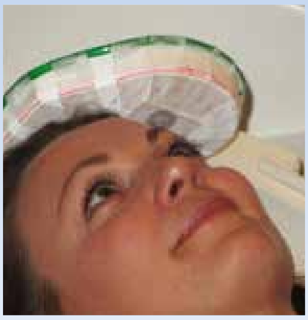
MagVenture *NEWS*

Special Edition: Interleaved TMS/fMRI

University of Zürich:
Finding the Link Between the Brain and the Mind

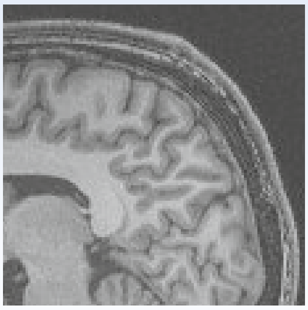
Danish Research Center for MR:
Interleaved TMS/fMRI is Our Entry Point into the Brain

University of California, Berkeley:
10 Quick Questions for Ian Cameron at
Helen Wills Neuroscience Institute



Interleaved TMS and functional MRI:
The Research, the Use, the Future

The MagVenture MRI Installation: What Does it Look Like?



MagVenture
Versatility in Magnetic Stimulation

We've only just begun ...

The idea of entering the brain to find the link between mind and brain is fascinating – What could possibly be more intriguing than entering the human brain and see how decisions are made?

What began as mainly a diagnostic tool is now rapidly moving into a new field with new promising and exciting possibilities for treatment that are emerging all over the world. I can honestly say that this journey, which I embarked on more than 25 years ago, has by far exceeded my wildest expectations: Not only are we now able to stimulate the brain, we can also see what actually happens in the brain while we are doing it! This, in other words, is what interleaved TMS-fMRI is all about.

Much has happened since we launched our first MRI coil, the MRi-B88. The interaction between the MR-scanners' static magnetic field and the dynamic magnetic field from the transducer-coil generates heavy mechanical forces on the structures of the coil. Handling these forces in a safe and reliable way is one of the main technological challenges in fMRi/TMS. The new MRi-B91 coil is more robust and can provide more stimuli per session then ever before. Image quality, accurate positioning and better integration with the head coil are other important challenges.

Our customers have, by moving from 1,5, 3, 5 and and now also 7 Tesla scanners, taken giant technological leaps. At MagVenture, we try our best to keep up with the pace by constantly improving our existing products and taking the necessary technological steps to ensure that we will also be the preferred supplier tomorrow.

The TMS/fMRi-solutions planned for tomorrow will address issues such as cooling of the coil in order to sustain more stimuli (full rTMS treatment protocols), reducing sound pressure per stimuli, better focusing in the brain, and improved reliability and support for advanced stimulus waveforms.

It's an ongoing process, and we simply could not have done this without our customers who are always willing to engage in not only interesting technical discussions, but also product and acceptance tests and even joint developments. Without the input and help from all you researchers out there we would not have been where we are today!

We strongly believe that the solid and dedicated work of research done today will prepare the future ground for improving therapies. Understanding the difference between the healthy and the impaired brain will help us determine the best therapies and medications and it may help us to refine rTMS treatment protocols.

With this special edition of the MagVenture newsletter we hope to push the knowledge sharing within the field of TMS and fMRI just a bit further.

For those of you who do not work within this field today, it is our hope that this newsletter can bring you some insight and inspiration as to what this combined technology can be used for.

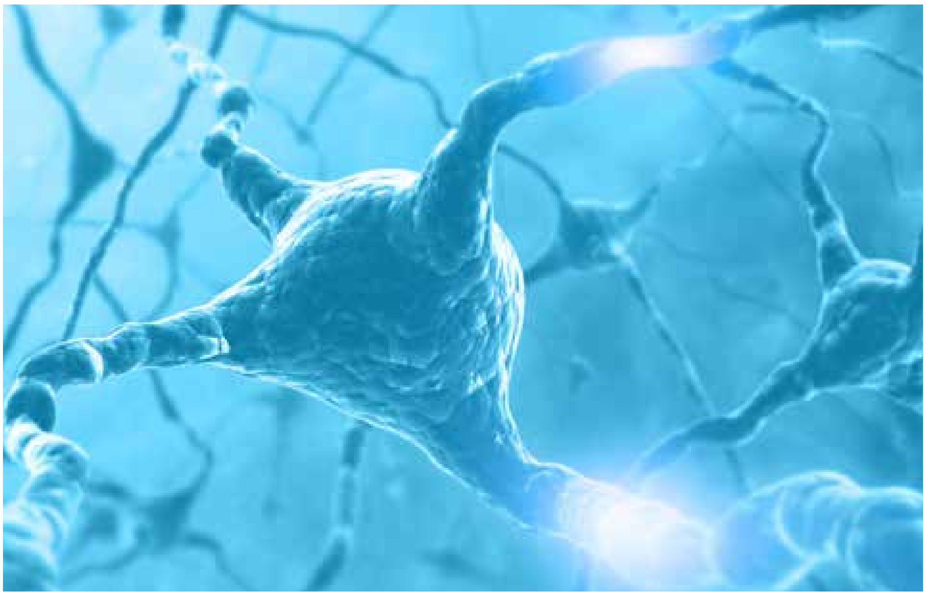
Stig Wanding Andersen
CEO, MagVenture

Table of contents

Editor-in-Chief: Gunnar Hallsson
Editorial Group: Lilja Astrup, Anne-Mette Damon, Kim Kristiansen & Jesper Groth
Layout: Anne-Mette Damon

