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MAX PLANCK INSTITUTE
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THE SOCIETY FOR THE STUDY OF
NEUROPROTECTION AND
NEUROPLASTICITY

FACULTY of MEDICINE
DEPARTMENT of
NEUROSCIENCES

International
School of Neurology

Seminars

Functional Imaging and Neurorehabilitation

Department of Neurosciences
University of Medicine and Pharmacy "Iuliu Hatieganu"
Cluj-Napoca | Romania
in cooperation with
Max Planck Institute for Neurological Research
Cologne | Germany

NOVEMBER 26-28, 2012
"Ion Minea" Auditorium / Clinic of Neurology
CLUJ-NAPOCA | ROMANIA

Welcome Address

It is a pleasure to welcome you to the 4th edition Seminars of the Neurosciences Department, "Functional Imaging and Neurorehabilitation", November 26th, 27th and 28th, 2012. The seminars are hosted by the Department of Neurosciences, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Haţieganu", Cluj-Napoca, Romania.

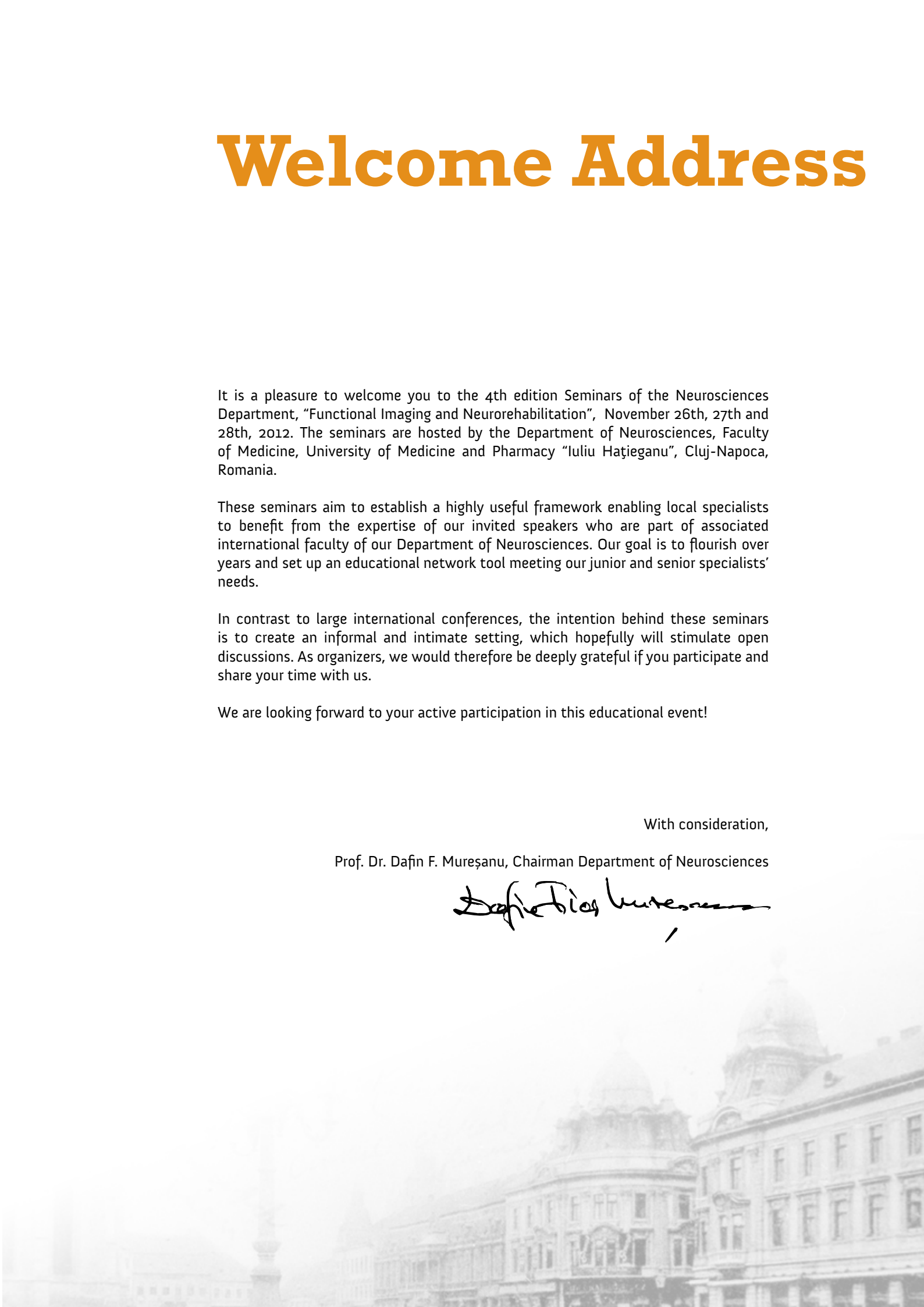
These seminars aim to establish a highly useful framework enabling local specialists to benefit from the expertise of our invited speakers who are part of associated international faculty of our Department of Neurosciences. Our goal is to flourish over years and set up an educational network tool meeting our junior and senior specialists' needs.

