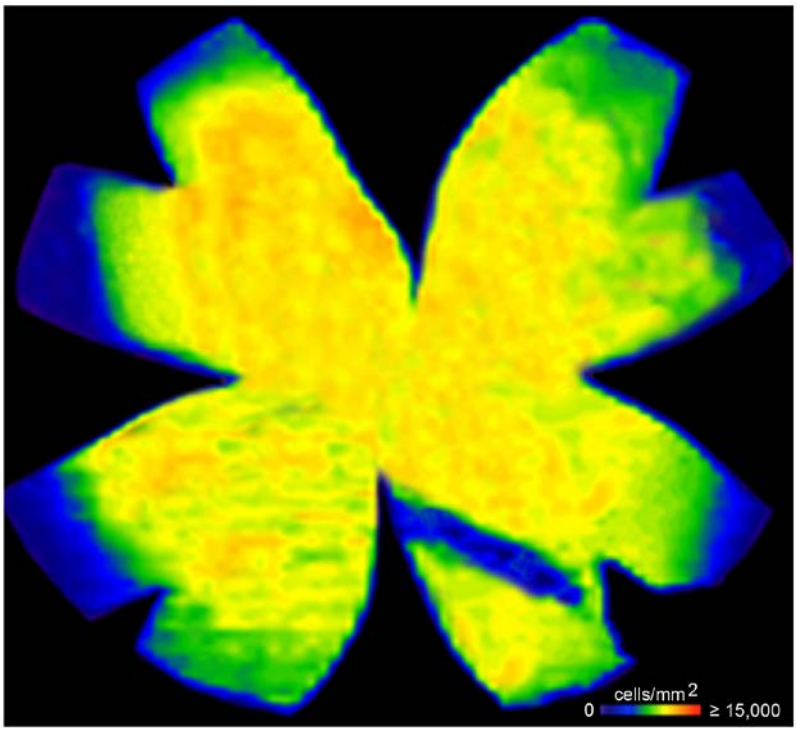
Annual Report

2015

Department of Neuroscience
Uppsala University



Cover Picture:
"Isodensity map of Brn3a$^+$ retinal ganglion cells on whole-mount post- natal day 4 chicken retina"

Photo captured by Caridad Galindo-Romero and edited by Mohammad Harun-Or-Rashid, Developmental Neuroscience

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INTRODUCTION

The activities of the Department of Neuroscience at Uppsala University Faculty of Medicine continue to cover a broad range of basic and clinical research as well as education about the nervous system. During 2015 the Department had around 170 employees excluding PhD students, postdoctoral fellows and clinically active researchers. In total approximately 300 people are active at the department. More than one-fourth of the staff is of overseas origin, enhancing the Department's international profile. Moreover, the clinical research groups engage numerous clinicians; these are employed by the University Hospital, but have their teaching and research affiliated to the Neuroscience Department. The pre-clinical research groups are concentrated within the facilities of Uppsala University Biomedical Center, while clinical research groups are distributed in different buildings in the main University Hospital campus including the House of Psychiatry, which from 2015 also offer space for Child and Adolescent Psychiatry.

The Department of Neuroscience is the result of a merger of 14 independent departments in 1998. One prime purpose of forming a joint Department of Neuroscience, from several preclinical and clinical neuroscience-oriented departments, was to strengthen interactions within neuroscience research in the clinical and preclinical disciplines in Uppsala. With time and despite different academic cultures in administration, teaching and research, we now are of the opinion that the Department has been able to consolidate a unified organization, and found synergies in teaching and areas for cooperative research, without losing the identity of each clinical and preclinical discipline.

Research

In the Department's effort to focus its activities it was decided to identify and support strategic research areas of common interest and significance: i) to build upon already existing strong and promising research areas; ii) to build workable bridges between preclinical and clinical research; and iii) to create opportunities for innovation by bringing together research groups from a wide range of disciplines. The importance of conceptual focus on strategies, combined with pro-active measures by the Department is identified as being important for strengthening the scientific impact, increasing national and international recognition as well as for increasing success rates in the competition for major national and international funding.

Despite substantial cut-backs in national funding we were awarded nearly the same amount of external grants as previous years, offering good hope of continued success in our research for the years to come. The Department of Neuroscience is one out of twelve Departments in the disciplinary domain of Medicine and Pharmacy. During the year 2015 we increased our research activities from 10.8 % to 11.2 % of the total activity estimated within the Disciplinary Domain and the financial result for the research sector was in large balanced as reviewed.

The Department has faced challenges when three group leaders were appointed positions at other departments and moved both their groups and research from the Department. It is of course enormously satisfying when members of the Department are able to get prestigious positions against national and international competition and we wish our former Department colleagues all the best luck and that this will open up for extended collaborations. We acknowledge that the Department must be a dynamic arena and that we must work as a

stepping stone for continued careers of our staff and students at all levels. In this perspective we are particularly pleased to see that two of our young colleagues who are active at the department were granted the prestigious *"Young investigator grant/Unga forskare"* from the Swedish Research Council.

Information and Department retreats

The annual "Neuroscience" day with information and scientific presentations was as usual held in March, to spread information and support intra departmental contacts. The topics were research at the department and how to write a winning grant application. As usual newly recruited researchers presented themselves and their research and the event ended with a banquette. The newly inaugurated pedagogic award "*Neuropriset för bättre lärande*" was awarded for the first time.

In August the Department again held a local one-day Uppsala retreat, this time at the new Hotel von Kraemer in conjunction with the new national resource Skandion Clinic for proton beam cancer therapy. The spectacular building formed an inspiring setting for this one-day event focusing on Department organization and leadership with connection to the shift of head of the Department that occurred later in October 2015.

The annual Teaching conference "*Lärarhalvdag*" was also held in August 2015. The half-day conference invited all staff involved in teaching, both teachers and course administrators, and focus was on examination and criteria-based evaluation of students. The successful meeting was held in the main auditorium of the new House of Psychiatry.

The media presence of the Department's researchers has been high and daily updates regarding the Department's activities in various areas have continued to be presented on the Department website during 2015. These updates are often based on internet searches, mainly in national and international media websites, of material published elsewhere on the activities of the Department's scientists and teachers in the community. This news service has become popular for increasing in-house information on the external activities of the Department. The 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.

Undergraduate and Graduate Education

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 2015, amounting to 17 % of the total budget. The Department's courses for medical students in 2015 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 on integrating basic and clinical sciences.

The Department has extensive responsibilities within the Physiotherapy and Speech Pathology and Therapy programmes. The Physiotherapy has adapted a revised curriculum and launched a new version of the program during 2015, where Behavioural Medicine is integrated with Physiotherapy. The Department has also considerable commitments within the

Biomedicine, Nursing and Pharmacy programmes, and plays 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, which was given for the sixth time in the autumn of 2015. This Masters programme has been developed by the Department in collaboration with other departments within the medical and pharmaceutical faculties and is one of the most appreciated Master programs at the faculty with a high international popularity. It attracted more than one third of international tuition fee students that were also successful in achieving study-stipends in completion among both national and Uppsala University stipends. The program has a high success rate with as many as 33 out of 36 students who received their Master Degree during 2015.

In total we educate more than 600 full-year student equivalents at the Department and 15 students received their doctoral degrees at the Department during 2015. Of these, 9 were males and 6 females, 7 students were from the clinical research areas and 8 students were from the preclinical research area.

Conclusions

The year 2015 has continued as a fruitful but challenging period thanks to the work of the qualified and dedicated staff of the Department. Our continuing efforts to increase cross-collaborations of research in a supportive departmental milieu and to facilitate teaching as well as administration have been particularly rewarding.

Uppsala, February 21st 2016

Ted Ebendal, PhD
Professor (emeritus Oct 1st 2015)
Head of Department

Finn Hallböök, PhD
Professor
Head of Department (from October 1st, 2015)

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Bryndis Birnir, teacher representative (from 150701)
Cecilia Yates, representative for technical/administrative personnel
Bejan Aresh, graduate student representative (to 150930)
Sören Spörndly-Nees, graduate student representative (from 151001)
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Karin Nordström, student representative (to 150930)
Frida Axén, student representative (from 151001)
Jan-Erik Borg, student representative (from 151001)

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Director of undergraduate studies

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Mia Ramklint
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DISSERTATIONS 2015

Botling, Taube, Amelie: Ophthalmology, *"Molecular and epidemiological studies on eyes with pseudoexfoliation syndrome"*.

Eriksson, Anders: Functional Pharmacology, *"Functional and Molecular Characterization of Centrally Expressed Genes Associated with Obesity"*.

Henrik Johansson: Physiotherapy, *"Exercise induced breathing problems in adolescents"*.

Krishnan, Arunkumar: Functional Pharmacology, *"Evolution of the G protein-coupled receptor signaling system: Genomic and phylogenetic analysis"*.

König, Niclas: Regenerative Neurobiology, *" Reconnecting the CNS and PNS with Stem Cell Transplantation"*.

Lagman, David: Pharmacology, *"Evolution of vertebrate vision by means of whole genome duplications: Zebrafish as a model for gene specialisation"*.

Lövenhag, Sara: CKF Västerås, *"Substance use in relation to psychiatric symptoms and psychosocial adversities in clinical and community samples of Swedish adolescents."*.

Nilsson, Emil: Functional Pharmacology, *"Genome wide methylation analysis and obesity related traits"*.

Nyholm, Lena: Neurosurgery,*"Quality systems in neurointensive care"*.

Päären, Aivar: Child and Adolescent Psychiatry, *"Long-Term Health Outcome of Adolescent Mood Disorders, Focus on Bipolar Disorder"*.

Solstrand, Dahlberg, Linda: Functional Pharmacology, *"Assessment of Function, Structure and Working Memory in Adolescents with a Recent Diagnosis of Eating Disorder"*.

Trolle, Carl: Regenerative Neurobiology, *"Motion vision processing in fly lobula plate tangential cells"*.

Vahlberg, Birgit: Physiotherapy, *"Physical Functioning, Body Composition and Exercise in elderly community-living individuals with stroke"*.

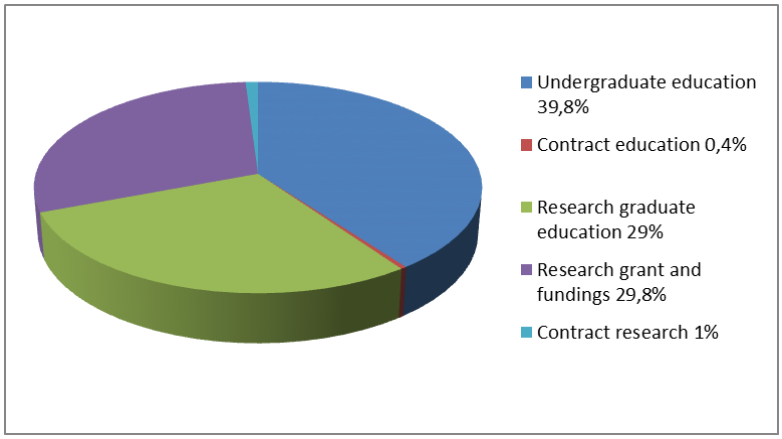
Wan, Saudi, Wan, Salman: Physiology, *" Role of Melatonin, Neuropeptide S and Short Chain Fatty Acids in Regulation of Duodenal Mucosal Barrier Function and Motility "*.

Åkerblom, Hanna: Ophthalmology, *"Retinal morphology and function in prematurely-born children at school age"*.

Finance 2015

Total revenues 2015: 152 656 000 Swedish krona

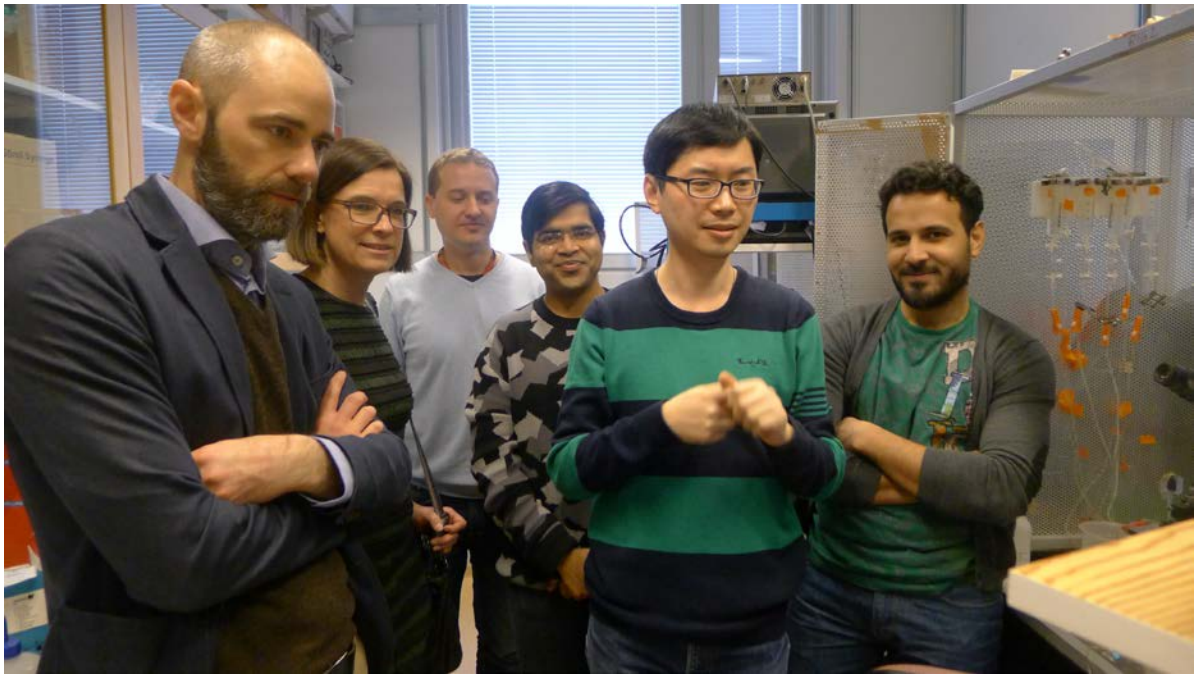
Undergraduate education 39,8%	60 815
Contract education 0,4%	561
Research graduate education 29%	44 293
Research grant and fundings 29,8%	45 447
Contract research 1%	1 540
	152 656



Research grants and funds: 45 447 000 Swedish krona

Name	Research grants KKR
Vetenskapsrådet	17119
FORMAS	2131
Socialstyrelsen	2216
STINT	414
Hjärnfonden	3196
Barncancerfonden	300
Kungliga vetenskapsakademin	2100
Beijerstiftelsen	738
Stiftelsen Major Gösta Nyholm	4662
EU	4358
Biogen	800
AFA försäkring	593
Diabetes Wellness	812
Jeanssons stiftelser	500
Fredrik och Ingrid Thurings stiftelse	500
Hållsten	813
Åhlén-stiftelsen	1120
svenska parkinssonförbundet	370
Selanders stiftelse	450
Åke Wibergs stiftelse	300
other	1 955

SCIENTIFIC REPORTS



Zhe Jin, second from right, presents results from Bryndis Birnirs research group Molecular Physiology och Neuroscience to Fredrik Sjögren and Anna Hemlin from the Brain Fundation, In the background; Sergiy Korol, Amol Bhandage and Omar Babateen, also from the group Molecular Physiology och Neuroscience. Link to the research group: http://www.neuro.uu.se/forskning/fysiologi/molekylar_fysiologi_och_neurobiologi/. Uppsala University, BMC.

