UMF
UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE IULIU HAŢIEGANU CLUJ-NAPOCA

FACULTY of MEDICINE
DEPARTMENT of
NEUROSCIENCES

Facultatea de Medicină Cluj

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RoNEURO

Seminars

Department of Neurosciences
University of Medicine and Pharmacy "Iuliu Hatieganu"
Cluj-Napoca | Romania

Non-invasive Brain Stimulation
New strategy for Brain Recovery

DECEMBER 8TH 2017

RoNEURO INSTITUTE FOR NEUROLOGICAL RESEARCH AND DIAGNOSTIC /
CLUJ-NAPOCA | ROMANIA | MIRCEA ELIADE 37

WELCOME ADDRESS

It is a pleasure to welcome you to the 47th edition Seminars of the Neurosciences Department, „Non-invasive Brain Stimulation – New strategy for Brain Recovery", December 8th, 2017. The seminar is hosted by the Department of Neurosciences, Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy ,Cluj-Napoca and "RoNeuro" Institute For Neurological Research and Diagnostic.

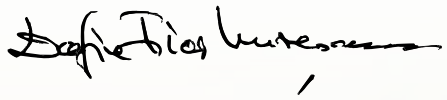
This seminar aims to establish itself as a highly useful framework that will enable local specialists to benefit from the expertise of our invited speakers who are part of associated international faculty of our Department of Neurosciences Cluj-Napoca, Romania and RoNeuro Science network. Our scope is to flourish over years and set up an educational vector aiming to meet 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, Faculty of Medicine,
University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj Napoca, Romania



ORGANIZERS

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Nanoneurosciences and
Neuroregeneration

RoNEURO
Institute for Neurological
Research and Diagnostic


SPEAKERS

SPEAKERS

WOLF DIETER HEISS /GERMANY

Wolf-Dieter Heiss 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 Minnessota, Minneapolis, USA.

In 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.

In 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 Univerity in Krems, Austria, since 2009 Adjunct Professor at the McGill University in Montreal, Canada, and since 2013 Associate Professor, Dept of Neurosciences, Univ. Iuliu Hatieganu, Cluj, Romania. In December 2014 he received Dr. honoris causa of Univ. Iuliu Hategianu, Cluj, Romania.

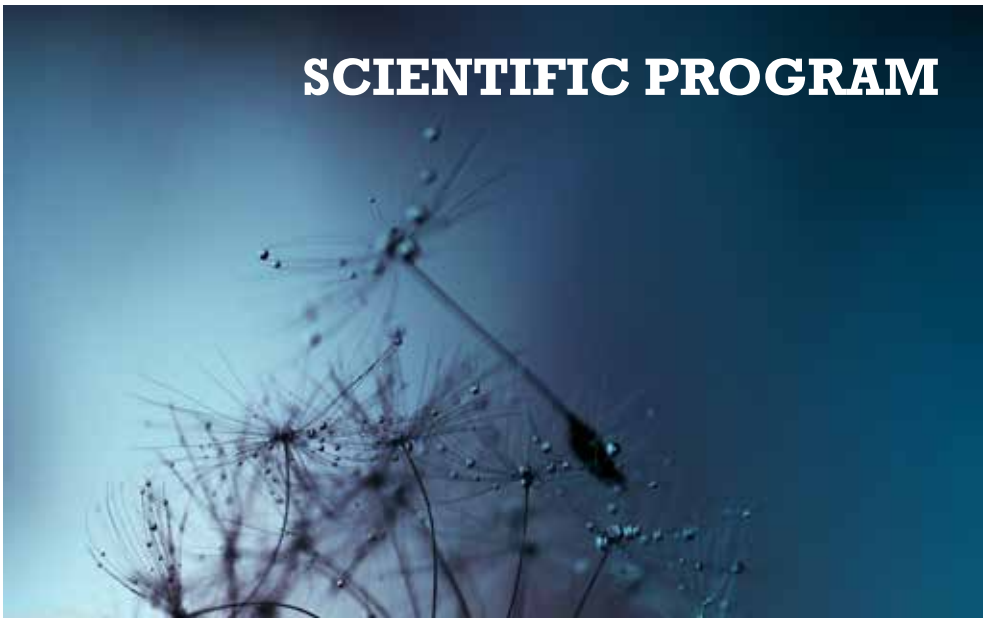
SPEAKERS

ALEXANDER HARTMANN /GERMANY

Alexander E.L. Hartmann is Professor of Neurology at the University of Bonn (Germany) and member of the Faculty of the University of Witten-Herdecke.

