MULTIMODAL TRASNCRANIAL MAGNETIC STIMULATION IN THE STUDY OF BRAIN AND COGNITION

Biomedicum Helsinki, Lecture Hall 2, March 24th-25th 2011

Summary

Transcranial magnetic stimulation (TMS) is a non-invasive brain research method that allows temporally and spatially accurate stimulation of the human brain. This workshop brought together a number of leading scientists to discuss the most recent advances in the use of TMS together with other brain imaging methods and of their applications in the study of the human brain. It provided an excellent possibility also for young scientists to present their most recent findings in the field. The workshop also presented a "Juhani Hyvärinen" –lecture by an eminent neuroscientist, Acamedician Riitta Hari. Juhani Hyvärinen (+1983) was a distinguished Finnish neuroscientist whose pioneering studies on the function of the parietal cortex were ground breaking influencing brain research still today.

The meeting was opened by the organizers, Prof. Stephen Jackson and Prof. Synnöve Carlson who also chaired the sessions of the two-day workshop. The speakers of the first day were Sven Bestmann (UK), Roland Chusaj (Germany), Matthew Rushworth (UK), Tuomas Neuvonen (Finland), Antti Pertovaara (Finland), Juha Silvanto (Finland) and Mark George (USA). The day ended with a poster session during which the participants of the workshop had a possibility to go through the posters and talk with their presenters. The posters were in the same area where lunch and coffee was served, so participants had plenty of time to go through them.

The second day started with a visit in BioMag Laboratory that is located in the Meilahti campus area, a 5 min walk from the meeting venue. The visit was hosted by the head of the BioMag laboratory, Doc. Jyrki Mäkelä, who first gave an introductory lecture about the laboratory. The visitors were then guided through the area by young reseachers who work in BioMag laboratory. They demonstrated the stimulation of the motor cortex on a subject with the navigated TMS system. Visitors could also see on video presentations how stimulation of the left inferior frontal cortex (Broca's area) disrupts speech production.

After the visit in BioMag laboratory, participants returned to the meeting area. The meeting continued with talks from Henry Hannula (Finland), Riikka Möttönen (UK) and Marcello Massimini (Italy). Then three poster prices were awarded to the best posters. The best posters were chosen by Zoltan Vidnyánszky and Sven Bestmann and were given to JeYoung Jung (Korea/UK), Johanna Metsomaa (Finland) and Satu Jääskeläinen (Finland). The last speaker of the meeting was Riitta Hari, who delivered the "Juhani Hyvärinen" -lecture.

Scientific content and discussion of the event

The first speaker *Sven Bestmann* talked about the assessment of state-dependent inter-regional causal influences using TMS and fMRI. He pointed out that while it is difficult to assess the impact of TMS on networks of interconnected regions, such impact can now be studied by new approaches that combine TMS with neuroimaging methods, such as functional magnetic resonance imaging (fMRI). He told that fMRI can detect the spatial topography of local and remote TMS effects and that these effects may vary with psychological factors such as task-state. By combining TMS with neuroimaging techniques allows to understand the physiological underpinnings of TMS, and the neural correlated of TMS-evoked consequences on perception and behaviour. This can provide powerful new insights about causal interactions among brain regions in both health and disease.

The session continued with a talk by *Roland Chusaj*. He replaced Jacinta O'Shea who had to cancel participation due to an illness. Roland Chusaj told about the different ways how to handle TMS related artefacts in simultaneous EEG recordings.

The third speaker *Matthew Rushworth* talked about the top-down and inhibitory control over the posterior brain regions exerted by the prefrontal cortex. They had tested the effects of TMS to two subareas of the prefrontal cortex, the inferior and medial frontal cortex on activity recorded from more posterior brain systems that are associated with motor selection and visual selection. TMS to the inferior frontal gyrus inhibited the other brain areas, and, in certain circumstances, facilitated motor or visual selection-related activity. The medial frontal cortex also exerted a top-down influence over motor selection and even over inferior frontal cortex and the manner in which it, in turn, influenced the motor system.

