## PLENARY LECTURES

### L1
### PRIMARY VISUAL CORTEX – RECEPTIVE FIELD PROPERTIES AND FEEDFORWARD AND FEEDBACK INPUTS

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Numerous psychophysical, behavioural and neurological studies implicate the mammalian primary visual cortex as the 'seat' of visual perception. Seminal work of Hubel and Wiesel published mainly in the 60-ties of the previous century, lay down foundations for the feedforward model of receptive field properties of individual neurons in the primary visual cortices of mammals with frontally positioned eyes (e.g. domestic cats and primates). The feedforward model has been somewhat modified by the discovery (mainly in the 70-ties of the previous century) of the parallel information channels in the retino-thalamo-cortical pathway. To this day, the excitatory feedforward model remains the mainstay of our thinking about the mechanisms underlying the processing of information in the primary visual cortices. To a large extent, the excitatory feedforward hierarcho-parallel associational cortico-cortical connections are underpinning our understanding of properties of neurons in numerous 'higher-order' visual areas. Only in the last two decades or so a number of studies attempted to examine the role of numerically massive feedback pathways originating from the higher-order visual cortical areas in determining the responsiveness and at least some receptive field properties of neurons in the primary visual cortices.

### L2
### FROM NOCICEPTORS TO CHRONIC PAIN

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The IASP (Int. Ass. Study of Pain) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Since its publication in 1979 this definition has been widely accepted notwithstanding that it was predefined in 1964 in Harold Merkey's Ph.D. thesis "An Investigation of Pain in Psychological Illness" (H.M. was the chairman of the IASP task force searching for the definition). Fortunately the psychological bias of the definition did not prevent in the last decades an ever increasing investigation into the modes of operation of the nociceptive system including its physiological as well as its pathophysiological aspects. As will be outlined in this lecture considerable progress has been made in identifying the characteristics of nociceptors and of the pathways along which they send their signals to the cortical centers responsible for the conscious sensation of pain. Less progress has been made in elucidating the mechanisms, both physical and psychological, responsible for turning an acute pain into a chronic suffering particularly when the tissue damage has long gone or when it was not present in the first place. Even less progress can be reported regarding the mysteries of acute and chronic neuropathic pain, which according to the IASP taxonomy group is "pain caused by a lesion or disease of the somatosensory nervous system". The reasons for our ignorance and possible ways to reduce it will be discussed.

### L3
### THE ROLE OF VOLTAGE-GATED CALCIUM CHANNELS IN REGULATING THE EXCITABILITY AND DISCHARGE BEHAVIOR OF MOTONEURONS

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The discharge behavior of mammalian motoneurons is governed by a complex interplay between the excitatory and inhibitory synaptic inputs they receive and the cells' intrinsic electrical properties. Motoneurons express a host of voltage-gated channels that can dramatically alter the transmission of synaptic current to the soma and the integration of different synaptic input systems. Of particular importance are the Cav1.2 and Cav1.3 channels that are a major source of the persistent inward current (PIC) that amplifies excitatory synaptic input and supports repetitive firing. Indeed, PICs provide an intrinsic source of excitatory drive that is larger than those associated with any of the synaptic input systems studied to date. Whereas PICs can be rapidly inactivated by a hyperpolarizing input, they are ideally suited for both supporting sustained muscle contractions in posture and for providing a major source of the alternating 'drive' to motoneurons during locomotion. In my lecture, I will review our studies conducted over the past decade on the biophysical properties of Cav1.2-1.3 channels using electrical, immunocytochemical and optical methods. My goal is to elucidate how the properties of these channels studied in reduced, *in vitro* preparations can account for many of the complex behaviors of motoneurons observed in intact animals and in man.

### L4
### AUTISM AND THE SVZ: A SITE FOR MECHANISMS?

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Based on a wide-ranging profile of autism-relevant behaviors, the BTBR T+tf/J (BTBR) mouse is the most widely accepted mouse model of idiopathic autism. Recent work from this lab indicated a widespread disturbance in the molecular composition of the extracellular matrix in the subventricular zone of the lateral ventricles (LV-SVZ) in BTBR,

compared to C57BL/6J (control) mice. Deep reductions in heparan sulfates (HS), linear polysaccharides that interact with a range of growth and guidance factors in the LV-SVZ, and in laminin, suggest a potential mechanism/location for the disturbed hodology of the autistic brain. Evaluation of this hypothesis involved 4 pairs of autism-diagnosed individuals (ADI) with age- and sex- (all male) matched typically developing (TD) controls. In the TD controls, HS levels declined sharply with increasing age, consonant with a particular function for HS in the developing brain. Overall, ADI had significantly less HS than TD, but this difference was most profound in the younger samples, disappearing in the age 60+ pair. Laminin levels were consistent for TD, but extremely variable for ADI. We now have a total of 18 ADI-TD age- and sex-matched pairs, and are examining gene expression and DNA methylation profiles in the LV-SVZ of individuals diagnosed with autism. We expect that changes localized to the LV-SVZ will provide greater specificity concerning epigenetic factors involved in the brain dysfunctions associated with the disorder.

**L5**

**DATA SHARING AND DATA PUBLICATION**

**De Schutter E.**

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Despite regulation supporting sharing of scientific data and extensive investment in neuroinformatics database infrastructure very little data is actually being shared in most subfields of neuroscience. I will first discuss reasons why data sharing often fails in practice, referring to personal experience as computational neuroscientist and co-editor in chief of Neuroinformatics. I will then argue that the main problem is a lack of clear incentives to share data. An obvious incentive can be authorship, but it is often not practical or appropriate for the scientists who collected the data to become co-authors of original articles that report results derived from the data. Recently, an alternative has become available under the form of data publication. Initially this was mainly seen as a procedure to make publicly released data collections citable by providing a doi. But several journals, including Neuroinformatics, have now introduced the concept of a data article. This is a paper that just describes how the data was collected and how it is made available, but does not include any interpretation or conclusions. The advantages and attractiveness of the data article format will be discussed.

**L6**

**BUILDING BLOCKS OF THE THALAMUS**

**Acsády L.**

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The basic computational unit of the thalamus, the glomerulus, was described exactly 50 years ago, by the late János Szentágothai. The essence of the glomerulus is a giant excitatory terminal which establishes multiple synapses on thalamocortical neurons. This synaptic arrangement evolved to secure faithful information transfer between a well-defined sensory input and the cortex. Recent ultrastructural and physiological investigations of several thalamic nuclei in the rodent and primate brains, however, revealed a rich diversity of excitatory terminals and actions in the thalamus. The data showed that only a minority of the thalamus is dedicated to faithful relay of sensory information. Large thalamic regions are driven exclusively by the cortex, whereas in others large excitatory terminals are entirely missing and are replaced by giant inhibitory terminals of extrathalamic origin. Convergence of large excitatory terminals with different origin on single thalamocortical cells has also been found and the size and complexity of the excitatory terminals displayed great nucleus specific variations These data suggests that the computations performed by individual thalamic regions is not necessary a simple relay and display considerable nucleus specific variability. Revealing the basic computational units of different thalamic nuclei also allow us to resolve the biological basis of neurological diseases involving the thalamus.

**L7**

**THE MIRROR NEURON SYSTEM**

**Rizzolatti G.**

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An exciting discovery in neurosciences over the last years has been that of a mechanism that unifies action perception and action execution. The essence of this mechanism – the mirror mechanism – is the following. Each time individuals observe an action done by others, a set of neurons that code that action are activated in the motor system. Since the observers are aware of the outcome of their motor acts, they also understand what the others are doing without the necessity of an intermediate cognitive mediation. In my talk, I will describe first some new discoveries on the mirror mechanism in the monkey. I will present then evidence that humans possess the mirror mechanism and that the anatomical location of parieto-frontal mirror networks of the monkeys and of humans closely coincide. Subsequently I will discuss the limits of the mirror mechanism in understanding others. I will stress that the mirror mechanism is, however, the only mechanism that allows a person to understand others' actions "from the inside" giving the observing individual a "first-person" grasp of other individuals' motor goals and intentions.

