Concept and future of neuromodulation therapy: with examples of repetitive Transcranial Magnetic Stimulation (rTMS) for aging related disease

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Definition of neuromodulation

Neuromodulation is a kind of treatment that alters the activity of nerves by the targeted delivery of stimuli, such as electrical or chemical agents, to specific nerve areas of the body. Its function is to normalize or regulate the function of nervous tissue. Neuromodulation is an evolving therapeutic approach that may involve a range of electromagnetic stimuli, such as magnetic fields (rTMS), electrical currents, or direct injection of drugs into the subdural space (intrathecal drug delivery). Emerging applications include targeted introduction of genes or gene modulators and light (optogenetics), which, by 2014, have been demonstrated at least in mammalian models, or for the first time in human data.

The definition of neuromodulation is to change the patient's nerve function by selectively applying signals (such as chemical stimulation or electrical reagents) to the target neuron location in the body. This is done to normalize the activity of the patient's nervous tissue or to improve regulation*(Hallett, 2000; Nitsche et al., 2008)*. Neuromodulation is an emerging research field in drugs that use various electromagnetic stimulation or drugs directly instilled into the subdural space (intrathecal administration). It can be divided into two categories: invasive methods and Non-invasive method.

Invasive method

Invasive methods can be divided into invasive electrical methods and invasive chemical methods. In invasive neuromodulation methods, it can be divided into two methods: spinal cord stimulation and deep brain stimulation*(Nitsche et al., 2008).*

The implantable electrode used for electrical stimulation first appeared in 1980, and its technology and use are still evolving so far. For forty years, spinal cord stimulation has become a common method of invasive neuromodulation therapy. This method usually conducts electrical stimulation at a frequency of 20–200 Hz, and studies are experimenting with new stimulation parameters, such as the use of a 10 kHz and 500Hz stimulation sequence *(Ansarinia et al., 2010)*.

Meanwhile, the choice of the patient is the most important. Candidates need to pass strict psychological and medical examinations to ensure that these patients can have a good resistance to

their pain syndrome. When the implantation procedure is complete, the patient will return to the device to turn on the device and program it.
Deep brain stimulation(DBS) can be used to help people with movement problems, including Parkinson's disease, dystonia, and tremor. DBS treatment is different from the spinal cord stimulation mentioned above. It has a variety of sites in central nervous system to treat diseases, depending on the target*(Morten et al., 2007)*.
Invasive chemical methods rely on intrathecal drug delivery systems, which deliver small amounts of analgesics or anticonvulsants directly to the site of action. This method can deliver drugs to very precise areas of the body. Although chemical neuromodulation is mostly invasive, swallowing pills can be seen as a non-invasive option.
Regarding the neuromodulation of depression. There is no recognized treatment for depression so far. Studies have shown that 30% of depression patients are resistant to treatment. In this case, standard treatment therapies (ie, antidepressants, psychotherapy, and cognitive therapy) cannot be effective for depression patients. Of the patients who respond to antidepressant treatment, about two-fifths of patients will have residual symptoms in later life, and three-tenths of patients will not respond to treatment at all. Therefore, psychiatric researchers are looking for alternative methods that may involve electrical or magnetic stimulation, such as non-drug therapy electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), repeated transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS) as a treatment for depression*(Akhtar et al., 2016)*.

Non-invasive method

Non-invasive neuromodulation modulates brain neuron by applying physical methods, such as direct current, ultrasound and magnetic. Although these methods are not as effective as invasive method, they have the advantages of safety, easy operation and more acceptable so that they are highly available for elder people.

Transcranial direct current stimulation (TDCS)

TDCS influences brain excitability by applying a low level of continuous electrical current which is produced by electrodes placed on the scalp*(Ting et al., 2018)*. The current going from the anode to the cathode is not strong enough to activate action potential. The actual effect depends on the reaction of prior state of the cortex and current*(Filmer et al., 2014)*. The effectiveness of TDCS is approved on several aging related diseases, such as inhibiting γ-aminobutyric acid (GABA) neurons to relieve age-related decline in cognitive and motor function*(Summers et al., 2016)*.
Although its effectiveness has been approved, the consistency of every stimulation is easy to be affected due to its non-invasive feature. The possible influencing factors are i) individual difference, ii) motor and cognitive interference and iii) electric current influences*(Horvath et al., 2014)*.
The skull thickness and subcutaneous fat level are the influencing factors since direct current need to go through the skull and subcutaneous fat to stimulate the brain nerve. The cerebrospinal fluid density, and cortical surface topography are also influence the stimulation result of direct current. Some research suggests that taking active motor and cognitive activity during or following TDCS have negative effect with stimulation and even abolish the stimulation effect. This is very important for further TDCS treatment design and the possible reason is the direct current is too

slight. Besides, the current is easy influenced by hair thickness and sweat, resulting that the output of electrodes is determined.The direct current applying on brain is hard to control as well. These disadvantages have to be taken into consideration.

