Medical University of South Carolina: 10 questions for Dr. Mark George at the Brain Stimulation Laboratory

Dr Stubbeman TMS Psychiatry: TMS is the future of psychiatry practice

Rowan University: John O’Reardon: FDA clearance will help spread TMS even further

TMS BrainCare: The success rate is so high that it sounds too good to be true

*) MagVita TMS Therapy System® is FDA cleared for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.
The recent 510(k) FDA clearance to market our MagVita TMS Therapy system for Major Depressive Disorder was, obviously, received with much enthusiasm here in MagVenture. This clearance will enable us to bring our products and services to the clinical psychiatric TMS community in the US. The US is, nevertheless, not a new market for us. We have in fact been present in the research community for more than a decade, and have established ourselves as a strong collaboration partner by developing TMS research solutions including several “first mover” features to several of the largest and most prominent research institutions in the country.

Dr. John O’Reardon, Professor of Psychiatry at Rowan University, is one of these researchers and he has personally worked with MagVenture’s MagPro device for the past 7 years. In a new trial, Dr George and his team will, with the use of MagVenture devices, test whether prefrontal TMS works to treat depression in war veterans. When asked what he thinks of the fact that there are now four FDA cleared TMS devices on the market, he responds: “this is good news. A rising tide floats all boats and we have lots of boats now.”

Dr. Mark George of the Medical University of South Carolina in Charleston and a true TMS pioneer has used MagVenture equipment for several years. In a new trial, Dr George and his team will, with the use of MagVenture devices, test whether prefrontal TMS works to treat depression in war veterans. When asked what he thinks of the fact that there are now four FDA cleared TMS devices on the market, he responds: “this is good news. A rising tide floats all boats and we have lots of boats now.”

Dr. George’s reaction well reflects the positive responses we have received and the general consensus that this clearance will first and foremost help to disseminate TMS even further, and thus allowing more patients to receive the treatment.

Stig Wanding Andersen
CEO, MagVenture

*) MagVita TMS Therapy System® is FDA cleared for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.
1) How did you first become involved in TMS?
I first encountered TMS when I was doing a research fellowship in 1989 at University College London. I was doing brain imaging with PET and SPECT, and was interested in the brain regions involved in regulating emotion. When I saw John Rothwell [professor of neurophysiology at the Institute of Neurology at Queen Square, ed.] using TMS in his motor lab to study the motor system, I immediately wondered if we could use it to investigate brain circuits involved in emotion regulation, and perhaps even treat diseases like depression.

2) For you personally, what was your main reason for choosing to work with TMS?
Imaging alone was insufficient. Brain activity during a task or state could be due to the task or state, or could be the brain’s reaction to the core activity, or could be merely incidental.

3) How was TMS perceived in the ‘early days’?
Back then all of these ideas were heretical – regional neuroanatomy of depression, brain basis of emotion regulation, non-invasively and without causing a seizure stimulating someone out of depression.

I later did the first clinical work at the National Institutes of Health (NIH) in Washington, with Dr. Robert Post. The going was still rough as there was much skepticism – getting asked to leave an ECT meeting, and having my senior boss at the NIMH tell me I could not talk to the press about TMS as they did not want to ‘sully the NIH name.’

Wouldn’t it be great if we could get 70% remission with only a few hours work?
Mark George

4) Seen in the infamous hindsight, what would have been especially nice to know back then?
The FDA was concerned about TMS causing a seizure and the potential effects of lots of pulses. They thus limited our early studies in terms of the intensity of stimulation. We underestimated the number of pulses needed, and the number of weeks we needed to stimulate.

I wish we had been more aggressive in pushing the parameters of stimulation. I think we underdosed for well over a decade, and may be still underdosing.

5) What do you consider to be among the most profound discoveries made?
That it worked is truly amazing. We did double blind studies from the beginning, but I was always worried that the effects were not going to replicate for whatever reason. I was very pleased when Dr. Saxby Pridmore, whom I had never met and who was working in Tasmania, Australia, started replicating our results, and showing changes in a biomarker called the dexamethasone...
suppression test (DST) [DST is used to assess adrenal gland function by measuring how cortisol levels change in response to an injection of dexamethasone. In conditions such as depression, dexamethasone can prevent cortisol levels from going down, ed.].

