Research Perspectives in Clinical Neurophysiology

A position paper of the EC-IFCN (European Chapter of the International Federation of Clinical Neurophysiology) representing ~ 8000 Clinical Neurophysiologists in Europe

Clinical Neurophysiology (as defined by the IFCN) is ‘‘a medical specialty, or sub-specialty, concerned with function and dysfunction of the nervous system, caused by disorders of the brain, spinal cord, peripheral nerve and muscle, using physiological and imaging techniques to measure nervous system activity. When interpreted in relation to the clinical presentation of patients, data from these techniques can either diagnose or assist in the diagnosis of, neurological or psychiatric conditions and quantify, monitor and follow progression of such conditions. Clinical Neurophysiology also encompasses physiological methods for therapy of neurological and psychiatric disorders”.

Research in Clinical Neurophysiology

Clinical Neurophysiology encompasses a broad array of methods to study the peripheral and central nervous system, and targets virtually all diseases in neurology and psychiatry. Clinical Neurophysiology bridges basic neuroscience closely with clinical neuroscience. It is a typical translational part of brain research. Investigation of human brain function is possible from *single cell recordings* during epilepsy surgery or *deep brain stimulation* to recording activity of large-scale brain networks during *electroencephalography* (EEG), *magnetoencephalography* (MEG), *positron emission tomography* (PET), *Single Photon Emission Computed Tomography* (SPECT), or *functional magnetic resonance imaging* (fMRI). These investigations are often combined with psychophysical and neuropsychological investigations.

Methods:

- *Electroencephalography* (EEG) and *Magnetoencephalography* (MEG)
  Multichannel recording of brain electrical activity is a necessary adjunct to the diagnosis of epilepsy, and delineation of its type and frequency, and in the analysis of wake/sleep conditions and reduced states of consciousness. Refinement with modern source analysis methods will allow improved precision, in particular in conjunction with multimodal imaging. The introduction of ambulatory recording of EEG and video now means that patients can be recorded over days at home, improving yield and the patient experience. In cognitive neuroscience, EEG and MEG are the only real time recording techniques at present and so often essential for data acquisition and complementary to functional imaging, (the neurophysiological signals have a time discriminations thousands of times higher than techniques based on blood-flow/metabolism). Though EEG has been considered a clinical tool, over the last decade or so it has moved beyond this to be frequently used in neuroscience labs as well. (so far more than 135,000 publications in total)

- *Subdural and intracerebral EEG recordings.*
  These techniques are currently indispensable to define surgical targets during the pre-surgical assessment of pharmaco-resistant epilepsy. In an increasing number of cases, the electrode contacts used for recording can be subsequently used to perform micro-thermocoagulation procedures that can avoid major resection (therapeutically interventional neurophysiology).

- *Multimodal Evoked Potentials* (VEP, ERG, BAEP, SEP, MEP, LEP, AEP, etc.).
  These are employed in the diagnosis of the causes of sensory and motor disturbances, for instance in multiple sclerosis, in coma prognosis and in investigation of ophthalmic and auditory disease.

- *Multimodal Event-Related-Potentials* (ERPs).
  These long latency evoked potentials reflect cognitive processing and so allow the recording of brain responses during tasks involving different types of memory, problem solving, decision taking etc.

- *Intraoperative monitoring*

  Intraoperative monitoring of brain, spinal cord and nerve function during surgery is improving safety of these procedures and becoming mandatory medico-legally. Monitoring of ICU patients is becoming more widespread and standard. (22,000 publications)

  Intensive care brain monitoring

  Optimizing neurological care during emergency and intensive care treatment has become a priority through all age groups. In particular, neonatal brain monitoring with long term EEG is already a standard in most European tertiary level centers in neonatal intensive care. Brain monitoring is also a key component of pediatric and adult intensive cares, as well as an increasing used method in the emergency medicine of neurologically compromised patients.

- *Polysomnography*

  EEG, together with other measures (polysomnography), is the only way to accurately measure sleep stages and is the backbone of the diagnostic investigation of sleep disorders. (19,000 publications)

- *Electromyography, nerve conduction studies and reflexes (spinal, brainstem, transcortical)*

  Such studies are standard extensions of the neurologic examination to diagnose patients with anterior horn cell, peripheral nerve, neuro-muscular junction or muscle disorders and to determine the extent and severity of such conditions. Reflexes are of paramount importance for research as well as for evaluation of clinical conditions including muscle tone abnormalities. (82,000 publications)

- *Electromyography, quantitative motor unit studies, nerve conduction studies, channelopathies and reflexes (spinal, brainstem, transcortical)*

  Such studies are standard extensions of the neurologic examination to diagnose patients with anterior horn cell, peripheral nerve, neuromuscular junction or muscle disorders and to determine the extent and severity of such conditions. Quantitative motor unit studies such as motor unit number estimate (MUNE) are valuable endpoints in clinical trials on motor neuron diseases and motor neuropathies. Reflexes

are of paramount importance for research as well as for evaluation of clinical conditions including muscle tone abnormalities. Channelopathies can be diagnosed by excitability testing with threshold tracking providing information about the activity of a variety of ion channels, energy-dependent pumps and ion exchange processes activated during the process of impulse conduction in the nerve. (82,000 publications)

- *Autonomic and small fibre testing.*
  Neurophysiological techniques are used to record various parameters associated with autonomic disturbances including heart rate variability, postural blood pressure and cutaneous blood flow useful in the assessment of small fibre nerve damage, which can occur in diabetes and other conditions. Specialist techniques, (contact heat evoked potentials and laser evoked potentials) can assess the pathways from skin to brain involved in perception of pain.

