Basic and Clinical NEUROSCIENCE
Summer 2010, Volume 1, Number 4

Integrated Technologies Like Noninvasive Brain Stimulation (NIBS) for Stroke Rehabilitation; New Hopes for Patients, Neuroscientists, and Clinicians in Iran

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Article info:
Received: 1 May 2010
First Revision: 2 June 2010
Accepted:5 June 2010

Key Words:
Stroke,
Transcranial Direct Current Stimulation (tDCS),
Transcranial Magnetic Stimulation (TMS),

ABSTRACT

The applications of neurophysiological therapy techniques range far and few in the realm of modern day medicine. However, the concept of electromagnetic stimulation, the basis for many noninvasive brain stimulation (NIBS) techniques today, has been of interest to the scientific community since the late nineteenth century. Recently, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), two noninvasive neurostimulation techniques, have begun to gain popularity and acceptance in the clinical neurophysiology, neurorehabilitaion, neurology, neuroscience, and psychiatry has spread widely, mostly in research applications, but increasingly with clinical aims in mind. These two neurophysiological techniques have proven to be valuable assets in not only the diagnosis, but also the treatment of many neurological disorders (post-stroke motor deficits, tinnitus, fibromyalgia, depression, epilepsy, autism, ageing and parkinson's disease). Its effects can be modulated by combination with pharmacological treatment that has undergone resurgence in recent years. In this review we discuss how these integrated technology like NIBS for evaluation in the clinical evidence to date and what mechanism it work for stroke rehabilitation particularly. Then, we will review the current situation of stroke rehabilitation in Iran and new hopes that NIBS could bring for clinicians and patients in this nationally prioritized field.

1. Introduction

Modern brain imaging methods like magnetic resonance image MRI and Functional MRI (fMRI) are indispensible tools in neuropsychological research because they are completely non-invasive, yet offer high-resolution views of the brain's neural networks and allow us to assess the brain's underlying physiology. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are non-invasive brain stimulation (NIBS) technology that ad crucial functional dimension to studying the human brain in real time.

TMS is based on the principle of electromagnetic induction, as discovered by Michael Faraday in 1838. The development of TMS (Barker et al., 1985) has enabled safe and painless investigation of the motor cortex and the integrity of the central motor pathways. Interest in tDCS in clinical practice has been growing, however, the knowledge about its efficacy and mechanisms of action remains limited. Although, forms of DC stimulation have been used since the inception of modern electrophysiology (Aldini, 1804). tDCS gained popularity when it was applied by Priori et al (1998) to human subjects and was shown to influence cortical excitability.

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Reminiscent of the effects of repetitive TMS or tDCS can up- or down-regulate neural activity in the stimulated regions (Fregni and Pascual 2007, Pascal et al., 1994 and Maeda et al., 2000)

These techniques represent powerful methods for priming cortical excitability for a subsequent motor task, demand, or stimulation can optimize the plastic changes, leading to more remarkable and outlasting clinical gains in rehabilitation.

2. Basic Methodology of NIBS:

There have been a number of comprehensive reviews on the methodology and mechanism of NIBS in neuroscience (Bolognini et al., 2009, Fregni and Pascual 2007, Talelli et al. 2006 and Pascual et al., 2002).

The electric current in the coil in turn creates a magnetic field variation of 1.5 to 2 tesla (T) that penetrates the skull to about 1.5 to 2.0 cm and reaches the brain. The magnetic field then produces currents changing at rates up to 170 A/μs and induces electric fields in the cortex of up to about 150 V/m. That is, via electro-magnetic induction, TMS induces ions to flow in the brain without exposing the skull to an electric current.

There are different types of TMS coils. The round coil can be powerful, but it is not very focal, in the figure-of-eight coil, the magnetic fields at the intersection of the circles sum to make the stimulus more focal. Other types of coil were made to try to stimulate deeper regions of the brain, like the H-coil and another with the windings of the coil around an iron core rather than air.

TMS with a focal figure-of-eight coil can be used to demonstrate the gross somatotopy of the motor homunculus. Stimuli are applied at various scalp sites using a latitude/longitude based coordinate system referenced to the vertex, and the amplitude of MEPs evoked in contralateral muscles is measured.

