The Jikei University School of Medicine, Tokyo: TMS can change rehabilitation

University Hospital Inselspital Bern: A new approach for treating spatial neglect

Weill Cornell Medical College, New York: TMS is a crucial and promising tool for rehabilitation after stroke

TMS for rehabilitation: An overview

Clinic Elpis, Granada: We need to spread the message
TMS – new hope for stroke victims

According to WHO, cerebrovascular disease, more commonly known as stroke, is the leading cause of disability in adults and can without question be ranked as a global epidemic with the number of stroke victims expected to increase even further in the coming decade.

Stroke not only affects millions of people every day on a social, emotional and physical level, it is also a huge financial burden to society. Those who suffer – and survive – a stroke, will often face a life of physical and cognitive impairment as well as dependency on other people. Rehabilitation will in those cases be a way to try to regain former abilities.

Physical Therapy, Occupational Therapy and Speech Language Therapy are all established and well known within the field of rehabilitation for stroke victims.

An increasing number of researchers are now, however, also conducting studies which combine these established therapeutic approaches with TMS protocols. At MagVenture we also see an increasing demand for TMS stimulators that fulfill this exact purpose. We have therefore developed the MagPro R100 specifically for the stroke research market. It is an advanced 100 pps stimulator with several different operating modes which enables a one-handed operation, making it both ergonomic and effective.

In this issue of MagVenture NEWS you can read about the discoveries made by some of the most prominent researchers within this field:

Professor René Müri of University Hospital Inselspital Bern has, in a recent study, seen improvements in spatial neglect.

In Japan, Professor Masahiro Abo, who has worked for decades with TMS and rehabilitation, is certain that “we can achieve a breakthrough in various rehabilitation concepts which had otherwise reached a dead end”.

However, as Mar Cortes, M.D. from Weill Cornell Medical College also puts it, we must recognize the limitations of these various rehabilitation approaches, including TMS, and the need for more research.

Nevertheless, from Japan, USA and Switzerland the message is loud and clear: TMS has considerable potential and can, in combination with the therapeutic approaches mentioned above, improve neuroplasticity and thus help the patient regain functioning.

Stig Wanding Andersen
CEO, MagVenture

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For Professor Masahiro Abo, the discovery of TMS and how to use it for stroke rehabilitation has founded the path of his career which has so far resulted in several significant findings. But according to Professor Abo himself, the biggest ones are yet to be revealed.

Professor Masahiro Abo clearly remembers the first time he saw and used a magnetic stimulator:

– It was in 1998 while I was studying at the Department of Clinical Neuroscience, Karolinska Institute in Sweden. It was astonishing to see how easily the brain could be stimulated externally. I was certain that this instrument – in time – would change rehabilitation medicine; I remember it as if it was yesterday, he says.

In order to improve mild or moderate paralysis of the upper limbs resulting from stroke, it is particularly important to enhance the functions of the damaged side of the brain. Professor Abo’s theory was that this, along with exercise, could be achieved by using transcranial magnetic stimulation.

It took Masahiro Abo and his team four years to form theories in animal studies to determine the optimal stimulation sites for magnetic stimulation on stroke victims.

Extensive media coverage
– While we waited for the funding to fall into place we made all the necessary preparations such as the training of occupational therapists and physicians to make the therapy available not only at university hospitals but also at general hospitals, says Masahiro Abo.

Today, there are 12 institutions in Japan that can provide the therapy. Getting patients to sign up for the magnetic stimulation turned out to be no problem at all:

– Thanks to extensive coverage of the therapy in Japanese television, newspapers, and magazines, more than 3,000 chronic stroke patients visited our outpatient department over the following 18 months to receive magnetic stimulation, says Professor Abo.

Another 100 acute stroke patients also received magnetic stimulation, starting just three days after their stroke.