Clinical Neurology & Psychiatry

Clinical Neurology

Group leader: Anja Smits, Professor

Members of the group during 2015

Amalia Feresiadou, MD
Andreas Tolf, PhD student
Anja Smits, Professor
Anne-Marie Landtblom, Professor
Atle Melberg, Associate Professor (passed away in November 2015)
Birgitta Jakobsson-Larsson, PhD student
Dag Nyholm, Associate Professor
Elisabet Westberg, PhD student
Eva Kumlien, Associate Professor
Håkan Askmark, Adjunct Professor
Imad Halawa, MD PhD student
Ingela Nygren, MD PhD
Inger Boström, PhD
Jan Fagius, Associate Professor
Joachim Burman, MD, PhD
Johan Virhammar, MD, PhD
Johan Zelano, MD PhD
Krisztina Szalisznyo, MD Psychiatry
Kenney Roodakker, PhD student
Madelen Braun, MD
Makrina Daniilidou, PhD
Maria Zetterling, MD PhD
Marina Senek, PhD student
Paul de Roos, MD
Per Olov Lundberg, Professor em
Peter Grenholm, MD
Peter Mattsson, Associate Professor
Shala Berntsson, MD, PhD
Sten-Magnus Aquilonius, Professor em
Stergios Papadimitriou, MD
Svante Wallmark, PhD student
Tamador Elsir, PhD
Torsten Danfors, MD, PhD
Valter Niemelä, PhD student

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, low-grade gliomas and sleep are studied in collaboration with other centres.

Research groups:

Epilepsy

Members of the group: Torsten Danfors, MD, PhD, Imad Halawa, MD, PhD-student, Eva Kumlien, associate professor, Peter Mattsson, associate professor, Stergios Papadimitriou, MD.

Epilepsy is a common and serious disorder of the central nervous system, with a prevalence of approximately 0,5-1 % 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 co-medication with SSRI-type antidepressants. In a separate study, cardiological problems in persons with epilepsy, as a collaboration with the University of Linköping, are analysed.

Focal epilepsy – clinical characteristics, prognosis, prevention and search for biomarkers.
We are studying a cohort of patients with newly onset epilepsy Uppsala County. Data is 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 Transcranial Magnet Stimulation (TMS)
We are applying TMS 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.

After the sudden death of Atle Melberg in November 2015, the Clinical Neurogenetics group does not longer exist in its former state. Atle who has been the driving force of this group for more than 20 years, is immensely missed by many of us as a colleague, a close friend and an excellent clinical scientist.

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, PhD student, 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, in collaboration with pharmaceutical industry. The latest development are a dose dispenser for microtablets of levodopa and an intestinal gel with levodopa/ entacapone/carbidopa. 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, Andreas Tolf, PhD student, Evangelos Katsarogiannis, MD, 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) which was introduced to Scandinavia as a treatment for MS by our group. Since then more than 100 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 follow up of Swedish MS patients, diseases free survival was 68% at five years. Further work is currently being done to describe outcome of these patients.

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. Further studies are being made to explore the mode of action of HSCT.

Studies of MS epidemiology are performed, firstly 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. Analysis of occupational exposures and hormonal factors are now being planned at the international level.
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. The frequency of patients with MS lacking oligoclonal bands, an interesting subtype, are studied in the Swedish Multiple Sclerosis register, with start in Uppsala.
An imaging project is also started, evaluating the role of synthetic MRI in MS, including also a project with studies of unspecific white substance lesions in demyelination and ischemia.

Identification of biomarkers for patients with brain tumors and tumor-related seizures

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.

Gliomas are the most common type of primary brain tumors and consist of low- and high-grade gliomas. Low-grade gliomas in adults are called diffuse low-grade gliomas (DLGG). DLGG are tumors with malignancy grade II that constitute an “interface” between benign and malignant tumors. DLGG have an annual incidence of 1.5-1.8 per 100 000 inhabitants. In spite of a relatively long survival, DLGG will eventually develop into malignant gliomas with fatal outcome. Treatment consists of a combination of surgery, radiotherapy and chemotherapy, but the most effective therapeutic modality as well as the optimal timing of treatment is still a matter of debate. This dilemma is strongly related to the variety in natural course of disease and response to therapy between individual patients.

Overview of research activity during recent years:
1) Our clinical studies on DLGG focus on the application of advanced MRI and 11C-methionine PET for pre-operative evaluation, detection of early tumor progression and to monitor response to treatment. We are particularly interested in evaluating these results with respect to cognitive functions and epileptic seizures. We have recently developed a new method to visualize the extension of DLGG beyond radiological borders in en-bloc resected DLGG (Zetterling et al, in press). We will use this method for histological studies of tumor invasion in relation to radiological parameters.

2) Translational studies consist of affinity-based proteomics on tissue samples of high-grade glioma in correlation to response to therapy and survival, with focus on the role PROX1 (Elsir/Roodakker et al, submitted). PROX1 is a transcription factor involved in cell cycle regulation and progenitor cell differentiation. In addition, PROX1 has been ascribed an oncogenic role in several human cancers including brain tumors. Our aim is to identify predictive and prognostic biomarkers that can guide clinical decisions and, in a longer perspective, provide a ground for new biological-based treatments.

3) Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disorder characterized by retinal and CNS hemangioblastoma, pheochromocytoma, and clear cell renal

cell carcinoma. The VHL gene which is located on chromosome 3p25 and encodes for a 213 amino acid tumor suppressor protein, which is a key player in the regulation of the hypoxia response pathway and vital to tumor survival in low oxygen conditions. VEGF and other proteins in the HIF-signaling pathway are easily available and non-invasive candidates for plasma biomarkers of VHL disease. No published reports so far have shown a correlation of these proteins to prognosis or treatment outcomes in VHL disease. Blood samples of all patients with VHL disease at Uppsala University Hospital, together with relevant clinical and radiological data, have been collected since 2012. The measurements of plasma levels of relevant biomarkers are performed in collaboration with professor Lena Claesson-Welsh group at the Rudbeck laboratory and the SciLifeLab platform for solid-phase PLA, led by Dr Masood Kamali-Moghaddam.

Sleep medicine

Group leader: Anne-Marie Landtblom
Group members: Makrina Daniilidou, PhD, Inger Boström, PhD, Amalia Feresiadou MD, Simon Lidén, MD, Valter Niemelä PhD student

This group was established in Upsala during 2014 with internal collaborations with Dept of pediatrics. Dept of lung medicine and allergy and preclinical Dept of Neuroscience. We study diagnoses like narcolepsy, the Kleine-Levin syndrome (KLS) and idiopathic hypersomnia from a clinical, epidemiological and imaging perspective. We also study biomarkers in blood and CSF. The acitivities are performed in collaboration with Linköping University with input from Prof M Parttinen, Helsinki University and the group of E Mignot, Stanford. Some acitivities have connections with the national register of narcolepsy, NARK REG. Our epidemiological studies has so far concerned the occurrence of narcolepsy after Pandemrix vaccination and confirm an increased prevalence and further studies are ongoing. Imaging studies with fMRI and SPECT show interesting differences in KLS, and these studies are being later expanded to include narcolepsy. The differential diagnosing of teenagers with sleep disorders has been put in focus in speeches and articles.

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Clinical Neurophysiology

Neuromuscular Synapse

Group leaders:
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Members of the group during 2015:

Anna Rostedt Punga, Associate Professor
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Carl Johan Molin, PhD student
Evgenii Bogatikov, PhD student
Johan Widenfalk, Associate Professor

Collaborators:

The group of Prof Sonia Berrih-Aknin, INSERM, Paris, France is working together with "Neuromuscular synapse" in finding new biomarkers in MG.
Prof Amelia Evoli, Catholic University, Rome, is working together with the group on finding biomarkers in MuSK+ MG and on the preclinical model of MuSK+ MG.

Prof Markus Rüegg, Basel, Switzerland (pathophysiology of the neuromuscular synapse)
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The general aims of the research group are:

1. Elucidation of the pathogenic mechanisms underlying neuromuscular disorders, and establishment of biomarkers, with focus on myasthenia gravis (MG).
2. Development of an in-vitro neuromuscular junction (NMJ) on an electronic chip device.

Neuromuscular synapse and myasthenia gravis:

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 preclinical model of experimental autoimmune myasthenia gravis (EAMG), in the clinical setting with MG patients and on establishing an "NMJ on a chip" system.

Biomarkers

During the past year we have continued our expansion of data on circulating microRNAs in the sera of MG patients as biomarkers. The levels of the most sensitive biomarker, miR150-5p, were reduced in patients with immunosuppressive treatment. We also established the novel biomarker let7-family of miRNAs in MG patients with MuSK antibodies, which support the etiological differences between AChR antibody and MuSK antibody seropositive MG. These potential biomarkers in the sera of MG patients are important, since 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. Also, we will examine the effects in a longitudinal MG patient cohort before and after thymectomy and introduction of corticosteroids.
We have also performed a pilot study of supervised physical exercise in MG patients and concluded that the clinical course do not worsen due to moderate physical exercise. This study will be repeated in a larger cohort of MG patients to be able to draw more extensive conclusions.
Further, we have established neurophysiological parameters to assess the effects upon physical training (Molin&Punga, in press) that will be used in future studies of physical exercise in MG patients. The next step will be to evaluate the examination of neuromuscular ultrasound in trained and untrained healthy individuals to see whether muscle mass and nerve diameter are affected by high-resistance strength training.

Novel cutting-edge model systems to study diseases at the NMJ

We have been able to record postsynaptic spikes from generated muscle cells (myocytes) on a high-density electrode chip. The chip contains an array of 26.400 platinum electrodes at a density of 3265 electrodes per mm^2. A subset of 1024 electrodes can be read out simultaneously and can be stimulated through the 32 on-chip stimulation buffers. Recently, this model system was able to record large spikes along many axonal sites (Lewandowska et al, 2015). We are now expanding on this model to include motor neuron recordings, to finally reach an NMJ on a chip.

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

Development of Advanced Electrophysiological Methods

Group leaders: Erik Stålberg, Professor em.

Members of the group during 2015:

Erik Stålberg
Arne Sandberg

Collaborators:

S Nandedkar, USA
L Puuksa, Estonia
DB Sanders USA
J Kouyoumdjian Brazil
M Sonoo, Japan
Dr S Löseth, Norway

AIM: 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.

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, and a multicenter study has been undertaken. 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 reference values are published. Also, a needle manufacturer has 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.
The method for direct muscle stimulation is being evaluated in critical illness (together with Prof Larssons group, at Karolinska Institute). Data have been collected from a large group of critically ill patients to be published as a PhD thesis, Humberto Skott, Karolinska Hospital.
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). Surface EMG (neurography) from many muscles has also been tested for monitoring of ALS. This should be an easier technique than the so called MUNE methods.
A new way to obtained “normal” reference material from a large mixed group of patients, some of whom were found normal is under development. Comparison between this mathematical way and actual recordings will be made.

Abnormalities in the neurographic parameters F-waves are studied in relation to various diseases. Detailed studies of the sensitivity in carpal tunnel syndrome of different methods are in progress (with doc G Ahlsén, Örebro),

Prof em Erik Stålberg is involved in collaborations with J Navallas, Spain, S Nandedkar, USA and M Sonoo, Japan in developing new motor unit analysis techniques.
He is also involved in projects with prof DB Sanders USA and J Kouyoumdjian Brazil to improve the method of single-fiber EMG.

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Central and Somatosensory Nervous System

Members of the group during 2015

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

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.

Project 2: Transcranial magnetic stimulation in the evaluation of patients with epilepsy and brain tumors

Project leaders: Åsa Amandusson, Hans Axelson

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 initiated studies focusing primarily on different aspects of cortical excitability in healthy subjects and patients with seizures, epilepsy and brain tumors. We have developed a standardized semi-automatic method for ppTMS measurement and recently completed a methodological study comparing different ways of performing ppTMS.

Project 3: Neurophysiologic methods in intraoperativ monitoring (IOM)

Project leader: Hans Axelson, Dmitri Bouzarov

Intraoperative neurophysiology (ION) provides the surgeons with information regarding the location and function of nervous tissues such as sensor, motor and speech cortical areas and pathways. Work in progress is divided into three main topics

1) Analysis of retrospective data from motor threshold measurements during asleep supratentorial glioma surgery and determineing to what extent non-surgical factors (technical and physiological) influence the motor threshold that may produce false “warning” alerts during surgery.
2) Implementation of automatic motor threshold assessment during supratentorial glioma surgery for more time efficient and reliable motor threshold determination for both cortical and subcortical stimulation.
3) Development and implementation of additional tests of higher order cerebral functions during awake craniotomy such as memory, facial recognition and vision.

This project main aim is to provide neurosurgeons with more reliable intraoperative information on the integrity and location of “eloquent” nervous structure in the operating field in a time efficient manner.

Project 4: 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 are fairly common, especially in patients with a primary brain injury, but also in patients with, for exemple, 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 therefore we currently perform a study on this.
During 2015 we started a prospective 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 with severe sepsis 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 5: 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 nervous 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. However 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

Hermann Handwerker (1) T. Helås (2), E. Jørum (2), IP Kleggetveit (2), B. Namer(1), O. Obreja (1), K. Ørstavik (2), M. Schmelz (1), B. Turnquist (3), SG Waxman (4), C. Weidner (1).
1: Germany, Erlangen and Mannheim universities
2: Norway, Rikshospitalet and Trondheim University
3: USA, Univ. Minnesota
4: USA, Yale University

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Swedish Chapter of ILAE (Svenska Epilepsisällskapet)
Stiftelsen Epilepsifonden

Psychiatry

Psychiatry

Group leader: **Lisa Ekselius, Professor**

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Björn Milesson-Fors, PhD student
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Stefan Nasir, PhD student
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 within the Department: Lisa Ekselius (PI), Mimmie Willebrand, Caisa Öster, Josefin Sveen, Josefin Bäckström.

Collaborators: Professor Elna Marie Larsson, Department of Radiology, Uppsala University (UU), Malin Gingnell, MD, PhD, Dept of Psychology, UU, Professor Folke Sjöberg and Emelie Gauffin, MD, PhD student, 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-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. Specifically, the situation of parents of children with burns has been studied. As parent health is of vital importance for children's health, an Internet-based information and self-help programme is developed and evaluated for parents of children with burns.

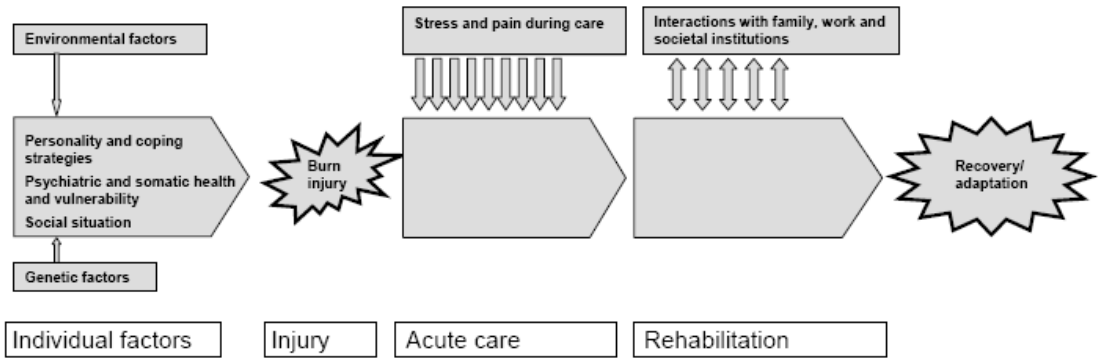

Figure 1. A model of trauma outcome.

II) Ongoing PhD projects within the "Personality and Individual Differences group"

Long-term outcome after pharmacological treatment in adult ADHD (Dan Edvinsson, PhD student);

Effect of CBT in hospital treated patients with depressive or anxiety disorders (Fredrik Folke, PhD student, med dr Per Söderberg and med dr Stefan Tungström, the General Psychiatric Clinic, Landstinget Dalarna, associate professor Timo Hursti, Dept of Psychology, UU).

Epidemiological studies of personality disorders (Efthymios Kouppis, med dr Emma Björkenstam and med dr Charlotte Björkenstam, University of California Los Angeles, Los Angeles, California, USA).

Chronic opioid treatment in chronic pain conditions: benefits and work ability versus addiction and abuse (MSc Hanna Ljungvall, professor Pernilla Åsenlöf, Dept of Neuroscience, UU, med dr Rolf Karlsten, Dept of Surgery, UU, professor Markus Heilig, Dept. of Clinical and Experimental Medicine, Linköping University).

