PLENARY LECTURES

L.1 Neuroimaging - neurophysiology and neuroanatomy *in vivo*

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Modern neuroimaging tries to describe the functional organization of the human brain at the level of large neuronal groupings, networks and systems. Magnetic resonance imaging (MRI) is now the structural and functional imaging modality of choice in imaging neuroscience. A systems level of description addresses how integrated brain functions are embodied in the physical structure of the brain. Recent advances in image based morphometry provide an unparalleled ability to examine clinical-functional-anatomical correlates. An exciting observation is the dynamic plasticity of function in normal brains and those of patients with neurological and neuropsychiatric disorders. Structural and functional brain maps should be viewed as dynamic, changing with development, ageing, and normal learning and with recovery of function after acute injury.

L.2 Neuronal synchrony, a code for relations - Jerzy Konorski Memorial Lecture

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The evaluation and encoding of relations among distributed neuronal responses are essential components of neuronal processes underlying cognition, memory formation and sensory-motor coordination. In complex brains multiple and rapidly changing relations need to be defined in parallel which requires highly flexible dynamic binding mechanisms. One option for the encoding of relations is the formation of conjunction specific neurons that respond selectively to particular constellations of activity in converging afferents. Another option is to label responses as related by synchronizing the respective discharges with a precision in the millisecond range. Synchronization enhances with high temporal resolution the saliency of the synchronized discharges and hence can be exploited for the selection and binding of responses. Experimental results suggest the following conclusions. 1) Precise synchronization is often associated with an oscillatory patterning of neuronal responses in the β and γ frequency range. 2) Both phenomena exhibit a marked state dependency and occur only when the cortex is in an activated state characterized by a desynchronized EEG. 3) Maintenance of this state requires release of acetylcholine acting on muscarinic receptors. 4) In sensory processing precise synchronization is likely to serve the selection and grouping of short response segments for further joint processing. 5) When neurons engage in oscillatory activity Hebbian modifications exhibit a marked phase sensitivity. Synaptic gain increases (decreases) when pre- and postsynaptic elements oscillate in phase (in counterphase) whereby phase offsets as small as 15 ms suffice to reverse the polarity of the synaptic modifications. 6) Synchronization of oscillatory activity occurs also in the absence of sensory stimulation and then appears to serve coordination of activity across cortical areas in the context of attention dependent processes such as task anticipation and short-term memory. It is suggested that these properties of synchronization are compatible with the hypothesis that it serves as a relation defining mechanism.

L.3 Integrative functions of spinal neurons

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Integrative functions of spinal neurones have been investigated for more than a century and each generation provides new information on these important functions. The earlier studies were mainly descriptive and provided examples of the multimodal input to spinal neurones, of the use of the same neurones for several purposes (multifunctional character), and of the flexibility in the use of spinal neuronal networks, with such notable phenomena as a phase- or state-dependent reversal of spinal reflexes. Most recent studies have focused on the mechanisms behind these phenomena and on possibilities of their use in treatment of various pathological states. We have been particularly interested in the operation of neuronal networks in which information from one source (afferent fibres or central neurones) is distributed to several neuronal subpopulations and in each of these is integrated with information from a variety of other sources and independently modulated. It will be shown that such arrangement may be particularly useful for the selection of pre-existing spinal neuronal networks and in ensuring a flexibility which does not require plastic changes within the networks. Similar arrangements may nevertheless also operate in brain structures involved in learning, such as the cerebral cortex, and would be worth to analyze in them.

L.4 Incentive motivation, conditioning and the integrative activity of limbic cortical-ventral striatopallidal systems

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Pavlovian conditioning has the potential to create multiple associative representations in the brain and pavlovian conditioned stimuli (CSs) profoundly influence appetitive (incentive motivational) behaviour in several distinct ways that depends upon the integrative activity of dissociable elements of limbic cortical-ventral striatopallidal circuitry. We have studied three of these pavlovian influences on motivated behaviour: discriminated approach, pavlovian-instrumental transfer (sometimes called pavlovian or conditioned motivation) and conditioned reinforcement. We have shown that pavlovian approach, as assessed in an autoshaping task, depends upon interactions between the anterior cingulate cortex and the nucleus accumbens core, and also upon interactions between the central amygdala and mesolimbic dopamine system. Pavlovian-instrumental transfer, the process by which pavlovian CSs potentiate goal-directed appetitive responses, also depends upon the central amygdala and nucleus accumbens core in a way that can be further modulated by increasing dopamine transmission in the nucleus accumbens shell. Conditioned reinforcement, by contrast, depends upon the integrity of the basolateral amygdala and nucleus accumbens core and is also profoundly potentiated by increased dopamine transmission in the nucleus accumbens shell in a way that is regulated by the central amygdala. These neurally dissociable conditioned influences on incentive motivational processes, especially but not only conditioned reinforcement, are of major importance in our understanding of the neural and psychological processes underlying drug addiction and may point towards the development of novel treatments of this complex neuropsychiatric disorder.

L.5 Neurons from human cord blood – the evidence

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Adult stem cell plasticity received strong experimental support. Moreover, their potential therapeutic use is supported by recent finding that transplanted bone marrow cells can be found in human brain. However, it is also argued, that adult stem cells can undergo rapid transformation *in vitro* and their capacity to transdifferentiate may be fortuitous. We have isolated a neural stem cell line from human umbilical cord blood (HUCB-NSC). Upon long term culturing HUCB-NSC: 1) retain normal, chromosomal pattern and 2) unchanged ability to proliferate and self-renew, 3) give rise to neurons, astrocytes and oligodendrocytes, 4) can differentiate into functional neurons *in vitro*, 5) upon transplantation can integrate into rats and mouse brain and differentiate into cells recognized by neuronal and astrocytic markers. Functional differentiation *in vitro* into neurons was proven by: 1) expression of functional proteins such as internexin, GluR2, D1AR, 5-HT1CR, AchRb, Gad65, Gad67, SV2 and TH (immunocytochemistry), 2) production of 5-HT and dopamine metabolites (HPLC), 3) presence of voltage and ligand-gated channels (patch-clamp electrophysiological recording). cDNA microarray analysis was employed to verify expression of stem- and neural-type genes in non-differentiated HUCB-NSC as compared to its starting population of CD34(-) mononuclears. An up-regulation of genes for several neural stem cell putative markers and neuron specific genes in HUCB-NSC including: Notch3, JAG2, FGFR1, ENO2, NGFR, NF 200kD, SV2 and Tau was shown.

L.6 Molecular and cellular cognition: Function and dysfunction

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Our laboratory is studying the biology of learning and memory. We are interested in the molecular, cellular and circuit processes that underlie the storage and recall of information. To accomplish this, we are using a variety of techniques including biochemistry, transgenic manipulations, pharmacology, *in vitro* and *in vivo* electrophysiology, neuroanatomical lesions and behavioral analysis. The focus of our studies has been on hippocampal dependent learning and memory. Our results implicate a variety of hippocampal mechanisms in learning and memory, including long-term and short-term plasticity, neuronal excitability and synaptic inhibition. We have found mutations that affect the induction of long-term changes in synaptic function and learning, and others that affect the stability of these synaptic changes and memory (but not learning). For example, our studies have demonstrated that the transcription factor cAMP responsive element binding protein (CREB) is critical for the formation of mammalian long-term memory. We have also studied the impact of these mechanisms in animal models of cognitive disorders. For example, we have recently showed that a mutation that causes Neurofibromatosis type I, a genetic disorder that affects one in 4,000 people world-wide, results in enhanced GABA inhibition in mice. This leads to deficits in synaptic plasticity that could account for the learning deficits associated with this disorder in mice and humans.

Jerzy Konorski Memorial Symposium: Integrative Activity of the Brain

Session A – Sensory integration and brain function

S.1 Organization of cell assemblies in the hippocampus

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Both J. Konorski and D.O. Hebb wondered about how information is processed and stored in neuronal networks. According to the "cell assembly" hypothesis, information is represented in the brain by groups of anatomically distributed neurons which come together briefly in synchronous spiking, and whose activity underlies both processing of external sensory input, and internal cognitive processes. Accordingly, neuronal populations should show an arrangement into synchronous groups, beyond that predicted by common modulation by sensory input. Using parallel recordings in the behaving rat, we found it was possible to predict the spike times of hippocampal pyramidal neurons from the spike times of simultaneously recorded neurons, better than from the animal's trajectory in space, or from a spatially-dependent theta phase modulation. The time window within which spike times were best predicted from simultaneous peer activity was 20-30 ms, suggesting cell assemblies are synchronized at this timescale. Because this temporal window matches the membrane time constant of pyramidal neurons, the period of the hippocampal gamma oscillation and the time window for synaptic plasticity, we suggest that cooperative activity at this timescale is optimal for information transmission and storage in cortical circuits.