Tuomas Neuvonen gave an overview about the use of TMS in diagnostics or research emphasizing that TMS offers time-locked, causal information about the role of the stimulated area. Therapeutic stimulation aims to modulate the excitability or synaptic activity either locally under the coil or remotely using a cortico-cortical or cortical-subcortical network. Carrying out a TMS experiment, performing diagnostics or attempting a therapeutic intervention require assumptions about the functional role of the stimulated brain area. He told about a novel way of combining diffusion tensor imaging (DTI), fiber tracking and TMS to investigate cerebral white matter networks and its microstructural properties. Combining TMS with anatomical connectivity and microstructural information from DTI has been demonstrated to offer valuable information in multiple applications in neurosurgery of rolandic tumors, stroke diagnostics and diagnostics cerebral palsy.

Antti Pertovaara told about novel experiments where TMS had been targeted to the prefrontal cortex (PFC) with the help of information obtained by diffusion weighted magnetic resonance imaging (DW-MRI) and probabilistic tractography. Combined use of DW-MRI and tractography allow investigating functional anatomy of the living human brain with high precision. A subarea of the PFC that was anatomically connected with the primary somatosensory (S1) cortical representation area of the tactile test stimulus in the hand thenar, was determined with tractography. He showed that navigated TMS of this PFC-S1 link attenuated somatosensory evoked potentials in S1 and suppressed tactile temporal discrimination ability in a somatotopic fashion. In subjects performing tactile WM task, a single TMS pulse applied to the PFC-S1 link during the memory maintenance period improved tactile WM, in spite of tactile interference during the retention period. Improvement of tactile WM by navigated TMS in this experiment was suggested to be due to increased top-down suppression of interfering somatosensory processing in S1 via the PFC-S1 link. These findings show that combining DW-MRI, probabilistic tractography and TMS increases specificity of the TMS and support the hypothesis that the PFC plays a role in tactile WM by gating sensory interference in S1.

Juha Silvanto discussed how the impact of TMS reflects a nonlinear interaction between the initial activation state of the stimulated cortex and the strength of the TMS pulse. He discussed experiments that had used fMRI-guided TMS in which state-dependency had been exploited to investigate neural selectivity in the visual cortex. He also described studies investigating the impact of TMS at different levels of initial state and TMS intensity. He argued that the nonlinear interaction between these factors can explain “paradoxical” functional facilitations induced by TMS. Furthermore, in a study in which TMS was used to probe cortical excitability in the visual cortex, qualitatively different results were obtained at low vs. high TMS intensities, indicating that the assessment cortical excitability was affected by the TMS intensity used to probe the neuronal population. He concluded that consideration of both the initial activation state and the TMS intensity are necessary for understanding TMS effects.

Mark George described how TMS can be used together with fMRI by performing ‘online’ (truly interleaved) studies at 3 T, and ‘offline’ studies where subjects are scanned before and immediately after TMS or sham stimulation. He described studies demonstrating that a combination of TMS and fMRI techniques may be useful in studying the effects of neuroactive drugs on specific brain circuits, or on how TMS affects emotion-regulating circuits. He described recent studies involving the online effects of an antidepressant/anticonvulsant, lamotrigine, or the offline regulation of

pain. In the lamotrigine study, Li and colleagues scanned healthy subjects in a double-blind, placebo-controlled, crossover design within the fMRI scanner on three different visits. They received both motor cortex and then prefrontal cortex TMS, while taking placebo, lamotrigine (LTG) or valproic acid (VPA). LTG and VPA had similar inhibitory effects on motor circuits, but differing effects on the prefrontal corticolimbic system. In the pain perception study, Borckardt and colleagues studied healthy adults who underwent an 8-minute thermal pain protocol with fMRI before and after rTMS treatment. TMS was associated with a 13.30% decrease in pain ratings, while sham was associated with an 8.61% decrease (p=.04). TMS was associated with increased activity in the posterior cingulate gyrus, precuneous, right superior frontal gyrus, right insula and bilateral postcentral gyrus. Activity in the the right superior prefrontal gyrus was negatively correlated with pain-ratings suggesting that it is involved in inhibitory circuits capable of pain reduction, which could explain the efficacy of TMS in pain management.

