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Clinical effects of non-invasive brain stimulation

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Summary

There are many types of non-invasive brain stimulation (NIBS) that can be considered for therapeutic intervention. Deep brain stimulation (DBS) can be highly successful, but it generally works by on-line effects, whereas NIBS needs to work by altering brain plasticity. With transcranial magnetic stimulation (TMS) used as a model of NIBS, the principles of brain plasticity are presented, and then TMS methods for producing excitability changes are reviewed. It is noted that multiple interventions are needed for significant therapeutic effects, and then principles and empirical data on multiple successive interventions are reviewed.

Keywords: *brain stimulation, transcranial magnetic stimulation, plasticity, Hebbian plasticity, gating, homeostatic plasticity, metaplasticity, repetitive transcranial magnetic stimulation, paired-associative stimulation*

Introduction

Non-invasive brain stimulation has a long history. Galvani discovered "animal electricity" in the late 18th century, and shortly thereafter in the early 19th century, his nephew, Aldini, used electricity to try to resuscitate the dead. The first clearly successful use was the development of electroconvulsive shock therapy (ECT) for mental illness in 1938. The explosion of new types of non-invasive stimulation was begun by Merton and Morton in 1980, when they showed that a brief, high voltage electrical stimulus (transcranial electrical stimulation, TES) could activate a focal part of the motor cortex and produce a muscle twitch. Physiologists jumped on this as a method to study the brain, and TES proved useful, but it is painful and that limited its use. Only 5 years later, Barker et al. showed in 1985 that it was also possible to stimulate the brain with a magnetic stimulus. As this was not painful, the field grew rapidly. Again, the method was first used for physiology, and there was also an immediate use in clinical neurophysiology to measure the integrity and speed of conduction in the corticospinal tract.

Around this time, deep brain stimulation (DBS) was proving successful in the treatment of essential tremor and Parkinson disease. The basic physiology of the transcranial magnetic stimulation (TMS) showed that it was possible to produce changes in brain excitability that outlasted the stimulation. The idea then arose that it was possible that non-invasive brain stimulation (NIBS) could also be used for therapy.

General principles

DBS certainly can be effective, but how it works is still not completely clear. There is one important observation, however, and that is that DBS works only when continuously used. It can have an immediate effect, and that effect might well cease immediately when the stimulation stops. There are some exceptions, but the general rule is clear. We know the brain operates in circuits, with information passing specifically from node to node. Moreover, some of this information is carried in oscillations in brain activity. So it seems that the on-line effect of DBS is due to the interruption of these circuits, either stopping them or modifying the oscillations. Lesions at the same targets of DBS have similar effects to DBS, and they would certainly disrupt circuits.

NIBS can also disrupt circuits while it is active, but, at least for something like TMS, it cannot be used continuously. Hence, efficacy would have to be based on another principle, that of plasticity. The brain is a highly plastic organ; it is constantly changing. Synapses change strength, new connections between neurons develop and old ones may disappear. People are constantly learning new things, new facts, new motor programmes; these all result from plastic changes in the brain. That the physiology showed that NIBS could induce plastic changes implied that it might be used for treatment. However, it is clear that the proposed mechanism is different from that of DBS. As an exception, there are situations when the effect of DBS takes some time to reach maximum efficacy and when the effect of DBS does not wear off immediately. This is most apparent in the treatment of dystonia. So there are situations in which DBS does produce a plastic change, but this does not seem permanent and generally is a minor aspect of its efficacy.

Range of devices

There is a large and growing list of devices and methods for NIBS. In this review, the emphasis will be on TMS, and the principles of plasticity that will be discussed will likely be the same for all devices. A brief listing of the devices is noted here.