University of Zürich: Finding the link between the brain and the mind

The Department of Economics at Zürich University hosts a small but prominent research group, headed by Professor Christian Ruff, focusing on Neuroeconomics and Decision Neuroscience. The group studies neural mechanisms of decision-making in perception and behavior as well as the effects of motivational factors (such as rewards and attention) on perception and action, respectively. A major method used to study these neural mechanisms is interleaved TMS/fMRI.



From correlated to causal neural activity

Traditional brain research has, through the means of Brain Imaging, shown that neural activity in different regions of the brain correlates with behavior, and that networks of regions may show joint activity changes, says Christian Ruff.

It has, for instance, been possible to measure correlated neural activity at two sites of the brain (the prefrontal and the visual cortex, for example) when participants perform a task, are in a specific state, or under specific conditions. How this activity is linked/connected or which activity causes the other has not been possible to measure for certain, however.

– With the use of interleaved TMS/fMRI we actually managed to show that there is a causal link between the two sites of the brain – the prefrontal and the visual cortex. This can be seen through manipulating the brain activity in one region (prefrontal cortex) by stimulating with TMS and concurrently examining how this stimulation affects the other site (visual cortex), Professor Ruff explains.

Changing the way we understand and treat mental disorders

Until now, Christian Ruff has used the visual cortex to show how this causal relationship between specific brain regions functions.
He anticipates that this approach can be used for many different targeted sites and that their findings might have an impact on the current therapies for different psychiatric disorders. One of the first signs of many mental disorders noticed by relatives and close friends is the impairment of social decision making, he says. Finding the causal links in the brain causing such altered behavior and understanding what brain processes may be deficient in the brains of patients suffering from psychiatric/neurological disorders could make it possible to refine therapies for these disorders.

> ***– With the use of interleaved TMS/fMRI we actually managed to show that there is a causal link between the two sites of the brain – the prefrontal and the visual cortex.***
>
> **Christian Ruff**

This can be done by specifically targeting the region – or regions – in the brain involved in a certain behavior that is affected by the disorder
.
– A deeper understanding of the causalities in the brain could help us optimize the already approved TMS therapy for depression by optimizing protocols as well as stimulation sites, says Christian Ruff.

Improving individual and collective decision-making

Is there a link between a better understanding of our brain and an improved society? – In brief, it might be possible in the future to optimize different aspects of our society if we gain a better, mechanistic understanding of the decision-making process, says Professor Ruff.

All social systems – the legal system, markets, the educational system, for instance – are based on assumptions about how people decide and interact with one another. Yet our understanding of these processes is not very

> ***It might be possible in the future to optimize different aspects of our society if we gain a better, mechanistic understanding of the decisionmaking process.***
>
> **Christian Ruff**

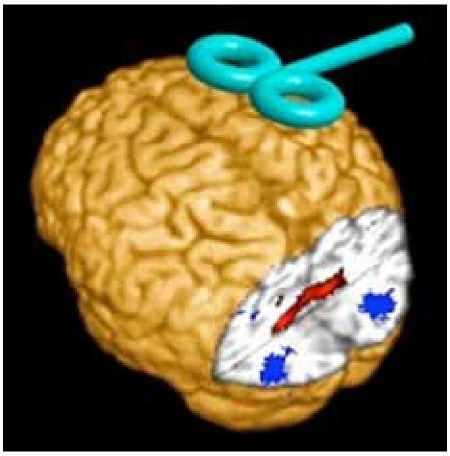
developed. We want to get a better understanding of how people make decisions and what influences these decisions.

Studying decision-making in the brain, in particular causal influences of motives processed in particular brain areas, can help us to obtain clearer knowledge in this respect. This can then lead to recommendations on how social systems should be structured to optimally suit the way people make decisions.

Ruff stresses that we are not yet at a point where his research can found the basis for recommendations, but his aim is to ultimately get there.

Hard work paved the way

In Christian Ruff's early years at Institute of Cognitive Neuroscience at University College London, he was determined to combine the two technologies of TMS and fMRI in order to show the causality of the functioning of the brain. Combining the two techniques was a technical challenge. And with no real standardized setup available, the research group had to solve many obstacles themselves within areas such as MR physics, equipment providers etc. Problems



Studying causal influences between brain regions: A target region is stimulated with TMS while fMRI is used to visualize the brain areas responding to neural impulses from the stimulated area.

with artifacts, timing, and control in a trial-and-error-manner were other issues the team had to solve.

Due to the difficult task of obtaining reliable and useful results it took 4 years before the first papers were published. This first paper ("Concurrent TMS-fMRI and psychophysics reveal frontal influence on human retinotopic visual cortex") is highly cited, due to the novelty of the technique and the results.

TMS/fMRI – a challenge with potential

Even today, Christian Ruff finds that interleaved TMS/fMRI is not a plug-and-play solution. It is rather complex to set up and obtain reliable results.