TMS: A breakthrough for rehabilitation
One of the major challenges of stroke rehabilitation is the improvement prognosis:

– In mild cases of post-stroke hemiplegia, improvements have typically stagnated approximately one month after onset. In severe cases, it has been after four months. For the severe cases, some factors may explain the poor improvement but the fact that mild and moderate hemiplegia does not improve after a month, even if the patients do retain some motility, has been inexplicable and unsatisfying, Masahiro Abo says and continues:

– With TMS at hand I believe we can achieve a breakthrough in various rehabilitation concepts which had otherwise reached a dead end.

Masahiro Abo

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TMS: A breakthrough for rehabilitation
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– With TMS at hand I believe we can achieve a breakthrough in various rehabilitation concepts which had otherwise reached a dead end. Since the impairment occurs in the central nervous system, namely the brain, an instrument which can stimulate the brain directly is needed. Magnetic stimulation allows you to either suppress or activate specific stimulation sites using different parameters, Professor Abo explains.

– If the regions of the brain that are important to recover from paralysis are found, we can increase the plasticity by combining quality training and magnetic stimulation to activate those particular sites, he states.

TMS and Physical training
– Along with TMS, occupational therapists also conduct one-on-one
training with the patients for two hours per day. Those who are able to will train for another hour or two. According to Professor Abo, it typically takes a week to achieve good movements. During the second week of training, these good movements will be imprinted into the brain.

For the patients, these sudden improvements can be quite a shock:

– They may not have been able to use chopsticks or hold a teacup for three years and suddenly they can do this after only a week of treatment. However, one must stay alert because the patient will tend to revert to the same bad movement that he has been doing for perhaps years, he says.

– Thorough instructions and high quality exercises are therefore necessary to keep the patient “on track”.

**TMS can reduce spasticity**

During his research, Professor Abo made another important discovery:

TMS can actually decrease the excitability of the anterior horn cells in the affected side of the brain to relieve spasticity.

– Spasticity is one of the major obstacles we struggle with when trying to improve paralysis. Decreasing them will produce a difference in motility, Masahiro Abo explains.

– Through the use of SPECT and fMRI we have proven that functions of the paralyzed side can be enhanced through magnetic stimulation and exercise.

**Unique concept: Combining MRI and rTMS**

When asked what it would take to establish TMS as a widespread tool within stroke rehabilitation, Professor Abo stresses the importance of creating the best possible training environment for patients suffering from post-stroke sequelae, which is a chronic condition stemming from the stroke.

– For example, magnetic stimulation is actively used in patients with aphasia resulting from stroke, he says.

We still need, however, to determine why transcranial magnetic stimulation can help decrease the spasticity of the impaired upper limbs.

– We have achieved good results after conducting magnetic stimulation on 400 patients. Now we need to determine, with the help of fMRI, whether it’s the left or right side of the cerebri that contributes to improving aphasia in patients. This treatment concept is called functional MRI-based therapeutic rTMS strategy, and we are the first in the world to introduce it, Professor Abo concludes.

We must, however, be patient and wait a bit longer before further details about Professor Abo’s groundbreaking research will be revealed.

**Blue Book: Professor Masahiro Abo**

Professor Masahiro Abo’s research on rehabilitation has so far resulted in

– 40 original articles and reviews (in Japanese).

– 17 papers on treatments with magnetic stimulation, see below.

University Hospital Inselspital Bern:
A new approach for treating spatial neglect

At the Division of Cognitive and Restorative Neurology at the University Hospital Inselspital Bern in Switzerland, Professor Dr. Med. René Müri and his research group are doing TBS research on patients suffering from spatial neglect. The goal is to improve neurohabilitation of spatial neglect by means of non-invasive brain stimulation.

Stroke is one of the main causes of acquired disability in adults, and the number of people affected by stroke is expected to increase further over the next decade. Those are the facts presented by the World Health Organization.

Spatial neglect, defined as the failure to detect, respond or orient to the stimuli located in the portion of space contralateral to the lesion, occurs in up to 43 per cent of all patients suffering from an acute right-hemispheric stroke and is as such a particularly disabling syndrome after stroke. Patients suffering from spatial neglect have a slower functional progress during rehabilitation, they stay in the hospitals longer and they have a decreased likelihood of being discharged home.

