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Basic and Clinical
NEUROSCIENCE

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Editorial:
Implantable Microsystems for High-Resolution Interfacing to the Brain

Almost a decade after the invention of the first semiconductor transistor in 1948, it took the revolutionary technology almost a decade to evolve from producing single devices to integrating only a few transistors as the first integrated circuit (IC) in 1958. Since then, integrated circuits have been in continuous progress for more than half a century as predicted by the well-known Moore's law. While integrated circuits still continue their progress with the same exponential pace, it is almost a decade that a new branch of science and technology has emerged, known as integrated microsystems. This can be taken as the natural technological evolution from individual circuit chips and non-circuit modules to complete systems with small physical dimensions and light weight. Integrated microsystems have opened windows of hope to providing efficient solutions to some of the problems that have not been resolvable by any other means whatsoever.

Among many kinds of microsystems being developed for a wide variety of applications, such as automotive industry, aerospace engineering, environmental monitoring, and defense systems, implantable biomedical microsystems are of increasing interest to both medical and engineering communities. This is mainly because of the capabilities such devices are expected to provide on the medical side, and also the technical challenges available on the engineering side. Examples of biomedical implants are pacemakers, cochlear implants, neural recording microsystems, and deep brain stimulators.

Electrically interfacing with the nervous system goes back to Benjamin Franklin's works no more than 250 years. Intra-cortical interfacing with the brain with high density and at the same time with high spatial resolution is, however, a rather new concept, being made possible by using unique capabilities advanced microtechnology has to offer. This technology is capable of implementing complex circuits with up to millions of transistors on silicon chips as small as a few millimeters on a side, realizing non-electronic structures such as probes and electrodes with sub-micron fabrication resolution, and finally integrating and packaging of all the electronic and non-electronic parts required to make a tiny implantable microsystem.

Implantable neural interfacing microsystems are known as powerful tools to enable neuroscientists perform high-density intra-cortical studies in the order of tens to hundreds and even thousands of parallel channels, and with high spatial resolution in the order of hundreds to tens of micrometers and even finer. It is also believed that such devices can successfully treat neural disorders such as epilepsy, paralysis, and Parkinson's disease, and even help effectively overcome deafness and blindness. On the non-medical side, researchers in cognitive sciences are among the other groups that anxiously await fully functional neural interfacing implants, using which they can talk to the brain and learn about how the signals sensed from the outside world are recognized.

Implantable microsystems designed and developed for intra-cortically interfacing with the central nervous system can be considered among the most sophisticated types of biomedical implants, possessing perhaps the most interesting applications. The extent of interest attracted to research in this area is clearly reflected in the daily increasing number of publications on the design and application of such devices. As evidence, Fig. 1 shows the exponential-like growth of papers and other relevant scientific and technical documents being published. This plot is the result of a search over Elsevier Scopus database for documents of any type with the words 'microsystem' and 'neural' in their titles, abstracts, or keywords.

An implantable neural interfacing microsystem, in general, comprises a microelectrode array (MEA), an analog front-end interfacing with the target tissue for recording and stimulation, and a radio frequency (RF) front-end for wireless interfacing to the external world. In order to be fully implantable, a neural interfacing microsystem needs to fulfill the following requirements:

Small physical size–No matter how powerful it is, it is evident that a microsystem needs to be small enough in size in order to be implanted in the brain without considerable damage to neighboring organisms and living tissues.

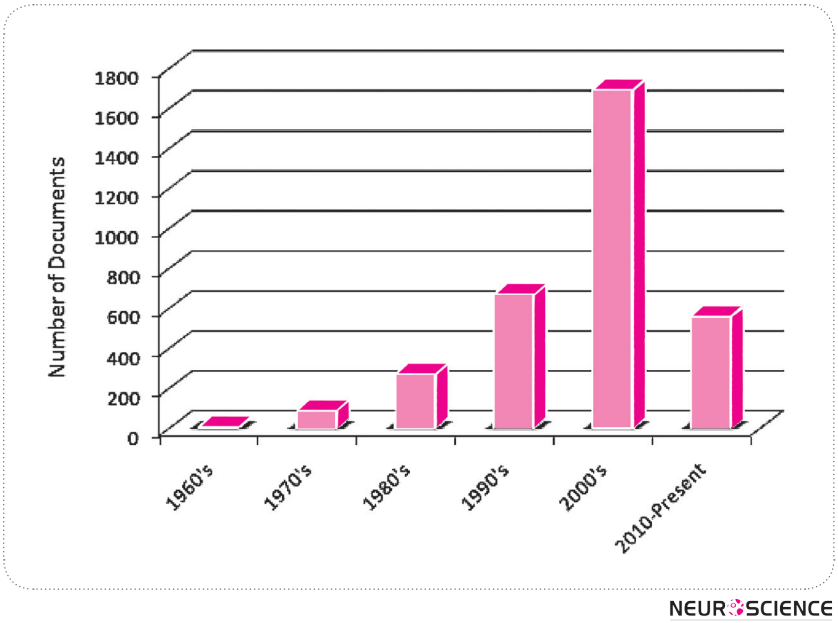

Figure 1. Number of scientific and technical documents published with the words 'microsystem' and 'neural' in their titles, abstracts, or keywords

Wireless operation–An implantable microsystem needs to bidirectionally communicate to an external set-up through wireless connection. Programming a neural interfacing implant to operate in the proper mode, setting parameters such as amplification gain and bandwidth for recording and the details stimulation pulses for stimulation necessitate the flow of data from the external side to the implant. In the reverse direction, one needs to transfer recorded neural data from the implant to the external setup, too.

Packaging– Electronic circuitry in an implant, need to be properly packaged and sealed in order to be protected from undesired chemical and electrochemical interactions with their surroundings. Moreover, packaging of an implant is sometimes necessary in order to protect the living body from the toxic materials used in the implant.

Biocompatibility–It is also of crucial importance to avoid bringing materials in touch with the body that might cause irritation, inflammation, or any other undesired reactions by the body. Even if the materials used for the development of an implant are not toxic, it is important to avoid unwanted reactions the body might show to the implant as a foreign object. For these reasons, implantable microsystems are either made out of biocompatible materials such as silicon, titanium, platinum, or gold, or encapsulated with materials such as silicone and parylene.

Over the past few decades, depth and breadth of research on the design, development, and employments of implantable neural interfacing microsystems has been expanding with an admirably rapid pace. These devices are expected to revolutionalize research in the near future not only in basic and clinical neuroscience, but also in so many other application areas.

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Letter to Editor:
Cheap Technology Like Transcrinal Direct Current Stimulation (tDCS) Could Help in Stroke Rehabilitation in South Asia

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Dear Editor, Stroke is caused by a disturbance in the supply of blood to the brain due to vascular pathology, thereby exhibiting a loss of brain function related its vascular territory. Stroke can be either ischemic or hemorrhagic. It is generally recognized that starting an individualized rehabilitation program as soon as possible after a stroke event, increases the chances of a patient recovering lost function sooner and to a greater extent.

Transcrinal direct stimulation (tDCS) is one type of Non Invasive Brain Stimulation (NIBS), which is a technology that holds promise for the future studies on diagnosis and therapeutic applications in different brain diseases. Major advances in this emerging field have been made relatively quickly, from new stimulation protocols for research to their application for the treatment of neurological and psychiatric diseases. But there is a serious question among developing countries with limited financial and human resources, about the potential returns of an investment in this field and regarding the best time to transfer this technology from controlled experimental settings to health systems in the public and private sectors.

With any new medical tool, the scientific community should ask what it offers that established methods do not in terms of diagnostic, prognostic, and therapeutic aspects of clinical practice. A new tool might have several benefits including: earlier establishment of a definitive diagnosis for a given clinical presentation, better prediction of the disease course, further support for sustained and intensive interventions, identification of the most suitable treatment strategy, and improvement of clinical outcome as a therapy itself. Current work indicates that NIBS may show promise in all of these areas.

Stroke is the third most common cause of death and the first leading cause of disability in developed and developing countries (American Heart Association, 2005). According to World Health Organization estimates, 5.5 million people died of stroke in 2002, and approximately 20% of these deaths occurred in South Asia (SA) (Feigin, 2005). Contrary to decline in the incidence of the disease in the Western population, the burden of the disease in SA countries (India, Pakistan, Bangladesh, and Sri Lanka) has inclined and is expected to rise (World Health Organization, 2007). Considering a high population, absolute number of stroke in SA would be in millions. Its consequences are myriad ranging form physical disability to death, to psychologic, social and economic consequences. These consequences do not only affect the individual or his/her family but also society as a whole.

There is not any published study showing that patients affected with stroke related disorder in SA receive any therapeutic treatment related brain stimulation. The main reason for this disparity is the lack of resources in such countries. We therefore propose a simple technique of brain stimulation that seemed long forgotten, but has received renewed attention, named transcranial Direct Current Stimulation (tDCS). This treatment is inexpensive, easy to administer, non-invasive and painless (Fregni & Pascual-Leone , 2007).

Advantages over tDCS by affecting a wider region of brain involving not only primary motor cortex but also premotor, supplementary motor, and somatosensory cortices, all of which have been shown to have a role in the recovery process in various studies (Nitsche et al., 2003). Stroke alters the balance between excitation and inhibition between the hemispheres, which suggests that

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down-regulation of the unaffected primary motor cortex (M1), may facilitate motor recovery following stroke (Fregni & Pascual-Leone , 2007).

tDCS is a NIBS technique in which two spongy electrodes, an anode and a cathode, are placed on the scalp after being soaked in saline solution. A current generator is connected to the two electrodes and delivers a low intensity electrical current thereby polarize membrane potential of neurons in stimulated area. Current that flows from the cathode to the anode have an inhibitory effect on the stimulated area while current that flows from the anode to the cathode is typically excitatory. The excitatory and inhibitory potentials tDCS can regulate are of great important in clinical applications (Fregni & Pascual-Leone , 2007, Nitsche et al., 2003 & 2008).

Two modes of tDCS have been used in human stroke rehabilitation studies, namely, anodal stimulation (increase in excitability) of the lesional hemisphere and cathodal stimulation (decrease in excitability) of the contralesional hemisphere. Proof-of- principle studies have been performed for both of these approaches using tDCS (Nitsche et al., 2008).

Thus, we have come to believe that tDCS might be a reasonable alternative therapeutic treatment for stroke in SA. The device to deliver tDCS is simple, can cost less than US$100 00 and can be manufactured locally. The equipment is fully reusable and utilizes one standard battery that can last several weeks. Furthermore, this treatment is easy to administer, and can be applied by technicians following appropriate instruction and training. Although further studies evaluating this method are warranted, tDCS might help to improve mental health in areas with poor resources (Nitsche et al., 2007).

Though tDCS are noninvasive by nature, tDCS technique is associated with potential risks that require certain precautions. If, however, the experienced investigator follows the appropriate guidelines and recommendations can be applied safely with minimal adverse effects ((Nitsche et al., 2003, 2008)).

The major limitation of tDCS is probably that it is not focal enough to map cortical functions precisely. Successful blinding of subjects and investigators is possible to conduct double blind and sham-controlled trials (Nitsche et al., 2007 and 2008).

Given the extensive health technologies available, it is often difficult for developing countries to decide which emerging technologies are best suited for their own needs with their current resources. In the long run, maintaining the life-style of neurologically impaired individuals can be extremely costly and time-consuming.

tDCS in clinical practice is promising as it gives another opportunity to modulate synaptic strength and brain function through top-down controlled manner, meaning that this intervention could be applied according to its patho-mechanisms and lesion locations of various clinical disorders. Moreover, by combining with bottom-up input like exercise or training, it could be used as additive therapeutic approach. Future Hopes for tDCS in clinical field would be developing more potent and disease-specific stimulation paradigm as well as training protocol for long-term therapeutic effect.

After a decade of speculation and experimentation, NIBS has not yet yielded any treatments that effectively alleviate any disorder. Despite this fact, interest remains high, perhaps due to the intuitive appeal of non-invasive stimulation and modulation of plastic neural circuits. Thus, intermittent treatments directed at the cortex may not be strong enough to provide meaningful change.

Conclusion

tDCS is useful technique to modulate and induce plastic changes in the brain thereby use it therapeutically in various disorders including stroke, which is worth to start to develop in South Asia in many aspect.

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Review Paper:
Methodological Dimensions of Transcranial Brain Stimulation with the Electrical Current in Human

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Non Invasive Brain Stimulation (NIBS).

ABSTRACT

Transcranial current stimulation (TCS) is a neuromodulation method in which the patient is exposed to a mild electric current (direct or alternating) at 1-2 mA, resulting in an increase or a decrease in the brain excitability. This modification in neural activities can be used as a method for functional human brain mapping with causal inferences. This method might also facilitate the treatments of many neuropsychiatric disorders based on its inexpensive, simple, safe, noninvasive, painless, semi-focal excitatory and inhibitory effects. Given this, a comparison amongst different brain stimulation modalities has been made to determine the potential advantages of the TCS method. In addition, considerable methodological details on using TCS in basic and clinical neuroscience studies in human subjects have been introduced. Technical characteristics of TCS devices and their related accessories with regard to safety concerns have also been well articulated. Finally, some TCS application opportunities have been emphasized, including its potential use in the near future.

1. Introduction

Throughout the previous decades, therapeutic stimulation modalities have made a great influence on paving the way towards treating a number of neuropsychiatric disorders. In the competitive field of achieving different ways to modulate the brain activity in a certain direction, there have been some other types of brain stimulation techniques including TMS (Transcranial Magnetic Stimulation), ECS (Electro Convulsive Stimulation) and DBS (Deep Brain Stimulation) in parallel with the presently focused technology, TCS (Transcranial Current Stimulation). TCS, the re-emerged way of brain stimulation, had been forgotten for a while after its discovery while it has been taken into consideration over the previous years. Hence, plenty of studies, pilot or proof-of-principle, have been carried out to investigate whether it can eventually result in a clinically approved application or not. Actually, a brilliant progress has been made and is still moving towards accomplishment in order to have its efficacy depicted as a beneficial method in both basic and clinical neuroscience. The present article provides a technical comparison among the recent modalities of brain stimulation and presents an introduction to the currently commercially available TCS devices illustrating some of their technical characteristics. Moreover, a brief discussion on TCS electrodes in addition to applications in basic studies where this method reveals as a potential method of choice will be made.

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2. Historical Overview

The rudimentary idea of 'therapeutic electricity' is relatively old if we consider the application of some animals, fish for instance, to treat some neurological disorders(Priori, 2003). Luigi Galvani and Alessandra Volta were two of such researchers who benefited from an animal source of electricity to do tDCS-based researches. As such, many fundamental studies were made until the 19th century by which TCS was developed as a technical method of brain stimulation. Eduard Hitzig (1867) who was one of the pioneers in utilizing the constant current to treat depression happened to notice involuntary movement of the subjects' eyes when doing his experiments. In collaborationwith an expert anatomist, Gustav Fritsch, Hitzig conducted other studies to verify such phenomenon. He ultimately demonstrated the correlation between stimulating different cortical areas and distinct responses in the contralateral limb (Gross, 2007; Pauly, 1983).

Later, Bishop and Erlanger (1926) conducted a related study on the effect of polarity on motor neurons, which led to the fact that the anodal stimulation would cause an increase in the membrane potential difference, while the cathodal one would result in a decrease of the same (Bishop & O'Leary, 1950). In the1960s, Bindman discovered that a 0.1–0.5 μA of electrical current would sufficiently produce a neural excitability shift in rat's cortex which remained for some hours after the stimulation was terminated(Bindman, Lippold, & Redfearn, 1962, 1964). Such an incidence evoked a considerable enthusiasm to modulate the brain excitability through brain polarization, which would cause a long-lasting result at the expense of a relatively short duration of stimulation.

Consequently, Lippold and Redfearn found many benefits of brain polarization to treat depressive disorders in patients, especially in those who had failed to respond to prior methods, including ECT (Electroconvulsive Therapy). This became more evident following the experiments on rats' cortex in collaboration with Bindman(Bindman, et al., 1964; Lippold & Redfearn, 1964; Redfearn, Lippold, & Costain, 1964). Taken in to account that all subjects were healthy , these investigators found that the anodal stimulation increases the alertness, mood and motor activity, while the cathodal one results in apathy and quietness(Lippold & Redfearn, 1964; Redfearn, et al., 1964). Costain continued to carry out some controlled experiments to further prove the efficacy of such a method(Costain, Redfearn, & Lippold, 1964). However, the desire to hold on the studies disappeared while trying to reach the analogous results (Arfai, Theano, Montagu, & Robin, 1970; Hall, Hicks, & Hopkins, 1970; Lifshitz & Harper, 1968) until the 1990s (indeed from 2000s)that TCS came back to both therapeutic and cognitive studies, specifically in human subjects. This approach started to offer new hopes after disappointing results came from pharmacological studies where psychotropic drugs failed to control refractory patients' symptoms.