– You must be very precise timing-wise and you need a lot of technical support. I think this is the major reason for researchers being hesitant about engaging in the field. People were also very cautious with fMRI in the beginning, remembers Professor Ruff.

He believes that once more research groups begin to use the technology and the set-up is easier and more standardized, interleaved TMS/fMRI will be employed more routinely and its many possibilities will find their way into numerous research and clinical applications.

Curriculum Vitae: Professor Christian Ruff

Professor Christian Ruff has a background as a neuropsychologist. His profound interest in cognitive science and the brain led him to a PhD position at the Institute of Cognitive Neuroscience, University College London, where he began researching the neural processes underlying the control of visual attention.

In order to show empirically which brain regions are involved in visual attention, he combined the already known technologies of TMS and fMRI.

This work led him to his current position as Professor at the University of Zurich, where he is now heading his group at the Laboratory for Social and Neural Systems Research (SNS-Lab) in the Department of Economics.

With a group of 4 post docs and 4 PhD students they research the neural mechanisms of human decision-making aided by, amongst other, interleaved TMS/fMRI.

More information at http://www.sns.uzh.ch/index.html

The TMS-fMRI experiments at the Laboratory for Social and Neural Systems Research at the University of Zürich are carried out on a Philips Achieva 3T whole-body scanner.

Danish Research Center for MR: Interleaved TMS/fMRI is our entry point into the brain

The Danish Research Center for Magnetic Resonance (DRCMR) at Copenhagen University Hospital Hvidovre has nearly 30 years of experience in magnetic resonance imaging (MRI) and is one of the leading brain imaging centres in Northern Europe. According to Professor Hartwig Roman Siebner the integration of MRI with other brain imaging modalities is one of its key focus areas. One of them is transcranial magnetic stimulation (TMS).

Professor Siebner has worked with TMS since the end of the 90's. During his time at the Institute of Neurology, UCL, London, in 2000-2002, he started working on combining TMS with functional MRI (fMRI).

– "Online" or interleaved TMS/fMRI – where the magnetic stimulation takes place inside the MR scanner and you actually depict what happens in the brain while stimulating, provides us with a huge opportunity to gain more knowledge about the functional connectivity of the brain, explains Hartwig Siebner.

TMS adds another dimension to existing technology

In his early days of research, Hartwig Siebner examined how TMS changes the cerebral glucose metabolism and cerebral blood flow with another method called positron emission tomography (PET). The PET method has some limitations. The temporal resolution is poor and the method exposes subjects to radiation.

– Compared to PET, fMRI gives us a superior spatial and temporal resolution, states Hartwig Siebner, – as fMRI facilitates studies of deeper parts of the brain and fMRI scans can be collected relatively fast. Moreover, the imaging technique relies on magnetic resonance without any radiation exposure.

A powerful way to map the structural connectivity, the "wiring" of the brain, is diffusion MRI (dMRI). The combination of TMS with fMRI, however, adds a complementary dimension because you can actually see how the communication is flowing through these "wires" (the axes of the neurons) that connect distant brain areas. With the use of TMS you can see how effectively the information flows through the connections. The structures might be malfunctioning even if the connections appear to be structurally intact.

New resources have revitalized the research

With the recent appointment of Axel Thielscher as Associate Professor at The Technical University of Denmark (DTU) and senior researcher at the DRCMR, the combined use of MRI and TMS has received a substantial boost.

– Compared to PET, fMRI gives us a superior spatial and temporal resolution.

Christian Ruff

Several researchers are currently conducting cutting-edge research within this specific field. Thielscher is, besides investigating the neural correlates of sensorimotor integration and motor control, working on solving the methodological challenges of interleaved TMS/fMRI.

Thielscher holds a PhD in Engineering and one in Human Biology, both from Ulm University (Germany). After a PostDoc at Brown University (RI, USA), he moved to the Max Planck Institute for Biological Cybernetics in Tübingen and founded his own research group working with 3 Tesla fMRI and TMS. – I was very fascinated by the fact that so little was known about TMS and what actually happens in the brain, explains Axel Thielscher. – I wanted to explore further the direct effects of TMS and how to use imaging to look at remote spreading of TMS. At DRCMR I can explore these particular areas and try to improve the methodology of the technique, he says, and adds that his background within both the technical aspects as well as human biology gives him a special advantage.

A PhD student at DRCMR volunteers for a test with the MagVenture coil MRi-B91 which is designed for use in MRI scanners with biphasic waveform standard mode.

Thielscher is dedicated to refining the technique to get better and more sensitive pictures and thus achieve more reliable results. As an example, Thielscher has a tremendous stake in upgrading from 2 to 3 Tesla scanners and solving the derived problems and challenges related to interleaved fMRI and TMS.

User-friendly future

Thielscher also stresses that it is paramount for the further diffusion of this combined technology that it becomes more integrated and easier to use. Today the set-up of interleaved TMS/fMRI is rather complicated and time-consuming to use. DRCMR therefore cooperates closely with MagVenture to make the combined technology of TMS and fMRI more user-friendly and to optimize the interleaved TMS outcome.