All in all, spatial neglect patients represent increased costs for the healthcare systems.

I think we can learn a lot of new aspects about spatial neglect and attention using non-invasive brain stimulation.

René Müri

New and effective protocol
– Spatial neglect is really a big problem in neurohabilitation because it is a negative predictor for outcome in terms of regaining functional independence. Thus, the need to find an effective way to treat spatial neglect is important, says Professor René Müri.

His division has investigated whether repeated application of continuous theta burst stimulation (cTBS) train could ameliorate spatial neglect.

– Previous treatment protocols used low frequency (mainly 1 Hz) repeated stimulation.

To apply a sufficient number of pulses (600 or more pulses), these protocols lasted between 20 and 30 minutes. Furthermore, most studies repeated the 1 Hz protocol five times a week over two weeks. So the whole procedure was very time consuming and not easy to apply in a clinical setting. TBS, which allows the same number of pulses within 45 seconds, is much easier to apply. Furthermore, TBS seems to have a very good effect on cortical plasticity, says Müri about the research being conducted by his research group.

Improvement for 3 weeks
When asked directly what surprised him the most during the TBS research on spatial neglect, Professor Müri answers that the researchers were impressed to find out that TBS had robust effects, especially after repeated applications.

Blue Book:
Professor Dr. Med. René M. Müri

Professor Dr. Med. René M. Müri is head of the Division of Cognitive and Restorative Neurology at the University Hospital Inselspital Bern, Switzerland, where he began in 2001. Professor Müri graduated as MD from University of Bern in 1984. He is a neurologist. Müri’s main interest lies within investigating the relationships between normal and deficient attention, perception, memory and language functions after brain lesion. In addition, he develops methods and techniques to improve neurorehabilitation. He is the author of 143 articles.

More information at
www.pubmed.gov
www.cclm.unibe.ch/content/research/research_groups/mueri/index_eng.html
In one study we showed that the effect of repeated TBS application [...] increased the positive effects on spatial neglect.

René Müri

Critiqued at first
Although time has proven that Professor Müri and his colleagues were on the right track to finding an effective treatment for spatial neglect, there have been "bumps on the road" in the past.

At the beginning when we first began to publish articles with our modified TBS protocol, we were often criticized for having modified the protocol that was first used in the human application of TBS. It took some years and more publications from other research groups to show that our protocol was efficient and produced even more stable effects than other protocols, says Müri.

What lies ahead
Despite the fruitful research within TMS/TBS being done so far by Müri and his research group, he stresses that the division will continue to do TMS research in the domain of spatial neglect and attention.

TMS research is important and has a twofold impact. Firstly, it allows for interfering with many processes in the cortical network as the high temporal resolution of TMS allows for studying the role of a certain region during attention. Secondly, repetitive TMS allows interfering with the network and attention and its interhemispheric interactions, emphasizes Müri and continues:

-- We are interested in finding out whether TBS is also efficient in the rehabilitation of aphasia and other cognitive disorders due to acquired brain injury.

René Müri is positive when it comes to discoveries waiting to be found within spatial neglect:

-- In the future, I think we can learn a lot of new aspects about spatial neglect and attention using non-invasive brain stimulation, ends Müri.

What is Theta Burst Stimulation (TBS)?

TBS makes it possible to induce strong and long lasting effects using a lower stimulation intensity and a shorter time of stimulation compared to conventional rTMS protocols.

There are two different TBS modalities:

**Intermittent TBS (iTBS):** 10 bursts are grouped and repeated every 10 seconds for a total duration of 191.84 seconds resulting in 20 trains with 600 pulses.

**Continuous TBS (cTBS):** Three pulses are being delivered at 50 Hz every 200ms. 200 burst are delivered without interruption for a total duration of 40.04 seconds resulting in 600 pulses.