3. Mechanism of Action

Based on recent neuroimaging studies, serving as a helpful tool for improving the efficacy of stimulation according to determination of targeted area, some main effects have been discovered to better understand the mechanism of tDCS. The imaging modalities such as positron emission tomography (PET)(Lang et al., 2005), functional magnetic resonance imaging (fMRI) (Baudewig, Nitsche, Paulus, & Frahm, 2001)and magnetic resonance spectroscopy(Arul-Anandam & Loo, 2009; Rango et al., 2008)can be considered in this category. These methods have proven some changes in the regional blood flow, glutamatergic neurotransmission and membrane function after stimulating the brain regions distal to the sites involved.

Noteworthy is that, the tDCS potentially changes the spontaneous firing rates without influencing the action potentials (Arul-Anandam, Loo, & Sachdev, 2009) and this is mainly due to the current densities being less than the action potential threshold of cortical neurons(Tehovnik, 1996; Wagner et al., 2007).Some studies have indicated that tDCS works successfully in stimulation since it changes the resting membrane potential while blocking the sodium ion channels through special drugs in order to decompose the changes in motor-evoked from the resting potential(Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003).

4. Different Brain Stimulation Modalities

Currently, there are a variety of brain modulation methods utilizing the electric and magnetic fields in order to alter the brain's activity. Some of these include, ECT (Electroconvulsive Therapy), VNS (Vagus Nerve Stimulation), TMS (Transcranial Magnetic Stimulation), DBS (Deep Brain Stimulation), Ultrasonic and Photonic stimulation.

In table 1, some of these modalities are being compared based on the interface, waveform and their general characteristics, stimulating machine and the approximate duration of stimulation. This is to provide an insight into technical properties of such methods. These descriptions partly prove the privileges of TCS over the other modalities.

For TCS in particular, the interface is defined as a saline soaked cotton pad containing rubber electrodes for conventional stimulation while some tiny set of electrodes are used for High-definition type. Conventional type electrodes' shape is usually square or rectangular and made of the materials mentioned. The working voltage of the TCS device here describes the threshold of stimulation in which the device is turned off in order not to exceed the outcome current. Also, the power consumption of the device has been noted as one of the possibly-stated characteristics. The duration also states the required period of time for the process to be carried out.

Table 1. Technical characteristics of different brain stimulation modalities

	Interface				Waveform		Stimulating Machine			Duration
	Shape	Size	Material	Other properties	A [1]	F [2]	V [3]	C [4]	P [5]	
TMS (Griskova, Hoppner, Ruksenas, & Dapsys, 2006; Speer et al., 2000; Wagner, Valero-Cabre, & Pascual-Leone, 2007)	Magnetic coil				Magnetic pulse		400-10K	4k-10k	5M	-
	Single circular loop/ figure-8 shaped	4-9 cm diameter (10-20 winding turns)	Wound copper wire	15-150 µH Inductance	1-4 Tesla	1-5 (Low); 10-20 (High)				
tDCS (Minhas et al.; Wagner, Valero-Cabre, et al., 2007)	Saline soaked cotton pads/ sponge patches covered with conductive gel/ array electrodes				DC current		To 66.7	To 2m	-	5-30 min.
	Square [6] Disk/pellet/ ring [7]	20-35 cm^2 [8]/ 12 cm^2 [9]	Cotton, Ag/AgCl, Ag	Current density: 24-29 µA/ cm^2	0.5-2 mA	-				
tACS (Minhas, et al.; Wagner, Valero-Cabre, et al., 2007)	Saline soaked cotton pads/ sponge patches covered with conductive gel/ array electrodes				Pulse train Square		30-35 p-p	0.1-4 m	-	5-30 min.
	Square [10] Disk/pellet/ ring [11]	25-35 cm^2 [12] /12 cm^2 [13]	Cotton, Ag/AgCl, Ag	Current density: 24-29 µA/ cm^2	0.5-2 mA	0.5-167 k				
DBS (Butson & McIntyre, 2006; Gimsa et al., 2005)	Metal Electrodes				Rectangular Pulse		-10 ¬_ -3	0.01-2 m	-	2-7 years (battery re-charge needed)
	Bar shaped	Approximately 1.27mm diameter,1.5mm height, 5.98 mm^2 surface	Stainless steel, Pt/Ir	Having conductivity 0.2 S/m	3 v	100-185				
ECT (Scott, 2009)	2 electrodes				Rectangular Pulse		600-1000 mC charge needed (Several hundred watts)			1-6 sec.
	cylinder having electrodes (relatively similar to TCS) in the end				~ 800 mA	~ 100				
Photonic (Zhang et al., 2009)	Red and Infrared light optrodes				650-900 nm Wavelengths	~ (100 ms)$^{-1}$	-	-	To 6.6 mW	Different [14]
	Bar-shaped	0.5-1.5 mm height	Platinum covered	Involving a volume of ~ 7.57 *10^5 um^3						
Ultrasound (Yoo et al., 2011)	Ultrasound Transducer				Ultrasound pulse		-			1-2 sec.
	Single Array	Variable	-	-	Isppa [15]= 12.6 W/ cm^2	690 PRF [16]= 10 Hz				

1. Amplitude
2. Frequency (Hertz)
3. Voltage (volt)
4. Current (Ampere)
5. Power (Watt)
6. Conventional tDCS
7. High definition tDCS
8. Conventional tDCS
9. High definition tDCS
10. Conventional tDCS
11. High definition tDCS
12. Conventional tDCS
13. High definition tDCS
14. Differs from 1 second at a distance of 5 feet, to 40 minutes in direct contact with the skin
15. Intensity of spatial-peak pulse-average
16. Pulse repetition frequency

5. TCS Requirements

Prior to start the procedure, the availability of the required materials should be carefully ensured. In the following, a set of essential materials is mentioned:

• TDCS device; the main component of the stimulation process comprises an electric apparatus which delivers the considered power to the target.

• Two sponge electrodes; the outer layer of the interface between the involved tissue and the power applying device.

• Two conductive rubber electrodes; the inner part of the sponge electrodes, supposed to deliver the applied current as a conductive medium.

• NaCl solution; the conductive solution used to obtain a better contact.

• Two rubber head bands; used to fasten and fix the electrodes on subject's head.

• 9V Battery (2x); the source from which the required power is generated.

• Cables; placed between the device and the electrodes, used to guide the electric power to the electrodes.

• Measurement Tape; used to determine the aimed place of stimulation and to locate the electrodes in order to have the desirable montage.

The following picture illustrates the required components of a common TCS device.

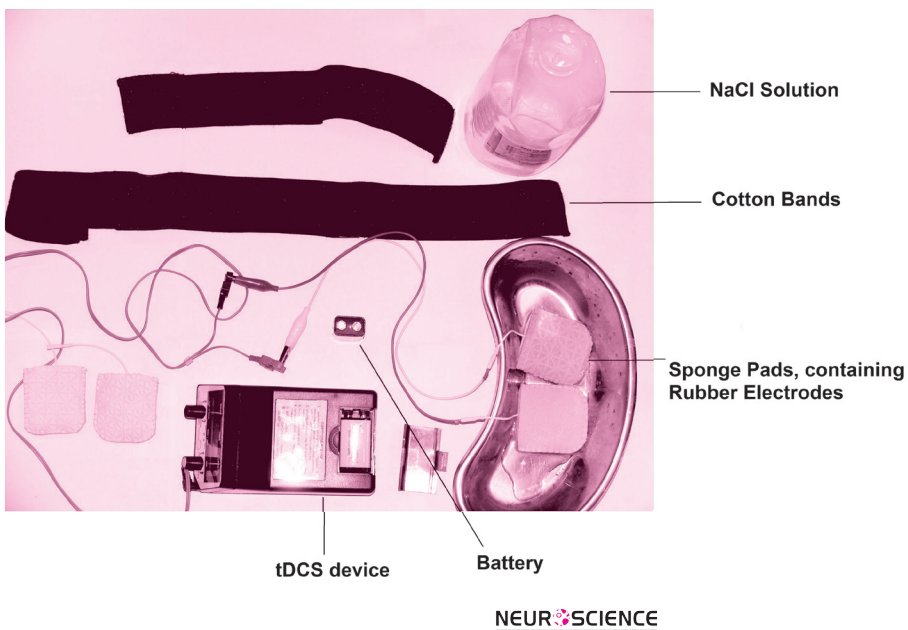

Figure 1. The preliminary TCS requirements

6. TCS Machine

Presently, there are many commercial types of TCS stimulators which have enabled some clinical and research applications. They can be categorized as off-label and on label devices. The on-label devices are particularly designed and then used for TCS and mostly tDCS due to their applicability for clinical trials, while the off-labels are used for TCS in addition to some other applications. In the following categories, there will be a brief description on some of these items, prior to summarizing them in table 2.

The front panel of an ideal TCS device is illustrated in the following figure to provide a view of its required parts.

On-Label Devices

6-1) Eldith stimulator – direct current (DC) stimulator used in clinical trials, in a hospital setting with the supervision of specialized personnel.

6-2) HDC series – programmable and portable device for tDCS treatment. The latest in this series is the HDCstim device.

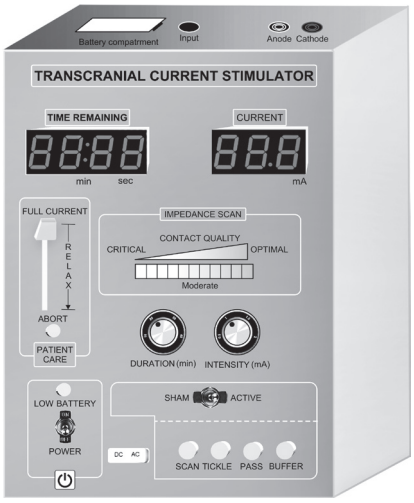

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Figure 2. A sample tDCS device; the "Time Remaining" part reverse counts the preset time; the "Current" part indicates the applied current intensity; Patient care can be dedicated to manually increase or decrease the intensity and abort the whole process if necessary; the "Impedance Scan" estimates the electrodes contact impedance and verifies its quality to optimize the place of electrodes, it will be optimal if the whole triangle gets colorful; "Duration and Intensity" knobs account for the preliminary stimulation adjustment. When set to the Active mode, Scan (scans and checks the contact's impedance), Tickle (applies an excess amount of current in cases of insufficient contacts), Pass (enables the main process of stimulation) and Buffer (isolates the device and electrical fields from environmental inputs –e.g. MRI) options should be adjusted, otherwise Sham mode should be selected; AC or DC types can be selected with the pertaining switch.

6-3) Soterix Medical stimulator: direct current (DC) generator used specially for delivering the required current to the target of the stimulation in both conventional and high definition type of stimulation.

6-4) Fisher Wallace Stimulator: a portable, safe and effective way for delivering a gentle, patented electrical current via sponge electrodes.

6-5) Trans-Cranial Stimulator: a portable, safe and easy-to-use device for delivering direct current to the scalp.

6-6) Starstim: a noninvasive wireless tCSneurostimulator used to perform electrical stimulation along with EEG monitoring.

Off-label TCS Devices

6-7) CESta – a high quality cranio-electro stimulation (CES) device capable of being promoted for use as tDCS, Micro-TENS or as a colloidal making device.

6-8) ActivaDose II Iontophoresis Delivery Unit – a delivery unit used to administer the prescribed soluble salts or other drugs into the body for medical purposes as an alternative to hypodermic injection.

Table 2. Summary of the commercially available TCS devices.

Usage type	On-label						Off-label	
Device Trademark	**Eldith (neuroConn)**	**HDC**	**Soterix**	**Fisher**	**Trans-Cranial-Technologies**	**Neuroelectrics**	**CESta**	**Activadose II**
Different available types	•DC-Stimulator •DC-Stimulator Plus •DC-Stimulator MR •DC-Stimulator MC	HDCstim (mostly)	• 1×1 tDCS-Stimulator • 4×1 Two Channel Stimulator •M×N Advanced System	Fisher Wallace Stimulator	Trans-Cranial	Starstim	CESta Stimulator	Activadose II Iontophoresis Delivery Unit
Stimulation Modalities	Conventional tDCS/ tACS	Conventional tDCS	Conventional tDCS/ tACS , HD-tDCS	Conventional tDCS/ tACS	Conventional tDCS	HD-tDCS	Conventional tDCS	Conventional tDCS
Company Reference	www.neuroconn.de/tdcs_en/	www.magstim.com/tdcs	www.soterixmedical.com	www.fisherwallace.com	www.transcranial.com	http://neuroelectrics.com/	www.mindalive.com/2_2	www.activatekinc.com/

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Eldith Stimulator

There is a variety of options in this category based on the DC/AC stimulation type, single/multi-channel device, clinical/personal at home use, etc. It should be noted that the basis of the design remains the same, although some physical and practical aspects of the device vary.

6-1-1) DC-Stimulator for tDCS

Supplied with a microprocessor-controlled constant current source, it serves two main modes of stimulation, including single (with a continuous stimulation, configurable fade-in and fade-out) and pulse one (cyclic turning on/off for the stimulation with a configurable pulse width and interval).

6-1-2) DC-Stimulator Plus for tDCS and tACS

Presenting two stimulation types of DC (unipolar) and AC (bipolar) in different modes of active and sham stimulation, four stimulation modes have been provided; ‘’tDCS’’(continuous stimulation, adjustable current of 0 to ± 4,500 uA ,duration 15-1,800 s , duration of fade-in/ fade-out 1-120 s) , ‘’Pulse’’ (cyclic turning on/off of stimulation, duration of complete pulse cycle/interstimulus interval (ISI) 300-2,000 ms, pulse width 200-(ISI-100), number of pulse cycles 1-500), ‘’Sinus’’(bipolar sinus waves adjustable current of 0 up to 3,000 uA , offset 0-±1,000 uA, frequencies of 0-250 Hz, adjustable phase 0-360 degree, duration 0-480 min), ‘’noise’’(normally distributed broadband low and high frequency noise, adjustable current of up to 1,500 uA, offset 0-±1,000 uA, duration 0-1,800 s, fade-in/fade-out period of 0-120 s)

6-1-3) DC-Stimulator MR

Equipped with the same facilities of the previous models, an extra amenity of MRI compatibility has been added, since no interference of the fMRI images during EPI sequence had been observed.

6-1-4) DC-Stimulator MC

7-Equipped with 4 programmable, microprocessor-controlled constant current sources using independent channels, it can serve various stimulation types including tDCS, tACS, CES[17], GVS [18] and tRNS[19]. This device is provided with the aforementioned modes of stimulation, including continuous, cyclical switching on and off, sinusoidal stimulation and their combination. The device is also fMRI compatible and neither makes nor takes any interference.

HDC Stimulators – HDCstim

This device has not only been provided with the previous models’ facilities, but also equipped with some other accessories in order to monitor the impedance of the contacts, to alarm in the case of insufficient contact. Generally, it has the ability to deliver DC stimulation to the target tissue, as well as the others.

Soterix Medical Stimulator

Offering a variety of devices, the overall idea of the design mostly remains the same as using a current generator. Unlike the others, it is equipped with the high definition type and benefits from some excess modes to technically simplify the whole process, such as monitoring the contact efficiency of the electrodes.

6-3-1) 1×1 tDCS Low-Intensity Stimulator

The Soterix Medical 1*1 line of low-intensity tDCS stimulator is mainly designed to produce low levels of DC current running through the two electrodes, the anode and the cathode placed on the target. It has several features to improve the safety of the process and to promote the subject comfort. These include, TRUE CURRENT, SMARTscan, RELAX and Pre-Stim TICKLE. In the SMARTscan mode, a continuous visual illustration of the electrodes’ quality is provided, before the stimulation or during it. In TRUE CURRENT mode, the supplied current is clearly depicted. In the TICKLE mode, a very weak current prior to tDCS may be applied in order to condition the skin. The RELAX mode also allows the clinician to reduce the current less than its preset given some exceptions such as the subject feedback. This includes two types of devices, the simple one and the ‘clinical trials’type which can be used to more conveniently perform many clinical investigations.

6-3-2) 4×1-C2 Multi Channel Stimulation Interface

Being an accessory to the isolated 2-channel stimulator, it is designed to be used with 5 leads where 4 leads (colored) are connected to an output of the stimulator,

17. Cranial Electrical Stimulation
18. Galvanic Vestibular Stimulation
19. Transcranial Random Noise Stimulation

and the remaining lead (white) is connected to the other output of the tDCS stimulator. This setup benefits from up to four modes including scanning, pass, tickle and buffer. In the first mode, the impedance between the surface of the electrode and the skin is scanned to find the optimized place of contact leading to a better current division among the electrodes.

In the second mode, the current will be delivered to the surface of the scalp and in the third mode, a small current will be applied through a selected electrode to lower its impedance if necessary. In the buffer mode, the electrodes will be isolated from the main circuitry of the apparatus, enabling the device compatibility with MRI and TMS.

6-3-3) M×N Advanced Neuromodulation Systems

As a non-invasive neuromodulation platform developed in M×N HD-tDCS stimulators (8-channel and 4-channel), this setup provides the clinician with control of electrode placement and the current, resulting in a novel noninvasive targeting. As such, the HD-targets and HD-explore systems enable the investigators to carry out automatic or manual dose optimization. The MXN system can be configured for effective DC stimulation without reportable sensation in most subjects. This system consists of multiple electrodes arranged in a special montage (4×1 for instance), resulting in more focal current delivery to the cortex.