There are some improvements in methodology of TMS and help to understand mechanism better. A recent pilot study from a research hospital in Berlin showed that the induced current activates nearby nerve cells in much the same way as currents applied directly to the cortical surface (Picht et al., 2008). Importantly, the magnetic field also does not affect the whole brain. The field reaches about 2-3 centimeters into the brain, and only directly beneath the treatment coil. With stereotactic MRI-based control, the precision of targeted TMS can be approximated to a few millimeters (Hannula et al., 2005). Recent development of navigated brain stimulation (NBS) is based on infra-red trackers, which allow the location of the coil to be continuously visualized on a 3D rendering of an individual MR image. It allows the coil location, rotation and tilting to be kept stable by using visual feedback and can monitor individual physical parameters on a sweep-to-sweep basis with sub-millimeter precision (Julkunen et al., 2009, Gugino et al. 2001; and Schmidt et al., 2009). This new technology is still expensive (more than hundred thousand dollars) and its applications in clinical settings need more scientific evidences.

Another method of NIBS is (tDCS) which delivers weak polarizing direct currents to the cortex via two electrodes placed on the scalp: an active electrode is placed on the site overlying the cortical target, and a reference electrode is usually placed over the contralateral supraorbital area or in a non-cephalic region. tDCS acts by inducing sustained changes in neural cell membrane potential: cathodal tDCS leads to brain hyperpolarization (inhibition), whereas anodal results in brain depolarization (excitation).

Differences between tDCS and TMS include presumed mechanisms of action, with TMS acting as neuro-stimulator and tDCS as neuro-modulator. Moreover, TMS has better spatial and temporal resolution, TMS protocols are better established, but tDCS has the advantage to be easier to use in double-blind or sham-controlled studies and easier to apply concurrently with behavioural tasks (for discussion of these methods, similarities and differences, see the review by Bolognini et al., 2009).

Though TMS and tDCS are noninvasive by nature, both stimulation techniques are associated with potential risks that require certain precautions. If, however, the experienced investigator follows the appropriate guidelines and recommendations [e.g., TMS (Rossi et al., 2009) and DCS (Nitsche et al., 2007 and Gandiga et al., 2006) both techniques can be applied safely with minimal adverse effects.

3. TMS Measurements:

There are series of objective measurements that could be obtained by TMS. These measurements have diagnostic values in evaluating cortical excitability and conduction time between different central nervous system areas. These measurements could also act as markers of changes in some certain neurotransmitters activity inside brain such as GABA, Glutamate or Dopamine.

3.1. Motor Threshold

Motor threshold refers to the lowest TMS intensity necessary to evoke MEPs in the target muscle when single-pulse stimuli are applied to the motor cortex. In most recent TMS studies, motor threshold is defined as the lowest intensity required to elicit MEPs of more than 50 μV peak-to-peak amplitude in at least 50% of successive

trials, in resting or activated (slightly contracted) target muscles (Rossini et al. 1994). TMS activates a mixed population of inhibitory and excitatory cortical interneurons, which can affect local and remote pyramidal tract neurons. The frequency, intensity, and coil orientation at which TMS pulses are delivered to the cortex significantly affect its consequences and its uses.

3.2. Motor Evoked Potentials (MEP)

When TMS is applied at intensities above motor threshold, the activation of excitatory interneurons can result in volleys of upper motor neuron activity, which subsequently activate the motor neurons of the spinal cord. The summed activity, an MEP, is measured via electromyography (EMG) from surface or needle electrodes over or in the muscles of interest or as descending volleys of direct (D) or indirect (I) waves recorded from epidural electrodes over the spinal cord, close to the pyramidal tract (Berardelli et al. 1999). The amplitude, area under the curve, and latency of MEPs are all used in various ways to measure motor cortical excitability.

One consequence of this is that the higher the intensity of the TMS stimulus, the larger the area of the MEP map. In addition, the higher the excitability of the cortical neurons, the easier it will be to stimulate them at a distance from the coil. The apparent area of the MEP map will be larger than if excitability is low. The movement evoked will be related to the first recruited muscle at the point of stimulation. If several muscles acting on the same joint are recruited simultaneously, then the MEP will depend on the strength and mechanical advantage of the muscles about the joint. Relatively discrete and reproducible movements can be evoked in distal hand muscles, but this is rarely possible for more proximal muscles because of their higher threshold. The reduced amplitude of MEPs is associated with a central motor conduction failure in many cases. Even in healthy people, however, the size and latency of MEPs show great inter- and intra-individual variability, leading to a broad range of normal values; therefore, results are qualitative rather than quantitative.

