Debating Deep Brain Stimulation

RECENT STUDIES ON THE DIFFERENT WAYS DEEP BRAIN STIMULATION (DBS) CAN BE APPLIED ARE BEGINNNING TO CATCH UP WITH WHAT IS CURRENTLY BEING PRACTISED

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The idea of surgery goes back at least 7,000 years, when boring holes in skulls was all part of a day's work for the unqualified surgeons of the Neolithic period. Archaeological evidence shows this primitive intervention was performed for health purposes, presumably to cure then-incomprehensible problems such as headaches and epilepsy. Given the archaic tools and limited breadth of their knowledge, it is remarkable that people back then had already made the leap of associating the brain with behaviour, albeit with a superstitious logic in which which a hole in the skull could provide an exit for the departure of the evil spirits responsible for such abnormalities.

Today, surgeons are a lot more delicate when they set out to alleviate the symptoms of neurological diseases like Parkinson's disease (PD). The surgical process known as deep brain stimulation (DBS) involves making a small hole in the skull through which to insert electrodes into a specific region of the brain. Electrical currents are then delivered to the targeted area from a neurostimulator placed elsewhere, usually the chest. The technique relieves the motor symptoms of PD, such as tremors and shaky movements, allowing patients to regain better control over their bodies in the long run, compared to conventional drug treatments like levodopa, in which the medication's effects wear off after five to 10 years.

Such extensive links between the brain and body would have baffled our ancestors, and they would have remained obscure to the generations who came after them. In fact, we still don't know how dopamine neurons in the brain degenerate and cause PD, although we can identify a few risk factors. So, while Deep Brain Stimulation (DBS) is a well-established form of therapy for PD and other neurological disorders like dystonia, our knowledge is accompanied by debates and differences of opinion about how it can be applied to sort out the mess in our brain circuitry.

Patient Selection

Conventional practice and the FDA's 2002 approval of DBS confine its use to treating late-stage patients whose symptoms cannot be controlled by medication. However, Prince of Wales Hospital in Hong Kong has been performing DBS on both early-stage and late-stage patients. The first patient to undergo the procedure at the hospital in 1997 was classified as being in the early stages of PD. "His cognitive abilities were fine, but one of his hands was suffering from tremors to the extent that he couldn't hold chopsticks or pick up a newspaper to read," recalls Professor Poon Wai Sung, Chair Professor and Chief of Division of Neurosurgery at the Department of Surgery in Prince of Wales Hospital at the Chinese University of Hong Kong.

This resonates with a landmark study known as EARLYSTIM involving researchers from French and German institutions, including the University Hospital Schleswig-Holstein in Kiel, Germany. The study's 251 participants were considered to have had PD at the young age of 45, and they manifested early motor complications. On average they were 52 years of age and they had lived with the condition for an average of 7.5 years. That differed from typical PD cases, who develop it later in their lives. The patients were divided into two groups. One underwent DBS and standard medical therapy, including levodopa. The other received only standard medical therapy.

The study's results showed that the quality of life of the group who had undergone DBS and medical therapy over a period of two years had improved by 26 percent. They demonstrated better mobility, increased ability to perform daily activities, and fewer side effects induced by long-term levodopa treatment. They were even able to reduce their levodopa intake after two years without any negative impact. In contrast, the quality of life of the group who underwent only medical therapy remained relatively unchanged, and their medication had to be increased by 21 percent to control their worsening symptoms.

The EARLYSTIM findings suggested a combination of neurostimulation and medical therapy was superior to just medical therapy alone, and that DBS could likewise benefit early-stage PD patients, instead of waiting until symptom control via medication proved completely inadequate. Details of the study were published online in *The New England Journal of Medicine* in February last year.

"In broad terms, there is medical consensus that, for most patients, the tipping point in recommending DBS occurs when the patient is in Hoehn-Yahr stage 3," says Associate Professor John Thomas, Medical Director and Senior Consultant at SMG Neuroscience Centre in Singapore and a Neurosurgeon at Mount Elizabeth Novena Hospital. The Hoehn-Yahr scale is a clinical rating system used to define PD stages. In Hoehn-Yahr stage 3, the patient's condition is between mild and moderate, with impairment in balance. But the patient is otherwise considered to be physically independent.

"The EARLYSTIM trial supported the use of DBS in very early stage 3. Since the response of patients to DBS is durable and long-lasting, it makes sense to make it available to them as soon as there is a reasonable certainty that it will improve their quality of life," he continues.