In contrast to large international conferences, the intention behind these seminars is to create an informal and intimate setting, which hopefully will stimulate open discussions. As organizers, we would therefore be deeply grateful if you participate and share your time with us.

We are looking forward to your active participation in this educational event!

With consideration,

Prof. Dr. Dafin F. Mureșanu, Chairman Department of Neurosciences



Organizers

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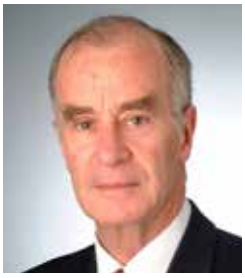
Speaker

Speaker



WOLF-DIETER HEISS /GERMANY

Wolf-Dieter Heiss, born 31.12.1939 in Zell am See, Austria, graduated in medicine from the University of Vienna, Austria, in 1965. He achieved his training in neurology, neurophysiology, psychiatry and nuclear medicine at the University hospital in Vienna and spent research fellowships at the MIT, Cambridge, USA, the Physiological Institute in Stockholm, Sweden, the Department of Physiology of SUNY, Buffalo, NY and the Department of Neurology of the University of Minnesota, Minneapolis, USA. 1976 he was appointed associate professor at the Department of Neurology of the University of Vienna. In 1978 he became director of the Center for Cerebrovascular Research of the Max Planck Institute for Brain Research and of the Department of Neurology of the City Hospital Cologne-Merheim, Germany. 1981 he was appointed as director at the Max Planck Institute for Neurological Research. 1985 – 2005 he was professor of neurology and chairman of the Department of Neurology of the University of Cologne and director of the Department of General Neurology at the MPI in Cologne. He was president of the International Stroke Society 1992-96, was on the board of directors of the Society for Cerebral Blood Flow and Metabolism, deputy editor of the Journal of Cerebral Blood Flow and Metabolism and at present is associate editor of the Journal of Nuclear Medicine and section editor of Stroke. He was chairman of the program committee of the European Federation of Neurological Societies (EFNS) 1998 - 2001 and was president of the EFNS 2001 – 2005. Since 2005 he is Visiting Professor at the Danube University in Krems, Austria, and since 2009 Adjunct Professor at the McGill University in Montreal, Canada.

Scientific Program

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Monday, NOVEMBER 26th, 2012
"Ion Minea" Auditorium / Clinic of Neurology

10:00 – 11:00	Functional and Molecular Imaging with Positron Emission Tomography / Wolf-Dieter Heiss (Germany)
11:00 – 12:00	Pathophysiology of Ischemic Stroke in Men: Imaging the Penumbra and Progressive Damage / Wolf-Dieter Heiss (Germany)

Tuesday, NOVEMBER 27th, 2012
"Ion Minea" Auditorium / Clinic of Neurology

10:00 – 11:00	Imaging for Selection of Patients for Efficient Treatment / Wolf-Dieter Heiss (Germany)
11:00 – 12:00	Functional Imaging in Rehabilitation: Changing Paradigms of Recovery / Wolf-Dieter Heiss (Germany)

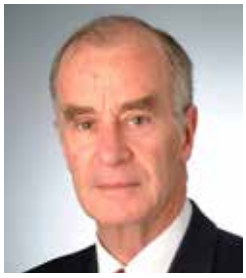
Wednesday, NOVEMBER 28th, 2012
"Ion Minea" Auditorium / Clinic of Neurology

10:00 – 11:00	PET Imaging in the Differential Diagnosis of Vascular Dementia / Wolf-Dieter Heiss (Germany)

Abstracts

Abstracts

FUNCTIONAL AND MOLECULAR IMAGING WITH POSITRON EMISSION TOMOGRAPHY



WOLF-DIETER HEISS
/GERMANY

Max Planck Institute for Neurological Research, Cologne, Germany

Positron Emission Tomography (PET) is an imaging technique which uses small amounts of radiolabeled biologically active compounds (tracers) to help in the diagnosis of disease. The tracers are introduced into the body, either by injection or by inhalation of a gas, and a PET scanner is used to produce an image showing the distribution of the tracer in the body.