Ultrasonic neuromodulation

Ultrasound neuromodulation influences brain excitability by delivering low-intensity ultrasound to nervous system tissue. During this process, the main mechanisms are acoustic radiation force (ARF) and cavitation*(Blackmore et al., 2019).* The ARF is a net force applied on brain tissue produced from mechanical wave of ultrasound, which attenuates in the tissue removing momentum of the wave*(Palmeri et al., 2011)*. Cavitation is generated from voids or bubbles within the tissue due to the periodic changes of ultrasound with the intensity exceeding the threshold. The bubbles produce acoustic emissions, jetting and streaming during this procedure, inducing bioeffects*(Blackmore et al., 2019).*

Ultrasound can only generate mechanical force and heat and its potential mechanisms in neuromodulation are i) membrane capacitance changes, ii) mechanosensitive channels, iii) sonoporation, iv) membrane waves and v) thermal effect. These mechanisms are briefly introduced below*(Blackmore et al., 2019)*.

Membrane capacitance is regards fixed and the nerve impulses transmit in the neuron. The mechanical force produced by ultrasound change the thickness, curvature, and the conformational state of the lipids in the membrane, leading to the changes of membrane capacitance, which result in the producer of action potential. The mechanosensitive channels theory illustrates that some ion channels, like two pore domain K+ channels, are shown sensitivity to various ultrasound degrees. Ultrasound can stimulate these sensitive ion channels to activate action potential. Sonoporation is defined as the opening of pores or other transport processes via acoustic stimulation. The physical pore, even the enhanced permeability of membranes, produced by ultrasound can provide a new channel for ion transport, resulting in potential changes. Membrane waves are proved associated with the nerve impulse, and when the membrane is close to phase transition, its interface waves is similar to nerve impulses, as well as the threshold for excitation. The heat generated by absorption ultrasound can induced infrared neural stimulation or some channels.

Different from the current mature nerve stimulation methods, using current or magnetic to stimulate nerve, ultrasound neuromodulation provides a new method, using mechanical force, to treat nerve related disease. Although the effectiveness of this method now is mainly approved in animal trial and rarely approved in aging related disease, it may have potential advantage in population aging challenging due to its unique mechanism.

Basic Principles and main effect of rTMS

Repetitive Transcranial magnetic (rTMS), one of the effective and representative neuromodulation therapies, is a classic approach on the treatment of central nervous or peripheral nervous system diseases.

The mechanism of rTMS is electromagnetic induction. When doctors activate the generator, there is a constantly changing current in coil produces a magnetic field oriented orthogonal to the plane of the coil. Since the skull is an insulator, there is almost no attenuation when the pulsed magnetic field penetrates.

And then, this field passes through the cerebral cortex area, generating a localized current in brain that stimulate nerve cells of target area which causes a change in transmembrane leading to depolarization or hyperpolarization of neurons so that they would be excitable*(Klomjai et al., 2015).*

There are some factors affecting rTMS: intensity, duration, frequency, stimulation site and coil types.

Firstly, Insufficient intensity may be useless, however, overdosing has been proved that results some side effects such as fainting, seizures, headache, etc. Duration depends on multiple diseases and its severity.

When it comes to frequency, we often define the high frequency is above 1 Hz which makes brain more excitable; low frequency is less than 1 Hz which makes brain less excitable.

Some articles proposed that, rTMS can increase or decrease the excitability of the corticospinal tract which affects cortical firing. This kind of cortical firing can provoke or inhibit the brain function depending on the excitability of interneurons *(Qiu, C et al.,2019)*. Apparently, it has been proved that the excitability of interneurons is dependent on frequency.

Interneurons exist in the cortical area of the brain. One is excitatory interneuron such as glutamatergic neuron that emits excitatory neurotransmitter; the other is inhibitory interneuron such as GABAergic neuron that emits inhibitory neurotransmitter. These two different types of interneurons have different electrophysiological properties which means high or low stimulation frequency makes them release neurotransmitter with high or low concentration affecting brain functions.