Today, the research at DRCMR focuses on functional connectivity in the human brain where Siebner and staff have moved the research field considerably. One of DRCMR's main applications of interleaved TMS-fMRI is the mapping of task and context-dependent connectivity patterns – in order to understand which parts of the brain are involved in performing specific tasks.

This approach capitalizes on the fact that TMS-evoked activity travels more easily along routes that are already pre-activated by natural ongoing brain activity, resulting in task dependent/context dependent stimulation effects.

Knowing what happens in the brain helps refine therapies

Since the brain acts differently in different states this state-dependent stimulation could be very relevant for therapeutic use and possibly help in refining TMS depression treatment in order to get higher response rates. Today, most of DRCMR's research within TMS/fMRI focuses on mapping the healthy brain. The multimodal research at the center has an impact on the future research in many derived areas, as the outcome is a greater knowledge of how the healthy brains works. The next logical step is to see how the impaired brain works.

Since interleaved TMS allows us to see how well the information flows through the brain one can also detect malfunctioning structures despite them being physically intact. This gives a better understanding of for example Alzheimer's and stroke.

Bio-markers help identify individual patient response

As TMS therapy is being explored in many diverse disease areas, mainly within psychiatric disorders, but also within areas such as stroke, it would be a tremendous step forward to be able to predict who will respond to TMS therapy and who won't. Siebner and Thielscher envisage that in the future it might be possible to use the interleaved TMS/fMRI as a biomarker to see if a patient is likely to respond to the treatment. This opens up for the possibility of prescribing personalized or more targeted therapies to each individual patient. What they can say for sure is that each brain is different, and that patients respond to TMS in different ways.

> ***– TMS is our entry point in to the brain network [...] Combined TMS-fMRI thus allows us firstly to see how the brain is connected and secondly whether the information is actually reaching its destination.***
>
> **Hartwig Siebner**

TMS/fMRI is worth the effort

The remaining challenge now is to spread the enthusiasm and motivate more research to apply interleaved TMS/fMRI in their research: – We need to get TMS combined with fMRI and bring it to a level where people can see that the outcome is worth the effort, say Siebner and Thielscher.

Multifocal TMS: not that far away

Besides tailored brain stimulation and studies of the impaired brain, a new frontier in interleaved/online TMS/fMRI is multifocal TMS. In this technique you stimulate two or more areas at the same time, and then examine how this adds up in the brain.

This, however, is yet to come.

The Danish Research Center for Magnetic Resonance (DRCMR)

DRCMR, founded in 1985, is located at Copenhagen University Hospital Hvidovre and hosts more than 70 researchers from different medical and non-medical disciplines. In addition to the extensive MR facilities, which include 5 whole-body MR scanners for human use and a 4.7 T pre-clinical Varian MR-scanner, the DRCMR offers two separate labs for TMS experiments, EEG experiments and 2 rooms for psychophysical testing equipped with the most modern technology in close vicinity to the MR facilities.

The research teams at DRCMR are pursuing cutting-edge biomedical, functional and structural imaging research which is supported by substantial national and international funding.

The focus of the DRCMR is threefold: 1) to provide first class clinical examinations with magnetic resonance (MR); 2) to advance the use of applied MR within both clinical research and basic science with a strong focus on neuroimaging; and 3) to work on methodological developments of MR and thus refining the technique.

More information at www.drcmr.dk

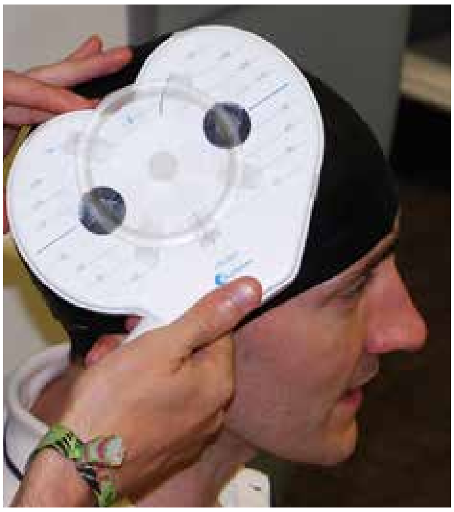
University of California, Berkeley :
10 quick questions for Ian Cameron at Helen Wills Neuroscience Institute

The Helen Wills Neuroscience Institute at University of California Berkeley, is an active, collaborative research community investigating fundamental questions about how the brain functions. Approaches from many disciplines (including biophysics, chemistry, cognitive science, computer science, genetics, mathematics, molecular and cell biology, physics, and physiology) are used to understand how the brain generates behavior and cognition, and how to better understand, diagnose and treat neurological disorders.

Ian Cameron, Postdoctoral Fellow at the University of California, Berkeley is conducting research with human volunteers, using functional Magnetic Resonance Imaging (fMRI) and Transcranial Magnetic Stimulation (TMS) to study complex brain functions such as decision making and the voluntary control over movement.

1) What is your main research-area of interest?
I study cognitive control. Specifically, I am interested in how neural signals related to the voluntary control over behavior can be mapped onto locations and networks in the brain.

2) How do you use TMS combined with fMRI in your research today?
I am looking at how TMS to the frontal cortex can alter fMRI signals in more sensory-related regions, such as the parietal and occipital cortex.