Henri Hannula talked about the applicability and reliability of navigated brain stimulation (NBS) TMS in neurosurgery in preoperative planning. He described how the navigated brain stimulation (NBS) TMS has been evaluated against perioperative direct cortical stimulation (DCS) in patients with brain tumors located in or adjacent to the motor cortex. In these studies NBS-TMS provides information usually only enabled by DCS and therefore allows pre-procedural planning in eloquent cortex surgery. In patient case studies the functional mapping data from NBS TMS system has been integrated via the OR-neuronavigation system into the surgical visual field of the neuronavigated surgical microscope. This method is reported to be a clinically a practical concept which supports safer and optimal resection of lesions near critical functional locations.

Riikka Möttönen described how TMS has been applied in language studies. The early stages of speech sound discrimination rely critically on the auditory system but whether the human motor system also contributes to speech perception is under debate. In a series of studies the role of the motor system in early automatic speech processing in the auditory cortex was studied by the combined use of low-frequency repetitive TMS, electroencephalography (EEG) and the “mismatch negativity” (MMN) paradigm. Disruption of the lip representation by TMS to the motor cortex suppressed the MMN responses, indicating that the motor cortex influences early automatic speech discrimination. In contrast, disruption of the hand representation did not suppress the MMN responses, suggesting that these influences are specific to the motor regions that control movements of the articulators. These studies suggest that

the human auditory cortex interacts with the motor representations of articulators during early speech processing.

Marcello Massimini gave an interesting talk about the use of TMS in studies on coma patients. He reminded that one can be disconnected from the environment and yet be conscious, as is the case, for instance, when one dreams, and that a key requirement for consciousness is that multiple, specialized cortical areas can interact rapidly and effectively (effective connectivity). He had employed TMS together with high-density EEG to measure effective connectivity at the bedside of brain-injured, non-communicating subjects. In vegetative state patients, who were open-eyed, behaviorally awake but unresponsive, TMS triggered a stereotypic, local response indicating a breakdown of effective connectivity, similar to the one observed in sleep. By contrast, in minimally conscious patients, TMS triggered rapidly changing, widespread responses similar to the ones recorded in healthy subjects during wakefulness and dreaming. Longitudinal measurements in subjects who gradually recovered consciousness showed that this change in the brain's capacity for internal communication occurred at an early stage before reliable communication could be established with the subject and before the spontaneous EEG showed significant modifications. He concluded that measuring cortical effective connectivity with TMS/EEG may represent a sensitive way to evaluate the brain's capacity for consciousness in brain-injured, non communicating patients.

The meeting ended with the "Juhani Hyvärinen" - lecture delivered by *Riitta Hari*. She started her lecture with historical notes of the influential work of the late prof. Juhani Hyvärinen in studying monkey parietal cortex with naturalistic stimuli. She then went on by discussing some human brain imaging studies (MEG, fMRI) with naturalistic auditory, visual, and tactile stimuli. She pointed out that much of our current knowledge of brain function derives from experiments applying accurately defined and controlled sensory stimuli that rarely exist in real life. Although setups with naturalistic stimuli have been criticized for being too loose to provide useful information about brain function, she argued in favor of taking the challenge to study brain function in settings closely resembling every-day conditions. She told about the use of naturalistic auditory, visual and audiovisual stimuli, such as cinema, in brain imaging studies. Also other persons' actions can be presented either visually or auditorily. She further told about new analysis tools that have unravelled the behavior of large-scale brain networks in a detail that could not have been derived from the behavior of single neurons or circumscribed brain areas activated in isolation.

Assessment of results and impact of event on future direction of the field

The workshop “Multimodal transcranial magnetic stimulation in the study of brain and cognition” brought together experts from the field who in their talks and discussions during the meeting told about many interesting recent advances that have been made by combining TMS with other brain research methods. For example, TMS together with high-density EEG recordings have provided new insight into the relationship between consciousness and cortical connectivity. Further, spatial cognition and attention relies on the function of large networks of brain areas that include areas in the frontal and parietal cortices. Concurrent TMS-fMRI and TMS-EEG studies have shed new light on how the frontal and parietal cortices modulate sensory processing and contribute to spatial attention and how lesions involving these networks produce the spatial neglect syndrome.

