Plasticity in the Human Motor System

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Key Words

Plasticity · Motor system, human · Transcranial magnetic stimulation · Transcranial direct current stimulation

Abstract

It is well recognized that the number and effectiveness of synapses in the adult brain change in response to learning and that similar processes contribute to the restoration of function after central nervous system damage. It is possible to use non-invasive methods of brain stimulation in humans (transcranial magnetic stimulation or transcranial direct current stimulation) to study and even manipulate these processes. Initial studies are now underway to test whether modification of synaptic plasticity by neurostimulation can improve the recovery of motor function in patients after stroke.

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Introduction

‘Plasticity’ is a term that can have many meanings, but is probably best defined as a long-term change in the effectiveness of connections between one part of the CNS and another [1]. This can involve changes in the efficiency of transmission at existing synapses between two sites or changes in the number of connections between them. In the developing brain these processes determine the

form and eventual connectivity of the CNS; in the adult brain they are thought to be important in memory or learning.

Changes in the effectiveness of transmission at existing synapses can occur in a variety of ways. Increasing transmission equates to raising the probability that the arrival of a neural spike at the presynaptic bouton will generate an outgoing spike in the postsynaptic neuron. This could occur, for example, by increasing the amount of neurotransmitter released by each presynaptic impulse. Alternatively, we could reduce the rate of reuptake of transmitter from the synaptic cleft so that it remains available for a longer time to activate postsynaptic receptors. At the postsynaptic site it might be possible to increase the efficiency of each receptor so that its ion channels stay open longer and they have a greater effect on the potential of the postsynaptic membrane; inserting more receptors into the membrane would have a similar effect. Finally, voltage-sensitive ion channels in the postsynaptic membrane could be inserted too, thus to amplify the changes in transmembrane voltage produced by initial activation of postsynaptic transmitter receptors.

All of these mechanisms (and more) are known to be used at various sites in the CNS. However, the most intensively studied are the processes of long-term potentiation (LTP) and long-term depression (LTD) that occur at excitatory glutamatergic synapses. These terms refer to the fact that short periods of patterned pre- and postsynaptic activity can lead to lasting changes in the effective-

ness of transmission across the synapse. Both LTP and LTD involve changes in presynaptic and postsynaptic structures, and this can vary at different synapses. LTD and LTP do not necessarily last forever; they are thought to be intermediate stages that can be complemented by anatomical changes such as growth of new synapses, which can take several hours to develop.

Changes in synaptic plasticity and synaptic number are thought to play a crucial part in the recovery of function after CNS damage. However, it is important to recall that it is unlikely that synapses evolved specifically to aid neurorehabilitation; they are too slow and too inadequate to ensure any survival advantage. It seems more likely that they evolved (and hence are best adapted) to promote learning and memory, and have only been secondarily recruited to repair injury after CNS damage. Thus, they may well not function particularly efficiently in neurorehabilitation, and this may perhaps account for the frequent examples of maladaptive plasticity (such as chronic pain) that can occur.

Summary of Neurophysiological Background

LTP and LTD can be induced artificially by repeated electrical stimulation of neural pathways. For example, in many systems, several hundred stimuli at a low frequency (e.g. 1 Hz) lead to a reduction in synaptic strength, whereas rapid stimulation (e.g. 100 Hz, or a theta burst pattern of 3–5 pulses at 100 Hz applied 5 times per second) increases connection strength. A different approach is termed ‘spike-timing-dependent plasticity’, in which a presynaptic impulse is paired with postsynaptic discharge. Repeated pairings can cause LTP or LTD, depending on the time between the stimuli. Classically, if the presynaptic input comes before the postsynaptic discharge, then the synapse is strengthened, whereas the opposite sequence will lead to depression.

In the field of motor control, the best evidence for an involvement of synaptic strengthening in normal learning came from experiments on rats that had been trained to produce a particular movement with one forelimb [2]. After training, the rats were killed and the primary motor cortex in each hemisphere (trained vs. untrained) was examined to test how easy it was to induce synaptic plasticity in intracortical pathways. It was more difficult to produce any LTP in the trained hemisphere than in the untrained hemisphere, suggesting that the process of learning changes synaptic plasticity. It was proposed that learning induces LTP in the trained hemisphere, making

it more difficult to produce further LTP by electrical stimulation. Interestingly, testing for LTD led to opposite results: it was easier to induce LTD in the trained hemisphere than in the untrained hemisphere.

Changes in synaptic connections can also be observed after injury. At a gross level, one sign of this is the change in motor cortical maps that can be seen after focal damage in animal experiments. Thus, a lesion of the hand area of the cortex in a monkey is accompanied by a shift in the representation of the hand into adjacent areas of the cortex [3]. This only occurs if the animals are given ‘therapy’ to make them use the affected hand, but not if the animals had no ‘therapy’. Thus, functional recovery appears to depend on a reorganization of the cortex. At a synaptic level, the reorganization involves changing the strength of existing synaptic connections as well as sprouting and the formation of new connections in the area surrounding the lesion. Although much of the change involves perilesional tissue, there are also effects on remote structures that have afferent or efferent connections to the lesioned site, such as on the premotor cortex or the opposite, undamaged, motor cortex.

