S25. TMS and depression

Chairs: E. Klein (IL), T.G. Bolwig (DK)

S25.1

Treating psychiatric symptom with TMS

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There is an assumption in some clinical research studies, particularly those using neuro-imaging, that a disturbance in discrete cortical regions is associated with distinct psychiatric symptoms or syndromes which may go across ICD-defined mental disorders. Such a hypothesis may be testable by TMS. The presentation will examine likely candidates for such testing in affective and psychotic disorders and produce a number of experimental paradigms that can be employed. Methodological issues, such as exact localization of the stimulation area and operational definition of syndromes, will be discussed. New data on the treatment of sixteen chronic hallucinators with 1Hz superior temporal stimulation will be presented as an example of such an approach.

S25.2

Magnetic seizure induction for the treatment of major depression

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Despite advances in psychopharmacological treatment, major depression remains a significant public health problem and a substantial proportion of patients fail to respond to conventional treatments. Electroconvulsive therapy (ECT) plays an important role in the treatment of the severely depressed, and especially those who do not respond to antidepressant medications, but its use is limited by cognitive side effects. Magnetic Seizure Therapy (MST) refers to the use of repetitive transcranial magnetic stimulation (rTMS) to perform controlled seizure induction under anesthesia. MST has the potential to limit the cognitive side effects of convulsive therapy by focusing seizure induction in specific cortical regions and avoiding current spread to areas implicated in amnestic side effects. MST will be explained and technological as well as clinical needs will be addressed. First results of this putative therapy in major depression will be reported and the general necessity for stimulating at higher amplitudes will be discussed.

S25.3

Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms?

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Potential therapeutic properties of repetitive transcranial magnetic stimulation (rTMS) have been suggested in several psychiatric disorders such as depression, mania, obsessive–compulsive disorder, posttraumatic stress disorder and schizophrenia. By inducing electric currents in brain tissue *via* a time-varying strong magnetic field, rTMS has the potential to either directly or trans-synaptically modulate neuronal circuits thought to be dysfunctional in these psychiatric disorders. To use rTMS optimally, it is most important to know how it is acting in brain tissue, i.e. knowledge concerning the putative neurobiological changes underlying the observed clinical effects. However, the limitations of human research necessitate preclinical studies in suitable animal models and basic studies at the cellular and molecular level to better understand how the induced intracerebral current density is regulated and which regulatory elements might serve as potential treatment targets. rTMS currently still awaits clinical routine administration although there is compelling evidence that it causes changes in neuronal circuits as reflected by behavioural changes and decreases in the activity of the hypothalamic-pituitary-adrenocortical system. Such alterations suggest regional changes in neurotransmitter/neuromodulator release, transsynaptic efficiency, signaling pathways and in gene transcription. Indeed, specific changes in the dynamic release patterns of biogenic amines, amino acids and the neuropeptide vasopressin in response to rTMS could be demonstrated by use of the in vivo microdialysis technique. Moreover, neuroprotective effects of rTMS and an increase in brain-derived neurotrophic factor (BDNF) gene expression were shown. Together, these changes are, in part, reminiscent of those accompanying antidepressant drugs. The data further suggest that a common molecular mechanism may underlie different antidepressant treatment strategies.

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S25.4

Slow rTMS in major depression and schizophrenia. Review of studies and implications for future research

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Recent studies have suggested that repetitive transcranial magnetic stimulation (rTMS) of the dorso-lateral prefrontal cortex (DLPFC) might be effective as a treatment for major depression (MD). One line of studies has reported the efficacy of high frequency rTMS (10–20HZ) to the left DLPFC, using focal stimulation. Our work has focused on the evaluation of low frequency (1HZ) non-fecal (round coil) rTMS to the right DLPFC. Using this approach, rTMS has been shown to be significantly more effective than sham stimulation in a double blind controlled study in 70 subjects with MD. At the end of 10 daily rTMS sessions Hamilton depression ratings (HDRS) were significantly lower in the rTMS group. Also, a significantly larger portion of patients had HDRS ratings <10 and did not need ECT. In a more recent study 28 subjects with MD were randomized to receive 1) right prefrontal rTMS with placebo medication (N=11) or 2) left prefrontal rTMS with placebo medication (N=10) or 3) active medication with sham rTMS (N=7). Ten daily treatments were administered over 2 weeks at 3HZ, 110% of motor threshold using a 80mm round coil (Magstim Rapid). Five patients (50%) in the left rTMS group but only one in each of the other groups, improved by more than 50% on their depression scores after 2 weeks of treatment. In this study left prefrontal rTMS at a frequency of 3HZ was superior to the other treatments and resulted in significant improvement in 5/10 patients. In contrast we failed to show therapeutic efficacy of rTMS in 31 schizophrenic patients using the same treatment protocol. In another study 46 normal volunteers were assessed for neuropsychological effects of one session of low frequency rTMS applied to the right or left DLPFC as compared to sham rTMS. In this double blind study, rTMS did not appear to have any adverse cognitive effects as assessed by several neuropsychological tests. Taken together all these suggest that low frequency (<5HZ) prefrontal rTMS may be selectively

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effective in MD without noticeable neuropsychological adverse effects, These results should however be viewed as preliminary. Furthermore the clinical relevance of these findings is not obvious since the effect size was small to medium. Thus more studies are needed to assess the long term efficacy and overall clinical benefit of rTMS in MD and characterize optimal treatment parameters. The studies were supported by grants from the Stanley Foundation and NARSAD.