Researchers may study these interneurons and finally determine the frequency used in rTMS. For example, the GABAergic interneurons, stimulation with low frequency might increase the efficacy of GABAergic inhibitions, because the stimulations did not change the firing rates of GABAergic interneurons but decreased the firing rates of pyramidal cells which belong to a kind of excitatory neurons. However, stimulation with high frequency increased both of them, and increase of excitatory neurons is higher than that of GABAergic neurons, therefore, stimulation of high frequency can provoke cortical firing. Therefore, by studying electrophysiological properties of interneurons, authors often define the high frequency is above 1 Hz (in clinical, doctors tend to use 5 Hz in most of case). Low frequency is less than 1 Hz which inhibit cortical firing. We all know that different areas of the brain are responsible for different functions. Therefore, stimulating different site with high or low frequency can achieve some therapeutic effect.

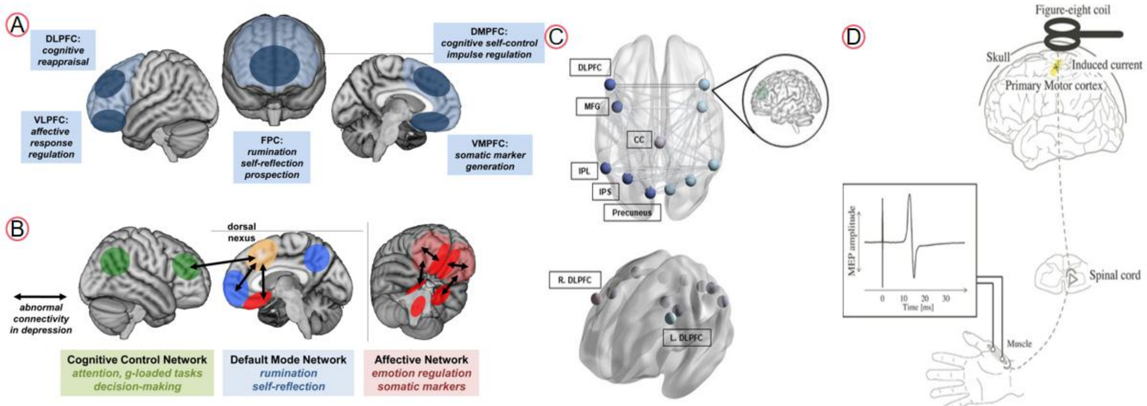

Figure 1.Cortical nodes and networks

(A) a network of prefrontal regions involved in the pathophysiology of depression. (B) Abnormal network activity in depression. (C) the frontoparietal network and sagittal view of the brain. (D) rTMS for Peripheral nervous system

DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; FPC, frontopolar cortex; MFG, middle frontal gyrus; IPL, inferior parietal lobe; IPS, inferior parietal sulcus; CC, corpus callosum; FPN, frontoparietal network; DMN, default mode network.

For example, the figure A demonstrated is a research of depression. Some authors contributed a network of prefrontal regions involved in the pathophysiology of depression *(Downar, J et al., 2013)*. By using PET-MRI, authors can figure out different function area and observe the abnormal activity of depression as shown in figure B. These function networks are marked in different colors and the red one means abnormal part.

It is generally believed that in in clinic, the left prefrontal cortex is under-excited and the right one is over-excited*(Kim et al., 2019)*. Doctors tend to use 10 Hz at LDLPFC and less than 1Hz at RDLPFC to treat patients.

Meanwhile, the stimulation site can reach deeper area which impact motor cortex and cerebellum so that it can control the legs or pelvic floor, which means it has potential in peripheral nervous system. As figure D shown, the stimulation led to depolarize and produce an action potential. If used in the primary motor cortex, the muscle activity can be recorded on electromyography referring to as a motor evoked potential *(Nojima and Iramina, 2018)*.

In order to satisfy different stimulation site, multiple types of coil have been produced. The circular coil originally used firstly. Subsequently, figure-8 coil was developed to satisfy more focal pattern of activation. Now, this kind of coil has commonly and commercially used in hospital. Four-leaf coil involved more areas can stimulate peripheral nerves. Double-cone coil is more comfortable because of its shape. As for H-core and crown, they can generate deeper magnetic penetration, so that they are utilized to deeper areas of brain even can control legs*(Deng et al., 2014)*. Therefore, rTMS is available for both central nerves and peripheral nerves system. It can not only use in some psychiatry and neurology diseases, but also use in relieving the pain and rehabilitation of stroke including motor and language function.

