



# NEUROSCIENCE CENTER

– ANNUAL REPORT 2010

Neuroscience Center Annual Report 2010

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## PREFACE BY THE DIRECTOR

From the beginning of 2010, the new law (Universities Act 558/2009) has increased autonomy of universities with regard to public administration. In line with this change, the University of Helsinki has considerably revised its internal administrative structure. The number of departments has been reduced, and increasing responsibilities for finances at the department level have been increased.

During this change the Neuroscience Center (NC) was regarded as sufficiently large to continue as an independent unit within the University. The new law and the renewed administration of the University have not caused marked changes in the daily operation of the NC. The main change has been in the rules and regulations of the NC, which have been revised to follow the general line implemented in the University. The revised rules and regulations emphasize the responsibility of the Director who now decides which groups will be recruited to the Center after the Scientific Advisory Board (SAB) and the Board have issued their recommendations. This enables the Director to develop the scientific profile of the Center and to handle the ensuing responsibility in a more explicit manner than in the previous administrative system. In general, the recruiting system has been made more flexible, enhancing possibilities for rapid decisions when needed in hiring talented personnel.

At the beginning of 2010, the SAB visited the Center during the mid-term evaluation of the groups. The Director and the groups received feedback of strengths and weaknesses, which will be very valuable in further development of the NC. All research groups were assessed as deserving of the continued support of the Center. The Adjunct Profes-

sor system was also discussed during the SAB visit. Based on the recommendation by the SAB, the Board accepted the conclusion that the Adjunct Professor system will be terminated at the end of 2010, and the released resources will be used to hire two new groups to the Center.

In response to an open international call for two new group leaders to the NC, 32 applications were received. A remarkable feature in this call was the clearly higher quality of the applications compared with previous NC calls. In particular, the proportion of excellent foreign candidates was clearly higher than earlier. As judged by the SAB and the Director, 8-10 candidates were highly competent to act as group leaders. Based on interviews of the shortlisted candidates by SAB members, Doctor Claudio Rivera and Doctor Sari Lauri were selected as group leaders from the beginning of 2011. Furthermore, with the help of Biocenter Finland financing, Doctor Vootele Vöikar was recruited in 2010 from the University of Zurich as the project leader of the Mouse Behavioral Unit. From the beginning of 2011, the NC comprises 14 research groups and 160 personnel.

The NC aims at developing in vivo studies that can be linked to mechanistic studies at the molecular/cellular level. In line with this research, behavioral studies on transgenic animal models belong to key areas of the NC. Furthermore, neuronal imaging led by Leonard Khirug is rapidly developing as an important core function within the NC. During 2010 the NC acquired a novel two-photon imaging system in cooperation with Neurotar Ltd. This in vivo imaging system when used in transgenic models where different cell types have been labeled allows studies on structural changes at the cellular level in



the living brain. Therefore, novel insights into molecular/cellular mechanisms of physiological and pathophysiological processes of brain are likely to be revealed with the help of the novel technology.

To profile current NC research and teaching, a few highlights have been selected in the Annual Report 2010. Satu Palva and Matias Palva write about their systems-level studies on human working memory (see the research highlight). The group has hypothesized that synchronization of cortical oscillations underlies working memory. The group has used magneto- and electroencephalography (M/EEG) during cognitive tasks to link neurophysiology and a cognitive operation. Using novel neuroinformatics tools to handle large datasets that have been developed in the group, they show synchronization of neuronal activity in functionally distinct cortical assemblies. The authors conclude, based on a series of studies, that dynamic large-scale cortical networks underlie the transient binding of anatomically distributed processes during working memory. The work is an excellent contribution to the basic problem of understanding how psychological phenomena arise from their neurophysiological substrates. Following the NC principle that expertise in research must

be applied in teaching, Satu Palva and Matias Palva have organized a course in systems neuroscience in the Master's degree programme in neuroscience MNEURO, containing a lecture series and a laboratory hands-on course (see the teaching highlight).

Tomi Taira writes about a related problem, but based on work at the molecular/cellular level. Inhibitory interneurons are known to orchestrate neuronal network activities and participate in synchronization of neural networks in both the developing and adult brain. Previous studies by the group have revealed that spontaneous network oscillations in the newborn brain are strongly regulated by kainate-type glutamate receptors (KARs). The group has now shown that KARs directly regulate interneuronal excitability by a G-protein-dependent mechanism. As in the case of the systems-level approach discussed above, the work of KARs provides insights into the biological basis of brain functions and cognitive processes. In addition to research, the electrophysiology groups at the NC have been very active for many years in organizing hands-on courses in their areas of expertise. The courses summarized by Tomi Taira (see the teaching highlight) have been extremely popular for students

within and outside of MNEURO because of the growing need to understand how molecular interactions are reflected in neuronal functions.

Two international conferences (NGF 2010 and HMGB1 2010 meetings) constitute highlights in research and doctoral training where Eero Castrén and Heikki Rauvala acted as major organizers and chairmen. The NGF meeting focused on neurotrophic factors in basic neuroscience and in research aiming at novel strategies to treat neurodegenerative diseases. The focus of the HMGB1 meeting was on inflammatory conditions within and outside of the nervous system, in particular the role of the HMGB1 protein in linking tissue injury and stress to activation of the innate immune response. Both conferences were successful in attracting an enthusiastic scientific audience where the most visible research groups of the conference topics presented their novel findings.

In conclusion, I would like to thank everyone at the NC, our collaborators, and the members of the Board and the SAB for their contributions to developing neuroscience research and teaching at the NC. I look forward to a successful year and important discoveries in basic neuroscience finding practical applications.



**Heikki Rauvala**  
*Director of the Neuroscience Center*



# HIGHLIGHTS 2010

## RESEARCH

### TUNING THE TONE IN DEVELOPING THE HIPPOCAMPAL NETWORK

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Neuronal excitability and the degree of neuronal synchrony are critical properties in determining the behavior of neuronal networks. Inhibitory interneurons orchestrate network activities by pacing, timing, and synchronizing neural circuits in the adult as well as the immature brain. Within the hippocampus, interneurons modulate the output of excitatory pyramidal neurons and granule cells of the dentate gyrus. Interneurons are essential for correct spike timing and synchronization of local oscillatory activity in cortical networks, including “cognitive” theta rhythms (4-12 Hz), gamma waves (25-100 Hz), and sharp-wave ripples (100-200 Hz), and their dysfunction is clearly implicated in pathophysiological phenomena such as epileptic-like activities with large synchronous seizure-like discharges at slower frequencies of 2-5 Hz.

During development neuronal circuits are constructed elaborately before the onset of experience-dependent plasticity. Spontaneous neuronal activity plays a central role in fine-tuning the developing synaptic contacts (Hanse et al. 2009). A critical factor for a given set of neurons to become functionally connected has been suggested to be the temporal coincidence of their activity, a process in which the GABAergic interneurons have an instrumental role. However, despite their vital role in neuronal functioning, surprisingly little is known about the development of the intrinsic firing properties of interneurons.

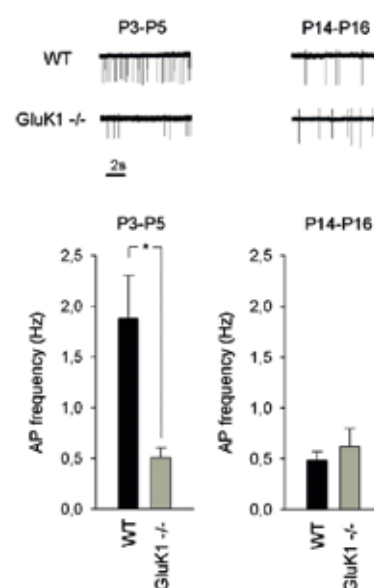
We have previously shown that the distinct, high-frequency spontaneous network oscillations seen in the newborn hippocampus (Palva et al. 2000) are strongly regulated by kainate-type glutamate receptors (KARs) (Lauri et al. 2005; 2006; Maingret et al. 2005; Juuri et al. 2010). We have now found that KARs can directly regulate interneuronal excitability via tonic inhibition of the medium-duration afterhyperpolarization (mAHP) by a G-protein-dependent mechanism, permitting a high interneuronal firing rate (Segerstråle et al. 2010). During develop-

ment the amplitude of the K<sup>+</sup> currents responsible for the mAHP increases dramatically because of decoupling between KAR activation and mAHP modulation, leading to decreased interneuronal firing.

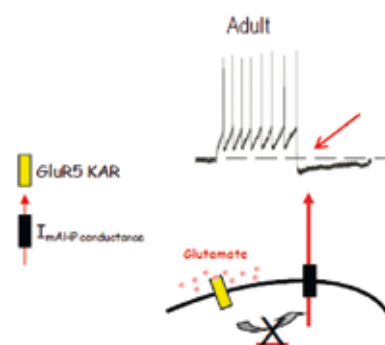
Since interneurons are the key players in setting the temporal coherence critical for synaptic plasticity and neuronal network oscillations, a mechanism that could switch the interneuronal firing pattern from “newborn” to “adult” type would have a substantial role in the activity-dependent maturation of the brain. Moreover, given that neuronal network oscillations are involved in a wide range of cognitive processes and sensory coding, the mechanism can provide intriguing insights into emergence of higher brain functions.

### References

- Hanse E, Taira T, Lauri S and Groc L (2009). Glutamate synapse in developing brain: an integrative perspective beyond the silent state. *Trends Neurosci.* 32: 532-537.
- Juuri J, Clarke VRJ, Lauri SE and Taira T (2010). Kainate receptor-induced ectopic spiking of CA3 pyramidal neurons initiates network bursts in neonatal hippocampus. *J. Neurophysiol.* 104: 1696-1706.
- Lauri SE, Segerstråle M, Vesikansa A, Maingret F, Mülle C, Collingridge GL, Isaac JTR and Taira T (2005). Endogenous activation of kainate receptors regulates glutamate release and network activity in the developing hippocampus. *J. Neurosci.* 25: 4473-84.
- Lauri SE, Vesikansa A, Segerstråle M, Collingridge GL, Isaac JTR and Taira T (2006). Functional maturation of CA1 synapses involves activity-dependent loss of tonic kainate receptor-mediated inhibition of glutamate release. *Neuron* 50: 415-429.
- Maingret F, Lauri SE, Taira T and Isaac JTR (2005). Profound regulation of neonatal CA1 rat hippocampal GABAergic transmission by functionally distinct kainate receptor populations. *J. Physiol.* 567: 131-142.
- Palva JM, Lämsä K, Lauri SE, Rauvala H, Kaila K and Taira T (2000). Fast network oscillations in the newborn rat hippocampus *in vitro*. *J. Neurosci.* 20: 1170-78.
- Segerstråle M, Juuri J, Lanore F, Piepponen P, Lauri SE, Mülle C and Taira T (2010). High firing rate of neonatal hippocampal interneurons is caused by attenuation of afterhyperpolarizing potassium currents by tonically active kainate receptors. *J. Neurosci.* 30: 6507-14.



**Figure 1.** GluK1 KARs regulate spontaneous interneuronal firing frequency in CA3 at P3-P5 but not at P14-P16, P denoting postnatal day (left panels). Data from on-cell recordings in interneurons show that the mean AP firing frequency of interneurons in P3-P5 GluK1 -/- mice (n=25) was significantly lower than that in wild type (WT) mice (n=16, p<0.05). Sample traces from WT and GluK1 -/- mice and summary statistics for P3-P5 data (right panels). Corresponding data from P14-P16 animals, showing no difference in AP firing rate between WT (n=8) and GluK1 -/- (n=10) mice at this age.



**Figure 2.** Scheme of developmental modulation of interneuronal mAHP (indicated by red arrows in voltage traces) by KARs. Note the much higher firing frequency in the newborn. See the text for details.

## NEURONAL SYSTEMS SUPPORTING HUMAN WORKING MEMORY

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Neuronal processing is spatially, temporally, spectrally, and functionally distributed. Identification of the neuronal mechanisms that coordinate this scattered and parallel activity into serial and capacity-limited cognitive operations is a major target in systems neuroscience. The quest for finding these systems-level mechanisms serves the broader goal of understanding how psychological phenomena arise from their neurophysiological substrates.

Cognitive tasks can be readily performed by healthy human subjects during noninvasive magneto- and electroencephalography (M/EEG). Unlike any other noninvasive neuroimaging approach, M/EEG signals directly reflect the underlying electrical activity in neuronal populations. Moreover, while the interpretation of M/EEG data is hindered by an inverse problem, state-of-the-art source reconstruction techniques can localize the neuronal sources reliably in an individual subject's brain anatomy.

Neuronal oscillations are ubiquitous at all levels of the nervous system and are the prime candidate for a mechanism for systems-level integration because they regulate local cortical excitability and co-

ordinate inter-areal functional connectivity in discrete time windows. We hypothesized that large-scale synchronization of human cortical oscillations underlies visual working memory (WM) retention. WM is an interesting cognitive task model because the memory retention period conceivably represents a stable, cognitively uniform, and experimentally well-isolable brain state. To characterize the systems-level mechanisms supporting WM, we developed a neuroinformatics platform for handling large M/EEG datasets and novel methods for data-driven mapping neuronal synchronization among cortical sources.

Fascinatingly, our approach revealed that during memory encoding, ongoing activity in functionally distinct cortical assemblies became synchronized in alpha (10-14 Hz), beta (14-30 Hz), and gamma (30-45 Hz) frequency bands. This synchronization represented a meta-stable brain state throughout the WM retention period and had a robust small-world network topology. Moreover, both local and inter-areal neuronal synchronization were dependent on the number of items held in memory and critically predicted individual behavioral WM capacity. Synchron-

ization within and among fronto-parietal and occipito-temporal networks was thus functionally significant and conceivably supported the attentional and representational functions of WM, respectively.

This series of studies provides evidence that dynamic large-scale cortical networks underlie the transient binding of anatomically distributed processing during working memory. This series of studies also constitute a "proof-of-concept" for using M/EEG in the identification of systems-level mechanisms linking neurophysiology and cognitive operations.

### References

- Palva JM, Monto S, Kulashekhar S and Palva S (2010). Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proc. Natl. Acad. Sci. U.S.A.* 107: 7580-85.
- Palva S, Monto J and Palva JM (2010). Topological properties of synchronized cortical networks during working memory maintenance. *Neuroimage* 49: 3257-68.
- Palva S, Kulashekhar S, Hämäläinen M and Palva JM (2011). Localization of cortical phase and amplitude dynamics during visual working memory encoding and retention. *J. Neurosci.*, in press.

## INTERNATIONAL CONFERENCES

### NGF 2010 CONFERENCE

The 10<sup>th</sup> International Conference on NGF (Nerve Growth Factor) and Related Neurotrophic Factors, NGF 2010, was organized in the Rantapuisto Conference Center in Helsinki on June 10-13, 2010. The conference was organized by the Neuroscience Center and the Finnish Centre of Excellence in Molecular and Integrative Neuroscience Research, and it was chaired by Professors Eero Castrén and Mart Saarma. The conference was attended by about 200 scientists worldwide who were interested in neurotrophic factors and neurodegenerative disorders. The first meeting of this biannual meeting series was organized in 1986 to honor Professor Rita Levi-Montalcini, Nobel Laureate and discoverer of the first neurotrophic factor. At the age of 101, Levi-Montalcini is still an active scientist and at the conference she provided her address, which was read during the opening ceremony.

The topic of the conference was “Neurotrophic Factors in Health and Disease”. Neurotrophic factors regulate neuronal survival, differentiation, and plasticity during development. In the adult brain, neurotrophic factors regulate neuronal plasticity and the formation of neuronal networks, and these are involved in learning, memory, and emotionality. Recent evidence indicates that these factors are

closely involved in the pathophysiology of neurodegenerative and neuropsychiatric disorders and in the treatment strategies for these diseases. These aspects were dealt with during the presentations and were enthusiastically discussed thereafter.

The organization of this conference in Helsinki and its success reflect the international recognition of the high quality of research on neurotrophic factors at the University of Helsinki, particularly at the Neuroscience Center and the Institute of Biotechnology.

### HMGB1 2010 CONFERENCE

HMGB1 (high-mobility group B1) has been identified as a key molecule linking tissue damage and stress to activation of innate immune mechanisms. HMGB1 is currently included in the group of molecules designated as DAMPs (damage-associated molecular patterns) or alarmins. HMGB1 is involved in the pathogenesis of a plethora of diseases in which acute or chronic inflammation plays a role such as sepsis, stroke, epilepsy, and rheumatoid arthritis.

The 4<sup>th</sup> International HMGB1 Symposium was organized in the main building

of the University of Helsinki on June 20-23, 2010. The conference was organized by the Neuroscience Center, Helsinki Graduate School in Biotechnology and Molecular Biology (GSBM) and Shino-Test/IBL International, and it was chaired by Professor Heikki Rauvala. The conference brought together about 100 scientists interested in HMGB1, other HMG-type proteins, and their receptors.

Cell regulation through extracellular HMGB1 (initially designated as “amphotericin”) has been extensively studied in physiological and pathophysiological contexts by the international scientific community during the last few years and was the focus of the meeting. In his keynote lecture, Professor Kevin J. Tracey discussed the recent intriguing findings that the autonomic nervous system controls extracellular HMGB1 levels and therefore affects inflammatory responses in peripheral organs. Other highlights of the meeting included lectures on the role of HMGB1 in the pathogenesis of stroke and epilepsy.