S.2 Beta frequency activity and attentional mode of the visual system

Wróbel A.

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In agreement with the old hypothesis that the descending feedback projections in the visual system might be activated during attention processes we have shown that in the cat, (1) cortico-geniculate feedback has a build-in potentiation mechanism acting at the beta frequency which activates thalamic cells and may thus lower the threshold for transmission of visual information; (2) the enhanced beta activity, as shown by chronic local field potential recordings, is propagated along the feedback pathway solely during attentive visual behavior; (3) this attention-related activity consists of 100-350 ms long bursts which appear simultaneously in cortical and thalamic sites involved in central vision and correlate also in time with gamma oscillatory events; (4) such bursting activity spreads to all investigated visual centers, including the lateral posterior-pulvinar complex and higher cortical areas; (5) the idle beta oscillatory rhythm observed in number of visual structures during non-visual situations changes towards a specific pattern of synchronization during attentive seeing. Similar data are obtained during visual behavior in humans. We suggest that observed pattern of beta activity represents temporary activated mosaic of functional connections needed for current visual scan. For example, it may produce background activation for gamma synchronization and perception. Our hypothesis for the role of the cortico-thalamic pathways in attentive perception may be easily applied for all stages of visual and possibly other sensory processing.

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S.3 Glutamate receptor mediated encoding and retrieval of paired-associate learning

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The "Integrative activity of the brain"[1] includes the capacity to represent the integrative relationships between separate items, i.e. paired-associate learning. It is often used to examine episodic memory in humans[2]. Animal models to date include the recall of food-caches by scrubjays[3] and the study of sequential memory[4]. In this presentation, I shall report a new paradigm in which rats encode, during successive sample trials, two paired-associates (flavours of food and their spatial locations) and display above chance recall of one item when cued by the other. In a first study, pairings of a particular foodstuff and its location were never repeated, so ensuring unique "what-where" attributes. Blocking NMDA receptors in the hippocampus, critical for the induction of certain forms of activity-dependent synaptic plasticit[5,6] impaired memory encoding but had no effect on recall. Inactivating hippocampal neural activity by blocking AMPA receptors impaired both encoding and recall. In a second study, two paired-associates were trained repeatedly over 8 weeks amongst novel pairs; hippocampal AMPA receptor blockade did not affect their recall.

Thus, unique "what-where" paired associates depend on encoding and retrieval within a hippocampal memory space with consolidation of the memory traces representing repeated paired-associates in circuits elsewhere[7].

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S.4 Blindsight in monkeys

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After lesions of striate cortex, primates can still detect and localize visual stimuli. I will review three aspects of this phenomenon in macaque monkeys. First, we found that macaques that received their striate lesions as infants had considerably more ability to detect and localize stimuli and discriminate movement than those that received their striate lesions as adults. Second, we suggest that the visual functions that survive striate lesions in macaques made in adulthood resemble those in human "blindsight". Third, we report that monkeys with striate lesions, like humans with striate lesions, are unable to discriminate direction of stimulus movement.

S.5 Integration of time and frequency information in the auditory cortex

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Complex auditory signals are characterized by spectral information in multiple frequency channels changing over time. Both time and frequency have to be encoded at high resolution for the auditory system to display its impressive performance. However, for complex objects and sound locations to be determined on the basis of this information, it eventually has to be integrated across both frequency and time. We propose that this integration is accomplished in higher areas of auditory cortex, and it is in fact this integration that is the major role of nonprimary auditory cortex. Different areas of cortex derive their functional specializations from the specific ways of how they integrate time and frequency information. We have found that neurons in the belt cortex surrounding the primary core areas respond better to band-passed noise bursts than to tones. They also prefer frequency-modulated sweeps to constant-frequency stimuli. The way these preferences are acquired is by means of nonlinear integration: Responses to the combination of different frequency bands are larger than the linear sum of the responses to each of the bands alone. Likewise, responses to the combination of temporal components, e.g. the syllables in a species-specific call, are larger than the linear sum of responses to each of the syllables alone. The proportion of neurons with such nonlinear combination sensitivity increases dramatically from core to belt. We expect that the kind and specificity of nonlinear integration changes further between belt and parabelt and differs between areas of the dorsal and ventral stream.

S.6 The role of area MT in perception and action

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It is widely accepted that the STS-region of the primate is involved in the perception of moving visual stimuli and in the control of visually guided eye movements (saccades and smooth pursuit). We are interested if and how this region is related to the control of visually guided arm movements as well. We trained rhesus monkeys to control a cursor on a screen by means of a two dimensional manipulandum and to perform tracking movements with moving targets, while keeping their gaze on a fixation point on the screen. In a first series of experiments we compared the activity of medio temporal area (MT) neurons in "Tracking" (motor) and "Replay" (visual). In "Tracking" conditions the monkey performed visually guided manual tracking movements in 3 different directions centered around the preferred direction of a MT neuron. In the "Replay" conditions the monkey held his arm stationary and the identical visual scene of the "Tracking" conditions, including fixation point, target and (replayed) cursor movement, was repeated. About the same number of units fired at higher rates in the "Tracking" and in the "Replay" conditions. The significant modulations of the activity in these cells shows, that the behavioural context of acting upon a moving stimulus is reflected in the activity of MT neurons. This result was confirmed in fMRI studies of human subjects. In a second series of experiments we perturbed MT activation by electrical microstimulation, while the monkey performed a "Bend-Tracking" paradigm. In this paradigm the target initially moved linearly downwards and then bent its trajectory to 1 of 4 directions. This change in direction coincides in time with the onset of stimulation current and with the target entering the center of the receptive fields at the site of stimulation. By comparing the trajectories of the monkeys hand in stimulated and non-stimulated trials, we found two main effects: 1) The reaction time to the change of target direction significantly increased with stimulation. 2) The direction of bend reaction was affected by microstimulation, in some cases in favour of the preferred direction of the stimulation site. Both results indicate the monkeys difficulty to act upon a moving stimulus with his hand on the basis of ambiguous motion information from area MT. Together these findings support the view that area MT is involved in the network that performs visuomotor transformations for acting upon moving.

Symposium – Cytokines in Brain Pathology

S.7 T cells traffic in the central nervous system

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Abstract not received

S.8 Nerve growth factor in the brain and cerebrospinal fluid of animal models of multiple sclerosis: a possible functional significance

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Nerve growth factor (NGF) is a neurotrophin normally present in the bloodstream, cerebrospinal fluid (CSF) and in developing and adult mammalian brains. NGF has been shown to exerts a crucial role in the survival and differentiation of brain cholinergic neurons and in promoting functional recovery of injured brain neurons. There is increasing evidence that NGF is also involved in immune and neuroimmune responses and in the recovery of neuroimmune-induced deficits. We have previously reported that NGF increases in CSF patients affected with Multiple Sclerosis (MS) and in rat brain with experimental allergic encephalomyelitis (EAE), one of the most used animal model of MS. More recently, using EAE rats we found that i.c.v. injected NGF is taken up by cells of the subventricular zone (SVZ) and transported into the parenchyma in proximity of damaged cells. The migratory activity of these cells is facilitated by the production of adhesion molecules and by the presence of glia radial cells expressing high-affinity NGF-receptors. Evidence that NGF is implicated in brain cell protection and repair occurring in EAE is supported by recent data obtained with marmoset, a non-human primates, affected with EAE and treated with intracerebral injection of NGF. The aim of more recent studies was to investigate the role of NGF in this neuro-immune pathology. These findings will be presented and discussed.

S.9 Nerve growth factor in rat ischemic brain

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Global transient cerebral ischemia induced by temporary cessation of systemic circulation in rats is a model for brain ischemia evoked by human cardiac arrest. Particularly sensitive to ischemia are pyramidal cells of CA1 region of the hippocampus. Exogenous application of neurotrophic factors, especially of nerve growth factor (NGF) to the brains of ischemic animals, considerably alleviates CA1 layer neurodegeneration. The mechanism of this beneficial action is not clear. The biological action of NGF is mediated by binding its high affinity receptor, TrkA. In addition, NGF reacts with a

low affinity receptor, p75, a common receptor also for other neurotrophins. The question of changes in endogenous NGF receptors in ischemic brain is a key problem in elucidating the mechanisms of neuroprotection exerted by exogenous NGF. The recent results of our investigations on changes in the cellular expression of NGF, its receptors and some other cytokines will be presented. The strong up-regulation of astroglial NGF receptors was demonstrated after ischemia especially in the region adjacent to the degenerating pyramidal neurons. Simultaneously it was found that the activated astroglia release NGF and also some proinflammatory substances, like interleukin-1beta. We hypothesize that the counteraction of proinflammatory substances prevents neuroprotection by endogenously released neurotrophin, and on the other hand we assume that the up-regulated astroglial TrkA receptor may be an important target for exogenous NGF.