GABA and depressive states (Louise Flood, MD student, professor Bryndis Birnir and Amol Bhandage, PhD student, Dept of Neuroscience, UU, med dr Janet Cunningham, associate professor Rpbert Bodén).

Psychiatric Epidemiology

Participants: Fotios Papadopoulos (PI), Georgios Makris, Jan Kask, Karin Tillman, Georgios Karamanis, Costas Adamidis, Mia Ramklint, Lisa Ekselius

Collaborators: Johan Reutfors, PhD and Professor Anders Ekbom, Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet; Ass. Professor, Alkistis Skalkidou, Department of Women's and Children's Health, Uppsala University; Richard White, PhD, Norwegian Institute of Public Health, Oslo, Norway; Professor Eleni Petridou, Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, Athens, Greece; Professor Dimosthenis Panagiotakos, Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

Our research focuses on epidemiological aspects of suicide, affective disorders, anorexia nervosa and gender dysphoria. We investigate predictors of both psychiatric and somatic outcomes.

Various aspects of suicide are studied using descriptive and analytical methods. Seasonality in suicides and perinatal depression is studied in particular with focus on the theoretical framework and possible clinical implications.

Retrospective register cohorts are utilized to study risk factors, mortality, comorbidity patterns and somatic outcomes. 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, Stefan Nasir, Hanna Spangenberg.

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, Professor Anna-Karin Wikström, Dept of Women's and Children's health, Assoc. professor Daniel Nowinski, Dept of Surgical Sciences, Professor Ata Ghaderi, Dept of Clinical Neuroscience, KI.

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?

Severe mental illness research

Participants: Bodén Robert (PI), Johan Bengtsson, Elin Thörnblom, Eric Clapham, Janet Cunningham, Lisa Ekselius, Eva Baghdassarian, Eva Lindström, Leif Lindström, Björn Milesson-Fors, Björn Nilsson.

Collaborators: Hans Axelson, Åsa Amandusson, Bryndis Birnir, dpt Neuroscience, UU, Erik Olsson, Department of Public Health and Caring Sciences, Elna-Marie Larsson, (Radiology), Dr Jakob Hedberg, and associate professor Magnus Sundbom, Surgical Sciences, UU, Gunnar Antoni, Dpt of Medicinal Chemistry, Division of Molecular Imaging; Caroline Wass, dpt of pharmacology, GU, Hatice Zora, SU, Associate professor Helle Kieler, biostatistician Lena Brandt, Dr Johan Reutfors, and professor Morten Andersen 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; Prof Jeff Daskalakis, CAMH, Toronto.

Our research projects encompass clinical studies as well as national register-based studies. Our projects focus on severe mental illness such as schizophrenia, bipolar disorder and

melancholic depression. In our clinical studies we investigate effect and mechanisms of different brain stimulation treatments for severe mental illness (ECT and rTMS). The assessments covers cognitive testing, brain imaging with MRI, PET as well as different neurophysiology assessment (ppTMS, NIRS, EEG with ERP, startle response, and HRV). 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 severe mental illness and the safety and effectiveness of psychotropic drug use.

Caring sciences

Participants: Lena Bergdahl, Jan-Erik Broman, Josefin Bäckström, Johan Dyster-Aas, Kristina Haglund, Lars von Knorring Agneta Markström, Christina Nehlin Gordh, Mia Ramklint, Caisa Öster.

Collaborators: Anne Berman, Department of Clinical neuroscience, Karolinska Institutet.

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

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.

II) Caring research in psychiatric care and mental health

Participants: Lena Bergdahl, Josefin Bäckström, Kristina Haglund, Christina Nehlin Gordh, Mia Ramklint, Caisa Öster.

Collaborators: 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

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 >520 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 >135 participants. This infrastructure is implemented in the psychosis department and in the ECT clinic and is linked to The autoimmune psychiatry clinic and to research projects concerning brain stimulation.

National Centre for Disaster Psychiatry (KcKP)

Participants Kerstin Bergh Johannesson (PI), Filip Arnberg, Cristina Bondjers, Martin Cernvall, Josefin Sveen, Mimmie Willebrand, Caisa Öster. Project assistants: Ida Hensler, Rebecca Altschul, Axelia Ahlund.

The National Centre 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 object 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 disasters 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, Martin Cernvall, Josefin Sveen.

Collaborators: Professors Christina Hultman and Unnur Valdimarsdottir, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet.

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 traumatic bereavement, 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. PhD student: Kristina Bondjers. Project assistant: Ida Hensler, Rebecca Altschul.

This project concerns psychological aspects of psychiatric morbidity 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 diagnosis 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. 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 symptoms of complex traumatic experiences.

Project leader: PhD Kerstin Bergh Johannesson.

Collaborators: Associate professor Doris Nilsson, associate professor Marie Wadsby, Örjan Dahlström, 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 symptoms of complex traumatic experiences. The validation was based on 781 individuals recruited from Linköping University, 83 patients from the psychiatric outpatient clinics of Akademiska sjukhuset in Uppsala and Tranås outpatient clinic and from homecoming Swedish soldiers.

Project 6. Effects of the mobile application PTSD Coach after a traumatic incident: a randomized controlled study.

Project leader: Kerstin Bergh Johannesson, PhD. Researchers: Filip Arnberg, Martin Cernvall, Josefin Sveen, Kristina Bondjers. Project assistants: Rebecca Altschul, Axelia Ahlund.

A majority of people will at some time during their lives be exposed to a traumatic incident, such as violence, abuse, threat, accidents or disasters. For some the exposure may cause the development of severe stress reactions.
Early and effective interventions can attenuate the suffering for the individual and decrease the cost for society. Access to information about common reactions, where to find support and knowledge about how to manage reactions can be valuable tools for individuals who for some reason do not have access to care.
PTSD Coach is a smartphone application which contains information about posttraumatic stress reactions, support for symptom management and information about where it is possible to seek support for help. The app has been developed by the National Center for PTSD, in collaboration with the Department of Defense's National Center for Telehealth and Technology in the United States. The American version of PTSD Coach is available for free downloading at App Store and Google Play.
KcKP has received the permission to translate and adapt the app into Swedish. A general object for the project is to increase the accessibility to evidence-based and cost effective interventions for individuals who have been exposed to traumatic incidents. The project aims to evaluate if the app can alleviate symptoms of posttraumatic stress and related unhealthiness in a Swedish population. A second object is to investigate factors that can explain and/or influence the effects of the intervention.

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Child & Adolescent Psychiatry

Group leader (temporary): Mia Ramklint, Associate professor

Members of the group during 2015:

Abdoulbaghi Ahmad, Associate prof.
Hannes Bohman, PhD
Nezar Ismet Taib, PhD student
Ulf Jonsson, Assoc. prof.
Anne-Liis von Knorring, Prof, emerita
Sandra Löfving-Gupta, PhD student
Mia Ramklint, Assoc. prof.
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Introduction

The research group in child and adolescent psychiatry is studying the development of psychopathology in children and adolescents as well as how psychopathology can be identified and treated. The research is based on a model in which biological, psychological and social risk/protective factors interact during growth and development of child psychiatric symptoms.

These risk and protective factors are studied in both epidemiological and clinical studies. Consequences of child psychiatric symptoms during adolescence are investigated through long-term follow-ups. Risk groups being studied include traumatized children and children who live in psychosocially disadvantaged environments as well as children with neuropsychiatric disorders. The research group is also studying the effect of interventions for defined risk groups. Research is conducted in both international and national collaboration with other research groups.

Experience of stress, emotional regulation and physiological stress reactions

Participants: Johan Isaksson (project leader), PhD, Vladislav Ruchkin, Assoc. professor, Mia Ramklint, Assoc professor, Frank Lindblad, Professor emeritus, Anastasia Karvouni, PhD student, Jacke Swartz, PhD

Collaborators: Kent W Nilsson, Centre for Clinical Research, Västerås, Ulf Högberg, Dept. of women and childrens' health, Helgi Schiöth, Functional Pharmacology, Dept. of neuroscience, Maria Hallerbäck Unenge, Gillberg Centrum, Gothenburg University

In this project, we study the physiological regulation and experience of stress in children. We examine how life events during pregnancy and the early years of life can influence the child's

physiological stress regulation as well as mental well-being in the long-term. We study children with attention deficit hyperactivity disorder (ADHD) and post traumatic stress disorder (PTSD) and how they experience and react to stress.

The research has shown that young people with ADHD estimate their stress as being higher than their peers. This applies especially to girls with ADHD. This is possibly a consequence of the symptoms' effects on everyday functions and/or is a result of inflexibility in the stress regulation system.

The body reacts to stress partly through the activation of the so called sympathetic nervous system, our ”fight or flight” system, and partly by a hormonal response conveyed through the pituitary to the adrenal gland where cortisol is released, called the HPA-axis. In the physiological stress response in children with ADHD, we have found an endogenous HPA-axis with lower levels of the stress hormone cortisol. An endogenous HPA-axis has previously been associated mainly with PTSD.

In our ongoing projects, we continue to explore the differences between boys and girls with ADHD. We examine the effectiveness of psychological treatment for ADHD and if treatment can minimize the perceived stress. We try to identify stress reactions related to PTSD as well as biomarkers for PTSD.

Consequences of Teenage Depression

Participants: Ulf Jonsson, Associate professor (project leader), Anne-Liis von Knorring, Professor emerita, Hannes Bohman, PhD, Aivar Pääre n, PhD

Collaborators: Tord Næssén, Professor, Department of Women’s & Children’s Health, Margareta Möller, UCF, Örebro, Inna Feldman, Department of Women’s & Children’s Health

In this long-term follow-up of depressed teenagers, we study the socio-economical effects and the consequences on mental and physical health of those who have suffered depression from an early age.

The follow-up is based on the large epidemiological survey of depression that was comprised of all the 16-17 year old high school students in Uppsala in the early 1990s. Participants were followed-up when they were 30-33 years old, and continued follow-ups are planned for the participants who are now in their 40s. Whatever consequences depression had is studied by comparing those with depression with non-depressed controls.

The research team has been able to show, among other things, that teenage depression increases the risk for worse mental and physical health in adulthood as well as a lower level of education and more psychosocial stress.

Risk factors for the development of child psychiatric problems

Participants: Vladislav Ruchkin, Associate professor (project leader), Mimmie Willebrand, Professor, Johan Isaksson, PhD, Frank Lindblad, Professor emeritus, Sandra Löfving-Gupta,

PhD student

Collaborators: 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;

In this project, we study risk factors for the development of antisocial behavior and alcohol abuse as well as examine the factors that influence this development after trauma. We study a particularly vulnerable group of children, i.e., institutionalized children, and we perform cross-cultural comparisons between children from different cultures.

Based on a bio-psycho-social model, psychopathology is developed through an interaction between biological, psychological and social risk factors. Risk factors can include genes, emotional attachment patterns, experiences of trauma and psychosocial factors such as poverty, crime and substance abuse.

Our research is characterized by a broad methodological variety, from genetic analyses to psychiatric epidemiological studies and clinical child psychiatric studies.

Children with traumatic experiences

Participants: Abdoulbaghi Ahmad, Associate professor (project leader), Frank Lindblad, Professor emeritus, Viveka Sundelin Wahlsten, Associate professor, Nezar Ismet Taib, PhD student

Collaborators:

We are studying children who have had traumatic experiences during their upbringing, their perception of these events, their perspective of trauma in relation to the perspective of adults and how they handle these experiences.

Based on a salutogenic perspective, we map the risk and protective factors for the development of post traumatic psychopathology such as post traumatic stress disorder (PTSD). We study the effect of preventative methods in risk groups and early treatment strategies for children with signs of disease. The research is carried out in collaboration with the University of Duhok in Iraqi Kurdistan, where children who have been victims of terror and war are identified, investigated and treated. Within the project, assessment instruments such as Genogram, HUTQ-C and PTSS-C were developed to assess children's traumatization and the intervention effect.

The research on childhood trauma also includes studies of sexual abuse, the psychosocial consequences of serious illnesses in childhood and how the child is influenced by an environment that is colored by their parents social and/or psychiatric problems.

Publications 2013-2015

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Stickley, A., Koyanagi, A., Ruchkin, V., Kamio, Y. Attention-deficit/hyperactivity disorder symptoms and suicide ideation and attempts: Findings from the Adult Psychiatric Morbidity Survey 2007. *Journal of Affective Disorders* 2016 Jan 1;189:321-8. doi: 10.1016/j.jad.2015.09.061. Epub 2015 Oct 22.

Agencies that support the work/ Funding

Swedish Council for Working Life and Social Research
Swedish Brain Foundation

Experimental Neuroscience

Developmental Genetics

Formation and Function of Neuronal Circuits

Group leader: Klas Kullander, Professor

Members of the group during 2015

Amilcar Reis, Post doc
Arthur Franca, PhD student
Atieh Tafreshiha, PhD student
Chetan Nagaraja, PhD student
Christiane Peuckert, Post doc
Ernesto Restrepo, Post doc
Fabio Caixeta, Post doc
Hanna Pettersson, Post doc
Henrik Boije, Post doc
Jörgen Jonsson, Post doc
Markus Hilscher, Guest scientist
Martin Larhammar, PhD student
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.
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 and two more were published in 2015, where we describe the the consequence of removing VAAT in the neuromuscular junction and in the dopaminergic system.

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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
EU FP7 Mindview
Swedish Brain Foundation
STINT

Neurodynamics

Group leader: Richardson N Leão, MD, PhD

Members of the group during 2015

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

Project 1: How brain oscillations are generated

Participants: Sanja Mikulovic, Ernesto Restrepo, George Nascimento, Richardson N. Leão

Theta oscillations is one of the most studied rhythms of the brain. However, this rhythm has wrongfully being correlate only to exploration or sleep. We have found that a much less studied form of form of theta, namely, type 2, is associated to mood. Moreover, we have found that these rhythms are generated in a part of the hippocampus that is not associated to movement. After dissecting the circuits responsible for its generation, we have modulated this rhythm using state-of-the-art optogenetic and chemogenetic methods in order to produce anxiolitic effects. These findings will serve to determine the influence of a hippocampal pacemaker on the synchronisation of limbic system. Besides, our discoveries will determine cellular targets for the control of mood disorders and will help to find targets for new anxiolitic agents.

Project 2. Mobile optical recording of neural activity

Participants: Sanja Mikulovic, George Nascimento, Richardson N. Leão

Optical methods are quickly becoming the choice for assessing activity of specific neuronal populations. The ability to identify and record from neurons during specific behavioral tasks has opened a whole new field in neuroscience. We have been developing methods using optical fibres for imaging neuronal activity (using genetically encoded activity probes). More recently, we have been working on the development of a miniaturised microscope that can be placed in the head of small animals such as mice. This novel approach will permit the study of neurons in situ while the animal freely performs behavioral tasks. These units will also be orders of magnitude cheaper than commercial microscopes. We can also assess deep brain regions with this method; hence, we will be able to study brain structures involved in Parkinsons and Alzheimers disease. In fact, we aim to assess brain regions affected by Alzheimers disease already in 2016 and study the effect of accumulation of Abeta peptides (found in Alzheimer patients) in these regions.

Publications 2013-2015

Mikulovic S, Restrepo CE, Hilscher MM, Kullander K, Leão RN. Novel markers for OLM interneurons in the hippocampus. Front Cell Neurosci.;9:201.

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Agencies that support the work/ Funding

Kjell och Märta Beijers Foundation
The Swedish Research Council

Sensory Circuits

Group leader: Malin Lagerström, Associate Professor

Members of the group during 2015

Marina Franck, postdoctoral fellow
Tianle Gao, postdoctoral fellow
Ida Waern, postdoctoral fellow
Bejan Aresh, PhD student
Fabio Freitag, PhD student
Elín Magnusdottír, PhD student
Jon Jakobsson, project student
Edda Blumel, 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 neuron, that respond to sensory stimuli e.g. heat, touch, pressure and tissue injury, and transmit 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 situ hybridization, electrophysiology, 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 is 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 additional aspects of the TRPV1 population.