- *Structural imaging*
  Magnetic resonance imaging (MRI) in clinical neurophysiology provides high resolution data of the brain for many functional purposes, e.g. guidance of electrode position for deep brain stimulation, dipole source calculation of multichannel EEG data and identification of epileptic foci. Ultrasound plays an increasing role in diagnostics of peripheral nerve and muscle disease, supplementary to MRI imaging and electrodiagnostics. Further new fields are the diagnostic ultrasound investigation of the brain in Parkinsons's disease. In focused ultrasound therapy non-invasive stereotactic brain surgery is performed during simultaneous thermosensitive MRI imaging. (4,800 publications)

- *Functional imaging*
  Functional MRI (fMRI) by using the BOLD and other technique provides a most promising link to brain physiology on a systems level). Though primarily a neuroradiological tool, it can be used simultaneously or in series with EEG to provide complementary information about brain structure and function. (107,000 publications)

- *Deep Brain Stimulation* (DBS):
  DBS is now a routine method approved in the EU for improving symptoms in movement disorders such as Parkinson's disease, dystonia and epilepsy. In DBS,

electrodes are implanted into nuclei such as the thalamus, subthalamic nucleus or other basal ganglia regions. Currently, new targets in the brain and novel stimulation protocols are being tested, to treat also other frequent diseases, such as epilepsy, intractable pain and a variety of psychiatric disorders. Future challenges encompass improvement of stimulation parameters, introduction of closed-loop stimulation, discharge for interruption of epileptic activity and seizure prevention by patterned brain stimulation, directional sensitive electrodes and others. (9900 publications)

- *Transcranial Brain Stimulation*:
  Transcranial magnetic stimulation (TMS) can be used for investigation of the functional properties of the nervous system. Direct continuous electrical stimulation of the brain by either weak alternating or direct current or pulsed short duration stimulation mediated by TMS allows the manipulation of brain function non-invasively for research, for clinical diagnosis and for the purpose of treatment of neurological and psychiatric diseases. Repetitive transcranial magnetic stimulation is now a standard treatment for depression, reimbursed by insurance in the US. It will be a main research task to further develop and refine these stimulation methods for treatment of other neurological diseases such as epilepsy, stroke sequelae and others. (14,000 publications)

- *Integrative multimodal assessments*
  Many of these techniques can be combined for more power including brain imaging in conjunction with electrophysiological techniques and clinical or behavioral measures.

- *Brain-Computer Interface* (BCI)
  BCI enables those with profound paralysis, e.g. Locked In Syndrome and some tetraplegics to communicate and/or control external manipulanda. (2,000 publications)

- *Clinical neurophysiology reducing the necessity for animal research:*
  Clinical neurophysiology in the context of recordings during epilepsy research or deep brain stimulation is important because it allows reducing the need of animal experiments. In particular when compared to non-human cognitive primate research it allows the design of much more complex experimental paradigms. In general this

research provides fundamental information on how the human brain works on levels from systems to cells.

Diseases:

Epilepsy

Stroke

Disorders of consciousness

Intraoperative monitoring

Movement disorders

Migraine

Multiple Sclerosis

Myasthenia

Tics

Dementia

Schizophrenia

Depression

Neuropathies and Myopathies

Motor neuron disorders

Spinal and nerve root disease

Sleep disorders

Pain

Neonatal seizures

Intensive care brain monitoring

Most promising Europe-wide future research topics

- Using invasive recordings in man during epilepsy monitoring or deep brain stimulation for acquisition of neurophysiological data.

  Implantation of invasive electrodes in patients with epilepsy or movement disorders provides a unique possibility to acquire data on human brain function with a high potential to reduce the amount of non-human primate research in this area. Hereby Europe-wide networks between clinicians and basic scientists would have a high potential for advancing knowledge of human brain function by minimizing animal studies.

- Providing data base infrastructure for collection of clinical data of rare patients.

  The prognosis of rare neurophysiological patients is frequently unclear due to the lack of a sufficient number or patients. Europe-wide studies could provide a sufficient number of patients. Clinical Neurophysiology seems to particularly well suited, many exact measures such as nerve conduction velocities etc. allow a quantitative follow-up, in conjunction with clinical and imaging data. A central EU-funded data-base would contribute to closing this knowledge gap.

- Interventional clinical neurophysiology

  Interventional clinical neurophysiology (transcranial and deep brain stimulation; focused ultrasound) provides a promising tool for treatment of many neurological and psychiatric diseases beyond the state reached so far. In particular improving the efficacy of transcranial stimulation methods requires a better understanding of underlying neurophysiology. A network bridging basic and human studies would advance this field to a great extent.

- Brain monitoring during intensive care

Brain-oriented care is rapidly advancing as a standard in the emergency and intensive care settings of all age groups. European academic centers have pioneered in this area for decades. In the past, European manufacturers of brain monitors have developed most of the technology that is currently sold around the world, hence Europe is in a clearly commanding position with strong competitive advantages. To continue European excellence in the field, there is a need to prospectively support building pan-European networks with clinical studies on brain monitoring, as well as to encourage their linkages with European-based medical device industry for the next generation brain monitors. Obviously, many clinical, technical and commercial challenges related to brain monitoring are shared by other modalities of neurophysiology, especially EEG, intraoperative monitoring, integrative multimodal assessments, invasive EEG studies, and multimodal evoked/event-related studies.

- Human Consciousness

  Human consciousness remains a major challenge in basic as well as in clinical neuroscience. Human consciousness depends on brain function. Impairment of consciousness may occur after focal or systemic brain lesions, after functional disturbances such as epilepsy or e.g. in the context of anesthesia. Inevitably, Clinical Neurophysiology at the interface to diseases can play a central role bridging basic neuroscience, neuropsychology, computational neuroscience and other areas by methods described above also incorporating aspects such as selective attention, memory, decision-making and task monitoring.