3) how long have you worked with the combination of TMS and fMRI?
4 months.

4) What caught your attention when you heard about TMS/fMRI?
As I was experienced with offline repetitive TMS followed by fMRI scanning, I became especially interested in the ability to study TMS influences on a trial-by-trial basis concurrently with event-related fMRI.

5) What has been the main obstacle in working with interleaved TMS/fMRI?
Positioning the coil and subject's head inside the MRI head coil, in order to get full brain coverage and allow for the monitoring of the subject's eyes using an eye-tracker. Everything has to fit in a confined space.

6) What has been the main discovery you have made using this technology?
The spatial resolution of TMS is remarkably precise. Moving the coil to a different location on frontal cortex by only 1 to 1.5 cm will produce very different activation patterns.

7) What do you hope to show/ obtain through your research by using this technology?
We hope that networks related to cognitive control can be mapped in part by applying TMS pulses to one region and measuring their influences in distal regions.

8) What impact could your research have on society?
It will allow us to examine the spread of TMS, and influences of TMS pulses on remote areas. This will allow us to directly study connectivity and map functional networks in the brain, even if the subject is at rest.

9) How will this technology be used 10 years from now?
I suspect that the development of new head-coil and TMS coil technology will allow for even more precise coil placement.

10) If you could give one piece of advice to researchers who consider interleaved TMS/fMRI, what would it be?
Consider the fMRI equipment, the head coil, and the position that the subject will lie in. Some experiments will be easier than others given these constraints.

Ian Cameron is here testing the MRI head coil with the MRi-B91 coil in place.

Helen Wills Neuroscience Institute

Neuroscience research at UC Berkeley spans four areas: Cellular & Molecular Neuroscience, Systems Neuroscience & Animal Behavior, Computational & Theoretical Neuroscience and Human Cognitive Neuroscience.

More information at http://neuroscience.berkeley.edu/

Interleaved TMS and functional MRI:
The research, the use, the future

Interleaved TMS concurrent with fMRI is a relatively new field within basic brain research. For an excellent overview of approaches of TMS combined with neuroimaging, consult with Siebner et al 2009[11].

This article provides an introduction to the field, including a brief update on selected research results the past 10 years and a look at the future of TMS/fMRI.

Interleaved TMS integrated with fMRI is used to study brain function connectivity in vivo and study how this connectivity may be changed by different interventions and pathologies. Connectivity is studied as regional Cerebral Blood Flow (rCBF) looking at blood oxygenation level-dependent (BOLD) contrast after TMS brain stimulation.

The test subject is placed inside an MRI scanner and exposed to TMS in different areas of the brain. The brain is then scanned and the process repeated in series as outlined in figure 1, until the experiment is finished.

A Siemens Magnetom Trio 3T scanner with a MagVenture MRi -B91 coil installed which makes it possible to expose the subject to repetitive Transcranial Magnetic Stimulation (rTMS) while being inside the scanner.

3 scans to elucidate whole brain activation patterns from 1-Hz TMS over left primary motor cortex. Both TMS excitation (110% motor threshold) and volitional movement of the same muscles caused blood oxygen level–dependent (BOLD) patterns encompassing known motor circuitry. The research team concluded that

A study along the same lines worked with induced vs. volitional movement[3]. TMS intensity was set to 50% MT and the subjects then performed volitional thumb movements that were acoustically triggered by the TMS coil clicks. Significant BOLD responses were observed in the motor system, in the bilateral audi-

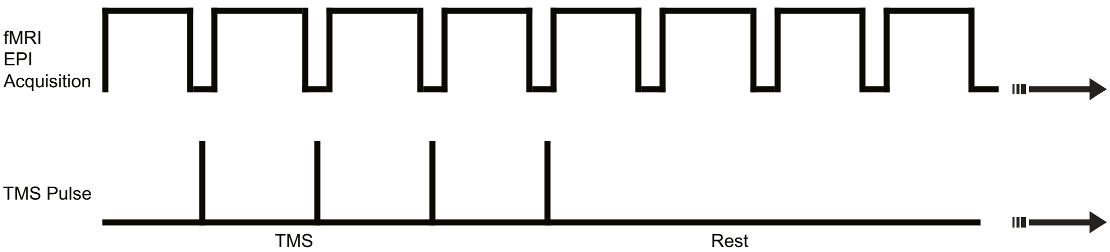


Figure 1: TMS pulses fMRI aquisition showing the process of interleaved TMS combined with fMRI.

No detectable difference between self-induced and TMS induced movements

Much attention has been devoted to study differences and similarities in rCBF between TMS stimulated movement of limbs compared to voluntarily movement (volition) of the same limbs[2-6].

In a study from 2005[2],TMS/fMRI was used on 11 subjects, each getting

the interleaved TMS/fMRI technique induced over primary motor cortex produces a whole brain pattern of BOLD activation similar to known motor circuitry from mimicked volitional movement, without any detectable differences. However, some differences may exist between time courses of BOLD intensity during TMS circuit activation and volitional circuit activation.

tory cortices, the ipsilateral inferior colliculus, and the bilateral insula (stimulated left M1/S1, SMA/CMA, thalamus ipsilateral to stimulated M1, bilateral putamen, and bilateral cerebellum). Volitional movement resulted in stronger BOLD response, but in a similar spatial activation pattern when compared to TMS induced BOLD response.

