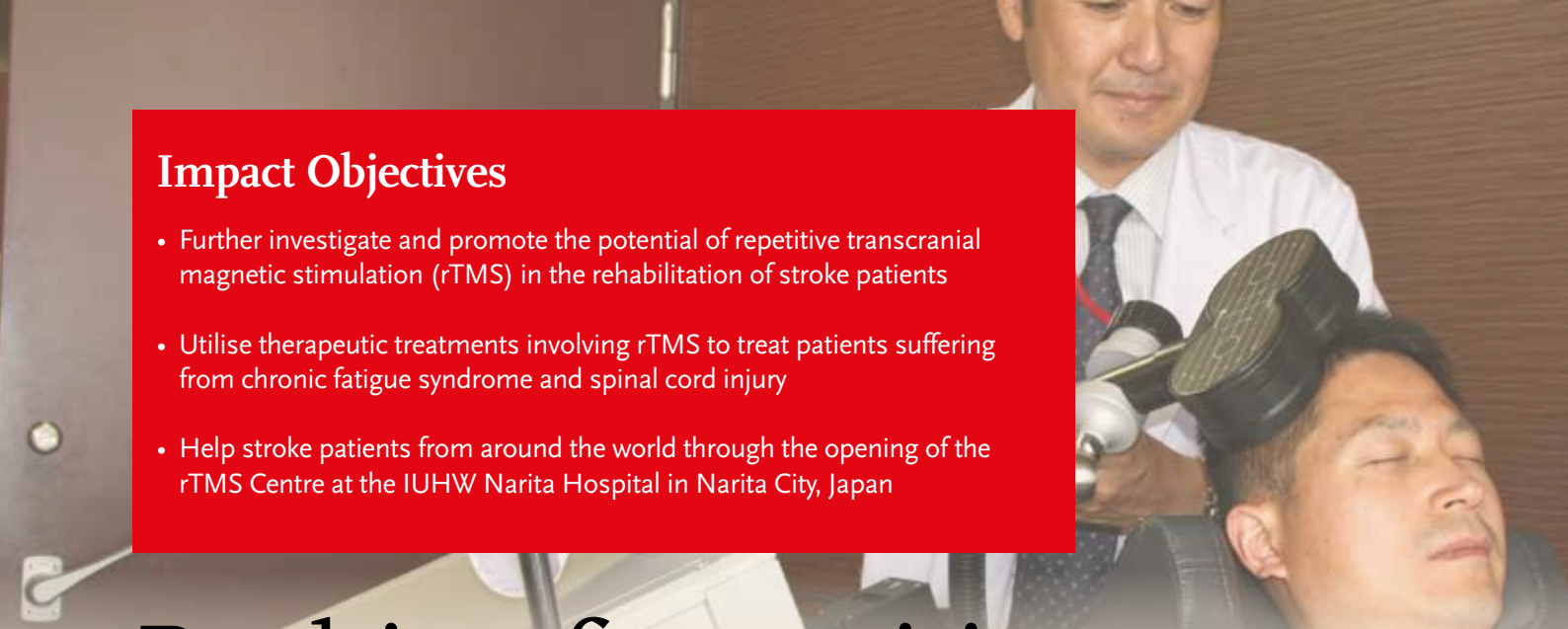

Impact Objectives

- Further investigate and promote the potential of repetitive transcranial magnetic stimulation (rTMS) in the rehabilitation of stroke patients
- Utilise therapeutic treatments involving rTMS to treat patients suffering from chronic fatigue syndrome and spinal cord injury
- Help stroke patients from around the world through the opening of the rTMS Centre at the IUHW Narita Hospital in Narita City, Japan

Pushing for positive changes for stroke patients

Professor Wataru Kakuda *believes repetitive transcranial magnetic stimulation (rTMS) therapy has the potential to help patients with stroke, spinal cord injury and chronic fatigue syndrome and is pushing for the treatment to become more widespread*

Could you begin by discussing your key research interests?

My current research interests include stroke rehabilitation, functional neuroimaging such as functional magnetic resonance imaging (MRI), near infrared spectroscopy (NIRS) topography and PET, non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS).

How did you come to work in the field of neurology?

In my university days, I found dealing with the brain the most exciting and challenging research area. I thought there were so many basic and clinical issues to be clarified in the field of brain medicine. That is the reason I started my medical career as a neurologist. At first, I was mainly engaged in acute management of stroke patients. However, later, I recognised that the field of neurorehabilitation, especially neurorehabilitation for post-stroke patients, has not developed satisfactorily. So many post-stroke patients are expecting a revolutionary improvement in terms of rehabilitation intervention and progress in the field of neurorehabilitation.