He was raised in Bremen (Germany) and trained in Medicine at the University of Würzburg and the University of Heidelberg (1964-1970). He specialized in Neurology in Baylor College of Medicine in Houston/Texas (1971-1973) and in Heidelberg/Germany (1973-1982). 1983 he became chief of the Cerebrovascular Section at the Dept. of Neurology of the University of Bonn. Since 2014 he is chief of the Diagnostic Unit (Electrophysiology, Ultrasound, Intraoperative Monitoring) at the Dept. of Neurosurgery of the Municipal Hospitals of Cologne.

His scientific interests are cerebrovascular diseases, intracranial pressure, magnetic stimulation of the central nervous system, ultrasound and electrophysiology of the brain.



SCIENTIFIC PROGRAM

SCIENTIFIC PROGRAM

FRIDAY, DECEMBER 8TH, 2017

10.00 – 10.40	Treatment of Acute Ischemic Stroke Wolf-Dieter Heiss
10.40 – 11.00	Imaging for Prediction of Recovery and Outcome after Stroke Wolf-Dieter Heiss
11:00 – 11.20	A proposed regional hierarchy in recovery of post-stroke aphasia Wolf-Dieter Heiss
11.20 – 11.50	Non Invasive Stimulation of the Brain 1 Alexander Hartmann
11.50 – 12.10	Coffee Break
12.10 – 12.40	Non Invasive Stimulation of the Brain 2 Alexander Hartmann
12.40 – 13.25	Non-invasive brain stimulation in rehabilitation after stroke Wolf-Dieter Heiss
13.25 – 13.50	Non-invasive repeated therapeutic stimulation for aphasia recovery: a multilingual, multicenter aphasia trial (NORTHSTAR) Wolf-Dieter Heiss
13.50 – 14.00	Summary: Is transcranial magnetic stimulation an effective therapy for aphasia? Wolf-Dieter Heiss and Alexander Hartmann
14.00 – 15.00	Lunch Break
15.00 – 18.00	Non-invasive Brain Stimulation – New strategy for Brain Recovery Scientific Symposium – UMF Days 2017 Alexander Hartmann

ABSTRACTS

TREATMENT OF ACUTE ISCHEMIC STROKE.

Wolf-Dieter Heiss

Ischemic stroke is the second most common cause of death worldwide and the third leading cause of the loss of disability-adjusted life years; however, treatment remains insufficient and is only successful during the first hours after the attack if reperfusion of the ischemic territory can be achieved. Thrombolysis resulting from the intravenous administration of recombinant tissue plasminogen activator (rt-PA) within 4.5 h significantly reduces the incidence of death or dependency at 3 to 6 months, but the benefit of its administration ceases between 4.5 and 6 h after the ictus.3 Attempts to recanalize occluded vessels after this time window by intra-arterial rt-PA or mechanical thrombectomy enhance reperfusion and have recently been shown to improve clinical outcome in carefully selected patients. However, the number of patients who may benefit from these reperfusion therapies is small and probably totals less than 20% of all stroke victims, even for those treated at specialized centers.

Therefore, many therapeutic strategies have been developed targeting the pathophysiological cascade that starts with ischemia and ultimately leads to irreversible tissue damage. Despite beneficial results obtained in the prevention of the development of infarcts and patient outcome following experimental ischemia, neuroprotective drugs have not shown efficacy in clinical trials. This failure to translate results from experimental studies to clinical application might be due in part to the use of inappropriate animal model and also to the design of human trials, which often do not consider the limited time windows of targeted steps in the pathophysiological cascade or the complexity of the biochemical and molecular mechanisms leading to ischemic brain damage. As a consequence, treatments directed at correcting one biochemical or molecular step in the pathophysiological cascade of ischemic cell damage have not been successful in stroke, warranting the testing of a multi-targeted therapy that includes compounds with effects on several of the associated pathophysiologic events. Additionally, also rehabilitative measures shouild be combined with treatment with multimodally acting drugs targetted on neuro-restoration to improve probability of recovery.

IMAGING FOR PREDICTION OF RECOVERY AND OUTCOME AFTER STROKE.