**L8**

**VISION RESTORATION AFTER BRAIN AND RETINA DAMAGE: THE "RESIDUAL VISION ACTIVATION THEORY"**

**Sabel B.A.**

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Vision loss after retinal or cerebral visual injury (CVI) is considered to be irreversible. According to the "residual vision activation theory" vision can be reactivated and partially restored. CVI is usually not complete but some structures are usually spared after damage: (1) areas of partial damage at the visual field border, (2) "islands" of surviving tissue inside the blind field, (3) intact extrastriate pathways, and (4) higher-level neuronal networks. But because of "non-use" in everyday life, the synaptic strength of these are impaired. However, residual structures can be reactivated by repetitive stimulation using different means: (1) visual experience, (2) visual training, or (3) non-invasive electrical brain current stimulation. They lead to the strengthening of synaptic transmission and synchronization of surviving cells (within-systems plasticity) and downstream neuronal networks plasticity. Reactivation induces synaptic plasticity is the basis for residual structures to become again engaged in every day vision and this (re-) activation effects outlasts the stimulation period, thus contributing in a last way to vision restoration and improvements in quality of life. In summary, partial blindness is not irreversible as previously assumed, but there is hope to regain (or restore) some of the lost vision through brain plasticity.

## SYMPOSIA
## S1. Neurophysiological and molecular mechanisms of pain

### S1.1
### THE BILATERAL JOINT-BRAIN CONNECTION: PAIN MECHANISMS AND NEURONAL CONTROL OF INFLAMMATION

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Major neuronal mechanisms of inflammatory joint pain are the peripheral and spinal sensitization. We addressed the role of proinflammatory cytokines in neuronal sensitization. A single injection of either TNF-α, interleukin-6, interleukin-1 β and interleukin-17 into the knee joint induced a slowly developing and long-lasting mechanical sensitization of the neurons mimicking longlasting inflammation-evoked sensitization. *Vice versa* the neutralization of these cytokines reduced hyperalgesia in antigen-induced arthritis. Neutralization of TNF-α significantly reduced mechanical and thermal hyperalgesia, neutralization of IL-1β reduced thermal hyperalgesia, neutralization of IL-17 reduced in particular mechanical hyperalgesia. Neutralization of IL-6 reduced mechanical hyperalgesia upon pretreatment. Spinal cytokines can contribute to inflammation-evoked spinal hyperxcitability. In particular IL-6 was rapidly increased in the spinal cord upon joint inflammation, and neutralization of IL-6 attenuated the development of spinal hyperexcitability. However, the nervous system also influences the inflammatory process. In antigen-induced arthritis in mice chemical sympathectomy or β-adrenergic blockers significantly reduced the magnitude of the acute phase of inflammation. Furthermore, neutralization of spinal TNF-α decreased the inflammatory process in the knee joint. These data suggest that the expression of inflammation is partly dependent on neuronal reflexes.

### S1.2
### NOVEL PHARMACOTHERAPY OF OSTEOARTHRITIS: TRPV1 AND CB1 RECEPTORS AS TARGETS FOR PHARMACOLOGICAL INTERVENTION

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Osteoarthritis (OA) is the most common degenerative joint disease, which leads to pain during joint loading and to chronic physical disability. The management of OA is often frustrating for both patients and physicians as adequate pain relief is difficult to achieve and no treatment modality seems to reverse the disease progression. Clearly, OA is a large, unmet medical need, there is a strong need to develop new treatments for OA. Considerable evidence has uncovered new mechanisms underlying the generation and transduction of pain, many of which represent new targets for pharmacological intervention. The endogenous agonist of cannabinoid receptor 1 (CB1), anandamide (AEA), also stimulates transient receptor potential vanilloid channel-1 (TRPV1) channels, which instead plays a key role in the induction of inflammation and the development of pain associated with OA. AEA degradation by fatty acid amides hydrolase (FAAH) limits its activity. Inhibiting FAAH, and TRPV1 with the same molecule might produce more efficacious anti-hyperalgesic actions than the targeting of FAAH or TRPV1 alone. An update of the relationship CB1 and TRPV1 channels and their possible implications for OA pain will also be provided. Bases for the possible future development of new therapeutic approaches that might be used for the treatment of pain will be suggested.

### S1.3
### SPINAL MICROGLIA ACTIVATION – IMPORTANCE FOR CHRONIC PAIN

**Mika J.**
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Pain may now be considered a neuro-immune disorder, since it is known that the activation of immune and immune-like glial cells in the dorsal root ganglia and spinal cord results in the

release of both pro- and anti-inflammatory cytokines, as well as algesic and analgesic mediators. Our studies underline an important role of cytokines (IL-1alfa, IL-1beta, IL-4, IL-6, IL-10, IL-18, fractalkine and CCL2); complement components (C1q); metaloproteinases (MMP-2, -9) and many other factors, which become activated under neuropathic pain. Another novel approach for controlling neuropathic pain can be pharmacological attenuation of glial and immune cell activation. It has been found that propentofylline, pentoxifylline, fluorocitrate and minocycline suppress the development of neuropathic pain. The other way of pain control can be inhibition of transcription factor synthesis (NF-kappaB); kinase synthesis (p38MAPK) and protease activation (MMP9). Additionally, since it is known that the opioid-induced glial activation opposes opioid analgesia, some glial inhibitors, which are safe and clinically well tolerated, are proposed as potential useful ko-analgesic agents for opioid treatment of neuropathic pain. Our results support the idea that targeting microglial activation represents a novel and clinically promising method for enhancing analgesic effects of opioids in neuropathic pain. Acknowledgments: Supported by grant 2011/03/B/NZ4/00042 and statutory funds.

**S1.4**

**NEUROBIOLOGICAL MECHANISMS IN MIGRAINE**

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Migraine is an episodic neurovascular disorder typically characterized by attacks of unilateral throbbing headache, autonomic dysfunctions and focal neurological symptoms. The initiation of migraine attacks is still enigmatic. While an essential role for the intracranial afferent innervation is widely accepted, the importance of cortical spreading depression inducing neurovascular inflammatory responses is disputed. Recent animal experiments indicate that a cascade of nociceptive events including the generation of gaseous mediators like nitric oxide species, which activate transient receptor potential channels and increase the release of calcitonin gene-related peptide, is involved in the trigeminal processing of nociceptive information possibly leading to migraine pain. A periodic weakening of endogenous inhibitory control systems may enable the dysregulation of central pain processing and constitutes a challenge for future routes of migraine therapy.

**S1.5**

**ASPECTS OF PAIN IN SPORT AND PHYSIOTHERAPY**

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Sport and physiotherapy involve issues of pain, including its theoretical, practical and therapy-related aspects. In sportsmen, pain plays an informative role to indicate the maximal load on the organism. In physiotherapy, pain shows the physiological limits of the patient's current readiness to manage rehabilitation loads. The wide spectrum of problems concerning pain in sport and physiotherapy may, due to advances in biology and medicine, become a new attractive area of scientific research. However, relatively few scientific papers deal with this subject. There are aspects of pain in sport and physiotherapy which remain rather unexplored, such as the effect of exercise on pain reception, the ability to tolerate pain during extreme physical stress, painkiller abuse, including by amateurs, pathophysiology of ischemia, individual sensory perception, and the placebo effect. Also, the synergic effects of physical, pharmacological and psychophysiological factors that modulate variability in pain perception or may have an effect on pain tolerance are not well understood. Better knowledge of this area, in addition to research impact, may have practical applications in the training process of sportsmen as well as persons who are physically active during their working life and after retirement. Pain in sport and physiotherapy can be expected to continue to gain in importance, given, in particular, the increasing number of active elderly people, especially in European countries.