6) Even though we are seeing very promising results, there are still some patients with MDD whose condition does not improve with TMS. Will it be possible for more patients to respond positively to the treatment?

I am an optimist. I am confident that we can and will continue to refine and improve TMS for treating depression, at least approaching the efficacy of ECT (60% remission). There are lots of candidate clues for improvement.

It is important to remember that many of the methods we use now for treating depression were educated guesses that have not been fully explored. These involve total dose (number of stimuli), different dosing regimens (multiple daily rather than once daily), frequency matching to the individual, or frequencies like theta burst that may be more powerful at changing the brain, better targeting, or combining TMS with talking therapy or special medications.

There is still a lot to work on. It would be unbelievable if our educated guesses turned out to be the best solutions.

7) What, within the field of TMS research for the treatment of MDD, do you consider to be among the biggest challenges you are facing today?

TMS for treating depression, as we do it now, is terribly inefficient, requiring many hours in the TMS chair. We need to figure out how to reduce this inefficiency and thus make it less costly, both to patients, doctors, and insurers. Wouldn’t it be great if we could get 70% remission with only a few hours work?

There are lots of studies with TMS in almost every major brain disease. Some of the more promising areas currently are acute or chronic migraine, pain (either post-surgical or chronic), OCD, PTSD and addictions.

8) With MagVenture’s recent FDA clearance for depression treatment, four FDA cleared systems are now available. What impact will this have in the US?

I think this is all good news. A rising tide floats all boats and we have lots of boats now. This means that not only one manufacturer has to do battle with insurance companies, but we now have a larger industry to fight these battles. I think this competition will drive down costs and spur competition and innovation.

9) Do you expect to see many new TMS treatments emerging in the next 10 years or so? Where do you see the most potential in terms of treatment?

Cooperative Study Protocol #556 is chaired by Dr. Jerry Yeseved at the Stanford VA and designed to test whether prefrontal TMS works to treat depression in veterans. It is thus more ‘realistic’ than the pivotal NIH, Neuronetics and Brainway trials, which were antidepressant medication-free studies in patients without substantial comorbidities.

The VA trial allows patients to stay on their medications, and many of them have PTSD and prior substance abuse.

MagVenture won the competitive bid for the TMS device. We hope to complete enrollment in the late spring of 2016.
Dr. Stubbeman TMS Psychiatry:  
TMS is the future of psychiatry practice

With a remission rate of 80%, Dr. Bill Stubbeman’s clinic attracts patients from across the USA, Japan and Canada who have struggled with depression for years. Stubbeman hopes that Theta Burst treatment in combination with neuronavigation will one day become the standard of care instead of the currently used protocols.

At his psychiatric clinic in West Los Angeles, Dr. Bill Stubbeman is treating patients suffering from refractory major depression. Five years ago he began offering TMS treatment at his practice after having extensively researched TMS and felt that it was the future of psychiatry practice. His patients have typically had a lifetime struggle with depression and have failed to receive benefits from medication or even Electroconvulsive Therapy.

“We have an 80% remission rate using a high frequency protocol combined with neuronavigation. All of our patients who have reached remission with TMS were previously severely refractory,” explains Dr. Stubbeman.

Usually the patients find his clinic after having well-researched TMS and neuronavigation, but he also gets referrals from colleagues who have been unable to bring their patients to remission.

“Many of my patients are skeptical when they first come to my clinic because nothing else has worked for them. Luckily, TMS has a low placebo effect, yet high remission rate. Education about TMS and attentive care allow patients to better evaluate TMS results. When nearing the end of treatment, all patients are generally amazed that the results are unbelievable yet real, and they hope that it lasts,” says Dr. Stubbeman who is afforded a lot of gratitude by patients finally in remission who are very appreciative of their treatment results.

When current patients are in remission or moving toward remission, that is a good day. When TMS is a known option for those who are not getting medication benefits, and they are in my office getting well, that’s a great day,” says Bill Stubbeman who is motivated by the fact that he is able to help people who have failed all other treatments get their lives back. Unfortunately TMS is not that well-known among psychiatrists.

“It is my impression that most psychiatrists in the USA are not very familiar with TMS and its high potential for treating patients who have failed everything else. Gradually, TMS is becoming more known to the general public through word of mouth and it is being covered on more and more insurance policies,” says Dr. Stubbeman.