Publications 2013-2015

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3. Gao T and Lagerström MC. The anti-inflammatory alkaloid *aloperine* in Chinese herbal medicine is potentially useful for management of pain and itch.
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4. 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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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.

Agencies that support the work/ Funding

Ragnar Söderberg Foundation
Swedish Research Council
The Konsul Th C Berghs Foundation
Uppsala University
The Brain Foundation
The Royal Swedish Academy of Sciences
The Olle Engkvist Foundation

Ophthalmology & Retina Biology

Ophthalmology

Ophthalmic Biophysics

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

Members of the group during 2015

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Kronschläger, Martin, MD, PhD, Ophthalmologist, Post-doc, part time
Malmqvist, Lars, Diploma of Medicine, PhD student, full time
Mar-Zoega, Gunnar, MD, MSc, Ophthalmologist, PhD student, part time
Merkoudis, Nikolaus, MD, Ophthalmologist, PhD student, part time
Sandberg-Melin, Camilla, MD, Ophthalmologist, PhD student, part time
Talibizadeh, Nooshin, MD, MSc, PhD student, full time
Yu, Zhaohua, MD, MSc, PhD student, full time

External collaboration 2015

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Löfgren, Stefan, MD, Docent, Ophthalmologist, St. Eriks Eye Hospital, KI
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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
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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, Nooshin Talibizadeh, 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, 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 undetected 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 an interactive digital visual acuity chart.

Participants: Anders Ohlsson, Christian Johansson, Svante Nilsson

Methods
Software that allows interactive visual acuity 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 20th 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 cause 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 2013-2015

Books
Manns F, Söderberg PG, Ho A Ophthalmic Technologies XXIV. SPIE Proc 2015;8930:
Manns F, Söderberg PG, Ho A Ophthalmic Technologies XXIV. SPIE Proc 2014;8930:
Manns F, Ho A, Söderberg PG Ophthalmic Technologies XXIII. SPIE Proc 2013;8567:

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ICNIRP, Stuck B, Schulmeister K, Sliney DH, Cesarini JP, Thomas R, Greinert R, Söderberg PG Icnirp guidelines on limits of exposure to incoherent visible and infrared radiation. Health physics 2013;105:74-91

ICNIRP: ICNIRP, Stuck B, Schulmeister K, Sliney DH, Cesarini, JP, Thomas R, Greinert R, Söderberg PG Icnirp guidelines on limits of exposure to laser radiation of wavelengths between 180 nm AND 1000 μm.. Health Physics, 2013; 105: 271-295

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Uppsala Läns Landsting research grants (ALF)

Paediatric Ophthalmology

Group leader: Gerd Holmström, MD, PhD, Professor

Members of the group during 2015

Eva Larssson, MD, PhD, Assoc Prof, Ophthalmologist
Dordi Austeng, MD, PhD, Ophthalmologist

Hanna Åkerblom, MD, PhD Student, Ophthalmologist
Anna Molnar, MD, PhD Student, Ophthalmologist
Dyrleif Petrusdottir, 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
Kerstin Rosander, researcher, Dept of psychology, Uppsala University
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 and geneticists (Prof Marie-Louise Bondesson and her team, Uppsala). Since 2009 - 2010 we have a 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. G Holmström is in charge of a national register for ROP, which has contributed a lot to research and improved knowledge.
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 these children in collaboration with paediatricians and psychologists. 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). Ophthalmological data on a national 6.5 year follow-up are now submitted to an American journal, and we are working on two regional projects on OCT and ERG in this group of children, in comparison with children born at term (PhD project Anna Molnar). A national follow-up at 12 years of age is about to start in March 2016.

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 has 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, was established in 2006. 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 (SNQ), 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). We have on-going projects regarding comparison of incidences of ROP during the last ten years.

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). The results of tudies on Multifocal ERG (MfERG) have recently been submitted to a scientific paper.

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

This study aimed to create a normal material in healthy children, regarding OCT and MfERG, to study the macular development during childhood. We also aimed 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. During 2015 one study on OCT in healthy children has been published in Acta Ophthalmologica(Anna Molnar et al) and one study on MfERG in Doucmenta Ophthalmologica (Anna Molnar).

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Agents that support the work/ Funding

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Gerd Holmström has got Marianne Bernadotte-medalj för mycket framstående insatser inom barnoftalmologisk forskning, 2015.

Glaucoma

Group leader: Curt Ekström, MD, PhD

Members of the group during 2015

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: Predictors for incident open-angle glaucoma in a Swedish population
Participants: Curt Ekström, Albert Alm

Background: Increased intraocular pressure, pseudoexfoliation, a positive family history and increasing age are established as the main risk factors for open-angle glaucoma in the Nordic countries, while knowledge of other potential risk factors is sparse.

Purpose: Predictors for incident open-angle glaucoma are studied in a sizeable 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. Information about incident cases is obtained by searching glaucoma case records. A specialist in glaucoma accomplishes classification of cases. Cox proportional hazards models are used to assess the relationship between potential risk factors and open-angle glaucoma.

Publications 2013-2015

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5. Ekström C, Botling Taube A. Pseudoexfoliation and cataract surgery: a population-based 30-year follow-up study. Acta Ophthalmol 2015; 93 (8): 774-777.

Agencies that support the work/ Funding

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KMA – Kronprinsessan Margarethas stiftelse for synhandikappade
Uppsala University, grants for PhD students

Retinal Stem and Progenitor Cell Development

Group leader: Finn Hallböök, PhD professor

Members of the group during 2015

Finn Hallböök, PhD professor
Henrik Ring, Med Mag PhD post doc and Adjunct
Sonya Stenfelt, MSc, PhD post doc (from Sept 2015)
Shahrzad Shirazi-Fard, MSc, PhD, post doc (early 2015)
Caridad Galindo-Romero, MSc, PhD, post-doc (January-July)
Maria Blixt, MSc, PhD student
Rashid Harun, MSc, PhD student
Minas Al-Baghdadi, Msc, PhD student
Marta Diaz-DelCastillo, Master student,
Dardan Konjusha, Master student, Research assistant.

The overall aim of our research is to understand how retinal neurons are formed during development. This knowledge is important for understanding retinal pathogenesis that leads to retinal degeneration or that triggers cell proliferation such as retinal gliosis or when the regulation of neurogenesis goes wrong and retinoblastoma develops.

We develop strategies for directing the *in vitro* development of human stem- or progenitor cells to bonafide human retina formed by 3D organogenesis. Such in vitro formed retinas serve as disease models. Such in vitro-formed 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-mammalian 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 human embryonic stem cells. We use the chicken embryo as a versatile *in vivo* experimental system that complements the human in vitro system. Furthermore, chicken is a species with an elevated regenerative capacity of injured retinal cells compared to that seen in mammals.

Project 1: Generation of retinal neurons

The project aims at understanding how early retinal neurons in the lineage of retinal 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 are now studying the role of the zinc-finger transcription factor Nolz1.
One important approach has been to establish methods for cell-specific lineage tracing and for transgene expression during embryonic development in the 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: Stenfelt, Blixt, Al-Baghdadi, Shirazi-Fard, Hallböök

Retinoblastoma is a rare childhood cancer that initiates during fetal development and is often diagnosed during the first years of life. It has features of an early cone retinal progenitor cell. Cones and horizontal cells are from the same progenitor and in animal models the cancer derives from horizontal cells. We have shown that the horizontal progenitors in the chicken retina do not activate any p53-cell cycle arrest or apoptosis in response to DNA damage. These progenitors may even perform a truncated terminal mitosis, leaving uneuploid cells that resist apoptosis. These cells in chicken retina lack the normal guard against cancer and resemble a cancer stem cell.
The overall aim of this research is to develop a human model based on the self-organising-3D-retinal cultures in vitro from human embryonic stem cells. Our chicken-based results will be translated to the human context in order to understand exactly what makes the cells prone to undergo carcinogenesis. Human ES cells with a retinoblastoma genotype will then be used for studying bonafide retinoblastoma tumorigenesis.

We have established the self-organising-3D-embryonic body cultures that produce pigmented retina but work still remains before we a proper laminated neural retina. However, we have identified the formation of the retinal progenitors cells that we hypothesize are the retinoblastoma cell-of-origin. A retinoblastoma hES cell genotype by iPSC from a patient with the familial form of Rb or by manibulating hES cells by CRISPR cas 9 - Rb loss of function. The chick work continues in parallel. We focus on the activation of p53 modulatory system in vivo and study both Rb loss of function as well as MYCN gain of function. Whole genome sequencing of retinoblastoma revealed that MYCN amplification even in the presence of wt Rb+ produces retinoblastoma. Our preliminary results show that chicken horizontal cells are less prone to go into apoptosis after over-expression of hCMYC/MYCN-T58A compared to other retinal progenitors.
Significance for childhood cancer: This project will be important to deepen the knowledge about the mechanisms of retinoblastoma carcinogenesis. Identifying the molecular mechanisms behind the cell of origin becomes increasingly important when treating children with therapeutic agents developed to target particular molecular pathways. With a deeper knowledge, we are able to aid in the development of complementary pharmacological treatments and a more successful outcome for the patients.

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

The overall hypothesis is depicted in figure 1 and addresses the observation that the outcome of injury or disease to the retina is dependent on how Müller cells respond to injury. After injury, the gliotic response of Müller cells includes de-differentiation, proliferation and depending on the species, differentiation and formation of new retinal cells including neurons and new Müller. In mammals the capacity to form neurons (the neurogenic capacity) has become limited and regeneration is much less or non-existing compared to fish, amphibians and to some extent birds, but nevertheless the mammalian Müller cells become gliotic and de-differentiate.

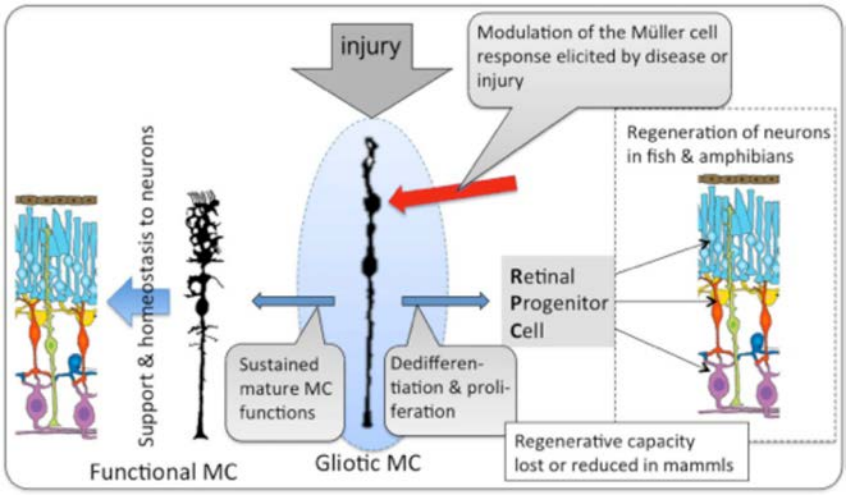

Figure 1. Injury leads to a gliotic response that may lead to de-differentiation and formation of a retinal progenitors (right blue arrow). The possibility to modulate the response (red arrow) may attenuate the de-differentiation and retain the support by mature Müller cells (left blue arrow).

The project aims at gaining control of the de-differentiation of Müller glia by the modulatory factors and signalling pathways that regulate this de-differentiation. We have found that the α2-adrenergic receptor agonist Brimonidine induces a robust negative feed-back regulation of the epidermal growth factor (EGF)-induced ERK-signalling in Müller cells. α2-Adrenergic receptor signalling therefore acts as a negative regulator of Müller cells during retinal injury and disease (Harun-Or-Rashid et al. 2015; Harun-Or-Rashid et al. 2014). The EGF receptor is an established drug-target with well-proven inhibitory or stimulatory reagents and combined with the novel mechanism of action for Brimonidine, as further investigated in this application. It may open for novel combinatory treatments of retinal disease or injury.

Our results reinforce the role for glial homeostatic functions during an injury or disease situation and the long-term outcome may be improved by reduced Müller cell- activation. Activated Müller cells become gliotic and may, in addition to attaining a progenitor role, also lose their vital homeostatic functions. The work in this proposal will forward the results that we have obtained using animal models and cells and bring it into the human cell system. We will primarily use a cell line with Müller cell characteristics as well as cells derived from human embryonic stem cells.

Project 4: Functional genetics using domestic animals

Participants: Ring**,** Shirazi Fard, 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 living among potential predators such 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

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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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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 has developed a free flight arena, which is big and bright enough for hoverflies to display conspecific interactions. By filming the flies with 2 cameras, we can reconstruct the 3D flight trajectories of flies in the arena.

We also have 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.

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

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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.*, 2015). 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 the human pancreatic islet GABA signalling. Building 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 obtain the 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 affinity for GABA is 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 an active research area.

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 Foundation

The Swedish Diabetes Foundation
The Swedish Children's Diabetes Foundation
ENABLE

Behavioural Neuroendocrinology

Group leader: Svante Winberg, Professor

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Fredrik Jutfelt, postdoc
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Laura Vossen, PhD-student
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Helen Nilsson, master student
Nikita Tjernström, master student
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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, Arshi Mustaffa, Gonzalo Andre and 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: 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: 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 4: Welfare, Health and Individuality in Farmed FISH: The WIN-FISH project

Participants: Svante Winberg[1], Leif Andersson[1], Marie-Laure Bégout[2], Ana Roque[3], Amedeo Manfrin[4], Morris Villarroel[5], Manuel Gesto[6].
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An ERA-net ANIHWA project

In modern aquaculture, fish are exposed to farming-inherent stressors that can be detrimental to animal health and welfare. However, it is increasingly clear that stress reactions are different for each individual and therefore, individuality should be included in the concept of animal welfare. Individual differences often take the form of suites of traits, or stress coping styles (SCS), where traits like sympathetic reactivity, aggression and the tendency follow and develop routines show positive relationships. In addition, these traits show a negative relationship with plasma cortisol levels and are also associated with differences in immune function. The main aim of the WIN-FISH project is to investigate the relevance of fish individuality when assessing fish welfare and performance under different culture conditions. The WIN-FISH consortium, consisting of 6 partners in 5 countries, will validate behavioral and physiological welfare indicators for sea bass, sea bream and rainbow trout at the individual and rearing unit level. This will generate new information about responses to environmental factors, knowledge that can be applied to improve husbandry and management practices. Modern recirculating aquaculture systems (RAS) related-stressors such as higher rearing densities and water quality parameters may challenge the welfare of fish. In WIN-FISH, health, welfare and production related effects of RAS rearing of sea bass and sea bream kept at different densities will be monitored. In order to account for individual variation, these studies will be performed on fish screened for SCS. Similarly, in flow through systems, health, welfare and production related effects of rearing densities will be further investigated in sea bream differing in SCS. It is also known that, in general, environmental enrichment has positive effects on animal welfare. WIN-FISH will investigate effects of environmental enrichment on rainbow trout with contrasting SCS. In an attempt to generate genetic markers for selective breeding to optimize performance and welfare of farmed Atlantic salmon, a genome-wide association analysis will be performed on salmon with divergent SCS, focusing on proactive fish differing in aggressive behavior. Finally, zebrafish will be used as a model to gain additional knowledge on mechanisms underlying SCS and aggressive behavior.

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Agencies that support the work/ Funding

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Pharmacology

Pharmacology

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Lars G. Lundin, docent, reader (lecturer) em.
Xesús Abalo, PhD, researcher
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Christos Gkolfos, project student
Gabriel Heras Arribas, project student
James Janani, project student
Joel Eggert, SOFOSKO student
Kilian Kuhn, exchange 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 involved in vision and in learning and long-term memory.
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, gene families involved in vision (such as the opsins, the light receptors) and gene families involved in learning and long-term memory (including glutamate receptors).

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: Christina Bergqvist, Helen Haines, David Lagman, 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. The effects of pancreatic polypeptide (PP) via Y4 are still obscure. 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 that are used to improve the structural model in collaboration with Dr. Hugo Gutierrez de Terán (Uppsala University). The results will facilitate drug development to reduce appetite.