Several enthusiastic presentations and discussions were held on the use of HMGB1 as a diagnostic biomarker, which is currently explored worldwide. Furthermore, successful treatment strategies based on HMGB1 targeting have been shown in several disease models and are expected to reach clinical trials in the forthcoming years.



## TEACHING

### LABORATORY COURSES IN SYSTEMS NEUROSCIENCE: MEG, EEG, AND MRI

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A laboratory course in human magneto- and electro-encephalography (M/EEG) was held for the first time in 2010. This hands-on course was preceded by a lecture series (in 2009) in systems neuroscience that covered the background of M/EEG approaches and their applications in cognitive neuroscience. During the course students performed M/EEG recordings on each other under supervision and learned the various stages involved in state-of-the-art electrophysiological brain imaging. Experiment design and data acquisition pitfalls were also discussed.

The course aimed at and succeeded in collecting publication-quality data that contributed directly to an active research project by the Palva group.

The data were subsequently analyzed by the course's participants in the follow-up course: Data Analysis and Management in Neuroscience. In the analysis course, the students learned to perform an array of data pre-processing, source reconstruction, and time-series analysis operations that lead to the final data visualization. Modern M/EEG research is technically and computationally intensi-

ve; properly guided hands-on experience in data acquisition and in the numerous analyses stages is critical for learning the method. Excitingly, at the end of the course, the students' analyses of their data and visualizations of the group data revealed novel neuronal correlates for conscious somatosensory perception and illustrated the hitherto poorly understood sequences of cortical activity that dissociate the neuronal processing of stimuli reaching sensory awareness from processing that remains unconscious.

### ELECTROPHYSIOLOGICAL APPLICATIONS IN NEUROPHYSIOLOGY

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Since 2003 the electrophysiology groups at the Neuroscience Center have annually organized a two-week hands-on course on *in vitro* electrophysiological techniques. During the course students learn basic skills in *in vitro* electrophysiological techniques (extra- and intracellular recordings, patch-clamp) as well as proper brain tissue preparation. Various experimental approaches (basic properties of hippocampal transmission, synaptic facilitation, epileptogenesis) are utilized to demonstrate the advantages and disadvantages of the different recording techniques (current-clamp, voltage-clamp, population responses, single-cell activity) in a "real-life" situation. By the end of the course, students are able to understand the possibilities and limitations of *in vitro* electrophysiological approaches in neuroscience research and to design experiments in which the techniques are applied in a relevant manner.

The course is nowadays extremely popular since the advances in molecular biology and genetics over the last decades have vastly increased the need to understand how molecular interactions and altered genomics are reflected in neuronal function. The high quality of teaching and the up-to-date techniques students can employ during the course have also resulted in an increasing number of international applicants; in 2010, altogether 6 of 9 students accepted to the course were from abroad or studying in the international programs at the University of Helsinki. The student-teacher ratio in the course is 2:1; thus, there is one senior scientist/PhD-level teacher / two students in the lab throughout the course. This guarantees continuous interaction between students and teachers, allowing an intense yet relaxed learning atmosphere.

## RESEARCH GROUPS

The mission of the Neuroscience Center is to conduct high-level, multidisciplinary research of the development, normal functions, and disorders of the nervous system. Research and teaching at the Neuroscience Center focus on the following four areas: molecular and cellular neuroscience, developmental neuroscience, cognitive and systems neuroscience, and basic research of nervous system diseases. All research groups work in at least one of these areas. In 2010, thirteen research groups worked at the Neuroscience Center.

### GROUP LEADERS



Matti Airaksinen



Eero Castrén



Pirta Hotulainen



Henri Huttunen



Kai Kaila



Leonard Khiroug



Sari Lauri



Anna-Elina Lehesjoki



Matias Palva



Pertti Panula



Heikki Rauvala



Tomi Taira



Vootele Vöikar

## GDNF FAMILY RECEPTORS, KCC2, AND NOVEL LRR PROTEINS IN NERVOUS SYSTEM DEVELOPMENT AND PATHOPHYSIOLOGY

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The Airaksinen group is currently investigating 1) the biology of the glial cell line-derived neurotrophic factor (GDNF) family in cutaneous and gastric innervation (Kupari); 2) the physiological role and regulation of the neuronal K/C-cotransporter KCC2, a key molecule in inhibitory neurotransmission (Blaesse et al. 2009), in particular, novel isoforms and mechanisms that drive KCC2 gene expression and how lack of KCC2 affects brain function (Markkanen, Uvarov); and 3) the physiological function of a novel family of neuronal leucine-rich repeat (LRR)-containing transmembrane proteins (LRRTMs) using genetically modified mice (Laakso, Paatero).

Using KCC2-deficient mouse lines created in the lab, previous studies have examined the specific role of hyperpolarizing inhibition in mouse behavior and

electrophysiology and have shown a novel structural role for KCC2 in spine development. Our work has identified a novel isoform of KCC2 that has a unique N-terminus, including a putative SPAK kinase-binding site (Uvarov et al. 2007). Analysis of expression and available mouse lines indicates that the new KCC2a isoform may support vital neuronal functions in the brain stem and spinal cord, whereas the major KCC2b isoform is responsible for the developmental shift of GABAergic responses. Recently, we showed that the two KCC2 isoforms are coexpressed in the neonatal brain and can form heterodimers (Uvarov et al. 2009) and that the postnatal induction of the KCC2b isoform is partly mediated via BDNF and Egr4 transcription factor (Ludwig et al. 2011).

The LRRTM family members are expressed by overlapping subpopulations

of CNS neurons. Previous studies have identified LRRTM1 as an imprinted gene and the first putative genetic influence on human handedness, making it a candidate gene for involvement in neurodevelopmental disorders. A cellular basis for this association was recently provided by a collaboration that identified LRRTM proteins as synaptic organizers (Linhoff et al. 2009). Consistent with this idea, LRRTMs localize to excitatory synapses and can induce presynaptic differentiation of contacting axons in vitro, and LRRTM1-deficient mice show altered distribution of excitatory synaptic markers in vivo. Moreover, LRRTM1- and LRRTM3-deficient mice show distinct behavioral phenotypes that are under investigation.



### Personnel

**Group leader:** Matti Airaksinen, MD, PhD, docent

**Post-doctoral fellows:** Anja Paatero, PhD;  
Pavel Uvarov, PhD

**Graduate students:** Jussi Kupari, MSc; Tiina Laakso, MSc; Marika Markkanen, MSc; Pavel Uvarov, MSc (PhD defence 18.6.2010)

**Technician:** Kaija Berg

### Selected publications

Ludwig A\*, Uvarov P\*, Soni S, Thomas-Crusells J, Airaksinen MS and Rivera C (2011). Egr4 mediates BDNF induction of KCC2 transcription. *J. Neurosci.* 31: 644-649 (\* equal contribution).

Blaesse P, Airaksinen MS, Rivera C and Kaila K (2009). Cation-chloride cotransporters and neuronal function. *Neuron* 61: 820-838.

Linhoff MW, Laurén J, Cassidy RM, Dobie FA, Nygaard HB, Airaksinen MS, Strittmatter SM and Craig AM (2009). An unbiased expression screen for synaptogenic proteins identifies the LRRTM protein family as synaptic organizers. *Neuron* 61: 734-749.

Uvarov P, Ludwig A, Markkanen M, Soni S, Hübner CA, Rivera C and Airaksinen MS (2009). Co-expression of neuronal K-Cl cotransporter KCC2 isoforms in neonatal brain. *J. Biol. Chem.* 284: 13696-704.

Uvarov P, Ludwig A, Markkanen M, Prunsild P, Kaila K, Delpire E, Timmusk T, Rivera C and Airaksinen MS (2007). A novel N-terminal isoform of the neuron-specific K-Cl cotransporter KCC2. *J. Biol. Chem.* 28: 30570-76.

Airaksinen MS and Saarma M (2002). GDNF family neurotrophic factors: receptor mechanisms, biological functions and therapeutic utility. *Nature Rev. Neurosci.* 3: 383-394.

## SIGRID JUSÉLIUS LABORATORY

### REGULATION OF NEURONAL PLASTICITY AND NEUROTROPHIN SIGNALING IN THE ADULT BRAIN

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Our group is investigating and developing ways of regulating neuronal plasticity and neurotrophic factor signaling in the central nervous system. We have recently been particularly interested in the ability of antidepressants and other drugs acting on the CNS to influence neuronal plasticity in the adult brain. We have previously shown a critical role of neurotrophin BDNF (brain-derived neurotrophic factor) and its receptor TrkB in learning, memory, and emotionality and demonstrated that neurotrophin signaling plays a critical role in the mechanism of action of several drugs, including antidepressants, opioid analgesics, and neuroprotective agents. We recently demonstrated that antidepressant drugs, by acting through the BDNF-trkB system, reactivate developmental-like plasticity in the adult cerebral cortex. We have investigated the epigenetic regulation of BDNF and other factors in adult plasticity and in response to adverse early life events. We have used cultured neurons, organotypic cultures, DNA microarrays, and epigenetic mechanisms to uncover the effects and mechanisms of neurotrophins and neuropsychiatric drugs in the brain. Future aims are to exploit our models to elucidate the roles of neurotrophins and the epigenetic regulation of the BDNF gene

in the normal brain as well as in neurodevelopmental and neuropsychiatric disorders, to understand the roles and consequences of neurotrophin-mediated plastic responses in drug action, and to develop new models to search for drugs that will influence the effects of endogenous neurotrophins on the brain.

#### Personnel

**Research director:** Castrén, Eero, MD, PhD, Sigrid Jusélius Professor in Neuroscience

**Post-doctoral fellows:** Vanina Dahlström-Heuser, PhD; Antonio Di Lieto, MD; Nina Karpova, PhD; Tomi Rantamäki, PhD (pharm); Ettore Tiraboschi, PhD

**Graduate students:** Yumiko Akamine, MSc; Henri Autio, MSc (pharm); Marie-Estelle Hokkanen, MSc; Juha Knuutila, MSc; Jesse Lindholm, MSc (pharm)

**Undergraduate students:** Arna Agustsdóttir; Hanna Antila; Emma Haapaniemi; Liisa Vesa

**Technician:** Outi Nikkilä

#### Selected publications

Maya Vetencourt JF, Tiraboschi E, Spolidoro M, Castrén E and Maffei L (2010). Serotonin triggers a transient epigenetic mechanism that reinstates adult visual cortex plasticity. *Eur. J. Neurosci.* [doi: 10.1111/j.1460-9568.2010.07488.x].

Sallert M, Rantamäki T, Vesikansa A, Anthoni H, Harju K, Yli-Kauhaluoma J, Taira T, Castrén E and Lauri SE (2009). BDNF controls activity-dependent maturation of CA1 synapses by down regulating tonic activation of presynaptic kainate receptors. *J. Neurosci.* 29: 11294-303.

Wu X and Castrén E (2009). Co-treatment with diazepam prevents the effects of fluoxetine on hippocampal neurogenesis. *Biol. Psychiatry* 66: 5-8.

Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, Castrén E and Maffei L (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science* 320: 385-388.

Rantamäki T, Hendolin P, Kankaanpää A, Mijatovic J, Piepponen P, Domenici E, Chao MV, Männistö PT and Castrén E (2007). Pharmacologically diverse antidepressants rapidly activate Brain-derived neurotrophic factor (BDNF) receptor trkB and induce phospholipase-Cy signaling pathways in mouse brain. *Neuropsychopharmacology* 32: 2152-62.

Castrén E (2005). Is mood chemistry? *Nat. Rev. Neurosci.* 6: 241-246.

Castrén M, Tervonen T, Kärkkäinen V, Heinonen S, Castrén E, Larsson K, Bakker CE, Oostra BA and Åkerman KEO (2005). Altered differentiation of neural stem cells in fragile X syndrome. *Proc. Natl. Acad. Sci. U.S.A.* 102: 17834-39.

Sairanen M, Lucas G, Ernfors P, Castrén M and Castrén E (2005). BDNF and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation and survival in the adult dentate gyrus. *J. Neurosci.* 25: 1089-94.



## REGULATION OF THE ACTIN CYTOSKELETON IN DENDRITIC SPINES

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Dendritic spines are small protrusions in neuronal dendrites, which is where the postsynaptic components of most excitatory synapses reside in the brain. Actin cytoskeleton is a structural element underlying specific changes in dendritic spine morphology and synapse strength. The proper morphology of spines and the appropriate regulation of actin cytoskeleton have been shown to be important for memory and learning. Defects in the regulation of actin cytoskeleton in neurons have been implicated in memory disorders. Regulation of the actin cytoskeleton by actin-binding proteins has been widely studied in motile cells, but corresponding information in dendritic spines is lacking.

Our aim is to investigate the molecular mechanisms of memory and learning by studying regulation of the actin cytoskeleton in dendritic spines.

Our main hypothesis is that fine regulation of actin cytoskeleton in neurons controls dendritic spine morphology and underlies the memory process.

Our group was assembled in March 2009. However, studies on actin cytoskeleton in dendritic spine morphogenesis had begun earlier (Hotulainen et al. 2009). In this earlier research, we elucidated the mechanisms of actin polymerization and depolymerization dur-

ing dendritic spine morphogenesis. Now, we continue this work by studying other types of actin binding proteins, namely actin cross-linking proteins palladin and tropomyosin 4 and actin motor proteins myosin IIb and myosin X. We are also interested in phosphorylation of actin, a regulatory mechanism about which little is known. As model systems, we use cultured rat primary hippocampal neurons and acute slices. Spine morphology and motility, as well as actin dynamics in spines, are analyzed by using various microscopy techniques. In addition, we use electrophysiological approaches to study the role of actin regulation in neuron function. This will bring us closer to our aim of understanding molecular mechanisms of memory and learning.

### Personnel

**Project leader:** Pirta Hotulainen, PhD, docent, Academy Research Fellow

**Post-doctoral fellow:** Enni Bertling, PhD

**Graduate student:** Mikko Koskinen, MSc

### Selected publications

Hotulainen P and Hoogenraad CC (2010). Actin in dendritic spines: connecting dynamics to function. *J. Cell Biology* 189: 619-629.

Hotulainen P, Llano O, Smirnov S, Tanhuanpää K, Faix J, Rivera C and Lappalainen P (2009). Defining mechanisms of actin polymerization and depolymerization during dendritic spine morphogenesis. *J. Cell Biology* 185: 323-339.

Skwarek-Maruszewska A, Hotulainen P, Mattila PK and Lappalainen P (2009). Contractility-dependent actin dynamics in cardiomyocyte sarcomeres. *J. Cell Sci.* 122: 2119-26.

Bertling E, Quintero-Monzon O, Mattila PK, Goode BL and Lappalainen P (2007). Mechanism and biological role of profilin-Srv2/CAP interaction. *J. Cell. Sci.* 120: 1225-34.

Hotulainen P and Lappalainen P (2006). Stress-fibers are generated by two distinct actin assembly mechanisms in motile cells. *J. Cell Biol.* 173: 383-394.

Hotulainen P, Paunola E, Vartiainen MK and Lappalainen P (2005). ADF and cofilin-1 play overlapping roles in promoting rapid F-actin depolymerization in mammalian non-muscle cells. *Mol. Biol. Cell.* 16: 649-664.

Bertling E, Hotulainen P, Mattila PK, Matilainen T, Salminen M and Lappalainen P (2004). Cyclase-associated protein 1 (CAP1) promotes cofilin-induced actin dynamics in mammalian nonmuscle cells. *Mol. Biol. Cell* 15: 2324-34.



## PROTEIN-PROTEIN INTERACTIONS IN NEURODEGENERATIVE DISEASES: MECHANISMS, IMAGING AND THERAPEUTIC TARGETS

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Alzheimer's disease (AD), the most common form of dementia, is quickly becoming the most expensive disease of our time. It was recently estimated that the current annual worldwide expenditure for dementia care (~450 billion €) equals 1% of global gross domestic product (GDP). Currently, only symptomatic treatment options are available for AD. Despite substantial research efforts, our understanding of the cellular and molecular pathobiology of AD as well as other neurodegenerative diseases remains limited. Most recent AD research has focused on how to reverse or delay the cerebral amyloid pathology typically seen in AD patients and in animal models of AD. Because of its complexity, AD needs to be approached from various perspectives.

The functionality of the cell depends critically on protein-protein interactions (PPI), particularly on the formation of multi-protein complexes. The traditional methods for studying PPIs rely on steady-state analysis of protein complexes that have been extracted from their native cellular environment. This is a significant shortcoming for functional studies. We use Protein-fragment Complementation Assays (PCA), a novel group of methods that allows studying dynamics of PPIs in

live cells and tissues to understand the basic molecular mechanisms involved in pathophysiology of neurodegenerative diseases. Currently, our focus is on the  $\beta$ -amyloid precursor protein (APP) and microtubule-associated protein Tau, molecules involved in amyloid plaque and neurofibrillary pathologies in AD, respectively. We are also interested in proteins involved in the development of synaptic pathology in AD, such as caspases and their synaptic substrates. Our technology platform allows various types of approaches, including mechanistic studies and screening for novel small-molecule modulators of PPIs. Ultimately, we aim to develop novel molecular imaging and reporter tools to study degenerative molecular interactions in live neurons and intact brain tissue.