Could you offer a little background about repetitive transcranial magnetic stimulation (rTMS)?

At first, TMS (non-repetitive TMS) was used as an investigative procedure for the functional condition of the brain. Some researchers studied the response of the brain to TMS in certain neurological disorders. However, in the late 1990s, it was found that TMS could change local neural activity as a neuromodulation intervention when TMS is applied in a repetitive manner as rTMS (repetitive TMS). After 2000, expecting this neuromodulation effect with rTMS, some researchers started to apply rTMS therapeutically for patients with depression, stroke, Parkinson's disease and more.

A number of stroke patients have already received rTMS therapy at some medical institutions (the number of institutions where rTMS can be performed is still small. For example, in Japan, only about 20 hospitals provide rTMS therapy continuously and commonly). However, rTMS therapy has been more commonly and more widely applied for patients with depression. In addition, since 2010, rTMS has been applied for many neurological and psychiatric conditions as a therapeutic tool, although some were carried out as part of a clinical study.

Are there any surprising results or developments you can reveal or any concepts and theories which you have had confirmed through your investigations so far?

For upper limb hemiparesis after stroke, we provided rTMS therapy combined with upper limb motor training. One surprising result was that in some patients, motor function of the affected upper limb dramatically improved with rTMS application after only 15 days, although the function didn't respond to any other rehabilitative interventions for several years. For the patients, it was the first time in several years that they experienced an improvement in motor function in the affected upper limb. From this experience, we now believe there remain neural plasticity to some extent in some post-stroke patients.

What are your hopes for the future of rTMS treatment?

My current biggest desire for rTMS therapy is that it will become familiar to all patients with stroke, spinal cord injury and chronic fatigue syndrome. I don't want patients to miss the potential to recover with rTMS application. We understand there is a strong necessity to let the patients know and understand this novel rTMS therapy. ▶

Solving a big problem

Researchers at Japan's ***International University of Health and Welfare*** *are investigating and promoting the potential of transcranial magnetic stimulation in the rehabilitation of stroke patients*

It is estimated that, worldwide, one in six people will have a stroke in their lifetime, and this statistic is on the rise. When a stroke strikes, blood supply to the brain is disrupted, which can cause oxygen starvation and brain damage. It can lead to permanent damage and is estimated to claim a life every six seconds. Naturally, rehabilitation is crucial for stroke patients and, if introduced rapidly enough, can assist in the improvement of symptoms. One researcher is exploring the potential of stem cell therapy as a treatment for stroke.

Professor Wataru Kakuda is based in the Department of Rehabilitation Medicine in the School of Medicine at the International University of Health and Welfare, Japan. Kakuda made a career change from neurologist to rehabilitation physician to assist in improving the prognosis for people who have suffered a stroke. 'There are so many disabled stroke patients for whom no effective rehabilitative intervention is available,' Kakuda explains. 'In other words, we cannot do anything for their symptoms after stroke. When I made my career change there were only a few researchers who studied and performed clinical research about rehabilitation for stroke patients. I thought the field of neurorehabilitation needed to be developed and that research in the field should be better promoted. The fact is, without neurorehabilitation research, outcomes for stroke patients would never improve. Therefore, I made a career change to rehabilitation physician and have been engaged in clinical study in order to discover effective rehabilitative interventions for stroke patients.'

REPETITIVE TMS

Kakuda and his team are investigating the potential of repetitive transcranial magnetic stimulation (rTMS) to be implemented in stroke rehabilitation. TMS is a non-invasive procedure that is typically used to help improve symptoms of depression. To do this, it uses magnetic fields to stimulate nerve cells in the brain. rTMS is another form of brain stimulation therapy used in the treatment of depression and anxiety. Kakuda explains more: 'The first report of TMS application for humans was published in the *Lancet* in 1985 by English neurologist Anthony Barker. He successfully moved the hand of the subject with TMS applied over the contralateral motor area of the brain. The mechanism of TMS is based on Faraday's Law of Induction. The current passing through a stimulating coil placed over the head can produce a magnetic field, which penetrates the skull and reaches the brain. After that, an ionic current is produced in the cerebral cortex by magnetic stimulation and the current stimulates the neuron in the cerebral cortex.'