In terms of delivering electricity directly, a current is produced between an anode and cathode on the surface of the

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brain, and electricity flows into the brain at the cathode and out at the anode. Stimulation of a peripheral nerve is most effective at a cathode, whereas stimulation of the brain is most effective under the anode. The early use of ECT was already mentioned in relation to the treatment of psychiatric disorder. It depends on producing a seizure, and multiple treatments may well be needed to have an effect. An oversimplified idea is that a seizure resets all brain activity, but it must also produce some plastic changes. A variation of ECT uses magnetic stimulation rather than electrical. Magnetic stimulation therapy (MST) produces seizures with more focal stimulation with hopes of fewer side effects [1].

As noted earlier, the first focal electrical stimulation was made with a brief, high voltage stimulus. This gets enough current to the surface of the brain to stimulate neurons and produce action potentials, but the stimulation of the skin is very strong and is painful. A variation of this method is delivery of a low voltage stimulus over a longer time, called transcranial direct current stimulation (tDCS). Much of the current is lost by being shunted within the scalp, but enough reaches the brain to alter membrane potentials of neurons and thus the probability of firing. There is such small current used that stimulation of scalp produces just a transient tingling; most of the time, there is no sensation noted. There are several variations of tDCS. One is where alternating current at various frequencies is given rather than direct current, transcranial alternating current stimulation (tACS). This appears to be able to influence oscillations in the brain as an additional effect. Another is transcranial random noise current stimulation, where fluctuations in current flow are random; there is less experience with this than the others.

TMS of the brain is done by passing a brief, high voltage current in a coil of wire generally placed tangential to the scalp. A magnetic field is produced perpendicular to the flow of current, which can penetrate the scalp and skull without loss of intensity. The magnetic field in the brain produces a flow of electric current in a loop mirroring that in the coil but flowing in the opposite direction. Note the current flow in the brain is therefore tangential to the surface of the brain, different from the direct electrical stimulation, which is perpendicular. (There is a similar difference in electroencephalography [EEG] and magnetoencephalography [MEG], EEG picking up mostly radial currents in the brain and MEG picking up mostly tangential currents.) Like TES, TMS acts by producing action potentials in neurons. Magnetic coils come in a variety of shapes, but the most common are two coils side-by-side in a figure-of-8 configuration. Since current flow in the brain mirrors that in the coils, where the coils meet the current adds and produces a small maximum, and hence the figure-of-8 coil can produce more focal stimulation than a single coil.

In some ways similar to tDCS, it is possible to affect the brain using strong static magnets [2]. Presumably such a produced magnetic field causes some membrane depolarisation.

There are a growing number of other new methods. One that has caught attention is “temporally interfering electric fields” [3]. A feature of all previously described methods is that the surface of the brain is most strongly affected, and influence falls off with depth. This method allows more stimulation at depth than surface. Two oscillatory electric fields are generated by separate stimulators and programmed to add only at a target in depth. Another new method, not electric or magnetic, is low intensity focused ultrasound [4]. High intensity focused ultrasound is used to make lesions, but low intensity can modulate activity, again with the possibility of greater effect at depth than at the surface. The ultrasound may work by influencing membrane polarisation, perhaps by interacting with channels in the membrane. It can be anticipated that this method will be actively pursued in coming years.

All the devices influence the brain by altering brain activity, either causing action potentials directly or modifying membrane potentials that would change the probability of action potentials being produced. The next consideration is how action potentials might lead to plastic changes.

