endocrine physiology. We have responsibility for the following student laboratory subjects: Blood pressure and ECG, dissection of sheep heart and spirometry.

Other Programmes: Physiology for civil engineers (6 hp), 15 students per year, we teach sensory and basic neural physiology, cardiovascular, respiratory, endocrine and gastrointestinal physiology

Course leader of Advanced course in human physiology (15 hp), 50 students per year. We teach sensory and basic neural physiology, cardiovascular, respiratory, endocrine and gastrointestinal physiology. This course contains 5 cases and the following laboratory subjects: neurological examination, nystagmus and temperature regulation.

Neuroanatomy

Functional Neuroanatomy for ***the Medicine programme,*** 200 students per year: The unit participates with lectures in functional neuroanatomy, and as PBL tutors, in Neurobiology, Homeostasis and Intervention (T3, 19,5 hp) and Clinical Medicine V (T8, 25,5 hp). The unit is also responsible for demonstrations in human brain anatomy (T3) and for the development and revisions of two PBL cases during the course Neurobiology, Homeostasis and Intervention.

Speech and Language Pathology programme: The unit is responsible for an integrated course in Anatomy and Physiology (T1, 6 hp) ca 35 students per year,. The focus of the course is in neuroscience, and the unit is responsible for lectures and for demonstrations in human brain anatomy.

Physiotherapy programme: The unit participates with lectures and group teaching in neuroanatomy, ca 100 students/year, during their first year course in Basic Anatomy.

Additional teaching: The unit gives lectures on functional neuroanatomy in the independent course Neurobiology (ca 20 students per year, 15 hp) at the Faculty of Science and Technology. The unit also gives lectures in Regenerative Neurobiology and Neuroplasticity in the master program course Advanced Neurobiology with Diseases of the Brain (ca 30 students, 15 hp).

Clinical Neuroscience Units

(Neurology, Neurosurgery, Neurophysiology and Rehabilitation Medicine)

An introduction in the clinical neurosciences is given during preclinical training, integrated with basic sciences such as neurobiology and neuroanatomy. The main course in clinical neurosciences takes place at semester 8/9 during clinical training. The course in clinical neurosciences consists of lectures, case discussions, seminars, practical training and individual supervision of students. The core curriculum in clinical neurosciences for medical students is based on national guidelines, which are defined by the Swedish network for teachers in neurology.

Undergraduate education with course leader responsibilities

1) Clinical neuroscience for Medical students, 180 students per year
The course in clinical neurosciences is part of Clinical Medicine V (comprising 25.5 hp), which is an integrated course in clinical neurosciences, ophthalmology, psychiatry and otorhinolaryngology. Mia Ramklint (psychiatry) has been the responsible teacher for Clinical Medicine V during 2014.
Course leaders: Anja Smits/Ann-Marie Landtblom (neurology); Per Enblad (neurosurgery), Kristin Elf (neurophysiology) and Christer Tengvar (rehabilitation medicine).
Block leader for neurology/neurosurgery/neurophysiology/rehabilitation medicine: Anja Smits

2) Neurology for students in Physiotherapy, 40-50 students per year

Dag Nyholm has been course leader for a two week- course (3 hp) in neurology for physiotherapists during 2014.

Undergraduate education with no course leader responsibility
Neurology is involved in undergraduate teaching at several other courses/programmes, such as: *Medicine programme (T3, T6, T9, 180 students per year),* lectures on "Muddy Points", "Neurological Examination", "Acute Neurology" for residents (AT-läkare) are given by Håkan Askmark, Eva Kumlien, Johan Zelano, Jimmy Sundblom; *Speech and Language Pathology programme (30 students per year),* lectures in neurology have been given by Paul de Roos and Anja Smits (3hp); *Biomedicine programme,* Johan Zelano lectured in neurology*; Nursing programme,* Jon Forsman, Paul de Roos and Johan Virhammar lectured neurology.

Ophthalmology

The Medicine programme: Ophthalmology is taught in an integrated course, Clinical medicine V, covering ophthalmology, ear-nose-throat, psychiatry, and neurology, neurosurgery and neurophysiology.
Teaching in ophthalmology includes lectures, seminars and clinical training/practice. Clinical training is organized at the ophthalmology clinic at the Uppsala university hospital and additionally at ophthalmology clinics in regional hospitals around Uppsala, to assure a good clinical exposure for the students. During the clinical training, the student cycles through a 1.5 week clinical rotation including auscultation with a consulting senior ophthalmologist, auscultation in vitreoretinal surgery, auscultation in cataract surgery and student consultation under the supervision of a qualified specialist in ophthalmology. There are also three multidisciplinary seminars taught together with specialists from departments of ear-nose-throat, psychiatry and neurology. At the end of the course, there is a practical and a theoretical examination, respectively.
Two 30 credit projects were tutored
Lars Malmqvist, RapiCSF - A fast test spectral contrast sensitivity, Medicine programme, UU, 130427
Jenny Sandström, Tablets as a vision aid for elderly with age-related macular degeneration, Medicine programme, UU, 140425