The brand new IUHW Narita Hospital in Narita City, Japan, is set to open in 2020 and will be equipped to offer rTMS therapy

> *There are so many disabled stroke patients for whom no effective rehabilitative intervention is available*

In TMS, a magnetic field is generated by an electric current flowing through a stimulating coil. This induces electric currents in the brain, stimulating neurons. In rTMS, the effect of the treatment on cortical excitability is dependent on the frequency of stimulation. For example, in high-frequency rTMS, there is a facilitatory affect, with an increase in cortical excitability, while low-frequency rTMS has a suppressive effect, and a decrease in cortical excitability is seen. Kakuda explains more: 'Low-frequency rTMS is defined as rTMS of less than or equal to 1 Herz. High-frequency rTMS is defined as rTMS of more than or equal to 10 Herz. Low-frequency rTMS can decrease local neural activity of the brain (which means it's suppressive), whereas high-frequency rTMS can increase the activity (which means it's facilitatory). Therefore, the effect of rTMS can be bi-directional based on the frequency of stimulation. When the activity of the pathologically hypoactive area of the brain needs to be increased therapeutically, high-frequency rTMS should be applied over the area. This neuromodulation effect of rTMS is mainly due to the changes in synaptic efficiency. For example, high-frequency rTMS can enhance synaptic efficiency in the stimulated areas of the brain.'

As such, the researchers determined that high-frequency rTMS should be used for up-regulation, with direct activation of the compensatory area, whereas low-frequency rTMS is appropriate for down-regulation, whereby neural activity in the hemisphere is contralateral to compensatory areas and there is a reduction of interhemispheric inhibition towards compensatory areas and disinhibition of compensatory areas and indirect activation of the areas. The team also found that with rTMS, neural plasticity should be enhanced prior to rehabilitative training. This is because, although the rehabilitative programme is the same, compensatory activity is facilitated and recovery of symptoms is also facilitated. 'Unfortunately, usual rehabilitation programmes without rTMS would not be enough to utilise residual neural plasticity and to promote compensatory mechanisms,' says Kakuda.

'We consider that rTMS should be applied in order to provoke and enhance compensatory mechanisms in the chronic phase of stroke. This means the rehabilitation programme including rTMS application can provoke compensatory mechanisms in chronic stroke patients and can produce functional recovery in the chronic phase.'

A POSITIVE COMBINATION

The importance of combining rTMS with rehabilitative training is invaluable, as Kakuda explains: 'If the brain is damaged due to stroke, some neurological symptoms like hemiparesis or aphasia can develop. However, the symptoms can improve gradually if rehabilitation is appropriately introduced. The reason for this recovery is that a compensatory mechanism can develop in the brain with rehabilitation. In other words, with the introduction of rehabilitation, some non-injured brain areas start to work by compensating for impaired neurological functions. Therefore, when rTMS is applied therapeutically for stroke patients, rTMS should be applied so the neural activity of compensatory areas can be facilitated.'

Looking ahead, the team's university, the International University of Health and Welfare (IUHW), is planning to open a new hospital in 2020, which will be called IUHW Narita Hospital in Narita City in the Chiba Prefecture of Japan. The hospital will have more than 600 beds and there will be more than 30 clinical departments, including a Department of Rehabilitation Medicine. 'At the Narita Hospital, there will be a rTMS centre where we can provide rTMS therapy for patients with various neurological disorders such as stroke, depression, spinal cord injury and so on. We would like to accept foreign patients who need rTMS therapy from all over the world,' Kakuda enthuses. 'We are planning to provide rTMS therapy as an inpatient treatment there. The centre in Narita will be the first rTMS centre in the Asian region and is expected to work as one of the largest and the most sophisticated centres for rTMS therapy in the world.'

A PROMISING FUTURE

This, combined with the team's exciting and encouraging results to date, is promising for stroke patients. So far, Kakuda and the team have successfully confirmed that rTMS is safe and feasible, and is effective for some patients with stroke, spinal cord injury and chronic fatigue syndrome. This means the researchers can confidently recommend this treatment to patients. The only difficulty is that the evidence supporting the usefulness of rTMS is not proved. The researchers' next step is for them to do so, as Kakuda explains: 'We are ready for the stage where the usefulness of rTMS therapy is confirmed by multiple institutes. Particularly, rTMS therapy for traumatic brain injury, spinal cord injury and chronic fatigue syndrome should be applied for more patients, since the number of patients treated with rTMS for such disorders is still very small,' Kakuda explains. 'From our experience of rTMS for some neurological disorders, rTMS therapy should be applied for more patients, more aggressively. Unfortunately, rTMS therapy is not well-known among patients. This means some patients may miss the chance of further recovery after stroke or spinal cord injury, since they don't have any information about rTMS therapy. In other words, there might be disabled patients who may be able to experience further recovery if rTMS therapy is introduced aggressively. We believe this is a big problem yet to be solved.' ●

Project Insights

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