An expensive treatment, but…
The price for a TMS treatment remains the Achilles’ heel for many patients, but according to Dr. Stubbeman it is also necessary to take into account the long term cost of psychiatric care, including therapy, medications, hospitalization, and loss of...
Dr. Stubbeman graduated with high honors from Princeton with a degree in Mechanical and Aerospace Engineering and received his MD from Columbia University. He began his training at UCLA as an Ear, Nose and Throat Surgeon specializing in auditory pathology, but his growing interest in the brain caused him to switch focus to psychiatry. He subsequently built a private psychiatry practice in West Los Angeles specializing in treatment-refractory psychopharmacology.

After realizing the potential of TMS to help patients that were beyond the reach of medication, he changed the focus of his practice to TMS treatment.

Dr. Stubbeman hopes to convince more doctors to use MRI-guided neuronavigation. With Neuronavigation you can plan stimulation areas and monitor the correct positioning of patient and coil.

All of our patients who have reached remission with TMS were previously severely refractory.

Dr. Stubbeman

More information at: www.drstubbeman.com
Dr. John O’Reardon, Professor of Psychiatry at Rowan University and noted researcher of neuromodulation techniques, welcomes the FDA clearance of MagVenture’s MagVita TMS Therapy System for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

In July 2015, MagVenture was the fourth and thus the latest TMS manufacturer to receive an FDA clearance. Dr. John O’Reardon, who has extensive research experience within the field of TMS, sees this as a positive development, both from the perspective of a researcher and a clinician. He believes that the clearance will not only provide a healthy competition to the market, but will also further encourage insurance companies to provide meaningful reimbursement for the procedure.

**Global perspectives**

On a global scale, John O’Reardon believes that the FDA clearance could also impact the dissemination of the TMS technology, both within clinical practice as well as in research. “More psychiatrists will start doing TMS and when good clinical results are observed this will create a strong word of mouth effect which will also encourage research specific to this particular device,” he says.

**Potential pricing advantages, reliable cooling and low noise**

John O’Reardon has been using MagVenture’s TMS equipment for the past 7 years. “From a psychiatrist’s point of view, MagVenture has some advantages,” he explains. “There are no extra costs for disposables. This shaped differently this is helpful. The noise level is reasonable. Also there has been little in the way of technical glitches, in my experience. It is important not to have these problems as you have a patient standing there waiting for treatment. The last thing you want is not to be able to do the session,” John O’Reardon stresses.

**ECT research led to TMS interest**

John O’Reardon’s interest in TMS emerged in the mid 90’s while doing a fellowship in Psychopharmacology and administering ECT. He read a report in Neuro Report which described the treatment of 6 patients using a new technology called TMS written by Mark George MD [see our interview on page 3, ed.]. It piqued his interest as for the first time it appeared possible to do brain stimulation in the office. “I saw the potential advantages over ECT which included time efficiency, convenience for the patient and lower side effects, including the absence of cognitive impairment,” he says.

In O’Reardon’s view, TMS will remain complementary to ECT but will not replace it. “ECT has the advantages of being more rapidly acting, more efficacious overall, and better if there...
is marked suicidality. TMS, however, will be earlier in the treatment algorithm than ECT with fewer side effects and may in fact work if ECT has failed. We found [Connolly et al, 2012 J Clin Psy, ed.] that there was 40% chance of success with TMS if ECT had already failed," he says.

**New TMS modalities**
Theta Burst, a patterned form of rTMS, is another treatment modality which John O’Reardon believes may ultimately have more promise than the standard 10Hz TMS protocol and further mentions sTMS (synchronized TMS) which is currently in trials and offers the potential of EEG-based TMS. According to Dr. O’Reardon, the possibility of at-home treatment may become a new frontier in treatment delivery as it would, obviously, be enormously convenient for the patient.

**Combination and augmentation approaches**
Another important issue will be the development of combined medication and psychotherapy strategies. There are two basic approaches here, combination and augmentation approaches. With a combination approach, an antidepressant and TMS are started together at the same time in the hope of a more complete result. In the augmentation approach, in the case of non-response or non-remission, TMS is added at 6 weeks to augment or enhance the antidepressant effect. Cognitive therapy can also be used to activate the prefrontal cortex immediately prior to TMS delivery to enhance its efficacy. This is a type of augmentation strategy for TMS but these approaches have yet to be studied, according to Dr. O’Reardon.