### Personnel

**Project leader:** Henri Huttunen, PhD, docent, Academy Research Fellow

**Graduate student:** Pranuthi Muggalla, MSc

**Undergraduate students:** Kai Kysenius; Niko-Petteri Nykänen; Prasanna Sakha

**Technician:** Milla Mustonen, MSc

### Selected publications

Huttunen HJ, Havas D, Peach C, Barren C, Duller S, Xia W, Frosch MP, Hutter-Paier B, Windisch M and Kovacs DM (2010). The acyl-coenzyme A: cholesterol acyltransferase inhibitor CI-1011 reverses diffuse brain amyloid pathology in aged amyloid precursor protein transgenic mice. *J. Neuropathol. Exp. Neurol.* 69: 777-788.

Tsoporis JN, Izhar S, Leong-Poi H, Desjardins JF, Huttunen HJ and Parker TG (2010). S100B interaction with the receptor for advanced glycation end products (RAGE): A novel receptor-mediated mechanism for myocyte apoptosis postinfarction. *Circ. Res.* 106: 93-101.

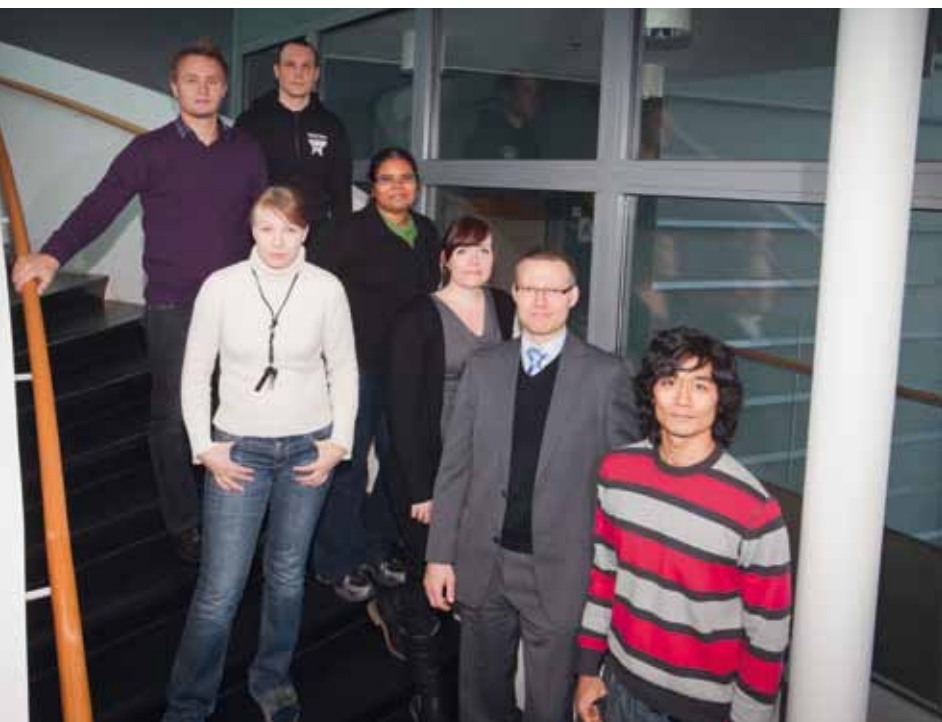
Huttunen HJ, Peach C, Bhattacharyya R, Barren C, Pettingell W, Hutter-Paier B, Windisch M, Berezovska O and Kovacs DM (2009). Inhibition of Acyl-coenzyme A: Cholesterol acyl transferase modulates amyloid precursor protein trafficking in the early secretory pathway. *FASEB J.* 23: 3819-28.

Shulga A, Blaesae A, Kysenius K, Huttunen HJ, Tanhuanpää K, Saarma M and Rivera C (2009). Thyroxin regulates BDNF expression to promote survival of injured neurons. *Mol. Cell. Neurosci.* 44: 528-534.

Huttunen HJ and Kovacs DM (2008). ACAT as a drug target for Alzheimer's disease. *Neurodegener. Dis.* 5: 212-214.

Huttunen HJ, Guenette SY, Peach C, Greco C, Xia WM, Kim DY, Barren C, Tanzi RE and Kovacs DM (2007). HtrA2 regulates APP metabolism through ER-associated degradation. *J. Biol. Chem.* 282: 28285-95.

Hutter-Paier B, Huttunen HJ, Puglielli L, Eckman CB, Kim DY, Hofmeister A, Moir RD, Domnitz SB, Frosch MP, Windisch M and Kovacs DM (2004). The ACAT inhibitor CP-113,818 markedly reduces amyloid pathology in a mouse model of Alzheimer's disease. *Neuron* 44: 227-238.



## MECHANISMS OF ELECTRICAL, IONIC, AND TROPHIC SIGNALING IN THE BRAIN

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Our research has focused on the role of ion-regulatory proteins in the control of neuronal excitability at the molecular, single-cell, network and in vivo levels.

(1) The neuronal chloride extruder KCC2, a key molecule in GABAergic inhibition, upregulated following neonatal seizures, which is the opposite of the seizure effects in the mature brain. Our work suggests age-dependent differences in the effects of neurotrophic factors on the trafficking of KCC2. (2) The neuronal carbonic anhydrase isoform 7 (CA7) has turned out to be a key molecule in seizure generation and a promising anticonvulsant drug target. Using a novel CA7 KO, as well as CA2 KO and double CA7/CA2 KO mice, we have examined the roles of these isoforms in neuronal pH regulation and in the establishment of excitatory bicarbonate-dependent GABA responses during hippocampal development. (3) Experimental febrile seizures (FS) cannot be evoked in the CA7 KO mice. The lack of FS is likely to be caused by a change in neuronal pH responsiveness, and not the absence of hyperthermia-induced hyperventilation. (4) We have shown that 5% CO<sub>2</sub> is a potent anticonvulsant in animal models and human epilepsy patients. (5) We have developed a novel rodent model

of birth asphyxia. Two-photon pH imaging in vivo as well as extracellular pH recordings have shown that birth asphyxia leads to a rise in both intra- and extracellular pH in the brain. Experimental birth-asphyxia seizures can be suppressed by preventing the fast rise in brain pH during recovery. A retrospective clinical study is in progress. (6) Using specific ablation of the cortical subplate in neonatal rats, we have examined activity-dependent structural and functional (EEG) development of the neocortex. (7) Our novel EEG techniques permit long-term monitoring of full-band EEG (Fb-EEG) activity in the neonatal intensive care unit, enabling a comparison of animal models and human neonates. Fb-EEG yields a valid indicator of the level of brain damage in preterm babies, providing guidance for decision-making related to therapeutic interventions.

### Personnel

**Research director:** Kai Kaila, PhD, Professor

**Coordinator:** Katri Wegelius, PhD

**Post-doctoral fellows:** Peter Blaesse, PhD; Eva Ruusuvaori, PhD; Else Tolner, PhD; Henna-Kaisa Wigren, PhD

**Graduate students:** Faraz Ahmad, MSc; Anne Blaesse, MSc; Mohamed Helmy, MB, BCh, MSc; Stanislav Khirug, MSc; Ilya Kirilkin, MD; Alessandro Marabelli, MSc; Nikhil Pandya, MSc; Martin Puskarjov, MSc; Anton Tokariev, MSc; Alexey Yukin, MSc

**Undergraduate student:** Mari Virtanen

**Technicians:** Briitta Haas; Merle Kampura, MSc

### Selected publications

Helmy MM, Tolner EA, Vanhatalo S, Voipio J and Kaila K (2011). Brain alkalosis causes birth asphyxia seizures, suggesting therapeutic strategy. *Ann. Neurol.* 2011 Feb. [Epub ahead of print].

Tolner EA, Hochman DW, Hassinen P, Otáhal J, Gaily E, Haglund MM, Kubová H, Schuchmann S, Vanhatalo S and Kaila K (2011). Five percent CO<sub>2</sub> is a potent, fast-acting inhalation anticonvulsant. *Epilepsia* 52: 104-114.

Khirug S, Ahmad F, Puskarjov M, Afzalov R, Kaila K and Blaesse P (2010). A single seizure episode leads to rapid functional activation of KCC2 in the neonatal rat hippocampus. *J. Neurosci.* 30: 12028-35.

Ruusuvuori E, Kirilkin I, Pandya N and Kaila K (2010). Spontaneous network events driven by depolarizing GABA action in neonatal hippocampal slices are not attributable to deficient mitochondrial energy metabolism. *J. Neurosci.* 30: 15638-42.

Blaesse P, Airaksinen MS, Rivera C and Kaila K (2009). Cation-chloride cotransporters and neuronal function. *Neuron* 61: 820-838.

Khirug S, Yamada J, Afzalov R, Voipio J, Khiroug L and Kaila K (2008). GABAergic depolarization of the axon initial segment in cortical principal neurons is caused by the Na-K-2Cl cotransporter NKCC1. *J. Neurosci.* 28: 4635-39.

Li H, Khirug S, Cai C, Ludwig A, Blaesse P, Kolikova J, Afzalov R, Coleman SK, Lauri S, Airaksinen MS, Keinänen K, Khiroug L, Saarna M, Kaila K and Rivera C (2007). KCC2 interacts with the dendritic cytoskeleton to promote spine development. *Neuron* 56: 1019-33.

Schuchmann S, Schmitz S, Rivera C, Vanhatalo S, Mackie K, Sipilä ST, Voipio J and Kaila K (2006). Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. *Nat. Med.* 12: 817-823.



## FUNCTIONAL AND MORPHOLOGICAL PLASTICITY OF TRIPARTITE SYNAPSE

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Synaptic networks constantly undergo plastic changes that are manifested as morphological and functional modulation of both excitatory and inhibitory synapses. While synaptic plasticity has been in the spotlight of neuroscience for some years now, its mechanisms remain poorly understood. A major challenge lies in uncovering the complex interactions between multiple chemical and electrical signaling pathways in the synapse. Fortunately, recent developments in optical and genetic methods are now offering an unprecedented opportunity to study these interactions and pathways in the highly relevant context of a living animal's brain.

The research by our group focuses on studying structural and functional plasticity of the synapse by utilizing a combination of advanced optical and electrophysiological techniques. We examine the synapse as a tripartite structure composed of a presynaptic neuron (terminal), a postsynaptic neuron (dendritic spine), and a perisynaptic astrocyte that enwraps the other two synaptic components and actively participates in the overall functional and morphological plasticity. Experiments are carried out in the intact brain of living animals, on brain slices, and on cultured neurons. Our methods include in vivo two-photon microscopic imaging, confocal microscopy, intrinsic optical signal imaging, patch clamp electrophysiology, local photolysis of caged compounds, calcium imaging, and total internal reflection fluorescence (TIRF) microscopy. We also develop new techniques, e.g. novel caged compounds, optical sensors based on fluorescent proteins, and methods for in vivo gene delivery to the neonatal rodent brain by non-ventricular plasmid microinjection and electroporation.

The main lines of our current research include 1) the role of structural changes in fine astrocytic processes in functional synaptic plasticity; 2) the role of mitochondrial signaling and Ca<sup>2+</sup> homeostasis in neurodegeneration, and the regulation of mitochondrial motility in relation to synaptic function; 3) pain-related mechanisms of P2X and TRPV1 receptor regulation; 4) activity-dependent trafficking of receptors and channels to the plasma membrane; and 5) mechanisms by which GABAergic synapses shift between inhibitory and excitatory modes of action.

### Personnel

**Group leader:** Leonard Khiroug, PhD, docent, Academy Research Fellow

**Post-doctoral fellows:** Julia Kolikova, PhD; Minna Niittykoski, PhD; Olesya Okuneva, PhD; Sergey Osmekhin, PhD; Evgeny Pryazhnikov, PhD; Svetlana Zobova, PhD

**Graduate students:** Artjom Dugan, BSc; Mikhail Kislin, MSc; Dmitry Molotkov, MSc; Dmytro Toptunov, MSc

**Undergraduate students:** Veronika Rezov; Elisabeth Tilli

**Visiting scientists:** Rasa Gabrenaite, PhD; Alexander Surin, PhD

**Visiting students:** Elisa Rech; Xiaoying Kang

### Selected publications

Molotkov D, Yukin A, Afzalov R and Khiroug L (2010). Gene delivery to postnatal rat brain by non-ventricular plasmid injection and electroporation. *J. Vis. Exp. JoVE* <http://www.jove.com/index/details.stp?id=2244>, doi: 10.3791/2244.

Khirug S, Pryazhnikov E, Coleman SK, Jeromin A, Keinänen K and Khiroug L (2009). Dynamic visualization of membrane-inserted fraction of pHluorin-tagged channels using repetitive acidification technique. *BMC Neurosci.* 10: 141.

Khirug S, Yamada J, Afzalov R, Voipio J, Khiroug L and Kaila K (2008). GABAergic depolarization of the axon initial segment in cortical principal neurons is caused by the Na-K-2Cl cotransporter NKCC1. *J. Neurosci.* 28: 4635-39.

Pryazhnikov E and Khiroug L (2008). Sub-micromolar increase in [Ca<sup>2+</sup>]<sub>i</sub> triggers delayed exocytosis of ATP in cultured astrocytes. *Glia* 56: 38-49.

Li H, Khirug S, Cai C, Ludwig A, Kolikova J, Afzalov R, Coleman S, Lauri S, Airaksinen M, Keinänen K, Khiroug L, Saarna M, Kaila K and Rivera C (2007). KCC2 interacts with the dendritic cytoskeleton to promote spine development. *Neuron* 56: 1019-33.

Tanaka K, Khiroug L, Santamaria F, Doi T, Ogasawara H, Ellis-Davies G, Kawato M and Augustine GJ (2007). Ca<sup>2+</sup> requirements for cerebellar long-term synaptic depression: role for a postsynaptic leaky integrator. *Neuron* 54: 787-800.

Kolikova J, Afzalov R, Giniatullina A, Surin A, Giniatullin R and Khiroug L (2006). Calcium-dependent trapping of mitochondria near plasma membrane in stimulated astrocytes. *Brain Cell Biol.* 35: 75-86.

Khirug S, Huttu K, Ludwig A, Smirnov S, Voipio J, Rivera C, Kaila K and Khiroug L (2005). Distinct properties of functional KCC2 expression in immature mouse hippocampal neurons in culture and in acute slices. *Eur. J. Neurosci.* 21: 899-904.



## SIGNALING MECHANISMS GUIDING FUNCTIONAL MATURATION OF GLUTAMATERGIC SYNAPSES

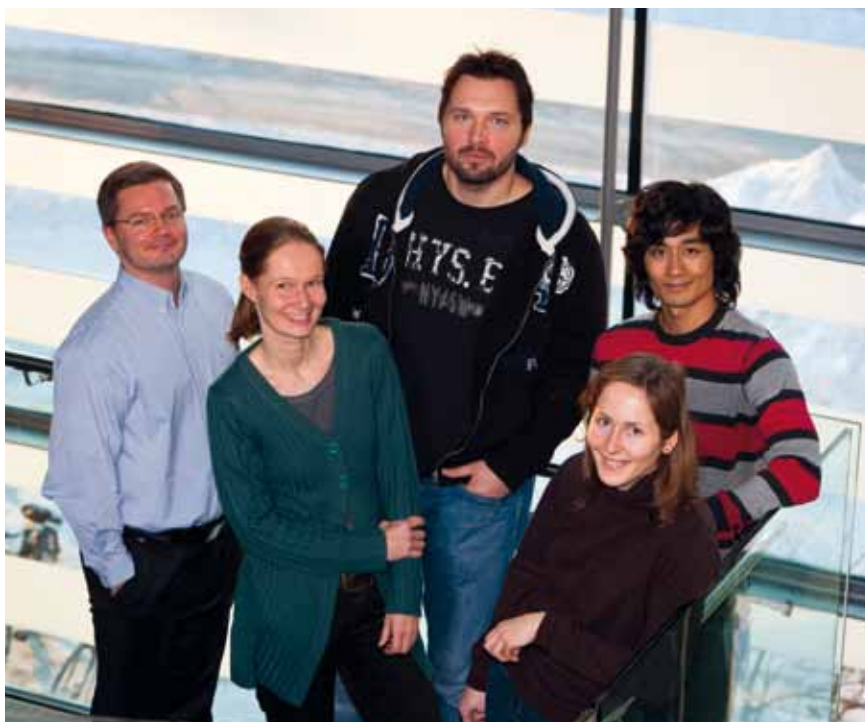
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Formation of neuronal circuits is a highly dynamic process of rapid and concurrent formation and elimination of synaptic connections. During this early development immature neuronal networks typically display spontaneous, rhythmic activity, which is thought to be instrumental in the development of synaptic circuitry.

Exactly how activity shapes synaptic connectivity during development and the molecular mechanisms underlying these processes remain largely unknown. The key questions focus on the cellular and molecular mechanisms that link electrical activity to changes in synaptic structure and how these are regulated during development. To shed light on the process, we have investigated the glutamate receptor mechanisms to detect specific patterns of endogenous activity in the immature hippocampus as well as in the downstream signaling cascades converting receptor ac-

tivity into long-lasting synaptic imprints. Our experimental approach involves the use of in vitro electrophysiological techniques in combination with pharmacological and local genetic manipulation of neuronal activity in various neonatal hippocampal preparations.