## S2. Synaptic plasticity and neuronal environment

**S2.1**

**BDNF PROTEOLYTIC PRODUCTS: DIVERSITY OF EFFECTS ON CELLULAR PLASTICITY**

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The neurotrophin brain-derived neurotrophic factor (BDNF) is involved several aspects of neuronal development and plasticity ranging from cell proliferation and survival to regulation of neuronal shape and synaptic long-term modifications. BDNF occurs in mammals in three different isoforms, a precursor, a truncated form and the mature form. Recent animal and cellular studies showed that mature and pro-BDNF elicit opposite biological effects, leading to the hypothesis that an incorrect balancing of the different isoforms may lead to a different outcome in brain functioning or even cause a pathological effect. We recently found a dysregulation in the levels of the three BDNF forms, including truncated BDNF, in serum from patients affected by schizophrenia, autism or multiple sclerosis. Since the biological role of truncated BDNF is unknown, we investigated its physiological functions using cultured rat hippocampal neurons and found that it has different effects on neuronal survival, dendritic and axonal development and synaptic activity with respect to mature BDNF and pro-BDNF.

**S2.2**

**ACTIVITY-DEPENDENT MOTILITY OF PERISYNAPTIC ASTROCYTIC PROCESSES: LINKS TO FUNCTIONAL SYNAPTIC PLASTICITY**

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Astrocytes are generally accepted as important players in synaptic function and development. On the other hand astrocytes *in vivo* have a very complex 3D structure, which is shaped by their numerous and highly ramified thin peripheral processes. Morphology of perisynaptic astrocytic processes (PAP) is subject to constant remodeling, for instance, long-lasting PAP retraction in hypothalamus is known to alter synaptic transmission and deficiency in PAP movement can prevent dendritic spine formation and synaptic maturation. The PAP motility is likely to be actin-based since they are known to contain actin and actin-related proteins. We use actin-binding deficient Profilin-1 (abdProf-1) as a genetically-encodable tool to selectively suppress activity-dependent morphological plasticity of astrocytes in combination with membrane targeted form of GFP (LckGFP) to trace PAPs precisely. This approach combined with astrocyte-specific viral gene delivery allows us to learn how suppressed morphological response of astrocytes can affect synaptic function in the mouse brain.

**S2.3**

**MMP-9, AN EXTRACELLULAR PROTEASE IN CONTROL OF SYNAPTIC PLASTICITY**

**Kaczmarek L.**

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The last twenty five years of intense research have provided convincing evidence for a role of regulation of gene expression in control of long-term neuronal plasticity, including learning and memory. Following our discovery (in late eighties) of c-fos activation in those phenomena, it has been well documented that c-Fos and its functional form, AP-1 transcription factor, play the major role learning processes. Recently, an extracellular proteolytic system, composed, inter alia, of tissue inhibitor of matrix metalloproteinases, TIMP-1 and matrix metalloproteinase-9, MMP-9, has emerged as a major AP-1 target in the brain neurons responding to enhanced neuronal activity. Structural remodeling of the dendritic spines and synapses is essential for synaptic plasticity, underlying learning and memory. We have found that in the rodent hippocampus both MMP-9 protein and its transcript are associated with dendritic spines, where they can undergo activity-driven local translation and locally released MMP-9 enzymatic activity controls the morphology of the spines. Functional inactivation of MMP-9 affects synaptic plasticity and blocks late phase of long-term potentiation as well as hippocampus- and amygdala-dependent learning. In aggregate, these results point to a novel molecular mechanism of synaptic function that operates extracellularly.

**S2.4**

**IMPACT OF METALLOPROTEASES ON SYNAPTIC AND E-S PLASTICITY IN THE HIPPOCAMPAL MOSSY FIBER – CA3 AND AC PATHWAYS**

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Learning and synaptic plasticity is known to involve activity of metalloproteinases (MMPs). Recently, we investigated impact of MMPs on mossy fiber-CA3 (mf-CA3) projection, where LTP is NMDAR-independent and presynaptic, and showed that MMP blockade disrupted LTP maintenance. Using *in situ* zymography we showed that LTP induction enhances gelatinases activity. Moreover, by means of gelatin zymography, immunohistochemistry and immunofluorescent staining we have shown that this was due to *de novo* synthesis and activation of MMP-9 (but not MMP-2). Next we found that manipulations in endogenous MMP-9 affected LTP in the mf-CA3 projection. Intriguingly, in slices from both MMP-9 KO and overexperssing rodents, LTP maintenance was nearly abolished. In KO group, LTP could be rescued by administration of active MMP-9. This suggests that LTP maintenance in mf-CA3 pathway requires fine-tuned MMP-9 activity. Neuronal plasticity may involve also changes in excitability and we addressed this issue in associational/commissural synapses formed between CA3 pyramidal neurons. We found that MMPs (MMP-3 and gelatinases) inhibition significantly reduced EPSP-to-spike (E-S) and spike coherence upon LTP indution. Altogether, we show that MMPs play a crucial role in controlling various facets of neuronal plasticity in the mf-CA3 hippocampal projection. Support: NCN grant N N401541540.

## S3. Across experimental and clinical neurophysiology

**S3.1**

**ELECTROPHYSIOLOGICAL DIAGNOSTICS OF MYASTHENIA AND MYASTHENIC SYNDROMES**

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Contemporary diagnostics of neuro-muscular (n-m) transmission disorders (including myasthenia and myasthenic syndromes)

comprises: (1) Pharmacological testing with edrophonium or neostigmine, (2) Immunological investigations of antibodies against AChR, MuSK and Ca channels, (3) Electrophysiological examinations: repetitive nerve stimulation (RNS) and electromyography of single muscle fibre (SFEMG) with jitter evaluation. When discussing the RNS, the physiological pathology of changes occurring during this test in the n-m junction is presented, as well as the effect of temperature on n-m transmission and the problem of n-m block selectivity. An optimal selection of muscles for such studies is proposed, taking into consideration that in n-m transmission disorders the sensitivity is higher in the proximal muscles than in the distal ones. Methods of activation of the changes looked for is discussed and an optimal investigation programme proposed. A typical myasthenic electrophysiological pattern is presented as well as that typical of Lambert-Eaton syndrome and congenital myasthenia. SFEMG method is discussed and its usefulness in diagnosing n-m transmission disturbancies. Finally, specificity and sensitivity of procedures employed in n-m transmission disturbancies is compared.

**S3.2**

**INTERHEMISPHERIC ASYMMETRY OF THE N20 SUBCOMPONENT LATENCY: NEW PARAMETER OF MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS IN HEALTHY ADULTS**

**Kinalski R.**

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For quantification in SI units the effects of sensory inputs influenced the poststroke interhemispheric sensorimotor disintegration the tools and procedures of clinical neurophysiology are needed. Detailed statistical analysis have proved that in healthy adults latency of N20 peak onset (N20o) recorded from one contralateral parietal (CPc) hemisphere is the best standard parameter for normal values. Such responses are also evoked in ipsilateral parietal (CPi) hemisphere. Stimulating right (R) then left (L) median nerves and using cephalic CP-Fz recording montage we have recorded (rec) SEPs simultaneously from CPc and CPi in the adult healthy right handed 9 men and 11 women of different age (39.16 ± 12.56 years) and height (H) (173.32 ± 10.18cm). In comparison with N20 the N20o latency mean values (LMV) to CPi were significantly longer both for R ($P$=0.001) and for L ($P$=0.008). Irrespective to side of stimulation and recording only the LMV of N20o correlated with H (Corr): R-recCPc-Corr $r$=0.53, $P$=0.008. R-recCPi-Corr $r$=52, $P$=0.007. L-recCPc-Corr $r$=68, $P$=0.0004. L-rec-CPi-Corr $r$=0.55; $P$=0.007.