René Müri and his colleagues used the modified cTBS protocol (see reference below):
Three pulses delivered at 30 Hz repeated with intervals of 100 ms. A train of 801 pulses (267 bursts) lasts 44 s.

**Literature:**
Mar Cortes, M.D. and Clinical Scientist at the Non-invasive Brain Stimulation and Human Motor Control Laboratory at Burke Medical Research Institute, has chosen to explore the use of neuromodulatory interventions such as Transcranial Magnetic Stimulation. Her main research interest is understanding neural plasticity and its clinical implications in relation to the human motor systems and, ultimately, to develop novel and individualized rehabilitation strategies to promote motor recovery and improve quality of life of patients with disabilities.

– I was working as a trained physical medicine and rehabilitation doctor in a Neurorehabilitation Hospital in Barcelona treating patients suffering from neurological disorders such as stroke and spinal cord injury when I came to realize the need to better understand the mechanisms of brain plasticity in order to promote motor recovery and to create individualized therapies for patients with paralysis, says Mar Cortes.

New project receives NIH funding
To Mar Cortes, understanding that the plasticity of the central nervous system is also present at the spinal cord level has been one of her most important discoveries so far.

This has furthermore led to the development of a technique which combines repetitive TMS with peripheral stimulation to up-regulate spinal cord excitability.

– The NIH has funded the project, which will now be used for individuals with spinal cord injury in order to strengthen the spare connections left after the injury, Mar Cortes explains.

Both rTMS and Transcranial Direct Current Stimulation (tDCS), are promising neuromodulation methods that can lead to long-lasting improvements in motor behavior.

Mar Cortes

Recovery of motor function through therapy and TMS
In the laboratory at Weill Cornell Medical College, Mar Cortes is currently studying the recovery of motor function after injury to the central nervous system.

– After injury, this function can be strengthened through activity-based therapy (motor training) or neuromodulatory interventions such as transcranial magnetic or direct current brain stimulation, she says.

– We investigate the role of controlled motor activity and non-invasive stimulation techniques, in promoting corticospinal plasticity, and its relation with motor recovery by using a combination of behavioral and electrophysiological techniques to address those questions.

A useful, non-invasive tool for studying post-stroke rehabilitation
According to Mar Cortes, TMS can not only quantify the functional state of corticospinal pathways, but also the changes and reorganization occurring after brain injury and during the motor recovery process. These measurements are particularly
The Cool-40 Rat Coil is developed with leading researchers and is the first of its kind on the market. The coil enables you to perform actual repetitive TMS protocols on rodents and obtain replicability and reliability in your research. The special coil design gives you:

- Increased focality
- High intensity and high frequency
- A large number of pulses.

Other TMS limitations may include low spatial resolution. This can, however, be improved by pairing it with a sophisticated neuronavigation system.

All in all it is important to understand the limitations of TMS and interpret the results along with clinical findings, says Mar Cortes.

**Coming up: Spinal Associative Stimulation**

As for the future, exciting studies are currently in the pipeline:

- We are presently conducting a research study which will investigate the therapeutic possibilities of Spinal Associative Stimulation (SAS) for patients with incomplete spinal cord injury, explains Mar Cortes.

The focus of this study is to increase spinal excitability, strengthen spared connections following the injury, and consequently voluntary activation of the leg muscles to help people suffering from spinal cord injury in chronic stages after the injury onset.

We are confident that we can further advance the promising therapeutic value of combined non-invasive stimulation therapies to enhance motor and functional recovery following incomplete spinal cord injury, says Mar Cortes, who also believes that TMS and tDCS in the next 5 to 10 years will be a valuable tool for treating neurological and psychiatric conditions such as stroke, spinal cord injury, Parkinson’s disease, chronic pain, and depression.

**Limitations must be recognized**

Mar Cortes does, however, underline the need to understand the limitations of TMS: The MEP responses are for example highly variable between subjects, healthy or with neurological diseases, which may limit the interpretation of the results as well as its therapeutic use in patients with disabilities.