Our current main research interests are as follows: 1) the physiological functions and developmental regulation of kainate-type ionotropic glutamate receptors in the immature hippocampus; and 2) the activity-dependent mechanisms guiding presynaptic maturation at developing glutamatergic synapses. We aim to understand how the fast Hebbian and the slow, homeostatic plasticity mechanisms operate in the developing circuitry and how they might control the transition from immature to mature presynaptic function.



### Personnel

**Project leader:** Sari Lauri, PhD, docent, Academy Research Fellow

**Graduate students:** Marko Sallert, MSc; Aino Vesikansa, MSc

**Undergraduate students:** Prasanna Sakha; Juha Simola

**Technical staff:** Marina Tibeikina, MSc

### Selected publications

Hanse E, Taira T, Lauri S and Groc L (2009). Glutamate synapse in developing brain: an integrative perspective beyond the silent state. **Trends Neurosci.** 32: 532-537.

Sallert M, Rantamaki T, Vesikansa A, Anthoni H, Harju K, Yli-Kauhaluoma J, Taira T, Castrén E and Lauri SE (2009). Brain-derived neurotrophic factor controls activity-dependent maturation of CA1 synapses by downregulating tonic activation of presynaptic kainate receptors. **J. Neurosci.** 29: 11294-303.

Huupponen J, Molchanova S, Taira T and Lauri SE (2007). Susceptibility for homeostatic plasticity is downregulated in parallel with maturation of the hippocampal synaptic circuitry. **J. Physiol.** 581(Pt 2): 505-514.

Vesikansa A, Sallert M, Taira T and Lauri SE (2007). Activation of kainate receptors controls density of functional glutamatergic synapses in the area CA1 of hippocampus. **J. Physiol.** 583(Pt 1): 145-157.

Lauri SE, Vesikansa A, Segerstråle M, Collingridge GL, Isaac JTR and Taira T (2006). Functional maturation of CA1 synapses involves activity-dependent loss of tonic kainate receptor-mediated inhibition of glutamate release. **Neuron** 50: 415-429.

Lauri SE, Segerstråle M, Vesikansa A, Maingret F, Mülle C, Collingridge GL, Isaac JTR and Taira T (2005). Endogenous activation of kainate receptors regulates glutamate release and network activity in the developing hippocampus. **J. Neurosci.** 25: 4473-84.

Lauri SE, Bortolotto ZA, Bleakman D, Ornstein PL, Lodge D, Isaac JTR and Collingridge GL (2003). A role for Ca<sup>2+</sup> stores in kainate-dependent synaptic facilitation and LTP at mossy fibre synapses in the hippocampus. **Neuron** 39: 327-341.

Lauri SE, Bortolotto ZA, Bleakman D, Ornstein PL, Lodge D, Isaac JTR and Collingridge GL (2001). A critical role of a facilitatory kainate autoreceptor in mossy fibre LTP. **Neuron** 32: 697-709.

## MECHANISMS OF NEUROLOGIC DISEASE: FROM GENE MUTATION TO MOLECULAR PATHOGENESIS

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Our research aims at understanding the molecular basis of human inherited disorders through identification of the underlying defective genes, followed by functional analyses of the gene product in cellular and animal models. The research focuses on disease mechanisms in progressive myoclonus epilepsy (EPM1), on gene identification in inherited rare central nervous system disorders, and on molecular genetics of idiopathic epilepsy.

The focus in the EPM1 project has been on the characterization of the role for cystatin B (CSTB) as a regulator of neuronal survival during oxidative stress and stereological analysis of disease progression in brains of *Cstb*<sup>-/-</sup> mice. Our data define a novel pathophysiological mechanism related to EPM1, whereby CSTB deficiency couples oxidative stress to neuronal death and degeneration, and suggest that intact CSTB-cathepsin B signaling is critical for maintaining cellular homeostasis under oxidative stress conditions. Stereological analyses have shown that early microglial activation precedes neuronal death and is a central contributor to EPM1 pathogenesis.

Following the identification of a novel gene, *MFSD8*, underlying neuronal ceroid lipofuscinosis (NCL), we have revealed that *MFSD8* mutations are a rather common cause for NCL worldwide. The search for novel genes underlying progressive neurodegenerative disorders in children using SNP-chip-based homozygosity mapping followed by next-generation sequencing of candidate regions resulted in identification of several novel candidate genes whose role in disease is dissected further.

In collaboration with Professor Holger Lerche, we characterized a novel *de novo* *SCN2A* gene missense mutation identified in a patient with early-onset epilepsy and later appearing episodic ataxia, myoclonus, and pain. We showed that the mutation leads to pronounced gain of function in the brain sodium channel NaV1.2 encoded by *SCN2A*. Thus, hyperexcitability of NaV1.2 may be associated with other symptoms besides seizures.

### Personnel

**Research director:** Anna-Elina Lehesjoki, MD, PhD, Professor

**Senior scientist:** Outi Kopra, PhD, docent

**Post-doctoral fellows:** Anna-Kaisa Anttonen, MD, PhD; Tarja Joensuu, PhD; Kaisa Kettunen, PhD; Olesya Okuneva, PhD; Anne Polvi, PhD; Jaana Vesterinen, PhD, docent

**Graduate students:** Maria Kousi, MSc; Mervi Kuronen, MSc; Inken Körber, Dipl.Biol.; Anni Laari, MSc; Otto Manninen, MSc; Saara Tegelberg, MSc; Auli Sirén, MD

**Undergraduate students:** Markus Lommi; Katariina Mattila, BM; Minnamari Talvitie, BSc; Isa Uski, BSc

**Technicians and other technical staff:** Paula Hakala; Hanna Hellgrén; Sinikka Lindh; Teija-Tuulia Toivonen

### Selected publications

Liao Y, Anttonen A-K, Liukkonen E, Gaily E, Maljevic S, Schubert A, Bellan-Koch A, Petrou S, Ahonen VE, Lerche H and Lehesjoki A-E (2010). *SCN2A* mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus and pain. **Neurology** 75:1454-58.

Dibbens LM, Michelucci R, Gambardella A, Andermann F, Rubboli G, Bayly MA, Joensuu T, Vears DF, Franceschetti S, Canafoglia L, Wallace R, Bassuk AG, Power DA, Tassinari CA, Andermann E, Lehesjoki AE and Berkovic SF (2009). *SCARB2* mutations in progressive myoclonus epilepsy without renal failure. **Ann. Neurol.** 66: 532-536.

Kousi M, Siintola E, Dvorakova L, Vlaskova H, Turnbull J, Topcu M, Yuksel D, Gokben S, Minassian B, Elleder M, Mole S and Lehesjoki A-E (2009). Mutations in *CLN7/MFSD8* are a common cause of variant late-infantile neuronal ceroid lipofuscinosis. **Brain** 132: 810-819.

Lehtinen MK, Tegelberg S, Schipper H, Su H, Zukor H, Manninen O, Kopra O, Joensuu T, Hakala P, Bonni A and Lehesjoki A-E (2009). Cystatin B deficiency sensitizes neurons to oxidative stress in progressive myoclonus epilepsy, EPM1. **J. Neurosci.** 29: 5910-15.

Joensuu T, Kuronen M, Alakurtti K, Tegelberg S, Hakala P, Aalto A, Huopaniemi L, Aula N, Michelucci R, Eriksson K and Lehesjoki A-E (2007). Cystatin B: mutation detection, alternative splicing and expression in progressive myoclonus epilepsy of Unverricht-Lundborg type (EPM1) patients. **Eur. J. Hum. Genet.** 15: 185-193.

Siintola E, Topcu M, Aula N, Lohi H, Minassian BA, Paterson AD, Liu XQ, Wilson C, Lahtinen U, Anttonen AK and Lehesjoki AE (2007). The novel neuronal ceroid lipofuscinosis gene *MFSD8* encodes a putative lysosomal transporter. **Am. J. Hum. Genet.** 81: 136-146.

Alakurtti K, Weber E, Rinne R, Theil G, de Haan G-J, Lindhout D, Salmikangas P, Saukko P, Lahtinen U and Lehesjoki A-E (2005). Loss of lysosomal association of cystatin B proteins representing progressive myoclonus epilepsy, EPM1, mutations. **Eur. J. Hum. Genet.** 13: 208-215.

Anttonen AK, Mahjneh I, Hämäläinen RH, Lagier-Tourenne C, Kopra O, Waris L, Anttonen M, Joensuu T, Kalimo H, Paetau A, Tranebjaerg L, Chaigne D, Koenig M, Eeg-Olofsson O, Udd B, Somer M, Somer H and Lehesjoki AE (2005). The gene disrupted in Marinesco-Sjögren syndrome encodes SLL1, an HSPA5 cochaperone. **Nat. Genet.** 37: 1309-11.



## SYSTEMS-LEVEL MECHANISMS OF PERCEPTION, COGNITION, AND ACTION IN THE HUMAN BRAIN

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All human behavior: perception, cognition, and action, emerges from intricate, multiscale neuronal interactions among brain regions. Accumulating data also suggest that disorders of these interaction networks can be the causal factor in many brain diseases. The aim of the Palva group is to characterize and identify neuronal network-level mechanisms that underlie the binding of anatomically, temporally, and spectrally scattered neuronal activity into coherent perception, cognition, and action. Synchronized network oscillations that reflect rhythmic millisecond-range temporal correlations of neuronal activity are known to modulate neuronal interactions and regulate network communication. They are thus a strong candidate mechanism for systems-level neuronal coordination and the main topic of the Palva group research. The functional role of network oscillations in the human brain can be studied noninvasively with magneto- and electroencephalography (MEG and EEG), which have the required millisecond-range temporal resolution. During 2007-2009 we developed a neuroinformatics approach for mapping all recordable (~105) cortex-wide neuronal interactions by using combined MEG/EEG and source reconstruction techniques that reveal the cortical structures underlying the MEG/EEG signals. We have used this approach to characterize the networks that underlie the maintenance of object representations in working memory and to predict the individual behavioral working memory capacity. We now aim to identify the dynamic network interactions that underlie perception, attention, and sensory awareness and their putative abnormalities in several brain diseases.

### Personnel

**Project leader:** Matias Palva, PhD, docent

**Post-doctoral fellow:** Satu Palva, PhD

**Graduate students:** Shrikant Kulashekhar, BSc;  
Simo Monto, MSc (Tech) (PhD defence 29.4.2010);  
Santeri Rouhinen, MSc

**Undergraduate students:** Onerva Korhonen;  
Ina-Maria Naukkarinen; Jonatan Panula

### Selected publications

Palva S, Monto J and Palva JM (2010). Topological properties of synchronized cortical networks during working memory maintenance. *Neuroimage* 49: 3257-68.

Monto S, Palva S, Voipio J and Palva JM (2008). Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans. *J. Neurosci.* 28: 8268-72.

Monto S, Vanhatalo S, Holmes MD and Palva JM (2007). Epileptogenic neocortical networks are revealed by abnormal temporal dynamics in seizure-free subdural EEG. *Cereb. Cortex* 17: 1386-93.

Palva S and Palva JM (2007). New vistas for alpha-frequency band oscillations. *Trends Neurosci.* 30: 150-158.

Palva JM, Palva S and Kaila K (2005). Phase synchrony among neuronal oscillations in the human cortex. *J. Neurosci.* 25: 3962-72.

Palva S, Linkenkaer-Hansen K, Näätänen R and Palva JM (2005). Early neural correlates of conscious somatosensory detection. *J. Neurosci.* 25: 5248-58.

Linkenkaer-Hansen K, Nikulin VV, Palva S, Ilmoniemi RJ and Palva JM (2004). Prestimulus oscillations enhance psychophysical performance in humans. *J. Neurosci.* 24: 10186-90.

Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J and Kaila K (2004). Infralow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proc. Natl. Acad. Sci. U.S.A.* 101: 5053-57.



## MODULATORY NEUROTRANSMITTER SYSTEMS AND THEIR ROLE IN BRAIN DISEASES

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The modulatory neurotransmitters activate G protein-coupled receptors, which share signal transduction systems in cells. In addition to regulating key physiological functions, these systems are involved in human mental and neurological diseases. We are particularly interested in the histaminergic system, which interacts with other systems in regulation of, for instance, sleep, diurnal rhythms, feeding, and addiction.

In a mouse model, lack of histamine in the brain of histidine decarboxylase-deficient mice was associated with an altered ethanol-induced locomotor response. H3 receptor antagonists inhibited the ethanol-evoked conditioned place preference, whereas an agonist did not. Acute stimulatory response by ethanol was also modulated by H3 receptor ligands. An antagonist increased ethanol activation, while agonist pretreatment diminished it. The inhibition of ethanol reward by H3 receptor antagonism implies that H3 receptor is a potential target to suppress compulsory ethanol seeking. In a postmortem human study, H3 receptor radioligand binding was higher in the

prefrontal cortex of schizophrenic brains than in control subjects, suggesting that histamine through this receptor may regulate cortical functions important in psychiatric diseases.

The target cell populations of neurotoxins that in humans cause Parkinson's disease were identified in the zebrafish brain. The two tyrosine hydroxylases in the zebrafish brain showed complementary expression patterns. Translation inhibition of the PARK6 gene (PINK1) important in early-onset Parkinson's disease led to decreased neuron numbers in the same cell groups, expressing either TH1 or TH2 as the neurotoxin MPTP. A decline in neuron numbers was associated with decreased locomotor activity of the fish, suggesting that these neurons are functionally important. Inhibition of PINK1 translation also rendered the fish sensitive to subeffective doses of MPTP, indicating interactions of genetic and environmental factors relevant in Parkinson's disease. Using microarray analyses, several novel signaling pathways related to PINK1 knockdown were identified and verified functionally.

### Personnel

**Research director:** Pertti Panula, MD, PhD, Professor

**Post-doctoral fellows:** Yu-Chia Chen, PhD; Kaj Karlstedt, PhD; Hisaaki Kudo, PhD; Yaroslav Lyubimov, PhD; Saara Nuutinen, PhD; Svetlana Semenova, PhD

**Graduate students:** Raphaela Kaisler, MSc; Madhusmita Priyadarshini, MSc; Stanislav Rozov, MSc; Maria Sundvik, MSc; Jenni Vanhanen, MSc

**Undergraduate students:** Tiia Ojala; Pauliina Toivonen

**Technicians:** Noora Kanerva; Henri Koivula, BSc; Anna Lehtonen, BSc; Susanna Norrbacka

**Visiting scientists:** Piotr Podlasz, VMD, PhD; Michalis Pavlidis, PhD, Professor

### Selected publications

Nuutinen S, Vanhanen J, Pigni MC and Panula P (2010). Effects of histamine H3 receptor ligands on the rewarding, stimulant and motor-impairing effects of ethanol in DBA/2J mice. *Neuropharmacology* Oct 31. [Epub ahead of print].

Sallinen V, Kolehmainen J, Priyadarshini M, Toileikyte G, Chen YC and Panula P (2010). Dopaminergic cell damage and vulnerability to MPTP in Pink1 knock-down zebrafish. *Neurobiol Dis.* 40: 93-101.

Jin C, Karlstedt K and Panula P (2009). Altered histamine H<sub>3</sub> receptor radioligand binding in postmortem brain samples from subjects with psychiatric diseases. *Br. J. Pharmacol.* 157: 118-29.

Kudo H, Liu J, Jansen EJ, Ozawa A, Panula P, Martens GJ and Lindberg I (2009). Identification of proSAAS homologs in lower vertebrates: conservation of hydrophobic helices and convertase-inhibiting sequences. *Endocrinology* 150: 1393-99.

Nuutinen S, Karlstedt K, Aitta-Aho T, Korpi ER and Panula P (2009). Histamine and H3 receptor-dependent mechanisms regulate ethanol stimulation and conditioned place preference in mice. *Psychopharmacology* 198: 381-6.

Sallinen V, Sundvik M, Reenilä I, Peitsaro N, Khrustalyov D, Anichtchik O, Kaslin J and Panula P (2009). Hyperserotonergic phenotype after monoamine oxidase inhibition in larval zebrafish. *J. Neurochem.* 109: 403-415.

Sallinen V, Torkko V, Sundvik M, Reenilä I, Khrustalyov D, Kaslin J and Panula P (2009). MPTP and MPP+ target specific aminergic cell populations in larval zebrafish. *J. Neurochem.* 108: 719-31.



## CELL SURFACE AND EXTRACELLULAR MATRIX MOLECULES IN NEURONAL DEVELOPMENT, PLASTICITY, AND DISORDERS

**Heikki Rauvala**  
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Our group focuses on mechanisms of neuronal development and plasticity. Based on neurite outgrowth assays, we have previously isolated, cloned, and produced as recombinant proteins two ligands of heparan sulfate proteoglycans, HB-GAM (heparin-binding growth-associated molecule; pleiotrophin) and HMGB1 (high-mobility group B1; amphoterin).

Recent studies have shown that HB-GAM regulates migration of neurons in the developing brain through binding to the transmembrane proteoglycan syndecan-3 (N-syndecan). Furthermore, syndecan-3 acts as a cell surface receptor for GDNF (glial cell-derived neurotrophic factor)-family neurotrophic factors.