Clinic application and treatment of rTMS areas

In practiced clinic application, rTMS can be used in multiple diseases, especially in psychiatry and neurology, it has proposed relatively mature treatment methods.

For example, anxiety is generally considered to be caused by hyperfunction of the right prefrontal cortex, and it is usually treated with low frequency rTMS. Epilepsy is caused by the excitement of the cerebral cortex, also used low frequency rTMS. On the contrary, patients with PTSD need to be treated with high frequency rTMS (usually 10 Hz) at RDLPFC.

More importantly, rTMS can be used to treat some diseases for elder people for its non-invasion. For example, Alzheimer’s, stroke, insomnia is common in older people. For patients with motor impairment after stroke, the affected side is used high frequency, the contralateral side is used low frequency. Therefore, 0.6Hz and 10Hz stimulation are used at RDLPFC or LDLPFC respectively.

Tinnitus is defined as the hallucination of sound, and there is no corresponding acoustic or mechanical correlation in the cochlea*(Han et al., 2021)*. It may be associated with auditory trauma, chronic hearing loss, emotional stress or spontaneous development and it is highly related to the age(Oosterloo et al., 2020; Piccirillo et al., 2020). Moreover, the prevalence of tinnitus in adults is about 10-15% all around the world*(Weise, 2011)*, and more than 20% elderly population suffers from tinnitus*(Oosterloo et al., 2020)*. Repetitive transcranial magnetic stimulation (rTMS), as a non-invasive intervention, the electromagnetic pulse is transmitted to the scalp of the patient through the coil. Eventually, some of this energy is transmitted through the skull and affects the activity of the underlying nerve tissue. Therefore, the potential mechanism of tinnitus makes the disease a good candidate for the inhibition of rTMS.

In a case study*(Ridder and Dirk, 2005)*, the researchers conducted rTMS guided by positron emission tomography and computed tomography (PET-CT) on a white man with a history of bilateral tinnitus for more than 30 years. After receiving rTMS, the patient changed tinnitus perception temporarily for 48 hours. However, the patient's hearing level did not completely return to normal after treatment, and tinnitus recurred after stopping rTMS treatment, which means that it was not cured.

To avoid the chance of single case and the influence of placebo, the results of another randomized controlled trial are more convincing*(Marcondes et al., 2010)*. In this parallel design, 20 patients were randomly stimulated with active or placebo in the left temporal cortex for 5 consecutive days. Treatment outcomes were assessed using the Tinnitus Handicap Inventory. Ethyl cysteinate dimmer-single photon emission computed tomography (SPECT) imaging was performed before and 14 days after rTMS.

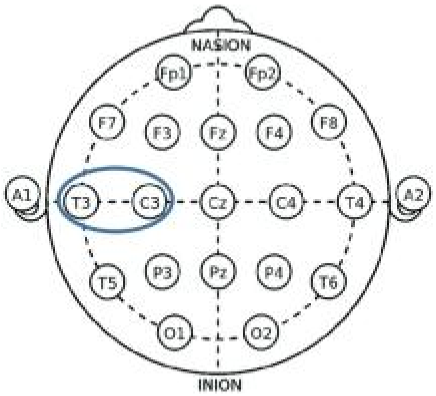

Figure 2, 10-20 international EEG system.

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The stimulation site corresponding to the scalp projection of the secondary AC was identified by placing the anterior junction of the two coil wings halfway between T3 and C3/T5 (10-20 international EEG system). Compared with the control group, the severity of tinnitus was significantly reduced 5 days after rTMS. After active rTMS, the single photon emission computed tomography (SPECT) imaging showed that the temporal gyro activity decreased in the lower left and right parts, while the limbic system activity increased, mainly in the right part. A negative electron emission tomography study showed that the asymmetry of metabolic activity in auditory cortex decreased after rTMS.

Furthermore, we cannot distinguish to what extent these changes are related to rTMS, or whether they more reflect a reduction in tinnitus severity. One limitation of this study is the control condition. Because the false coil only imitates the sound of active rTMS, but lacks the sense of body membrane, it is not an optimal control condition. In addition to that, a randomized, double-blind, crossover, placebo-controlled trial of 1 Hz rTMS was conducted in 16 patients with chronic tinnitus also got the same result*(Rossi et al., 2007)*. Finally, 8 of 14 responders improved significantly. But there were also two patients who withdrew because of the temporary deterioration of tinnitus.