Fisher Wallace Stimulator

This device is specifically equipped with an AC delivering source which can supply 0-4 mA output current. It has been designed to work on patented frequencies of 15/500/15000 Hz with the pulse width of 33 microseconds, where the maximum charge per pulse will be 0.13 micro coulombs. The setup has also been provided with On/Off Time Per Burst of 50 milliseconds and 16.7 milliseconds, respectively. Its configuration can be simply changed to tDCS application for investigational studies. It is mainly based on conventional tDCS model having saline soaked sponge pads and its current density can be altered using a knob which can both be used to determine the current intensity or turn the device on/off.

Trans-Cranial-Technologies

This device can provide a direct current of 0.5 to 2 mA in 0.1mA increments; it can be used for up to 30 minutes with countdown current display. Meanwhile, it can monitor and display actual current and electrode quality; it also ramps up in a slow manner to raise the subject's comfort through conditioning the skin. Moreover, automatic abort has been added in cases of excessive resistance to prevent skin irritation.

Starstim

Multi-channel programmable tCS is capable of performing current-controlled tDCS, tACS and tRNS in sham or user-defined waveforms. It can stimulate and record at the same time using the same electrodes which provides the user with a visualized EEG monitoring. It is equipped with EEG data output and Bluetooth 2.1 communication set, while is compatible with different operating systems of Windows and MAC. Finally, it can provide a maximum current of ±2 mA per electrode while recording EEG signals at a specific sampling rate.

CESta Stimulators

Analogous to the prior models, it is equipped with the essential accessories to deliver DC current to the aimed tissue. It has the ability to check the connections to estimate the skin impedance in order to find the possible deficiencies in the electrodes' contact. It is also provided with some presumed function libraries, prepared in some tables, to determine the required specifications of stimulation according to the patient's disorder.

Adding to the above specifications and function, Micro-TENS stimulation, tDCS, Colloidal Silver production and Synchronization with the company's Digital Audio-Visual Integration Device (DAVID) and other types of Portable and Lightweight (PAL, PAL36)devices can be considered as CESta stimulator's functions.

ActivaDose II Iontophoresis Delivery Unit

The ActivaDose II Iontophoresis Delivery Unit is indicated for the administration of soluble salts or other drugs into the body for medical purposes as an alternative to hypodermic injection in situations when it is advisable to avoid the pain of needle insertion and drug injection and to minimize the infiltration of carrier fluids, or to avoid the damage caused by the needle insertion when tissue is traumatized.

It only works at a continuous stimulation mode and is able to provide the required current up to 4 mA in a ramp up manner with an adjustable duration.

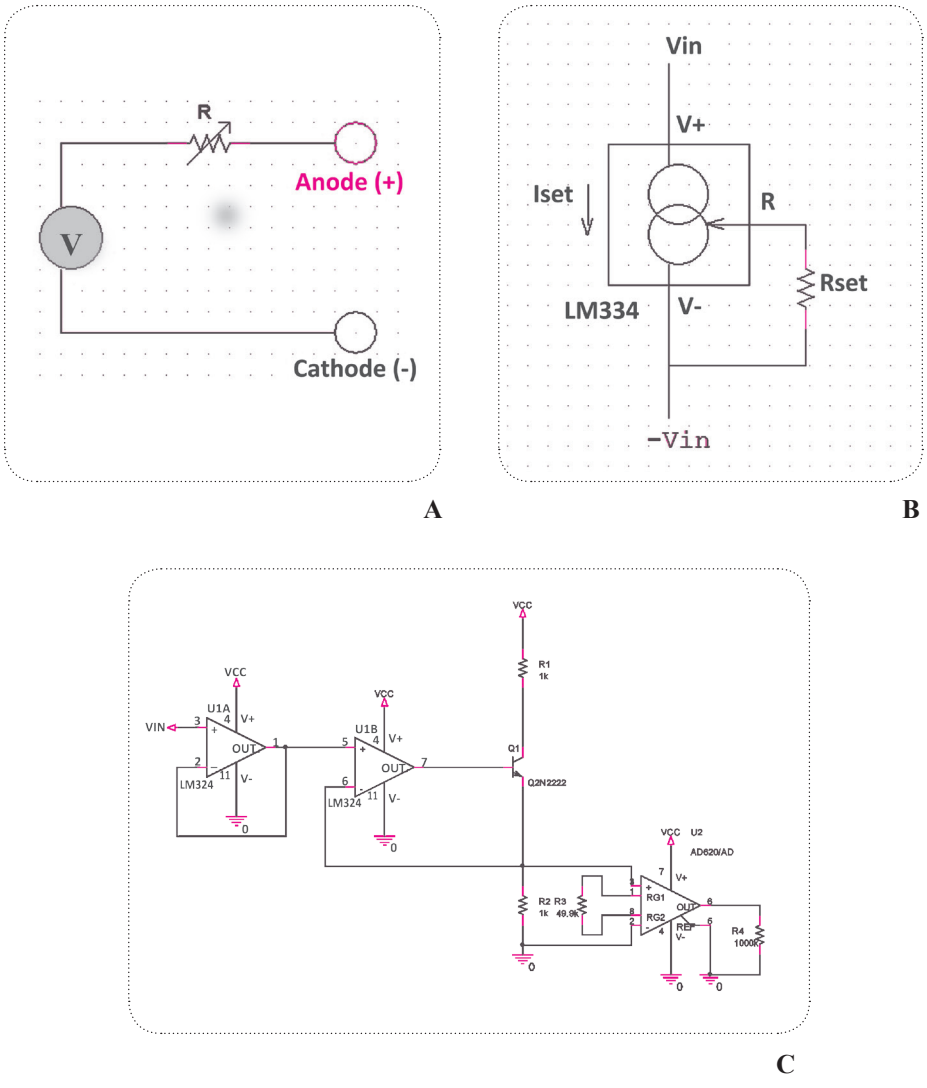

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Figure 3. TCS Fundamental sample circuits a) Circuit model, b) Integrated circuit implementation using LM334, c) Feedback implementation.

7. Circuitry and Schematics

The key feature in designing a TCS device is the use of an adjustable current regulator, which contains different parts of electronic components. A simple tDCS device can be assumed as a current source. Voltage and current regulators, LM334 and LM317 for instance, which usually provide an output of constant voltage or current respectively, regardless of the changes in other characteristics of the circuit including input voltage current or load conditions are used to supply the required output current for the stimulation process. There are two main implementation techniques: linear and switching each of which has some advantages and disadvantages. Simpler design and lower cost are the most important advantages of the linear current regulator, in contrast to switching types which have complicated design and more electronic parts. A favorable efficiency and low weight of switching regulators are the key advantageous factors for such a portable device. A linear regulator employs an active (BJT or MOSFET) pass device (series or shunt) controlled by a high gain differential amplifier whereas a switching regulator converts the DC input voltage to a switched voltage applied to a power MOSFET or BJT switch.

Common switching regulators mainly include Buck (step-down), Boost (step-up), Buck/Boost (step-down/step-down). Moreover, the TCS apparatus usually retains the advantage of boost topology in which the volt-

age will rise until it reaches the final threshold to supply the aimed current.

Linear regulators generally include integrated current source (LM334) and Operational amplifiers.

Another common fashion of generating current is using voltage to current converters which is used by some commercially available devices. In this method, an input voltage will be modified in order to transform into the adjusted current.

8. Conventional vs. High Definition TCS

There are mainly two separate types of transcranial current stimulation techniques including conventional and High-definition TCS. Conventional transcranial direct current stimulation (tDCS) supplies weak direct currents (260 mA-2 mA) applied to the scalp via rectangular sponge patches (nominally 25-35 cm2) covered with conductive gel(F. Hummel et al., 2005; Iyer et al., 2005; Marshall, Molle, Siebner, & Born, 2005; Nitsche & Paulus, 2000). Once conventional type had been invented and used to perform studies to investigate the efficacy of TCS, it showed to suffer from poor spatial precision as it involves a broad region of cortex owing to skull dispersion. A newer design called high definition tDCS (HD-tDCS) provides a focal current delivery to discrete regions of cortex and to avoid diffuse spatial resolution. In this approach, multiple (more than two) smaller gel electrodes, instead of using two large pads, are used to target specific cortical structures. The HD-tDCS can be performed via different montages. One of the possible electrodes configurations is the 4×1 HD-tDCS montage in which 4 electrodes are placed around a central one; thus, a set of 5 electrodes is used to deliver the required current to the cortex, which results in higher focality as compared to the conventional type (Caparelli-Daquer E et al., 2012). Both types tend to modulate the brain activity to cause a decrease or an increase in pain and sensory experience as well as offering some other possible effects(Borckardt et al.).

9. Alternating vs. Direct Current Stimulation

Since more than a decade ago, abundant studies with various designs have been carried out to investigate the possible effects the low-intensity (sub-threshold) current stimulation on cortical excitability, but great proportion of it has been dedicated to direct rather than alternating current stimulation. In fact, the only difference they have is regarding their current type, which is simply alternating in tACS and direct in tDCS while the required apparatus and other accessories remain the same. The two ways often cause different effects in brain and its functions, the main objective of the performed studies.

The recent studies performed in the previous decade (2000s to 2010s) reveal the tDCS efficacy through various achievements including, significant effects on visual recognition memory task in Alzheimer disease (Boggio et al., 2009),decreasing tics in two patients with Tourette syndrome(Mrakic-Sposta et al., 2008), decrease in craving for alcohol (Boggio, Sultani, et al., 2008) , significantly reduced craving for some foods (Fregni et al., 2008), reduction in subjects' propensity to punish unfair behavior (Knoch et al., 2008), increased recognition memory (Ferrucci et al., 2008), significantly reduced depression scores (Boggio, Rigonatti, et al., 2008; Fregni, Boggio, Nitsche, et al., 2006),increased sleep efficiency and decreased arousals(Roizenblatt et al., 2007), decreased reaction time (Boggio et al., 2006) and improvements of motor functions (Fregni, Boggio, Santos, et al., 2006) in Parkinson's Disease and decreases in Epilepsy seizure frequency (Fregni, Thome-Souza, et al., 2006), improvement in accuracy of the picture naming task (Monti et al., 2008), decreased reaction time (F. C. Hummel et al., 2006) and significant motor improvement(Boggio et al., 2007; Hesse et al., 2007) have been the outstanding attempts in Stroke patients' clinical trials in addition to the novel opportunities in the future perspective.

Over the recent decades, some alternating current stimulation clinical trials have investigated the visual phosphene induction in healthy subjects (Kanai, Chaieb, Antal, Walsh, & Paulus, 2008), the improvement in implicit motor learning task in healthy subjects (Chaieb, Antal, Terney, & Paulus) and assessed this technique's effects on patients suffering from generalized anxiety disorder (Roy-Byrne et al.). Additionally, this approach has succeeded to lead to a significant difference in the average pain intensity in spinal cord injury patients (Tan et al., 2006),(Capel, Dorrell, Spencer, & Davis, 2003), significant difference in beta-endorphin levels (Gabis, Shklar, & Geva, 2003), EEG alterations in alpha and beta band frequencies (Schroeder & Barr, 2001) and finally, improvements in attention (Southworth, 1999).

10. TCS Electrodes

One of the noteworthy aspects of a TCS study is indeed the possible electrode-gel parameters according to their main characteristics including size, shape and materials for the electrodes, and also the required chemical composition and volume of the gel.

It should be noted that, these parameters are mainly for HD-tDCS type and the electrodes of the conventional type are completely different, as they are simple sponge pads containing rubber electrodes (figure 4) and soaked in a saline solution (NaCl 0.9%)(Ben Taib & Manto, 2009).

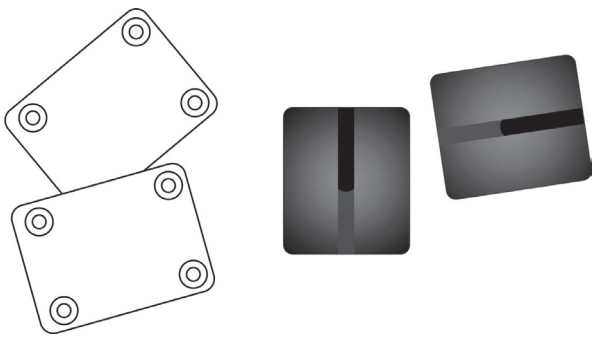

Figure 4. Sponge Pads (left) containing rubber electrodes (right)

Various pad shapes and sizes have been tested to rebut the common opinion of a considerable difference in electrical stimulation's tolerance ((Forrester BJ, Petrofsky JS., 2004). Moreover, the application of NaCl solutions in the range of 15 to 140 mM to sponge electrodes is proven to possibly cause no pain to the subject and to be perceived as comfortable during the tDCS trial (Dundas, Thickbroom, & Mastaglia, 2007).

In fact, all these efforts are made to achieve the appropriate solid-conductor and to partly guarantee the most desirable electrode durability, skin safety and subjective pain. There have been some experiments related to HD-tDCS to discover the most appropriate electrodes for stimulation, as items have recently been examined in well-designed investigations.

A collection of five types of solid-conductor (figure 5) (Ag pellet, Ag/AgCl pellet, rubber pellet, Ag/AgCl ring and Ag/AgCl disc) and seven conductive gels (Signa, Spectra, Tensive, Redux, BioGel, Lectron and CCNY-4) were identified and examined. Finally, the Ag/AgCl ring in combination with CCNy-4 gel resulted in the most favorable outcomes.

Under anode stimulation, electrode potential and temperature rises generally occurred in all electrode-gel combinations except for both Ag and rubber pellet electrodes with Signa and CCNY-4 gels. Sensation results however, are shown to be independent of stimulation polarity (whether to use anode or cathode).

Ag/AgCl ring electrodes were found to be the most comfortable followed by Ag, rubber and Ag/AgCl pellet electrodes across all gels(Minhas, et al.).

Figure 5. Different solid-conductor shapes and materials (Ag pellet, Ag/AgCl pellet, rubber pellet, Ag/AgCl ring, Ag/AgCl disc respectively).

11. TCS Montages

A tCS montage is a protocol determining the state of the stimulator device either in active or sham mode. Among protocol's parameters, the most important is the electrode positioning which depends on the goal and design of the study. Typically, there are two types of positioning, bilateral and unilateral. Unlike the bilateral positioning in which both electrodes are placed on scalp,in unilateral, only the active electrode is placed on the scalp and the reference is placed mostly on supraorbital area or shoulder, contralateral to the active electrode (generally, in unilateral design the reference electrode can be placed anywhere except the scalp). In other words, bilateral

stimulation can be performed with the two electrodes (anode and cathode) on analogous regions of the right and left hemisphere while the unilateral montage comprises positioning the active electrode on the DLPFC and the cathode on the contralateral supraorbital.

Of note, Nitsche et al., have provided an overview of the recent studies introducing different aspects of their protocols as well as details on their montage (Nitsche et al., 2008). Placing the stimulation electrode on M1 or hand area and the reference electrode on the contralateral orbit alters the brain activity of the subjects depending on the polarity of stimulation. As noted, with cathode being the active electrode, the excitability of the involved area reduces, while anodal excitability enhances after the anodal stimulation in basic neurophysiology applications. Moreover, this montage can enhance β-band in motor cortical excitability after the anodal stimulation while it is reduced after the cathodal one using the intramuscular coherence analysis (Power et al., 2006). While using anode as the active electrode, placing the stimulation electrode on S1 and the reference on contralateral orbit is shown to result in laser-evoked pain perception diminution in cathode stimulation and improve the spatial acuity. Active electrode on Oz and the reference on Cz results in visual perception threshold elevation using the cathodal stimulation (Antal, Nitsche, &Paulus, 2001) and reduction in phosphine threshold by anodal stimulation (Antal, Kincses, Nitsche, & Paulus, 2003). When placing anode on Cp5 and the reference electrode on the contralateral orbit, the stimulation leads to an enhancement in language learning (Floel, Rosser, Michka, Knecht, & Breitenstein, 2008).

Studies with unilateral vs. bilateral electrode positioning have reemphasized theimportance of the reference electrode's position in later analyses. The positioning of electrodes is normally based on the 10-20 international EEG system which is represented in figure 6.

12. Safety Concerns

Currently, the required current for stimulation is 1 to 2 mA at maximum and the clinical devices usually guarantee not to exceed this level to let the procedure remain innocuous for the patients. When applying a 1 mA direct current via two electrodes of 7×5 cm in size, the amount of the electrical current will predict an axial and tangential cortical current density of approximately 0.093 A/m2 and 0.090 A/m2, respectively, (Zaghi, Acar, Hultgren, Boggio, & Fregni).