Young students presented their recent work as posters and had the possibility to discuss their studies with more experienced participants during the poster session and during other times of meeting, as well, since the posters were located in the area were the lunch and coffee was served. A joint dinner was served to the participants allowing further time for discussions during the two-day meeting.

On the second day of the meeting, a visit to the near-by BioMag laboratory was arranged. During this visit the participants could see in practice how the NBS-TMS system works. The visitors saw demonstrations (by video recording) of the NBS-TMS that when targeted to the left inferior frontal cortex (Broca´s area) produced disruption of speech production.

The meeting also provided a possibility for the young participants to enquire possibility to work in the laboratories of the more senior participants. Such enquiries were already made e.g. regarding the BioMag laboratory.

A special issue of Experimental Brain Research on the topic of ‘Recent Advances in Brain imaging of Human Sensorimotor function’ will be edited by Prof. Stephen Jackson. This special issue will present papers from speakers and poster presenters also of the Helsinki meeting,

Final Program

	"MULTIMODAL TRASNCRANIAL MAGNETIC STIMULATION IN THE STUDY OF BRAIN AND COGNITION" PROGRAMME		
Date	Activity	Time	Venue
24th March	Registration / Mounting of the posters	8.00-9.00	Biomedicum Helsinki
	Opening of the workshop Stephen Jackson and Synnöve Carlson	9.00-9.15	Lecture Hall 2
	Sven Bestmann Assessing state-dependent inter-regional causal influences using TMS and fMRI	9.15-10.00	Lecture Hall 2
	Roland Csuhaj New solutions for the TMS-EEG research	10.00-10.45	Lecture Hall 2
	Break	10.45-11.00	Section B2
	Matthew Rushworth Combining imaging with interference techniques to look at interactions within neural circuits for behavioural inhibition	11.00-11.45	Lecture Hall 2
	Lunch break	11.45-13.00	Section B2
	Tuomas Neuvonen Combining anatomical connectivity and TMS in the study of human brain	13.00-13.30	Lecture Hall 2
	Antti Pertovaara Facilitation of tactile working memory by top-down suppression from prefrontal to primary somatosensory cortex in humans	13.30-14.15	Lecture Hall 2
	Juha Silvanto TMS intensity and initial activation state interact in nonlinear manner: implications for the assessement of function and excitability	14.15-15.00	Lecture Hall 2
	Coffee break	15.00	Section B2
	Mark George Combining TMS with fMRI – An update on recent work with offline and interleaved studies in depression and pain	15.15-16.00	Lecture Hall 2
	Poster presentations	16.00-17.00	Section B2
	Roland Csuhaj New solutions for the TMS-EEG research Algol Diagnostics / Brain Products	17.00-18.00	Lecture Hall 2
	Dinner	19.00-22.00	House of the Estates
25th March	Visit to BioMag Laboratory Hosting Jyrki Mäkelä	9.00-10.00	Helsinki University Central Hospital
	Henri Hannula Electric-field-guided Transcranial Magnetic Stimulation in cortical mapping	10.15-11.00	Biomedicum Lecture Hall 2
	Riikka Möttönen Auditory-motor interaction during speech perception: combined rTMS and EEG experiments	11.00-11.45	Lecture Hall 2
	Lunch break	11.45	
	Marcello Massimini TMS/EEG measures of effective connectivity in coma patients	13.00-13.45	Lecture Hall 2
	Best Poster Price	13.45	Section B2
	Coffee break	13.50	Section B2
	Presenting the Juhani Hyvärinen lecturer Synnöve Carlson	14.10	Lecture Hall 2
	Riitta Hari: Juhani Hyvärinen Lecture Studying brain function in naturalistic conditions	14.15-15.00	Lecture Hall 2
	Closing of the workshop		Lecture Hall 2