Recent studies have shown that the PP receptor Y4 is associated with childhood obesity and adult body weight. We are now investigating the complicated genetics of this gene which displays both copy number variation (CNV) and single nucleotide polymorphisms (SNPs). We have recently confirmed that the gene copy number correlates with obesity.

Project 3: Evolution of vision in vertebrates

Participants: Xesús Abalo, David Lagman

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, respectively. A surprising conclusion from these comparisons is that colour vision arose before dim-light vision. We have also found specialization between duplicated genes with regard to timing and location of expression in the eye in zebrafish. Interestingly, zebrafish eyes are more complicated than those of mammals in that the zebrafish has a larger repertoire of genes. Furthermore, some duplicates differ in the circadian cycle. Thus, the genome doublings have facilitated elaboration of vertebrate vision by supplying additional gene copies that have evolved 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: Evolution of memory molecules

Participants: Helen Haines, Christina Bergqvist

Learning and long-term memory are exceedingly complex processes involving multiple types of receptors and ion channels and a large repertoire of proteins that modulate their activities. So far, most studies have used rat and mouse as model systems to characterize the molecular mechanisms. However, such complicated machineries can best be understood by taking an evolutionary approach to deduce how they have originated and become so complicated. We are therefore investigating how and when the gene duplications took place that have generated the gene families involved in learning and memory. We have already found that many of the gene families expanded in the early vertebrate genome doublings, and that zebrafish often have more gene copies than mammals. Future studies will combine phylogenetic analyses with comparisons of expression patterns in the brain, primarily aiming to compare zebrafish and chicken with rat/mouse.

Project 6: 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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Stiftelsen Olle Engkvist Byggmästare
Stiftelsen Facias

Honours

Dan Larhammar is 3rd vice president of the Royal Swedish Academy of Sciences 2015-2018 and chairperson for the the Academy's Education Committee.

Dan Larhammar organized a Wenner-Gren Symposium on "Co-evolution of receptors and ligands" in Stockholm 9-12 Sept. 2015.

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

Xesús Abalo organized the "1st Scientific Meeting" of the "Spanish Scientist in Sweden Association" celebtated in Stockholm, on April 30th 2015.

Functional Pharmacology

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

Senior leaders: Madeleine Le Grevés, Lecturer, Michael Williams, Associate prof. and Christian Benedict, Associate prof. sleep group.

Members of the team during 2015

Helgi B. Schiöth, professor,
Robert Fredriksson, associate professor,
Madeleine Le Grevés, lecturer, course leader
Christian Benedict, researcher, associate professor
Michael Williams, researcher, associate professor
Samantha Brooks, affiliated researcher
Staffan Uhlén, researcher
Sonchita Bagchi, post doc
Pleunie Högenkamp, post doc
Vanni Caruso, post doc
Mathias Rask-Andersen, post doc
Jonathan Cedernaes, post doc
Lyle Wiemerslage, post doc
Jessica Mwinyi, post doc
Arunkumar Krishnan, PhD student (defended 2015)
Sahar Roshanbin, PhD student
Olga Titova, PhD student
Sofie Hellsten, PhD student
Emil Nilsson, PhD student (defended 2015)
Anders Eriksson, PhD student (defended 2015)
Emilie Perland, PhD student
Linda Solstrand Dahlberg, PhD student (defended 2015)
Colin Chapman, PhD student
Frida Rångtell, PhD student
Nathalie Bringeland, PhD student
Sarah Voisin, PhD student
Wei Zhou, PhD student
Marcus Bandstein, PhD student
Sofia Kanders, PhD student
Hao Cao, PhD student
Andreas Johansson, PhD student, part-time
Maria Ling, PhD student, part-time
Björn Sundberg, PhD student, part-time

General: The team studies pharmacological, genetic and behavioural aspects and 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 team 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 2015: We have been very productive in 2015 with more than 30 papers published. We continued to publish papers in high impact journals during 2015. This includes papers in *Genome Med* (Voisin et al.), *Genome Biology* (De Luc et al.), *J Clin Endocrinol Metab* (Cedernaes et al.), *Mol. Endocrinol.* (Williams et al.), *Diabetes* (Cedernaes et al.), *Pharmacol Rev.* (Hamann et al.), *Brain Behav Immun* (Machado et al.), *Alzheimers Dement* (Benedict et

al.) and a comment in *JAMA Intern Med* (Cedernaes et al.). According to DIVA, this team is currently the most productive unit at the department of neuroscience considering the total impact of the published papers during the last four years. This is also evidenced by the fact that Schiöth has the highest cumulative impact of all researchers in the neuroscience department, followed by Benedict during the past 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 a high number of citations, and the total number of citations received by Schiöth HB (Google Scholar) was above 2000 during 2015. Schiöth has published 28 papers (23 original papers and 5 reviews) that have received more than 100 citations. Schiöth is on Thomson Reuters list of the worlds "*most influential researchers*" based on citations.
Grants: The unit for functional pharmacology has been very successful during year 2015 in receiving external grants. The unit had three VR-projects 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 years in 3 years. Fredriksson had also a VR-NT project grant for 0.4 mSEK/year on "Functional characterization of novel amino acid transporters". Benedict has been awarded a young researcher VR-M grant (5 mSEK; only 27 out of 320 applications were approved) and a Novo Nordisk excellence award for endocrinological research (5mDKK) to conduct studies about the role of sleep on health. Fredriksson had also a VR-NT senior researcher grant for salaries of 1.2 mSEK/year, 3 + 3 years. Cedernaes has an international post doctoral grant for 3 years or about 1 mSEK per year about sleep as well as several other smaller grants. Schiöth also has a grant at Hjärnfonden of 0.5 mSEK/year for studies on biomarkers and Benedict another for 0.5 mSEK/year for sleep research. Fredriksson had 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. AFA has granted Benedict/Schiöth 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, bioinformatics, human labs including sleep labs. 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 focusing increasingly on genetics and pathology. We have a fly (drosophilia) lab 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. Benedict has been able to build his own research group within this unit, currently including two PhD students, one medical postdoc, one master student, and several term students. Benedict utilizes a fully equipped sleep lab to study the effects of sleep and sleep deprivation on psychological and metabolic health. The team also performs 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. The molecular biology lab has well a 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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Caruso V, Sreedharan S, Carlini VP, Jacobsson JA, Haitina T, Hammer J, Stephansson O, Crona F, Sommer WH, Risérus U, Lannfelt L, Marcus C, Heilig M, de Barioglio SR, Fredriksson R, Schiöth HB. (2016) mRNA GPR162 changes are associated with decreased food intake in rat, and its human genetic variants with impairments in glucose homeostasis in two Swedish cohorts. Gene. S0378, 00106-2.

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Cedernaes J, Schiöth HB, Benedict C. (2015) Determinants of shortened, disrupted, and mistimed sleep and associated metabolic health consequences in healthy humans. Diabetes. 64, 1073-80.

Agencies that support the work/ Funding

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Åke Wikberg Foundation,
Magnus Bergvall Foundation,
Tore Nilsons Foundation,
AFA

Functional Neurobiology (Motions and Emotions Lab)

Group leader: Åsa Mackenzie, Associate Professor. Recruited as Professor in Molecular Physiology to the Dept of Organism Biology and moved the research group there June 1, 2015.

Members of the group during 2015 (January to June):

Åsa Konradsson Geuken, Researcher
Emma Arvidsson, Post doc
Nadine Schweizer, PhD student
Stéfano Pupe Johann, PhD student
Thomas Viereckel, PhD student
Julia Pedersen, PhD student
Bianca Vclek, Bachelor student

Research:
Our research interests are focused around brain functions that are important for regulating *motions and emotions* 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.*

Publications 2013-2015

1. Ethanol affects limbic and striatal presynaptic glutamatergic and DNA methylation gene expression in outbred rats exposed to early-life stress.
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Åke Wibergs stiftelse
Major Gösta Lind Minnesfond
The Swedish Research Council
ERA-NET Neuron: Mental Disorders
Uppsala University

Neuropsychopharmacology

Group leader: Erika Comasco, Ph.D.

Members of the group during 2015

Lars Oreland, Prof. em.
Jarmila Hallman, Prof.
Aniruddha Todkar, PhD student
Megha Bendre, MSc/ PhD student
Maria Vrettou, MSc/ PhD student
Simone Toffoletto, MD
Wout Boon, Erasmus student
Kristina Holmberg, MSc student
Julia Breedh, MD student
Simone Wanderoy Blemings, Bachelor

student
Sara Abdullah, Bachelor student
Avesta Saaid, Bachelor student
Gianpaolo Coscia, Bachelor student

Research during 2015 has been focused on the psychoneurobiology of psychiatric disorders, comprising:
- clinical research on gonadal hormone changes and women's mental health, using a complementary approach including genetics, endocrinology, neurophysiology and neuroimaging;
- translational research on (epi)gene-by-environment interaction mechanisms related to alcohol use disorder, including experiments with rodents as well as human population-based and clinical samples, with a special focus on the adolescence period.

Publications 2013-2015

1. Ethanol affects limbic and striatal presynaptic glutamatergic and DNA methylation gene expression in outbred rats exposed to early life stress. Vrettou M, Granholm L, Todkar A, Nilsson KW, Wallén-Mackenzie Å, Nylander I, Comasco E. *Addiction Biology* (2015)
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9. Treatment with serotonin reuptake inhibitors during pregnancy is associated with elevated corticotropin-releasing hormone levels. Hannefors A-K, Hellgren C, Schijven D, Iliadis S, Comasco E, Skalkidou A, Olivier JDA, Sundström-Poromaa I. *Psychoneuroendocrinology* (2015)
10. Henrik Sjöbring and the concept of individual psychology in psychiatry. Oreland L. *Ups J Med Sci* (2015)
11. Exploring possible association between DβH genotype (C1021T), early onset of conduct disorder and psychopathic traits in juvenile delinquents. Isaksson J, Grigorenko EL, Oreland L, Af Klinteberg B, Koposov RA, Ruchkin V. *Eur Arch Psychiatry Clin Neurosc* (2015)
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HTTLPR, and MAOA-uVNTR. Nilsson KW, Comasco E, Hodgins S, Oreland L, Åslund C. *International Journal of Neuropsychopharmacology* (2014)

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15. Haplotype tag single-nucleotide polymorphism analysis of the vesicular glutamate transporter genes in severely alcoholic women. Comasco E, Hallman J, Wallén-Mackenzie Å. *Psychiatry Research* (2014)
16. Emotional fronto-cingulate cortex activation and brain derived neurotrophic factor polymorphism in premenstrual dysphoric disorder. Comasco E, Hahn A, Ganger S, Gingnell M, Bannbers E, Oreland L, Wikström J, Epperson CN, Lanzenberger R, Sundström-Poromaa I. *Human Brain Mapping* (2014)
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19. Serotonin transporter genotype by environment: studies on alcohol use and misuse in human and non-human primates. Todkar A, Nilsson KW, Oreland L, Hodgins S, Comasco E. *Translational Neuroscience* (2013)
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21. Three-way interaction effect of 5-HTTLPR, BDNF Val66Met, and childhood adversity on depression: a replication study. Comasco E, Åslund C, Oreland L, Nilsson KW. *Eur Neuropsychopharmacology* (2013)
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23. The father of botany on the flora of mental disorders. Oreland L. *Lakartidningen* (2013)
24. Effect of gene, environment and maternal depressive symptoms on pre-adolescence behaviour problems - a longitudinal study. *Child Adolesc Psychiatry Ment Health* (2013) Agnafors S, Comasco E, Bladh M, Sydsjö G, deKeyser L, Oreland L, Svedin CG

Books/book chapters

1. Om barns sjukdomar i början av 1800-talet. Professor Pehr Afzelius föreläsningar Morbi infantum med kommentarer. Blomquist H, Jonsell R, Oreland L. Publisher: Medicinhistoriska museet (2014). ISBN 978-91-637-5652-8
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

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Märta Lundqvist foundation

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 2015

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, Professor
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
Inger Ståhl-Myllyaho, NICU Technician
Parmenion Titsopoulos, Neurosurgeon, PhD Student
Maria Zetterling, MD, PhD, Neurosurgeon

Undergraduate students and project researchers

Erik Degerman (30 hp MD program)
Jonathan Holm (30 hp MD program)

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, 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, CBF pressure autoregulation status (PRx), intracerebral neurochemistry changes (e.g. energy metabolic perturbations and biomarkers), neurophysiology (e.g. post traumatic seizure activity), brain temperature and 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. A mobile CT scanner with a xenon CBF device makes it possible to measure regional CBF bedside at the NIC unit.

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) and 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 are 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 provides 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 2015
For main results in 2015 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 Myllyaho.

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, animal 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 2015

For results in 2015 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 demonstrated 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 2015:

Marklund N (2015) Host of the European Association of Neurological Surgeons ***(EANS) Training Course***, Uppsala, January.

Marklund N (2015) ***Glia Meeting***, July 15-18, Bilbao, Spain.

Marklund N (2015) ***EANS Meeting***, Madrid, Spain, October 18-21 (invited speaker).

Hillered L (2015) Microdialysis for protein biomarker monitoring in the neurointensive care setting (invited plenary speaker). ***The 35th Herbert Olivecrona Symposium***, Karolinska University Hospital Solna, Stockholm, Sweden, December 4, 2015.

Rostami E (2015) Bedside monitoring of cerebral blood flow and metabolism in patients suffering from subarachnoid hemorrhage usin Xenon-CT and microdialysis (invited plenary speaker). ***The 35th Herbert Olivecrona Symposium***, Karolinska University Hospital Solna, Stockholm, Sweden, December 4, 2015.

Marklund N (2015) ***Portuguese Neurocritical Care Meeting***, Dec 4-5, Coimbra (invited speaker).

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Uppsala University Faculty of Medicine
Selander Foundation

Developmental Neuroscience

Molecular and Genetic Analysis of Experimental Traumatic Brain Injury

Group leader: Ted Ebendal, Professor (emeritus from October 1st, 2015)

Members of the group during 2015

Ted Ebendal, Ph.D., Professor
Charlotte Israelsson, Dr. Med. Sci., Researcher
Annika Kylberg, Research Engineer

When a traumatic brain injury (TBI), afflicts a person, for example 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. 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. Using an experimental TBI model in mice we have shown that 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 particularly strong expression levels among various chemokines and their receptors linked to specific cells in the immune system. After TBI, the chemokines and their receptors have shown central roles in the immune system with both inhibitory and promoting effects. Thus, an induced trauma shows differences in temporal expression levels which differ both in time and regarding the strength of the response but also among the interacting pathways.

Therapeutic approaches have so far been unsuccessful in patients suffering from trauma. 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 their resulting effect on the network of chemokines and 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.

Project 1: Outcome of treatment strategies in TBI

After TBI, the distribution of the chemokine *Cxcl10* gives reactive clusters of cells revealed by *in situ* hybridization. These clusters appear in the penumbra zone, but also at some distances from the primary injury as well as contralaterally, although to a minor extent. In our comparative studies of mouse models of TBI and neurodegenerative diseases, we saw apparent clusters of *Cxcl10*-expressing cells representing plasmacytoid dendritic cells. Treatment strategies applicable for several brain-damaging disorders and diagnosis thus become obvious. As a primary focus, we have tested several compounds with anti-inflammatory actions in order to find candidate therapies for TBI with reducing effects in postinjury inflammation. Two of the investigated compounds have caught our attention so far. Both are affecting leucocytes and block as well as boost different immune-related molecules. One is the cytostatic cyclophosphamide, a well-known pharmaceutical substance impairing leukocytes and in use in patients with cancer or systemic lupus erythematosus, has given promising results. The compound showed robust reductions in injury-induced transcripts, reminiscent of those seen in the injured *Ccr2*-/- mice. In particular, the agent seems to block the recruitment and activation of antigen-presenting conventional dendritic cells. The other is a compound already in phase II studies for rheumatoid arthritis. It has given promising results in our TBI experiments and are undergoing further investigations.