Real time monitoring of Cerebral Blood Flow

TMS used with Continuous Arterial

Spin Labeling (CASL), which makes it possible to measure the regional cerebral blood flow (rCBF), has also shown promising results[4].

The study showed the feasibility of interleaving rTMS stimulation with CASL imaging. In contrast to combining TMS with PET, this novel combination offers a better temporal and spatial resolution and does not utilize radiation.

The results presented demonstrate that the sensitivity of the employed CASL method was good enough to detect rCBF changes already at relatively low TMS intensities of 100% motor threshold (i.e., just eliciting finger twitches).

Extending the research to look at connectivity and networks

The effect of a continuous train of TMS applied to left dorsal Premotor cortex (PMd) and whether this would trigger context-specific activity shifts in remote premotor areas during externally but not internally guided movements was also studied[5]. The context-dependent effects of left PMd stimulation on motor activity in remote right-hemispheric cortical regions point to a critical involvement of left PMd in mapping external cues on appropriate movements. TMS increased rCBF in these cortical areas only for responses relying on a pre-learned associative visuomotor mapping but not for freely selected responses.

The data further suggests that the left PMd becomes part of a functional network comprising right-hemispheric and mesial motor regions that supports arbitrary visuomotor mappings with the left non-dominant hand.

Concurrent TMS-fMRI have been used to reveal causal interactions between remote but interconnected areas of the human brain by showing that circuits originating in the human frontal eye field could modulate activity in retinotopic visual cortex, in a manner that differentiates the central and peripheral visual field[9, 10].

TMS/fMRI shows the spread of locally applied TMS

Interleaved TMS/fMRI has been used to study connectivity in the human visual system[1]. Neurons are connected to other neurons; stimulation of one population of cells will evoke responses in synaptically connected brain regions. Thus, the area of the brain stimulated by TMS will affect activity in specific brain networks.

> ***Although TMS is only applied locally, the effects of TMS spread through existing connections within the cortical visual system.***

TMS applied to the occipital pole targeting striatal cortex resulted in activity in the lateral temporaloccipital region in both right and left hemispheres. Activity along the intraparietal sulcus was also registered. These are regions known to be visually responsive. Thus, although TMS is only applied locally, the effects of TMS spread through existing connections within the cortical visual system.

Sham TMS influences task performance

A recent study has examined whether pre-stimulus sham TMS can facilitate target detection[6]. The study showed that sham TMS caused a facilitation of reaction times when preceding the target stimulus by 150, 200, and 250 ms. Earlier and later time windows were not effective. Also, positioning the TMS coil ipsilateral instead of contralateral relative to the target stimulus improved the reaction times.

It could hereby be concluded that the clicking sound from sham TMS will influence task performance in multiple ways.

Helping refine therapeutic use of TMS

Interleaved TMS/fMRI has also been used to investigate the effects of lamotrigine (LTG) and valproic acid (VPA)[7]. These drugs are used to treat both depressions and bipolar disorder. Results indicate that both LTG and VPA have network-specific effects on effective connectivity within motor and corticolimbic circuits.

When TMS was applied over the motor cortex, both LTG and VPA reduced TMS specific effective connectivity between primary motor (M1) and pre-motor cortex (PMd), and between M1 and the supplementary area motor (SMA). When TMS was applied over prefrontal cortex, however, LTG alone increased TMS-specific effective connectivity between the left dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC).

In summary, LTG and VPA both inhibited effective connectivity in motor circuits, but LTG alone increased effective connectivity in prefrontal circuits. This suggests that interleaved TMS/fMRI can assess region- and circuit-specific effects of medications or interventions.

TMS to induce spatial neglect-like effects

A precisely timed pulse of transcranial magnetic stimulation (TMS) applied over the right posterior parietal cortex (PPC) can produce temporary visuo-spatial neglect-like effects[8].

During neglect-like behavior, the fMRI maps showed decreased neural activity within parieto-frontal areas. Such areas will often have lesions or be otherwise dysfunctional in patients with left neglect (e.g. often seen in stroke patients). Vertex TMS induced behavioral effects compatible with leftward response bias and increased

> ***Refining the technique and improving the usability is an on-going exercise.***
>
> ***Fortunately, a lot of research groups are more than happy to engage in this exercise and help [...] push the research even further.***

BOLD signal in the left caudate (a site which has been linked to response bias).

A few bumps on the road remain

Recent efforts have focused on how to validate interleaved TMS for fMRI studies and considerable energy has been put into resolving hardware issues from both users and manufacturers alike to reach solutions fit for proper research. Researchers ask for a plug and play solution, which has been very difficult to accommodate for the manufacturers of TMS equipment, due to the complexity of the technique.

> ***The integration of TMS with fMRI provides us with a unique tool to study human brain functional connectivity in vivo and assess how it can be altered by certain interventions, behaviors, or pathologies.***

Combined efforts between research groups and MagVenture, has led to the introduction of a complete system solution. This system comprises the TMS butterfly coil, modified stimulators, filters etc. and addresses all the sources of artifacts.