3.3. Short-Interval Intracortical Inhibition (SICI) and Facilitation (SICF)

Exploiting TMS's preferential activation of interneurons and transsynaptic activation of pyramidal tract cells has allowed for a better characterization of inhibitory and facilitatory mechanisms operating within M1. Paired pulse stimulation delivered through the same magnetic coil over M1, where a suprathreshold test stimulus (TS) is preceded by a subthreshold or suprathreshold conditioning stimulus (CS) can be used to gain insight into the relative contribution of local inhibitory and excitatory inputs to M1 pyramidal tract cells. The CS can cause an increase in MEP amplitude (facilitation, SICF) or decrease in MEP amplitude (inhibition, SICI) compared with the MEP evoked by the TS alone.

3.4. Silent Period

TMS-pulses delivered during active tonic muscle contraction of approximately 5 s with the instruction to maintain contraction at least 2 s after the stimulus. For instance, the duration of the cortical silent period or the TMS-induced delay in voluntary movement can be used to map inhibitory effects of TMS (Thickbroom et al. 1996). Measures of cortical inhibition MEP measures represent the net facilitatory effect of a TMS pulse. Two methods provide complementary information on the excitability of cortical inhibitory circuits. The silent period is the period of suppressed EMG activity that follows an MEP evoked in actively contracting muscle. It is due to a combination of spinal and cortical effects. The extra period of inhibition is due to suppression of cortical excitability, probably through the action of a long lasting GABA-B-ergic IPSP (Werhahn et al. 1999). Measurements of the duration of the silent period are thought to give an estimate of the excitability of this system. The silent period is evoked by relatively high stimulus intensities. However, a different inhibitory system can be activated at much lower intensities. Kujirai et al. (1993) demonstrated that the MEP evoked in resting muscle could be suppressed if it was preceded by a subthreshold stimulus given 1–5 ms earlier.

4. Diagnostic Implications of TMS

One area in which TMS has contributed to the understanding of the neurobiological basis of motor disorders has been the evaluation and diagnosis of psychogenic paralysis. The patterns of findings in these studies can help to localize the level of a lesion within the nervous system, distinguish between a predominantly demyelinating or axonal lesion in the motor tracts, or predict the functional motor outcome after an injury. The abnormalities revealed by TMS are not disease-specific and the results should be interpreted in the context of other clinical data. Some TMS findings can be quite useful for an early diagnosis (eg, multiple sclerosis, Bell's palsy, psychogenic paresis, plexus neuropathy) and prognostic prediction (eg, multiple sclerosis, stroke, cervical spondylosis). Such a finding may result in more objective diagnostic criteria for this disorder. Theoretically, a thorough characterization of neurophysiological abnormalities in this disorder may lead to interventions targeting these abnormalities and, hence, better treatment. However, what TMS can add to detailed, serial neurological exams has yet to be ascertained.

4.1. Diagnosis

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5. Mechanisms of NIBS Actions

Exactly which neural elements are activated by TMS and the mechanisms of neuronal stimulation remains unclear and might be variable across different brain areas and different subjects (Pascual et al., 2002).

The mechanisms underlying long-term effects of TMS are incompletely understood, but they could be analogous to long-term potentiation (LTP) or depression (LTD) seen in the hippocampus after repeated activation of synaptic pathways (Hoffman et al., 2002, Wang et al., 1999 and Huang et al., 2005). In addition, modulation of neurotransmitter levels seems to be a contributing factor. The neurotransmitter systems involved include the inhibitory GABAergic system (Donoghue et al.,1996 and Hess et al., 1996) as well as the excitatory glutamatergic system with activation of NMDA receptors (Hess et al., 1996). TMS may result in changes in endogenous neurotransmitters (GABA and glutamate) and neuromodulators (DA, NE, 5-HT, ACh) which play a pivotal role in the regulation of the neuronal activity in the cerebral cortex (for review, Hasselmo et al., 1997). A focal increase of dopamine in the striatum was indeed demonstrated in healthy human after sub-threshold 10 Hz rTMS applied to the ipsilateral primary motor cortex (Strafella et al., 2001) or dorsolateral prefrontal cortex (Strafella et al., 2003).