Plasticity mechanisms

Plasticity is the capability to change, and the brain is constantly undergoing plastic changes. Acquiring a new memory or new motor skill is a plastic change. Plastic changes arise from changes in synaptic strength, changes in neuronal excitability, birth and integration of new neurons, and formation and dissolution of new synaptic connections. Non-invasive brain stimulation can cause plastic changes itself and also change the state of a brain region so that subsequent processes, such as further stimulation or natural learning, will be more or less successful. Changes in synaptic strength can be due to changes pre- or post-synaptically, and there are often parallel changes in excitability of the neuron membrane itself [5]. Changes post-synaptically are in the number or subunits of the receptors, and changes of the neuron are due to alterations in ion channels. Basic science studies of synaptic plasticity have identified a set of synaptic plastic changes due to the rate of synaptic activity. In the simplest experiments, rapid rates such as more than 10 Hz lead to an increase in synaptic strength, called long-term potentiation (LTP), and slow rates such as 1 Hz lead to a decrease in synaptic strength, called long-term depression (LTD). Reversal of LTP is called de-potentiation, and reversal of LTD is de-depression. NIBS, mimicking these techniques, can produce similar changes in excitability. If the excitability of the brain is changed, then a subsequent similar intervention might have a different effect. In that circumstance, plasticity has changed. Plasticity of plasticity is called metaplasticity.

If a region of brain has increased excitability with increased synaptic strength, increased neuronal excitability and increased activity, further attempts for plastic changes will be enhanced. The opposite will happen if there is decreased excitability and activity. This is called gating [6] and follows the principles of Hebbian conditioning, specifically the Bienenstock-Cooper-Munro (BCM) rule (fig. 1). There is a problem with this process. For example, if increased excitability leads to more excitability, it might well spiral out of control. Such metaplasticity is non-homeostatic. Fortunately, there is an opposite process that intervenes when excitability changes become extreme; this is called homeostatic metaplasticity. With homeostatic metaplasticity, if activity is low, interventions will tend to increase excitability and if activity is high, interventions will tend to

decrease excitability. The BCM rule and homeostatic plasticity can be put together with the BCM rule in mid-range and homeostatic plasticity at the high and low ends [7–9] (Fig. 1).

There is another process of Hebbian conditioning that describes changes in synaptic strength depending on the precise timing of action potentials in the presynaptic and postsynaptic cell, called spike-time dependent plasticity. In the most common situation, if the presynaptic activity is in the few ms before the postsynaptic activity, then the synaptic strength will be increased and if in the few ms after, the strength will be decreased. This is the origin of the phrase, "neurons that fire together, wire together." However, this process is dependent on the particular cells, and some synapses are opposite, called anti-Hebbian. The cell biology underlying these processes is still incompletely known [10].

TMS stimulation paradigms for producing plastic changes

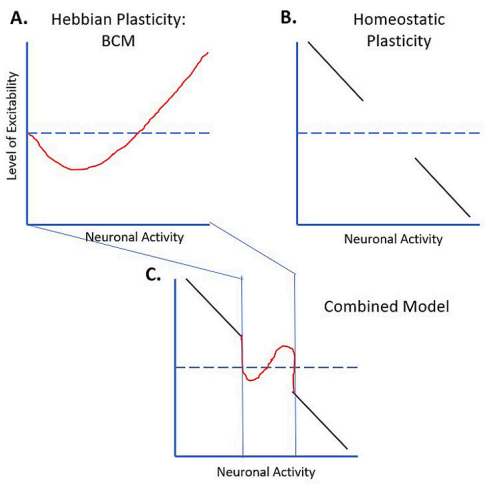
The simplest technique is repetitive TMS (rTMS). Slow rates, such 1 Hz, will lead to reduction of excitability and fast rates, such as 10 Hz or 25 Hz, will lead to increased excitability [11]. With rapid stimulation, excessive stimulation could cause a seizure and safety guidelines are available which, if followed, will allow rapid stimulation to be given safely [12]. Excitability is easily checked in the motor system with the amplitude of the motor evoked potential (MEP). Whether slow and rapid effects as seen in the motor system are always translated to other parts of the cortex is not certain. Studies of the increase and decrease in excitability show behaviour similar to LTP and LTD, respectively. As it is not certain that LTP and LTD actually underlie the changes, usually these are referred to as LTP-like and LTD-like, respectively.