**TMS ‘dream machine’**
When asked to define his ‘TMS dream device’, John O’Reardon describes it this way: “It would be more compact, cheaper, provide an all-in package including theta burst, with a coil curved better to fit the shape of the head, with guidance from research as to how to optimize the TMS effect with medications and psychotherapy, and ability to deliver a treatment protocol in 1/5th of the time currently needed.”

---

**John O’Reardon**

Dr. John O’Reardon received his medical degree from University College Cork in Ireland in 1984. He is board-certified in primary care in Ireland and the UK.

He completed his residency in Psychiatry at the University of Pennsylvania. Post-residency he did Fellowships in Psychopharmacology and Cognitive Therapy.

His areas of interest clinically are treatment-resistant mood disorders and neuromodulation therapy (ECT, TMS, DBS, VNS, dTMS, sTMS and tDCS). Research wise his main interest has been the development of new neuromodulation treatments.

He has been involved in large scale trials in TMS, VNS, DBS, sTMS and tDCS. He has over 100 scientific publications, including 29 in the TMS field.

More information at: [www.rowan.edu/som/index.php](http://www.rowan.edu/som/index.php)
35 years ago, Robert McMullen, MD opened his private practice in general psychiatry on the West Side of New York City. In 2010, he added TMS depression treatment to his long list of treatments.

Being a psychiatrist, Dr. Robert McMullen found himself looking for a way to treat his many patients suffering from major depressive disorder who did not respond to the medication he prescribed to them. To Dr. McMullen, TMS was the solution. “I was first interested in TMS because I had been reading about its benefits for years, and I needed an alternative for the many patients who failed to achieve full remission from antidepressants,” says Robert McMullen of his decision to finally invest in TMS equipment to make the – at the time – novel treatment available to his many patients.

No per-use fee
“The purchase price of the TMS equipment that I first bought was very expensive, and it has actually cost me a lot of money that I had to pay a fee to the company for every treatment I did. I am therefore very pleased that it is now possible to get FDA cleared TMS equipment from other manufacturers such as MagVenture who do not operate with a ‘per-use fee’. That makes a big difference to me and my practice,” says Robert McMullen.

The success rate is so high that it sounds too good to be true, so many psychiatrist do not believe it.

Robert McMullen

TMS is worth travelling for
So far, around 300 patients with major depressive disorder have undergone TMS treatment at TMS BrainCare. “What has sustained us has been the enormous benefits, as well as long acting benefits, for so many of my patients,” says Robert McMullen, who in the past five years since he first began to offer TMS has been treating men and women of all ages from all over New York City and even further away.

Robert McMullen

MD Robert McMullen graduated from Georgetown University Medical School in Washington DC in 1976.

He is founder and owner of TMS BrainCare in New York. For 35 years he has had a private practice in general psychiatry. He treats patients with a wide range of mental illnesses. He specializes in the treatment of mood disorders and anxiety disorders and is particularly experienced with the treatment of resistant depression.

In 2010, he began offering TMS treatment.

More information at: www.tmsbraincare.com
50% success rate
Only a few of Dr. McMullen’s patients have to travel a long distance to get to the clinic. However, even to those patients who have a long commute, the benefit is so large that it is worth it, he explains. The high success rate of over 50% also explains why the patients willingly pay for the treatment themselves even though it is not covered by their insurance.

“It makes it more affordable for patients if we charge them $100 and accept that as full payment if we cannot collect from insurance. We are much more likely to have a patient agree to treatment if they only have to pay $100 per treatment,” says McMullen who sees great advantages in the research currently being done with Theta Burst Stimulation (TBS) which can shorten the treatment time by more than 30 minutes per session.

“If I could use TBS for many of my patients, it would make it much easier to just charge $100 per treatment,” says McMullen.

Number of treatments is important
The usual and FDA cleared full treatment protocol for TMS depression treatment is 5 treatments a week for 6 weeks, but McMullen believes that the number of treatments is what is important. Therefore he is open towards giving the treatment less often.

“If the distance and logistics are very difficult for my patients, I will allow them to come in much less frequently – if for example the patient is only able to come in once a week, that patient will in my belief still benefit from the treatment. It will just take longer to get the full benefits of the treatment,” says McMullen.