Some studies have aimed to clarify the cellular mechanisms of tDCS over the motor cortex (Nitsche et al., 2003 and Liebetan et al, 2002). Furthermore, anodal stimulation had a significant positive effect on I-wave facilitation. I-waves are modulated by GABAergic drugs and ketamine, an NMDA-receptor antagonist, but not by ion channel blockers (Nitsche et al., 2000 and Liebetan et al, 2002) thus implicating effects on inhibitory synaptic pathways in the mechanism of action of anodal stimulation. In simple terms, tDCS does not cause resting neurons to fire; it rather modulated the spontaneous firing rate of neurons by acting at the level of the membrane potential. This quality distinguishes tDCS from other stimulation techniques, which excite neurons directly, such as TMS/rTMS, conventional TES or electroconvulsive therapy in research.

In summary, the mechanism of action of tDCS is not completely clear but appears to involve a combination of hyper- and de-polarising effects on neuronal axons as well as alterations in synaptic function.

6. Stroke in Iran

Stroke is the third leading cause of death and the first in serious adult disabling diseases in most countries. More than 750,000 Americans suffer strokes each year and the number of death reaches 150,000 annually. It would be terrifying to know that every 45 seconds someone suffers a stroke and every 3 minutes somebody dies from the disease. That stroke is one of the most disabling and fatal diseases among the Iranian old and even middle age population and it continues to be a major public health problem.

Unfortunately, there is no reliable data about incidence and mortality-morbidity rate of stroke in Iran and it seems Iran's health ministry has difficulties in gathering this information especially from the remote and smaller cities because of not having an integrated data system available. But, In a study on stroke patients admitted to the emergency department of a large university (Shariati) hospital in Tehran during a one year period (Sikaroodi, et al., 2008a); there were no significant differences between stroke characteristics in Iran and western countries.

In the United States, of the surviving patients (about 75-80% of total stroke victims/year), 30% need help for usual activities of daily living, 20% need help for ambulation, and 16% need institutional care; Only one third of patients return to an independent life. Although there is no precise estimation of financial burden of stroke in Iran, considering diagnostic and therapeutic costs, short and long term care expenses, lost productivity (as well as hidden costs), it should be at least 4 billion US $/year (author's consensus opinion).

Regarding to significant negative impact of stroke on public health and social economy, it has become one of the major priorities in many countries to establish stroke related services with three main missions:

1- Primary and secondary prevention,

2- Reducing mortality rate, and,

3- Improving survivors' independence in daily activities.

For these purposes development of specialized, well organized and coordinated medical facilities that provide comprehensive services in every phases of stroke is crucial for every heath care system. But, unfortunately, unlike the situation for heart diseases (with many good and well equipped centers), there are almost no specialized hospitals or services for stroke patients in Iran. Some hospitals do not even admit stroke patients and in some hospitals, patients do not receive a multidisciplinary therapy. The reason is, of course, unavailability of appropriate facilities, to do more or severe deficits in team working between different involved specialities. This lack of an integrated approach in which acute care should be linked with early rehabilitation as well as comprehensive assessment of medical problems, active physiological management, skilled nursing and early setting of rehabilitation plans, has led to a great waste of prevention and rehabilitation potentials in stroke fields.

Meanwhile, there are physicians, physiatrists, and neurologists with especial interest in stroke, and most of the laboratory and diagnostic imaging techniques, and nearly all of the therapeutic measures are available inside the country.

The main shortcomings are:

1. Lack of precise statistical data about stroke in Iran,

2. Lack of a national stroke guidelines for management of stroke in acute and chronic phases,

3. Lack of specialized and coordinated centers (such as Stroke Centers) for the acute treatment of stroke,

4. Insufficient number of stroke neurologists and lack of stroke nurses,

5. Uncoordinated activity with neurosurgeons, psychiatrists, cardiologists, radiologists, physical therapists, and anesthesiologists, and

6. Lack of sophisticated rehabilitation facilities and centers.

These defects in stroke treatment network in Iran have placed a great deal of economic burden on Survivor's family and health care system. Among all these deficits, investment on stroke rehabilitation is one of the most cost effective prioritized and doable interventions. Bearing in mind, in a reasonable setting of stroke management, only one third of patients return to an independent life; the importance of Stroke rehabilitation will be highlighted. While one of high priorities, stroke rehabilitation is largely neglected in our country. The reasons are:

1. Facilities are not available in many areas,

2. Are relatively expensive; and

3. Are not delivered in a service package and multidisciplinary way.

Also, rehabilitation is still not considered seriously by many physicians, partly due to not observing the evidence of its effectiveness in their everyday practice.