S.10 Cytokines and chemokines in the CNS during EAE

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Multiple sclerosis (MS) is an inflammatory disease characterized by damage to CNS myelin. Myelin protein-specific CD4+ T cells secreting proinflammatory Th1 cytokines and chemokines are thought to coordinate an autoimmune response in the CNS. Women with MS develop disease twice more often than men. The basis for gender bias in MS is unclear; accumulating evidence suggests hormonal factors may be involved. Increased levels of sex hormones produced during pregnancy have been shown to associate with significantly reduced severity of MS. A shift towards Th2 cytokine production has been demonstrated during pregnancy and high dose estrogen therapy, and is thought to be the primary mechanism by which estrogen suppresses development of experimental autoimmune encephalomyelitis (EAE), an animal model for MS. However, low dose estrogen treatment is equally protective in the absence of a significant shift in cytokine production. Cytokine deficient mice were treated with estrogen to determine if a shift in Th2 cytokine production was required for protective effects of hormone therapy. Estrogen effectively suppressed development of EAE in IL-4 and IL-10 knockout mice. Decrease in disease severity was accompanied by a reduction in inflammatory cytokines and chemokines in the CNS. There was also a profound decrease in the frequency of TNF-alpha producing cells in the CNS and periphery. Therefore, we propose that one mechanism by which estrogen protects females from the development of cell-mediated autoimmunity is through a hormone dependent regulation of TNF-alpha production.

S.11 IL-15 and IL-18 in patients with multiple sclerosis

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Il-15 is a cytokine produced by monocytes/macrophages sharing several biological activities with IL-2. IL-15 induces T cell proliferation, enhances NK cell cytotoxicity and stimulates B cells to proliferate and secrete immunoglobulins. IL-18 plays an important role in Th-1 response through its ability to induce IFN-gamma production in T cells and NK cells. Because of these properties it is reasonable to assume that these cytokines may play a role in the immunopathogenesis of MS. We have measured IL-15 and IL-18 levels in the serum and CSF of 21 patients with relapsing-remitting form of MS, 9 with active gadolinium enhancing lesions in MRI,12 without enhancing lesions and compared results with the control group. IL-15 and IL-18 concentration in the CSF and sera were measured by ELISA. There was a significant increase of IL-15 in the sera of MS patients in comparison with the control group. The levels were highest in patients with active gadolinium enhancing lesions. There was also a highly significant increase of both IL-18 CSF and serum levels in MS patients. In patients with active MRI lesions the levels of IL-18 in CSF and serum were significantly higher in comparison with the lesions found in patients without enhancing lesions. The results suggest involvement of IL-15 and IL-18 in immunopathogenesis of MS especially in the active stages of the disease.

S.12 Cytokines in stroke

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Stroke is characterized by brain tissue damage associated with the development of inflammatory response. The inflammatory processes observed in stroke are thought to be aggravated by pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-a), interleukin-1beta (IL-1b) and IL-6 produced by resident brain cells and the invading activated monocytes. The number of functions ascribed to pro-inflammatory cytokines in stroke is increasing. These include: leukocyte activation and recruitment from peripheral blood to the ischemic brain area, cytotoxicity, induction of changes in coagulation and fibrinolysis, induction of hepatic synthesis of acute phase proteins. On the other hand - they may enhance regeneration and recovery in the injured brain on several ways, e.g. by stimulation of revascularization, induction of nerve growth factor release by astrocytes, induction of differentiation of neurites and increase of the number of sodium-dependent channels in neurons. Data indicate that the production of cytokines is genetically controlled and influenced by many polymorphisms e.g: VNTR IL-1RN polymorphism, IL1-beta C-511T polymorphism, IL1-alpha G+4845T polymorphism, IL-6 G-174C polymorphism, and TNF-alpha A308G polymorphism. Results of studies suggest that genetic variation at the cytokines loci in Polish stroke patients population is a genetic factor that influence the clinical course of the disease.

Jerzy Konorski Memorial Symposium: Integrative Activity of the Brain

Session B – Cognitive and emotional integration

S.13 Awareness of action

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Our research investigates the proposal that the sensory consequences of movement are predicted by forward models of the motor system. It is proposed that the sensory prediction can be compared with the actual sensory feedback from movement and the results of this comparison can be used to determine the source of the sensation. This predictive system enables the consequences of self-produced events to be cancelled relative to external events and allows us to distinguish self- and externally produced events. It has been proposed that an impairment of this predictive mechanism could give rise to certain symptoms experienced in schizophrenia. If self-produced sensations are interpreted as being generated by an external source, then thoughts

might be interpreted as external voices (auditory hallucinations) and self-produced movements might be interpreted as externally generated (delusions of control). Psychophysical studies have shown that the sensory consequences of self-produced movement is attenuated perceptually relative to external sensations in normal control subjects but not in psychotic patients with auditory hallucinations and delusions of control. Functional neuroimaging studies have demonstrated that the perceptual attenuation of self-produced events may be mediated by attenuation of activity in the somatosensory cortex and the anterior cingulate cortex. Furthermore, evidence suggests that the cerebellum is involved in signalling the sensory discrepancy between the predicted and actual sensory consequences of movement. Over-activation of this neural network may underlie delusions of control, according to the results of a recent study that investigated delusion of control experiences in the normal brain.

S.14 Drug dependence as an impairment of the mechanism of drive satisfaction ("antidrive")

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Addiction is a complex brain disorder characterized by the compulsive out-of-control drug seeking and drug taking behavior, and by the risk of relapse even after a prolonged period of abstinence. The behavior of an addicted person becomes progressively focused on obtaining and using drugs despite serious negative consequences. This disorder may have its source in a disturbed balance of drive-related behaviors which control appetitive reactions aimed at seeking contact with an addictive substance. To understand how the motivational processes are changed with the development of dependence, one must consider the mechanism of drive satisfaction and satiation states that occur in relation with the consummatory reflex. When given drive is satisfied, the state of fulfillment occurs. This state may be a result of a so-called "antidrive" mechanism. While the drive activity is characterized by general activation and tension, the drive satisfaction state ("antidrive") is characterized by relaxation and relief. When a particular drive is satisfied, the operation of other drives become possible. Here, we postulate that dysfunction of drive satisfaction ("antidrive") leads to a sustained activation related to the current drug-related drive, which suppresses the operation of other drives. In effect, uncontrolled compulsive appetitive behavior is released, and the operation of other drives is restrained thus forcing the organism to focus on drug-related drive.

S.15 Auditory cortical processing and memory in the monkey

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The paucity of information regarding the cerebral substrates and mechanisms of high-level auditory processing in primates is a serious obstacle to deciphering the neural basis of human language as well as of human auditory perception and memory generally. To help fill this gap, we are conducting a multidiscipinary program of neuroacoustic research in the monkey. The initial results suggest the following tentative picture regarding the functional organization of the auditory system. Cortical auditory tissue occupies the full extent of the superior temporal gyrus (STG) as well as portions of the inferior parietal, prefrontal, and limbic lobes. Several of these auditory areas overlap with previously identified visual areas in a pattern consistent with the notion that the auditory system, like the visual system, contains separate corticocortical streams for processing stimulus quality, location, and motion. This proposal is supported by the anatomical connectivity within the auditory system, which contains both ventrally directed and dorsally directed projections out of the tonotopically organized auditory areas in the caudal part of the superior temporal gyrus (cSTG). The rostral part of this gyrus (rSTG), a key component in the putative stream for processing sound quality, displays a striking columnar pattern of metabolic activity during passive listening to auditory stimulation. This consists of adjacent thick and thin columns representing ipsilateral and contralateral auditory inputs, respectively, and a third, thin, unactivated column. Also, whereas cSTG always shows greater activation in the right hemisphere than in the left, rSTG shows left-hemisphere "dominance" during listening to monkey vocalizations but not other acoustic categories. This asymmetrical response to vocalization is due in part to suppression of the right rSTG by the left *via* the forebrain commissures. In addition to a role in perception, rSTG is critical for the recognition of trial-unique sounds, as assessed by the effects of removing it on delayed matching-to-sample with short (<1 min) delays. This auditory memory ability may depend on interaction between rSTG and ventromedial prefrontal cortical areas, to which it projects directly *via* a pathway that courses just dorsal to the amygdala and rostral hippocampus. Like rSTG removal, medial temporal removal also impairs auditory memory ability, but it does so apparently by interrupting the rSTG-prefrontal pathway rather than by disrupting long-term auditory memory, which has not yet been demonstrated in the monkey.