Strange sounding treatment with magnets
Even though depression treatment with TMS is successful, the success is ironically enough also keeping the number of referrals to McMullen’s practice down. TMS is simply too good to be true, believes McMullen who still gets almost half of his patients from his own practice, although other psychiatrists are finally beginning to refer their patients who do not respond to antidepressants to TMS treatment.

“It has been slow for other psychiatrists to begin to refer to me, although this is picking up. I think that referrals are difficult because of three things. First, the success rate is so high that it sounds too good to be true, so many psychiatrists do not believe it. Secondly, it is difficult to induce a patient to go to a strange doctor for a strange sounding treatment with magnets that cost thousands of dollars with no guarantees that there will be results. And thirdly, TMS is not as widely known and accepted as ECT. It is always surprising to me that some people will choose to have ECT rather than TMS,” says McMullen and concludes that he would definitely like to promulgate TMS more.

FDA cleared*: MagVenture’s MagVita TMS Therapy System® for treating Major Depressive Disorder

Benefits include:

• Very low operating costs: no per-use fees or costly disposable components to the system.

• Safety and efficacy rates that are equivalent to other FDA cleared rTMS devices, including a simple design and workflow for optimal ease of use.

• FDA cleared and CE approved.

More information at www.magventure.com

*) MagVita TMS Therapy System® is FDA cleared for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.
MagVenture donates new TMS coil to humanitarian hospital in Ukraine

For the past 5 years, The Gerontology Institute at the National Academy of Medical Sciences of Ukraine has successfully been using a MagPro stimulator from MagVenture for the rehabilitation of patients suffering from stroke and head injuries (including members of the anti-terrorist association). MagVenture has now donated a new Cool-B65 coil as well as a super flex arm for the institute.

Above, Dr. Alexandra Semenova from the Gerontology Institute is seen with the new MagVenture Cool B65 coil.

Paired-Pulse Composer for MagPro X100

With this program it is possible to set all the upper and lower randomization ranges and create a randomized paired pulse protocol within these ranges which can be executed on a MagPro X100. The protocol can easily be exported to a CSV file format, where it is possible to customize a protocol before loading it again. An unlimited number of protocols can be saved and loaded again at a later stage. Press play and the protocol is executed on the MagPro. In order to get fully reliable research results, the realized outcome of the paired-pulse protocol is displayed.

It is possible to choose between monophasic, biphasic and half sine waveforms as well as current direction. Further, a specific randomized protocol is easily repeated with a different Motor Threshold ratio. Reports of all the executed protocols including the realized outcome of the MagPro can be printed.

Upcoming TMS courses

What: TMS Workshop
When: 7-9 December 2015
Where: Danish Research Centre for Magnetic Resonance, Hvidovre, Denmark

What: Advanced TMS Symposium
When: 10-12 March & 22-24 September 2016
Where: San Fransisco, USA

What: Maastricht TMS Certification Course
When: 26-27 May 2015
Where: Maastricht University, The Netherlands

New A/P coil available

Due to increased use of our Cool D-B80 coil and a derived increased interest in conducting double-blinded clinical research studies with this exact coil, MagVenture introduces an A/P version (Active/Placebo). The Cool D-B80 A/P coil functions as both active (A) and placebo (P) coil. The symmetrical design with no indication of active vs. placebo side makes it ideal for double-blinded studies.

It has a simple software set-up allowing for blinding of both the patient and the operator. With a built-in orientation-switch to determine which side of the coil to be placed towards the patient, the software tells the operator whether to turn the coil or not. The coil has an adjustable output for current stimulation of the patient’s skin synchronously with the magnetic stimulation pulses.

MagVenture at rehabilitation convention

The European Congress of Neuro-Rehabilitation (ECNR) takes place in Vienna on December 1-4.
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 and k150641). The intended use is treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

k061645, k091940: The intended use is for 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 (except the above cleared intended use).

For further information please contact MagVenture.

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

Follow MagVenture at LinkedIn

MagVenture A/S
Lucernemarken 15
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
Schmelzerstraße 25
47877 Willich
Germany
Phone: +49 (0) 2154 814 56 50
infodeutschland@magventure.com

www.magventure.com

© MagVenture A/S • 511-0301 • www.magventure.com