In fact, the optimal stage at which DBS can provide the greatest benefit is based on more than just medical information. "It is fair to offer DBS if medical therapy is not achieving adequate symptom control for the patient. The adequacy of symptom control is a subjective impression that comes from the patient – it depends on his or her personal goals and ambitions in terms of mobility. So it differs between patients," adds Professor Thomas.

Imaging Technology

Developments in imaging technology have also expanded the ways in which DBS surgery is carried out on different types of patients. One such study concerns the role of intra-operative MRI in "asleep" DBS surgery.

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MOUNT ELIZABETH NOVENA HOSPITAL, SINGAPORE

DBS is conventionally an "awake" procedure during which patients are given a local anaesthetic. Combined pre-operative MRI and CT brain scans first help to determine the targets where the electrodes should be placed. A stereotactic frame guides the electrodes to these targets. During the surgery, microelectrode recording (MER) allows surgeons to listen to neuronal activity from the brain structures to distinguish them from one another. That helps the surgeons to place the electrodes more accurately. The crucial testing of the electrodes and their effects can thus be done when the patient is awake.

But a trial last year by researchers at the Oregon Health and Science University in the US dispensed with the traditional MER. Asleep DBS was performed on 60 patients under general anaesthetic. Of these, 33 had PD.

As with conventional practice, pre-operative MRI images were taken to identify electrode target sites and the trajectory of electrode placements was planned. Pre-operative CT scans of the brain anatomy were then fused with the MRI images, and the composite scans were used for surgical navigation. However, instead of MER, a second intra-operative CT scan was done after the electrodes were placed, and merged with the pre-operative scans to check for off-target errors. This was used to confirm the accuracy of electrode placements. The subsequent paper published in the *Journal of Neurosurgery* in August last year indicated that the accuracy was comparable to the results of awake DBS using MER.

"Intra-operative MRI has been reported in a number of centres where it has been available for several years. But its cost benefit has not been shown to be superior to the routine procedure. Neither are the surgical results," confirms Professor Thomas. "Such studies are variations on the theme of some kind of intra-operative imaging as an additional verification step to intra-operative stimulation and recording," he adds.

"Opinions on this are split 50:50. Some believe the best targeting is achieved using MER, particularly for younger patients who are in the early stages of the disease. In addition, putting electrodes accurately in the anatomy is one thing. The other thing is to use the same electrodes to test their effects," says Professor Poon. "Perhaps there are surgeons for whom time is money, and it is more cost effective to treat three asleep DBS cases in one day with patients under general anaesthesia than one awake DBS case," he posits.

Asleep DBS

The practice of asleep DBS varies too. Some patients are anxious and stressed about being awake during an operation on their brain. Beyond PD, patients with dystonia and resultant jerky movements may prove difficult subjects for precise awake DBS. Asleep DBS is less stressful for patients, and suitable for those unable to comply with the logistics of an awake procedure. Yet, while the idea of skipping general anaesthesia when undergoing brain surgery may seem daunting, the case for awake DBS remains strong.

"The awake procedure is preferred by most surgeons, as the additional information from recording and stimulation increases the surgeon's confidence that the electrodes are on target. Compared to an awake procedure, asleep DBS does not allow the surgeon to make such a detailed neurophysiological recording, in which routine electrical firing patterns of nerves in the brain are recorded by the surgeon, or intra-operative testing, in which the effects of the electrical current introduced into the brain are observed. However, the results appear comparable in a number of studies," states Professor Thomas, who typically performs asleep DBS on young children with dystonia, but who has also done so on several adult PD cases.

"If the patient can tolerate it, testing the effects of the electrodes when he or she is awake is an advantage," says Professor Poon. "We do not use asleep DBS for PD at Prince of Wales Hospital, but we do so for dystonia if the patient is moving around and liable to break the hardware during the surgery. So the decision also depends on the patient," he adds.

While such studies of DBS are yet definitive, they contribute to the pool of exploratory research about it and its other applications. The different ways DBS is performed during PD treatment are just the tip of the iceberg, and its use is currently being explored for other neurological diseases and psychiatric disorders, such as depression, Alzheimer's, and even anorexia nervosa.

At the same time, like other medical conditions when research and clinical practice are considered in the context of one another, it doesn't necessarily mean that all practices always develop alongside research. As Professor Poon puts it, "A breakthrough comes when it becomes a scientific statement. But, naturally, changes in practice are also informed by clinical experience, and they can be quite independent." Our Neolithic ancestors, with the primitive surgical tools they learned to use to make holes in skulls, would doubtless agree. GHT

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