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

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 remodelling. 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 chemoattractant protein-1) and *Ccl12* (monocyte chemoattractant 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.

Publications 2013-2015

1. Israelsson C, Kylberg A, Bengtsson H, Hillered L, **Ebendal T**. 2014. Interacting chemokine signals regulate dendritic cells in acute brain injury. PLoS One 9(8):e104754. doi: 10.1371/journal.pone.0104754.

2. Israelsson C, Kylberg A, Björklund U, **Ebendal** T. 2015. Anti-inflammatory treatment of traumatic brain injury with Rabeximod reduces cerebral antigen presentation in mice. J Neurosci Res. 93(10):1519-1525.

Honours

Ted Ebendal was awarded the older Gustaf Adolfus Medal (Hedlinger) in Gold by the Board of Uppsala University in 2015.

Regenerative Neurobiology

Group leader: Elena N. Kozlova, Assoc. Professor

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Ali Inan El-Naggar, SOFOSKO student
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External Collaborations

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International: Dr Christian Berens, Dept Microbiology, Univ Erlangen-Nuremberg, Germany; Prof Vladimir Berezin and Dr. Stanislava Pankratova, Panum Institute, Copenhagen Univ, Denmark; Prof Eugen Lukanidin, Danish Cancer Soc Res Ctr, Copenhagen, Denmark; Prof Thomas Knöpfel, Imperial Coll, London, UK; Prof Harry Heimberg, Diabetes Research Center, Brussels, Belgium; Prof Su-Chun Zhang, Waisman Ctr, Univ Madison, WI, USA; Prof Kevin Eggan, Harvard Stem Cell Inst, Cambridge, MA, USA; Dr. Peter Shortland, Sch Sci and Health, Univ Western Sydney, Australia; Prof Emmanuel Hermans and Dr. Ronald Deumens, Dept Pharmacol, Cathol Univ Louvain, Brussels, Belgium; Prof Varda Shoshan-Barnatz and Dr. Adrian Israelson, Dept Life Sci and Nat Inst Biotechnol, Ben-Gurion Univ Negev, Beer-Sheva, Israel; Dr. Joep Saura, Biochem Molec Biol Univ, Sch Med, Univ Barcelona; Dr. Inez De Greef, Treeway, Rotterdam, The Netherlands; Dr. PJ Anand, Alcyone Inc., Concord, MI, USA; Dr. Ivo Lieberam, MRC Ctr Dev Neurobiol, King's Coll, London, UK; 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 three long-term objectives:

- Promote functional recovery after spinal root and spinal cord injury.
- Develop novel strategies using nanomaterial and cell based treatment of amyotrophic lateral sclerosis (ALS).

- Exploit the beneficial potential of neural crest stem cells for cell supportive and cell protective purposes with focus on endangered motor neurons in ALS, and on endogenous or transplanted insulin producing beta-cells.

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

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 overall objective is to restore functions that are lost following spinal cord injury with a focus on sensory loss and dysfunction after plexus avulsion injuries.

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. In for example traffic or fall accidents these roots can be avulsed from the spinal cord. The injured axons are unable to re-enter the spinal cord, and as a result, the patient suffers 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 have shown that human neural progenitor cells implanted at the site of avulsed and re-attached dorsal roots support functional regeneration of sensory axons into the host spinal cord (Hoeber et al, 2015). This process appears to be the result of stem cell mediated growth permissive “gaps” in the glial boundary at the dorsal root-spinal cord interface. Our current research aims to determine the mechanisms underlying this ingrowth and optimize its outcome. 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 injuries to the spinal cord.

Nanomaterial and stem cell replacement for treatment of ALS

We have developed a novel delivery system based on mesoporous silica nanoparticles for release of small peptide mimetics of bioactive/therapeutic molecules in the organism (Stem Cells Transl Med, 2013; Nanomedicine, 2014). The results of these studies can contribute to the development of a tunable, locally implantable delivery system for neuroregenerative purposes. We are currently employing this system for our research on spinal root and spinal cord injury as well as for delivery of novel neuroprotective agents in experimental models of amyotrophic lateral sclerosis (ALS), a lethal disorder characterized by progressive paralysis due to death of upper and lower motor neurons.

Our ALS research is carried on mouse and human neural cells harboring a mutation of superoxide dismutase (SOD)1, a commonly used model of human ALS. For early stage disease, our aim is to identify novel neuroprotective agents and deliver them *in vivo* using agent loaded nanoparticles. For late stage disease replacement of lost motor neurons their functional integration is the ultimate objective. For this purpose our aim is to generate human embryonic stem cell-derived motor neuron progenitors according to good manufacturing practice (GMP), implant them into the a model of spinal motor neuron degeneration together

with nanoparticles loaded with motor neuron specific differentiation factors. To promote outgrowth of implanted motor neurons to denervated muscles nanoparticles loaded with neural regeneration stimulating factors are placed at strategic sites between spinal cord and muscle.

Boundary cap neural crest stem cells for regenerative medicine

We have shown that growth, survival and function of mouse and human insulin producing cells in the pancreas are promoted if the cells are cultured or transplanted together with murine boundary cap neural crest stem cells (bNCSC), a transient cell population residing at the junction between dorsal roots and spinal cord during embryonic development (Lau et al, 2015; Grapensparr et al, 2015). The beneficial effects of bNCSCs require direct cell-cell contact with beta-cells through cadherin-catenin connections (Ngamjariyawat et al, 2013). Our 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, who have lost large amounts of their insulin producing cells. Given the translational relevance of these results we intend to generate human bNCSC and explore their cell supportive and cell protective potential.

Recently bNCSCs were also shown *in vitro* to protect motor neurons subjected to excitotoxic challenge (Schizas et al, unpublished, as well as motor neurons harboring a an ALS-associated mutation in the gene for superoxide dismutase (SOD)1 (Aggarwal et al, submitted). We aim to determine the mechanisms underlying these effects and translate them into *in vivo* models of motor neuron degeneration.

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Stiftelsen Olle Engkvist Byggmästare

Physiotherapy

Group leaders: Pernilla Åsenlöf, PhD, PT, Professor

Members of the group during 2015

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Lena Zetterberg, PT, PhD
Ylva Åkerblom, PT, PhD-student

Physiotherapy research at Uppsala University is strongly linked to the clinic and hence characterised by patient-centred approaches and clinical intervention studies. Research activities focus on physical activity, physical exercise, and activities training and their contribution to enhance health in various clinical populations. 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 behaviours likely to improve a number of health outcomes and reduce all-cause mortality. In subjects with chronic conditions 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 main research aims are to identify prerequisites for physical activity and physical capacity in subjects with chronic conditions and young and geriatric populations as well; investigating reasons for physical inactivity and physical limitations, investigating fall prevention interventions, identifying simple tests to measure physical capacity, and developing and evaluating rehabilitation interventions. Current research includes studies on chronic obstructive pulmonary disease (COPD), asthma, sleep apnoea, rheumatoid arthritis,

heart diseases, dysfunctional breathing, exercised induced breathing problems, subjects with stroke, Parkinson' disease, Multiple sclerosis, Charcot-Marie-Tooth disease, cervical dystonia, myasthenia gravis, amyotrophic lateral sclerosis (ALS), acute and chronic pain, and elderly people with increased fall risk.

A significant feature of our research is the integration of behavioural medicine. 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 pain 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. 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.

Ccollaborators include researchers from the fields of physiotherapy, clinical psychology, clinical physiology, pulmonary medicine, psychiatry, pain and anaesthesiology, rheumatology, addiction medicine, cardiology, neurology, epidemiology, gerontology, nutrition, and surgical sciences.

Ongoing main projects 2015

Ambulatory oxygen in patients with COPD who desaturate during exertion – A multicenter study in the Nordic countries (AMBOX-study).

In patients with COPD several ongoing studies are investigating; muscle function, maintenance of physical activity, long term follow up patients with COPD, and prevalence of pulmonary rehabilitation within primary care in Sweden

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

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.

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.

Physical function and activity in patients with total knee arthroplasty three months after operation.

Validation of outcome measures in canine physical rehabilitation and physiotherapy.

ALS/MNS and pain.

Stepped care and tailored pain management in primary care.

Physical activity and health related behaviour change in sleep disordered breathing and insomnia.

Integration of patients' innovations in a web-based intervention targeting physical activity in rheumatoid arthritis.

Chronic opioid treatment in chronic non-cancer pain: benefits and work ability versus risks and opioid use disorder

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Uppsala County Council Research Fund
ALF
Uppsala-Örebro Research Fund
The Stroke Research Fund
The Swedish Rheumatism Association

Speech and Language Pathology

Group leader: Monica Blom Johansson, PhD

Members of the group during 2015

Per Alm, PhD, senior lecturer
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Klaudia Ceder, research assistant
Margareta Gonzalez Lind, PhD student
Martina Hedenius, PhD, senior lecturer
Margareta Jennische, PhD, associate professor
Cecilia Nakeva Von Mentzer, PhD, junior lecturer
Ingrid Sör, research assistant

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.

In the beginning of 2015, Birgitta Johnsen, SLP, became honorary doctor of the Faculty of Medicine with the motivation: with crucial importance for Uppsala University through pioneering work Birgitta Johnsen developed speech-language pathology as an academic discipline in Sweden, implemented science into clinical practice and initiated and actively participated in the establishment of the speech-language pathology program. (”Birgitta Johnsen har med avgörande betydelse för Uppsala universitet genom pionjärarbete utvecklat logopedin som akademisk ämnesdisciplin i Sverige, omsatt vetenskap i klinisk verksamhet samt initierat och aktivt medverkat till inrättandet av en logopedutbildning.”)

Another important aspect of the research activities during 2015 was the establishment of a new Speech and Language Lab within our department, with state of the art facilities for multimodal recordings and studies involving audio, video, EMG, EGG, and electroencephalography (EEG), as well as transcranial electric stimulation.

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

Participants: Martina Hedenius (PI). Collaborators: Joanne Arciuli. Sven Bölte, Juha Kere, Janne von Koss Torkildsen, Martin Ingvar, Lars Nyberg, Jonas Persson.

This project explores the role of statistical/procedural learning and memory consolidation in language and reading development. It also investigates the compensatory potential of declarative memory in the case of statistical/procedural learning impairments. The research questions are addressed with both behavioral and brain imaging techniques, including (functional) Magnetic Resonance Imaging and Diffusion Tensor Imaging.

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.

The acquisition of aided communication may 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 under the leadership of Professor Stephen van Tetzchner, University of Olso. A large corpus of utterances produced with communication aids by children aged 5-15 years has been obtained and is actually being analysed to be published as a reference guide on aided communication development both for research and clinical use.

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. During 2015 the studies have focused on multimodal "micro-analysis" of the speech motor symptoms of stuttering, including electromyography (EMG) and electroglottography (EGG). The results are being prepared for publication, and provide a new outline of the nature of this speech motor

disorder. The frontline progress of the research on stuttering in Uppsala has been acknowledged by key note presentation invitations at the world conference on stuttering research in Lisbon 2015 and the international conference on stuttering in Barcelona February 2016.

Project 4: Aphasia and communication in everyday life as perceived by significant others

Participants: Monica Blom Johansson, Marianne Carlsson, Per Östberg, Karin Sonnander

This project focuses the communicative rights of individuals with aphasia and their ability to be active participants in their social environment and in the community. In this last part of the project in particular, the significant others of individuals with aphasia are in focus including their own health and everyday life situation, how they could contribute to increase autonomy and social participation of individuals with aphasia and what support they may need themselves.

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)

This 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, Mathias Hällgren, PhD Linköping University, Klaudia Ceder, research assistant

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 indicates that the test appears to be sensitive for predicted perceptual difficulties of different consonant contrasts.

Project 7: Listening difficulties in children with language impairment, 2016-2018

Participants: Cecilia Nakeva von Mentzer, Jennie Pihlgren, Elsa Erixon, Sofie Järlesäter (Teamet för hörselimplantat, Akademiska sjukhuset) David R Moore, Cincinnati Children's Medical Hospital

The aim of this project is to investigate mechanisms involved in speech and auditory processing children with normal hearing between 7 to 12 years of age who have or have not been diagnosed with language impairment. The overall objective is to test the hypothesis that some children with language impairment have 'listening difficulties' (LiD) that are not detectable using conventional pure tone audiometry. The long-term goal with the planned research is to improve speech understanding in children with language impairment.

Project 8: Computer-assisted reading intervention in children with Down's syndrome

Participants: Cecilia Nakeva von Mentzer, Margareta Jennische, Nelli Kalnak

This projects aims to investigate whether it is possible to support reading development in children with Down's syndrome (DS). Graphogame is an Internet based reading program with a phonics approach originally developed for children with dyslexia. It offers child friendly exercises for beginning readers, i.e. grapheme-phoneme correspondence training, blending of phonemes into words and segmenting words in phonemes, and has recently proven successful for children with hearing loss. In the current study we will examine whether children with Down's syndrome may benefit from such an Internet-based reading intervention.

Project 9: Early support and conversation training for significant others of persons with aphasia

Participants: Monica Blom Johansson, Klaudia Ceder, Ingrid Sör, Per Östberg (associate professor, KI),

Given the important role of close relatives in the rehabilitation of people with stroke and aphasia, it is of great importance to help them to be a support for the person with aphasia. A six-session intervention aims to flexibly provide the significant other with emotional support, individualized information about stroke and aphasia, and conversation training according to their specific needs and ability to assimilate the information and training given. The feasibility of the intervention has been tested in a pilot study. To get a comprehensive understanding of the intervention outcome several validated and reliable outcome measures are used to cover linguistic and communicative ability, activity, social and societal participation, life satisfaction and psychological health in addition to specific environmental and personal factors. Data is collected before and after treatment, and at 6 and 12 months post-stroke onset.

Project 10: A longitudinal study of persons with aphasia and their life partners

Participants: Monica Blom Johansson, Klaudia Ceder, Ingrid Sör, Per Östberg (associate pro fessor, KI)

The aim of this project is to increase the knowledge about how aphasia and its psychosocial consequences evolve/change over time for people with aphasia and their life partners, and the factors that can affect their life situation and adjustment process. The participants are

followed during several years with data collection undertaken at inclusion (as close as possible to the stroke event but at most two months post-onset), 3, 6, 12, 18, 24, 36, 48, 60 and 120 months post-onset. Several validated and reliable outcome measures covering linguistic and communicative ability, activity, social and societal participation, life satisfaction and psychological health as well as of some environmental and personal factors are used in order to get a comprehensive understanding of the participants life situation.The same instruments as in project 9 are used.

Project 11: Swedish adaptation of the Comprehensive Aphasia Test (CAT) – an European CATs project

Participants: Members of the Swedish adaptation group are Monica Blom Johansson, Klaudia Ceder, and Ingrid Sör; Ingrid Behrns and Francesca Longoni (University of Gothenburg); Per Östberg (KI).

The Collaboration of Aphasia Trialists (CATs) is an action of the European Collaboration in Science and Technology (COST). CATs consists of several working groups which work on aphasia-related research topics. One of them is developing/translating/adapting aphasia assessment tools comparable across different languages. An ongoing project is the adaptation of the Comprehensive Aphasia Test (CAT) to fourteen different languages, including Swedish. For each adaptation process, national interdisciplinary teams work accordingly with the previously agreed upon guidelines. To ensure comparability across the various languages, the adaptations are matched according to underlying linguistic variables such as word and sentence length, word frequency, imageability, morphological complexity, grammatical structure, and spelling regularity. Since some of the languages lack the necessary background data on variables such as imageability and frequency, studies are being conducted in order to establish these data. When the adaptation process is completed, each language version of the CAT will be standardized and normed.