In addition to heparin/heparan sulfates, HMGB1 binds to the immunoglobulin superfamily protein RAGE (receptor for advanced glycation end-products), which mediates the neurite outgrowth-promoting signal of HMGB1. In addition to growth cone migration, HMGB1/

RAGE regulates migration and proliferation of many cell types during development, tumor spread, and inflammation. Studies on HMGB1/RAGE have resulted in a novel research line, where communication of neurons with immune cells is explored.

AMIGO (amphoterin-induced gene and orf) has been identified as an HMGB1-induced gene in hippocampal neurons using ordered differential display. AMIGO defines a novel gene family with three closely related members (AMIGO, AMIGO 2, and AMIGO 3) belonging to both LRR (leucine-rich repeat) and Ig (immunoglobulin) superfamilies of cell surface proteins.

Physiological and pathophysiological roles of HB-GAM, HMGB1/RAGE, and the AMIGOs are examined using the mouse and the zebrafish as model organisms. The signaling mechanisms of the proteins are elucidated using methods of molecular cell biology and structural biology.

### Personnel

**Research director:** Rauvala, Heikki, MD, PhD, Professor, Director

**Post-doctoral fellows:** Mikhail Paveliev, PhD; Ari Rouhiainen, PhD; Li Tian, PhD

**Graduate students:** Marjaana Kiiltomäki, MSc; Juha Kuja-Panula, MSc; Evgeny Kuleskiy, MSc; Lauri Mankki, MSc; Päivi Vanttola, MSc; Xiang Zhao, MSc

**Technicians:** Erja Huttu; Seija Lågas; Eva-Liisa Saarikalle

### Selected publications

#### HB-GAM/N-syndecan (syndecan-3)

Bespalov MM, Sidorova YA, Tumova S, Ahonen-Bishop A, Magalhães AC, Kuleskiy E, Paveliev M, Rivera C, Rauvala H and Saarma M (2011). Heparan sulfate proteoglycan syndecan-3 is a novel receptor for GDNF, neurturin, and artemin. *J. Cell Biol.* 192: 153-169.

Hienola A, Tumova S, Kuleskiy E and Rauvala H (2006). N-Syndecan deficiency impairs neural migration in brain. *J. Cell Biol.* 174: 569-580.

#### HMGB1/Ig superfamily proteins/ AMIGO

Rauvala H and Rouhiainen A (2010). Physiological and pathophysiological outcomes of the interactions of HMGB1 with cell surface receptors. *Biochim. Biophys. Acta* 1799: 164-170.

Tian L, Rauvala H and Gahmberg CG (2009). Neuronal regulation of immune responses in the central nervous system. *Trends Immunol.* 30: 91-99.

Tian L, Lappalainen J, Autero M, Hänninen S, Rauvala H and Gahmberg CG (2008). Shedded neuronal ICAM-5 suppresses T-cell activation. *Blood* 111: 3615-25.

Rouhiainen A, Tumova S, Valmu L, Kalkkinen N and Rauvala H (2007). Pivotal Advance: Analysis of proinflammatory activity of highly purified eukaryotic recombinant HMGB1 (amphoterin). *J. Leukoc. Biol.* 81: 49-58.

Rouhiainen A, Kuja-Panula J, Wilkman E, Pakkanen J, Stenfors J, Tuominen RK, Lepäntalo M, Carpen O, Parkkinen J and Rauvala H (2004). Regulation of monocyte migration by amphoterin (HMGB1). *Blood* 104: 1174-82.

Kuja-Panula J, Kiiltomäki M, Yamashiro T, Rouhiainen A and Rauvala H (2003). AMIGO, a transmembrane protein implicated in axon tract development, defines a novel protein family with leucine-rich repeats. *J. Cell Biol.* 160: 963-973.



## ACTIVITY-DEPENDENT DEVELOPMENT AND PLASTICITY IN THE HIPPOCAMPUS

**Tomi Taira**  
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During development our brain evolves from a sparsely connected set of nerve cells into a finely tuned neuronal network capable of delicate information processing. Spontaneous electrical activity, i.e. electrical events emerging within the neuronal network itself rather than being evoked by external inputs, provides important cues for the precise neural connections to be formed, but we have only just begun to understand the elaborateness of this process. Our project aims at elucidating the activity-dependent mechanisms that regulate development and plasticity of neuronal connections in the mammalian brain and how these mechanisms contribute to the functional maturation of neuronal networks. We employ a multi-methodological approach using a combination of electrophysiological, molecular biological, and imaging techniques. Moreover, a wide range of experimental models (*in vitro*, *in vivo*) are used in parallel, providing an immediate, physiologically relevant framework for our studies. We have recently identified a new kainate-type glutamate re-

ceptor (KAR) that regulates presynaptic maturation in developing hippocampal neurons (Lauri et al. 2006). It provides a novel mechanism for activation of 'silent' synapses during early development and is thus likely to play a critical role in the formation of functional synaptic connections in the hippocampus. At the level of the neuronal network, KARs via modulating synaptic inputs to both interneurons and pyramidal cells regulate synchronous activity in the developing hippocampus. Interestingly, this kind of activity is probably linked to certain stages of early sleep. The level of neuronal network activity can in turn have a critical impact on the maturation of the hippocampal circuitry. Our work has demonstrated that the density of glutamatergic synapses is rapidly regulated by the overall levels of neuronal activity in the intact immature hippocampus. This regulation is strongly dependent on the developmental stage of the tissue, and it appears to have different 'critical periods' for excitatory (glutamatergic) and inhibitory (GABAergic) synapses.

### Personnel

**Group leader:** Tomi Taira, PhD, docent

**Post-doctoral fellows:** Vernon Clarke, PhD;  
Svetlana Molchanova, PhD

**Graduate students:** Johanna Huupponen, MSc;  
Juuso Juuri, MSc; Natalia Luchkina, MSc;  
Mikael Segerstråle, MSc; Marina Tibeikina, MSc

**Undergraduate students:** Teemu Hirvonen;  
Ragani Velusamy

### Selected publications

Segerstråle M, Juuri J, Lanore F, Piepponen P, Lauri SE, Mülle C and Taira T (2010). High firing-rate of neonatal hippocampal interneurons is due to attenuation of afterhyperpolarizing potassium currents by tonically active kainate receptors. *J. Neurosci.* 30: 6507-6514.

Hanse E, Taira T, Lauri SE and Groc L (2009). Glutamate synapse in developing brain: an integrative perspective beyond the silent state. *Trends Neurosci.* 32: 532-537.

Sallert M, Rantamäki T, Vesikansa A, Anthoni H, Harju K, Yli-Kauhaluoma J, Taira T, Castrén E and Lauri SE (2009). Brain-derived neurotrophic factor controls activity-dependent maturation of CA1 synapses by downregulating tonic activation of presynaptic kainate receptors. *J. Neurosci.* 29: 11294-303.

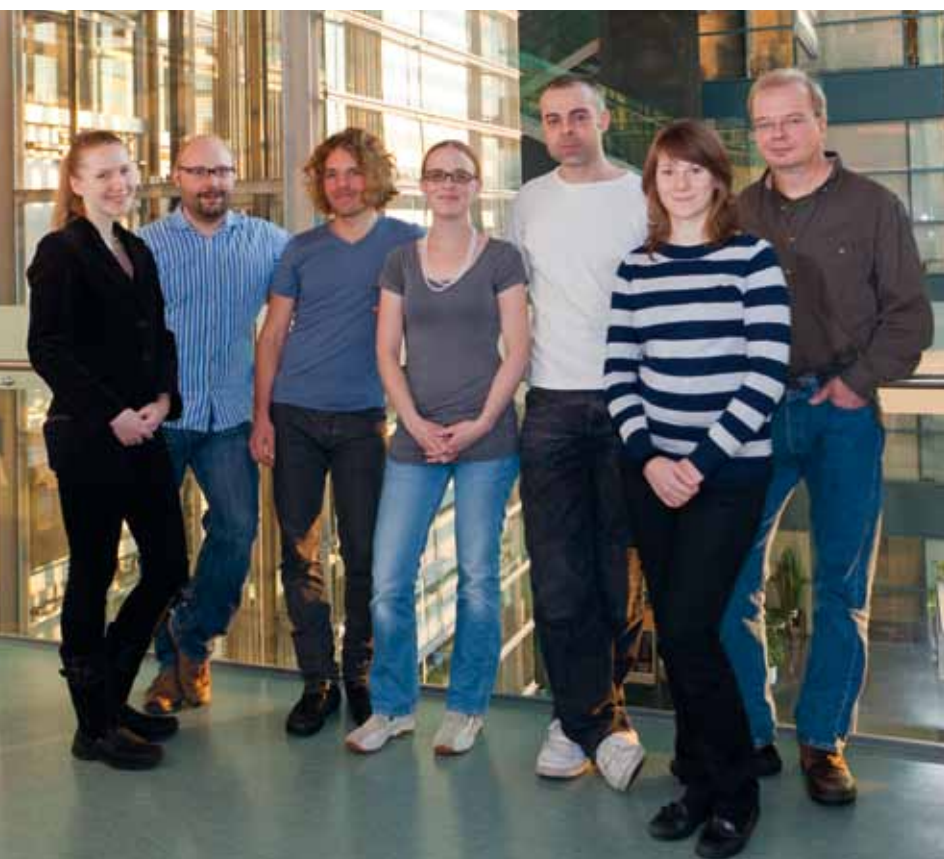
Lauri SE, Vesikansa A, Segerstråle M, Collingridge G, Isaac J and Taira T (2006). Functional maturation of CA1 synapses involves activity-dependent loss of tonic kainate receptor-mediated inhibition of glutamate release. *Neuron* 50: 415-429.

Lauri SE, Segerstråle M, Vesikansa A, Maingret F, Mülle C, Collingridge G, Isaac J and Taira T (2005). Endogenous activation of kainate receptors inhibits glutamatergic transmission and modulates network activity in the developing hippocampus. *J. Neurosci.* 25: 4473-84.

Lauri SE, Lämsä K, Pavlov I, Riekkö R, Johnston B, Molnar E, Rauvala H and Taira T (2003). Activity-blockade induces formation of functional synapses in the newborn rat hippocampus. *Mol. Cell. Neurosci.* 22: 107-117.

Lämsä K, Palva M, Ruusuvaara E, Kaila K and Taira T (2000). Synaptic GABA activation inhibits AMPA/kainate receptor-mediated bursting in the newborn (P0-P2) rat hippocampus. *J. Neurophysiol.* 83: 359-366.

Palva M, Lämsä K, Lauri SE, Rauvala H, Kaila K and Taira T (2000). Fast network oscillations in the newborn rat hippocampus *in vitro*. *J. Neurosci.* 20: 1170-78.



## EFFECTS OF GENETIC BACKGROUND, SEX, AND ENVIRONMENT ON MOUSE BEHAVIOR – REFINEMENT OF PHENOTYPING METHODS

**Vootele Vöikar**  
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Use of mice in biological research is increasing. The mouse has evolved to be a model organism of choice for investigation of genetic mechanisms of physiology and pathology in mammals. Behavioral investigation is an essential part of the phenotypic analysis of genetically modified mice. However, basic analysis of mouse behavior in laboratory conditions warrants further attention to guarantee reliable interpretation of mutant phenotypes.

The focus of our studies will be on the role of genetic background and sex in mouse behavior. However, environment plays a critical role in the development and expression of behavioral traits. Therefore, the impact of various environmental manipulations at different developmental stages will be addressed. The aim is to characterize conditions with positive or negative stimulation and the possible strain- and sex-specific effects of these factors. A notable innovation in behavioral phenotyping will be an application of novel automated systems. For this purpose, we plan to invest in validation of the Intellicage. This equipment allows long-term monitoring of mice in social groups in their home-cage, and, more importantly, application of different learning paradigms without handling of the animals. Stereotactic lesions, pharmacological interventions, and transgenic manipulations will be applied for further investigation of behavioral mechanisms.

Our research is anticipated to lead to enhanced understanding of cognition and emotion in mice. Such knowledge will contribute to better modeling and analysis of psychiatric and neurological disorders, but also to improving animal welfare.

### Personnel

**Project leader:** Vootele Vöikar, MD, PhD

**Post-doctoral fellow:** Natalia Kuleskaya, PhD

### Selected publications

Endo T, Maekawa F, Vöikar V, Haijima A, Uemura Y, Zhang Y, Miyazaki W, Suyama S, Shimazaki K, Wolfer DP, Yada T, Tohyama C, Lipp HP and Takeyama M (2011). Automated test of behavioral flexibility in mice using a behavioral sequencing task in IntelliCage. **Behav. Brain Res.**, in press.

Richter SH, Garner JP, Zipser B, Lewejohann L, Sacher N, Touma C, Schindler B, Chourbaji S, Brandwein C, Gass P, van Stipdonk N, van der Harst J, Spruijt B, Vöikar V, Wolfer DP and Würbel H (2011). Effect of population heterogenization on the reproducibility of mouse behavior: a multi-laboratory study. **PLoS One** 6: e16461.

Krackow S, Vannoni E, Codita A, Mohammed AH, Cirulli F, Branchi I, Alleva E, Reichelt A, Willuweit A, Vöikar V, Colacicco G, Wolfer DP, Buschmann JUF, Safi K and Lipp HP (2010). Consistent behavioral phenotype differences between inbred mouse strains in the IntelliCage. **Genes Brain Behav.** 9: 722-731.

Vöikar V, Colacicco G, Gruber O, Vannoni E, Lipp HP and Wolfer DP (2010). Conditioned response suppression in the IntelliCage: assessment of mouse strain differences and effects of hippocampal and striatal lesions on acquisition and retention of memory. **Behav. Brain Res.** 213: 304-312.

Vöikar V, Polus A, Vasar E and Rauvala H (2005). Long-term individual housing in C57BL/6J and DBA/2 mice: assessment of behavioral consequences. **Genes Brain Behav.** 4: 240-252.

Vöikar V, Vasar E and Rauvala H (2004). Behavioral alterations induced by repeated testing in C57BL/6J and 129S2/Sv mice: implications for phenotyping screens. **Genes Brain Behav.** 3: 27-38.

Vöikar V, Koks S, Vasar E and Rauvala H (2001). Strain and gender differences in the behavior of mouse lines commonly used in transgenic studies. **Physiol. Behav.** 72: 271-281.



## ADJUNCT PROFESSORS

The Neuroscience Center may also have joint research programs and activities with other parts of the University of Helsinki and with other universities, research centers, or related units. The Neuroscience Center collaborates with four Adjunct Professors to expand and deepen the research and teaching areas. The Adjunct Professors were selected for a three-year period starting in 2008.

### STRUCTURAL BIOLOGY OF TARGETS RELEVANT TO NEUROSCIENCE

**Adrian Goldman, PhD, Professor**

Institute of Biotechnology, University of Helsinki  
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### NEUROBIOLOGICAL BASIS OF DYSLEXIA: SUSCEPTIBILITY GENES AND REGULATORY NETWORKS

**Juha Kere, MD, PhD, Professor**

Karolinska Institutet, Sweden; Haartman Institute, University of Helsinki, and Folkhälsan Institute of Genetics, Helsinki  
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### REGULATION OF ACTIN-DRIVEN MORPHOLOGICAL PROCESSES IN NEURONS AND RADIAL GLIA

**Pekka Lappalainen, PhD, Professor**

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### NEUROBIOLOGICAL MECHANISMS OF MEMORY IMPAIRMENT IN ALZHEIMER'S DISEASE

**Heikki Tanila, MD, PhD, Professor**

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# TEACHING AT THE NEUROSCIENCE CENTER

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Tomi Taira

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Strong investment in research-based teaching is one of the central strategies of the University of Helsinki. The position of the NC as an interdisciplinary research institute gives it a unique opportunity to successfully promote this task. Neuroscience courses are being organized at both the Viikki and Meilahti campuses.

The NC provides a wide range of neuroscience teaching that integrates recent research with undergraduate and graduate courses. Lectures, seminars, and laboratory courses are designed in collaboration with experts in teaching techniques to ensure high efficacy and quality of teaching.

All courses organized by the NC are in English. Currently, teaching provided by the NC equals the credits required for minor subject studies in neuroscience (25 ECTS cr), for a doctoral degree (60 ECTS cr), or for a major in the international Master's Degree Programme in Neuroscience, MNEURO (120 ECTS cr). Thus, our teaching packages give excellent opportunities to study neuroscience for both undergraduate and postgraduate degrees. Students from several faculties and universities are also able to select individual courses from our curriculum.

Members of the Neuroscience Center are also closely connected to graduate schools funded by the Ministry of Education and the Academy of Finland. Eight of the NC group leaders belong to the Management Board of the Finnish Graduate School of Neuroscience (FGSN).