Workshop - Introduction to Neurophysiology of Appetite

S.16 Different flavors of body weight regulation

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The prevailing new views of body weight regulation consider weight regulation in terms of the long-term maintenance of energy balance. Thus a stable body weight would be a result of dynamic equilibrium between energy intake and expenditure. Numerous controlling mechanisms and factors are involved. Research attention focuses on mechanisms controlling ingestion of calories and nutrients (appetite) on one side of the equation and those controlling body adiposity and heat production and dissipation (metabolism, endocrine and autonomic systems, behavior) on the other side. Furthermore, an interaction between the environment and a large number of susceptibility genes could affect energy balance at any level, from metabolism, through neural processing of metabolic signals, to neural processing of environmental signals and behavior. The most important function of the regulatory system may not be the control of body weight *per se*, but rather a balanced control of energy intake and expenditure. The integrative and control neural system involves the hypothalamic nuclei that receive information from areas in the forebrain and, in turn, project to the cortical areas and brain structures controlling endocrine, sympathetic and parasympathetic systems. Problems of appetite disturbances and obesity are thus multifaceted and can be tackled only by a concerted multidisciplinary approach involving psychology, behavior, neurophysiology, pharmacology, endocrinology and genetics.

S.17 From sensation to consciousness: Pleasure is the fifth influence of universe

Cabanac M.
Laval University, Quebec, Canada

There is experimental evidence showing that sensory pleasure and consciousness emerged with reptiles. A postulate is presented according to which consciousness keeps the quadri-dimensional structure of its sensory origins. The four dimensions are quality, intensity, duration, and hedonicity. The above postulate would explain the phylogenetic origin of pleasure as the common currency in the trade-offs for access to the behavioral final common path. Pleasure, is analog to a force which moves the brain (the infinite complex) and may be considered as the 5th influence in the known universe. Thus, all our behaviors are motivated by the quest for pleasure, either as a reward or as an expectation.

S.18 Development of food preferences in cats

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Development of food preferences depends on, among others, an experience with a particular food during an early period of animal's life. Two contradictory mechanisms have been described: the primacy effect and the novelty effect. The primacy effect means that an animal in the later period of life prefers its rearing diet, that is, the diet which it ate during the early period of its life. The novelty effect means the preference to a novel diet. Recently, an attempt to explain the "primacy-novelty" contradiction has been made on domestic cats, using nutritionally balanced diet and a learning situation with instrumental conditioning paradigm. Cats were deprived of a variety of food tastes in early period of their lives. It has been found that different reward values of different kinds of food are responsible for differing performance in a task using instrumental conditioning for food reward. On the other hand, neither the nutritive value of the diet, nor discriminative abilities of the cat, or possible difficulties in differentiation of instrumental responses, are responsible for this differing performance. The different food reward values reflect the different palatabilities of the food tastes in the task. It may be concluded that an inborn food preference is revealed in later period of life if the taste environment is homogeneous, that is, restricted to one kind of food in early life. Thus, either the primacy effect or the novelty effect can be observed, depending on the use of different kinds of food in later period of cat's life.

S.19 Quantitative genetics of energy expenditures and body mass

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Quantitative genetic analyses revealed that unlike behavioral traits, energy expenditures are characterized by low narrow sense heritabilities. This suggests that traits related to energy management have been closely and consistently associated with Darwinian fitness, and therefore, was subject to strong, natural selection resulting in low genetic variance. Furthermore, artificial selection experiments on laboratory mice suggest that at least in small mammals a substantial increase in daily movement distances can be achieved by increasing running speed, without remarkable increases in food consumption. On the other hand, however, there are good evidences for the existence of positive, genetic correlations between basal rate of metabolism (BMR) and metabolic costs of maintenance of internal organs (such as heart, liver, kidneys and small intestines) associated with energy assimilation and therefore, the regulation of body mass. Also, there appears to be a positive, genetic correlation between BMR and maximum metabolic expenditures sustained over long periods of time (SusMR). Thus, despite low heritabilities, the differences in food consumption and body mass between "active" and "sedentary" individuals are mediated by genetic architecture of BMR and SusMR.

S.20 Polymorphism of the leptin (LEP) and leptin receptor (LEPR) genes - effects on body composition

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In 1953 Kennedy proposed a theory of food intake regulation, so-called lipostatic model. He assumed existence of a factor coming from the adipose tissue, which is produced in proportional level to the stored fat. Generated signals influenced the appropriate brain region and decreased the food intake (a negative-feedback loop). In 1973 Coleman et al. described a model of the two autosomal recessive mutations ob/ob (ob-obesity) and db/db (diabetes) in obese mice, which were correlated with some phenotype features like morbid obesity, hyperphagia and decrease in energy expenditure. In 1994 Zhang et al. identified by positional cloning the ob gene and its product - leptin, and described mutation resulting in ob/ob phenotype. Intensive studies led to the identification of the leptin receptor gene. The effect of point mutation in its sequence is abnormal splicing and finally the db/db phenotype. Both genes, ob and db are recognized as good QTL (quantitative trait loci) candidates. In our studies we analysed the effects of known pig leptin gene mutations (T3469C and G3714T) and also searched for the new ones. So far, we have identified polymorphic sites in the leptin receptor gene, localised in exon 4 and intron 3. Moreover, we analysed C/EBP and CREB genes, coding the transcription factors, which play a key role in adipogenesis and control of the leptin expression.

S.21 Cytokines and feeding

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Cachexia is characterized by a decrease in feeding, and it is thought that the cytokine tumour necrosis factor-alpha (TNF) is largely responsible for this. Administration of certain other cytokines (especially interleukin-1, IL-1) to animals decreases feeding. TNF is less effective. Thus cytokines are thought to be involved in the hypophagia that occurs during sickness. However, cytokine antagonists do not completely prevent the hypophagia associated with infections so that other factors may be involved. Our studies on the mechanism of this action of IL-1 have failed to demonstrate roles for the catecholamines, serotonin, histamine and a number of other neurotransmitters, as well as neuropeptides, such as corticotropin-releasing factor, neuropeptide Y, cholecystokinin, and the melanocortins that are known to affect feeding. However, cyclooxygenase (COX) does appear to be critical, because the responses can be ameliorated by COX inhibitors, or the lack of genese for COX. Such studies have shown that both COX1 and COX2 are involved, but probably not COX3. Because COX2 induction occurs in the cerebral endothelia, this may explain how cytokines that cannot pass the blood-brain barrier are able to affect behaviour. Behavioural studies suggest that IL-1 may affect motivation.

Jerzy Konorski Memorial Symposium: Integrative Activity of the Brain

Session C – Neuronal mechanisms and pathways in learning and memory

S.22 Cellular mechanisms and local network properties of the prefrontal memory system

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The functional architecture of the cerebral cortex, including that of the prefrontal cortex, was one of the *major foci* of Jerzy Konorski's many interests. In Kornorski's time, it had been firmly established that lesions of the dorsolateral prefrontal cortex in primates alter performance on spatial delayed response tasks. However, little was understood of the cellular and circuit basis of the functions carried out by dorsolateral prefrontal cortex. My presentation will address the cellular basis of dorsolateral function, explain its relationship to the human working memory system, and argue it's central importance in cognition. I will emphasize the stimulus-independent sustained activation of neurons in the dorsolateral prefrontal cortex and their content - specific coding of information ("memory fields") and suggest that these properties constitute the fundamental cellular basis of the brain's information processing capacity. In particular, findings from contemporary neurophysiological studies, both *in vivo* and *in vitro*, have identified excitatory and inhibitory operations of neurons in identified local circuits that provide a cellular and mechanistic basis for these aforementioned neuronal properties. The talk will emphasize advances in understanding prefrontal function that had their roots in Konorski's time.

Reviews

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Goldman-Rakic P.S. (1999) The physiological approach: Functional architecture of working memory and disordered cognition in schizophrenia. Biol Psychiatry 46: 650-661.

S.23 Morphological aspects of the integrative function of the claustrum

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The claustrum is a telencephalic structure which possesses reciprocal connections with various areas of the cerebral cortex. According to these connections somatosensory, visual and auditory zones of the claustrum have been described. Neurons located in these zones are mostly unimodal. However, positron emission tomography and fMRI studies strongly suggest that the claustrum is deeply involved in cross-modal transfer of information of more than one sensory modality. That function is based on very specific neuronal systems of the claustrum: (1) claustral projection neurons which form the ascending limb of the claustrocortical neuronal loop, (2) cortical projection neurons which send axons to the claustrum-descending limb of the claustrocortical loop, (3) neurons of the thalamus and brain-steam with axons terminating in the claustrum and (4) claustral interneurons which show the great diversity of structure and biochemical specifity. The role of these neuronal systems in the cross-modal transfer of information is still not clear.