Despite a common concern assuming the process probably dangerous, it generally does not cause considerable adverse effects, although it has some, including decreased heat and cold sensory thresholds and a marginal analgesic effect for cold pain thresholds when using HD-tDCS technique. No meaningful effects on mechanical pain thresholds and heat pain thresholds are usually

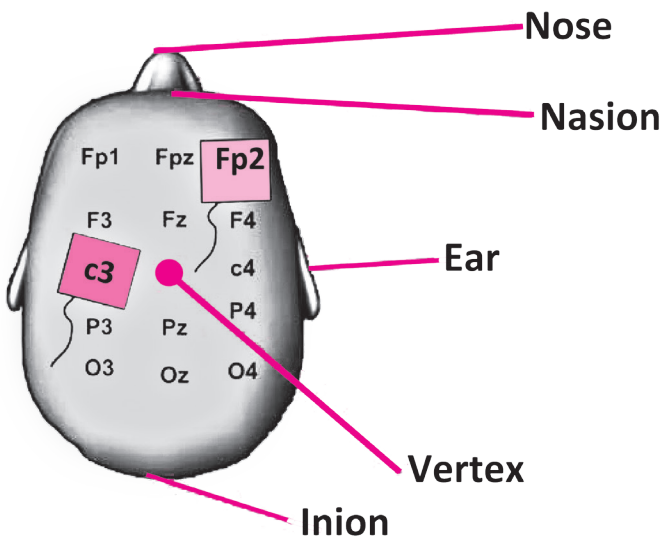

Figure 6. The 10-20 International EEG system is used to determine electrodes placement. For instance, to perform the anodal stimulation of dorsolateral prefrontal cortex the anode (active electrode) should be placed over F3 or F4 depending on the study.

observed(Borckardt, et al.). In the conventional type, a group of healthy subjects and patients were examined to determine what kind of TCS-related problems they may report. The most common reported adverse effect turned out to be the tingling sensation. In addition, the light itching sensation under the stimulating electrodes was considered as an undesirable effect. However, after the stimulation, infrequent headache, nausea and insomnia were rated as negative effects. The former sets of effects had mainly influenced the healthy group, while the latter were mostly reported by the patients(Poreisz, Boros, Antal, & Paulus, 2007).

13. Methodological Design for TCS Studies

Typically the design of a study TCS-involved is a straightforward procedure in which the main target is generating reliable and valid data in order to measure the effects of TCS in a certain neurocognitive function. There are some critical questions (Figure 7) which must be answered in order to create a study design based on an a priori hypothesis and the main question. We have created a diagram based on these critical questions (CQ) to show the roadmap of a complete methodological design of such a study (Figures 7 to 9).

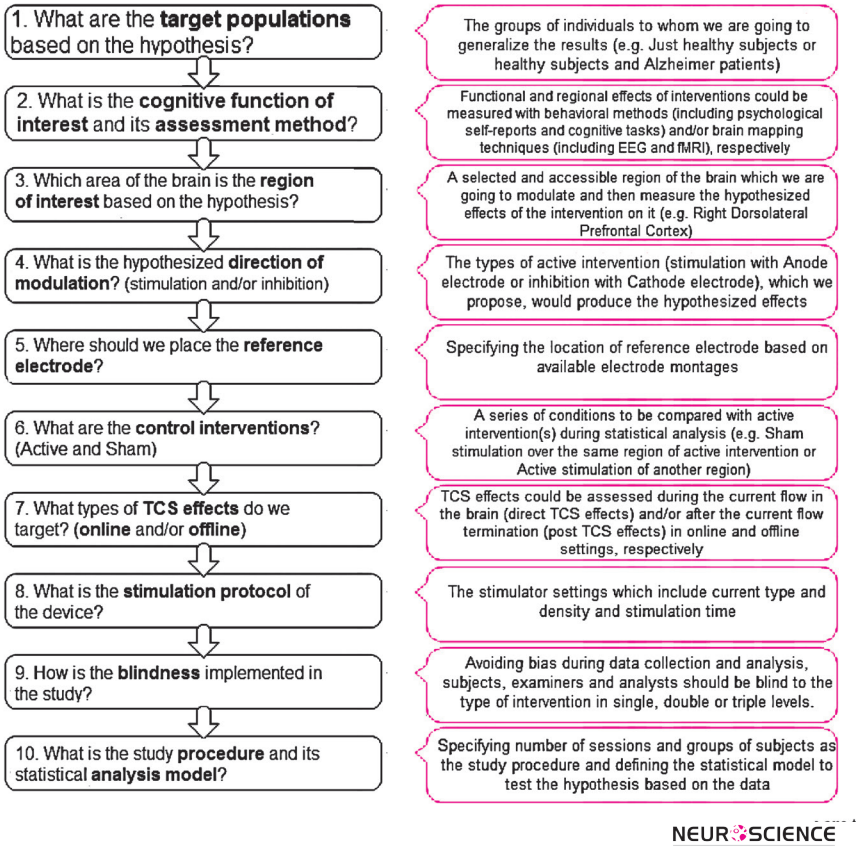

Figure 7. The critical questions which need to be answered to generate a roadmap when designing a TCS-included study. Red boxes are the brief descriptions of each bold phrase, which is the important keywords of each critical question.

13.1. The Roadmap

A normal study-design consists of six major steps (Figure 8), which would be based on the hypothesis and the main goals of the study. The first step is the answer to the critical questions 1 to 3. Generally, there are two main types of studies: studies with single (e.g. Normal People) or multiple target populations (e.g. Normal Controls and Alzheimer's Patients). Normally, if the purpose of a study is to investigate the effects of TCS in different conditions (for instance the hypothesis that TCS exerts positive effects on working memory performance in normal people), single-target is the method of choice. On the other hand, when the purpose is to determine differences of TCS procedure effects in different targets (for example, the hypothesis that TCS increases work-

ing memory performance in Alzheimer's patients with better efficacy compared to normal subjects), the second method (two target populations) should be applied. Whether we choose single-target or multiple-targets, the rest of the roadmap is mostly the same; however, in order to generate appropriate comparable data in a multiple-target design, we must divide it into the same number of separate single-target designs and compare their data to make the final decision of the experiment. This division brings on the sample matching concern, which means all the samples should be two by two matched.

After specifying the target populations we have to decide on the neurocognitive function of interest and its assessment method. Behavioral methods (e.g. Questionnaires) and brain mapping techniques (e.g. EEG) are two types of assessments could be used alongside TCS. The last process of this step is determining the region of interest (ROI) on the brain. Most of the time results from previous TCS or TMS studies are used to find the appropriate region to intervene.

13.2. Intervention Types

The second step is to choose the intervention types to use in the study, which is directly related to the critical questions 4 through 6. This step is divided into three inner steps illustrated in the second box of Figure 8. "Active" and "Control" are the two categories of intervention typeswhich their specification should be fixed in the first (CQ 4, 5) and second (CQ 6) inner steps, respectively.

In the first inner step we have to specify the active interventions from two available choices; anodal and cathodal, and after that to determine the place of reference electrode based on the "Electrode Montage" in which we should choose montage of electrodes placement from three types of montages: 1: Double Monopolar Montage in which two active electrodes (contralateral to each other) would be placed on the scalp and one reference electrode outside the scalp. 2: Monopolar Montage which is the same as the first type with only one active electrode on the scalp. 3: Bipolar Montage in which both active and reference electrodes would be placed on the scalp.

The second inner step is to decide on the control interventions. There are two types of control interventions: "Active Control" and "Sham Control". Active control refers to an intervention different from (but with regard to) the active intervention, which divides into three types: different stimulation of the same region (e.g. if the active intervention is anodal over F3, a possible active control could be cathodal over F3); same stimulation of the contralateral region (e.g. if active intervention is anodal over F3, a possible active control could be anodal over F4); same stimulation of another region (e.g. anodal over F3 for active and anodal over O4 for control).

Considering all types of the available active and control interventions, combinations of a variety of them seems possible however, only one of these combinations (permutations) would be used in a study, which suggests that we must choose this combination carefully and make a decision based on our hypothesis, goal and previously published articles. After specifying the "combination of interventions", we then have to decide on the electrodes location according to brain regions. We should find their exact position based on landmarks or an international standard in order to be comparable with other studies. MRI-guided measures and international the 10-20 standard for electrode positioning are the two systems which are widely used in intervention studies. Final part is about specifying the size of each electrode. Normally, 5 x 5 or 5 x 7 cm2 electrodes are used.

13.3. Session Design

Session Design is the third step in the process of designing a TCS study. In this step, the procedure of each session and the experimental protocols of the study should be designed to give answer to the seventh critical question. At first, the target TCS effect should be determined which is the outcome of our decision on incorporating offline, online or mix of both protocols.

In an online protocol, the assessment procedure is performed during the intervention, which requires counterbalanced (across subjects) sessions with respect to the intervention types in order to generate enough data for measuring the effects of intervention during a certain cognitive process. In contrast, the assessment task in the offline type is performed either post to intervention or in a pre-post procedure meaning that it would be performed both before and after the intervention. The combination of offline and online designs is another possibility which is a good candidate for an advanced procedure design as we can measure the effects of both the stimulation and assessment tasks at the same time. Mostly, in this type of design, online stimulation is conducted immediately after offline one or vice versa (e.g. ten minutes of offline stimulation followed by ten minutes of online stimulation).

13.4. Stimulation Protocol

In this step (Forth step), the technical settings of stimulator should be set. At first, one should decide whether

to use alternating or direct current and then distinguish the current features (intensity for direct currents and intensity and frequency for alternating currents). Then the duration of the intervention, which is divided into stimulation time and ramping time, should be defined.

13.5. Blindness

The fifth step is about our approach to blind the study, which is a response to the CQ 9. Typically, blindness means putting subjects, examiners and/or analysts unaware of the intervention types of each session in order to be able to measure "placebo effects". Blindness comes in three levels: the single-blinded design, means that only subjects are blinded to the conditions while double blind means that in addition to subjects, examiners are also blinded and triple-blindedmeans that all subjects, examiners and data analysts are blinded to the conditions.

13.6. Study Type and Analysis Model

The final step (Step 6) is dedicated to our decision about using "multiple groups" or "multiple sessions" design for the each target population in the study and is a response to CQ 10. In a "multiple groups" design, at first several groups should be defined based on the intervention types selected in previous steps (i.e. if the intervention types are active anodal and sham control, we should define two groups: one for active anodal and the other for sham control intervention) after which the random samples (subjects) from the target population must be assigned to each group. This procedure implicitly encompasses a case control study. Unlike multiple groups, in multiple sessions we would deal with only one group in which for each intervention type at least one session per subject is needed. This design leads to a crossover study with randomized sessions with respect to intervention types. Each one of these designs has its pros and cons, meanwhile the major concerns in multiple sessions are the carryover effect and habituation. Knowing the probable effects of intervention could help us to get around the carryover effect, but in order to deal wisely with the habituation problem we must choose the assessment task cautiously.

The output of a TCS study strongly depends on the statistical methods which show whether there are significant differences between Active and Control results. Therefore, the final decision (Inference and Outcome) in a study design depends on its statistical analysis model. We have to extract all the random variables generated by our choices in previous steps and create a statistical model based on them. Two simple and widely used statistical models are Student t-test and ANOVA.

13.7. Multiple Stimulations

All we explained in this section so far is about designing a research study, but what should we do to use TCS in clinical practice? Unfortunately, there is no comprehensive answer to this question and further studies are needed to create a universal protocol, but because a clinical protocol requires at least a multiple stimulation design, we decided to analyze the assumptions and requirements of multiple stimulation studies. There are three assumptions about TCS in a multiple stimulation design, explained in figure 9: Accumulativeness of TCS effects, Escalation in TCS effect durability and Time dependence of TCS therapeutic effects.

14. TCS as a Method of Choice for Neurocognitive Studies

There have been abundant studies investigating the efficacy of the tDCS which mostly intend to reach to the clinical application chances to be used as treatment. TDCS could also be used during the basic cognitive studies to provide causal inferences regarding the functional human brain mapping in both normal and clinical population. TDCS as a safe and inexpensive intervention method has received serious attention from different cognitive laboratories. But, non-focal and distributed electrical stimulation of tDCS in both superficial and deep brain regions made regional functional inferences very hard. There is a wide spectrum of cognitive functions under investigation with regard to the potential effects of TCS. Different methodological settings and "unpublished negative findings" have left some inconsistencies between the available evidences in different cognitive domains. nevertheless, there remain serious hopes for using TCS as a safe and portable cognitive modifier in a near future(Ekhtiari & Bashir, 2010).

15. TCS as a Method of Choice for Treatment

There have been some therapeutic results in some experiments in this field; hence this method has offered hope for being efficacious and safe in some clinical applications.

Possible clinical applications mainly include Parkinson's disease, tinnitus, fibromyalgia, epilepsy, migraine, fluent aphasia and post-stroke motor deficits (Been, Ngo, Miller, & Fitzgerald, 2007). It might also be useful to apply this method to treat some psychological disorders such as depression, anxiety disorders and schizophrenia.

In PD (Parkinson's disease), tDCS has been demonstrated as a beneficial way to affect the working memory inpatients depending upon the intensity and the site of stimulation which is justified by the local increase in excitability(Boggio, et al., 2006). In treating (focal) epilepsy both tDCS and rTMS have been used to directly affect the neocortical (epileptogenic) area to result in an impermanent reduction in seizures' frequency, usually lasting to several weeks(Paulus, 2009). Additionally, some recent studies have revealed that, the cathodaltDCS will be a good choice for treating epilepsy and dystonia(Nitsche, et al., 2003). Some experiments have also suggested that the cathodaltDCS over V1 might be an effective prophylactic therapy in mi-

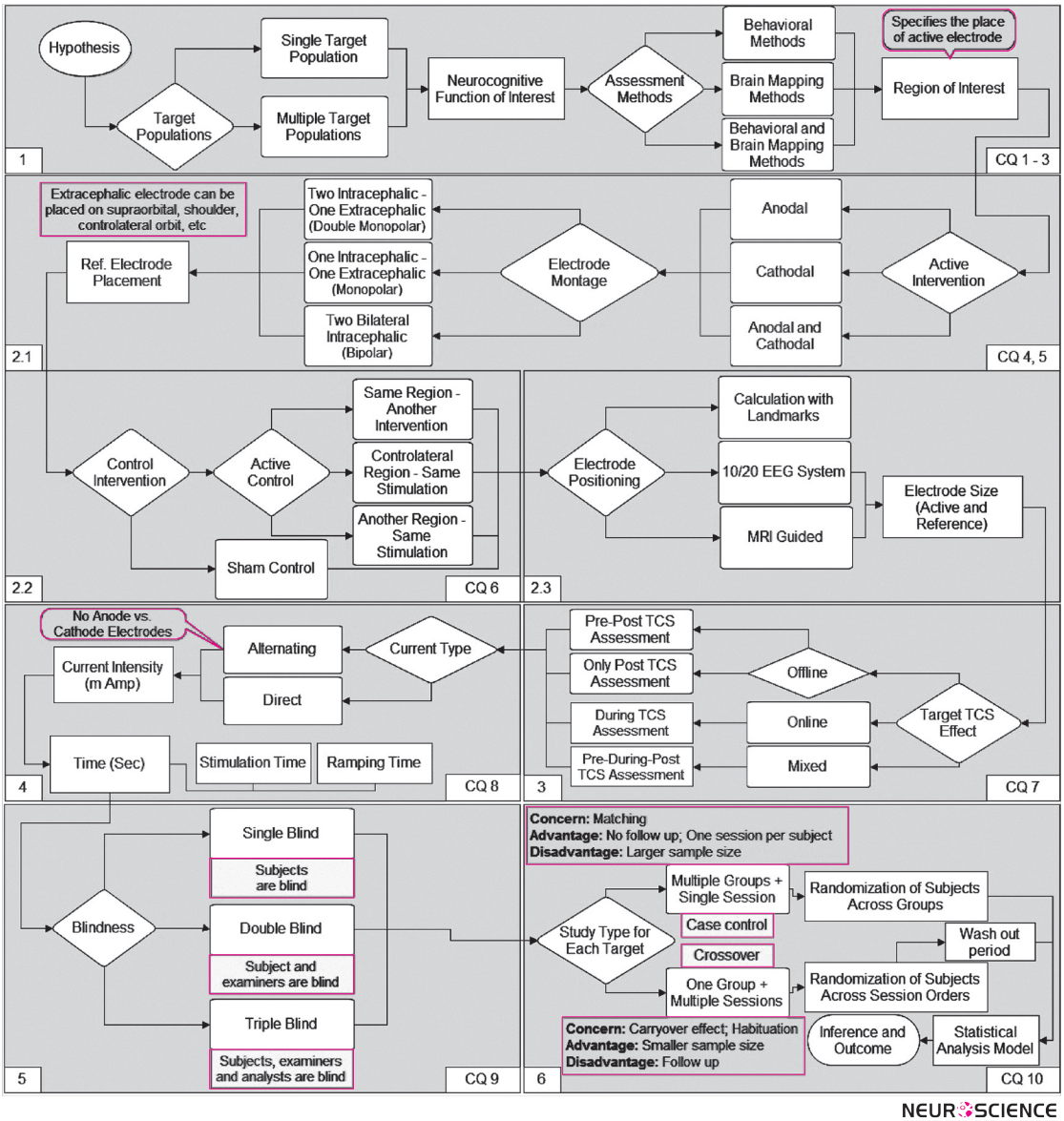

Figure 8. The roadmap to design a study which measures TCS effects in six steps: 1. Concept Design: Determining the total number of the target populations, which separates study into two directions: single target population vs. multiple-targets population in which each target should be dealt with separately as a single-target study (Critical Question (CQ) 1-3), then specifying neurocognitive function of interest, its assessment method, and region of interest. 2. Intervention Types: Choosing the intervention type to use in the procedure. 2.1. Specifying Active intervention (CQ 4) and reference electrode placement base on Electrode Montage. 2.2. Choosing a combination of control interventions (CQ 5). 2.3. Positioning the electrodes on the head based on a standard system and specifying the size of each electrode. 3. Session Design: Designing the procedure of each session based on our choice for the Target TCS Effect. 4. Stimulation Protocol: Setting the stimulator's properties such as current intensity (CQ 8). 5. Blindness: Clarifying the blindness status of the people involved in the experiment (CQ 9). 6. Study Design: Determination of single group vs. multiple groups design, its randomization and the statistical model to analyze the results.