## COURSES ORGANIZED BY THE NEUROSCIENCE CENTER

### 920015 Basic Methods in Neural Cell Culture

3 ECTS credits

Responsible person: Pirta Hotulainen

Participants: 8

### 920007 Basic Mechanisms of Nervous System Disorders

3-6 ECTS credits

Responsible person: Anna-Elina

Lehesjoki, Pentti Tienari, Outi Kopra

Participants: 73

### 920017 Laboratory Works in Systems Neuroscience: MEG, EEG and MRI

5 ECTS credits

Responsible person: Satu Palva

Participants: 5

### 920018 Data Analysis and Management in Neuroscience

3 ECTS credits

Responsible persons: Satu Palva and

Matias Palva

Participants: 4

### 920022/52098 Phenotypical Characterization of Transgenic Animals

3 ECTS credits

Responsible person: Kai Kaila

Participants: 29

### 920009/52265 Introduction to Neurobiology

5 ECTS credits

Responsible person: Kai Kaila

Participants: 46

### 920001 Introduction to Molecular and Cellular Neuroscience

6 ECTS credits

Responsible person: Heikki Rauvala

Participants: 43

### 920002 Developmental Neuroscience

3 ECTS credits

Responsible person: Eero Castrén

Participants: 38

## NEUROSCIENCE SEMINAR SERIES

The Neuroscience seminar series, organized regularly since 2003, has proven to be an important instrument of scientific exchange as well as student education. In 2010, a total of 21 seminars were held by international and Finnish research scientists, ranging from young independent researchers to prominent senior scientists. Speakers are usually invited by the Neuroscience Center group leaders, and seminars cover a broad range of topics from neuroscience to cell biology. The audience of 30 to 50 people consists of graduate students, postdoctoral fellows, and senior faculty members. Guest speaker presentations are always followed by questions from the audience and lively discussions. For PhD students, regular attendance and active participation in the seminars count as points towards their study plan. In addition to the main presentation, each invited speaker is encouraged to spend time with a number of group leaders individually, engaging in more in-depth discussion of recent findings and mutually interesting scientific questions.

12.3. **Marjo Goette** (Novartis Pharma, Switzerland): High-content screening and imaging-based assays with primary neurons at the Lead Finding Platform

19.3. **Rebecca Klein** (Duke University Medical Center, Durham NC, USA): Age-dependent modulation of synaptic integrity in human apoE targeted replacement mice

26.3. **Dmitry Ossipov** (Olympus Europa Holding, Hamburg, Germany): In vivo brain imaging by means of two-photon microscopy

29.3. **Graham Barrett** (University of Melbourne, Australia): The p75 neurotrophin receptor negatively regulates the cholinergic system in the CNS; relevance in a mouse Alzheimer model

9.4. **Pavle Andjus** (Institute for Physiology & Biochemistry, University of Belgrade): Benchmarking for Amyotrophic Lateral Sclerosis research with Neurobiophysical means

13.4. **Thomas Blanpied** (University of Maryland School of Medicine, Baltimore, MD USA): Single-molecule imaging of perisynaptic actin

16.4. **Giovanni Colacicco** (Institute of Anatomy, University of Zurich): Stereotaxic lesions and home cage environment - refining assessment of mouse behaviour

30.4. **Dante R. Chialvo** (Dept. of Physiology, UCLA, USA): The brain at the edge

21.5. **Corette Wierenga** (Max Planck Institute of Neurobiology, Germany): Imaging inhibitory synapse formation and plasticity

26.5. **Minisymposium on optical brain imaging *in vivo***

Overview of optical imaging methods and applications (**Leonard Khirug**, Neuroscience Center, Helsinki)

Plasticity in visual cortex studied with optical imaging (**Ettore Tiraboschi**, Neuroscience Center, Helsinki)

Epileptiform activity visualized using intrinsic optical signal (**Artyom Dugan**, Neuroscience Center, Helsinki)

Down to details: Questions and Answers session (**Ivo Vanzetta**, Université de la Méditerranée Aix-Marseille, France)

3.6. **Kevin Staley** (Departments of Pediatrics and Neurology, University of Colorado, Denver, USA): Neuronal ion transport, GABA-mediated synaptic signaling, and neonatal seizure therapy

17.6. **David B. Mount** (Harvard Medical School): Molecular physiology of K-Cl cotransport

10.8. **Robert Kelsh** (University of Bath, Great Britain): Pigmentation and associated disorders in zebrafish

11.8. **Maximiliano Suster** (SARS Center, Bergen, Norway): Genetic dissection of sensory-motor circuits

12.8. **Harold Burgess** (National Institute of Health, Bethesda, MD, USA): Sensorimotor gating in larval zebrafish

14.9. **Benjamin Peng** (Division of Life Science, Hong Kong University of Science and Technology): Local and global signaling in neuromuscular synaptogenesis

24.9. **Anthony J. Bell** (Redwood Center for Theoretical Neuroscience, UC Berkeley, USA): Emergence and submergence in the nervous system

**Irene Miguel-Aliaga** (Department of Zoology, University of Cambridge, UK): Intestinal neurons in *Drosophila*: Does the body rule the mind or does the mind rule the body?

8.10. **Andreas Lüthi** (Friedrich Miescher Institute, Switzerland): Defining the neuronal circuitry of fear

**Apar Jain** (EMBL Monerotondo Mouse Biology Unit, Italy): Dissecting behavioral patterns and their neural circuits involved in fear and anxiety

19.11. **Francisco Xavier Castellanos** (The Phyllis Green and Randolph Cowen Institute of Pediatric Neuroscience, NYU Child Study Center, New York): TBA



## CORE FACILITIES

Sophisticated technologies used in modern neuroscience require centralization of core facilities used by several research groups within and outside of the Neuroscience Center. Transgenic methods allow dissection of normal and abnormal behavioral mechanisms; the rationale to start the Mouse Behavioral Unit was in the context of mouse transgenesis. The Zebrafish Core Facility provides another important model organism for neuroscience research, in particular for developmental and behavioral neuroscience and for disease models. The zebrafish project operates on both the Meilahti and the Viikki campuses, serving as an example of active intercampus operations. The Neuronal Cell Culture Unit, a key facility of the Neuroscience Center, is used by groups from both campuses.

### MOUSE BEHAVIORAL UNIT

**Vootele Vöikar**  
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Mouse genetic models play a key role in the investigation of molecular pathways underlying normal biological functions or pathological states. The models require extensive analysis at various levels of complexity. Behavioral testing is an important approach in comprehensive studies aimed at understanding psychiatric and neurological diseases. The analysis of mouse behavior in laboratory conditions is undergoing rapid evolution, and a growing need exists for expertise in this field. The Mouse Behavioral Unit was started in 1998 to provide research groups in neurobiology with the possibility of characterizing their mutant mice. Since then, the Unit has substantially expanded its repertoire of available tests and models. The systematic work to improve and refine the methods has been recognized locally and internationally. We have therefore received an increasing number of collaboration requests. The test battery for behavioral phenotyping involves assessment of motor behavior (coordination, spontaneous activity), muscle strength (grip strength),

nociception (hot/cold plate, tail withdrawal, plantar test, automated von Frey, paw-pressure analgesia), sensorimotor gating (prepulse inhibition of acoustic startle reflex), emotional behavior (elevated plus maze, light-dark exploration, open field, Y-maze, forced swim test), social behavior (dominance tube test, resident-intruder test), and learning and memory (spatial navigation in water maze, fear conditioning, conditioned taste aversion, novel object recognition, social transmission of food preference). A comprehensive laboratory animal monitoring system allows for long-term (24-72 h), automated, and non-invasive collection of several physiological and behavioral parameters (activity, food and water consumption, metabolic performance) simultaneously. Recent installation of the newly developed system for home-cage monitoring (IntelliCage) has extended the Unit's abilities. This "behavioral micro-laboratory" allows automated individual assessment of spontaneous and cognitive behavior of the mice in social settings with minimal human interference. This high-throughput approach to behavioral screening could markedly increase the speed of experiments and optimally standardize housing conditions and experimental procedures with normal and genetically modified mice. In addition to the phenotyping of mutant mice, basic re-

search with commonly used inbred strains is carried out to establish baseline values and to validate the models. These studies provide important background information for interpretation of data. Specifically, we are interested in the interactions of genetic background, sex, and environment in modulation of behavioral patterns. The Unit is awaiting new animal facilities to accommodate the space requirements and other specific needs of a mouse behavioral laboratory.

#### Personnel

**Post-doctoral fellow:** Natalia Kuleskaya, PhD

**Graduate student:** Jesse Lindholm, MSc (Pharm)

### NEURONAL CELL CULTURE UNIT

**Eero Castrén**  
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The Neuronal Cell Culture Unit develops methods for the culture of primary neuronal cells and provides Neuroscience Center groups and other research groups in the Helsinki region with cultured neu-



rons. The neurons provided by the Unit include embryonic rat and mouse hippocampal and cortical neurons, cerebellar granule neurons, peripheral ganglia neurons, hippocampal slice cultures, and neuronal and embryonic stem cells. The Unit has facilities for transfection and viral transduction of gene constructs to primary neurons and slice cultures. In addition, the Unit provides cells and training related to production and handling of primary neuronal cultures to investigators in other institutes and campuses, including Biomedicum. Centralization of primary neuronal culture activity is important in providing continuity and in improving the quality and consistency of these cultures. Furthermore, a core facility saves in expenses by optimizing the use of cells and cell culture materials.

### Personnel

Technicians: Seija Lågas; Outi Nikkilä

## ZEBRAFISH UNIT

Pertti Panula  
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Fast embryonic development, transparent embryos, and the availability of a large number of mutants have rendered zebrafish one of the favorite models in developmental biology. Rapidly increasing knowledge of the zebrafish genome has also enabled efficient identification of important genes in this species. Most studies on zebrafish thus far have concentrated on identifying early developmental phenotypes from mutation screens. The research carried out at the Neuroscience Center focuses on new methods utilizing high-resolution confocal and two-photon imaging of developing neuronal networks, and automated quantitative behavioral analysis. These methods are combined with use of translation inhibition with morpholino oligonucleotides, selection of new mutants from mutation screens, and studies on mutants produced with targeted lesions in genomes (TILLING) or zinc finger technology. One of the goals is to extend efficient phenotype analysis to a phase in which the CNS produces complex behaviors. Current projects aim at determining the roles of

newly identified genes, the mutations of which produce severe human neurological diseases. Models of human diseases related to disorders of the aminergic neuronal systems are also being developed. The methods used include gene cloning and expression analysis, translation inhibition, developmental analysis using microscopy and gene arrays, high-resolution imaging, and automated behavioral techniques. The recent addition of aquarium space allows genetic studies and maintenance of mutant and transgenic fish strains. The core facility provides services to all universities and research institutions in Finland and cooperates with companies interested in screening drug candidates. The core facility also arranges basic and advanced courses in zebrafish methods, with internationally recognized teachers.

### Personnel

**Post-doctoral fellows:** Hisaaki Kudo, PhD; Yu-Chia Chen, PhD; Svetlana Semenova, PhD; Maarit Hölttä-Vuori, PhD

**Graduate students:** Maria Sundvik MSc; Madhusmita Priyadarshini, MSc

**Undergraduate students:** Gabija Toleikyte; Pauliina Toivonen; Olli Tiainen; Henri Puttonen

**Fish manager:** Henri Koivula, BSc

**Technician:** Susanna Norrbacka, BSc

# NEUROSCIENCE CENTER RESEARCH AND CENTRES OF EXCELLENCE

The national strategy for centres of excellence in research has been jointly developed with the Academy of Finland and the Finnish Funding Agency for Technology and Innovation.

The centre of excellence programme is one form of research funding for promoting the development of creative research environments. All centres of excellence in research represent the cutting edge of their respective fields. Candidates for centres of excellence include research units or researcher training units, comprising one or several high-quality research teams with shared and clearly defined research goals, which are at or have the potential of reaching the international forefront of their field.

## FINNISH CENTRE OF EXCELLENCE IN COMPLEX DISEASE GENETICS

The group led by Professor Anna-Elina Lehesjoki is one of the seven research groups forming the Centre of Excellence in Complex Disease Genetics (CoECDG) of the Academy of Finland. Research within the CoECDG aims at dissecting the genetic background of some common diseases and their trait components by combining special expertise with the sample resources accessible to the CoECDG investigators. The CoECDG builds on accomplishments of the Centre of Excellence in Disease Genetics of the Academy of Finland (in 2000-2005), but has a more extended research program to reflect developments in the field as well as its own research progress: from Mendelian diseases to complex traits. The CoECDG combines diverse expertise of eight group leaders across institutes in Finland, Sweden, and the UK. The CoECDG was chosen for funding in the Academy of Finland's Centre of Excellence programme in 2006-2011.

### DIRECTORS OF THE RESEARCH TEAMS

Docent Anu Jalanko  
(National Institute for Health and Welfare)

Professor Juha Kere  
(UH and Karolinska Institutet)

Professor Jaakko Kaprio  
(UH and National Institute for Health and Welfare)

Professor Kimmo Kontula (UH)

Professor Anna-Elina Lehesjoki  
(UH and Folkhälsan Institute of Genetics)

Professor Aarno Palotie  
and Joe Terwilliger  
(UH and Sanger Center (AP))

Docent Samuli Ripatti  
(UH and National Institute for Health and Welfare)

## FINNISH CENTRE OF EXCELLENCE IN MOLECULAR AND INTEGRATIVE NEUROSCIENCE RESEARCH

CoE in Molecular and Integrative Neuroscience Research focuses on trophic factors in the mechanisms of neuronal development, plasticity, and disorders. Groups of the CoE have complementary expertise in the fields of molecular/cellular neuroscience, neurophysiology, neuropharmacology, and systems neuroscience. The aim is to create a multidisciplinary international CoE in basic and translational neuroscience.

### DIRECTORS OF THE RESEARCH TEAMS

Professor Mart Saarma  
(chairman; Institute of Biotechnology)

Academy Research Fellow  
Urmas Arumäe  
(Institute of Biotechnology)

Docent Claudio Rivera  
(Institute of Biotechnology and  
Department of Biosciences)

Professor Kai Kaila  
(Department of Biosciences and  
Neuroscience Center)

Professor Heikki Rauvala  
(Neuroscience Center)

Professor Eero Castrén  
(Neuroscience Center)

Docent Matti Airaksinen  
(Neuroscience Center)

# ADMINISTRATION

Administration of the Neuroscience Center (NC) is determined by the Board and the Director. An important administrative body of the NC is the Scientific Advisory Board, which promotes the NC's scientific activities.

## THE BOARD

The Board discusses the target program, its personnel plan, and the budget, and approves the annual report. Based on the statement of the Scientific Advisory Board, the Board makes a proposal to the Rector of the University to appoint the Director. The Board issues a statement about the Director's decision to add a research group to the Center. Furthermore, the Board decides on the strategic lines of teaching. The Rector appoints the members of the Board for a four-year term. The Board had three meetings last year.



### THE BOARD 1.5.2008 – 30.6.2010

#### Chair of the Board

Professor Kiello Haahtela,  
Faculty of Biological and Environmental Sciences

#### Vice-Chair

Professor Pekka Männistö, Faculty of Pharmacy

#### Members of the Board

Professor Timo Erkinjuntti, Faculty of Medicine

Director Antti Haapalinna, Orion Pharma

Professor Teija Kujala, Faculty of Behavioural Sciences

Professor Outi Vainio, Faculty of Veterinary Medicine

Professor Anu Wartiovaara, Faculty of Medicine

Student Mikko Berg, student representative

Student Miia Lehtinen, student representative

Master of Science Mikael Segerstråle, student representative

Master of Science Lauri Mankki, personnel representative

### THE BOARD 1.7.2010 – 31.3.2014

#### Chair of the Board

Dean, Professor Risto Renkonen, Faculty of Medicine

#### Vice-Chair

Professor Kiello Haahtela, Faculty of Biological and Environmental Sciences

#### Members of the Board

Director Antti Haapalinna, Orion Pharma

Professor Teija Kujala, Faculty of Behavioural Sciences

Professor Outi Laitinen-Vapaavuori, Faculty of Veterinary Medicine

Professor Pekka Männistö, Faculty of Pharmacy

Docent Pentti Tienari, Faculty of Medicine

Docent Henri Huttunen, personnel representative

Research technician Outi Nikkilä, personnel representative

Master of Science Tuomas Aivelo, student representative

Student Juha Lempiäinen, student representative

#### Deputy members

Professor Timo Erkinjuntti, Faculty of Medicine

Docent Iiris Hovatta, Faculty of Medicine

Professor Kari Keinänen, Faculty of Biological and Environmental Sciences

Professor Christina Krause, Faculty of Behavioural Sciences

Professor Olli Peltoniemi, Faculty of Veterinary Medicine

Research director Jukka Sallinen, Orion Pharma

University lecturer Outi Salminen, Faculty of Pharmacy

Postdoctoral researcher Saara Nuutinen, personnel representative

Master of Science Lauri Mankki, personnel representative

Master of Science Miika Pihlaja, student representative

Student Markus Lammi, student representative

## DIRECTOR

The Director is responsible for the development of the Center and its scientific profile and plans the target program, the personnel plan, and the budget. The Director also participates in NC's scientific activities and oversees the preparation of matters for discussion by the Board and the Scientific Advisory Board and the execution of decisions. The Director makes the decision to add a research group to the NC. The Director of the NC is Professor Heikki Rauvala.

## ADMINISTRATION DIRECTOR

The Administration director is responsible for the NC's administration and finances. The Administrative services unit and maintenance personnel are subject to the authority of the Administration director. The Administration director of the NC is Anna Mattila, MSc.