S.24 The encoding of prediction errors by dopamine cells during Pavlovian conditioning

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Konorski was the first to suggest a process by which synaptic plasticity could mediate learning when in 1948 he proposed that Pavlovian learning is a function of the activity in the neurons activated by the conditioned stimulus and the rate of change in the activity of the neurons excited by the unconditioned stimulus. However, contemporary theories of associative learning argue that learning is controlled by a prediction error, which encodes the discrepancy between the actual reinforcer and the reinforcer predicted by the conditioned stimuli. Recordings from the ventral tegmentum during appetitive Pavlovian conditioning suggest that prediction errors may be encoded by the activity of dopamine cells. Unexpected but not predicted reinforcers drove the dopamine cells, and stimuli paired with a predicted reinforcer in the absence of a dopamine response were not effective conditioned excitors. Conversely, stimuli paired with a depression of the baseline dopamine activity, caused by the omission of an expected reinforcer, functioned as conditioned inhibitors. Moreover, both condition excitors and inhibitors activated the dopamine cells in manner that corresponded to their capacity to mediate higher-order learning. Taken together, these results suggest that the dopamine cells propagate the prediction errors generated by both primary and conditioned reinforcers to the forebrain.

S.25 Unity from duality

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When, in the primeval sea, creatures first began to crawl, "right" and "left" came into being, yielding neuronal nets to control response to the sidedness of stimuli. In the half billion years of moving and sensing, two brains have evolved, the right and the left; and human experience now shows them to be roughly equivalent, potentially independent, conscious entities. This dramatic fact is evidenced by "split-brain" patients and by numerous cases of therapeutic removal of either hemisphere. Equally dramatic, of course, is that there is not the slightest sign of this duality in everyday experience, the right and left visual fields are seamlessly knit, and cross purpose is absent in the moment to moment operation of the two cerebral hemispheres. This unity is constantly synthesized by the 100,000,000 fibers passing from each hemisphere to the other; the vastness of that interchange emphasized upon comparison with the mere 1,000,000 fibers conveying all the visual world from each eye. With the large distances in the human brain some 100+ ms may commonly transpire for one hemisphere to send to and receive a response from the other. Efficiency thus demands that most neuronal calculation occur within rather than between hemispheres, thereby promoting differences in the characteristic capabilities of each alone, i.e., "hemispheric specialization". Despite this there is a bewildering bilaterality of activation revealed by fMRI for most cognitive tasks. In the absence of the forebrain commissures brainstem systems can be shown, in macaques, also to participate in the unification of behavioral result from the actions of the separated hemispheres. The system favors synthesis from congruent (visual) input to the two hemispheres; but in the face of incompatible hemispheric input, one hemisphere consistently comes to dominate the response, to "seize" control.

S.26 Pattern of interconnections between the temporal and prefrontal association cortices

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Pattern of interconnections between the temporal and prefrontal association cortices examination of the intracortical connections with the fluorochrome and BDA axonal transport showed, that there are several hierarchically organized association areas in the temporal cortex of the dog brain. The first order association cortex is located in the anterior part of the composite posterior area (CPa) and posterior sylvian area (SP). Intracortical connections originating in the parasensory visual and auditory cortex converge in these areas. The second bimodal association cortex was found in the anterior-most part of the anterior ectosylvian gyrus (area CE), where projections from the auditory (EP) and somatosensory (PoC) areas converge. Higher order association cortex, with convergence of three sensory modalities, was identified in the areas SD and SA of the sylvian cortex. Areas SD-SA are distinguished with the high density of intracortical connections from the auditory and visual association areas and, additionally, connections from the area CE. The somatosensory representation reaches the SD-SA cortex through the indirect intracortical projection of the area CE. Only the higher order association cortex (SD-SA) has strong bi-directional connections with the prefrontal association cortex (PFC). These connections are focused on the dorsolateral part of PFC that seems to be a distinct site of convergence of various types of connections, with a special preference of the temporo-prefrontal one.

Comparison of the organization of dog's and primate's temporo--prefrontal afferents reveals a significant difference. In the dog's brain, the dorsolateral PFC part is mainly related the associative, polimodal fields of the highest order. In contrast, in the monkey brain, the temporo-prefrontal connections originate also from those cortical fields that perform the lower level processing of sensory information. Reciprocal connections also terminate in various parts of the prefrontal cortex.

S.27 Remembering visual motion: cortical mechanisms

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The ability to store visual information for brief periods of time is fundamental to successful execution of visually guided behaviors. In this talk, I will examine neuronal mechanisms underlying temporary storage of one of the important features of the visual stimulus, its direction of motion. I will describe recent experiments single-cell recordings carried out in monkeys during the performance of working memory for motion tasks that demonstrate that cortical area MT, specialized in processing of visual motion, also participates in the circuitry underlying its storage. I will also provide evidence that the activity of MT neurons during the execution of these memory tasks is strongly modulated by the top-down influences.

Symposium – Neuroimmune Biology

S.28 The nuroimmune regulatory network

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That a healthy mind is fundamental to general well being has been recognized since prehistoric times and proverbs analogous to "Healthy body - healthy mind" exist in many languages. Scientific inquiries with regards to mind-body interactions commenced over a century ago. Hans Selye discovered that stress activates the hypothalamus-pituitary-adrenal-thymus axis, which results in the development of the "general adaptation syndrome". This syndrome is characterized by elevated resistance of stressed animals to diverse insults. Andor Szentivanyi and colleagues described that hypothalamic lesions prevent anaphylactic death in guinea pigs. This was the first experimental evidence for the sweeping regulatory power of the nervous system over violent, life threatening immune reactions. Miklos Jancso and coworkers established that the nervous system also controls the inflammatory response. In the seventies and eighties a handful of laboratories started to re-examine various aspects of neuroimmune-interaction. It was established that pituitary hormones have the capacity to stimulate, inhibit and modulate immune responses. Placental and pituitary hormones are also involved in the development of the immune system and maintenance of immunocompetence. Lymphoid organs are innervated and neurotransmitters and neuropeptides are important regulators of immune and inflammatory reactions. It became apparent that immune derived cytokines and nerve impulses serve as feedback signals towards the neuroendocrine system. Evidence was produced, indicating that immune reactions may be conditioned in the classical pavlovian sense. Evidence is increasing rapidly for the physiological role of cytokines and of immunocytes in the function of various organs and tissues, and in reproduction. It is also becoming obvious that Selye's general adaptation syndrome really corresponds to the acute phase response. This is a multi-faceted and highly coordinated systemic defence reaction, which involves the conversion of the immune system from a specific, adaptive mode of reactivity to a rapidly amplifiable, poly-specific reaction mediated by natural immune mechanisms. Immunological (poly)specificity is assured by profoundly elevated levels of natural antibodies and liver-derived acute phase proteins. Much has been learned about the regulation of cell activation, growth and function from immunological studies. Burnet's clonal selectional theory designated the antigen as the sole activator. Bretcher and Cohn recognised first that at least 2 signals are required. This was followed by numerous studies on cell-to-cell interaction within the immune system and led to our current understanding of the importance of cell adhesion molecules and cytokines in cell activation and proliferation. This, coupled with the available information about the mechanisms of action of hormones and neurotransmitters, of signal transduction and nuclear regulatory pathways paves the way to understanding how higher organisms function in their entire complexity. It is now apparent that the Nervous- Endocrine- and Immune-Systems form a systemic regulatory network, which is capable of regulating all aspects of bodily functions in health and disease. Thus, Neuroimmune Biology provides new foundations to Biology.

S.29 Experimental peritonitis as a model for investigations of interactions between the immune and opioid systems

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We have shown that the accumulation of exudatory leukocytes in peritoneal cavity of an irritant-injected mice or fish (but not frog) may be inhibited by morphine co-injection perhaps due to opioid-binding induced desensitisation of leukocyte receptors for some chemotactic factors. *In vitro* binding of MOR and DOR (but not KOR) inhibited migration of mice and fish (but not frog) leukocytes to zymosan-activated serum. We made attempts to characterise the profile of endogenous opioids and their receptors in Swiss mice with zymosan-induced peritonitis. During the first 24 hours of inflammation the peritoneal cells exhibited increased mRNA level

of MOR but not KOR, and increased level of mRNA for proenkephalin and prodynorphin but not proopiomelanocortin. A massive accumulation of Met-enkephalin in the focus of inflammation (both in the leukocyte homogenates and peritoneal fluid) was accompanied by its local synthesis in exudatory cells and by influx from distal lymphoid and neurohormonal centres. The latter was suggested by a significant Met-enkephalin decrease in hypothalamus and striatum, peripheral blood and local lymph nodes. In contrast, the local decrease of beta-endorphin and dynorphin was recorded in the focus of inflammation. Their sudden decrease in hypothalamus and the increase in striatum accompanied this.