Patterned stimulation methods can lead to faster changes in excitability. Theta burst simulation (TBS) is characterised by bursts of three stimuli at 50 Hz given at 5 Hz. Continuous TBS (cTBS) delivered for periods even as short as a minute can lead to decreased excitability. Intermittent TBS (iTBS) is given in 2-second trains, every 10 seconds. In just a few minutes, there will be a robust increase in excitability. Quadripulse stimulation (QPS) delivers bursts of four pulses every 5 seconds for 30 minutes [13]. The interval between the stimuli in the bursts vary; short intervals, optimally about 5 ms (QPS5), will lead to excitation and longer intervals, optimally about 50 ms (QPS50), will lead to inhibition. TBS and QPS changes of excitability are also LTP-like and LTD-like.

Another popular method for making a plastic change is paired-associative stimulation (PAS) [11]. In this technique the median nerve is stimulated and then paired with a single TMS to the motor cortex. Pairs are given repetitively at frequencies between 0.01 and 0.25 Hz. If the TMS is shortly after the input to the motor cortex from the median nerve stimulation, with an interval between median nerve stimulation and TMS of about 25 ms, then there will be an LTP-like effect. If the TMS is shortly before the median nerve input, for example with an inter-stimulus interval of 10 to 15 ms, then there will be an LTD-like effect. The size and direction of the effect seems to follow the spike-time dependent plasticity rule of Hebbian conditioning as described above.

All of the effects described here last only about 30 to 60 minutes. This obviously would be inadequate if a therapeutic effect is desired. If someone wanted to learn a motor skill and practiced just once for a few minutes, it would be unlikely that there would be any long-term learning. There must be repetitive practice and over time, there is a more enduring memory. This is similar with any TMS-induced plastic change. Where therapeutic effects have been found, the TMS has been given multiple times. What is the physiology underlying the more enduring change? The short-term change after a single TMS session appears to be spontaneously reversible. Presumably a long-term change would be due to more enduring synaptic changes or even circuit changes.

Figure 1: Principles of brain plasticity. The level of excitability of a region of brain is plotted as a function of baseline neuronal activity. A. The gating type of Hebbian plasticity. If neuronal activity is increased, further attempts to increase excitability can succeed, but if neuronal activity is decreased, then excitability will decrease. B. Homeostatic plasticity. With more extreme changes of neuronal activity, a background of increased activity will lead to decreased excitability while a background of decreased activity will lead to increased excitability. C. A combined model of Hebbian plasticity and homeostatic plasticity with the idea that Hebbian plasticity operates with small changes in neuronal activity and homeostatic plasticity will operate with larger changes. BCM refers to the Bienenstock-Cooper-Munro Rule. See text for more discussion. Figure is modelled after part of figure 3 in [7].



Lessons from motor learning

Excitability of the motor cortex was assessed with TMS during learning of a motor sequence in a serial reaction time task [14]. That there is a sequence is not revealed to the subject, but as they get faster with the movements, they eventually realise there is a sequence. During the early learning, the excitability of the motor cortex gradually increased, but then reduced after the sequence was appreciated. When practicing a sequence on a piano over 5 days, there was a gradual increase in excitability of the motor cortex over this time period [15]. A model of long-term learning and practice is the ability of the blind to read Braille. The excitability of the finger representations involved in reading was assessed by the size of the representation, and they were enlarged [16]. The full size of the representations was maintained by continuing practice, since

they shrank after stopping for a few days [17]. Thus, it does appear that a more enduring change can indeed be recognised by a change in excitability.