Table.1 Compare of three studies.

rTMS tinnitus	Simone 2007 (Rossi et al., 2007)	Kleinjung 2005 (Kleinjung et al., 2005)	Kim, Hyun 2015 (Kim et al., 2015)
No of patients	14	14	61
Treatment duration	5 days	5 days	4 weeks
rTMS frequency/length of the train/No of stimuli	1 Hz (1200 stimuli/day)	1 Hz (2000 stimuli/day)	1 Hz (600 stimuli/day)
Stimulus intensity (% of RMT)	120%	110%	90%
Coil type	Figure of eight	Figure of eight	Figure of eight
Individual neuronavigation	PET guided	PET guided	-
Percentage of responders	35%	78.6%	50.8%

Above all, it can be seen from three cases that rTMS can relieve tinnitus symptoms in a short time to a certain extent, which may be related to the neural regulation of tinnitus. Besides, each experiment claims that patients have improved, although their effects are quite different. However, the limitations still exist, we cannot completely exclude the psychological factors, and the treatment effect is very limited, and cannot be cured totally. Especially for the elderly, long-term treatment will increase their burden of life.

For Mild Cognitive Impairment, which can be considered as an intermediate stage between the expected cognitive decline of normal aging and the pathological decline of dementia, there is one group carried out a 4-year prospective cohort, study, and the patients were treated with 5-Hz Repetitive Transcranial Magnetic Stimulation*(Trebbastoni et al., 2016)*. TMS is delivered through a high-frequency electromagnetic stimulator by trains of 10 stimuli and 120% of resting motor threshold (rMT) intensity, which is connected to a figure eight coil placed above the primary motor area.

Table.2 Compare between MLC and tinnitus.

	rTMS tinnitus, Simone 2007[8]	**rTMS aMCL, Alessandro 2016[11]**
No of patients	14	40
Treatment duration	5 days	4 years
rTMS frequency/length of the train/No of stimuli	1 Hz (1200 stimuli/day)	5 Hz (1000 stimuli/day)
Stimulus intensity (% of RMT)	120%	120%
Coil type	Figure-of-eight	Focal coil
Individual neuronavigation	PET guided	No
Target brain area	Between T3 and C3/T5	Primary motor area

Controlled study	Randomized, crossover, double-blind (placebo TMS with a sham coil)	20 healthy controls
Crossover	Yes	No
Percentage of responders	35%	--
Duration of effects after the last rTMS application	Two weeks	--
Correlations between rTMS and clinical characteristics	The beneficial effects of rTMS on tinnitus are independent of mood changes	5 Hz rTMS may be a neurophysiological marker for Alzheimer conversion in MCI

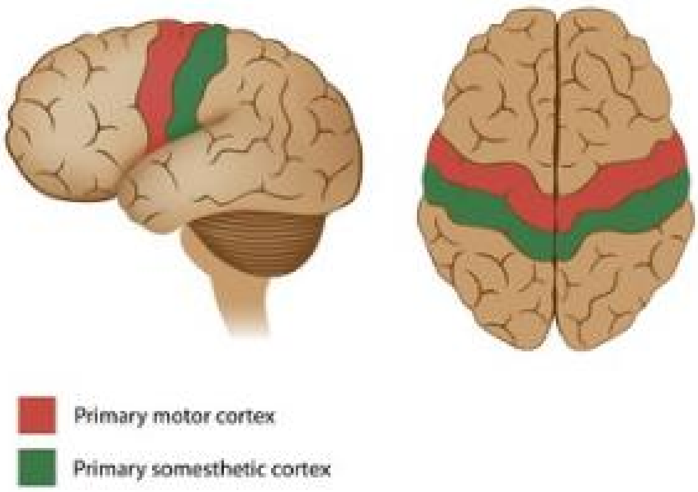

Figure.3 Primary cortex
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In the end of it, thirty-five aMCI patients completed the study; 60% of them converted to Alzheimer. There was a significant increase in motor-evoked potential (MEP) amplitude in healthy controls from the seventh, but not in amnestic mild cognitive impairment (aMCL) group. Moreover, a suggestive hypothesis is that we can take 5 Hz rTMS as a neurophysiological marker for Alzheimer conversion in MCI. Identify patients who have converted to Alzheimer from individuals diagnosed with MCI. Also give us an early warning of Alzheimer.