**S3.3**

**APPLICATION OF SURFACE ELECTROMYOGRAPHY IN DIAGNOSTICS OF MUSCLES MOTOR UNITS DYSFUNCTION DURING OVERLOADING AND IN STANDING POSITIONS**

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Surface electromyography (sEMG) recorded bilaterally starts to be applied the same frequently as invasive needle EMG in confirmation of certain muscle- or spine-related motor units disorders. In 30 patients with clinically recognized myofascial pain (bilateral trigger points-TRPs), mean sEMG amplitude recorded from trapezius and cervical or lumbar axial muscles at rest was increased (>25 μV instead of 15 μV indicating increased tension) what in turn decreased their ability to maximal contractions. No pathology in motor transmission was found. Coexistence of characteristic spontaneous activity in needle EMG recordings with TRPs presence was observed. In 40 office-workers dysfunction of trapezius muscle was the most responsible for cervicogenic headache when recordings of sEMG were performed and again the same at rest-maximal contraction pattern of motor units dysfunction was found. Differentiation of sciatica and pseudosciatica patients with clinical examinations especially when they complain of pain during prolonged standing is difficult. However sciatica ($n$=11) was characterized with significant increase of mean sEMG amplitude recorded especially in distal muscles on affected side during tandem position. It was related to decrease in sEMG "fluctuations" frequency more than in pseudosciatica ($n$=9) patients in normal and standing positions. ENG was pathological only in sciatica patients.

## S4. Cortico-subcortical interactions in different behavioural states

**S4.1**

**BRAIN STATE-RELATED ACTIVITY OF SEPTO-HIPPOCAMPAL NEURONAL NETWORK**

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Biologically relevant synchronous discharges of assemblies of pyramidal neurons result from coordinated activity of oscillating neuronal networks. Cortical oscillating networks include different types of GABAergic interneuron, which are known to innervate different subdomains of pyramidal neurons. Interneurons contribute to different cortical rhythms by firing at different phases of field oscillations. The cortical network oscillators are embedded in larger oscillating networks comprising subcortical structures, such as the basal forebrain. An example

of this kind of cortico-subcortical network is the hippocampus reciprocally connected with the medial septum belonging to the basal forebrain corticopetal system. The medial septum innervates the hippocampus through cholinergic, GABA-ergic and glutamatergic projections and receives a prominent GABA-ergic innervation from the hippocampus. Additionally, the GABA-ergic septo-hippocampal cells specifically target the GABA-ergic interneurons, implying a role in hippocampal rhythmogenesis. Extracellular recording and juxtacellular labelling of hippocampo-septal GABA-ergic neurons and septo-hippocampal neurons *in vivo* have provided insight into their functional properties, including firing patterns of identified neurons during different, brain state-dependent hippocampal oscillations.

**S4.2**

**CORTICO-THALAMIC MODULATORY PATHWAY**

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The lateral geniculate nucleus (LGN) relays visual information from the retina to the primary visual cortex (V1). In addition to glutamatergic fibers from the retina, the neurons in the LGN are innervated by glutamatergic fibers descending from V1. Although corticothalamic feedback fibers outnumber fibers ascending from the retina 10:1, the excitatory drive they provide is quite limited due to the dendritic location and low transmitter release probability of the synapses. While feedback is below the threshold for initiating action potentials, it could modulate the transfer of information to V1. This modulation could provide a mechanism for attention to emphasize behaviorally relevant sensory input. To investigate a role in attention we first identified that the vesicular glutamate transporter type 1 (VGLUT1) is important for the normal function of the feedback neurons and then proceeded to test mice with deficient VGLUT1 expression in a behavioral task that assesses visual attention. EPSCs of corticothalamic origin, measured in whole-cell patch-clamp in LGN slices, were absent in VGLUT1 knock-out mice. In heterozygous VGLUT1 mice, corticothalamic synapses had altered short-term plasticity. When VGLUT1-heterozygous mice were subjected to the 5-Choise Serial Reaction Time Task, they had reduced performance in spatially divided attention and inhibitory response control. This could be an effect from an altered corticothalamic modulation of the thalamic relay.

**S4.3**

**CORTICAL DETERMINATION OF TEMPORAL STRUCTURE OF SPIKE TRAINS IN THE CAT'S LATERAL GENICULATE AND PERIGENICULATE NUCLEI**

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Feedback projections from the, so called, "higher-order" to the "lower order" structures are common feature of sensory systems. Those projections were proposed to control the flow of sensory information from the periphery to the cortex. The cortico-thalamic feedback of the mammalian visual system was extensively studied, yet we are still far away from understanding neuronal and network mechanisms engaged in this modulatory influence. In our earlier studies with cortical cooling as a method of reversible elimination of cortical input to thalamus, we have shown that cortical feedback modulated response magnitude and influenced receptive field organization of neurons in both lateral geniculate (LGN) and perigeniculate (PGN) nuclei. Elimination of the cortical input modified spontaneous firing rate of thalamic neurons, decreasing, as expected, activity of the relay LGN cells, and, surprisingly, increasing the activity of PGN interneurons. Our recent studies show that despite of different effects of the cortical feedback on spontaneous firing rate, elimination of cortical input similarly affects inter-spike intervals within bursts generated by LGN and PGN cells, increasing their length. These results suggest similar cellular mechanism underlying direct cortical influence exerted on the LGN relay cells and PGN interneurons.

**S4.4**

**STATE RELATED CHANGES OF INFORMATION FLOW IN THALAMO-CORTICAL PATHWAYS**

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Depending on the level of arousal identical sensory stimuli result in different neuronal and behavioral responses. This effect may depend on thalamo-cortical network mechanism directing sensory information to the cortex either through a first-order or higher-order thalamic relay nuclei. Using multichannel chronic recordings from the thalamo-cortical part of the somatosensory system of behaving rats, we have shown that in low arousal the information flow reaches primary sensory (S1) cortex mainly *via* first-order ventral posteromedial (VPM) nucleus and that a higher-order relay – posterior medial nucleus (PoM), receives this information later, *via* feedback input from S1. In contrast, during high arousal substantial part of the sensory information flow to S1 is passed also through the PoM nucleus. We propose that direct opening of peripheral inputs transmission through PoM follows the release of this nucleus from feed-forward inhibition exerted by zona incerta. This mechanism may serve to supply fast sensory information about salient stimuli not only to S1 but also, in parallel, to higher order sensory and motor cortices in order to facilitate behavioral reactions. Although such mechanism may lower the accuracy of detailed stimulus feature processing but may play a vital role during dangerous situations. Research was supported by the National Science Centre grant N N401 533040.

## S5. Bioactive lipids and mitochondria: Key players in the pathogenesis of Alzheimer's disease (AD)

### S5.1
### MITOCHONDRIAL DYSFUNCTION – THE MISSING LINK BETWEEN AGING AND SPORADIC AD?

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The non-Mendelian sporadic Alzheimer's disease (AD) is the most frequent form of dementia diagnosed worldwide. The most important risk factor to develop sporadic AD is aging itself. Next to hyperphosphorylated Tau, intracellular amyloid beta (Aβ) oligomers are known to initiate a cascade of pathological events ranging from mitochondrial dysfunction, synaptic dysfunction, oxidative stress, and loss of calcium regulation, to inflammation. All these events are considered to play an important role in the progressive loss of neurons. The molecular mechanisms determining the balance between Aβ production and clearance during the progression of the disease are not well understood. Furthermore, there is cumulating evidence that Aβ formation impairs mitochondrial function. On the other hand, mitochondrial dysfunction, in particular increased formation of mitochondrially derived reactive oxygen species, promote Aβ formation. We propose that mitochondrial dysfunction, which is well-known to increase with age, is an initial trigger for Aβ production. A vicious cycle is initiated that originates from mitochondrial dysfunction, implying that AD can be viewed as an age-associated mitochondrial disorder. The proposed mechanism sheds new light on the pathophysiological changes taking place during the progression of AD as well as in the aging process.

### S5.2
### TARGETING MITOCHONDRIA IN ALZHEIMER'S DISEASE: EFFECTS OF OMEGA 3 FATTY ACIDS

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Increasing evidences suggest that mitochondrial dysfunction plays an important role in the pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD). Alterations of mitochondrial efficiency and function are mainly related to failure of enzyme activities of mitochondrial complexes from the electron transport chain leading to oxidative stress, deficits in cellular bioenergetics and finally neuronal death. More recently, structural changes of the mitochondrial network were related to bioenergetic dysfunction, and the consequences are a matter of intensive research. The essential role of mitochondrial bioenergetics and the unique trajectory of alterations in brain metabolic capacity enable a bioenergetic- centric strategy that targets disease-stage specific pattern of brain metabolism for disease prevention and treatment. Recently, high fish intake or dietary supplementation with omega-3 fatty acids (n-3 FAs) has been linked to reductions in the risk of developing AD and to delayed cognitive decline in patients with very mild AD. However, the underlying cellular and molecular effects of n-3 FAs are poorly described. Here, we present new data demonstrating protective effects of n-3 FAs on bioenergetic function. Since mitochondrial dysfunction represents an early event in disease progression, more studies are needed that focus on therapeutic strategies starting before severe progression of the disease.