Want to study effects and action mechanisms of TMS on rats? Apply TMS directly on rodents with the new Cool-40 Rat Coil from MagVenture

The Burke Rehabilitation Hospital has been affiliated with The New York Hospital-Cornell University Medical College since 1968.

Research conducted include the Dementia Research Laboratories and the Molecular Neurobiology Laboratory.

In addition, the institute conducts research into pulmonary disease, head injury, stroke, Parkinson’s disease and other neurological disorders.

**More information at www.burke.org**

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**More information at www.burke.org**
**Stroke:** The loss of brain function due to a disturbance in the blood supply to the brain. A stroke is either caused by ischemia (lack of blood flow i.e. due to a blood clot) or hemorrhage (bleeding of the blood vessels).

**Post-stroke:** Various diseases which often follows an acute stroke (sequela), for example spasticity, motor deficit, visuospatial neglect, and aphasia.

Traditional stroke rehabilitation deals with these main concepts:

**Physiotherapy (PT):** To improve moving and balance issues, strengthen muscles for walking, standing and other activities.

**Occupational Therapy (OT):** To manage daily activities such as eating, bathing, dressing, writing or cooking.

**Speech-Language Pathology (LSP):** To re-learn language skills (talking, reading and writing) and improve swallowing problems.

**Neuroplasticity**

Neuroplasticity has replaced the formerly-held position of the brain being a physiologically static organ. Research within rehabilitation has shown that the brain cells may only be temporarily damaged, not killed. Furthermore, they can regain functioning. Sometimes, one part of the brain will “take over” to cover for another region which has been damaged by the stroke.

Humans have structural redundancies which mean that several areas of the brain are prepared to do the same function. This allows neural compensation (residual neural tissue takes over a lost function, also known as cortical reorganization) and recovery (restoring the function of injured brain tissue by excitation).

Research shows that repetitive Transcranial Magnetic Stimulation (rTMS or TMS) can improve neuroplasticity and thus function, partly by enhancing cortical reorganization and producing potent changes in cortical excitability.

**rTMS protocols in stroke rehabilitation**

Most research focuses on combining TMS with Physiotherapy, Occupational Therapy, and Speech Language Therapy.

Common TMS protocols used in stroke rehabilitation research:

- Low-frequency rTMS (around 1 Hz) over the unaffected hemisphere in order to restore defective inhibition.
- High-frequency rTMS (5 Hz or more) over the affected hemisphere in order to reactivate hypoactive regions.
- Theta Burst Stimulation (TBS) which is a form of TMS which induces strong and long lasting effects using a lower stimulation intensity and a shorter time of stimulation compared to conventional TMS – see also page 6.
For the past two years, Luis Navío has offered TMS for depression treatment at his clinic in Granada in Southern Spain. The results are very promising.

**What made you decide to invest in a depression system?**
– We believe that TMS is a very important tool to treat a mental illness such as depression, but without the side effects from antidepressants.

**Have you had any previous experience with TMS?**
– No, we have not had any prior practical experience with TMS. We did not have any hesitations entering the field, though, as we knew that TMS is very safe. It has been used a lot of times and if you follow the protocol, everything will be ok. As I mentioned, it is our first contact with this technique so we are currently working on improving our protocols along with three doctors, two psychiatrists and one doctor in neurophysiology.

**Have you treated any patients so far? And what results did you get?**
– Yes, we have already treated patients. The results we are getting are hopeful. The patients have improved their state of mind.

We typically see that their mood improves, and they get more energy. Their interest and pleasure in most activities increase and this improvement is kept over time.

**What do your patients think?**
– When our patients come to the clinic, they don’t understand how TMS can actually improve the brain. So usually they feel apprehensive at first, but once they start to feel better, they just love TMS.

**Can you give an example of a patient receiving treatment?**
– The last patient we had had not been working for 6 months but was able to return to his job after receiving TMS.