Positron Emission occurs when a proton rich isotope (unstable parent nucleus, e.g. 11C, 15O, 18F) decays and forms a neutron, a positron and a neutrino. After traveling a short distance (3-5mm), the positron emitted encounters an electron from the surrounding environment. The two particles combine and "annihilate" each other, resulting in the emission of two gamma rays in opposite directions of 0.511 MeV each. The image acquisition is based on the external detection in coincidence of the emitted gamma-rays. Many lines of response connecting the coincidence detectors are drawn through the object and used in the image reconstruction. The tomograph's reconstruction software then takes the coincidence events measured at all angular and linear positions to reconstruct an image that depicts the localization and concentration of the radioisotope within a plane of the organ that was scanned.

The concept of emission and transmission tomography was introduced by David E. Kuhl, Luke Chapman and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others finally leading to large multi-ring scanners and combined imaging devices as PET/CT and PET/MRI. PET is both a medical and a research tool used in clinical neurosciences and in pre-clinical studies using animals, where it allows repeated investigations in the same subjects. However, PET imaging uses short lived isotopes the production of which requires a cyclotron, and molecular tracers which are synthetized and labeled in a dedicated radiochemistry unit.

PET neuroimaging is based on an assumption that areas of high tracer uptake are associated with high brain activity. The flow of blood to different parts of the brain, which is correlated with high brain activity, has been measured using the tracer oxygen-15 labeled water. However, because of its 2-minute half-life, O-15 must be piped directly from a medical cyclotron for such uses, which is difficult. One of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of labeled 2-fluorodeoxy-D-glucose (FDG) for measuring energy metabolism made PET a widely applicable clinical tool, especially in oncology. Since brain pathologies affect metabolism of both glucose and oxygen, measurement of regional glucose use by FDG-PET is a promising diagnostic tool in many disorders. Several radiotracers have been developed for PET that are radioligands for specific neuroreceptor subtypes for dopamine D2/D3 receptors, for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme).

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These agents permit the visualization of neurotransmission in a plurality of CNS diseases. Novel probes for in vivo PET imaging of neuroaggregates in human brain permit amyloid imaging as a marker of early degenerative cognitive impairment (Alzheimer disease).
The utilization of biological probes labeled with short lived radioisotopes makes PET a powerful tool to image function, blood flow, metabolism, transmitter activity, receptor distribution, enzymatic activity, gene expression and other molecular variables in the brain. The high sensitivity allows PET to measure concentrations of molecules in the nano- and picomolar range without affecting the biochemical system being investigated. The wide versatility has made PET an important tool for experimental and clinical neuroscience.

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PATHOPHYSIOLOGY OF ISCHEMIC STROKE IN MEN: IMAGING THE PENUMBRA AND PROGRESSIVE DAMAGE