### S5.3
### MicroRNA-125b (miRNA-125b) REGULATION OF 15-LIPOXYGENASE (15-LOX) EXPRESSION AND THE GENERATION OF NPD1 FROM DHA: A POTENTIAL CONTRIBUTOR TO THE PATHOGENESIS OF ALZHEIMER'S DISEASE (AD)

**Lukiw W.J.**

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In the human central nervous system (CNS), plasma membranes are normally enriched in docosahexaenoic acid (DHA). Membrane bound DHA is liberated by phospholipase A2 (PLA2), that is subsequently converted into a 10,17S-docosatriene known as neuroprotectin D1 (NPD1). The DHA-to-NPD1 conversion appears to occur *via* the actions of 15-lipoxygenase (15-LOX). In the hippocampal CA1 region of Alzheimer's disease (AD) we observe significant up-regulation in the activity of several phospolipases, including cytosolic phospholipase A2 (cPLA2), and significant deficits in the abundance of both 15-LOX and NPD1. Expression of 15-LOX appears to be regulated epigenetically and post-transcriptionally by the actions of a brain enriched, NF-kB-regulated miRNA-125b which binds to the 3'-untranslated region (3'-UTR) of 15-LOX mRNA, and down-regulates 15-LOX expression. 15-LOX down-regulation, and a deficiency in neurotrophic NPD1 may be explained by the actions of a single NF-kB-up-regulated miRNA-125b, part of a mis-regulated family of inducible, NF-kB-sensitive miRNAs in AD brain. The actions of a pathologically up-regulated miRNA-125b, and other pathogenic miRNAs, may be neutralized using anti-NF-kB and/or anti-miRNA-125b strategies, thereby returning 15-LOX and NPD1 expression back to homeostatic levels.

**S5.4**

**CERAMIDE/SPHINGOSINE-1-PHOSPHATE IN CELLS SURVIVAL AND DEATH: IMPLICATION IN ALZHEIMER'S DISEASE**

**Strosznajder R.P.[1], Czubowicz K.[1], Gąssowska M.[2], Cieślik M.[2]**

*[1]Department of Neurosurgery, [2]Department of Cellular Signalling, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland*

Ceramide and sphingosine-1-phosphate (S1P) are very active sphingolipid messengers which play a crucial role in regulation of neuronal cells survival and death. Alternation of ceramide/S1P rheostat is related to several pathological disorders including Alzheimer's disease. Ceramides are involved in cells proliferation, differentiation and apoptotic death, while S1P enhances cell proliferation and antagonizes apoptosis. S1P regulates cellular processes by binding to five specific G protein coupled-receptors (S1PR1-5). The aim of the study was to investigate the molecular processes of neuronal death evoked by ceramide and the role of S1P in neuroprotection. Our study indicated that ceramide enhanced significantly the level of free radicals and decreased neuronal cells (SH-SY5Y) viability through inhibition of PI3-K/Akt pathway. Ceramide also decreased anti-apoptotic (Bcl-2) and increased pro-apoptotic (Bax, Hrk) gene expression. Exogenously added S1P increased the viability of cells through S1PR (1-3) receptors-dependent mechanism. S1P also increased Bcl-2 gene expression and decreased the gene expression of Hrk protein. Summarizing, our study indicated that the action of ceramide and S1P on mitochondria may control neuronal fate and may play a crucial role in neurodegeneration and neuroprotection.

## S6. Neurobiology of invertebrates

**S6.1**

**NEURAL CONTROL OF BODY PATTERNING IN CEPHALOPODS: FROM BEHAVIOR TO GENOMICS**

**Tublitz N.J.**

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Cephalopods, a class of mollusks that includes octopus, squid, cuttlefish and nautilus, are among the most fascinating organisms in the animal kingdom. They are legendary for their intelligence, learning capacity, incredible behaviors and motor plasticity. Their large brain, and neural circuitry provides the neural foundation for the remarkable behavioral plasticity exhibited by these creatures. This talk will begin with a brief overview of cephalopods including some of their most important and unique characteristics. The major part of the lecture will focus on the cellular and molecular regulation of Body Patterning Behavior, the ability of these organisms to produce static and dynamic body displays within 500 milliseconds and arguably their most amazing behavior.

**S6.2**

**THE ROLE OF BRP PROTEIN IN SYNAPTIC PLASTICITY IN THE VISUAL SYSTEM OF *DROSOPHILA***

**Pyza E., Górska-Andrzejak J., Woźnicka O.**

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Bruchpilot (BRP) protein is a scaffolding presynaptic protein that has been detected in the nervous system of *Drosophila melanogaster*. BRP assembles a presynaptic active zone and is responsible for calcium channel clustering and release of a neurotransmitter from synaptic vesicles. We have used the antibody nc82 against BRP to visualize presynaptic elements of tetrad synapses formed between the photoreceptor terminals and postsynaptic cells in the first optic neuropil (lamina) of the *Drosophila* optic lobe. In the lamina several circadian rhythms have been detected including rhythms in plasticity of synapses and neurons. The aim of this study was to examine whether BRP protein is involved in the circadian plasticity of tetrad synapses in the lamina. We have examined the BRP level, measured as the fluorescence intensity of immunolabeling, at different times of a light/dark (LD 12:12) regime and constant darkness (DD). We have found that BRP oscillates during the day. In LD 12:12 its level increases two times, in the morning and in the evening. However, these two peaks in BRP abundance are regulated differently. The morning peak is predominantly regulated by light since it is not present in norpA7 phototransduction mutant but it also depends on the circadian clock gene per. In turn the evening peak is regulated by the brain pacemaker. This peak is present in DD as well as in the norpA7 in LD but is absent in clock gene mutants.

**S6.3**

**NEUROTRANSMITTERS AND OTHER FACTORS REGULATING INSULIN PRODUCING CELLS IN THE *DROSOPHILA* BRAIN**

**Nässel D.R.**

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Insulin-like peptides (ILPs) and growth factors (IGFs) not only regulate development, growth, reproduction, metabolism, stress resistance, and lifespan, but also certain behaviors and cognitive functions. ILPs, IGFs, their tyrosine kinase receptors and downstream signaling components have been largely conserved over animal evolution. Eight ILPs have been identified in *Drosophila* (DILP1-8) and they display cell and stage specific expression patterns. One insulin receptor, dInR, is known in *Drosophila* and most other invertebrates. Nevertheless the different DILPs are independently regulated transcriptionally and appear to have partly distinct functions, with some redundancy. I will discuss what is known about regula-

tion of production and release of DILPs in *Drosophila* with focus on insulin signaling in the daily life of the adult fly. Under what conditions are DILP-producing cells (IPCs) activated and which factors have been identified in control of IPC activity in flies? The brain IPCs that produce DILP2, 3 and 5 are targeted by a leptin-like molecule and DILP6 from the fat body. Also a few neurotransmitters and neuropeptides, like serotonin, octopamine, GABA, short neuropeptide F (sNPF), corazonin and tachykinin-related peptide have been identified as regulators of IPCs in *Drosophila*. I also discuss physiological conditions under which IPC activity may be regulated, including nutritional states, stress and diapause induction.