Project 12: Supporting Communicative Participation of Individuals with Aphasia

Participants: Lise Randrup Jensen (PI) (Univ. of Copenhagen); Monica Blom Johansson; Elisabeth Ahlsén and Charlotta Saldert (University of Gothenburg); Jytte Isaksen (Denmark); Madeleine Cruise, Simon Horton and Carol Pound (UK); Nina Simmons-Mackie (US)

This network includes nine members and its purpose is mainly to study and/or develop good ways of evaluating Supported Conversation of Adults with Aphasia (SCA) with respect to underlying theories, participation and quality of life. The project also involves hosting the Nordic Aphasia Conference in Copenhagen 2017.

Publications 2013-2015

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2. Hedenius M, Ullman MT, Alm PA, Jennische M, Persson J, 2013. Enhanced recognition memory after incidental encoding in children with developmental dyslexia. PLoS One 8, e63998.

3. Alm PA, Dreimanis, K. Neuropathic pain: transcranial electric motor cortex stimulation using high frequency random noise. Journal of Pain Research. 2013;6:479-486.

4. Alm PA, Karlsson R, Sundberg M, Axelson HW. Hemispheric lateralization of motor thresholds in relation to stuttering. PLoS One. 2013;8:e76824.

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6. Nakeva von Mentzer, C., Lyxell, B., Sahlén, B., Wass, M., Lindgren, M., Ors, M., & Uhlén, I. (2013). Computer-assisted training of phoneme-grapheme correspondence for children who are deaf and hard of hearing: Effects on phonological processing skills. International Journal of Pediatric Otorhinolaryngology.

7. Nakeva von Mentzer, C., Lyxell, B., Sahlen, B., Dahlström, O., Lindgren, M., Ors, M., Kallioinen, P., & Uhlen, I. (2014). Computer-assisted reading intervention with a phonics approach for children using cochlear implants or hearing aids. Scandinavian Journal of Psychology, 55(5), 448-455.

8. Nakeva von Mentzer, C., Lyxell, B., Sahlen, B., Dahlström, O., Lindgren, M., Ors, M., Kallioinen, P., & Uhlén, I. (2014). The Phonics Approach in Swedish Children using Cochlear Implants or Hearing Aids: Inspecting Phonological Gain. Journal of Communication Disorders, Deaf Studies & Hearing Aids 2(3).

9. 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

10. Jennische, M. & Zetterlund, M. (2015) Interpretation and Construction of Meaning of Bliss-words in Children. Augmentative and Alternative Communication, 31(2): 97–107. DOI: 10.3109/07434618.2015.1036117

Reviews 2013-2015

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)
Kungliga Vetenskapsakademien (Project 1)
Faculty of Medicine at Uppsala University (Project 3)
Strokefonden (Project 4)
The Swedish Research Council, Humanities and social science (Project 5)
Tysta skolan (Project 6)
Svenska Dyslexistiftelsen (Project 7)

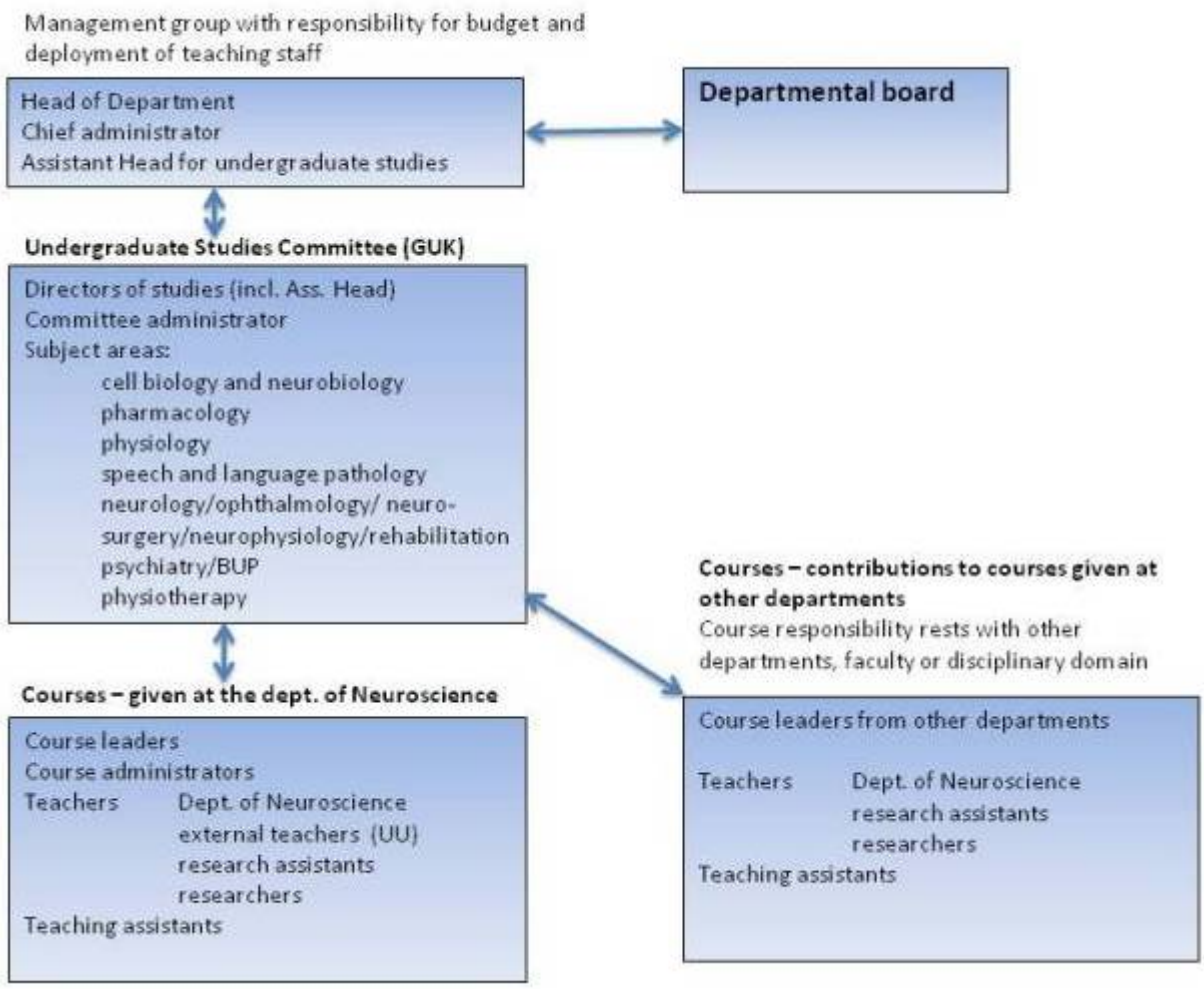
FORTE: Swedish Research Council for Health and Working Health Care (Project 7)
Stiftelsen Sävstaholm (Projekt 8)
Morins donation (Project 10)
Afasifonden (Project 11)

UNDERGRADUATE STUDIES 2015

Mia Ramklint, senior lecturer and researcher in Psychiatry,
teaching Child and Adolescent Psychiatry in course Clinical Medicine IV,
for students of Medicine Programme.
Mia Ramklint has also been awarded the title excellent teacher.

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 (Grundutbildningskommitteen, GU).



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 2015:

Seven major subject areas with director of studies
- Cell biology and neurobiology (C&N)
  Finn Hallböök until October, then Dan Larhammar
- Pharmacology (FA)
  Robert Fredriksson
- Physiology (FY)
  Olle Nylander
- 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 2015 a half-day teaching conference was held at the Psychiatry building on 24th August for all involved in teaching at the department. The conference focused on criteria-based assessment with guest speakers from KUUP, the unit for Quality Enhancement and Academic Teaching and Learning (Emma Lundkvist and Geir Gunnlaugsson). The Department's own Eva Wenngren presented a report on the Physiotherapy programme's practical experience of introducing criteria-based assessment.

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.

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 Pettersson
NHoI, Neurobiology, Homeostas and Intervention	3NR137	Madeleine Le Grevès	Neil Ormerod
Clinical Clerkship	3NR012		
Clinical Medicine V/ Clinical Medicine IV	3NR008/3NR014	Mia Ramklint	Gunneli Ekberg
	Neurology	Ann-Marie Landtblom	Sari Thunberg
	Psychiatry	Mia Ramklint	A.-C. Fält
	Ophthalmology	Gerd Holmström	Gunneli Ekberg
Child and Adolescent Psychiatry	3BP001	Mia Ramklint	A.-C. Fält
Communication skills	3PS053/54	Mia Ramklint	A.-C. Fält
Biomedicine			
Molecular Cell Biology	3MU123	Finn Hallböök	Karin Nygren
VBE - Tissue Biology with Embryology	3MU122	Finn Hallböök	Karin Nygren
Neurobiology	3MU132	Klas Kullander	Neil Ormerod
Pharmacology with medicinal chemistry	3MU150	Robert Fredriksson	Neil Ormerod
Comparative medicine	*3MU143*	Madeleine Le Grevès	Neil Ormerod
Master's programme in biomedicine			
Advanced Neurobiology	3NR600,	Bryndis Birnir / Zhe Jin	Karin Nygren
Drug Target Identification and Evaluation	3NR380	Helgi Schiöth	Karin Nygren
Master's Degree Project in Biomedicine	3MU230	Lina Thorvaldsson (examinator)	Karin Nygren
Laboratory Project in Biomedicine	3MU015/3MU130	Helgi Schiöth (examinator)	Karin Nygren
Research training in biomedicine and laboratory animal science	3NR730	Madeleine Le Grevès	Neil Ormerod
Nursing			
Nursing and medical science within psychiatric care	3PS040	Caisa Öster	A-C Fält
Specialist nursing			
Psychiatry	3PS300	Caisa Öster	A-C Fält
Nursing in Psychiatry/Mental Health I	3PS301	Caisa Öster	A-C Fält
Nursing in Psychiatry/Mental Health II	3PS302	Kristina Haglund	A-C Fält
Advanced Nursing Study within Psychiatric Care	3PS303	Caisa Öster/Kristina Haglund	A-C Fält
Degree Project in Psychiatric Care	3PS304	Caisa Öster	A-C Fält
Speech and language pathology			
Basic Concepts of Anatomy, Physiology and Pathophysiology	3LG020	Elena Kozlova	Anki Gustafsson
Professional Logopedics I	3LG110	Nadina Laurent	Anki Gustafsson
Professional Logopedics II	3LG111	Sofia Ögefeldt	Anki Gustafsson
Nervous System Disorders in Adults	3LG024	Per Alm	Anki Gustafsson
Child Logopedics 1	3LG210	Maria Krüger-Vahlquist	Anki Gustafsson
Speech Impairment: Stuttering. Head and Neck Cancer	3LG404	Per Alm/Sofia Ögefeldt	Anki Gustafsson
Clinical Child Logopedics 1	3LG610	Maria Krüger-Vahlquist	Anki Gustafsson
Speech Pathology in Congential Nervous System Disorders	3LG214	Monica Blom Johansson	Anki Gustafsson
Voice Pathology	3LG215	Sofia Ögefeldt	Anki Gustafsson
Speech Pathology in Acquired Nervous System Disorders	3LG216	Monica Blom Johansson	Anki Gustafsson
Speech Pathology in Language and Reading Disorders in School-Aged Children	3LG217	Cecilia Nakeva von Mentzer	
Clinical Voice Pathology,	3LG613	Maria Krüger-Vahlquist	Anki Gustafsson

Professional Logopedics III	3LG112	Nadina Laurent	Anki Gustafsson
Clinical Course: Stuttering	3LG615	Maria Krüger-Vahlquist	Anki Gustafsson
Clinical Speech Pathology in Acquired Nervous System Disorders in Adults	3LG620	Maria Krüger-Vahlquist	Anki Gustafsson
Clinical Speech Pathology in Congenital Nervous System Disorders	3LG619	Maria Krüger-Vahlquist	Anki Gustafsson
Clinical Speech Pathology in Language and Reading Disorders	3LG621	Maria Krüger-Vahlquist	Anki Gustafsson
Professional Logopedics IV	3LG113	Nadina Laurent	Anki Gustafsson
Master's Thesis in Speech and Language Pathology	3LG503	Per Alm, Monica Blom Johansson	Nadina Laurent
Advanced Clinical Logopedics (elective)	3LG616	Monica Blom Johansson	Anki Gustafsson
Advanced Theoretical Speech and Language Pathology	3LG617	Monica Blom Johansson	Anki Gustafsson
Physiotherapy			
Physiotherapy I	3PT011	Ann Sundbom/Pernilla Åsenlöf	Stefan Pettersson
Physiology and Anatomy I	3PT012	Svante Winberg	Stefan Pettersson
Physiotherapy I: Health Behaviour and Research	3PT013	Charlotte Urell	Stefan Petterssib
Anatomy II	3PT021	Ann Månsson	Stefan Pettersson
Physiotherapy II	3PT022	Helena Igelström/Ewa Wenngren	Stefan Pettersson
Anatomy II: Muscles and Joints	3PT023	Ann Månsson	Stefan Petterson
Physiotherapy II: Movement, Biomechanics and Functional Anatomy	3PT024	Ewa Wenngren	Stefan Pettersson
Physiotherapy III: Acute and Subacute Conditions	3PT031	Johanna Holmbäck	Stefan Pettersson
Neuroanatomy and Physiology Related to Pain and Stress	3PT032	Camilla Ekwall	Stefan Pettersson
Psychiatry	3PS034	Mimmie Willebrand	A-C Fält
Physiotherapy in Neurological Disorders, Theory and Practice	3SG036	Camilla Ekwall	Stefan Pettersson
Phys. in Pain and Musculoskeletal Dysf., Theory and Clinic	3SG096	Christina Emilsson	Stefan Pettersson
Basic Physiology Related to Pain and Stress	3SG037	Cecilia Norrbrink	Stefan Pettersson
Neurology	3SG069	Dag Nyholm	Stefan Pettersson
Paediatrics and Physiotherapy in Paediatrics	3SG086	Eva Gåve	Stefan Pettersson
Physiotherapy in Patient Care, Theory and Practice	3SG027	Johanna Holmbäck	Stefan Pettersson
Clinical Education in Physiotherapy, Elective	3SG029	Camilla Ekwall	Stefan Pettersson
Research Methodology II	3SG087	Sara Holm	Stefan Pettersson
Rehabilitation ...in patients with Non-communicable diseases	3SG081	Margareta Emtner	Stefan Pettersson
Research Methodology III/Research plan	3SG091	Mikael Andersson	Stefan Pettersson
Health and Health Promotion	3SG072	Sören Spörndly-Nees	Stefan Pettersson
Physiotherapy and Geriatric Care	3SG068	Marie Sandström	Stefan Pettersson
Research Methodology IV/Bachelor's Thesis	3SG090	Karin Hellström	Stefan Pettersson
Physiotherapy for Adults with Neurological Disorders	3SG093	Lena Zetterberg	Stefan Pettersson
Degree Thesis in Physiotherapy, Advanced Level	3SG094	Cathrin Martin	Stefan Pettersson
Clinical Course in Physiotherapy for Exchange Students	3SG074		Stefan Petterson

Within the faculty of pharmacy

Pharmacy (bachelor's programme)			
Physiology	3FF112	Olof Nylander	Stefan Pettersson

Within the disciplinary domain of science and technology

Biology/Molecular biology			
Neurobiology	1BG207	Malin Lagerström	Neil Ormerod
Civil engineer chemistry/technology			
Physiology and Molecular Cell Biology	3FF158	Olof Nylander	Stefan Pettersson

Elective courses

Within the faculty of medicine

Psychotraumatology	3PS038	Kerstin Bergh Johannesson	A-C Fält
Medical history	3NR501	Eva Ahlsten	Stefan Pettersson
Laboratory Animal Science	3FD130	Madeleine Le Grevès	Neil Ormerod
Exploring the Brain I	3NR201	Klas Kullander	Stefan Pettersson
Exploring the Brain II	3NR202	Klas Kullander	Stefan Pettersson
Psychiatry	3PS050	Caisa Öster	A-C Fält
Advanced Course in Neuroscience Care	3NR009	Niklas Marklund	Sari Thunberg
Research Methods	3LG501	*Therese Glatz (Psychology)*	Anki Gustafsson
Evaluation of Scientific Reports	3LG517	*Ebba Elwin (Psychology)*	Anki Gustafsson
Clinical Supervision	3LG927	Maria Krüger-Vahlquist	Anki Gustafsson
Paediatric Swallowing and Feeding	3LG935	Margareta Gonzalez Lindh	Anki Gustafsson
Sports Medicine and Sports Rehabilitation	3SG007	Charlotte de Belder Tesséus	Stefan Pettersson
Advanced Course in Neuroscience Care	3NR009	Niklas Marklund	Sari Thunberg
Behavioural Medicine: Theory and Practice within Health Care	3SG089	Annika Bring	Stefan Pettersson
Advanced Physiotherapy: Theory and Method	3SG085	Cathrin Martin	Stefan Pettersson

Laboratory courses

Advanced Course in Developmental Genetics	Several	Karin Nygren
Advanced Course in Neuropharmacology	Several	Karin Nygren
Elective Course in Neuroscience	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 of the courses were either new or substantially revised in 2014 and 2015. Five courses in the Bachelor’s programme were given from our department: 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 with assistance from Jörgen Jonsson 10 hp), Pharmacology and medicinal chemistry (new 2015) (course leader Robert Fredriksson and Charlotta Wallinder (dept of Medicinal chemistry) and the course on Experimental animal welfare (new 2014). The department contributes significantly to the course in physiology (Olle Nylander/Markus Sjöblom, 16,5 hp).