The „ischemic penumbra“ defines tissue which is perfused below the level for functional failure but above the level leading to irreversible morphological damage. Penumbra tissue has the potential for functional recovery provided that local blood flow can be reestablished, but irreversible damage will develop without sufficient reperfusion depending on the interaction of severity and duration of ischemia. Differences in selective vulnerability of neurons as well as differences in perfusion in small tissue compartments are responsible for a considerable heterogeneity in patterns of injury.
With acute flows below the threshold of energy required for maintenance of basic housekeeping (20 % of pre-occlusion values), injury in the core is a direct consequence of energy failure resulting in terminal depolarization of cells and is established within a few minutes after onset of ischemia. During the subsequent subacute phase the irreversible damage expands into the penumbra: Multiple electrical and biological disturbances interact in the progression of irreversible damage. They are triggered by periinfarct spreading depression-like depolarizations (PIDs), which require increased energy for activated ion exchange pumps. The increased glucose and oxygen demand cannot be met by the restricted flow to the penumbra leading to hypoxia and stepwise increase in lactate. The pathogenetic cascade triggered includes among others: release of excitatory and inhibitory neurotransmitters, activation of ion channels, influx of calcium, free radical formation, nitric oxide generation. Usually within 6 to 8 hours all the penumbra is converted into irreversible infarct. In a delayed phase secondary phenomena may contribute to additional tissue damage.
One successful application of PET was regarding the transfer of the concept of the penumbra into the clinical management of acute ischemic stroke. Experiments in baboons and cats in the 70s and 80s defined blood flow values for functional disturbance and irreversible morphological damage, which could also be established by PET in patients with acute stroke. The progression of irreversible damage, the core of ischemia, into the functionally impaired area, the penumbra, could be followed in experimental models. Also the potential for recovery of these areas with reperfusion within the time window was demonstrated in these models, a result which formed the basis for thrombolysis and other reperfusion therapies. In animal models tracers for neuronal integrity were tested which are useful for early detection or irreversible tissue damage. These tracers can help in therapeutic decisions and in the prediction of malignant course after occlusion of large arteries. In the assessment of subacute and chronic pathophysiological changes after stroke results from animal experiments indicated the importance of neuroinflammation, which can be visualized as microglia activation, for progression of damage into areas primarily not affected by ischemia and for prognosis of functional deficits. These inflammatory changes might also play an important role in increased amyloiddeposition and might therefore be involved in the development of poststroke dementia. In this context the identification of the area of

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irreversible damage, and its distinction from the penumbral zone, i.e. tissue with impaired function but reserved morphology, may improve the estimation of the potential efficacy of various therapeutic strategies. Whereas positron emission tomography is the gold standard for detection of the penumbra, other imaging modalities especially PW-DW-MRI may be used for this purpose and for the selection of patients who might benefit from strategies combining intervention against acute pathophysiological mechanisms with support of neuroplasticity and neurorepair. The impact of imaging modalities might even be increased by the advent of combined MRI PET equipment and the introduction of more sophisticated molecular tracers into clinical application.

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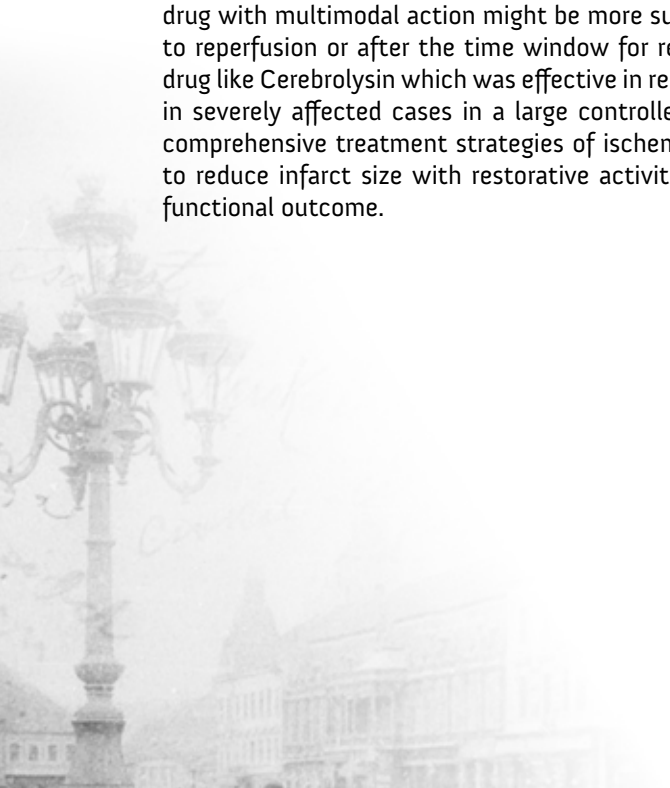
IMAGING FOR SELECTION OF PATIENTS FOR EFFICIENT TREATMENT