Testing and Inducing Synaptic Plasticity in Human Motor Cortex: Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

The advent of painless and non-invasive transcranial methods for stimulating the brain has opened the possibility of interacting directly with processes of synaptic plasticity in humans. Two methods are now in common use, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS). At the present time neither has specific approval for use from the FDA in the USA, and both have to be used under local license review board procedures. This is not the case in the rest of the world.

A TMS stimulator consists of a large electrical capacitance that is attached to a coil of several turns of copper wire. When the circuit is made, the capacitor discharges through the wire, causing a strong current (around 2,000 A is typical) to flow for about 1 ms. This current produces a large equally transient magnetic field that is of the same size as that in an MRI scanner. The magnetic field penetrates the scalp and skull easily, and because it changes so rapidly (from 0 to a very high value, then back again to 0 in 1 ms), it induces electrical (‘eddy’) currents in the brain under the coil. Effectively, the time-varying magnetic field ‘carries’ the electrical stimulus from the coil

across the barrier of the skull and scalp into the brain. The induced current pulse lasts about 200 μ s and is similar in amplitude to that produced by a conventional electrical stimulator applied directly to the surface of the brain [4].

The magnetic field falls off rapidly with distance from the coil so that it is usually assumed, unless the stimulus intensity is very high, that neural activation is limited to elements in the cortex or subcortical white matter. The most likely target of the stimulus is axons of neurons rather than their cell bodies or initial segment regions. Measurements of the strength-duration time constant to produce output from the motor cortex are consistent with this idea [5]. However, since many or most of these axons will have synaptic connections in the cortex, a single stimulus is capable of setting up cascades of activity in cortical circuits that outlast the stimulus pulse by many milliseconds.

A variety of axons belonging to different populations of neurons are activated under the coil. Some are local to the area of cortex under the coil, others project axons to or from the site of stimulation; some will be excitatory, others inhibitory. The final outcome might be complex and quite unlike the normal organized patterns of activity that occur in natural behaviours. However, some selectivity arises from the fact that different neurons have different thresholds to electrical stimulation. Low intensities of stimulation will therefore activate a much more limited population of neurons than higher intensities.

A TMS stimulator can produce single pulses of stimulation or trains of very many pulses at a variety of rates. If a single pulse is applied over the hand area of motor cortex, then it will produce a twitch of the hand muscles on the contralateral side; if the same stimulus is applied over the occipital cortex, then subjects may report seeing phosphenes, small transient patches of light in the visual field. Stimuli over other areas of the brain appear to have no obvious effects. However, this does not mean they are not stimulating the brain. In fact, a single pulse of TMS usually disrupts any processing that is going on at the time the stimulus is applied [6]. The reason for this is that the pulse synchronously activates many cells, which then discharge repeatedly for a short period of time. This disrupts their participation in any ongoing process for a period of about 50–100 ms. Normally, subjects do not note this transient interference with function, but if probed carefully, it can be revealed. For example, tactile thresholds can be transiently increased after a single TMS pulse to the sensory cortex [7].

Repeated TMS (rTMS) pulses are used to test and produce neural plasticity. As in animal work, several hun-

dred pulses at a low frequency (1 Hz) usually lead to a reduction in excitability, whereas high frequencies (>10 Hz) usually excite. Both effects outlast the stimulation by 30 min or more depending on the particular pattern and duration of TMS applied. In many protocols the effects do not occur if subjects are given an oral dose of a drug that interferes with NMDA receptors (an important component of the LTP and LTD effects in animals) so that the effects probably rely on LTP and LTD-like processes in the human brain [8].

A TDCS stimulator is a much simpler affair than a TMS stimulator. It consists only of a battery and a current regulator, attached by wires to two electrodes placed on the scalp. When the stimulator is turned on, a small constant current (1 mA) flows between the two electrodes. The duration of the stimulus varies, but typically the current is allowed to flow for many minutes (e.g. 10 min). TDCS is quite a different method of stimulating the brain than TMS; in fact, in many ways it does not 'stimulate' anything, it simply modifies patterns of ongoing activity. Thus, while TMS pulses depolarize axons and generate action potentials in cortical neurons, TDCS polarizes the neurons, increasing or decreasing their transmembrane potential by a few millivolts, while the current is present. This change in membrane potential will increase or decrease the mean firing rate of the neurons, depending on whether the stimulus depolarizes or hyperpolarizes the cell, respectively [9].