S.30 Melatonin modulates various aspects of chicken immune system activity

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Pineal gland is a vertebrate neuroendocrine organ involved in the transduction of the external photoperiodic information into a hormonal message, understood for all tissues and organs within the body. Its main hormone, melatonin (MEL), considered as a "biochemical substrate of darkness" exerts several regulatory effects, including the immunomodulation. To date, numerous experimental approaches have been undertaken to elucidate the mechanism(s) involved in this MEL action, which seems to be complex and dependent on a huge number of factors, including species and experimental protocol applied. Using exogenous MEL as a modulator of experimentally induced peritonitis in chickens, we have examined several parameters of their immune system function, together with the activity of the pineal AA-NAT, a key-enzyme in MEL biosynthesis. The results obtained have demonstrated a biphasic effect of exogenous MEL on the development of inflammation, expressed by the number and activity of the peritoneal leukocytes. The message(s) sent by the inflammation and/or MEL treatment are perceived by the secondary immune organs, resulting in the changes in splenocyte proliferation *in vitro*. Pineal gland function is also influenced, and in particular the nocturnal peak of AA-NAT disappears. Some of these effects seem to be mediated by the endogenous opioids, synthesized and secreted by immune cells under the influence of MEL.

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S.31 Brain cytokines as mediators of immune-CNS interactions

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Cytokines synthesized by brain cells could actively contribute to interactions between the immune and nervous systems if their production would be triggered by both peripheral immune signals and central neuronal signals. We have studied this possibility using as models the stimulation of peripheral immune cells by the endotoxin LPS, and the stimulation of hippocampal neurons during long-term potentiation (LTP) of synaptic activity. Administration of a low dose of LPS, which does not disrupt the blood brain barrier and that does not cause an endotoxic shock, induced IL-1b, IL-6, TNFb and IFNg gene expression in the brain. Increased accumulation of IL-1 and IL-6 mRNA transcripts was preferentially detected in the hypothalamus and hippocampus, while TNFa and IFNg gene expression was more marked in the thalamus-striatum. During LTP, a process considered to underlie certain forms of learning and memory, IL-1b, IL-1ra, IL-18 and IL-6, but no TNFa, gene expression was substantially increased, both *in vivo* and *in vitro*, effect that could be prevented by blockade of NMDA-glutamate receptors. Furthermore, blockade of IL-1 receptors resulted in a reversible impairment of LTP maintenance without affecting its induction. Interferance with endogenous IL-6 resulted in opposite effects. These results show that cytokine production in the brain can be induced by both peripheral immune and central neuronal signals. This dual control of cytokine production lead us to propose that interactions between cytokine-producing cells (glia and/or neurons) and stimulated neurons constitute a relevant step in CNS-immune system communication.

S.32 Local and systemic immune reaction in Parkinson's disease

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It is currently considered that a defect of genes combined with exposure to environmental factors may cause Parkinson's disease (PD). Multiple factors are involved in the pathogenesis of PD, including inflammation in affected regions in brain. In the past, high numbers of activated microglia cells in the substantia nigra have been reported. The occurrence of autoantibodies against neuronal structures, an elevated gamma delta T cell population and increased IgG immunity in cerebrospinal fluid to heat shock proteins have been found in PD. Cytokines (such as tumor necrosis factor alpha, interleukin 1 beta and interleukin 6) and apoptosis-related proteins were elevated in brain or cerebrospinal fluid in patients with PD. It is assumed that activated glial cells may participate in neuronal cell death in PD. An infectious cause for PD has been already discussed for years. In particular, some epidemiological evidences strongly suggest a possibility of an infection etiology of PD. Disturbed cellular and humoral immune functions in peripheral blood of patients with PD also have been reported. In advanced stages of PD the numbers of peripherial blood lymphocytes were decreased and mitogen responses were reduced. Also, in sera of untreated PD patients levels of immunoglobulins IgM and IgA were decreased and *in vitro* IgG production in B cells was reduced. Some immune abnormalities observed in PD may partially result from disordered immune regulation, in which neurotransmitters play an important role. Recent findings support the hypothesis that patients with PD have altered function of the immune system, but the precise role of such disturbances for the neurodegeneration is still unknown.

S.33 cDNA microarray analysis of differential gene expression in multiple sclerosis lesions

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cDNA microarray analysis offers simultaneous measurement of expression of thousands genes. We performed cDNA microarray analysis of CNS tissue from multiple sclerosis (MS) subjects in which different regions of active and silent lesions were compared. Major differences in gene expression (DGE) occurred between the lesion margin and lesion center in both active lesions studied (57 and 69 genes differentially expressed, respectively), whereas the margins and centers of silent lesions showed markedly reduced heterogeneity (only 11 and 2 genes differentially expressed, respectively).To compare differences between active and silent lesions, we performed DGE comparison of the pooled data from both types of lesions. The major DGE occurred at the lesion margin, 156 (26.5%), the greater number representing upregulated genes at the margin of active lesions (15%). Fourteen genes were found to be

significantly upregulated in marginal versus central zones in both active lesions examined. These genes comprised predominantly inflammation/immune-related factors. We also performed DGE analysis of pooled genes upregulated at the margin of active lesions and found that among the 50 genes showing differences, 9 (of 14) were identified in the previous analysis of overlapping differentially expressed genes. Thus, this DGE analysis has identified a new set of genes associated with lesion activity in MS which are expressed during lesion progression many of them not previously linked with the disease.

Jerzy Konorski Memorial Symposium: Integrative Activity of the Brain

Session D – Sensory integration and brain function

S.34 "Higher-order" visual cortical areas responsible for form/pattern processing modulate neuronal activities in the "lower" visual areas and superior colliculus

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In the cat, cytoarchitectonic areas 21a (presumed homologue of area V4 of primates) and areas 20a and 20b (presumed homologues of primate inferotemporal cortex) constitute some of the "higher-order" visual cortical areas involved in form/pattern analysis rather than motion processing. Selective reversible inactivation of area 21a or areas 20a and 20b resulted in significant changes in the magnitude of responses to visual stimuli of respectively a third or two-thirds of area 17 cells examined. Inactivation of area 21a resulted usually in a reduction in the magnitude of responses of area 17 cells while during inactivation of areas 20a and 20b decreases and increases were equally common. Changes in the magnitude of responses were often accompanied by changes in a number of specific receptive field characteristics of area 17 cells. Reversible inactivation of area 21a resulted also in significant changes (almost always reduction) in the magnitude of responses of over 60% of neurones in the ipsilateral superior colliculus (a motion rather than a pattern-processing structure). Some receptive field characteristics of collicular cells tested were also affected. Thus, projections from the higher-order form/pattern processing cortical areas appear to play important roles in determining the functional performance of neurones in primary visual cortex and in visual midbrain.

S.35 Mnemonic processing in the primary visual cortex

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Primary sensory areas are usually not implicated in memory functions. However, some memory tasks may require distributed processing that may also involve early levels of the sensory pathways. We trained macaques in a delayed match to sample task that required the monkey to remember both the orientation of a briefly presented grating and its retinal location, while the monkey had to maintain foveal fixation on a fixation spot. They were prepared for electrophysiological recordings (under ketamine plus xylazine anaesthesia) by implantation of a frame for carrying microelectrodes.With our behavioural paradigm, we found evidence for a role of the primary visual cortex in mnemonic processing in two ways: (1) At early stages of learning the task, when the monkey had learnt to perform a simple DMS task at one retinal location, the learning was highly retinal position specific, since it did not transfer to another location easily. (2) In our recordings from the striate cortex, many neurons showed significant differences to the same visual stimulus depending upon whether the stimulus is the sample or the match stimulus. When the same stimuli were presented on the receptive field as the monkey performed a simple fixation task and not a memory task, these differences were not evident. These experiments imply that mnemonic factors can modulate responses to visual stimuli as early as the striate cortex.