However, from the user's point of view, it still takes an effort to get sufficiently acquainted with the technology to obtain reliable and reproducible results. Therefore, refining the technique and improving the usability is an on-going exercise.

Fortunately, a lot of research groups are more than happy to engage in this exercise and help remove the occasional bumps on the road and hereby push the research even further.

The future brings more research using interleaved TMS/fMRI

The integration of TMS with fMRI provides us with a unique tool to study human brain functional connectivity in vivo and assess how it can be altered by certain interventions, behaviors, or pathologies.

Brain connectivity has until now been difficult to prove and quantify but interleaved TMS/fMRI is a groundbreaking tool which enables us to do just so. Not only are researchers provided with an entry point in to the brain, the future might also very well bring us cutting edge research to increase our understanding of the brain. This again might lead to Interleaved TMS/fMRI becoming a tool to refine the therapeutic use of TMS.

Interleaved / Integrated / Online / Concurrent / Combined TMS/fMRI?

They all refer to the same process: Stimulating the brain with magnetic pulses while depicting what happens in the brain at the same time with functional magnetic resonance imaging (fMRil).

The MRi-B91 coil from MagVenture.

References:

1. Halko MA, Eldaief MC, Pascual-Leone A. Noninvasive brain stimulation in the study of the human visual system. J Glaucoma. 2013 Jun-Jul;22 Suppl 5:S39-41. doi: 10.1097/IJG.0b013e3182934b31. PubMed PMID: 23733126.

2. Denslow S, Lomarev M, George MS, Bohning DE. Cortical and subcortical brain effects of transcranial magnetic stimulation (TMS)-induced movement: an interleaved TMS/functional magnetic resonance imaging study. Biol Psychiatry. 2005 Apr 1;57(7):752-60. PubMed PMID: 15820232.

3. Moisa M, Pohmann R, Ewald L, Thielscher A. New coil positioning method for interleaved transcranial magnetic stimulation (TMS)/functional MRI (fMRI) and its validation in a motor cortex study. J Magn Reson Imaging. 2009 Jan;29(1):189-97. doi: 10.1002/jmri.21611. PubMed PMID: 19097080.

4. Moisa M, Pohmann R, Uludağ K, Thielscher A. Interleaved TMS/CASL: Comparison of different rTMS protocols. Neuroimage. 2010 Jan 1;49(1):612-20. doi: 10.1016/j.neuroimage.2009.07.010. Epub 2009 Jul 14. PubMed PMID: 19615453.

5. Moisa M, Siebner HR, Pohmann R, Thielscher A. Uncovering a context-specific connectional fingerprint of human dorsal premotor cortex. J Neurosci. 2012 May 23;32(21):7244-52. doi: 10.1523/JNEUROSCI.2757-11.2012. PubMed PMID: 22623669.

6. Duecker F, Sack AT. Pre-stimulus sham TMS facilitates target detection. PLoS One. 2013;8(3):e57765. doi: 10.1371/journal.pone.0057765. Epub 2013 Mar 4. PubMed PMID: 23469232; PubMed Central PMCID: PMC3587629.

7. Li X, Large CH, Ricci R, Taylor JJ, Nahas Z, Bohning DE, Morgan P, George MS. Using interleaved transcranial magnetic stimulation/functional magnetic resonance imaging (fMRI) and dynamic causal modeling to understand the discrete circuit specific changes of medications: lamotrigine and valproic acid changes in motor or prefrontal effective connectivity. Psychiatry Res. 2011 Nov 30;194(2):141-8. doi: 10.1016/j.pscychresns.2011.04.012. Epub 2011 Sep 15. PubMed PMID: 21924874.

8. Ricci R, Salatino A, Li X, Funk AP, Logan SL, Mu Q, Johnson KA, Bohning DE, George MS. Imaging the neural mechanisms of TMS neglect-like bias in healthy volunteers with the interleaved TMS/fMRI technique: preliminary evidence. Front Hum Neurosci. 2012;6:326. doi: 10.3389/fnhum.2012.00326. Epub 2012 Dec 17. PubMed PMID: 23251130; PubMed Central PMCID: PMC3523259.

9. Ruff CC, Blankenburg F, Bjoertomt O, Bestmann S, Freeman E, Haynes JD, Rees G, Josephs O, Deichmann R, Driver J. Concurrent TMS-fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. Curr Biol. 2006 Aug 8;16(15):1479-88.

10. Heinen K, Ruff CC, Bjoertomt O, Schenkluhn B, Bestmann S, Blankenburg F, Driver J, Chambers CD. Concurrent TMS-fMRI reveals dynamic interhemispheric influences of the right parietal cortex during exogenously cued visuospatial attention. Eur J Neurosci. 2011 Mar;33(5):991-1000.

11. Siebner HR, Bergmann TO, Bestmann S, et al. Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul. 2009 Apr;2(2):58-80.

The MagVenture MRI installation
– What does it look like?

The MagPro installation for MRI consists of three main parts:
1) Equipment/storage room with MagPro unit
2) Scanner room with coil connected to MagPro unit
3) Control room.

The MagVenture MRi-B91 coil for interleaved TMS-fMRi is mounted in the coil holder device to ease the positioning inside the scanner.