Lessons from repeated sessions

There have not been many studies of repeated TMS sessions in normal subjects. Several studies have looked at two sessions with the objective of studying homeostatic plasticity. For example, in one such study, two sessions of PAS were given at a 30-minute interval [18]. If LTD-like PAS preceded LTP-like PAS, the effect of the LTP-like PAS was increased. If there were two LTP-like PAS interventions, the increase in excitability from the second PAS was always less than the first, and there was even a negative linear relationship between the two effects. In another study, excitatory rTMS (5 Hz) or inhibitory rTMS (1 Hz) preceded LTP-like or LTD-like PAS [19]. Interactions were always homeostatic; for example, after 5 Hz rTMS, LTP-like PAS actually decreased excitability. Another study showed that the interval between two "strong" LTP-like PAS sessions is crucial [20]. With a 10-minute interval, the second PAS prolonged the excitability effect; with a 30 minute interval there were increases of both magnitude and duration. However, at intervals of 60 minutes and 180 minutes, there was no effect of the second PAS.

Such studies have not necessarily looked at two sessions of TMS, but instead one TMS technique and physical practice. For example, in one such study, PAS at different intervals primed a motor learning task. If LTP-like plasticity was induced, then motor practice was ineffective, but if LTD-like plasticity was induced, then motor practice was enhanced [21]. Such studies show that when doing repeated sessions, care has to be taken not to have effects blunted by homeostatic mechanisms.

Repeated sessions beyond two, at least within 1 day, have been studied with transcranial direct current stimulation (tDCS). A standard session of 15 minutes of 1 mA of anodal current produced about 30 minutes of increased excitability [22]. If repeated over the course of the day at 20-minute intervals, the excitability lasted for more than 24 hours. If repeated at 3-hour intervals, there was no prolonged benefit. Hence, multiple sessions can produce longer effects, but timing is crucial. A similar experiment with cathodal stimulation for an inhibitory effect failed to show a prolonged effect with the 20-minute intervals [23], again showing that all details matter.

Therapeutic studies

All studies show that repeated sessions are needed [24, 25]. A review of the indications and the quality of evidence is in this recent review and will not be repeated here. The most successful indication is for the treatment of depression and some aspects of that will be noted in relation to underlying principles. Neuroimaging studies in depression show hypometabolism of the left dorso-lateral prefrontal cortex (DLPFC). The most common technique for treatment is high frequency rTMS over the left DLPFC. Ten to 30 sessions are needed over the course of several weeks. The use of iTBS rather than rTMS allows shorter sessions and it seems that multiple sessions in the same day may shorten the total time taken for the treatment. Successful treatment improves the hypometabolism and, interestingly, improvement in depression can also be produced by various forms of inhibitory stimulation of the right DLPFC. Hence it appears that interhemispheric balance may also be relevant for benefit.

Another demonstration of the importance of interhemispheric balance comes from treatment studies of left side neglect after right hemisphere stroke. Benefit can be obtained with multiple sessions of inhibitory stimulation of the left parietal area [26, 27] and the benefit appears to require an intact corpus callosum connecting the parietal areas [28].

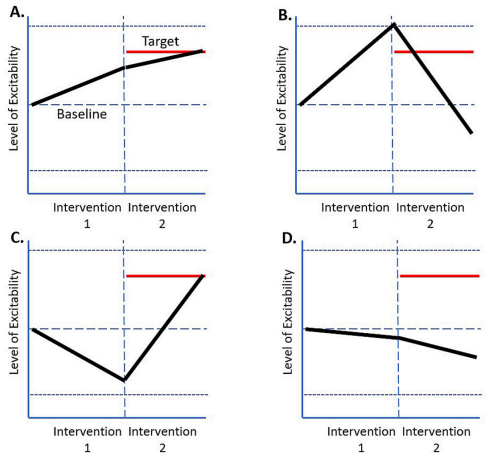
There is some evidence for benefit for the motor symptoms of Parkinson disease with high-frequency rTMS delivered to motor cortices bilaterally [24, 25]. Again, multiple sessions are needed. In one study, motor cortex excitability was tested before and after each rTMS session [29]. RTMS was delivered over both motor cortices and both DLPFCs at 25 Hz eight times over 4 weeks. Both gait and a complex arm movement task gradually improved, with benefit lasting 1 month. MEP threshold did not change at any time. MEP amplitude was tested at 120% of threshold. The amplitudes tested before the interventions went down very slightly over the sessions. MEP amplitudes immediately after the intervention increased about the same each time, and that increment correlated with the improvement in the speed of the arm task. However, despite clinical improvement, there was no significant change in motor cortex excitability.