A collaborative network between different disciplines involved in stroke rehabilitation is of outmost importance. Providing active rehabilitation measures and use of modern rehabilitation techniques (such as NIBS), may considerably lower the morbidity and economic burden of stroke for the victim, his/her family, socially, and nationally.

Since Stroke Centers are very costly and need a relatively long time to be established, providing stroke rehabilitation including NIBS departments (even a few in Tehran and big cities), may at least partially cover the present shortcomings in the management of stroke disabilities.

7. NIBS in Stroke Rehabilitation

TMS delivered to different levels of the motor system (neuraxis) can provide information about the excitability of the motor cortex, the functional integrity of intracortical neuronal structures, the conduction along corticospinal, corticonuclear, and callosal fibres, as well as the function of nerve roots and peripheral motor pathway to the muscles. The neurological deficit observed following acute stroke is largely due to the death of neuronal tissue in the affected region. Restoration of viable blood supply to this region, and resolution of perilesional edema and inflammation are factors possibly contributing to rapid recovery of function following stroke (Rossini et al., 2003). Another important consideration following stroke is the disruption of neuronal networks in undamaged brain regions that are remote from the original injury but are functionally connected, such as subcortical regions or the contralateral motor cortex. Originally, this concept was termed "diaschisis" and was proposed as a principle for recovery following brain lesions (von Monakow, 1914) but evidence of this has only recently been provided (Seitz et al., 1999).

Stroke alters the balance between excitation and inhibition between the hemispheres, which suggests that down-regulation of the unaffected M1 may facilitate motor recovery following stroke (Murase et al., 2004). The

ability of rTMS to modulate motor cortical excitability in a frequency-dependent manner has been exploited in studies investigating stimulation of either the affected or unaffected hemispheres of stroke patients. Depending on rTMS parameters, long lasting suppression or facilitation of cortical excitability can be induced: Low-frequency rTMS decreases cortical excitability (Pascal et al., 1994, 1999 and Maeda et al., 2000) and has been applied to the unaffected motor cortex to decrease hyperexcitability in chronic stroke patients (Takeuchi et al., 2005). A single session of 1 Hz rTMS decreased cortical excitability and transcortical inhibition, and led to a short-lasting increase in pinch acceleration of the paretic hand, while no change was seen following sham stimulation. In contrast, a recent study applied 3 Hz rTMS in conjunction with routine rehabilitation in acute stroke patients, and found that real, but not sham, stimulation decreased disability over a two-week period, although there was no increase in motor cortical excitability as predicted (Khedr et al., 2005). Favorable neurological effects have been reported after high-frequency rTMS in patients with stroke (Khedr et al. 2005 and Kim et al. 2006 and Yozbatiran et al. 2009).

In terms of safety, 20 Hz rTMS was well tolerated and in terms of behavioral effects, modest improvements were seen, for example, in grip strength, range of motion, and pegboard performance, up to 1 week after rTMS (Yozbatiran et al. 2009).

rTMS was a useful adjunct to conventional therapy for dysphagia after stroke (Khedr et al. 2009). High frequency rTMS reduces cerebral cerebral vasomotor reactivity, possibly as a secondary effect on autonomic control of cerebral hemodynamics. The effect of rTMS on cerebral hemodynamics should be carefully considered before proceeding toward a therapeutic application in stroke patients (Vernieri et al. 2009).

Because standard rTMS protocols exhibit post-stimulus effects of short duration, novel protocols such as theta burst stimulation (TBS), are promising approaches to enhance the effectiveness of rTMS. Although TBS protocols of the human prefrontal cortex seem to be safe in healthy subjects (Grossheinrich et al. 2009).