## SCIENTIFIC ADVISORY BOARD

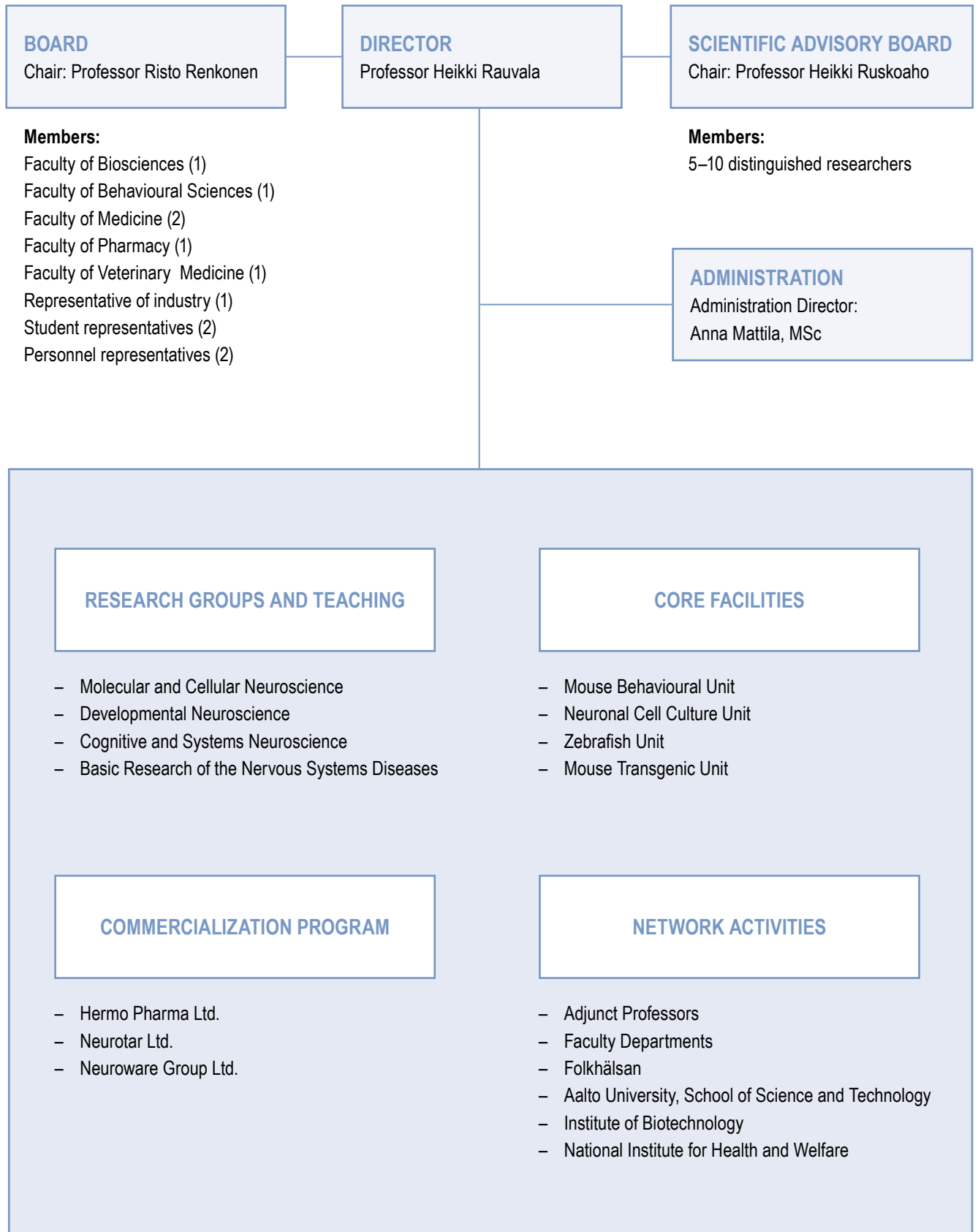
The NC has a Scientific Advisory Board that consists of leading experts of the field. This Board promotes the NC's scientific activities, issues statements on the competence of applicants for the positions of Director and Research directors, evaluates the NC's scientific activities, and formulates initiatives to start new activities in research and teaching.

The Scientific Advisory Board comprises a minimum of five and a maximum of ten distinguished researchers in the scientific fields represented by the NC. The Rector of the University of Helsinki appoints the members of the Board for a four-year term based on the proposal of the Board of Trustees. Currently, the Scientific Advisory Board consists of the following members:

<b>Chairman</b>
Professor Heikki Ruskoaho (Faculty of Medicine, University of Oulu)
<b>Members</b>
Professor Anders Björklund (Wallenberg Neuroscience Center, Lund University, Sweden)
Professor Thomas Perlmann (Ludwig Institute for Cancer Research, Karolinska Institute, Sweden)
Dr. Geneviève Rougon, Directeur (Institut de Biologie du Développement de Marseille [IBDM], Marseille, France)
Professor Erin Schuman (Max Planck Institute for Brain Research)
Professor Johan F. Storm (University of Oslo)
Professor Klaus Unsicker (University of Freiburg, Institute of Anatomy and Cell Biology)
Professor Wolfgang Wurst (Helmholtz Zentrum München)



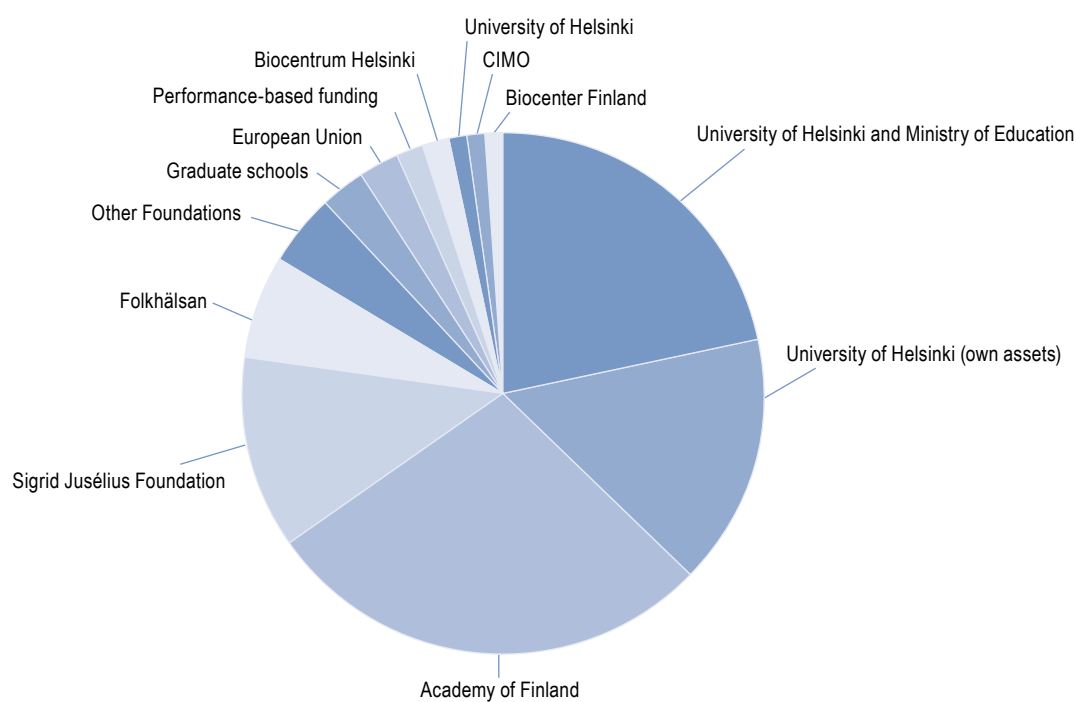
# ORGANIZATION OF THE NEUROSCIENCE CENTER



# FINANCES

Funding of the Neuroscience Center in 2010		In euros	%
<b>1. Basic funding</b>		<b>2 385 000</b>	<b>37,4</b>
	University of Helsinki and Ministry of Education	1 385 000	21,7
	University of Helsinki (own assets)	1 000 000	15,7
<b>2. Competitive funding</b>		<b>3 990 437</b>	<b>62,6</b>
	Academy of Finland	1 790 993	28,1
	Sigrid Jusélius Foundation	754 856	11,8
	Folkhälsan	404 966	6,4
	Other Foundations	277 944	4,4
	Graduate schools	179 485	2,8
	European Union	166 987	2,6
	Performance-based funding	104 781	1,6
	Biocentrum Helsinki	100 125	1,6
	University of Helsinki	75 400	1,2
	CIMO	68 400	1,1
	Biocenter Finland	66 500	1,0
<b>TOTAL</b>		<b>6 375 437</b>	<b>100,0</b>

## PROPORTION OF THE FINANCIERS OF THE TOTAL FUNDING IN 2010



# PERSONNEL

	Number	%	PY*	PY %*
Researchers	103	70	85	70
PhDs	53			
Graduate students	35			
Other research staff	15			
Undergraduate students	24	16	18	15
Laboratory technicians	16	11	15	12
Administration	3	2	3	2
Maintenance	2	1	1	1
<b>TOTAL</b>	<b>148</b>	<b>100</b>	<b>122</b>	<b>100</b>

\* person-years

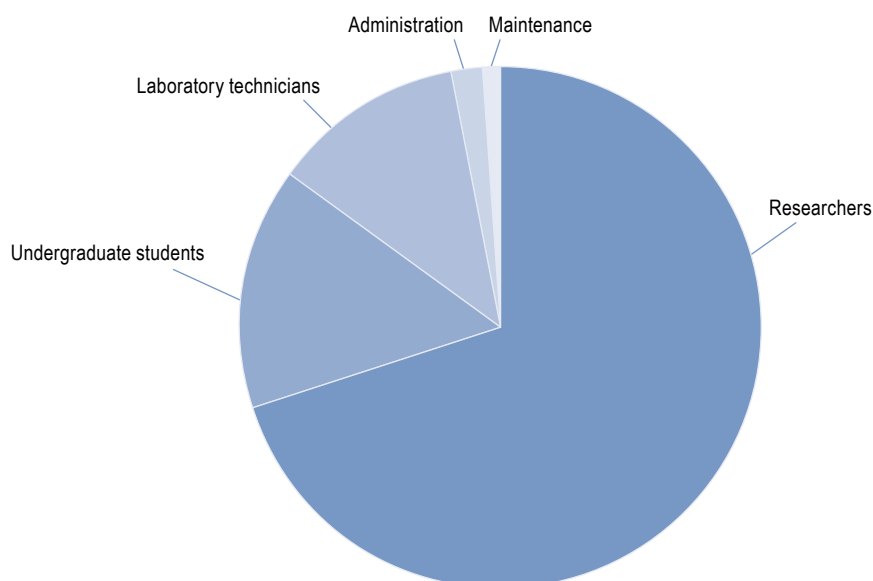
Proportion of foreign researchers in the category Researchers 45,6 %

Proportion of PhDs in the category Researchers 51,5 %

Proportion of women in the categories Researchers and Undergraduate students 52,8 %

Proportion of women of all staff 57,4 %

## PROPORTION OF STAFF CATEGORIES (PERCENTAGE IN PERSON-YEARS)



# STAFF MEMBERS

## GROUP LEADERS

Airaksinen, Matti, MD, PhD  
Castrén, Eero, MD, PhD  
Kaila, Kai, PhD  
Khirug, Leonard, PhD  
Lehesjoki, Anna-Elina, MD, PhD  
Panula, Pertti, MD, PhD  
Rauvala, Heikki, MD, PhD  
Taira, Tomi, PhD

## ADJUNCT PROFESSORS

Goldman, Adrian, PhD  
Kere, Juha, MD, PhD  
Lappalainen, Pekka, PhD  
Tanila, Heikki, MD, PhD

## PROJECT LEADERS

Hotulainen, Pirta, PhD  
Huttunen, Henri, PhD  
Lauri, Sari, PhD  
Palva, Matias, PhD  
Vöikar, Vootele, MD, PhD \*\*

## POST-DOCTORAL FELLOWS

Anttonen, Anna-Kaisa, MD, PhD \*\*  
Bertling, Enni, PhD \*\*  
Blaesse, Peter, PhD  
Chen, Yu-Chia, PhD  
Clarke, Vernon, PhD  
Dahlström-Heuser, Vanina, PhD  
Di Lieto, Antonio, MD \*\*  
Joensuu, Tarja, PhD  
Karlstedt, Kaj, PhD  
Karpova, Nina, PhD  
Kettunen, Kaisa, PhD \*\*  
Kolikova, Julia, PhD \*\*  
Kopra, Outi, PhD \*\*  
Kudo, Hisaaki, PhD  
Kuleskaya, Natalia, PhD \*\*  
Lyubimov, Yaroslav, PhD \*\*  
Molchanova, Svetlana, PhD \*\*  
Niittykoski, Minna, PhD  
Nuutinen, Saara, PhD  
Okuneva, Olesya, PhD \*\*  
Osmekhin, Sergey, PhD \*\*  
Paatero, Anja, PhD  
Palva, Satu, PhD  
Paveliev, Mikhail, PhD  
Polvi, Anne, PhD  
Pryazhnikov, Evgeny, MD, PhD  
Rantamäki, Tomi, PhD (pharm)  
Rouhiainen, Ari, PhD  
Ruusuvoori, Eva, PhD  
Semenova, Svetlana, PhD  
Tian, Li, PhD  
Tiraboschi, Ettore, PhD  
Tolner, Else, PhD  
Uvarov, Pavel, PhD \*\*  
Vesterinen, Jaana, PhD \*\*  
Wegelius, Katri, PhD  
Wigren, Henna-Kaisa, PhD  
Zobova, Svetlana, PhD \*\*

## GRADUATE STUDENTS

Ahmad, Faraz, MSc  
Autio, Henri, MSc (pharm)  
Helmy, Mohamed, MB, BCh, MSc  
Hokkanen, Marie-Estelle, MSc  
Huupponen, Johanna, MSc  
Juuri, Juuso, MSc  
Khirug, Stanislav, MSc  
Kiiltomäki, Marjaana, MSc  
Kislin, Mikhail, MSc \*\*  
Knuuttila, Juha, MSc  
Koskinen, Mikko, MSc  
Kousi, Maria, MSc  
Kuja-Panula, Juha, MSc  
Kuleskiy, Evgeny, MSc  
Kuronen, Mervi, MSc  
Körber, Inken, Dipl.Biol.  
Laakso, Tiina, MSc  
Laari, Anni, MSc  
Lindholm, Jesse, MSc (pharm)  
Manninen, Otto, MSc  
Markkanen, Marika, MSc  
Molotov, Dmitry, MSc  
Monto, Simo, MSc (Tech) \*\* (PhD defence 29.4.2010)  
Priyadarshini, Madhusmita, MSc  
Sallert, Marko, MSc  
Segerstråle, Mikael, MSc  
Sirén, Auli, MD \*\*  
Sundvik, Maria, MSc  
Tegelberg, Saara, MSc  
Tokariev, Anton, MSc  
Uvarov, Pavel, MSc \*\* (PhD defence 18.6.2010)  
Vanhanen, Jenni, MSc \*\*  
Vanttola, Päivi, MSc  
Vesikansa, Aino, MSc \*\*  
Yukin, Alexey, MSc  
Zhao, Xiang, MSc

## OTHER RESEARCH STAFF

Akamine, Yumiko, MSc  
Blaesse, Anne, MSc \*\*  
Dugan, Artjom, BSc \*\*  
Kaisler, Raphaela, MSc \*\*  
Kirilkin, Ilya, MD  
Kupari, Jussi, MSc  
Luchkina, Natalia, MSc  
Mankki, Lauri, MSc  
Marabelli, Alessandro, MSc \*\*  
Muggalla, Pranuthi, MSc  
Pandya, Nikhil, MSc \*\*  
Puskarjov, Martin, MSc  
Rozov, Stanislav, MSc  
Tibeikina, Marina, MSc \*\*  
Toptunov, Dmytro, MSc \*\*

## UNDERGRADUATE STUDENTS

Agústsdóttir, Arna  
Antila, Hanna  
Haapaniemi, Emma \*\*  
Hirvonen, Teemu \*\*  
Korhonen, Onerva \*\*  
Kysenius, Kai  
Kulashekhar, Shrikanth, BSc  
Lommi, Markus \*\*  
Mattila, Katariina, BM \*\*  
Naukkarinen, Ina-Maria \*\*  
Nykänen, Niko-Petteri  
Ojala, Tiia  
Panula, Jonatan \*\*  
Rezov, Veronika \*\*  
Rouhinen, Santeri  
Sakha, Prasanna  
Simola, Juha  
Talvitie, Minnamari, BSc \*\*  
Tilli, Elizaveta \*\*  
Toivonen, Pauliina \*\*  
Uski, Isa, BSc \*\*  
Velusamy, Ragani \*\*  
Vesa, Liisa  
Virtanen, Mari \*\*

## TECHNICIANS AND OTHER TECHNICAL STAFF

Berg, Kaija  
Haas, Britta  
Hakala, Paula  
Hellgrén, Hanna  
Huttu, Erja  
Kampura, Merle, MSc  
Kanerva, Noora \*\*  
Koivula, Henri, BSc  
Lehtonen, Anna, BSc \*\*  
Lindh, Sinikka \*\*  
Lågas, Seija  
Mustonen, Milla, MSc  
Nikkilä, Outi  
Norrbacka, Susanna  
Saarikalle, Eeva-Liisa  
Toivonen, Teija-Tuulia

## ADMINISTRATIVE SERVICES UNIT AND MAINTENANCE

Duus, Markus \*\*  
Lasanen, Seppo \*\*  
Luoto, Anu, MSc  
Mattila, Anna, MSc  
Rosenblad, Tarja

## OTHER STAFF

Laakkonen, Liisa, PhD  
Lahtinen, Ulla, PhD

\*\* working part of the year

# THESES

## MASTER'S THESIS

Liisa Vesa: TrkB hermokasvutekijäreseptori masennuslääkkeiden potentiaalisena vaikutuskohtana

## DOCTORAL THESES

Simo Monto: Dynamic correlations in ongoing neuronal oscillations in humans - perspectives on brain function and its disorders

Pavel Uvarov: Neuronal K-Cl cotransporter: Transcriptional mechanisms of KCC2 gene regulation

# PUBLICATIONS

Asiedu M, Ossipov MH, Kaila K and Price TJ (2010). Acetazolamide and midazolam act synergistically to inhibit neuropathic pain. **Pain** 148: 302-308.