S.36 Plasticity and specificity of cortical pathways and networks

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The function of a sensory area of the neocortex relies on specific input pathways, processing networks, and output projections. How do these pathways and networks arise during development and acquire their functional role? We have used a range of approaches to answer this question. The early development of pathways to and from a cortical area involves the expression of specific genes which guide axonal projections. Using high-density DNA microarrays, we have identified genes that are differentially expressed between sensory areas of cortex in neonatal mice (Leamey et al. 2002). The development of cortical networks is thought to be regulated by a combination of molecular and activity based cues. We have shown that altering the pattern of activity in brain pathways has dramatic effects on processing networks. Rewiring the brain in neonatal ferrets by inducing retinal projections to innervate the auditory pathway significantly alters various aspects of intracortical connections, leading to a map of visual space, orientation selective responses, and an orientation map in the rewired auditory cortex. Finally, behavioral studies of visually driven perceptual and conditioned fear responses in rewired ferrets and mice (Newton et al. 2002) demonstrate that the modality of inputs to the auditory thalamus can instruct the function of upstream areas and pathways. Thus, specific pathways to and from cortex are nonetheless plastic in function, and depend for physiological and behavioral instruction on input activity early in development.

S.37 Reactivity and plasticity of large synapses: mechanisms and possible role in integrative activity of central nervous system

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Abstract not received

Workshop - Neurobiology of Pain

S.38 Plasticity of the nervous system – a mechanism in chronic pain

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Experimental and clinical research shows that long lasting plastic changes of the nervous system are involved in the progressive chronicity of pain. Most of these include induced transcriptional processes as indicated by the expressions of Fos and Jun transcription factors. The following cases of neuroplasticity will be presented: 1) accumulation of Na^+-channels at sites of nerve injury; - involvement of the vanilloid receptor VR1 in inflammation induced nociceptor sensitisation; 2) potentiation of chemosensitivity of nociceptive nerve terminals by interaction of bradykinin and adrenergic receptors; 3) positive feedback amplification between the sensory nervous system and the immune system in neurogenic inflammation; 4) apoptosis of spinal dorsal horn neurons following peripheral nerve lesions; 4) long term potentiation (LTP) at synapses on spinal dorsal horn neurons following repetitive noxious afferent stimulation; 5) attenuation of the spinal opioid system following a peripheral nerve lesion; 6) wind up of the gain in spinal motor reflexes following prolonged noxious stimulation; 7) reorganization of somatosensory cortical maps following amputation and prolonged pain conditions. It is likely that these neurophysiological mechanisms contribute to the generation and maintenance of chronic pain. The modulation of some of this pathophysiology by psychological and behavioral processes (anxiety, depression, immobility) may further contribute to the chronicity of pain. Thus, any chronic pain may become a nervous system disease. Early preventive strategies have a high value in the clinical treatment of chronic pain.

S.39 Different pain mechanisms and response to treatment in patients with post herpetic analgesia

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Patients with post herpetic neuralgia (PHN) constitute a heterogeneous group with respect to painful symptoms. Some patients exhibit pronounced brush-induced allodynia and positive response to local anesthetic infiltration. Nerve blocks with local anesthetics and/or steroids were often used as a one of the method of treatment acute herpes zoster and PHN. In the group of patients with pathologically active or sensitized nociceptors it is also possible that subcutaneous infiltration of low doses of opioids could be beneficial. In this group of patients the intravenous and topical application of lidocaine, that blocks ectopic impulses in primary afferent nociceptors, provides considerable pain relief. Other group of patients with PHN complains spontaneous constant burning pain with or without concomitant hypoesthesia and/or shock-like pain. These symptoms can be produced by central central synaptic reorganization as a consequence of nociceptors degeneration. In these patients pharmacological treatment with antidepressants, anticonvulsants, opioid analgesics and NMDA-receptor antagonists can be beneficial. Furthermore, in some patients sympathetic stimulation can produce an alpha-2-adrenoreceptor-mediated activation of primary afferents. All these different mechanisms can operate in an individual patient with PHN. In this presentation clinical observations in chronic pain patients suffering from PHN will be shown.

S.40 The role of melanocortins and theirs receptors in nociception

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The melanocortin peptides, which include ACTH, alpha-melanocyte stimulating hormone, beta-MSH and gamma-MSH are derived from a precursor protein, proopiomelanocortin (POMC). There is a strong evidence that among POMC-derived peptides, melanocortins are the ones that exert a variety of immunomodulatory and anti-inflammatory activities, facilitate regeneration of injured nerves, have direct effect on nociception and interact with opiate system. The latter functions have recently attracted much interest since melanocortins are the target of the search for better antinociceptive drugs in chronic pain, especially inflammatory and neuropathic pain. The mechanisms underlying the biological actions of melanocortins in nociception are still largely unknown. Molecular cloning of specific receptors opened avenues to study melanocortin biology and physiology. Antagonists of MC receptors are useful tools for investigating the molecular mechanisms underlying melanocortin-associated effects. Better understanding of these mechanisms can lead to new therapeutic opportunities in the treatment of chronic pain. Clarification of the role of the melanocortin system in the development of neuropathic pain and explanation of the relationship between melanocortins and opioid system will expand our knowledge about the mechanisms of melanocortin action in chronic pain.

S.41 Functional organization of voltage-gated ionic chanels in visceral sensory neurons – specificity and pattern theories of pain

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Information from cardiac sensory receptors including cardiac nociceptors is transmitted by thoracic cardiac dorsal root ganglion (DRG) neurons. We have performed a series of experiments to find out whether the information from cardiac low threshold mechanoreceptors and cardiac nociceptors is conveyed by the same or by different DRG neuron population. For that purpose we have recorded the activity of cardiac afferent fibers, cord dorsum potentials evoked by stimulation of cardiac afferents, and voltage-gated Na+ and K+ currents in anatomically identified cardiac DRG neurons. We found that the majority of cardiac DRG neurons have similar functional properties with respect to their activation by sensory stimuli as well as the expression and kinetics of voltage-gated currents.

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Jerzy Konorski Memorial Symposium: Integrative Activity of the Brain

Session E – Molecular and integrative biology of behavior

S.42 Different systems of cortical rhythms are associated with distinct classes of attentive states. Studies in cat and monkey

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Studies on behaving cats have shown that several distinct classes of electrocortical rhythms exist, that accompany a variety of states and/or levels of attentiveness. Behavioural situations with focused attention are concomitant with rhythms in the 25-45 Hz frequency band (also called beta or gamma, depending on the authors). On the other hand, a different class of rhythms was observed, in the 14-20 Hz band during situations less often described in isolation, when the animal expects an event with high probability to occur, thus showing that the latter situation is quite separate from that of focused attention. Finally, in situations of "inattentiveness" of the animal, either spontaneous or of an apparently active withdrawal of attention (e.g. when the animal is in an instrumental conditioning task and receives the negative non rewarded stimulus), slow rhythms suddenly occur, likely to accompany an episode recalling "internal inhibition". In monkeys, similar data were obtained, with even several degrees in power of the 25-45 Hz band while the animal was working on a video-tracking test, depending on the successive episodes of this sensori-motor task. Given that part at least of these classes of rhythms were each shown to have a restricted cortical localization, and a particular thalamic nucleus simultaneously oscillating, we tend to extrapolate and conclude that various facets of attentiveness are each subtended by the activation of a separate thalamocortical system.

S.43 Gene expression as means to study information integration in the brain

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Understanding the levels and mechanisms of information integration in the brain remains as the major challenge for neurobiological research. Discovery of inducible gene expression evoked in neurons by brain response to external stimuli has greatly advanced our knowledge of information integration. In our own studies, we have first shown that L-glutamate, the major excitatory neurotransmitter, may activate gene expression in the brain. We have next shown, that glutamate-inducible c-fos, encoding a component of AP-1 transcription factors is activated in learning, and this activation can be used to map neurons in defined brain regions undergoing plastic changes. Using this approach, we have shown specific associations of cortical amygdala with establishment of fear memories, and medial/lateral/basolateral amygdala with anxiety. Hence inducible gene expression appears very useful in mapping brain regions whose activation has to be integrated in order to produce long-term learning. Another aspect of this problem is that careful analysis of patterns of inducible gene expression has allowed us to suggest that it may play various roles in the brain, such as maintenance of plastic changes, replenishment of proteins worn out during periods of massive enhancement of neuronal activity accompanying learning episodes, and finally integration of information at the neuronal nucleus level. Finally, studies on inducible gene expression can be used further to indicate molecular mechanisms of the information integration. In the case of c-Fos/AP-1 we have first identified timp-1 (tissue inhibitor of metalloproteinases-1) gene as AP-1 target in the brain, and then followed by showing that also MMP-9 (matrix metalloproteinase-9) is inducible in response to enhanced neuronal activity. This discovery has most recently been followed by showing that extracellular matrix synaptic proteins such as β-dystroglycan can by MMP-9 enzymatic targets, and their degradation can fulfil the retrograde messenger function at the synapse, allowing for very precise, local integration of information.