Hummel et al. (2005) studied stroke patients as they practiced an upper limb training task, the Jebsen-Taylor Hand Function Test or JTT. Performance time decreased significantly after stimulation, but not after sham stimulation, with greater improvement in tests requiring fine motor control than tasks involving proximal arm control. Stimulation increased the amplitude of MEPs recorded using recruitment curves and SICI was significantly reduced, suggesting that GABA receptor-dependent inhibitory processes were involved (Hummel et al., 2005). The significant correlation between improvement in JTT time and increased recruitment curve slope suggests that tDCS can influence motor cortical excitability and can improve skilled motor functions of the paretic hand in chronic stroke patients. Recent developments have led two research groups to suggest that cortical stimulation combined with motor training can lead to greater functional gains in stroke patients than rehabilitative training alone (Bütefisch et al., 2004; Hummel et al., 2005). Some activation in the uninjured brain could reflect adaptive cortical reorganization that promotes functional recovery, but some changes may be maladaptive and generate the emergence of behaviors, suppression of which would promote neurorehabilitation. These studies suggest that decreasing inhibition in the affected M1, and perhaps other motor related areas such as the dorsal premotor cortex, can unmask pre-existing, functionally latent neural connections around the lesion and contribute to cortical reorganisation (Takeuchi et al., 2005).

Contralesional neglect after stroke is not due to the lesion itself but primarily due to the hyperactivity of the intact hemisphere, and 1 Hz rTMS of the unaffected parietal lobe to suppress excitability of the intact hemisphere can improve contralesional visuospatial neglect after stroke (Oliveri et al. 2001). Naeser and co-workers (Naeser et al., 2002) have shown that patients with Broca's aphasia may improve their naming ability after 1 Hz rTMS of the right Brodmann's area 45 that is supposed to be overactivated in patients with unrecovered, non-fluent aphasia. These observations are transient and it is premature to propose them as realistic therapeutic applications. Nevertheless, rTMS of the region of interest detected in functional images could highlight the property of plastic changes of the cortical circuitry and hint at future novel clinical interventions.

Even though the duration of the off-line effects is frequently thought to be relatively short-lived, lasting minutes to hours depending on the duration and stimulation pattern of the rTMS train, there are suggestions of longer-lasting effects. A second train of rTMS applied even 24 h after a first one to the motor cortex has been shown to have a more robust effect on corticospinal excitability (Maeda et al., 2002). However, to date, there has been no systematic study of such a prediction, or of other critical aspects of the application of NIBS to injured brains. For example, the effects that strokes can have on perturbing the currents induced by TMS in the neural tissue are insufficiently experimentally tested, despite the well-known fact that after a stroke, numerous physiologic changes occur in the brain tissue, which can alter its electrical response properties. A computer-based model concluded that the distribution of TMS-induced currents can be severely disrupted by tissue changes associated with a stroke lesion (Wagner et al., 2006).

Since, tDCS has become quite well known for its simplicity, cost-affordability, and safety. As in the 1960s, there are still many fundamental unresolved questions concerning how various differences in brain anatomy induced by neurological disorders, such as stroke, influence the stimulating currents . Thus, although behavioral (Nitsche et al., 2002) and imaging studies (Nitsche et al., 2004b) suggest the 'brain effects' of tDCS, little has been done to quantify the current densities injected during stimulation, to compare them to published current density magnitudes necessary for neural stimulation, or to analyze how different stimulation parameters can influence the stimulating currents (Fregni and Pascual-Leone, 2007). The effects of a single tDCS session persisted for more than 25 min after the stimulation but returned to baseline levels during repeat testing 10 days later. In another study, patients with central pain from traumatic spinal cord injury experienced significant improvement 16 days after a course of tDCS treatment to the motor cortex (Nitsche et al. 2003). The improvement occurred following 5 consecutive days of anodal (but not sham) tDCS of 2 mA and it was proposed that this may have been due to a secondary modulation of thalamic nuclei activity.

Enhancement of excitability can be achieved with either high frequency rTMS or anodal-tDCS. Suppression of excitability can be accomplished with either low-frequency rTMS or cathodal-tDCS. A growing body of evidence from small clinical trials has demonstrated the efficacy of both approaches to induce considerable changes on cortical excitability, which often correlate with relevant clinical gains in motor functions.