Wolf-Dieter Heiss

Neuroimaging modalities may help to assess functional outcome and to predict the efficacy of rehabilitation in individual patients additionally to functional assessment scales such as NIHSS and others.

CT: The most widely used imaging procedure in acute stroke is CT, especially for differentiation between hemorrhagic and ischemic stroke, for localization of the lesion and for decision making regarding administration of potentially risky stroke therapies as thrombolysis. ASPECTS (the Alberta Stroke Program Early Computed Tomography Score) is a measure to quantify ischemic changes on CT within the territory of the middle cerebral artery (MCA) and can help select patients for acute intravascular treatment.

MRI: With diffusion-weighted imaging (DWI), the size of the lesion can be outlined early and DWI lesion volume significantly increased the power of prediction models. Diffusion tensor imaging (DTI) measures may also be used to predict outcome. The connectivity in networks as assessed by DTI is more important for outcome and recovery than the extent of the primary structural lesion.

Assessment of brain blood supply and cerebral perfusion

Inclusion of information from CT angiography contributed significantly more to outcome prediction than the ASPECTS score. Evidence of large vessel occlusion is crucial for improving outcome by early endovascular interventions. The final size of an infarct is also influenced by the extent and quality of collateral circulation to the affected brain area. The presence of robust collateral flow is best visualized by conventional angiography, but CT angiography as a non-invasive alternative has better spatial resolution than transcranial Doppler or MR angiography and can depict leptomeningeal collaterals.

The visualization of disturbed interaction in functional networks and of their reorganization in the recovery after focal brain damage is the domain of functional imaging modalities such as PET and fMRI. PET: Mapping of neuronal activity in the brain can be primarily achieved by quantitation of the regional cerebral metabolic rate for glucose (CMRGlc). Quantitative imaging of cerebral blood flow (CBF) is based on the principle of diffusible tracer exchange, using 15O-labeled water. PET detects and, if required, can quantify changes in CBF and CMRGlc accompanying different activation states of brain tissue. The regional values of CBF or CMRGlc represent the brain activity due to a specific state, task or stimulus in comparison with the resting condition, and color-coded maps can be analyzed or correlated to morphological images.

fMRI measures signals that depend on the differential magnetic properties of oxygenated and deoxygenated

hemoglobin, termed the blood-oxygen-level-dependent (BOLD) signal, which gives an estimate of changes in oxygen availability. The amount of deoxyhemoglobin in small blood vessels depends on the flow of well-oxygenated arterial blood (CBF), on the outflow of O2 to the tissue (CMRO2) and on the cerebral blood volume (CBV). fMRI images map changes in brain function and can be superimposed on the anatomical image.

Motor and somatosensory deficits: In most fMRI or PET studies involving active or passive movements, a widespread network of neurons was activated in both hemispheres. During recovery from hemiparesis, a dynamic bihemispheric reorganization of motor networks takes place. Ipsilateral cortical recruitment seems to be a compensatory cortical process related to the lesion of the contralateral primary motor cortex. The unaffected hemisphere actually inhibits the generation of a voluntary movement by the paretic hand. This effect of transcallosal inhibition can be reduced by repetitive transcranial magnetic stimulation (rTMS).

Post-stroke aphasia: Studies of glucose metabolism in aphasia after stroke have shown metabolic disturbances in the ipsilateral hemisphere caused by the lesion and contralateral hemisphere caused by functional deactivation (diaschisis). Patients with an eventual good recovery predominantly activated structures in the ipsilateral hemisphere.

NON INVASIVE STIMULATION OF THE BRAIN

Alexander Hartmann

According to the law of Farraday, the intensity change of a magnetic field causes an electric field in a conductive. In live cells, the intentional change of a magnetic field leads to depolarisation. If a magnetic field is applied to the brain and changes its intensity, the cells of the brain may be depolarized. Above a certain power level, this results in an electric current along the axons and even causes increased activity in the downstream organs such as muscular contraction.

Transcranial magnetic stimulation (TMS) of the brain is a technique which is used for both stimulation and inhibition of brain tissue activity. Repetitive TMS (rTMS) may either lead to stimulation of the underlying tissue if high frequency of > 5 Hz is used or inhibition of the depolarization if low frequency of 1 Hz is used. Depending on the type of the magnetic coil, the magnetic field can be used as being widespread for stimulation / inhibition of rather large areas such as brain lobes (as it is used in magnetically evoked potentials in neurologic diagnostics or therapy of depressions or autonomous headache) or ending in a sharp focus in about 20 mm depth oft the brain tissue to target one singular gyrus as it is used in presurgical mapping of the brain or therapy of neurologic disorders such as aphasia or central paresis.