**Do other clinics in Spain offer TMS for depression treatment?**
– Yes, there are others but the message should be spread more widely. We should all help tell about the obvious advantages of TMS, especially regarding the fact that there are no side effects to the treatment and that patients suffering from depression can actually get help and feel better. It’s a very simple message, really.

**Do other doctors know that you are offering TMS at your clinic?**
Yes, we know that a lot of our “colleagues” are watching us because there are such big expectations to TMS.

Quite often, clinics will also provide references to our clinic about TMS.

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Clinic Elpis, Granada:
We need to spread the message

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– When our patients come to the clinic, they don’t understand how TMS can actually improve the brain. So usually they feel apprehensive at first, but once they start to feel better, they just love TMS.

Luis Navio
SFN 2014
MagVenture will be present at the 44th Annual Meeting of the Society for Neuroscience taking place in Washington, DC 15-19 November.

30,000 neuroscientists from across the world are expected to join this premier venue for neuroscientists to present emerging science and explore new tools and technologies within global neuroscience.

Come visit MagVenture at booth 326 to learn more about our innovative solutions and hear what we can offer within TMS.

Technical training course
MagVenture recently held a technical training course aimed at technical staff at distributors and customers.

The course covered circuit descriptions, troubleshooting, module placement and safety handling with both lectures and hands-on activities.

MagVenture will repeat the training course in the fall of 2014. Please contact service@magventure.com for further details.

Service contracts
MagVenture now offers service contracts on MagPro units and coils. The contracts include maintenance, service and annual safety check of the MagPro unit and coils. The contracts typically apply to customers who do not have the possibility to conduct safety checks and maintenance on their own. MagVenture continues to offer service on a case to case basis. If you are interested in more information about the service contracts, please contact service@magventure.com.

Course in Clinical Use of TMS – September 25-26 2014
At Maastricht Brain imaging Center, Maastricht University

Maastricht University offers a two-day workshop with focus on the clinical applications of TMS. The course includes

- Academic sessions
- Hands-on training
- Individual feedback sessions on intended protocols or procedures
- Short presentations by researchers from the psychiatric and neurological fields about using TMS for psychiatric disorders and rehabilitation.

Place: MBIC/Scannexus Research site, Maastricht Brain Imaging Center, Maastricht University, The Netherlands.
Date: September 25-26, 2014
Number of participants: 20 maximum
Price: €400
Further information and registration: info@magventure.com
About MagVenture

MagVenture is a medical device company, established in 2007, specializing in non-invasive magnetic stimulation systems for depression treatment as well as for clinical examination and research in the areas of neurophysiology, neurology, cognitive neuroscience, rehabilitation, and psychiatry.

From its headquarters in Denmark, MagVenture develops and markets advanced medical equipment based on the use of pulsating magnetic fields.

MagPro magnetic stimulators are sold on the world market through direct sales subsidiaries in Germany and the USA, and through a global network of distributors in Europe, Asia, Middle East, and the Americas.

Regulations in the USA

In the USA federal law regulates the sale of Medical Devices through the US Food and Drug Administration (FDA). This is done to ensure safety and effectiveness. Devices which are permitted to be marketed for their intended use must either have a 510(k) or PMA clearance.

MagPro® stimulators R30, R30 with MagOption, X100, and X100 with MagOption are all FDA 510(k) cleared (k061645, k091940). The intended use is stimulation of peripheral nerves for diagnostic purposes.

The use of devices for other than their FDA cleared intended use is considered as investigational. Such use is only permitted if the Investigational Device Exemption (IDE) guidelines have been followed. For full information on this procedure, please consult FDA's website (www.fda.gov).

All investigational devices must be labeled in accordance with the labeling provisions of the IDE regulation (§ 812.5) and must bear a label with this statement:

"CAUTION Investigational Device. Limited by Federal (or United States) law to investigational use."

Please note that transcranial magnetic stimulation (TMS, rTMS) with MagPro stimulators is considered investigational in the USA.

For further information please contact MagVenture.

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