**S6.4**

**BIOLOGY OF NEUROPEPTIDE PROCESSING AND PRODUCTION IN THE FRUITFLY *DROSOPHILA***

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Neuropeptides synthesized by secretory neurons or interneurons in the CNS are important regulators of physiology, behaviour, and development. They are synthesized from larger precursor molecules by a specific set of enzymes. Combining the power of *Drosophila* neurogenetics with semiquantitative peptidomics, we are characterising the functional role of these processing enzymes. The results obtained so far are in line with genomic data suggesting that there typically is one major specific gene/enzyme for each processing step, which is in contrast to the situation in mammals. As expectable, many behavioural phenotypes in peptide processing mutants are reminiscent of known peptidergic phenotypes. Theoretically, processing enzymes represent an ideal cellular target to regulate divergent peptidergic signalling in the neuroendocrine and nervous system. The findings above make the fruitfly an ideal genetically and biochemically tractable model to test this hypothesis. Moreover, we will outline how these findings in concert with cell-specific genetic targeting could be used to identify new peptidergic phenotypes, as well as to analyse the function of "functionally redundant" peptides.

**S6.5**

**REGULATORY MECHANISMS OF *PERIPLANETA AMERICANA* NERVOUS SYSTEM FUNCTIONS**

**Lapied B.[1], Stankiewicz M.[2]**

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Cockroaches, mainly *Periplaneta americana*, are known to be suitable models for both fundamental and applied neurobiological research. Different preparations, used in electrophysiological experiments, can be extracted from its relatively accesible nervous system. Studies performed on (1) DUM (dorsal unapired median) octopaminergic neurons from the central nervous system and (2) neuronal cholinergic transmission revealed several complex regulatory mechanisms, which are for some of them very similar to those found in vertebrate nervous system. Differential regulation of membrane receptors and ion channels involved in the modulation and generation of DUM neurons pacemaker activity by phosphorylation/dephosphorylation (e.g., PKA, PKC, DARPP-32, CaMKinase II, PP12A) process have been now well characterized. Furthermore, more unusually, these intracellular signalling pathways seem to play important roles in the increase of sensitivity to neurotoxicants. In the same way, at cholinergic synaptic transmission level, the functional property of a negative muscarinic feedback has also been identified to play crucial influence in the modulation of the release of acetylcholine, which thereby reinforces compound toxic activity. All these data reveal exciting research area that could lead to improvement in the efficiency of insect pest management.

## S7. Higher order motor control and recovery of functions

**S7.1**

**ACTION OBSERVATION AS A TOOL FOR NEUROREHABILITATION OF MOTOR DEFICITS FOLLOWING STROKE**

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The mirror neuron system consists of a set of brain areas capable of matching action observation with action execution. One core feature of the mirror neuron system is the activation of motor areas by action observation alone. This unique capacity of the mirror neuron system to match action perception and action execution stimulated the idea that mirror neuron system plays a crucial role in the understanding of the content of observed actions and may participate in procedural learning. These features bear a high potential for neurorehabilitation of motor deficits following stroke. Since the first articles exploring this principle were published, a growing number of follow-up studies have been conducted in the last decade. Though, the combination of action observation with practice of the observed actions seems to constitute the most powerful approach. The existing studies analyzing the effects of this neurorehabilitative approach in clinical settings especially in the rehabilitation of stroke associated motor deficits will be summarized. Additionally, a perspective on the ongoing trials by our research group will be provided. The data obtained up to date showed significant positive effect of action observation on recovery of motor functions of the upper limbs even in the chronic state after stroke, indicating that

our approach might become a new standardized add-on feature of modern neurorehabilitative treatment schemes.

**S7.2**

**THE MIRROR SYSTEM IN HUMANS, MOTOR LEARNING AND RECOVERY OF FUNCTION**

**Buccino G.**

*Department of Medicine and Surgery, University of Magna Greacia in Catanzaro, Italy*

Not received

**S7.3**

**ENCODING MOTOR INTENTION IN MONKEY PARIETAL AND PREMOTOR CORTEX**

**Fogassi L.**

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Single neuron recording studies showed that in both ventral premotor cortex (VPM) and inferior parietal cortex (IPC) most neurons discharge in relation to goal-related motor acts and are involved in sensorimotor integration processes. More recently, a series of studies investigated the role of IPC and VPM in intentional actions, using a paradigm in which monkeys have to perform two types of actions, in order to assess whether the response of grasping neurons of the two areas are influenced by the final action goal. The results showed that grasping neurons of both regions activated differently according to the final goal of the action (eating or placing) in which grasping act was embedded, likely reflecting agent's motor intention. Furthermore, when the monkeys had to perform the same two actions but using different types of grip, many neurons showed an integration of grip and action goal coding. One of the most interesting findings of these studies is that both parietal and premotor mirror neurons show a differential activation depending on the action goal not only during the execution, but also during the observation of others intentional actions. This indicates that the parieto-premotor circuit underlying the organization of intentional actions also allow individuals to decode the motor intentions of others.

**S7.4**

**TASK-DEPENDENT DISSOCIATIONS BETWEEN TRANSITIVE AND INTRANSITIVE GESTURE REPRESENTATIONS: THE PROSPECTS OF RECOVERY FOLLOWING RIGHT VS. LEFT HEMISPHERE LESIONS**

**Króliczak G.**

*Institute of Psychology, Adam Mickiewicz University, Poznan, Poland*

There is compelling neuroimaging evidence for a common left-hemisphere praxis representation network supporting the control of meaningful actions. Yet, the idea of dissociable neural systems for tool use (transitive) and intransitive (symbolic) gestures was revived by reports of selective dissociations between imitation and pantomime of transitive and intransitive skills. Because the contribution of recognition and/or visuo-spatial deficits was not directly assessed, this study tested whether distinct representations support transitive and intransitive skills during their visual processing, and later imitation. The outcomes were then compared to the results of verbally-cued gesture pantomimes. Both perception and imitation of the two gesture categories activated common networks, different between the tasks. The areas engaged more during watching transitive pantomimes, and imitation of intransitive gestures, were found outside of these networks. Examples of single case dissociations will be also shown and discussed. All these findings support the idea that transitive gestures are more demanding to process and execute. Yet, they also show that it is imitation of intransitive gestures that relies on modulations outside of the praxis representation network. These outcomes shed some new light on the prospects of recovery following right vs. left, and lateral vs. medial brain lesions.

## S8. Neurobiology of autism

**S8.1**

**MUTATIONS OF Shank3 IN AUTISM AND MOUSE MODELS**

**Savonenko A.**

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Autism represents a spectrum of behavioral and cognitive disorders characterized by deficits in language development, social interactions, and repetitive behaviors. A significant fraction of ASD is caused by *de novo* or rare mutations, and the Shank3 gene is one of the genes with multiple mutations linked to this disorder. This link is confirmed in GWAS studies. Interestingly, ASD cases with Shank3 mutations are characterized by high variability of phenotypes ranging from severe cases of autistic disorder to milder variants with Asperger syndrome. Recently, a number of groups created different Shank3 knockout mice models attempting to reproduce effects of genetic perturbations discovered in ASD patients. Strategies employed by different groups have demonstrated that levels of Shank3 protein are decreased to different extent by knocking out different exons of the Shank3 gene likely due to transcription from spared intragenic promoters. The phenotypes of Shank3 mutant mice were diverse possibly reflecting variability of ASD symptoms in patients with Shank3 mutations. At the synapse, Shank3 interacts with multiple key players such as Homer, mGluRs, GKAP and cy-

toskeletal proteins suggesting that mutations of this protein would lead to multiple effects at the synapse involving perturbations in multiple molecular pathways. How different mutations and multiple synaptic pathways can evoke behavioral and cognitive phenotypes of autism remains a central challenge of research, and Shank3 mutations embody a good example of this problem.