Both cases above indicated that rTMS has a significant effect on the improvement of tinnitus symptoms and as suitable an early warning of Alzheimer's disease. But at the same time, we can notice these two studies also reflect many shortcomings, such as small sample size and low patient completion. The quantitative explanation of its conclusion is insufficient.

Pros and cons of rTMS

Next, we will focus on the disadvantage and advantage of rTMS to further explain, But actually because of rTMS is a very representative therapy in neuromodulation, so maybe be these properties are also associated with the whole neuromodulation therapy region.

Firstly, for the advantages, from the device picture, we can clearly know that it is a non-invasive therapy. This also means it will not create any painful for patients during the treatment. It is so important for the elder people. Besides it is so economical and with an excellent cost-effectiveness. Previous studies have elucidated that rTMS can provide long-term and sustained remission in patients with major depressive episodes of drug resistance and significantly improve patients' quality of life (QOL)*(Charnsil et al., 2012)*.
However, it also has a lot of disadvantage, improvable region. For example, although there were a lot of meta-analysis, cases reports or even RCT research for rtms, it is still insufficient for large-clinical-sampled and natural RCT research while compared with other drug therapy. Besides Like many neuromodulation therapies, its mechanism of action, pathway, and target sites are still not clear. The treatment is almost built on a black box. Finally, the current treatment methods for patients are always one symptom to treatment, which means their treatment plans are lack of personal optimization*(Sciortino et al., 2021).*

Future and trend of neuromodulation

Apart from rTMS, the traditional neuromodulation methods for aging related disease are often invasive and may lead to the risk of adverse effects. For example, deep brain stimulation is a common neurosurgical procedure to control some of the symptoms of Parkinson's disease by placing the electrode connected to a neurostimulator. However, the procedures carry the risk of hemorrhage and infection, which may cause unexpected problem to the brain area*(Doshi and Paresh, 2011)*. Endovascular neuromodulation appears in recent research which combines the technology of interventional neurology and neural engineering. The Stent rode is a recently developed miniaturized neural interface device which can record and activate the brain signal after being implanted inside the blood vessels*(John et al., 2019)*. The name of the device is derived from its element parts, the stent, and the electrode. The function of the stent is to provide support to the electrodes as a scaffold and the electrodes are fixed on the stent struts. The device can be implanted into the superior sagittal sinus, which is next to the brain, from the jugular vein using the percutaneous catheter venography. Then, it can transmit signal through a transvenous lead between the electrode and a receiver placed in the chest subcutaneously. Therefore, there is no need to do the operation directly in the brain for the implantation of this device. The current application of the device is mainly involved in the stroke and the intracranial hypertension treatment.
Instead of curing the above disorders, there are more potentials for the endovascular devices in neuromodulation application. There were already two case on two patients of 60s and 70s suffered from amyotrophic lateral sclerosis able to control texting and typing through their mind at a 92%accuracy rate after implanting the Stent rode as the control component with the eye-tracking devices*(Oxley et al., 2020)*. Therefore, the device has the potential to be delivered through the vein to the specific region such as prefrontal area, somatosensory and motor cortex, and the parietal regions to generate the deep brain stimulation such that there will be more neurological conditions able to be treated such as the Parkinson's disease and epilepsy*(Oxley et al., 2016)*. However, there are still need the breakthrough in the design of the endovascular devices before accessing the thalamus, fornix, nucleus accumbent, cingulate cortex and ventral capsule because the stent is not small enough to pass through the small blood vessels to reach those regions*(Teplitzky et al., 2014)*. Combining the micro or nano technology may make the device to be achievable to access to these

areas. Moreover, future work is needed in generating the more consistent cortical responses before the further research on the other application of neuromodulation.

To provide the more detailed stimulation to a certain region, for example the somatosensory cortex, high resolution and high-density electrodes are required to induce the specified percepts*(Flesher et al., 2016)*. So, there is still much more research on the brain signal decoding needed with respect to cognitive, emotional, sensory aspect and also the thought and memory to achieve the goal. With the rapid development of artificial intelligence and machine learning, the decoding process will become more effective, and the AI can be designed to a stimulator to provide more precise and detailed neuromodulation. In conclusion, the development of different aspect will bring more intelligent and personalized neuromodulation therapy methods including the rTMS for the aging-associated disease.

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