TMS to augment behavioural training

TMS may well be able to have therapeutic effects on its own, but another way of using it would be to "prime" the brain so that subsequent behavioural training would be better. In one such study of Parkinson disease, 5 Hz rTMS was given over the leg motor area prior to 30 minutes of treadmill training to improve gait [30]. There was also a sham control rTMS group. Sessions were repeated 12 times over 4 weeks. Both groups improved, but the real rTMS group did much better. These investigators also studied brain excitability but focused on measures of inhibition. Patients were studied before the whole series of trainings and then again at the end. They found increases in motor threshold, lengthening of the cortical silent period and increase in the amount of short intracortical inhibition in both groups, but statistically more in the real TMS group. These changes bring the patients toward normal brain excitability. This does indicate a plastic change of the motor system.

In such studies, there is an important question in relation to getting a maximum effect. Should TMS priming be excitatory, to take advantage of gating, or should it be inhibitory to take advantage of homeostatic metaplasticity (fig. 2)? A recent study tackled that problem by comparing 1 Hz, 25 Hz, and sham rTMS as priming prior to treadmill training to improve gait in patients with Parkinson disease [31]. There were 12 sessions over 3 weeks; subjects were studied before the intervention, and 1 day, 1 month, and 3 months after the intervention. The 1 Hz and 25 Hz rTMS groups both produced more improvement in fastest walking speed, the timed-up-and-go test, and the MDS-UPDRS III than the sham group, and these effects were enduring for 3 months. The behavioural improvements in both real

Figure 2: Effects on the level of excitability of a region of brain with two successive interventions. Baseline level of excitability is the dashed line, and the upper and lower bound of a homeostatic window are dotted lines. The red line is the target of increased excitability. (The red line is pictured within the homeostatic window, but theoretically with multiple interventions a target might be achieved higher than the original upper bound.) A. Two successive excitatory interventions remaining in the range of Hebbian plasticity. B. Two successive excitatory interventions where the first intervention increases excitability to the maximum; in the second stage homeostatic plasticity is operative and the excitability level declines. C. Initial inhibitory intervention of substantial magnitude. The second intervention trying to increase excitability follows a homeostatic principle and the increase in excitability is also substantial. D. Initial small inhibitory intervention. Following principles of Hebbian plasticity, an attempt to increase excitability would be unsuccessful and might actually decrease the excitability. See text for more discussion.



rTMS groups were correlated with prolongation of the cortical silent period and increase in the short interval intracortical inhibition. The physiological changes were generally larger in the 25 Hz group than the 1 Hz group but did not reach statistical significance. The plastic change produced in this study is similar to that of the Yang et al. study [30], but with the methods here the effect is seen to last up to 3 months after the intervention. The authors interpreted the results to indicate that gating could have occurred with 1 Hz as well as 25 Hz, but the 1 Hz intervention could have asymmetrically pushed the inhibition far enough to enter the range where homeostatic plasticity would be operative. This is clearly a valuable study and more work of this sort will be helpful in optimising rehabilitation and therapeutic protocols.

Conclusion

It is clear that repeated use of rTMS (as the focused example of NIBS here) can have therapeutic effects and that it can lead to plastic changes of brain that can be enduring long after the stimulation has ended. Repeated use is needed, as changes from single interventions are only short-lasting. Why does NIBS lead to plastic changes when DBS does not? Perhaps because NIBS has its primary effect on cortex while DBS has its primary effects in deep structures. Or perhaps because NIBS is intermittent and DBS is continuous, and with continuous stimulation there is habituation. There is much more to learn.

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Potential competing interests
No conflict of interest relevant no this article was reported.

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