**S8.2**

**AUTISM AS A SYNAPTOPATHY: BEHAVIORAL STUDIES IN GENETIC MOUSE MODELS**

**Wöhr M.**

*Behavioral Neuroscience, Philipps-University of Marburg, Marburg, Germany*

Autism is a neurodevelopmental disorder characterized by abnormal reciprocal social interactions, communication deficits, and repetitive, stereotyped patterns of behaviors. While the causes of autism remain unknown, the high concordance between monozygotic twins supports a strong genetic component. Genome-wide and pathway-based association studies led to the identification of several susceptibility genes for autism, many of which code for proteins involved in synapse formation and function, including the NLGN and SHANK genes families. NLGN genes code for postsynaptic cell adhesion molecules, Neuroligins, that bridge the synaptic cleft by forming heterophilic complexes with their presynaptic binding partners, Neurexins. SHANK genes code for scaffolding proteins located in the postsynaptic density of excitatory synapses. To test the hypothesis that mutations in NLGN and SHANK gene family members contribute to the symptoms of autism, we evaluated various mutant models for behavioral phenotypes with relevance to autism, focusing on social communication, namely ultrasonic vocalizations and the deposition of scent marks, which appear to be two major modes of mouse communication. Results indicate that mice lacking Neuroligin or Shank family members display an autism-like behavioral phenotype, including social communication deficits. Often, these deficits are paralleled by cognitive dysfunctions, such as impaired object recognition. Our studies support the notion that autism is a synaptopathy.

**S8.3**

**EXTRACELLULAR MATRIX ALTERATIONS IN BTBR MOUSE MODEL OF AUTISM**

**Meyza K.**

*Laboratory of Emotions Neurobiology, Nencki Institute of Experimental Biology, PAS, Warsaw, Poland*

Autism spectrum disorders (ASD) are a group of behaviorally defined neurodevelopmental disorders characterized with three core symptom clusters: social behavior impairments, deficient communication and increased repetitive behaviors. The etiology of the disease remains poorly understood as many factors seem to contribute to ASD phenotype. Several mutations in genes encoding synaptic proteins have been linked with aberrant social behaviors in mouse models of autism. The condition of the synapse relies not only on the expression of these proteins but also on the state of the extracellular millieu surrounding it. The extracellular matrix (ECM) regulates formation and maturation of dendritic spines, scaffolding and presentation of growth factors to newly born neurons as well as migration of neurons and axons to their designated brain regions both during development and adulthood. The aberrant expression of its components may lead to neuropathologies observed in patients diagnosed with ASD. Here we have looked at the expression of ECM components (laminin and heparan sulfate) in the brains of BTBR T+tf/J mice, the best-studied mouse model of ASD, displaying not only behavioral deficits but also neuroanatomical features resembling those of ASD patients. We found the expression markedly decreased as compared with highly-social c57BL/6J mice, which opens an entirely new field of search for molecular basis and biomarkers of their autistic-like behaviors.

**S8.4**

**ANIMAL MODEL OF AUTISM INDUCED BY PRENATAL EXPOSURE TO VALPROIC ACID: TRANSLATIONAL VALIDITY**

**Schneider T.**

*Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK*

Autism is a neurodevelopmental disorder characterised behaviourally by impairments in social interaction, verbal and nonverbal communication, and by restricted, repetitive patterns of behaviour, interests, and activities. I will present one of the best characterized animal models of autism induced by prenatal exposure to valproic acid (VPA). Rodents exposed to VPA on the 12th day of gestation show several brain abnormalities, resembling those found at autopsy and imaging studies of autistic patients as well as long-term behavioural deficits including decreased sociability, hyperactivity, stereotypic activity, increased anxiety, lower sensitivity to pain, and diminished acoustic prepulse inhibition; and several molecular and immunological aberrations, e.g., altered functioning of opioidergic, serotonergic, dopaminergic, and glutamatergic systems, and decreased cellular immunity. Observed aberrations are more prominent in males and can be reversed by environmental enrichment. Similarities in behavioural, anatomical, biochemical and immunological pathology in autism and VPA rodents suggest the utility of this model for defining common pathways for dysregulation of normal developmental patterns and assessing the time course and sources of vulnerability to autism. I will show recent empirical and theoretical applications of VPA model towards better understanding and potential new treatments for autism.

## S9. RNA binding proteins, microRNAs and local protein synthesis in nervous system function

### S9.1

### DYNAMIC REGULATION OF mRNA TRANSLATION IN NEURONS BY FMRP AND microRNAS

**Muddashetty R., Gross C., Yao Y., Nalavadi N., Warren S.T., Bassell G.J.**

*Department of Cell Biology, Emory University School of Medicine, Atlanta, GA, USA*

Long term synaptic plasticity underlying learning and memory is believed to require the reversible and dynamic regulation of local protein synthesis, which is dysregulated in fragile x syndrome, the most common form of inherited intellectual disability and autism. Fragile x syndrome is caused by the loss of the Fragile X Mental Retardation, FMRP, an mRNA binding protein involved in the regulation of local protein synthesis at synapses. We elucidated a cooperative role and dynamic interaction between the Fragile X Mental Retardation, FMRP, and microRNAs to repress translation at synapses, which can be rapidly de-repressed in response to activation of gp1 metabotropic glutamate receptors. One FMRP target mRNA of interest has been postsynaptic density-95, PSD-95, which is localized to dendrites and can be translated at synapses in response to activation of mGluRs. More recent work has revealed the role of other microRNAs to regulate FMRP target mRNA translation that appears important for control of neuronal excitability. We speculate that fragile x syndrome may result from synaptic protein imbalances due to dysregulation of microRNA-mediated control that is important for control of neuronal development, excitability and plasticity.

### S9.2

### PERSISTENT TrkB SIGNALING TO MNK ACTIVATES A TWO-STAGE TRANSLATIONAL SWITCH UNDERLYING *IN VIVO* LTP MAINTENANCE

**Bramham C.R.**

*Department of Biomedicine and KG Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway*

Long-term synaptic plasticity requires stimulus-evoked changes in protein translation. However, the dynamics of translational control post-stimulus are little understood. We report that LTP maintenance at excitatory synapses in live rats requires repetitive BDNF activation of TrkB over hours. TrkB signalling to the MAP kinase-interacting kinases (MNKs) mediates sustained eIF4F translation initiation complex formation through a two-stage mechanism. In early LTP maintenance, MNK triggers release of the CYFIP1/FMRP repressor complex from the 5'-mRNA cap, coupled to translation of FMRP-regulated mRNAs. In late LTP maintenance, MNK switches to regulate the canonical translational repressor 4E-BP2 specifically within the synaptic compartment. This delayed release of 4E-BP2 is associated with synapse-specific polyribosome formation and enhanced dendritic mRNA translation. In MNK knockout mice, both CYFIP1 and 4E-BP2 repressor complexes are disrupted. Hence, sustained TrkB-MNK signalling drives the sequential activation of distinct forms of cap-dependent translation, culminating in synapse-specific translation and LTP maintenance.

### S9.3

### MicroRNA FUNCTION IN SYNAPSE DEVELOPMENT AND PLASTICITY

**Schratt G.M.**

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The proper development of synapses in the mammalian central nervous system is critical for cognitive functions, and aberrations lead to neurological disorders, e.g., intellectual disability, autism and schizophrenia. We have recently identified miRNAs that are important during various stages of excitatory synapse development in hippocampal neurons, such as dendritic arborization and spine maturation. Our current research explores the mechanisms of activity-dependent regulation of these miRNAs at the level of transcription, processing and subcellular localization. Furthermore, we characterize the role of activity-dependent miRNA regulation in different forms of synaptic plasticity, as well as the implications for higher cognitive functions and homeostasis, using genetically modified mice. Potential links to the above mentioned neurological disorders will also be discussed.

### S9.4

### RIBONUCLEOPARTICLES IN DENDRITIC ARBOR DEVELOPMENT

**Jaworski J.**

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Dendrites are the main site of information input into neurons. Development of a dendritic tree is multistep and very complex process, which is tightly regulated by combination of extracellular cues and execution of intrinsic genetic program. An important cellular process for proper dendritic arbor development is local production of key structural proteins in response to neuronal activity and trophic factors. This so called local translation requires transport and storage of translationally dormant mRNAs along dendrites in form of ribonucleoparticles. The data form overexpression and knockdown experiments will be presented, supporting important role of selected components of ribonucleoparticles, e.g., ZBP1 and Staufen 1 in proper development of dendritic arbors of hippocampal neurons. Using ZBP1 and its target, b-actin mRNA,

as examples I will show how, on a molecular level, ZBP1 contributes to dendritic growth. Finally, evidence for a positive role of protein kinases such as Src and mTOR in regulation of ZBP1-dependnet dendritic growth will be presented. This work is supported by ICGEB grant no. CRP/POL11-02.