Carta F, Temperini C, Innocenti A, Scozzafava A, Kaila K and Supuran CT (2010). Polyamines inhibit carbonic anhydrases by anchoring to the zinc-coordinated water molecule. **J. Med. Chem.** 53: 5511-22.

Castrén E and Rantamäki T (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. **Dev. Neurobiol.** 70: 289-297.

Castrén E and Rantamäki T (2010). Role of brain-derived neurotrophic factor in the aetiology of depression: implications for pharmacological treatment. **CNS Drugs** 24: 1-7.

Erdinc OO, Joensuu T, Ilgen-Uslu F, Bebek N, Ozkara C, Tutkavul K, Gunduz A, Lehesjoki AE and Baykan B (2010). Unverricht-Lundborg disease in Turkey: Delineating the phenotype between cystatin B mutation positive and negative cases. **J. Neurol. Sci.-Turk.** 27: 1-11.

Gyarfas T, Knuutila J, Lindholm P, Rantamäki T and Castrén E (2010). Regulation of brain-derived neurotrophic factor (BDNF) and cerebral dopamine neurotrophic factor (CDNF) by anti-parkinsonian drug therapy in vivo. **Cell. Mol. Neurobiol.** 30: 361-368.

Haiko J, Laakkonen L, Juuti K, Kalkkinen N and Korhonen TK (2010). The ompTins of *Yersinia pestis* and *Salmonella enterica* cleave the reactive center loop of plasminogen activator inhibitor 1. **J. Bacteriol.** 192: 4553-61.

Horn Z, Ringstedt T, Blaesle P, Kaila K and Herlenius E (2010). Premature expression of KCC2 in embryonic mice perturbs neural development by an ion transport-independent mechanism. **Eur. J. Neurosci.** 31: 2142-55.

Hotulainen P and Hoogenraad CC (2010). Actin in dendritic spines: connecting dynamics to function. **J. Cell Biol.** 189: 619-629.

Huttunen HJ, Havas D, Peach C, Barren C, Duller S, Xia WM, Frosch MP, Hutter-Paier B, Windisch M and Kovacs DM (2010). The acyl-coenzyme A: cholesterol acyltransferase inhibitor CI-1011 reverses diffuse brain amyloid pathology in aged amyloid precursor protein transgenic mice. **J. Neuropathol. Exp. Neurol.** 69: 777-788.

Hölttä-Vuori M, Salo VTV, Nyberg L, Brackmann C, Enejder A, Panula P and Ikonen E (2010). Zebrafish: gaining popularity in lipid research. **Biochem. J.** 429: 235-242.

Juuri J, Clarke VRJ, Lauri SE and Taira T (2010). Kainate receptor-induced ectopic spiking of CA3 pyramidal neurons initiates network bursts in neonatal hippocampus. **J. Neurophysiol.** 104: 1696-706.

Karpova NN, Rantamäki T, Di Lieto A, Lindemann L, Hoener MC and Castrén E (2010). Darkness reduces BDNF expression in the visual cortex and induces repressive chromatin remodeling at the BDNF gene in both hippocampus and visual cortex. **Cell. Mol. Neurobiol.** 30: 1117-23.

Kestilä M, Ikonen E and Lehesjoki A (2010). Suomalainen tautiperintö. **Duodecim** 126: 2311-20.

Khirug S, Ahmad F, Puskarjov M, Afzalov R, Kaila K and Blaesle P (2010). A single seizure episode leads to rapid functional activation of KCC2 in the neonatal rat hippocampus. **J. Neurosci.** 30: 12028-35.

Kukko-Lukjanov TK, Lintunen M, Jalava N, Lauren HB, Lopez-Picon FR, Michelsen KA, Panula P and Holopainen IE (2010). Involvement of histamine 1 receptor in seizure susceptibility and neuroprotection in immature mice. **Epilepsy Res.** 90: 8-15.

Lahti L, Knuutila JEA and Kaski S (2010). Global modeling of transcriptional responses in interaction networks. **Bioinformatics** 26: 2713-20.

Lehesjoki A (2010). Cystatin B. In: Encyclopedia of Movement Disorders (eds. Kompolti K and Verhagen L), pp. 273-275. Oxford, Academic Press.

Lehesjoki AE and Gardiner RM (2010). Unverricht-Lundborg disease and ceroid lipofuscinoses. **Epilepsia** 51: 76-76.

Leo JC, Elovaara H, Bihan D, Pugh N, Kilpinen SK, Raynal N, Skurnik M, Farndale RW and Goldman A (2010). First analysis of a bacterial collagen-binding protein with collagen toolkits: promiscuous binding of YadA to collagens may explain how YadA interferes with host processes. **Infect. Immun.** 78: 3226-36.

Leo JC and Goldman A (2010). Jacks of all trades? Probably not. The E. coli Eib proteins bind IgG Fc. **Mol. Immunol.** 47: 1870-72.

Liao Y, Anttonen AK, Liukkonen E, Gaily E, Maljevic S, Schubert S, Bellan-Koch A, Petrou S, Ahonen VE, Lerche H and Lehesjoki AE (2010). SCN2A mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. **Neurology** 75: 1454-58.

Louhivuori V, Vicario A, Uutela M, Rantamäki T, Louhivuori L, Castrén E, Tongiorgi E, Akerman K and Castrén M (2010). BDNF and TrkB in neuronal differentiation of Fmr1-knockout mouse. **Neurobiol. Dis.**, epub 2010 Nov 1.

Lyubimov Y, Engstrom M, Wurster S, Savola JM, Korpi ER and Panula P (2010). Human kisspeptins activate neuropeptide FF2 receptor. **Neuroscience** 170: 117-122.

Moise L, Liu J, Pryazhnikov E, Khiroug L, Jeromin A and Hawrot E (2010). K(v)4.2 channels tagged in the S1-S2 loop for alpha-bungarotoxin binding provide a new tool for studies of channel expression and localization. **Channels** 4: 115-123.

Molotkov D, Yukin A, Afzalov R and Khiroug L (2010). Gene delivery to postnatal rat brain by non-ventricular plasmid injection and electroporation. **J. Vis. Exp. JoVE** <http://www.jove.com/index/details.stp?id=2244>, doi: 10.3791/2244.

Nuutinen S, Karlstedt K, Aitta-aho T, Korpi ER and Panula P (2010). Histamine and H3 receptor-dependent mechanisms regulate ethanol stimulation and conditioned place preference in mice. **Psychopharmacology** 208: 75-86.

Palmu K, Stevenson N, Wikstrom S, Hellstrom-Westas L, Vanhatalo S and Palva JM (2010). Optimization of an NLEO-based algorithm for automated detection of spontaneous activity transients in early preterm EEG. **Physiol. Meas.** 31: N85-N93.

Palva JM, Monto S, Kulashkhar S and Palva S (2010). Neuronal synchrony reveals working memory networks and predicts individual memory capacity. **Proc. Natl. Acad. Sci. U. S. A.** 107: 7580-85.

Palva S, Monto S and Palva JM (2010). Graph properties of synchronized cortical networks during visual working memory maintenance. **Neuroimage** 49: 3257-68.

Panula P (2010). Hypocretin/orexin in fish physiology with emphasis on zebrafish. **Acta Physiol.** 198: 381-386.

Panula P, Chen YC, Priyadarshini M, Kudo H, Semenova S, Sundvik M and Sallinen V (2010). The comparative neuroanatomy and neurochemistry of zebrafish CNS systems of relevance to human neuropsychiatric diseases. **Neurobiol. Dis.** 40: 46-57.

Panula P and Nuutinen S (2010). Histamine and H3 receptor in alcohol-related behaviors. **J. Pharmacol. Exp. Ther.**, epub 2010 Sep 23.

Perälä N, Peitsaro N, Sundvik M, Koivula H, Sainio K, Sariola H, Panula P and Immonen T (2010). Conservation, Expression, and Knock-down of Zebrafish *plxn2a* and *plxn2b*. **Dev. Dyn.** 239: 2722-34.

Rantamäki T and Castrén E (2010). Riittääkö että masennuslääke vain otetaan. **Dosis** 26: 209-213.

Rauvala H and Rouhiainen A (2010). Physiological and pathophysiological outcomes of the interactions of HMGB1 with cell surface receptors. **Biochim. Biophys. Acta** 1799: 164-170.

Ruusuvuori E, Kirilkin I, Pandya N and Kaila K (2010). Spontaneous Network Events Driven by Depolarizing GABA Action in Neonatal Hippocampal Slices are Not Attributable to Deficient Mitochondrial Energy Metabolism. **J. Neurosci.** 30: 15638-42.

Saarinen A, Mäyränpää MK, Lehesjoki AE and Mäkitie O (2010). Low-density lipoprotein receptor-related protein 5 (LRP5) variation in fracture prone children. **Bone** 46: 940-945.

Saarinen A, Saukkonen T, Kivelä T, Lahtinen U, Laine C, Somer M, Toiviainen-Salo S, Cole WG, Lehesjoki AE and Mäkitie O (2010). Low density lipoprotein receptor-related protein 5 (LRP5) mutations and osteoporosis, impaired glucose metabolism and hypercholesterolaemia. **Clin. Endocrinol.** 72: 481-488.

Sallinen V, Kolehmainen J, Priyadarshini M, Toleikyte G, Chen YC and Panula P (2010). Dopaminergic cell damage and vulnerability to MPTP in *Pink1* knockdown zebrafish. **Neurobiol. Dis.** 40: 93-101.

Segerstråle M, Juuri J, Lanore F, Piepponen P, Lauri SE, Mülle C and Taira T (2010). High firing rate of neonate hippocampal interneurons is due to attenuation of afterhyperpolarizing potassium current by tonically active kainate receptors. **J. Neurosci.** 30: 6507-14.

Sharifi A, Kousi M, Sagné C, Bellenchi GC, Morel L, Darmon M, Hulková H, Ruivo R, Debacker C, El Mestikawy S, Ellender M, Lehesjoki AE, Jalanko A, Gasnier B and Kyttälä A (2010). Expression and lysosomal targeting of CLN7, a major facilitator superfamily transporter associated with variant late-infantile neuronal ceroid lipofuscinosis. **Hum. Mol. Genet.** 19: 4497-514.

Sipilä S, Blaesse P and Kaila K (2010). Development of GABAergic signaling: from molecules to emerging networks. In: *Oxford Handbook of Developmental Behavioral Neuroscience* (eds. Blumberg M, Freeman J and Robinson S). Oxford University Press, New York.

Sirén A, Polvi A, Chahine L, Labuda M, Bourgoin S, Anttonen AK, Kousi M, Hirvonen K, Simola KOJ, Andermann E, Laiho A, Soini J, Koivikko M, Laaksonen R, Pandolfo M and Lehesjoki AE (2010). Suggestive evidence for a new locus for epilepsy with heterogeneous phenotypes on chromosome 17q. **Epilepsy Res.** 88: 65-75.

Spulber S, Rantamäki T, Nikkilä O, Castrén E, Weihe P, Grandjean P and Ceccatelli S (2010). Effects of maternal smoking and exposure to methylmercury on brain-derived neurotrophic factor concentrations in umbilical cord serum. **Toxicol. Sci.** 117: 263-269.

Tammimäki A, Käenmäki M, Kambur O, Kuleshkaya N, Keisala T, Karvonen E, García-Horsman JA, Rauvala H and Männistö PT (2010). Effect of S-COMT deficiency on behavior and extracellular brain dopamine concentrations in mice. **Psychopharmacology** 211: 389-401.

Tolner E, Hochman D, Hassinen P, Otáhal J, Gaily E, Haglund M, Kubová H, Schuchmann S, Vanhatalo S and Kaila K (2010). Five percent CO<sub>2</sub> is a potent, fast-acting inhalation anticonvulsant. **Epilepsia**, epub 2010 Sep 30.

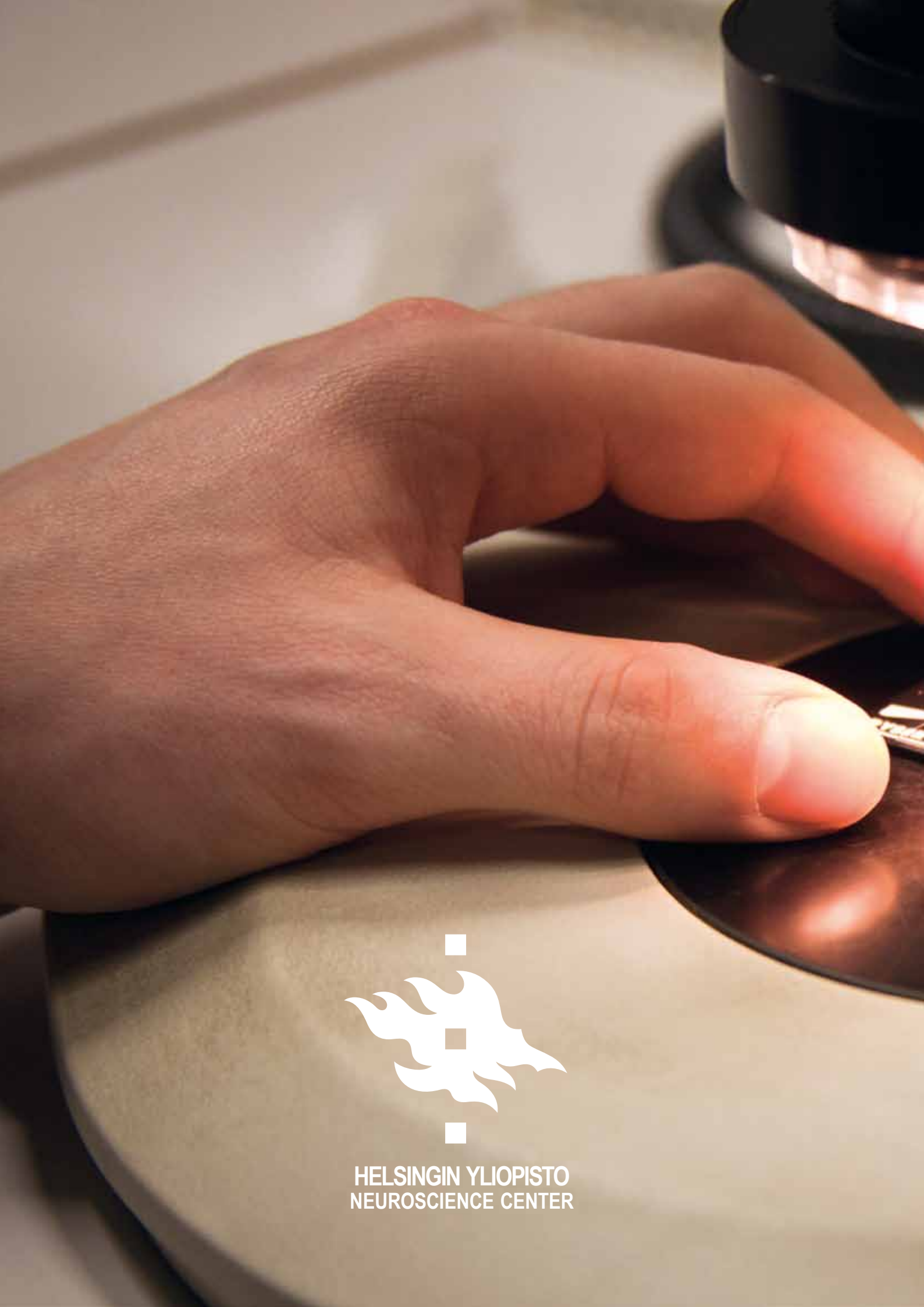
Tsoporis JN, Izhar S, Leong-Poi H, Desjardins JF, Huttunen HJ and Parker TG (2010). S100B interaction with the receptor for advanced glycation end products (RAGE): a novel receptor-mediated mechanism for myocyte apoptosis postinfarction. **Circ. Res.** 106: 93-U197.

Vanhatalo S and Kaila K (2010). Emergence of spontaneous and evoked EEG activity in the human brain. In: *The Newborn Brain: Neuroscience and Clinical Applications* (eds. Lagercrantz H, Hanson M, Evrard P and Rod C), pp. 229-244. Cambridge University Press.

Viitanen T, Ruusuvuori E, Kaila K and Voipio J (2010). The K<sup>+</sup>-Cl<sup>-</sup> cotransporter KCC2 promotes GABAergic excitation in the mature rat hippocampus. **J. Physiol.** 588: 1527-40.







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