Brain Stimulation and its Role in the Assessment and Management of Movement Disorders

Ayan K. Dey, MD, PhD Candidate, Institute of Medical Science, Faculty of Medicine, University of Toronto

Dr. Robert Chen

This article shares the transcript of a recent interview with Dr. Robert Chen, senior scientist and staff neurologist at the Toronto Western Research Institute. Dr. Chen specializes in movement disorders and his research focuses on investigating the pathophysiology of movement disorders and the action mechanism of brain stimulation techniques for the treatment of movement disorders such as Parkinson's disease.

UTMJ: Could you briefly describe your career path and what brought you to studying movement disorders?

RC: I went to medical school in England after high school as that's how the British system is set up. I completed my first three years at Cambridge and that is actually when I first became involved in research. My first research project was in the field of reproductive immunology. Then I started my clinical training in London, which is when I started becoming interested in neurology, clinically. I liked the detailed neurological exam, and using my knowledge of anatomy and physiology to deduce a localization and diagnosis. After finishing my internship in London, England, I came to Canada. In Canada, I completed a Master's degree under the supervision of Dr. Peter Ashby who was a neurologist and neurophysiologist based in Toronto. It was during this time that I was introduced to neurophysiology research and also to movement disorders. I found movement disorders very interesting and again I was mainly drawn to the clinical aspect. I was fascinated by seeing all the different types of movement disorders in patients and trying to figure out the right diagnosis. After my research year, I began my residency in internal medicine at Queens University, followed by specialty training in neurology at Western University wherein my interest in movement disorders continued to grow. After residency, I did a fellowship at the NIH where I continued to research movement disorders using combination of neurophysiology and imaging. After completing my fellowship I was recruited to a faculty position in Toronto where I have been practicing ever since 1998.

UTMJ: Brain stimulation is currently an area of great interest in the field of neuroscience, could you describe what brain stimulation refers to?

RC: Broadly speaking, there are two types of brain stimulation; invasive and non-invasive. My research program focuses on both types of stimulation. In non-invasive brain stimulation, no surgery is required. The most popular form of non-invasive brain stimulation is transcranial magnetic stimulation or TMS for short. TMS involves applying a magnetic coil to the surface of the head which generates a magnetic field which passes through the scalp and induces a current at the target site, thus stimulating the brain. Depending on the frequency used, TMS can be used to stimulate or inhibit a given area. That said, TMS can be used to simulate the effects of a focal lesion in a human subject. Another type of non-invasive stimulation is called transcranial direct current stimulation. This does not actually produce neuronal activation but biases the neuronal membrane. As for invasive brain stimulation, the most well-known form is deep brain stimulation or DBS. DBS involves implantation of an electrode into the brain. In the context of movement disorders, this electrode is generally put into the basal ganglia. These electrodes are typically connected to an implanted pulse generator which consists of a battery pack. These generators provide continuous stimulation but can also be programmed to give intermittent pulses.

UTMJ: How did you become interested in brain stimulation for the study of movement disorders?

RC: I got introduced to magnetic brain stimulation during my masters but at that time, our understanding of brain stimulation was very rudimentary. Then during residency after attending a few neurology conferences, I started becoming interested in using brain stimulation to study the motor cortex. Nevertheless, it was mainly during my fellowship at the NIH that I

Corresponding Author:
Ayan K. Dey
Email: ayan.dey@mail.utoronto.ca

further developed my knowledge of brain stimulation using transcranial magnetic stimulation (TMS) and how to use it to study brain plasticity in the context of movement disorders. It was at this time that I truly started to appreciate the value of brain stimulation for exploring the pathophysiology of movement disorders and the potential to use it therapeutically.

UTMJ: At present, what role does non-invasive forms of brain stimulation play in the assessment and management of movement disorders such as Parkinson's disease? Do you see it as more of a research tool, assessment tool or treatment option?

RC: Well, I think all of these apply. As a research tool it has been very useful. It has been used to understand brain excitability and plasticity, to further understand the pathophysiology of Parkinson's disease and how treatment options such as deep brain stimulation work. It also has a limited role as a diagnostic tool, for example, distinguishing some types of parkinsonism from typical Parkinson's disease. TMS has also been examined as a treatment option. Currently repetitive TMS (rTMS) is an approved treatment option for medication resistant depression in both Canada and the US. There have also been a number of studies that have looked at using TMS as a treatment for Parkinson's disease with a recent meta-analysis showing that it is benefit when given in addition to conventional drug treatment. That said, while TMS seems like a promising treatment option, more work needs to be done in the form of definitive, large randomized control studies to establish efficacy.

UTMJ: Building on the idea of TMS as a treatment option, how does TMS differ from DBS for the management of Parkinson's Disease? From my understanding DBS has been largely successful for treating those with drug resistant Parkinson's Disease. Do you think TMS could ever replace DBS?

RC: I think they have very different roles. Deep brain stimulation as you mentioned is very effective for those found to be suitable for it. However not everyone is suitable for the surgery. For some individuals the risk of mortality or morbidity is too high. Moreover as it is invasive, the procedure is inherently more risky with risk of hemorrhage or infection. So DBS is really for more advanced patients in whom medial therapy is insufficient. On the other hand, TMS, if proved efficacious by further research, can be applied much more widely. The number of people who could potentially benefit from TMS would be far greater because it is a non-invasive treatment. However because it is a non-invasive procedure, the effects of TMS are not permanent and thus patients often require multiple sessions to produce a lasting effect. Thus, I do not think it will ever replace DBS but it could be used as an adjunctive treatment for additional effect.