An essential issue to take into account, when applying these NIBS protocols to a damaged human brain, is related to the concept of homeostasis (that is the human's brain ability to regulate changes in synaptic plasticity as to avoid drastic changes in its function). Therefore homeostasis is likely to respond definitively and forcefully to artificial and functionally non-specific changes in network activity such as those probably induced by NIBS. Homeostatic plasticity (i.e., the dependency of the amount and direction of the obtainable plasticity from the baseline of a neuronal network) is increasingly recognized as regulatory mechanism for keeping neuronal modifications within a reasonable physiological range. Here, NIBS could be influential for driving longer-term consolidation of new network patterns. The choice of the more suitable time window for NIBS intervention likely needs careful examination in order to exclude maladaptive cortical responses, which could interfere with or even suppress the effects of the behavioral therapy.

8. NIBS for Stroke Rehabilitation in Iran

Needless to say, when planning to solve any problem, there is need for precise statistics and measurements to evaluate the situation and assess effectiveness of interventions. A new Iranian National Stroke Database and Registry (INSDR) Protocol has been introduced recently (presented at 6th world stroke congress in Vienna, Sikaroodi, et al., 2008b), proposing a unified-user friendly and culturally validated method for data collection, as a four A4 pages work sheath in a HTML format for uploading in web-pages. Demographic data, and findings in general and

Figure 1. Multidisciplinary stroke rehabilitations in Iran. Combination of brain stimulation technology to other conventional methods of rehabilitations in a team work is an essential element to reach to long lasting treatment outcomes.

neurologic examinations, laboratory and imaging data, and pre- and post stroke Barthel and Modified Rankin Scale were included. Nearly all of the data is entered by checking boxes (only a few items need to be entered as text), and the average time for completing each form is 45 minutes. The database is both shareable and comparable, and we think it may help to perform multicenter/national/international studies on stroke, more easily.

Fortunately, from 10 active NIBS centers (all rTMS equipped) in Tehran (3 academic sites in medical university hospitals) and 3 centers in other cities (Shiraz, Yazd and Isfahan), 2 centers are mainly devoted to multidisciplinary stroke rehabilitation and others usually accept referred stroke cases from stroke rehabilitation centers. All of these sites agree on the undeniable acute effects of rTMS on stroke patients (personal communication with center's heads); but, most of them emphasize on the serious need for multidisciplinary rehabilitation work on the patients to obtain sustainable results.

Of course, in order to establish multi level centers dedicated to stroke rehabilitation utilizing NIBS, health authorities and decision makers should provide careful national guidelines and regulations, and provide facilities needed for many different training courses, and finally issue certifications for the approved staff and centers who will do the great job. INSDR along with specialized neuropsychological assessments and neuroimaging protocols could provide a monitoring system for further evaluation and follow up long term effects of different protocols of NIBS in Iran to upgrade and revise national protocols periodically.

9. Summary

The major limitation of tDCS is probably that it is not focal enough to map cortical functions precisely. Furthermore, it cannot produce temporally focused effects like TMS. On the other hand however, the application is simple. Successful blinding of subjects and investigators is possible to conduct double-blind and sham-controlled trials. Despite these promising results, some limitations of TMS need to be noted. Critically, after stroke, there is a change in the local anatomy and the lesion evolves in time to formation of scar tissue and, particularly in the case of cortical damage, larger cerebrospinal fluid spaces. Because the conductance of cerebrospinal fluid (CSF) is 4 to 10 times higher than that of brain tissue, scar formation and larger CSF spaces modify the geometry and magnitude of the electric field induced by rTMS, and stimulation of the lesioned hemisphere can become difficult to predict unless careful modeling is done (Lancaster et al., 2004).

The diagnostic and therapeutic potential of both tDCS and TMS is undeniable. Although both treatments have their detriments, with further research and recognition, useful techniques could be developed to promote the integration of these neurostimulation methods into clinical settings. Greater understanding of the mechanisms of action of each approach is necessary in order to optimize their combined use in rehabilitation and realize the promise of a more effective means to promote functional recovery after brain injury. NIBS technologies are located in their first steps to act as a reliable effective treatment modality for neurological patients; and in this stage, developing countries such as Iran, based on their available experiences and understructures, could have a good role in scientific promotion of this field and therefore utilize NIBS benefits for their patients. In the long run, maintaining the life-style of neurologically impaired individuals can be extremely costly and time-consuming. But, NIBS brings new hopes for cost effective interventions to improve patient's quality of life in Iran and the world.

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