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. 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, the students can choose freely from other courses, and are able to specialize in their field of interest. They also complete a master's thesis 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 thirteen). Twenty-nine each year in 2012, 2013 and 2014. In 2015, only 17 non-paying students were accepted, partly because of an increase in the number of accepted fee-paying students 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 with two courses; Advanced Neuroscience (15 credits) given by the Physiology unit and Preparation for Research with Focus on New Drug Targets (15 credits) given by the Functional Pharmacology unit. Other courses in the first year are Homeostasis and Endocrine Disorders with a Focus on Major Diseases (15 credits) from the Department of Medical Cell Biology, and 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. The Department of Neuroscience also coordinates the Master Thesis projects.

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

Assurance of quality
Between 2013 and 2015, the master programme was evaluated by the Swedish Higher Education Authority. and a substantial work has been done under 2014 and 2015 to address the comments made in the evaluation 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 have also been new lectures added to the common seminar series for all the master programme at the Medical Faculty, and the structure of this seminar will be revised during 2016 to introduce a flipped-classroom pedagogy and more group discussions on ethical topics. The organization of the examination of the Master thesis projects has been revised so that there now are four 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 societal 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 Medical Faculty and our program is represented by Lina Thorvaldsson.

Development of teaching and learning
Our teachers are recruited from the teaching staff and researchers from 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.

Students from other universities have often not taken any course in laboratory animal science, which can cause problems for those wishing to do master thesis projects that include animal research. As a solution to this, we have developed a course of 15 credits that combines the laboratory animal science course with a laboratory project. This course is offered as an alternative during the third semester, and will provide the students with an opportunity to gain the Felasa certificate that allows them to perform animal experimentation.
Starting in the autumn of 2016, the students will also have the opportunity to do the same laboratory animal science course as a part of their master thesis, if they choose to do a longer thesis of 45 credits. The option to do a thesis of 45 credits is also new. Previously, the students could not to longer theses than 30 credits. However, we noticed that many students were doing laboratory projects in the third semester that continued into the master thesis in the fourth semester, and decided to offer them the opportunity to do a longer project.

Internationalization

The proportion of students with an international background decreased with the introduction of the tuition fees in 2011, but has increased steadily since then. 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 and in 2015 were back to two thirds. Thirteen tuition-fee paying students were accepted in 2015. Among the thirty new students admitted in the autumn of 2015, nineteen had an international background (they came from Spain, India, the Netherlands, Romania, Greece, Syria, Germany, Great Britain, Iran, Indonesia, Iraq and China). The proportion of non-paying students from EU countries have also increased over the years, possibly as a result of the increased awareness of European students that studies in Sweden are free and of high quality.

The Speech and Language Pathology Programme

The eighth class (LK12) of speech and language pathologist (SLP) (27 students) graduated in January and 40 new students were admitted to the program in the spring semester (35 females and 5 males).

In addition to regular courses, two courses at advanced level in ‘Paediatric Swallowing and Feeding: Assessment and Management’ 7.5 hp and ‘Clinical Supervision’, 7.5 hp were given during 2015. In addition to the first course, an international symposium was arranged with Professor Joan C Arvedson: ‘Pediatric Swallowing and Feeding Assessment and Intervention’ with 70 participants.

Development of teaching and learning

The National meeting for education in speech and language pathology in 2015 was hosted in Lund with participants, teachers and students from all Speech and language pathology programmes in Sweden. The meeting discussed common problems and possible collaborations.

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 "Counseling skills" by Johan Waara, Director of studies at the Department of Psychology. His lecture and seminar with a focus on the dialogue between supervisor and student were very much appreciated. 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.

Eleven students have been doing their elective course on advanced level, 7.5 hp or part of their master thesis abroad (Great Britain or France).

Broadened recruitment

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

The Medicine Programme

A revision of the programmes curriculum was introduced during 2013 - 2014 that mainly dealt with the clinical semesters (7-11). This revision resulted in a period of "double teaching" in the spring of 2015, when both the old and the new versions of the Department's main course in the clinical stages of the programme were given concurrently. This period was challenging for the Department's teaching and administrative staff, but was judged to have been a success.

The Department played a major role in the discussions and preparations for the new and revised curriculum and continues to contribute to the development of the programme through representatives in the programme committee. 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 and pedagogical responsibility for *Clinical Medicine IV*, semester 8. The Department's teaching commitments include integrated preclinical-clinical neuroscience, neurology, neurosurgery, clinical neurophysiology, rehabilitation medicine, psychiatry and ophthalmology.

The Department further participates in the program with teaching in 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 exercises 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 spring of 2015 the Physiotherapy programme (UP 14) started its second semester following the 2014 curriculum (UP 14). Fifty students were admitted to the programme. Twenty-five students graduated in the spring and 33 students in the autumn of 2015. All having followed the curriculum of 2005.
Twenty-seven students were registered to write the thesis of 15 credits on the one-year Master's Programme.

Development of teaching and learning

Throughout 2015 the process of creating a new curriculum, with the aim of implementing and integrating a behavioural medicine profile in the programme, continued. All teachers were involved in some way, e.g. creating new course plans or planning new assignments.
The working process of the development of UP 14 was 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, assured the progress of the work in three phases: Phase 1 entailed a period of "planning and professional development"; Phase 2 "development of curriculum"; and, Phase 3 "implementation of the new curriculum".

Spring 2015 saw the start of phase 3 with the second semester of the new programme.
The first two courses in the spring semester of 2015 were given for the first time, with a new assignment on how to coach and guide a person in changing their physical activity behaviour being introduced. This innovative assignment is an excellent example of integrating knowledge of behavioural medicine with expertise in physical activity. Course evaluations showed a positive response.

The teachers in the second semester of UP 14 also implemented a range of new pedagogical elements in their courses, with an increase in activity-promoting forms of teaching, which encourage students to take greater responsibility for their own learning.

In parallel with the start of the second semester of UP 14, preparations for the third semester with start in the fall 2015, continued.

All teachers participated in an internal education course on gender issues in teaching and literature, arranged by the head of the programme´s steering committee, senior lecturer Karin

Hellström. The programme's teaching staff was also invited to attend the educational courses, seminars and workshops offered by the Division for Development of Teaching and Learning.
A majority the programme's teachers attended the yearly “Teachers´ Learning Day” at the Department of Neuroscience, which had the theme “Criteria for examination”. Eva Wenngren made a well-received presentation based on the programme's experience of putting criteria-based assessment into practice.

In order to disseminate and expand knowledge of behavioural medicine and methods of integrating behavioural medicine with our education in physiotherapy, the programme provided extensive opportunities for professional development and training, in the form of seminars and face-to face discussions with course leaders. These efforts were led by Professor Pernilla Åsenlöf and senior lecturer Annika Bring, project manager for UP 14.

Assurance of quality

Efforts towards the assurance of quality in the physiotherapy programme continued during 2015, including: theoretical and clinical activities among the staff; evaluation of clinical training; course evaluations; as well as self-evaluations. The results were compiled and formed the basis of an analysis of the programme in terms of strengths, weaknesses and need for change.

Clinical training

Finding trainee posts for clinical practice for our students was accomplished.
Efforts and fundings in regard to finding trainee posts for the new physiotherapy course in the fall semester of 2015 were performed during the spring semester of 2015. Teachers and staff travelled to different regions (Gävleborg, Karlstad, and Hudiksvall) and 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.
Annual meetings for clinical supervisors formed part of our on-going efforts to maintain a high level of quality in the trainee posts during 2015.
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 decided to give our internationalisation efforts a lower priority during 2015, due to the demands of implementing the new curriculum. However, one student did his elective clinical practice in Austria. The programme also received one physiotherapy student from Liverpool who did clinical practice at the University Hospital (Akademiska sjukhuset).

Broader recruitment

The programme has about 40% male students. We aim to recruit more students with immigrant backgrounds in order to reflect the patients 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

Karin Vemhäll from the hospital in Falun and Christian Adolfsson from Mälargården 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 13 students were in the Programme in Psychiatric Care, based at the Dept. of Neuroscience, in the spring of 2015 and, 16 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 2014–2015 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

During the autumn semester we have introduced more problem based learning in the programme. This was useful for the students learning both assessed by themselves and was also reflected in the examinations. Clinical examinations (OSCE’s) of professional competence at an advanced level have been used in the programme for several years. Main focus is on assessment of communication skills, as this is one of the most central competences in psychiatric nursing and we continuously develop performances and assessments with help of student and teachers evaluation.

Clinical training

Trainee posts for clinical practice for the students have been arranged in collaboration 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 and the moment *"Omvårdnad och medicinsk vetenskap inom psykiatrisk vård comprising 7.5 hp"* provides knowledge of psychiatry and mental health in medical as well as caring sciences. The focus 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

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 moment 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 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

During 2015 the previous course has been remodelled to fit in as a moment in three courses in semester one, four and six in the nursing programme. In addition we have been developing a new eligible course in semester five which starts in 2016. It is a challenge to acquaint students with psychiatry and psychiatric care in the short time available and much work has been on improving student- and teacher-guides.

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 2015, touching on topics ranging from Laboratory animal science to Medical history. 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.

The Department's courses in psychiatry and aimed at professionals working in related disciplines, such as social work, continued in popularity.

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: 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. Klas Kullander is course leader.

Neurobiology, 10 hp, the Biomedicine Programme: This course, given for the second time in 2015, is scheduled 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 was 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 and Jörgen Jönsson, 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 2015 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 (CMB) in the Biomedicine programme, 2nd semester; Tissue biology with Embryology (VBE) 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. During the autumn of 2015 Finn Hallböök took over as head of the Department and the preparations and role as course leader for the CMB spring 2016 course was taken over by Henrik Ring

The biomedicine VBE course is given in collaboration with Dept's IMBIM and Med Cell Biology. Within the Tissue biology course, embryonic development is used as a primer for understanding the establishment of specialized tissues in the vertebrate embryo.

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 110 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, supervision responsibility for 3 seminars and six case-based seminar groups per semester.

Several lectures are given in other courses such as Laboratory Animal Science, Neurobiology for both the biomedicine programme and the medicine programme, 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). Madeleine Le Grevès is course leader and Robert Fredriksson was director of studies in pharmacology during 2015. This course is given twice a year with around 90 students each time. Personnel at the unit give lectures in pain and analgesia as well as vascular pharmacology, lead PBL cases and seminars, and organize examinations.

In addition we participate 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 course leader. This course is run entirely within the unit with a few invited lecturers.

In the Biomedicine programme, Madeleine Le Grevès leads the recently revised course in Comparative Medicine (5 hp), which is now given in the autumn semester for approximately 40 students. The course provides theoretical knowledge and practical skills in laboratory animal science, covering topics such as: 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 share responsibility with the department of medical chemistry for the course “Pharmacology with medicinal chemistry”, 12 hp, with Robert Fredriksson as course leader. This was a new course for 2015 held for the first time in the autumn semester.

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

Robert Fredriksson has been a major participant in our group and taken a leading role in the department's teaching activities, as course leader, director of studies and as a lecturer. Robert left the department at the end of 2015 to take up a position as Professor in the Department of Pharmaceutical Biosciences at Uppsala University's Faculty of Pharmacy. We wish him well in all his future endeavours.

Medical History

The aim is to disseminate knowledge of 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 third term are shown the exhibitions on a guided tour of the Medical History Museum. The guides are Henry Johansson, Bertil Karlmark, Lars Oreland and Mats Westman. Every half year, nursing students, during their first term, are given a guided tour of the museum. The guides are Eva Ahlsten, Urban Josefsson, and Bertil Karlmark. Pharmacy 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 sixth course in Medical History was performed during spring 2015. As in 2013 and 2014 Eva Ahlsten was the leader of this course. The teachers were doctors, a psychologist, a mid-wife, 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 given lecture. The subjects of the course, besides an

introduction of common medical history, were psychiatric history, pharmacology, epidemics and vaccinations, 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-two 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, 19.5 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 and universities) at undergraduate and graduate level, particularly lectures concerning the distinction between science and pseudoscience but also various aspects of neurobiology and pharmacology.

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 transport proteins and transport mechanisms over the cell membrane, the autonomic nervous system (including the enteric nervous system), 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.

Neuroanatomy

Medicine programme (230 students per year): The unit participates with lectures in functional neuroanatomy in Communication, Nerves and Psyche (T1, 5 hp), Neurobiology, Homeostasis and Intervention (T3, 19,5 hp) and Clinical Medicine V (T8, 25,5 hp). The unit also participates as PBL tutors in Neurobiology, Homeostasis and Intervention (T3, 19,5 hp) and Clinical Medicine V (T8, 25,5 hp).

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

Biomedical programme (50 students per year): The unit participates with lectures in neurohistology in Tissue Biology and Embryology (T3) and neuroplasticity in Neurobiology (T3).

Physiotherapy programme (80 students per year): The unit participates with lectures, group teaching and examination in neuroanatomy 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

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 p project works were tutored

Lars Malmqvist, RapiCSF - A fast test spectral contrast sensitivity, Medical program, UU, 130427

Jenny Sandström, Tablets as a vision aid for elderly with age-related macular degeneration, Medical program, UU, 140425

Biomedicine programme: Ophthalmology is taught during half a 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 that are given annually.

Practical Optics: This 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 opthalmology 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.

ST-project tutored
During 2015 one ST-project was tutored and examined:
Julia Henrikssan, Dept. of Ophthalmology, Hudiksvalls sjukhus, Comparison of estimates of best corrected visual acuity between measurements with a digital chart and the ETDRS chart, respectively.
Tutor: Professor Per Söderberg

Project work
During 2015 on project work was co-tutored with the Master Programme in Computer and Information Engineering
Digitalization of Visual Acuity Testing, Anders Ohlsson, Christian Johansson, Svante Nilsson

International teaching
Undergraduate program, College of Optometry, University of Houston, Houston, Texas, USA Structure, function and pathology of the lens, Per Söderberg. Annual lectures.

Undergraduate- and Masters- and Graduate program, Dept. of Biomedical Engineering, University of Miami, Miami, Florida, USA, Laser Safety.

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 according to the national evaluation scheme required by the national Swedish residents' educational organisation, IPULS, and with a 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 and child and adolescent psychiatry. During 2015 the program was changed and we doubled the courses, teaching psychiatry at semester 8 and 9, and teaching child and adolescent psychiatry at semester 8, 9 and 10. We also teach the subjects communication skills and medical psychology, and also for communications skills we had doubled courses this year. Communication skills and medical psychology 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, 8 and during 2015 also at semester 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 1, 4 and 6.

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 students' evaluations as a basis for revising and developing our courses and pedagogical methods.

Development of teaching and learning

During the 2015 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 2015 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.

The end