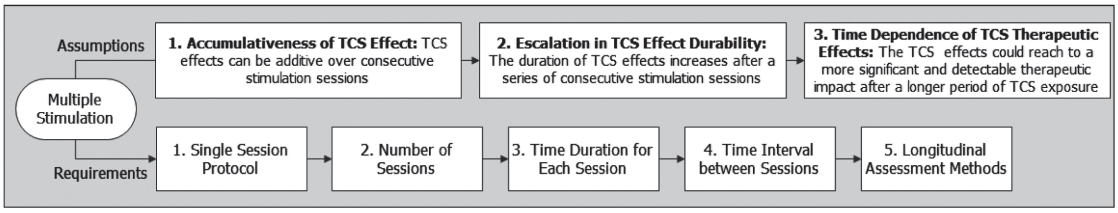

Figure 9. Assumptions and requirements in a multiple stimulation study design.

graine and this is perhaps according to the pain control(Antal, Kriener, Lang, Boros, & Paulus). With regard to the putative positive effects anodal tDCS may have on the aphasic patients, a study has depicted a meaningful improvement in language treatment due to a decreased processing time during a picture naming task by the fluent aphasic participants, when administrating anodal tDCS on the left hemisphere of head(Fridriksson, Richardson, Baker, & Rorden).Recently, researchers have made a significant progress, stressing alterations in resting membrane potential, spontaneous neural firing rates, synaptic strength, cerebral blood flow and metabolism subsequent to the tDCS which portrays a potential avenue in near future due to the meaningful positive effects on major depressive disorder (MDD)(Arul-Anandam & Loo, 2009).

16. Future

As any field of application of tDCS has been experimental and not clinical until today, there are many possible chances for tDCS to flourish in treating both neuropathic and neurocognitive disorders in the near future(Bashir, Sikaroudi, Kazemi, Forough, & Ekhtiari, 2010). Although tDCS was temporarily forgotten due to fast paced progress in pharmacotherapy and other types of brain stimulation, it has started to revive again. Given the fact that TCS is much simpler and more available than any other types and requires only a direct current supply and some electrodes, this modality has found its way toward clinical applications. These methods generally include the same as mentioned in the previous section varying mainly in neuropsychological disorders. Thus, future studies can be correlated with molecular, neurophysiological and imaging techniques in order to determine the optimized solution for each disorder, in cases of current strength, durability, polarity and potential combinations with other types of brain stimulations or pharmacological interventions. As such, neuroimaging techniques are a possible way of finding the correlation between the individualized effects of the tDCS on the brain and the stimulation itself with varying properties. There are also some studies to verify the computational phantoms role in predicting the current distribution in different brain areas during tDCS and this may lead to provide insights on a more accurate prediction of the involved brain regions. On the other hand, since HD-tDCS is one of the demanding fields on which there have not been sufficient investigations, it might be a great chance to carry out more studies in order to discover its efficacy, even further than the conventional type. Furthermore, this tool can be potentially beneficial to enhance language and mathematical abilities, concentration, problem solving, working memory and coordination as it facilitates the more accurate and justified modulation of the brain activity.

17. Conclusion

In conclusion, TCS is a safe, portable, noninvasive and painless method of brain modulation in which the alteration of brain excitability is intended through transmitting a small amount of current, direct or alternating, through a determined area of the brain. This intervention leads to a change in neural membrane potentials based on the polarity of the applied electrodes. Considering the ease, availability and tolerability of TCS for brain activity modulation, this modality has played a crucial role in offering hope to treat different types of neurocognitive disorders as compared to the other neuromodulation methods. Thus, there are a variety of commercial devices and other amenities which encourage researchers to run carefully designed pilot studies. There are several potential clinical applications for this technique based on which current studies are making progress to establish approved therapeutic interventional approaches to treat refractory neurocognitive disorders.

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Corticospinal Facilitation of Erector Spinae and Rectus Abdominis Muscles During Graded Voluntary Contractions is Task Specific: A Pilot Study on Healthy Individuals

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ABSTRACT

Introduction: In this study we compared transcranial magnetic stimulation (TMS) elicited motor evoked potentials (MEPs) in a postural (bilateral low back extension: BLBE) and a respiratory (forced expiration during breath holding: FEBH) task.

Methods: Using TMS of the left motor cortex, simultaneous patterns of corticospinal facilitation of the contralateral erector spinae (ES) and rectus abdominis (RA) muscles during graded voluntary activation were compared in seven healthy subjects.

Result: The facilitation pattern demonstrated task dependency by showing that MEP amplitudes in the ES muscle tended to be smaller at any given contraction level in the FEBH task than in the BLBE task.

Discussion: The results suggested a linear-type relationship between the size of MEPs with increasing background contraction of ES and RA in the BLBE task. However, both muscles showed a plateau effect with higher background contractions (>50% of maximum) during the FEBH task. The varied response of ES and RA across these two tasks reinforces the importance of task specific training in clinical settings.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive and pain free tool for the assessment of an individual muscle or a muscle group's pattern of corticomotor facilitation. (Lagan, Lang, & Strutton, 2008; Mortifee, Stewart, Schulzer, & Eisen, 1994). TMS studies suggest the existence of direct corticomotor input to the abdominal muscles (Plassman & Gandevia, 1989), and back muscles (Ferbert, Caramia, Priori, Bertolasi, & Rothwell, 1992). The role of these muscles in fine control trunk movements and their role in providing core stability of the spine make it of interest to examine their corticomotor excitability during graded voluntary tasks. Corticomotor excitability of trunk muscles can be studied by examining the amplitude of motor-evoked-potentials (MEPs) by TMS during graded voluntary contractions of these muscles. An increase in corticomotor excitability produces synaptic facilitation which coincides with an increase in MEP amplitude (Mazzocchio, Rothwell, Day, & Thompson, 1994; Nielsen & Petersen, 1995). The observed facilitatory modification could reflect changes in synaptic excitability in the cortex, in the spinal cord or at both sites.

Literature indicates that the pattern of corticomotor facilitation varies for different muscles across a range of voluntary background contractions. For example, maximum facilitation of the first dorsal interosseus (FDI)

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muscle (Hess, Mills, & Murray, 1987) in the hand and tibialis anterior (Turton & Lemon, 1999) in the lower limb occurs at less than 20% of the maximum voluntary contraction (MVC). TMS studies on abdominal muscles to date have produced conflicting results. While some studies indicate a similarity between facilitation patterns of the abdominal oblique muscles and intrinsic hand muscles (Plassman & Gandevia, 1989), other studies suggest a more linear facilitation profile, reaching a peak between 30-40% MVC (Tunstill, Wynn-Davies, Nowicky, McGregor, & Davey, 2001). A similar facilitation pattern illustrating a gradual increase in facilitation profile has also been reported for the erector spinae (ES) muscle (Nowicky, McGregor, & Davey, 2001).

A number of studies have indicated that the facilitation patterns of muscles may also vary according to the voluntary task (Gandevia, McKenzie, & Plassman, 1990; Hauptmann, Skrotzki, & Hummelsheim, 1997). According to Datta and colleagues, simple abduction of the index finger resulted in larger MEPs of the FDI than a power grip (Datta, Harrison, & Stephens, 1989). Additionally, Flament and colleagues found larger MEPs of the FDI during complex tasks compared to simple index finger abduction (Flament, Goldsmith, Buckley, & Lemon, 1993). In both studies, the voluntary activation of the FDI was kept constant by monitoring the surface electromyogram (sEMG). In a more recent study, Hasegawa and colleagues described a lower TMS threshold and larger MEP amplitudes in the FDI during the precision grip compared with the power grip (Hasegawa, Kasai, Tsuji, & Yahagi, 2001). This suggests that the type and nature of a voluntary task can have a considerable impact on facilitation patterns of involved muscles. Clinical literature has developed a large body of evidence supporting the presence of task specificity in trunk activation and core stability within functional tasks (Hall, Tsao, MacDonald, Coppieters, & Hodges, 2009; McCook, Vicenzino, & Hodges, 2009). However, the extent to which corticomotor patterns of activation reflect this functional bias is not known.

Research using TMS has demonstrated evidence of independent task specific activation of trunk musculature (Hodges, Butler, Taylor, & Gandevia, 2003; Kuppuswamy et al., 2008). However, there is no supporting evidence illustrating simultaneous (co-contraction/co-activation) patterns driven centrally for antagonistic muscle groups of the trunk for specific functions.

This study was designed to explore the relationship between the facilitation patterns and level of background voluntary contraction in two different tasks. Specifically, it was aimed to compare the pattern of corticomotor facilitation of the contralateral erector spinae and rectus abdominis (RA) muscles during graded voluntary activation in a postural (bilateral low back extension - BLBE) and a respiratory task (forced expiration during breath holding - FEBH).

Hypotheses

Within the BLBE experimental task, there will be a linear relationship between the facilitation pattern of a single muscle (ES and RA) and the intensity of the background voluntary contraction.

Within the FEBH experimental task, there will be a non-linear relationship between the facilitation pattern of a single muscle (ES and RA) and the intensity of the background voluntary contraction.

2. Methods

2.1. Subjects

Ethical approval for this study was obtained from the Monash University Human Research Ethics Committee. All subjects gave their written informed consent, in accordance with the Declaration of Helsinki. Seven healthy subjects (3 male, 4 female), all right-handed, aged 31-48 years (38.28 ± 7.3), with no history of neurological disease or back pain, were recruited for the study.

2.2. Electromyographic Recordings

Prior to the application of electrodes, the skin was prepared using a standard procedure. Surface electromyography (sEMG) was recorded using 2cm round self-adhesive pre-gelled surface electrodes (Skintact®, Innsbruck, Austria) positioned on the right RA muscle at the mid trunk level immediately superior to the umbilicus and approximately 3 cm from the midline, and right erector spinae muscle 5cm lateral to the midline at the level of L2-L3. sEMGs were filtered (below 10 Hz and above 500 Hz) and amplified (x 1000) before being sampled (1 kHz) by a computer for storage and analysis (Powerlab, AD instruments Pty Ltd, Australia). The possibility that the electrodes picked up sEMG from other muscles cannot be excluded but is thought to be minimal.

2.3. Transcranial Magnetic Stimulation (TMS)

TMS was delivered with MagStim 200 stimulator (Magstim Company, Ltd, UK) through a 20cm figure-of-eight hand-held flat coil. The optimal stimulation

position ('hot spot') was searched over the left cortex (1.5 cm anterior and 3 cm lateral to vertex) at which the MEPs could be simultaneously recorded from both ES and RA muscles.

Figure 2A illustrates the individual (small circles) and the average (square symbol +/- SD) optimal stimulation locations (hot spots) over the left motor cortex (referenced to vertex).

As in previous TMS studies reporting difficulties in eliciting resting MEPs in trunk muscles (Ferbert, et al., 1992; Nowicky, et al., 2001; Taniguchi & Tani, 1999), intentional voluntary contraction of trunk muscles was used to facilitate the elicitation of MEPs by TMS (Strutton, Theodorou, Catley, McGregor, & Davey, 2005).

Threshold to TMS was determined for each task with the subject in a seated position maintaining a weak contraction (15% MVC) of the specified muscle, i.e. ES for the BLBE task and RA for the FEBH task. Threshold was assessed as the lowest intensity of TMS that produced 3 out of 5 successive MEPs of both muscles (ES and RA) exceeding 50 μV peak-to-peak amplitude (Rossini et al., 1994). Subsequent experimental trials were conducted using a stimulus intensity of 1.2 times this threshold value.

2.4. Experimental Protocol

Pilot work determined the best position to produce reliable, sustained, and graded levels of two different tasks: BLBE and FEBH. The most comfortable position for activation was supported sitting in a semi-reclined podiatry chair (Figure 1). In both tasks subjects were instructed to vary their effort between randomly nominated intensities of 0% MVC, 25% MVC, 50% MVC, 75% MVC and a maximum (100%) contraction. Maximum contraction was defined as the maximum voluntary contraction output achievable in that session. Subjects used feedback of the EMG signal from the primary muscle relative to the task (ES for the BLBE task and RA for the FEBH task) to modulate their effort through the specified contraction forces. Subjects underwent a brief training session, and then practiced both tasks before each experimental trial. The task order was varied randomly between subjects.

During the BLBE or FEBH task, subjects were able to view the integrated EMG response for performance feedback on the ES or RA muscles via a computer screen directly in front of them (Figure 1), whilst MEPs were simultaneously recorded from both ES and RA muscles. Target levels were indicated on the integrated EMG screen to demonstrate the required contraction intensity

Figure 1. Experimental setup illustrating subject positioned in semi-reclined chair viewing EMG feedback on computer monitor and task specific cues whilst undergoing TMS on the left motor cortex.

for the primary muscle for each specific task. A second investigator was present throughout to encourage the subject to produce optimal levels of stable contraction. In the FEBH task subjects were instructed to breathe out forcefully against their closed glottis in an expiratory Valsalva manoeuvre for about 3 seconds. In the BLBE task subjects were instructed to arch the low back by contracting the ES muscle. They were instructed not to hold their breath during the BLBE task. Five contraction levels (0, 25, 50, 75 and 100% MVC in a random order) were conducted in each of the two tasks. Eight magnetic stimuli were delivered per contraction level with a random interval averaging approximately one stimulus every 4 seconds, totalling in 5 x 8 stimuli per task. An auditory signal cued the subject into a 2.6 second lead time to perform the desired output for the appropriate muscle activation prior to magnetic stimulation. Subjects were given a short rest period in between stimuli and between contraction levels.

2.5. sEMG Analysis and Statistics

sEMG signals were analysed using LabChart 7 data acquisition software (Adinstruments Pty Ltd, Australia). Eight raw MEP responses together with corresponding full-wave rectified records at each contraction level were averaged. The mean voltage levels of the averaged rectified MEP were measured at each level of contraction. The latency of the MEP was determined as the interval between the stimulus and the first positive inflection, above background sEMG levels, of the rectified MEP.

Facilitation patterns were produced by plotting the mean voltage level of the rectified MEP against the mean voltage level of the pre-stimulus sEMG. Statistical comparisons were made using a three-factor repeated measure ANOVA (2 muscles × 2 tasks × 5 background contractions), alpha level was set at 0.05.

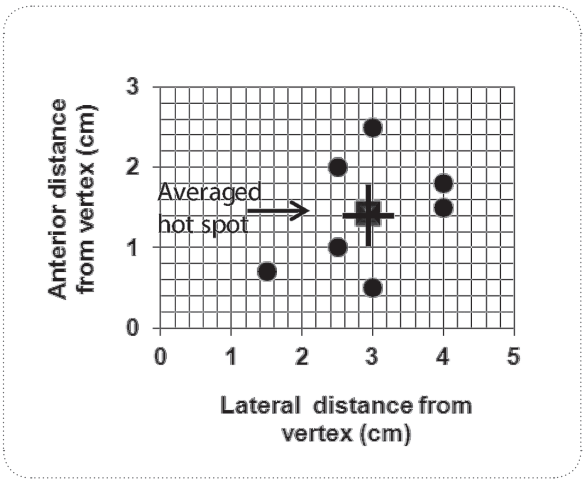
3. Results

3.1. Active olds and Latency of Responses

In all seven subjects it was possible to evoke simultaneous responses in both ES and RA muscles while maintaining a weak contraction (15% MVC). Mean (±SE) threshold stimulation used to produce MEPs, while maintaining a weak contraction (15% MVC) of the specified muscles was 71.0±4.7. This ranged from 55 to 81% of the maximum stimulator output (MSO). The mean (±SE) magnetic stimulation intensities used to produce MEPs during experimental tasks was 85±5.7 % MSO.

Compared to reported latencies at rest, voluntary contraction of the ES and RA muscles resulted in a reduction in MEP latencies as follows (Figure 2B): Right ES: 15.4±0.75 ms (BLBE task) and 16.49±0.95 ms (FEBH task), Right RA: 18.17±1.3 ms (BLBE task) and 18.64±0.95 ms (FEBH task).