S25.5

Transcranial magnetic stimulation and depression

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Transcranial Magnetic Stimulation (TMS) has been used in the therapy of depression during the last 6 years. No direct comparison between ECT and TMS has been made. ECT and TMS both use electrical energy to induce neuropsychiatric change. Up to date there are few trials comparing ECT with TMS. Grunhaus et al (2000) looked at non-responders to unilateral ECT and found no difference in response to either bilateral ECT or TMS while they found ECT significantly more effective than TMS for patients with psychotic depression. The current delivered with TMS generators can be directed to particular regions (rTMS) while ECT involves all regions of the brain. rTMS may be given as high frequency stimulation (higher than 1 Hz) and as low frequency or single-stimulation TMS (0.25 to 1.0 Hz). Using low frequency rTMS Klein et al 1999 found evidence for short-term efficacy of this modification in patients with recurrent major depression. Using high-frequency rTMS George et al 1997 found a small difference in antidepressant effect in patients having active rTMS to the left dorsolateral prefrontal cortex compared with sham-rTMS.

A recent study (Lisanby et al 2001) demonstrated that rTMS may be used in such a way that generalised seizures are induced and are therapeutic.

The antidepressant effect of rTMS should be considered further optimising stimulus frequency, intensity and magnetic coil placement, which has not yet been optimised. Further a biological heterogeneity among patients treated with rTMS may also contribute to differing efficacy across clinical studies.

S25.6

Transcranial magnetic stimulation as a tool for assessment and modulation of cortical excitability in patients with major depression

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Introduction: Since its introduction (Barker et al., 1985), single-pulse transcranial magnetic stimulation (sTMS) has been widely used as a noninvasive technique to evaluate brain function in health and disease. More recently, repetitive transcranial magnetic stimulation (rTMS) was introduced as a tool for modulating brain activity. High frequency rTMS (3Hz and higher) has been shown to enhance cortical excitability while low frequency (1Hz) rTMS has been reported to transiently inhibit focal cortical areas. The capacity of rTMS to alter cortical excitability may play an important role in mechanisms of its antidepressant effects. However, the relationship between stimulus location, frequency and treatment outcome is still not clear and objective measures that could help to optimize treatment are lacking. Objective: To study changes in cortical excitability following rTMS treatment in patients with major depression (MD) and their relationship with rTMS parameters and treatment outcome.

Methods: Forty eight consenting subjects with MD were randomized to receive 1) right prefrontal rTMS with placebo medication (N=21), or 2) left prefrontal rTMS with placebo medication (N=16) or 3) active medication with sham rTMS (N=11). Patient groups were further divided into subgroups according to the frequency of rTMS: 1) Twenty four patients received ten daily rTMS treatments at 3Hz frequency and 110% motor threshold intensity; 2) Thirteen patients received ten daily rTMS treatments at 10Hz frequency and 100% motor threshold intensity. Severity of depression was blindly assessed before, during and after treatment. In order to assess the effect of rTMS on cortical excitability, the resting motor threshold (rMT), silent period threshold (SPT), silent period duration (SPD) and amplitude of the motor evoked potential (MEP/M- wave amplitude ratio) in response to sTMS were evaluated before and after the treatment.

Results: Left prefrontal 3Hz rTMS was superior to the other treatments. Following two weeks of left rTMS a significant increase of the left motor cortex MEP/M wave amplitude ratio was evidenced in the patients who improved but not in those who failed to improve ($p<0.05$). No changes were observed in the patients who received right or sham rTMS.

Conclusions: The antidepressant effect of rTMS seems to be associated with increase of the left hemisphere excitability. Objective measures of cortical excitability could help to optimize treatment and might become a useful predictor of treatment outcome.

S26. Neuromuscular abnormalities in schizophrenia – a consequence of central or peripheral mechanisms

Chairs: H.Y. Meltzer (USA), F.-A. Wiesel (S)

S26.1

Neuromuscular abnormalities in psychosis; implications for nosology, neurodevelopment and neurotransmitter abnormalities

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Some but not all patients with schizophrenia, schizoaffective disorder, and to a lesser extent, bipolar disorder and psychotic depression, have been reported to have various abnormalities of the neuromuscular system, including: 1)small-moderate increases in plasma creatine kinase (CK) activity of skeletal muscle origin during a brief period associated with recent onset of delusions and hallucinations; 2)various types of morphologic abnormalities of skeletal muscle fibers, including denervated fibers and increased fiber type grouping; 3)increased branching and sprouting of subterminal motor nerves and increased motor unit territory; 4) motor nerve conduction deficits; and 5) infant and childhood gross motor abnormalities. These findings suggest a possible neurodevelopmental etiology. The commonality of these abnormalities across psychotic illnesses suggests nosologic overlap. Massive increases in plasma CK activity with antipsychotic drugs, particularly atypical antipsychotic drugs, have been reported in a small proportion of patients. The discovery of 5-HT2A receptors in skeletal muscle cell, along with other data, raises the possibility that serotonin is important for neuromuscular abnormalities in psychosis.

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