Stroke is responsible for about 5.7 million deaths per year worldwide and is the leading cause of disability. In about 80 % stroke is caused by ischemia, i.e. critical reduction of cerebral blood flow to the brain mostly as a result of thrombotic or embolic occlusion of supplying arteries. In ischemic stroke the sudden decrease of regional blood flow is responsible for functional deficits and triggers a cascade of pathophysiological mechanisms leading to tissue damage. However, the contribution of these different pathophysiological mechanisms to the size of the final infarct and to the severity of the clinical deficits is different with the initial lack of blood supply causing most of the damage. As a consequence of the complex cascade leading to infarction therapeutic strategies are limited and must be adapted to the time course of ischemic cell damage. The most effective – and up to now only approved – treatment is reperfusion achieved by thrombolysis in the first hours after the attack, but the wide application of this strategy is limited by its time window, an increased risk of symptomatic brain hemorrhage and relevant exclusion criteria. Several imaging modalities (e.g. PW-DW MRI) may be useful to select patients who can benefit from reperfusion therapy – iv or ia thrombolysis and interventional reperfusion strategies – even after the usually recommended time window has passed, but results are still controversial. Despite all these efforts the total number of stroke victims benefitting from reperfusion therapy is still limited. Therefore there is an urgent need for therapeutic interventions targeted at biochemical and molecular mechanisms which contribute to the progression of ischemic damage over a longer time period. However, up to now all the clinical trials performed with neuroprotective agents and other means to interfere with one defined pathogenetic step have failed despite promising results in various stroke models. A drug with multimodal action might be more successful in stroke treatment in addition to reperfusion or after the time window for recanalization procedures has elapsed. A drug like Cerebrolysin which was effective in reducing mortality and improving outcome in severely affected cases in a large controlled trial therefore might have a place in comprehensive treatment strategies of ischemic stroke, which combine acute efforts to reduce infarct size with restorative activities to promote repair and improve final functional outcome.



Abstracts

FUNCTIONAL IMAGING IN REHABILITATION: CHANGING PARADIGMS OF RECOVERY

Acute cerebrovascular disease is still the leading cause of disability, despite incidence rates have decreased in some countries over the last years. Only a limited number of patients with ischemic stroke can profit from acute treatment and / or can achieve satisfactory recovery during rehabilitation. The outcome after a stroke is determined by several factors including severity of initial deficits, size of infarct, the type of arterial occlusion, existence of collateral perfusion and additional damage to the brain, but also general factors as age and comorbidity play an important role. For the prediction of the chance for recovery imaging modalities have been increasingly applied and significant relationships between outcome and size of infarcts on CT or DWI, pattern of arterial occlusion, extent of collateral flow and injury to fiber tracts were described.

Imaging of functional activation by fMRI or PET shows the brain regions involved in special tasks and can detect changes in the functional networks. Especially when lesions affect the primary cortical centers various patterns of activation in the respective functional network are observed which are related to the severity of the damage and to the extent of recovery of disturbed function. Recovery of motor, but also of higher brain functions, e.g. language is affected by the involvement of the network in the hemisphere contralateral to the infarct. In many instances a high activity of this contralateral network inhibits the reintegration of primary ipsilateral centers and thereby impairs functional improvement. By several brain stimulation techniques, e.g. repetitive transcranial magnetic stimulation and direct current stimulation the inhibitory effect of contralateral areas can be reduced or homolateral areas can be excited. These changes in the activation pattern might be supportive for rehabilitative measures and in combination may improve outcome after stroke.

Abstracts

PET IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF VASCULAR DEMENTIA

WOLF-DIETER HEISS
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S. ZIMMERMANN-MEINZINGEN
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Aging leads to a small loss of cortical neurons, but to a significant reduction of synapses, dendrites and myelinated fibres. These age-related changes may cause some cognitive impairment, brain atrophy and frontally accentuated diffuse decrease in metabolism. In pathological disorders leading to dementia, most frequently degenerative Alzheimer's disease, cerebrovascular disease or a combination of both, the changes are more severe, affect predominantly specific regions and result in significant loss of neurons. The differential diagnosis of these disorders is based on symptoms of cognitive and memory impairment and is supported by results of neuropsychological tests and of imaging. Whereas computed tomography and magnetic resonance imaging are able to detect morphologic lesions, these modalities cannot determine functional consequences of the underlying pathologies. Positron emission tomography allows imaging of the localized and / or diffuse metabolic disturbances responsible for cognitive impairment and dementia, and is effective in differentiating vascular from degenerative dementia, as Alzheimer's disease. It can also detect inflammatory changes and their interaction with amyloid depositions for the development of mixed dementias after stroke. Imaging of neurotransmitters and of synaptic function additionally yields insight into disease specific pathophysiology. Despite the broad clinical application of PET is limited, this technology has a great impact on research in dementia.

Notes

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