A



B

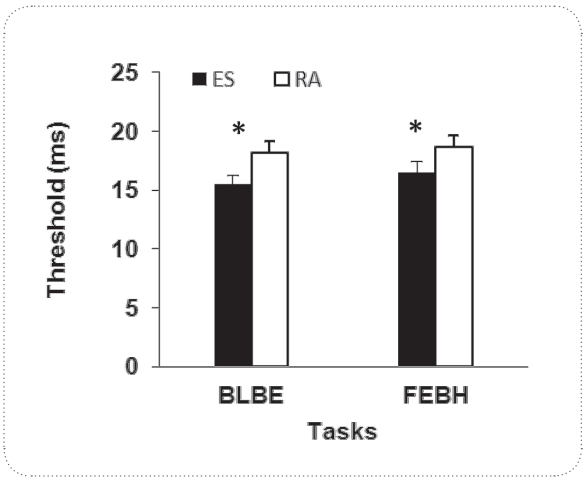


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Figure 2. (A) Location of optimal stimulation for the elicitation of maximum MEPs from both ES and RA muscles in sitting position. The small circles represent individual stimulation locations (n = 7) and the square (+/- 1 SD) represents an average stimulation location. (B) Group mean latencies of MEP responses for BLBE and FEBH tasks in the right ES and RA muscles. Error bars indicate 1 S.E.M. * indicates P<0.05.

3.2. Facilitation of MEPs

Figure 3 illustrates single subject averaged MEP responses from ES and RA muscles during both BLBE and FEBH tasks at different background contraction levels. Voluntary contraction of the trunk muscles in the two tasks produced an increase in MEP amplitude with increasing voluntary contraction. In this representative example, the MEPs appear to increase more linearly with contraction force during the BLBE task than the FEBH task.

3.3. Task Dependent Differences in Voluntary Activation

The normalized facilitation patterns were determined for each subject individually as a percentage of the maximum MEP amplitude achieved over both tasks. During the BLBE task, there was a linear relationship between voluntary contraction of the ES and RA muscles and size of MEPs (Figure 4A and 4B, middle panels). Any increase in background voluntary contractions coincided with an increase in MEP amplitude. For the FEBH task this increase plateaued during the last three levels of voluntary contractions (50, 75 and 100% of MVC)

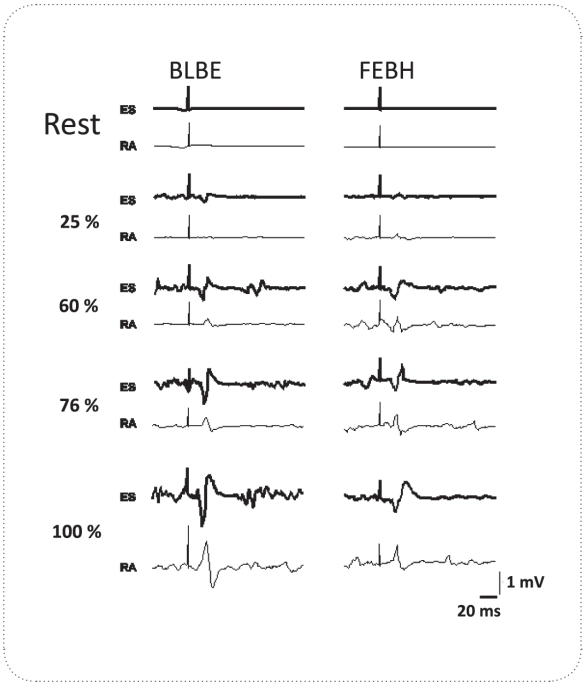

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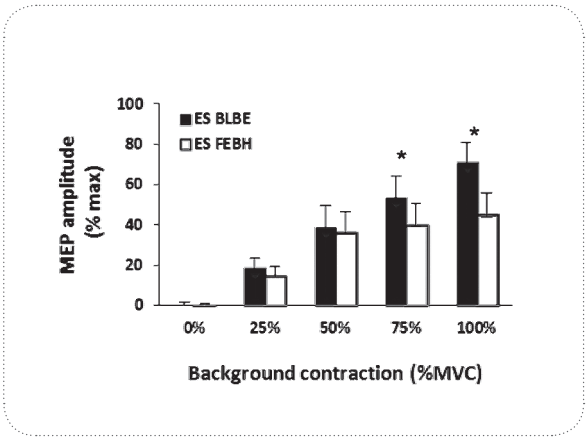
Figure 3. Single unrectified MEP responses to TMS of the left motor cortex at increasing levels of voluntary contraction in the right erector spinae (ES) and rectus abdominis (RA) muscles in a representative subject. Left column illustrates MEP responses during the BLBE task; right column illustrates MEP responses during the FEBH task. Increasing levels of EMG and MEP amplitude can be seen over the four levels of voluntary contraction during the BLBE task. For the FEBH task this increase plateaued during the highest two levels of voluntary contractions.

(Figure 4A and 4B, middle panels). When normalized to the maximum level of contraction achieved over both tasks, the MEP amplitudes in the facilitation pattern for the right ES during BLBE were consistently higher in the BLBE than in the FEBH task. This difference was only significant ($p<0.05$) in higher levels of background contractions (75 and 100% of MVC) (Figure 4A upper panel). RA muscle follows a similar trend at 100% of MVC ($p<0.05$) but this facilitation pattern has an opposite trend during lower levels of background contraction. Accordingly, the MEP amplitudes in the facilitation pattern for the right RA during FEBH were significantly higher ($p<0.05$) at 25 and 50% MVC than during the BLBE task (Figure 4B upper panel).

Since the maximum levels of voluntary EMG produced in the two tasks were different, comparison of normalized facilitation patterns between the two tasks may be misleading. The facilitation patterns were examined based on the absolute values of the responses (Figure 4A and 4B, lower panels). Similar to the normalized results for the BLBE task, a linear relationship between the absolute MEP amplitude and the absolute background EMG activity was observed (Figure 4A and 4B lower panels). A plateau effect in absolute MEP amplitude was also observed with increasing absolute background EMG activity in the FEBH task (Figure 4A and 4B lower panels). These results mimic the facilitation patterns observed in the normalized data.

A



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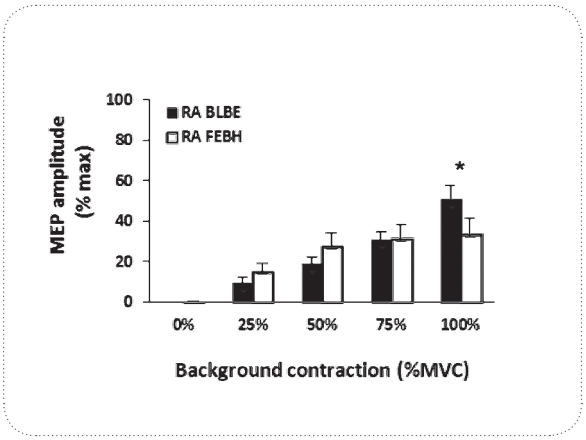

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Figure 4. Normalized group mean patterns of facilitation of MEPs at different levels of voluntary activation in the right ES muscle (4A, upper panel), and in the right RA muscle (4B, upper panel); Same data presented in a way to better visualise task differences in the right ES muscle (4A, middle panel) and in the right RA muscle (4B, middle panel); Note that the facilitation pattern during the FEBH task tends towards a plateau at around 50% MVC levels. Absolute group mean pattern of facilitation of MEPs with increasing voluntary effort in the right ES (4A, lower panel) and in the right RA muscle (4B, lower panel). Distance (double arrow) indicates relative EMG amplitudes at the MVC for the two muscles across the BLBE and FEBH tasks. Error bars indicate 1 S.E.M. * indicates $P<0.05$.

As expected, for the BLBE task where the ES is the prime mover, higher levels of ES contraction were produced compared to the FEBH task. The voluntary EMG amplitude of ES at MVC was significantly larger for the BLBE task (1.4± 0.06 mV) than for the FEBH task (1.1±0.01 mV) (Figure 4A, lower panel, double arrow).

Similarly, in the FEBH task, where the RA plays a major role, higher levels of contraction of RA were produced compared to during the BLBE task. The voluntary EMG amplitude of RA at MVC was significantly larger for the FEBH task (0.86± 0.02mV) compared to the BLBE task (0.44±0.01 mV) (Figure 4B, lower panel, double arrow).

4. Discussion

This study has shown that TMS of the motor cortex can be used to assess simultaneous voluntary activation of the superficial trunk flexor and extensor muscles over a wide range of contraction strengths. The tasks performed in this study are representative of the daily usage of ES and RA muscles.

The results of this study support previous evidence (Ferbert, et al., 1992; Plassman & Gandevia, 1989) demonstrating that corticomotor input to the trunk muscles can be activated by TMS over the motor cortex. Each stimulus produces a descending volley in the corticomotor tract, which can excite different spinal motor neuron pools to produce MEPs in the sEMG recordings from skeletal muscles. The overall excitability of the corticomotor pathway between the stimulus and the target muscle is directly related to the amplitude of the resulting MEPs. Changing inputs to the system (e.g., voluntary contraction of the target muscles) will result in synaptic facilitation, increasing the overall excitability and the amplitude of the resulting MEP (Mazzocchio, et al., 1994; Nielsen & Petersen, 1995).

4.1. Threshold and Latency

It has been suggested that it is more difficult to elicit MEPs in paraspinal and abdominal muscles than in limb muscles (Nowicky, et al., 2001; Taniguchi & Tani, 1999). During a relaxed state, MEPs could not be elicited in all subjects. However, it was possible in all seven subjects to evoke simultaneous responses in both ES and RA muscles while subjects maintained a weak contraction (15% MVC). This finding supports the conclusion of Strutton and colleagues, which indicated that intentional voluntary contraction of paraspinal muscles enabled MEPs to be elicited routinely by TMS (Strutton, et al., 2005). In this study simultaneous MEPs were evoked in both ES and RA muscles using a 20 cm flat figure-of-eight coil placed over the left cortex, an average of 1.5 cm anterior and 3 cm lateral to vertex (Figure 2A), so that the induced current flowed medially and mainly in the left cortex.

In agreement with published literature, latency times during background voluntary activity of both ES and RA in either task were shorter than the latencies of these muscles at rest (Hess, et al., 1987). The latency of MEP to TMS over the motor cortex in active ES and RA suggests that the MEP in these trunk muscles is mediated by a fast conducting corticomotor pathway. This latency is longer in active RA than ES which simply suggests a longer pathway for descending signals. This is consistent with current knowledge of neuroanatomical descending pathways (Ferbert, et al., 1992; Nowicky, et al., 2001).

4.2. Patterns of Facilitation and Task Specificity

It was hypothesized that within the BLBE experimental task, there would be a linear relationship between the facilitation pattern of a single muscle (ES and RA) and the intensity of the background voluntary contraction. This study shows a graded linear pattern of MEP facilitation with increasing voluntary effort in the BLBE task for both ES and RA muscles. This finding supports previous research which proposed linear relationship between levels of background contractions and levels of corticomotor facilitation within a specific task (Nowicky, et al., 2001; Tunstill, et al., 2001).

It was hypothesized that within the FEBH experimental task, there would be a non linear relationship between the facilitation pattern of a single muscle (ES and RA) and the intensity of the background voluntary contraction. During the FEBH task, this study showed a non-linear facilitation pattern with a plateau at higher levels of background voluntary contraction for both ES and RA muscles. This finding suggests task specificity and is in agreement with other research which proposed task dependency of facilitation patterns in trunk muscles (Nowicky, et al., 2001; Tunstill, et al., 2001) and limb muscles (Lemon, Johansson, & Westling, 1995).

A number of studies have previously examined variation in facilitation patterns between proximal and distal limb muscles within a given task (see (Schieppati, Trompetto, & Abbruzzese, 1996; Taylor, Allen, Butlere, & Gandevia, 1997). Turton and Lemon (1999) reported that in the distal first dorsal interosseous (FDI) muscle, the facilitation pattern was greatest at lower levels

of voluntary contraction (10% MVC), while the more proximal muscles (biceps and deltoid) had more linear patterns for a specified task. They suggested a distal to proximal gradient of corticomotor innervations. Given that this study only examined responses from axial muscles (ES and RA); we were unable to identify change in facilitation patterns relative to a specific muscle location.

4.3. Limitations of Study

The most significant limitations of this study were its cross-sectional design, imposing restrictions on the interpretation of observed associations. Any cause and effect could not be established. This is a pilot study on seven healthy individuals hence findings cannot be extrapolated to larger populations of healthy individuals or people with neurological or musculoskeletal conditions.

4.4. Clinical Applications

To our knowledge, this study is the first to use TMS of the motor cortex to simultaneously assess voluntary contraction of trunk flexor and extensor muscles.

The motor cortex provides a critical contribution to postural control (Deliagina, Beloozerova, Zelenin, & Orlovsky, 2008). It has been shown that inhibition of the motor cortex can reduce postural activity of the trunk muscles associated with voluntary limb movements (Hodges, et al., 2003). As cortical regions contribute to postural control, it could be speculated that deficits in postural activation, such as observed in people with low back pain, may be associated with changes in the excitability and organisation of the motor cortex. These parameters have previously been reported as altered in patients with low back pain (Strutton, et al., 2005).

The results of this study demonstrate the co-activation and close synchrony of ES and RA during both postural and respiratory tasks, with increased activity in both muscle groups arising from voluntary contraction of just one muscle group. Clinically this suggests that a targeted training program addressing one muscle group (e.g. RA) may have a facilitatory effect on motor function in the opposing muscle group (e.g. erector spinae). The plateau effect in MEPs (cortical facilitation) observed at higher levels of voluntary contraction in the FEBH task suggests that maximum voluntary effort may be unnecessary to achieve maximum cortical facilitation in this task. However, for the postural task examined in this study (BLBE), no plateau effect was observed. The varied response of both ES and RA across the two tasks examined in this study reinforces the importance of including training across a range of tasks within a rehabilitation program, and identifying relevant task specificity for function.

5. Conclusion

This study has shown that the synchronous recording of MEPs in trunk muscles of healthy individuals provides valuable information on changes occurring at the level of the central nervous system, such as threshold to TMS, facilitation patterns and task specificity of a muscle's activity. Investigations such as this offer further insight into the neurophysiology underlying trunk motor control and could be used to explore efficacy of rehabilitation strategies addressing postural control dysfunction.

6. Acknowledgements

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The Effects of Bilateral Subthalamic Nucleus Stimulation on Cognitive and Neuropsychiatric Functions in Parkinson's Disease: A Case-Control Study

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ABSTRACT

Introduction: Parkinson's disease is one of the most disabling diseases which by electrode implantation and stimulation of subthalamic nucleus (STN), much progress has been made in the treatment of drug resistant patient. This new method of neurosurgery may have some neuropsychological side effects on the patients. The main aim of this study is to evaluate the effects of this kind of treatment on the different neuropsychological aspect of patients.

Methods: The case-control study designed for comparing two groups of patients with Parkinson's disease. Thirty patients, who underwent electrode implantation and Deep Brain Stimulation (DBS), compare with 60 patients treated with antiparkinson's drugs. These two groups matched in age, sex, Parkinson's disease duration and Parkinson's severity scores. Measurements: the UPDR scale was used to assess the severity of the Parkinson's severity. Beck Depression Inventory questionnaire (BDI) and Hamilton Anxiety Rating Scale questionnaire (HARS) were used to evaluate the depression and anxiety consequences of DBS.

Mini Mental Status Examination (MMSE) and Clock Drawing Test (CDT) were used to evaluate the cognitive and executive function of the study subjects.

Results: patients with STN stimulation showed lower level of anxiety and depression, however, the cognitive status were more deteriorated in study subjects than control group.

Discussion: Patient with DBS surgery have to be followed up for neuropsychiatric symptoms particularly for the cognitive deterioration in long term period.

1. Introduction

Parkinson's disease is one of the most prevalent movement disorders throughout the world. In recent years, considerable pharmacological and surgical progress has been made in the treatment of this disabling disease. The major sites of dysfunction in Parkinson's disease are the subthalamic nucleus (STN) and substantia nigra (SN), which are two components of the basal ganglia (BG)(Joseph J & Tolosa, 2007; Sadock B, Sadock J, & A, 2009; Sadock B, Sadock J, & V, 2007). The loss of dopaminergic neurons in the SN results in hypokinetic symptoms secondary to overactivity of the STN and globus pallidus (GPi) via the indirect pathway and hyperkinetic movement caused

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by overactivity of the direct pathway(Joseph J & Tolosa, 2007; R.F & I, 2005; Sadock B et al., 2007). Subthalamic deep brain stimulation (DBS) is one of the most important interventions in functional neurosurgery and has transformed the treatment of advanced or drug resistant Parkinson's disease(Baltuch GH & MB, 2007). STN as a driving source of the BG plays an important role in the pathogenesis of Parkinson's disease(Heo et al., 2008). In addition to the importance of this structure in motor coordination, the STN regulates cognition and emotion; stimulation of this site can cause emotional or cognitive changes(Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). Despite the effect of STN stimulation on controlling the motor symptoms of Parkinson's disease, the effects of this procedure on cognition and mood are not well-established. One study has shown that, three years after surgery, two cognitive variables became worse (category fluency and total score of fluency). Apathy and thought disorders were also worsened. The major behavioural changes documented in this study includes two transient aggressive impulsive episodes, one suicide, four suicide attempts, one case of permanent apathy, one case of transient severe depression, four psychoses (one permanent) and five cases of hypomania (one permanent)(Funkiewiez et al., 2004). The location of the electrode may have an impact on mood changes. In one case report, right DBS alone elicited several episodes of acute depressive mood changes. The electrode on the left was within the inferior STN, whereas the right electrode was marginally superior and lateral to the intended STN target within the fields of Forel/zona inserta(Stefurak et al., 2003). Sometimes, this may cause manic symptoms or suicidal behaviour (Burkhard et al., 2004; Herzog et al., 2003). Although DBS deteriorates cognitive function and mood disorders such as depression, anxiety or improving in these symptoms; important challenges persist in the development of this type of treatment. In recent years, some studies have been designed to address the effects of DBS on cognitive function and mood changes (Benabid, 2003; Chan et al., 2009; Fields et al., 2003; Peron et al., ; Rothlind, Cockshott, Starr, & Marks, 2007; Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000; Schneider et al., 2003; Temel et al., 2006).