S.44 The "emotive brain", the noradrenergic system and memory consolidation

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Jerzy Konorski was among the first to attempt a neurophysiological model to account for how motivation and attention influence perception, learning and memory. He proposed that there were two interacting brain systems - the emotive and the cognitive. Now we know that neuromodulatory systems covarying with psychological states modulate cortical arousal, influence sensory processing and promote synaptic plasticity. To study the role of the locus coeruleus noradrenergic system (LC) in memory, we use a foraging task where rats associate an odor with reward in only 3 trials, resulting in a memory trace lasting at least 1 week. The prelimbic cortex (PLC) proved to be one of the few regions showing increases in c-fos after this learning. A beta-antagonist, injected in PLC 2 h after the odor-reward training produced amnesia. This suggests that the LC is implicated in a late phase of memory processing in this region and that PLC is part of a neural circuit activated during the consolidation of odor-reward association memory. To characterize the temporal dynamic, we recorded unit activity in PFC during and after learning. A population of cells showed dramatic change in firing rate related to the learning experience. Some cells showed increases during the intertrial interval with an incremental increase after each trial until the rat reached asymptotic performance. Simultaneous recording from LC and PFC in an operant olfactory discrimination task showed that LC responses to the CSs always precede those in PFC suggesting that NE plays a role in PFC plasticity.

S.45 A 3-neuron network demonstrating associative plasticity

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We investigated modulatory role of individual serotonergic neurons in a network consisting only of three interconnected neurons. Mechanosensory neurons in the snail *Helix* sp. form a glutamatergic synapses with the withdrawal interneurons. Spikes in sensory neurons were paired or explicitly unpaired with activation of the modulatory serotonergic cell. It appeared that the activity in a single serotonergic cell in a pairing-specific way changed the amplitude of the monosynaptic glutamate-mediated responses in withdrawal interneurons. Reducing situation further, to an "artificial synapse" modelled by glutamate application to the soma of synaptically isolated interneurons, we showed that the serotonin applications can elicit a long-term increase of the glutamate responses. Infusing BAPTA, a selective Ca^{2+} chelator, into the postsynaptic interneuron completely blocks the serotonin-induced increase what clearly demonstrates involvement of Ca^{2+} in this form of plasticity. Optical Ca^{2+}

imaging from the individual interneurons during intracellular "reinforcing" stimulation of a single serotonergic cell directly showed increase of calcium in postsynaptic cell in this model situation without concomitant changes in membrane potential. Bath applications of serotonin also elicited an increase of intracellular Ca^{2+} concentration in interneurons. Thus, intracellular activity of only one neuron can serve as a reinforcement in this small network.

S.46 Nature of diencephalic amnesia studied in mice with genetic lesion of the mamillary bodies

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Mammillary bodies and mammillothalamic tract represent a part of a Papez neural circuitry that has been implicated in severe memory disturbances in patients with Korsakoff's syndrom. However, the specific role of mammillary bodies in memory functions remains controversial being often considered as just a functional extension of the hippocampal memory system. To study this issue we used mutant mice that have no mammillothalamic tract and medial mammillary nuclei due to the lack of Foxb1 winged helix gene expression in the developing nervous system. Foxb1 mutant mice were unable to learn hippocampal-dependent spatial memory tasks in Morris watermaze and Barnes circular maze. However, they had no impairment in other hippocampal memory tests such as spatial reference learning in radial arm maze and contextual fear conditioning. On the other hand, Foxb1 mutants were deficient in working memory task, such as 8-arm radial maze. Thus, the genetic lesions of medial mammillary nuclei and mammillothalomic tracts produce learning and memory deficits distinct from the damage of hippocampus. Our results suggest that mammillary nuclei are involved in specific set of cognitive tasks which require coupling the output of hippocampal memory system to thalamo-cortical working memory system.

S.47 Trace competition at retrieval: Evidence from taste- and fear-conditioning

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In many instances of conditioning, multiple associative traces could be formed over time, all referring to the same conditioned (target) stimulus. Furthermore, when an associative conditioned trace is retrieved, the subject's brain might be forced to make a choice among the competitive traces, only one of which subsequently prevails to control the overt behavior after the specific retrieval experience. I will illustrate such processes of trace competition, and their consequences as far as the stability of the trace is concerned. I will also discuss some of the molecular mechanisms involved. This will be done using data from two experimental systems: conditioned taste aversion in the rat, and fear conditioning in the Medaka fish. Elucidating the rules that govern trace competition and the fate of the trace after retrieval, could cast light on the nature of persistence and stability of memory traces, and might contribute to the development of methodologies to modify long-term traces.

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S.48 Cognitive function in normal chronological aging

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The aim of the study was the analysis and assessment of cognitive functioning of hundred-year-old people. Three cognitive verbal functions of the left hemisphere were selected: -narrative discourse, -interpretation of proverbs, -verbal fluency. Right hemisphere mechanisms were represented by: Tower of London Test, Witwicki's Puzzles, Benton Memory Retention Test and visual recognition of nonsense in the pictures. Nine normal aging hundred-year-old people and 14 members of control group (normal aging 65-years old people of similar gender, level of education and environmental factors) participated in the study. Results: in both groups there is diverse profile of cognitive functions. Hundred-year-old people reveal some problems with eyesight and hearing, as well as limitations of motor efficiency and selective cognitive difficulties. The members of control group have most troubles with proverbs interpretation and the best results in recognition of nonsense.

S.49 Time and language - Critical remarks on diagnosis and training methods of temporal-order judgement

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For decades studies have shown that children with language-learning impairments, children and adults with dyslexia as well as patients with brain injuries to the left hemisphere with aphasic syndromes have difficulties in identifying the correct order of rapidly presented stimuli. This association of temporal processing abilities and language competence is discussed on the phonological level. The ability to discriminate certain consonant-vowel syllables such as /pa/, /ta/ and /ka/, or /ba/ and /da/ is based on the temporal analysis of rapidly occurring components in the speech signal. Over the last years studies have been published claiming that an improvement of linguistic competence can be achieved through the training of temporal processing abilities. Discussing the empirical findings, some critical points have to be defined: First, the employed diagnostic and training methods vary between studies which make comparisons difficult. Second, several training modules are used in parallel. Effects of the temporal-processing training cannot be isolated. Third, often only mean differences between groups and before/after treatment are presented. The success in training of individual cases (or subgroups) is not documented. Fourth, the positive transfer from an improvement in computer-based language tests to complex communication has not been shown. Possible approaches for detecting the possible causal relation between the time and the language domain are discussed.

S.50 Subjective present and two modes of thinking

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Synchronization tapping has been used as the simplest system for examining the timing mechanism in sensory-motor coupling. The most interesting phenomenon observed in this task is the negative asynchrony, of which the subject himself is unaware. This phenomenon where the onset of each tapping precedes the onset of the stimulus by several tens of milliseconds means the subjective present is emerged in a time region that includes the future. In our research, applying a dual task method, the relationship between such anticipatory response and higher brain functions, such as attention and working memory, was investigated. The results revealed two modes of anticipation. In the inter stimulus-onset interval (ISI) range of 450 to 1,800 ms, an automatic response that was not affected by attentional resources was observed and was based on feed-forward dynamics. In the 2,400 to 3,600 ms range, the response showed a trade-off relationship in the allocation of attentional resources. The magnitude of synchronization error (SE) between tap onset and stimulus onset in this region was scaled by the ISI and a feedback dynamic was suggested. These results revealed for the first time the presence of two modes of anticipation in synchronization tapping, from the viewpoint of time perception. Accordingly, the emergence of the subjective present in sensory-motor coupling can be regarded as a dual process between implicit and explicit thinking.

S.51 Time and timing in cognitive processes: Clinical and experimental evidence

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Neuropsychological studies have indicated that the temporal order (TO) of two stimuli can be properly reported if they are separated by an interval of at least 40 ms. This gap defines the temporal order threshold (TOT). In series of studies we tested individual differences in the ability to perceive TO, to answer the following questions: 1) can it be influenced by the stimulus modality or the applied experimental procedure? 2) are there any gender or generation differences? 3) are the specific language disorders related to TOT? We tested young healthy volunteers, centenarians, patients with brain lesions and monochannel cochlear implant recipients. In young healthy adults, TOT was around 40 ms, independently of the stimulus modality and experimental procedure (inter- vs. intrahemispheric stimulation). Women needed longer gap than men to identify correctly the TO. In centenarians the typical TOT was nearly 4 times prolonged, probably as the result of chronological aging. Patients with left hemisphere lesions and Wernicke's aphasia showed significantly prolonged TOT (up to ca. 120 ms). The similar elevation of TOT accompanied auditory comprehension deficits in cochlear implant users. To conclude, TOT seems to be mediated by the universal supramodal neuronal mechanism, which is strongly related to the subject's sex, age and linguistic competencies.

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