Transcranial direct cortical stimulation (tDCS) using a low conductance voltage applied to the skull by an anodal and a cathodal electrode is able to stimulate the brain in rather large areas. It is discussed whether this is an alternative to TMS.

The lecture will focus on the following topics:
- Physical basics of magnetic and electrical brain tissue stimulation
- Practical approach to TMS for mapping of the brain
- rTMS and tDCS as therapeutic instruments for neurologic diseases
- Practical approach to rTMS and tDCS for therapy of neurologic diseases
- Robotic TMS

A PROPOSED REGIONAL HIERARCHY IN RECOVERY OF POST-STROKE APHASIA

Wolf-Dieter Heiss

Activation studies in patients with aphasia due to stroke or tumours in the dominant hemisphere have revealed effects of disinhibition in ipsilateral perilesional and in contralateral homotopic cortical regions, referred to as collateral and transcallosal disinhibition. These findings were supported by studies with selective disturbance of cortical areas by repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers and in patients with focal brain lesions. Both, collateral as well as transcallosal disinhibition might be relevant for the compensation of lesions within a functional network. From these data a hierarchical organization of recovery of aphasia after stroke and of compensation of language defects due to brain tumours can be deduced, by which the reactivation of undamaged network areas of the ipsilateral hemisphere usually lead to better outcome than the involvement of homotopic contra-lateral regions. rTMS can be used to identify areas relevant for speech production and might play a role in treatment strategies targeted at modulating the activity of contralateral homotopic areas of the functional network which might interfere with language recovery.

NON-INVASIVE BRAIN STIMULATION IN REHABILITATION AFTER STROKE

Wolf-Dieter Heiss

The functional deficit after a focal brain lesion is determined by the localization and the extent of the tissue damage. Since destroyed tissue usually cannot be replaced in the adult human brain, improvement or recovery of neurological deficits can be achieved only by reactivation of functionally disturbed but morphologically preserved areas or by recruitment of alternative pathways within the functional network. The visualization of disturbed interaction in functional networks and of their reorganization in the recovery after focal brain damage is the domain of functional imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Longitudinal assessments at rest and during activation tasks during the early and later periods following a stroke can demonstrate recruitment and compensatory mechanisms in the functional network responsible for complete or partial recovery of disturbed functions. Imaging studies have shown that improvements after focal cortical injury are represented over larger cortical territories, an effect which appears to be dependent on the intensity of rehabilitative training. It has also been shown that the unaffected hemisphere in some instances actually inhibits the recovery of ipsilateral functional networks and this effect of transcallosal inhibition can be reduced by non-invasive brain stimutation.

Non-invasive brain stimulation (NIBS) can modulate the excitability and activity of targeted cortical regions and thereby alter the interaction within pathologically affected functional networks; this kind of intervention might promote the adaptive cortical reorganization of functional networks after stroke. Non-invasive brain stimulation (NIBS) uses direct current (DCS: excitation under the anode, inhibition under the cathode) or repetitive transcranial magnetic stimulation (rTMS: excitatory at high frequency, inhibitory at low frequency). Since recovery from poststroke deficits seems to be more effective in patients who recover function in the ipsilateral perilesional area, NIBS trials aimed to activate this region: this effect can be achieved by excitatory NIBS (high frequency repetitive transcranial magnetic stimulation, rTMS; intermittent theta burst stimulation, iTBS; anodal transcranial direct current stimulation, tDCS) to reactivate the perilesional area or by inhibitory NIBS (low frequency rTMS or cathodal tDCS) to reduce increased activities in the contralesional homologous areas.

DCS as well as rTMS were applied in combination with rehabilitative measures in order to improve various symptoms after stroke, especially motor deficits and aphasia. In both applications recovery was improved with combined treatment in comparison to standard therapy without NIBS. All types of NIBS were used in rehabilitation of motor deficits after stroke and positive effects on recovery were observed. Among the different modalities low-frequency inhibitory stimulation of the motor cortex in the contralateral non-affected hemisphere seems to be the most prominent approach, but large controlled trials are still missing.