Deep brain stimulation by electrode neurosurgery is a new technique for the treatment of Parkinson's disease and some other neuropsychiatric disorders such as obsessive compulsive disorder,(Abelson et al., 2005) TIC disorder(Flaherty et al., 2005)and refractory depression(Mayberg et al., 2005). This method of treatment has recently been initiated for the treatment of Parkinson's disease in Iran. DBS surgery is one of the most expensive surgeries, and is partially been paid by the Iranian Ministry of Health. Rasool Akram Hospital in Tehran, the capital city of Iran, is the only academic centre in Iran in which DBS surgery has been conducted science now. Despite being a pioneering centre in the surgery of patients with Parkinson's disease, this is the first study performed to study the neuropsychological and cognitive effects of DBS carried out at this facility. Our purpose is to evaluate the effects of DBS on the psychiatric complaints (anxiety and depression) and cognitive function of these patients.

2. Methods

2.1. Study Design

We used a case-control design in which patients with Parkinson's disease treated with the DBS technique were compared with patients suffering from Parkinson's disease who were treated with antiparkinson's drugs. In all of the case group the electrodes located bilaterally in the STN during stereotactic surgery.

This case-control study was performed at the Rasool Akram Hospital in Tehran, Iran. At the beginning of this study, only 30 study subjects were with Parkinson's disease periodically attended the clinic after surgery in the study centre. The mean time after DBS surgery in these group were 31.43 months, After completion of the recruiting phase for the case subjects, two control subjects were selected for every case subject; therefore, 60 control subjects were recruited. The control group was selected by matching subjects according to age (±2 years), gender, duration of Parkinson's disease (±2 years) and the severity of disease according to the UPDR scale (± 5 points). The control group samples had not been candidate for DBS due to several possible reasons like preferring medication instead of surgery, fear of surgery, financial problem and lack of insurance support.

2.2. Surgical and MRI Procedures

The Leksell-G Stereotactic head frame was fixed to the patient's skull under local or general anesthesia parallel to the orbitomeatal plane. Then the patient was transferred to MRI suite, where special sequences were obtained on a 1.5 Tesla machine (Philips Gyroscan). The series of images were taken pre-operatively included: 3-dimentional MR T1-weighted and MR T2-weighted coronal and axial images and inversion recovery (IR) without any gantry tilt.

The localization of the initial STN (Subthalamic nucleus) target was calculated by stereotactic software (Ste-

reonauta Plus, Madrid, Spain Version II) on coronal and axial T2-weighted images (the center of hypointensity of STN on T2 Weighted MRI image) acquired orthogonally to Anterior Commissure-Posterior Commissure axis (AC–PC axis) crossing the anterior limit of the Red Nucleus. Then the initial target coordinates (X, Y, Z) were plotted on the T1-weighted image with contrast to find a safe trajectory for insertion of DBS electrode (avoiding intracranial vessels or ventricles).

In the operating room, five microelectrode trajectories were inserted into the brain and simultaneous electrophysiological monitoring was performed. After finding the optimal location for stimulation based on the length of STN recorded, effects and side-effects to acute macro stimulation, the permanent leads were implanted and fixed.

It's demonstrated that the degree of clinical improvement after DBS largely depends on the accuracy of electrode placement. The small size, ovoid shape, and oblique disposition of the STN and the individual variability in the STN situation are responsible for spatial inter-individual fluctuations of the real patient's target, which might significantly differ from the theoretical statistical target.

For calculating the location of the STN, a line drawn from the anterior commissure (AC) to the posterior commissure (PC) and calculates the mid commissure point (MCP) (Mansour ParvareshRizi & Bakhti., 2010), then DBS and MRI parameters including the target coordinates (X, Y, Z) and the distances from MCP to the center of STN in all three axes, on both sides were calculated for each patient. According to this method the anatomic location of STN identified from MCP. The average locations are About 11.05 mm for X axis, 3.18mm for Y axis and 3.68 for Z axis.(Mansour ParvareshRizi & Bakhti., 2010)

2.3. Measurements

All study subjects provided fully informed consent. The study instruments included a demographic questionnaire, the Hamilton Anxiety Rating Scale (HARS) for detecting the severity of anxiety(Hamilton, 1959), the Beck Depression Inventory (BDI) for detecting depression symptoms and severity, the Mini Mental Status Examination (MMSE) for evaluating cognitive function. The Clock Drawing Test (CDT) with the Mendez scoring method was completed by self-report(Mendez, Ala, & Underwood, 1992), as well as by interviewing and examining the cognitive function of the subjects. The past psychiatric history of all patients was investigated and recorded on the demographic questionnaire. All instruments were completed when the study subjects were in the "on" phase. ("on" phase in control subjects, means taking medication and "on" phase in case subjects means the DBS device was on)

The severity of disease was measured by the UPDR scale at two points. The first was in the "off" condition of drug treatment in both groups. The score under these conditions was registered in the patient's medical documents and used in this study. The second assessment, which was conducted by the researcher, was in the "on" condition when the surgery had been performed for the DBS group with concurrent drug treatment and in the control group when subjects were taking medication at the recommended dose.

This study was approved by the Ethics Research Committee of the Tehran Psychiatric Institute.

The authors declare no conflicts of interest in conducting this study.

3. Results

We enrolled 90 subjects in this study, with 30 patients in the case group (Parkinson's disease with DBS therapy) and 60 patients in the control group (Parkinson's disease with pharmacotherapy). The mean time after DBS surgery in these group were 31.43 months (minimum duration was 3 months and maximum duration was 96 months). (Table 1)

Table 1 shows the demographic characteristics of the participants and the severity of Parkinson in both groups in "on" and "off" condition. The study sample, in both the case and control groups, was matched for age, gender, duration of disease and severity index.

The Parkinson severity in "off and on" conditions were 54.73 and 12.93 in DBS group (case group); 55.66 and 14.8 in drug group (control group) which shows the efficacy of both intervention, however, the difference between two groups were not significant in either condition. (Table 1)

Since the HARS, CDT and MMSE results were not normally distributed in our sample (Table 2), we used the nonparametric Mann Whitney U test for comparing scores.

In the assessment of mood and anxiety, the mean ranks of the HARS scores were 40.75 and 47.88 in the case and control groups, respectively (P = NS). The mean ranks of the BDI scores were 43.42 and 46.54 in the case

Table 1. Demographic features of the study sample (n=90).

	Case (n=30)/ Control (n=60)	Min	Max	Mean (SD)	Sig	T	Df
Age	DBS	40	71	51.23 (7.15)	0.879	0.284	NS
	DRUG	36	67	50.78(7.04)			
Sex	DBS	Male = 25 (83.3%) Female = 5 (16.7%)			0.687	0.203	NS
	DRUG	Male = 51 (85 %) Female = 9 (15%)					
Parkinson Duration	DBS	7	16	10.65(2.85)	0.708	1.524	NS
	DRUG	5	16	9.67(2.90)			
UPDRS on	DBS	5	23	12.93(4.52)	0.786	-1.781	NS
		7	30	14.80(4.76)			
UPDRS off	DRUG	34	92	54.73(13.50)	0.263	-0.351	NS
		34	88	55.66(11.03)			
DBS duration (months)	Case	3	96	31.43			

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The Mann Whitney U test showed no significant difference in the HARS scores between patients with DBS and those on pharmacotherapy (Mann Whitney U = 757.5, z = -1.22). No significant difference was seen in the BDI scores in the two groups (Mann Whitney U = 837.5, z = -0.536).

In the assessment of cognitive function, the mean ranks of the MMSE scores were 39.22 in the case group and 48.64 in the control group (p = 0.096). For the CDT scores, the mean rank was 36.33 in the case group compared with 50.08 in the control group (p = 0.015) (Table 4).

Table 2. Tests of normality for study variables.

	UPDRS off	UPDRS on	HARS	BDI	MMSE	Clock Test
Mean ±SD	55.36±1.18	14.18±4.74	12.92±7.03	13.46±12.45	28.26±1.87	17.86±2.92
K.S. test P. value	0.145	0.233	0.016	0.140	0.001	0.000

K.S: Kolmogorov-Smirnov , SD: Standard Deviation

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Table 3. Mann Whitney U test results on neuropsychological features in DBS and pharmacotherapy cases.

	Case/Control	N	Mean ± SD	P.value **
HARS	DBS(Case)	30	11.50 ± 5.57	0.222
	Drug(control)	60	13.63 ± 7.6	
BDI	Case	30	12.8 ± 7.34	0.592
	Control	60	13.8 ± 7.25	

*Number ** Mann Whitney U test

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Table 4. Mann Whitney U test results on cognitive status in DBS and pharmacotherapy cases.

	Case/Control	N	Mean ± SD	P.value **
MMSE	Case	30	27.5 ± 2.55	0.096
	Control	60	28.63 ± 1.29	
Clock test	Case	30	16.7 ± 4.55	0.015
	Control	60	18.43 ± 1.3	

*Number ** Mann Whitney U test

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In the assessment of neurocognitive function, the Mann Whitney U test showed a significant difference between the DBS and pharmacotherapy groups in terms of the CDT scores ($p<0.05$, $z = -2.428$, Mann Whitney U = 625.000), but the test showed no significant difference in the MMSE scores between the two groups (Mann Whitney U = 711.500, z = -1.667).

For evaluating the past history of mental illnesses, the study samples of the case and control groups were divided into two groups, with and without past psychiatric history. There was no significant difference ($\chi 2 = 1.4$, df = 1).

4. Discussion

This study was carried out on subjects within 30 months of performing DBS using a case-control study design.

The main findings of this study showed that psychiatric problems, including depression and anxiety, do not occur to a significantly greater extent in patients treated with DBS compared to those given pharmacotherapy. Nevertheless, cognitive changes were detected after DBS intervention. The MMSE scores were not different significantly between the two groups, but the CDT score was increased in the DBS group.

Although the severity of anxiety and depression was not different, the scores were lower in the DBS group. Increasing the sample size may make it possible to detect differences. In previous case report studies, DBS (subthalamic electrode implementation) was associated with depressive symptoms and suicidal ideation (Berney et al., 2002; Stefurak et al., 2003). In a study carried out by Funkiewiez (2004), the results showed that, after three years, mood improved and cognitive function showed no significant changes (Funkiewiez et al., 2004). Deep brain stimulation treatment bilaterally in the globus pallidus internus substantially improved symptoms of depression as measured by the Hamilton Rating Scale of Depression(Kosel et al., 2007). Chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus has resulted in marked improvement in chronic and refractory depression(Mendez et al., 1992). Therefore, the current controversy could be accounted for partly by the location of the electrodes implemented in deep brain tissues(Stefurak et al., 2003).also whether the electrode located in the dorsal or ventral part of STN may associated with different effects on motor symptoms and affect, dorsal stimulation of STN may cause less variable motor response and more improvement in UPDRS motor rating, this effect likely achieved by selectively stimulation and modulation of sensorimotor territory of STN or afferent projection. Ventral stimulation of STN may change limbic function and associated with more positive affect and emotions so whether the electrode more contact with the ventral or dorsal part of STN, may cause different effect on mood and affect of patients.(Greenhouse et al.)

In the assessment of cognitive function, the effect of subthalamic DBS was not significant, although lower scores were seen in the MMSE in the DBS group than in patients treated with pharmacotherapy. This may have been due to the high degree of cortical appraisal in the MMSE. DBS in the STN does not involve cortical areas; therefore, MMSE scores may not be affected by the DBS procedure. However, it could be speculated that the sample size was insufficient and that increasing the study sample size may decrease MMSE scores in the DBS group.

On the other hand, the CDT scores in the DBS group were lower than in the pharmacotherapy group, and this difference was significant. It is reasonable that, in the DBS group, performing some procedures involving basal ganglia structures may have revealed some cognitive impact mainly related to subcortical areas and executive functions. The CDT evaluates subcortical cognitive functions, and this result could be reasonable, even with the rather small sample size used in this study (Nair et al., 2010; Peters & Pinto, 2008; Pinto & Peters, 2009).

In a study performed in Texas, an association was also detected between the location of the tip of the electrode and cognitive and memory functions (York, Wilde,

Simpson, & Jankovic, 2009). Kosel et al. showed that, after 15 months of follow-up, DBS in the STN and DBS in the GPi were associated with reduced cognitive abilities such as verbal fluency and working memory(Kosel et al., 2007). DBS surgery performed for essential tremor resulted in a decrease in semantic memory and visual memory(Baltuch GH & MB, 2007).

Regarding to neurocognitive squeal, different anatomical locations have been tried. Some research showed that cognitive processing was lower in STN stimulation compared with GPi stimulation; nevertheless, there were no significant differences in motor functions between GPi and STN stimulation. Therefore, in addition of motor outcomes, the neurocognitive results should be considered in surgery procedure(Follett et al., 2010), but the other research showed that long term motor efficacy of STN implants has been up to 8 years, compare to 5.5 years for GPi implants (Albanese & Romito) and no difference in mood and cognitive outcome of these two methods (GPi versus STN).(Okun et al., 2009; Okun et al., 2003; Weaver et al.)

It can be concluded that DBS surgery could have a neuropsychiatric and cognitive impact which must be followed by the management team. Appropriate medical and non-medical intervention should be considered in these cases.

Because of the limited number of people candidate for surgery and DBS, we couldn't assess subject before and after DBS and it takes long period of time.

It didn't possible to turn OFF device in case group for neurocognitive assessment in OFF status because of moral reason.

In subsequent studies, a more powerful study design with a structural interview for axis one diagnosis and evaluation (According to DSM-IV TR) and a completed neuropsychology battery will be employed to evaluate the long-term impact of DBS surgery.

Regarding to socio- economic situation of the two groups, it could be mentioned that the case subjects may have been in higher level which could afford for the expensive DBS surgery, however, it is not clear that the socio-economic conditions could have any significant effect on the neuropsychiatry impact of DBS intervention.

6. Authors Contribution

Reza Mahdavi designed and conducted the study, data collection and drafting the article. Seyed Kazem Malakouti contribute the conception and designed the study and revised critically the article. Gholam Ali Shahidi contribute the design and revised the article. Parvaresh contribute the conception and reviewed the article.

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The Polarity-Dependent Effects of the Bilateral Brain Stimulation on Working Memory

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ABSTRACT

Introduction: Working memory plays a critical role in cognitive processes which are central to our daily life. Neuroimaging studies have shown that one of the most important areas corresponding to the working memory is the dorsolateral prefrontal cortex (DLFPC). This study was aimed to assess whether bilateral modulation of the DLPFC using a noninvasive brain stimulation, namely transcranial direct current stimulation (tDCS), modifies the working memory function in healthy adults.

Methods: In a randomized sham-controlled cross-over study, 60 subjects (30 Males) received sham and active tDCS in two subgroups (anode left/cathode right and anode right/cathode left) of the DLPFC. Subjects were presented working memory n-back task while the reaction time and accuracy were recorded.

Results: A repeated measures, mixed design ANOVA indicated a significant difference between the type of stimulation (sham vs. active) in anodal stimulation of the left DLPFC with cathodal stimulation of the right DLPFC [$F(1,55)= 5.29$, $P=0.019$], but not the inverse polarity worsened accuracy in the 2-back working memory task. There were also no statistically significant changes in speed of working memory [$F(1,55)= 0.458$,$P=0.502$] related to type or order of stimulation..

Discussion: The results would imply to a polarity dependence of bilateral tDCS of working memory. Left anodal/ right cathodal stimulation of DLPFC could impair working memory, while the reverser stimulation had no effect. Meaning that bilateral stimulation of DLFC would not be a useful procedure to improve working memory. Further studies are required to understand subtle effects of different tDCS stimulation/inhibition electrode positioning on the working memory.

1. Introduction

Working memory refers to a the ability responsible for the limited and temporary storage and processing of information for manipulating, recalling or association with other incoming information. According to the central executive model (Baddly, 1986), an attentional control system should be responsible for the strategy selection, control and co-ordination of the various processes involved in short-term storage and more general processing tasks. An important characteristic of this system is a limitation of resources and variations in processing, storage and functions (Salmon. et. al, 1996).