The Biomedicine Programme: Ophthalmology is taught during one day. The teaching includes lectures.
SK-courses: SK-courses are national courses, constituting a mandatory part of the national curriculum for specialist training in Sweden with participants from all specialist clinics in Sweden. Ophthalmology at Uppsala university contributes to national Ophthalmology training with the SK-courses Practical optics and Paediatric ophthalmology.
Practical Optics: The course covers physical characteristics of light, effects of light and laser on the eye, geometrical optics and ophthalmic instruments. Thirty-seven lectures are scheduled over the course of one week. The course includes practical training with optical instruments used in clinical ophthalmology in three half-day sessions. At the end of the course, there is an examination seminar.
Paediatric ophthalmology and strabismus: The course covers aetiology, diagnosis and treatment of diseases in paediatric ophthalmology, as well as strabismus in adults and children. There are several seminars and case presentations, in addition to traditional lectures. There is also practical training of students with patients.

Additional teaching: Ophthalmology also contributes with lectures on specific topics in the nurse specialist education, the orthoptist education and the masters program at the Department of Neuroscience.

Assurance of quality

For each course in the Medicine and Biomedicine Programmes, clinical and the theoretical training are separately evaluated by the students in writing.

The SK-courses are evaluated by the national evaluation scheme required by the national Swedish residents' educational organisation, IPULS, and by specific evaluation that covers the content and the teaching of each lecture.

Psychiatry

(Psychiatry and Child and Adolescent Psychiatry)

Medicine programme: The unit of psychiatry has course leader responsibility for teaching psychiatry during *Clinical Medicine V*, at semester 8-9, and course leader responsibility for teaching child and adolescent psychiatry during *Clinical Medicine VI*, at semester 9-10. We also teach the subjects communication skills and medical psychology. These subjects are part of the course *Professional Skills and Communication*, that continue through the whole programme. Within this course we give lectures and provide practical training at semester 1, 3, 4 and 10. Finally, we give solitary lectures at different courses, such as about neurotrauma at the introductory neuroscience course *Communication, Nerves and Psyche*, at semester 1, and about neuropsychological development, at the course *Growth and Development* and *Homeostasis and Endocrinology* at semester 2, and about emergency psychiatry during *Emergency Treatment II*, at semester 11.
Nursing programme: The unit for Psychiatry is responsible for the mandatory course "Nursing and Medical Science within Psychiatric Care" at semester 4.

Specialist Nursing programme in psychiatric care: The unit for psychiatry is responsible for the specialization in Psychiatric care within the specialist-nursing programme, 60 credits.

Physiotherapy programme: One week is allocated to psychiatry, consisting in lectures.

Biomedicine programme: As part of the course *Diseases – Clinical Survey* we teach psychiatry during one week each year.

Speech and Language Pathology Programme: As part of the course *Nervous System Disorders in Adults* we teach psychiatry during one week each year

Freestanding courses: We have a distance-learning course in *Psychiatry*, 15 credits, that has become very popular, with more than 200 applicants each year.

Assurance of quality

Our teaching is conducted in accordance with the Uppsala University pedagogic programme. We use pedagogic methods that aim to activate the students, both Problem Based Learning (PBL), case-methodology and seminars for reflection; and our teachers are educated in working with these methods. A lot of effort has been put into strengthening of the constructive alignement between goals, teaching methods and examinations. We use

studentevaluations as a basis for revising and developing our courses and pedagogical methods.

Development of teaching and learning

During the 2014 further efforts were made to improve teaching and learning
These efforts included:

- Pedagogic education of teachers and clinical tutors.
- Producing web-based educational materials, with lectures and interactive learning tasks, as a complement to other teaching and as a web-based course.
- Working with examination forms. During 2014 we introduced, at the medicine programme, a clinical examination, based on a psychiatric consultation role-play with an actor. We have developed two Objective Structured Clinical Examinations' (OSCE), in the Specialist Nursing programme.
- We have developed three Inter Professional Learning (IPL) tasks for students from the medicine, the nursing and the specialist nursing programmes.

Clinical training

Medical and nursing students had their clinical training at the University hospital, Division of psychiatry.