Equipment/storage room

The MagPro unit is placed in the equipment/storage room. Power supplies and similar equipment for the scanner are also located in this room which is placed next to the actual scanner room.

Waveguides are led from the equipment room to the actual scanner room, using a a penetration panel for cable access through the wall.

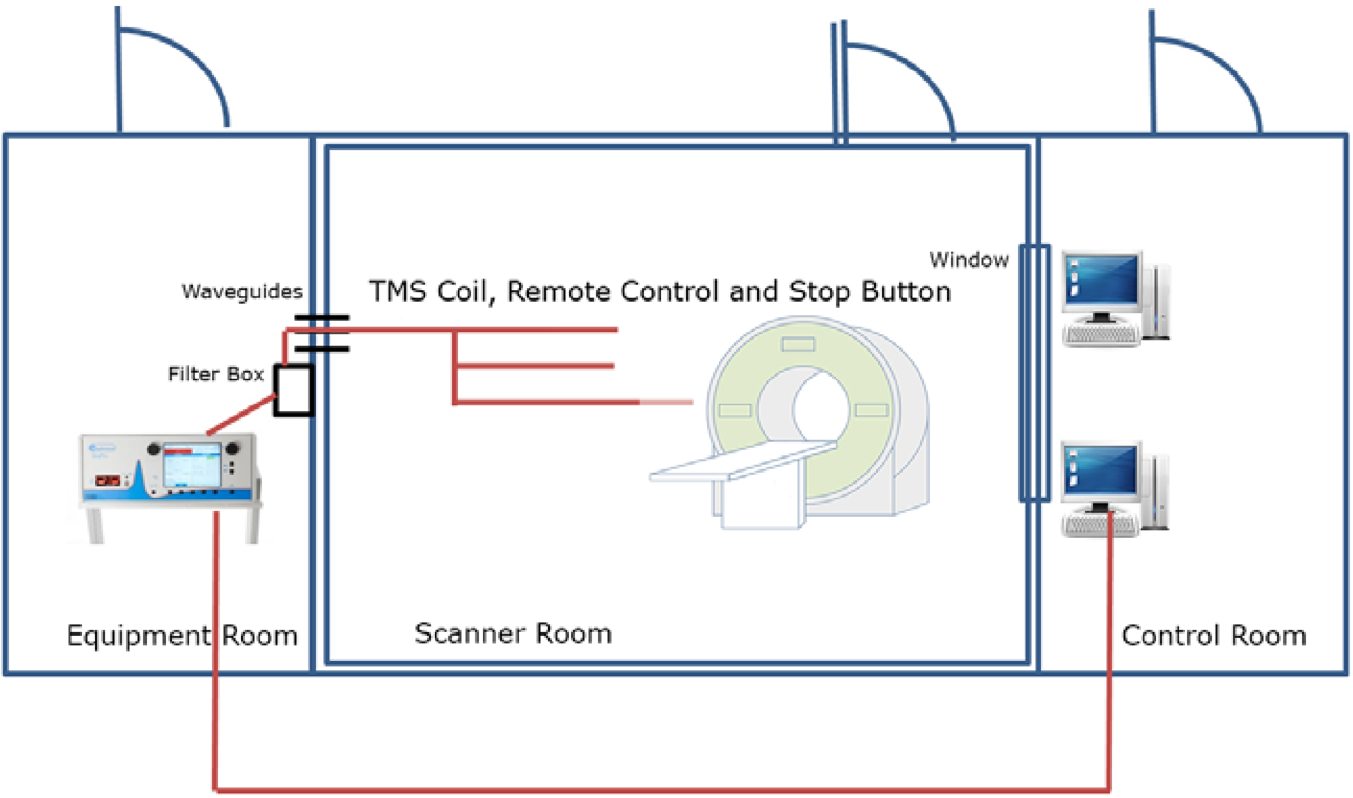
Scanner room

The scanner room is shielded against Radio Frequency (RF) interference. It is designed as a Faraday cage with full metal shielding in all walls, doors, ceiling and floor and has a metal laminated mesh window.
Inside the scanner room, the actual coil, a handheld remote control and a patient "panic button" is installed, all connected to the MagPro unit using a cable guide through a waveguide on the penetration panel.

The cable from the MagPro consists of a special extension cable with a Filter Box that prevents the RF signals to enter the scanner room via the coil cable.

Control room

The control room holds the PC's controlling the MagPro, scanner etc. The MagPro can be controlled from a PC with MagVenture's External Control Program and can be integrated into the existing scanner software.



The equipment room with the MagPro and the control room are in some cases located in the same room.

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.

Get the latest news on Magnetic Stimulation – sign up for the MagVenture Newsletter at
www.magventure.com

Follow MagVenture at
LinkedIn

MagVenture A/S
Lucernemarken 15
DK-3520 Farum
Denmark
Phone: +45 4499 8444
info@magventure.com

MagVenture, Inc
303 Perimeter Center North
Suite 300
Atlanta GA 30346
USA
Phone: +1 888-MAGPRO-4
infousa@magventure.com

MagVenture GmbH
Rheinstrasse 7
41836 Hückelhoven
Germany
Phone: +49 (0) 2433 970 290
infodeutschland@magventure.com

www.magventure.com