UTMJ: Have there been any clinical trials aimed at assessing the efficacy of TMS? If so, what is the additional benefit of TMS beyond what can be provided by conventional pharmacological treatment?

RC: Most trials involving TMS introduce it as an add-on therapy for patients who are already on medication. Most of these trials focus on the motor symptoms of Parkinson's Disease such as tremors and thus use the Unified Parkinson's Disease rating scale as a primary outcome measure. In this regard, preliminary studies have demonstrated some additional benefit of combination therapy using TMS and medication relative to medication alone. However there is recently interest in assessing whether TMS can help manage some of the non-motor symptoms of Parkinson's Disease such as constipation, fatigue, numbness and depression which are not as effectively managed by drug therapy. Indeed, a small number of trials have reported reductions in depression symptoms in those with Parkinson's disease following repetitive TMS. Nevertheless, to date very few studies have investigated the effect of TMS on other non-motor symptoms and thus further study is needed to see if TMS would be of benefit. Overall it is premature to definitively claim whether TMS is of additional benefit, but preliminary results are promising.

UTMJ: Is TMS affordable? Is the added benefit clinically significant enough to warrant the additional cost?

RC: A TMS machine itself is not very expensive relative to other medical equipment. The main expense when using TMS is that someone has to be there to administer TMS….so there is a personnel cost, with sessions running between 20-30 minutes or more. Also because it requires patients to travel to a treatment site, often repeatedly, there is also a significant time investment and cost of travel on the part of the patient. These costs add up as a typical treatment course would be 10 sessions over 2 weeks or 20 sessions over 4 weeks. That said, at present most medications are cheaper than TMS but what we are trying to still determine is if TMS can bring clinically significant benefit beyond what can be achieved by medication. On that note, there are lower cost non-invasive tools such as transcranial direct current stimulation which can be bought at a significantly lower price and may potentially be safe and feasible for home use by the patient with proper training. There are ongoing studies looking into this.

UTMJ: Are there any long term side effects of repeated TMS or brain stimulation?

RC: TMS has been around since the mid-1980s and so far there are no known long-term side effects. Nevertheless, there are some possible risks that we do explain to patients before treatment. The most concerning risk is the induction of seizures. Previous studies have reported that seizures can be induced by rTMS. This is mainly related to the parameters used; namely the intensity and frequency of the pulses. For this reason there are currently guidelines to limit the stimulation parameters to make it safe. Thus the risk of seizure induction is very low in practice. There are also concerns regarding the sound of the machine so we provide earplugs to participants.

UTMJ: What do you feel has been the overall impact of brain stimulation technology and what do you see in the future?

RC: Deep brain stimulation (DBS) certainly has changed the management of patients with movement disorders as it has been used to effectively treat individuals who have significant complications with medication. DBS is also being investigated in a number of other conditions such as depression and Alzheimer's disease. Looking into the future, I believe there will be significant innovations in DBS. Currently, what we use is an open loop system. In an open loop system, we set parameters which we test clinically and then program into the device. In the future what I think will happen will be the development of close loop systems where the intensity and timing of stimulation will vary based on real-time patient data gathered through biosensors. In this way the device will set its own parameters that are optimized for a given patient and will be capable of automatically adjusting parameters as needed. Another technology that I see in the horizon is the use of brain computer interface wherein patients will be able to control assistive devices using brain signals.

UTMJ: What about advanced brain imaging techniques such as functional MRI and diffusion imaging? How do you feel they have contributed to the management of brain disorders?

RC: Functional and diffusion imaging tools are excellent research tools that have helped improve our understanding of a lot of neurological disorders. With functional MRI informing us about changes in functional connectivity in the brain and diffusion imaging helping us visualize changes in white matter tracks. These tools are now starting to play a bigger role in clinical decision making. For example, neurosurgeons may now use fMRI and diffusion imaging when planning their operations so as to minimize side effects arising from disruption of important tracts or brain regions. Overall, while MRI has been around for a long time, I can see these newer techniques gradually becoming more integrated into clinical practice with time, in addition to being very useful in research.

UTMJ: Finally, it has been proposed that as technology becomes more rooted in the management and assessment of disease we are losing touch with behavioural and functional outcome measures – do you agree with this? If so, what are some of the consequences?

RC: I would say no. Having said that, I would say we do need to be careful in our overall approach. We need to remember to treat the patient not the "scan". Sometimes imaging markers, while informative, may not directly relate to the clinical status of the patient. For example, an MRI or positron emission tomography (PET) scan may improve without corresponding improvements symptoms reported by the patient. Also there is an increased danger of over-interpreting abnormal physiological/imaging parameters. Treating a patient with abnormal readings may or may not actually improve clinical outcomes. This is because abnormal readings could represent many things. It could be a compensatory response or a consequence of a disease rather than the cause. So I think one needs to be careful in interpreting the meaning of abnormal test results. It is important to always relate test results to the clinical status of the patient. Nevertheless, I think technology if we use it properly can help us identify surrogate and subclinical markers of disease before more overt clinical markers appear. If such markers can be developed and proven to be reliable, treatment can begin earlier which may in turn improve clinical outcome. Ultimately, one has to keep in mind, what really matters is the clinical outcome.

UTMJ: That concludes the interview questions. Thank you Dr. Chen.

RC: My pleasure.