Like rTMS, TDCS leads to long-lasting after-effects on the cortex beneath the stimulating electrodes. Several minutes of anodal stimulation (positive electrode over the area of interest) will increase excitability for about 30 min, whereas 10 min of cathodal stimulation (negative electrode over the area of interest) will reduce excitability for the same period. Exactly how TDCS produces these long-term effects is unclear. One possibility is that if anodal stimulation depolarizes the postsynaptic neuron, the neuron is more likely to fire in response to any presynaptic input. This will tend to reinforce any ongoing patterns of input that lead to synaptic plasticity. Indeed, work in animal experiments has shown that depolarization of postsynaptic cells can increase the effectiveness of either LTP induced by a train of high-frequency stimulation pulses [10] or spike-timing-dependent plasticity induced by pairing presynaptic inputs with postsynaptic discharge [11].

The advantage of TDCS is that the stimulus cannot be perceived by the subjects, and therefore it is very easy to 'sham' treat individuals. TMS, in contrast, always makes a loud click and produces a mild scalp sensation when the

pulses are given, and is therefore more difficult to 'sham'. However, TMS is more focal than TDCS. Because of safety concerns about electrical burns to the scalp, TDCS electrodes are very large (approx. 35 cm²) so that the point of activation is not well defined.

Effects of rTMS and TDCS on the Healthy Human Brain

The after-effects of rTMS and TDCS can be measured in various ways including effects on fMRI activation patterns or behavioural performance. For example, 1,500 pulses of motor cortex TMS at a frequency of 1 Hz and an intensity subthreshold for evoking any visible movement of the body reduce the excitability of the motor cortex for 20–30 min after the end of the rTMS. Electrophysiologically this is detected as a reduction in the size of the muscle twitch that is evoked by a single standard suprathereshold TMS pulse [12]. Behaviourally it leads to a small increase in the reaction time of movements made by the opposite hand [13]. The same occurs after 10 min of anodal TDCS. If rTMS or TDCS is applied to the occipital cortex, the threshold for inducing phosphenes by a single TMS pulse is reduced, and contrast sensitivity is enhanced [14].

From the point of view of possible therapeutic applications in rehabilitation, it is interesting to note that rTMS and TDCS can also influence the speed at which subjects can learn tasks. Thus, anodal TDCS can improve performance in the serial reaction time task [15], and both rTMS and TDCS can increase the rate at which subjects can learn to make rapid finger movements [16].

Finally, it is important to note that the effects of rTMS and TDCS may not be confined to the sites of stimulation. Because both forms of stimulation change the activity in axons that connect to other areas, changes in excitability can be observed at distant points. Effectively, there is a change in the function of interconnected information loops [17].

Application of rTMS and TDCS in Rehabilitation after Brain Damage

Recovery of patients after stroke depends to a large extent on behavioural modifications that allow tasks to be performed successfully even though they are performed quite differently than before the damage. However, it is increasingly recognized that there is considerable poten-

tial for plastic reorganization of neural connections in the brain to produce some restoration of function that allows the relatively normal performance of everyday tasks. rTMS and TDCS may be able to play a useful role in this process of restorative neurology.

A number of studies have been performed to test whether a single session or multiple sessions of rTMS of the motor cortex can improve the recovery of arm and hand function in the acute and chronic phases after stroke [18]. Two approaches have been used: in the first, an excitatory rTMS protocol is applied to the affected hemisphere in order to increase its contribution to recovered movements; in the second, inhibitory rTMS is applied to the non-stroke hemisphere in an attempt to prevent it from inhibiting the activation of the stroke hemisphere and again improve the involvement of the stroke hemisphere in movement.

Single-session studies in which the motor performance of patients has been examined before and after rTMS have generally shown an about 10% improvement compared to placebo rTMS in chronic patients; there have been no single-session studies in acute cases, given the day-to-day variation in their symptoms. Daily treatments for 1 or 2 weeks have also been applied in order to produce an effect that might last days or months. Both chronic and acute studies have been successful with 10–20% improvements in hand and arm function lasting several weeks after the stroke. However, these are rather small-scale studies, and far more work needs to be done to define exactly which parameters of stimulation are optimal for individual patients as well as to define the time after stroke in which this type of therapy might be most effective.

At the present time there are very few studies of the potential usefulness of similar therapeutic approaches in aphasia or dysphagia. To date, TMS has been mostly used for assessing the potential role of the undamaged hemisphere in recovery. In dysphagia, it appears that a recovery of swallowing occurs mainly in response to increased activity in the non-stroke hemisphere. The situation is slightly less clear in aphasia. However, using TMS in its 'virtual lesion' mode has revealed that left hemisphere activation in aphasic patients is more consistently critical for the performance than right hemisphere activity. The implication from a therapeutic viewpoint would be that it might be more successful to try to increase excitability in the non-stroke hemisphere in patients with dysphagia, whereas the opposite might be true (increase excitability in the stroke hemisphere or decrease activity in the non-stroke hemisphere) in aphasia [19].

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