## S.10 Recovery of the brain function after stroke

### S10.1

### VISUAL FIELD DEFECTS IN PATIENTS WITH ISCHEMIC STROKE: CHARACTERISTICS, CONSEQUENCES, AND ACUTE MANAGEMENT

**Tatlisumak T.**

*Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland*

Ischemic brain damage along the visual pathways frequently manifest with visual field defects. Most occipital lobe infarcts lead to homonymous hemianopia. Additionally, cognitive problems are often present. Visual field defects caused by occipital lobe infarction are often permanent causing long-term disability in vision and in daily life activities. Patients lose environmental control, give up their activities, have difficulties in reading and watching, lose their driving licence, are prone to accidents, and working-age patients often have to give up their work. Approximately 20–30% of ischemic stroke patients have some degree of visual field defect. Only half of these patients recover, most recovery occurring within 3 months. IV thrombolysis is the only approved acute treatment in ischemic stroke, but most patients having an occipital infarction score low on neurologic scores and do not usually receive thrombolysis. We have recently described that thrombolysis was safe in these patients and was associated with high rates of improvement. Future efforts must concentrate on disseminating thrombolytic therapy in this patient group and developing effective rehabilitation methods for reducing the burden of the disease, but current treatment options are limited.

### S10.2

### NON-INVASIVE BRAIN STIMULATION IN VISION IMPAIRMENT AFTER STROKE: THE REVIS NETWORK

**Gall C.[1], Rossini P.M.[2], Tatlisumak T.[3], Waleszczyk W.J.[4], Speck O.[1], He H.[5], Sabel B.A.[1]**

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Non-invasive brain stimulation is a promising tool in treatment of visual impairment. The aim of the 'Restoration of Vision after Stroke' (REVIS) network is to determine if non-invasive current stimulation may also have a positive impact on vision restoration in patients with post-chiasmatic visual pathway lesions. In particular, the potential of non-invasive current stimulation in ameliorating vision impairment following stroke is the key issue addressed by the REVIS study group. Within the REVIS network a number of small sample, randomized, controlled, clinical studies including patients with post-chiasmatic lesions due to monohemispheric, ischemic or hemorrhagic stroke were initiated by clinical partners from Germany, Italy and Finland. The network also includes a basic neuroscience project that studies neuronal network reorganization in the cat visual system after stroke (Poland). Beyond the European network, a collaboration with the Institute of Automation at the Chinese Academy of Science was established. This contribution presents the overall aims of the network activity, the rational of the clinical endpoint selection and preliminary findings.

### S10.3

### ATTENUATION OF INFLAMMATORY RESPONSE AFTER STROKE ALLOWS TO RETAIN BRAIN PLASTICITY

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Despite indications that brain plasticity may be enhanced after stroke, we have described impairment of experience-dependent plasticity in rodent cerebral cortex neighbouring the stroke-induced lesion. There is increasing evidence showing that inflammation accounts for stroke progression. Once activated, inflammatory cells can release a variety of cytotoxic agents that may induce more cell damage as well as disruption of the blood-brain barrier and extracellular matrix. We have shown that chronic treatment with anti-inflammatory drug ibuprofen restored plasticity of cortical representation of vibrissae induced by whisker deprivation. We have also the upregulation cyclooxygenase-2 (COX-2) and other proinflammatory factors, i.e. IL-1 and tumor necrosis factor TNFα shown in the acute poststroke phase. Since TNFα is one of the key players in stroke progression, we decided to reduce the TNFα signalling by introduction into the brain soluble TNFα receptors 1 that will compete for TNFα with receptors localized in the brain tissue. We have shown that such approach undertaken simultaneously with the stroke was successful in preserving the poststroke brain plasticity. Supported by Polish National Science Centre Grant: N N401 098739.

### S10.4

### NEUROPHYSIOLOGICAL TECHNIQUES TESTING BRAIN CONDUCTIVITY

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Different brain areas are thought to be integrated into large-scale networks. Recent approaches for investigating structural organization and functional coordination within these networks involve measures of connectivity among brain areas. Transcranial magnetic stimulation (TMS) can be used to analyze the functional state of the cerebral cortex, discovering changes in its excitability, connectivity and plasticity which may have occurred through processes such as learning or recovery from a lesion. We review studies using *in vivo* functional brain connectivity technologies. TMS-EEG studies have begun to describe the nature of the TMS-evoked EEG responses in order to broaden the comprehension of the activation mechanisms of TMS. Several studies have proved the power of TMS-EEG by displaying many data about the excitability or connectivity of the brain. Particularly, it has been proposed that the very first part of the TMS evoked EEG response displays the excitability of the stimulated cortex while its spatio-temporal distribution over the scalp displays the spread of activation to other cortical areas – *via* intra and inter-hemispheric cortico-cortical connections as well as to sub-cortical structures and spinal cord *via* projection fibres – that means the effective connectivity of the stimulated area. Finally effective connectivity may be considered as the union of structural and functional connectivity. These studies provide insights into the relationships between brain structure and function.

## S11. A CARE lecture

**S11.1**

### ETHICAL AND LEGAL ASPECTS OF EXPERIMENTING ON ANIMALS

**Turlejski K.**

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In my presentation I am going to review the present the state of law concerning research on animals in the European Union and Poland in particular. I am going to refer relate the status of implementation of the EU Directive 2010/63 in Poland and other EU. Next I will review the major changes in standards of the laboratory animal husbandry, process of ethical evaluation and control over scientific experiments that implementation of the new Directive 2010/63/UE of the European Union Council and European Parliament is going to impos. Lastly, I will compare numbers of animals used for animal research in various European countries, the spectrum of species used and the most problematic directions and objects of scientific research on animals from the point of view of the new Directive. In conclusion, I will try to describe the possible impact of the new Directive on animal research in Europe.

## POSTER SESSIONS
## P1. Neurochemistry and pharmacology

**P1.1**

### EXTRACELLULAR alpha-SYNUCLEIN INDUCES CALPAIN-DEPENDENT OVERACTIVATION OF CYCLIN--DEPENDENT KINASE 5 IN PC12 CELLS

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α-Synuclein (ASN) secreted from neurons into the extracellular space affects the homeostasis of neighboring cells, but the pathophysiology of extracellular ASN remains largely unknown. The aim of the present study was to analyze the role of cyclin dependent kinase 5 (Cdk5) in molecular mechanism of extracellular ASN toxicity. We found that exogenously applied ASN evoked apoptotic cell death in a significant population of dopaminergic PC12 cells. ASN induced rapid and long-lasting calcium influx and activation of calcium-dependent enzymes, including caspase-3, nitric oxide synthase and calpain. ASN-induced calpain activation leads to cleavage of Cdk5 activator p35, and subsequently to formation of p25 and Cdk5 overactivation. Moreover, we showed that exposure of PC12 cells to ASN increased Cdk5 activity by enhancement of its phosphorylation at Tyr15. Calpeptin, an inhibitor of calpains, and inhibitors of Cdk5, Roscovitine and BML-259, prevented ASN-evoked apoptosis and cell death, indicating the involvement of Cdk5 in mechanism of ASN toxicity. Our data showed that alterations in calcium homeostasis and modulation of calcium-dependent enzymes by extracellular ASN may contribute to the early stages of pathogenesis in Parkinson's disease and other synucleinopathies.Supported by a grant from The National Science Centre 2012/05/B/NZ3/02047.

**P1.2**

### IMIPRAMINE-REVERSED ELEVATION OF Hsp72 EXPRESSION IN THE BRAIN OF RATS IN THE CHRONIC MILD STRESS MODEL OF DEPRESSION

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Heat shock proteins HSP70 play a protective role against stress-induced damage of cells. We assessed the expression of inducible Hsp72 in the prefrontal cortex (PFC) and hippocampus (HIP) of male Wistar rats subjected to the chronic mild stress (CMS), the procedure inducing depression-like symptoms, and subsequently