In poststroke aphasia several studies attempted to restore perilesional neuronal activity in the injured left inferior frontal gyrus by applying excitatory high frequency rTMS or iTBS or anodal tDCS to small series of patients in the chronic stage: They showed favorable effects in speech performance for several weeks to a few months. Only one study coupled ipsilesional anodal tDCS to language therapy in chronic nonfluent aphasia and observed improved speech / language performance for 1 week to 2 months. Most NIBS studies in poststroke aphasia employed inhibitory low frequency rTMS for stimulation of the contralesional pars triangularis of the right inferior frontal gyrus (BA 45) in order to reduce right hemisphere hyperactivity and transcallosal inhibition on the left Broca's area. Most studies reported single cases or small case series with chronic poststroke aphasia without any control condition and beneficial effects on speech performance lasting for several months. Only a few controlled studies including sham stimulation were performed in chronic stage after stroke. A controlled trial with inhibitory cathodal tDCS stimulation of the non-dominant right Wernicke area in patients with subacute global aphasia resulted in some improvement of comprehension in the treatment group. In one controlled randomized study changes in PET activation pattern in the subacute course were related to the clinical improvement. The shift of the activation pattern to the dominant hemisphere induced by inhibitory rTMS over the right inferior frontal gyrus could be demonstrated in the PET activation studies and correlated to improved performance in aphasia tests. NIBS might be a treatment strategy which could improve the effect of other rehabilitative efforts.

With NIBS positive effects were also obtained in hemineglect, memory dysfunction and cognitive decline after stroke. A combination of NIBS with multimodally acting drugs with neurotrophic efficacy might might improve chances for recovery.

NON-INVASIVE REPEATED THERAPEUTIC STIMULATION FOR APHASIA RECOVERY: A MULTILINGUAL, MULTICENTER APHASIA TRIAL (NORTHSTAR)

Wolf-Dieter Heiss

Noninvasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) has been used in case series and small randomized controlled trials to improve recovery from poststroke aphasia in combination with speech and language therapy. Results of these studies suggest possible clinical efficacy and an excellent safety profile. Therefore, a larger international multicenter proof-of-concept trial was launched, to directly compare the safety and efficacy of rTMS, tDCS, and sham stimulation as adjuvant therapy to speech and language therapy in subacute poststroke aphasia. In the 4 participating centers, subacute stroke patients with aphasia are randomized between 5 and 30 days after ischemic stroke to either receive rTMS, tDCS, or sham stimulation in combination with a daily 45 minutes speech and language therapy session for 10 days. Efficacy is evaluated at 1 and 30 days after the last of the 10 treatment sessions using 3 outcome measures, validated in all participating languages: Boston naming test, Token test, and verbal fluency test. Additionally, adverse events are recorded to prove safety. In this study, a total of 90 patients will be recruited, and data analysis will be completed in 2016. This is the first multilingual and multinational randomized and controlled trial in poststroke aphasia and if positive, will add an effective new strategy for early stage poststroke aphasia rehabilitation.

SUMMARY: IS TRANSCRANIAL MAGNETIC STIMULATION AN EFFECTIVE THERAPY FOR APHASIA?

Wolf-Dieter Heiss and Alexander Hartmann

- Aphasia is a common deficit after ischemic stroke affecting about one-third of patients. Speech and language therapy in poststroke aphasia has limited efficacy.
- Functional neuroimaging by PET has demonstrated that a lesion of primary language areas activates perilesional and contralateral regions of the speech-specific functional networks.
- Long-term recovery of language function is related mainly to reactivation of primary or perilesional areas of the dominant hemisphere. Contralateral homolog areas have an inhibitory effect on the reintegration of perilesional ipsilateral regions into the functional network.
- Depending on the frequency, repetitive transcranial magnetic stimulation (rTMS) can exhibit inhibitory or excitatory effects on the cortex, which can be imaged by PET.
- Results from case reports, case series and small controlled trials suggest that inhibitory rTMS on contralateral homolog areas is able to improve language function in aphasics but a large controlled trial is necessary to prove the clinical efficacy of this therapeutic strategy.
- Alternative strategies of noninvasive stimulation techniques, such as excitatory rTMS, anodal and cathodal transcranial direct current stimulation and theta burst transcranial magnetic stimulation need to be investigated.

Notes

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