According to Baddley (1992), working memory transiently stores and processes information underlying attention. These comprise functions such as learning, language and reasoning which are supported with complex

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cognitive operations. Furthermore, it plays a critical role in cognitive processes which are central to one's daily life. Several brain regions are shown to be involved in working memory processing. They include dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus, hippocampus, globuspallidus, caudate nucleus, putamen, amygdala (Sadleir, Vannorsdall, Schretlen, Gordon, 2010), dorsal occipital area, frontal eye field, intraparietal sulcus, inferior temporal gyrus, posterior middle frontal gyrus, and the superior parietal lobule (Pessoa et al., 2002). Functional neuroimaging studies however have suggested a dominant role for DLPFC in this respect (Paulesuet. al, 1993). This area becomes highly activated when precise information monitoring for spatial, non-spatial, verbal and visual stimuli is required (Funahashi et al., 1993). Meanwhile, the medial parts of prefrontal cortex contribute to the maintenance and retrieval of the recently encoded information (Zimmer, 2008, Mottaghy et al. 2000).

Transcranial Direct Current Stimulation (tDCS) is a non-invasive method to manipulate the cortical activity using a continuous weak electric current induced by large electrodes placed on the scalp of the subject (Nitsche, et al., 2008). The amount of the electrical current going to the brain is enough to cause focal and prolonged, but yet reversible shifts on cortical excitability (Wagner et al., 2007, Miranda et al., 2006). These manipulations have diverse effects on brain functioning, depend on site, polarity and size of the stimulation (Javadi & Walsh, 2012). This method has been proposed to be applied for the rehabilitation of working memory deficits seen in mental or neurological disorders such as Alzheimer, depression or Parkinson's Diseases (Ferrucci et al, 2008; Kalu et al, 2012; Boggio et al, 2006), while more evidence is required to support this application. A growing body of evidence has substantiated that different tDCS electrode positioning result in various modulatory effects both normal subjects and patients (Boggio et al., 2006; Ferrucci et al, 2008; Fregni et al., 2005; Marshall et al., 2005). Fregni et al. (2005) found that 1 mA of online anodal tDCS over the left DLPFC for a period of 10 minutes, enhances the accuracy of the 3-back working memory task, compared to sham and cathodal tDCS applied to the same area. However, bilateral tDCS stimulation of DLPFC during the modified Sternberg working memory task either for the anodal or cathodal stimulation, increases reaction time (Marshal et al, 2005). Ohn et al. (2008) assessed the working memory during 30 minutes under 1 mA anodal tDCS stimulation applied to left DLPFC. They identified a linear improvement of the working memory over time. In a similar report, a 2 mA tDCS stimulation was shown to improve the working memory in patients with Parkinson's Disease, whereas 1 mA stimulation led to no significant effect (Boggio et al. 2006). Ferrucci et al. (2008) showed that either the anodal or cathodal stimulation over the cerebellum did not alter the working memory proficiency in Sternberg's test. In another study, they reported that one anodal session of temporal cortex in patients with Alzheimer's Disease improved memory performance, whereas the impact of applying several sessions of stimulation on long-term improvement remained controversial. More recently, Mulquiney, et.al (2011) have found that the anodal tDCS over the left DLPFC may significantly improve the performance speed in a 2-back working memory task, while this is not shown to have effects on the accuracy of performance. These finding would imply that effect of tDCS heavily depend on various variables, including: the side, the power, the polarity of stimulation.

Taken the above insights together, the aim of the current is to investigate any possible effects of the simultaneous excitation of the bilateral DLPFC on working memory.

2. Methods

2.1. Participants

Sixty healthy college students (30 male) were recruited from Shahid Beheshti University. Participants were randomly assigned into two subgroups (15 female in each) with respect to the side and polarity of the stimulation, i.e. left anodal/ right cathodal vs. left cathodal/ right anodal stimulation of the DLPFC. The mean and standard deviation of age for the groups were; 22.3 years, (sd= 0.86) And 21.2 years, (sd=0.67). The difference in age was not significant. Participants gave an informed consent form for taking part in the study. All of them met the inclusion criteria for tDCS (Nitsche et al, 2008), and none had previously experienced tDCS experiments. Exclusion criteria were substance abuse, history of serious head injury, or any other serious medical condition interfering with tDCS application or working memory performance.

2.2. Design

The study had a single-blinded 2x2x2 repeated measure design. Each participant underwent two sessions with at least 3 days interval to minimize any potential carry over effect of stimulation. They received active or sham tDCS stimulation for 20 minutes while performed the task just before and after to the stimulation. The stimulation session's order was randomized and counterbalanced across

participants to overcome the learning effect on the outcome measures. A same 2-back working memory task was used in all pre/ post assessments. This task is a sensitive measure to cognitive changes in a variety of disorders and has minimal learning effects, making it an ideal task for repeated testing (Maruff et al., 2009; Mulquiny et al., 2011). All stimulation sessions were carried out by the same researcher.

2.3. Procedure

Participants were briefed about the procedure at the beginning of each session. The location of right and left DLPFC were determined based on Dasilva et al.'s (2011) method. Each participant was instructed to response to a computerized working memory task by pressing button 1 or 2 as he or she decided whether each figure was identical to the one presented two earlier in the sequence. They were instructed to press the key 1 if the presented figure was the same as the figure presented two stimuli previously, and if not to press the key 2.

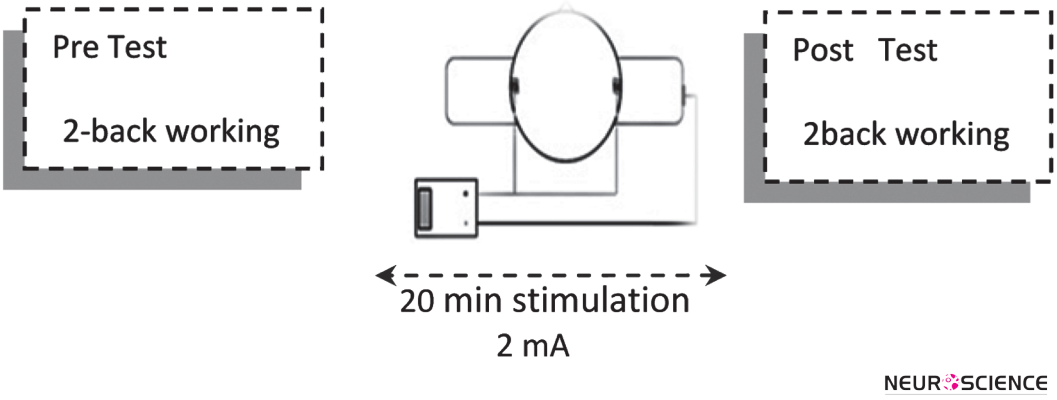


Figure 1. Sequence of task presentation and stimulation. Participants were first required to perform 2-back working memory task. Then the tDCS stimulation was applied over left and right DLPFC, during 20 minutes. Finally, post 2-back working memory task was assessed.

2.4. Measures

2.4.1. Working Memory Task

A visual sequential 2-back figure working memory (Mull & Seyal, 2001) was used in this study. Subjects were presented with a pseudo-random set of six figures. The stimuli were generated using the MATLAB software. A 2-back working memory task, is considered as an active task, since the working memory should be continuously updated (Zimmer, 2008). Subject were asked to press the key 1 if the presented figure was the same as the figure presented two stimuli previously, and if not, press the key 2. One hundred figures which were divided into six different series were prepared in the task and totally 20 correct responses were obtained from each set. Figures were presented randomly and sequentially while for each figure the subject had to memorize it then press the key 1 or 2 based on what image he or she sees in the next sequence. Subjects' speed as well as correct responses was recorded. The applied 2-back working memory task remained the same for all participants.

2.4.2. Stimulation

Stimulation was applied with a battery-driven device (Activa Dose Iontophoresis manufactured by ActivaTek), which was capable of delivering the anodal, cathodal direct current and sham direct current required for this study. Direct current was delivered through two 25 cm2 (5×5) electrodes, covered by sponge pad soaked in sodium chloride solution. The stimulator was set to fade in and out over a period of 30s at the beginning and the end of the stimulation session.

2.4.2.1. Active Stimulation

Active stimulation was applied at 2 mA. The left cathodal/right anodal stimulation was conducted with the anode placed over the right DLPFC and cathode over the left DLPFC, and in the reverse order for the left anodal / right cathodal stimulation. The electrodes were positioned with an elastic band according to electrode placement measuring method.

2.4.2.2. Sham Stimulation

During sham stimulation by positioning electrodes as same as active tDCS condition a constant current faded in for 30 s before being immediately faded out for 30 s, and the tingling sensation associated with tDCS was noticeable only for the first 1 min. This coding and setting required the subject to be blind, resulting in a single-blinded experiment.

2.4.3. Statistical Analysis

For both accuracy and speed, we conducted a 2 × 2 × 2 ANOVA repeated measure (pre/post × electrode position× stimulation) of participants' working memory. We conducted a general linear model repeated measures analysis on the factors working memory scores (pre vs. post) and tDCS stimulation condition (active vs. sham stimulation) was employed. To determine more specifically whether the accuracy after tDCS differed in stimulation condition paired samples for the intra group active versus sham comparisons, two-tailed analysis with significance level of $P < 0.05$, not adjusted for multiple comparisons were performed. The dependent variables were checked for the normal distribution.

3. Results

3.1. Results of Working Memory Accuracy

Repeated measure-ANOVA revealed that the effect of "stimulation" condition was significant [F (1, 55) = 5.29, P=0.019]. Similarly, the interaction of "order" ×"stimulation" × "electrode position" [F(1,55)=2.404 P=0.045] was significant (table2). To overview this finding we should consider the differences which are outlined in Figure2. Post-hoc Paired t test showed that there was significant differences between the accuracy in post stimulation conditions (sham vs. active) only in the left anodal/ right cathodal tDCS stimulation [t=-2.894, df=28, P = 0.007], but not in the left cathodal/ right anodal tDCS stimulation [t = 0.497, df=27, P= 0.623]. Independent samples t tests did not reveal significant differences between the post stimulation results of active or sham types of electrode positioning (figure 2).

Table 1. Means and standard error of mean (SEM) for accuracy and speed on 2-back visual working memory outcome measures

		Active stimulation		Sham stimulation		Statistics within a group	Statistic Between group
		Pre-tDCS	Post-tDCS	Post-tDCS	Post-tDCS		
Accuracy	Anodal left/ Cathodal right/	6.7±1.8	6.2±1	6.8±2	7.2±1.1	0.007[a]	0.082
	Cathodal left/ Anodal right	6.7±0.9	7.1±0.9	7.6±1	6.9±0.9	0.623	
Speed	Anodal left/ Cathodal right	232±74	174±41	202±47	152±10	n.t.	n.t.
	Cathodal left/ Anodal right	242±95	180±20	236±15	174±10	n.t.	

n.t., not tested; statistic between groups is independent samples t test electrode positioning. Statistics within a group are paired samples t test post active versus post sham tDCS.

[a] P>0.05.

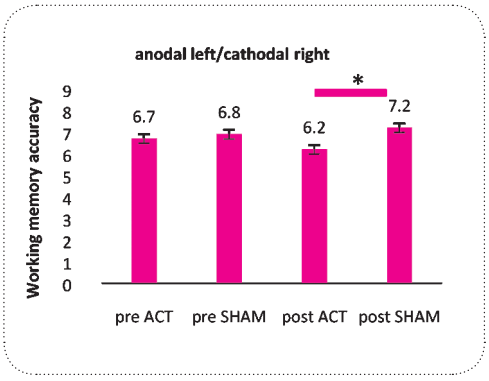
3.2. Results of Working Memory Speed

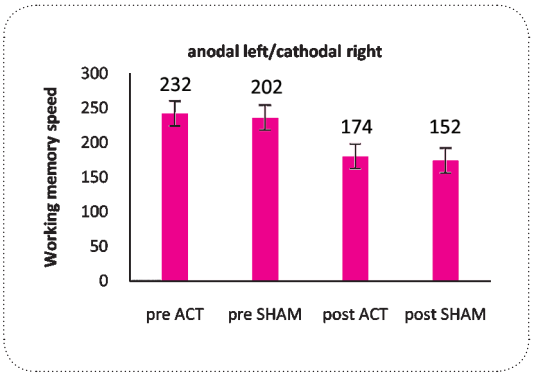
For the working memory speed, repeated measure-ANOVA revealed that there was no significant effect of "stimulation" [F(1,55)= 0.458 ,P=0.502] or interaction of "stimulation" × "order" × "electrode position" [F(1,55)= 0.123, P=0.728] (table2). There was a significant effect of "order" [F(1,55)= 0.458 ,P=0.000]. As presented in figure 3, this difference was due to the familiarity with procedure of the test in which the speed of performance increases in post-test. This result indicates that participants were not significantly faster in responding neither in the active (Anodal and Cathodal) stimulation nor sham trials (table 1/figure 3) and the response speeds were similar when participants responded in pre and post of stimulation setting(table 1/figure 3).

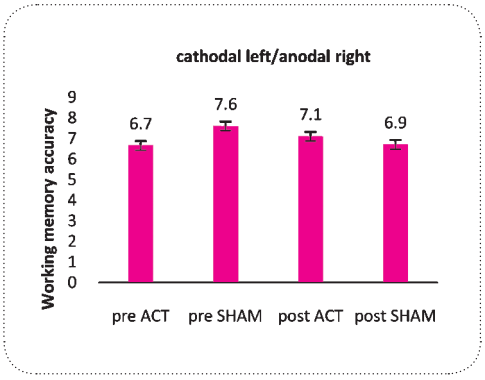
Table 2. Results of the repeated measure of ANOVAs used to compare accuracy and speed of the anodal left/cathodal right and cathodal left/anodal right of DLPFC groups.

	Factors	*F* statistic	*P* value
Working memory accuracy	**Stimulation**	**F** (1,55) = **5.29**	**0.019**
	Stimulation* Electrode position	F (1,55) = 0.018	0.894
	Order	F (1,55) = 0.572	0.453
	Order* Electrode position	F (1,55) = 0.423	0.518
	Order*Stimulation	F (1,55) = 0.156	0.312
	Stimulation*Order*Electrode position	**F** (1,55) = **2.404**	**0.045**
Working memory speed	Stimulation	F (1,55) = 0.458	0.502
	Stimulation* Electrode position	F (1,55) = 0.313	0579
	Order	**F** (1,55) = **39.03**	**0.000**
	Order* Electrode position	F (1,55) = 0.154	0.696
	Order*Stimulation	F (1,55) = 0.49	0.825
	Stimulation*Order*Electrode position	F (1,55) = 0.123	0.728

Boldface highlights important comparisons







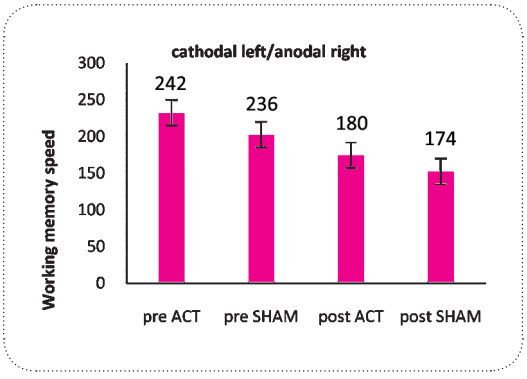


Figure 2. Absolute change of visual working memory revealed in post active and post sham conditions in left anodal/right cathodal tDCS stimulation of normal subjects (t test, P = 0.007). There are no differences between conditions in cathodal left/anodal right (t test, P> 0.05). Data are represented as mean ± SEM.

Figure 3. There is no significant difference in the mean speed between conditions (sham vs. active stimulation) in both protocols. Data are represented as mean ± SEM.

4. Discussion

We attempted to investigate the effects of the bilateral stimulation of the DLPFC on working memory. Our results indicated that the left anodal / right cathodal stimulation of the DLPFC impaired the accuracy of the task performance as compared to the sham stimulation of the same area. Both stimulation types had no effects on the speed of working memory performance. Our results were incongruent with previous studies (Fregni et al, 2005; Ohn et al, 2008; javadi & walsh, 2011; Javadi & Cheng, 2011), which showed that anodal stimulation of the left DLPFC enhances the working memory performance.

These data raises the question of whether the difference in our results with previous studies is due to the type of stimulation electrode position. In other words, could simultaneous stimulation of right DLPFC with left DLPFC interferes with the working memory performance.

Incongruent with literature about brain stimulation effects on working memory, the present study showed that the left anodal stimulation of DLPFC with simultaneous cathodal stimulation of right DLPFC not only failed to enhance the accuracy performance of the participants, but also decreased the accuracy in their working memory performance. Though, we should consider to the role of the cathode electrode applied over the right DLPFC.

Some neuroimaging studies (Funahashi et al, 1989, 1990, 1991; Salmon et al, 1996) have demonstrated the right DLPFC activation during a visual working memory task. Likewise, some other report have showen that this region is involved in working memory (D'Esposito et al, 1998; Smith and Jonides, 1999). Moreover, lesion studies (Goldman & Rosvold, 1970; Bauer & Fuster, 1976; Funahashi, Bruce, & Goldman- Rakic, 1993) have indicated that when this area is damaged, the working memory is notably affected. It has been found that transcranial magnetic stimulation (TMS) of the right DLPFC with disruption of function, results in impaired visual working memory capacity (Oliveri et al., 2001; Turatto, Sandrini, & Miniussi, 2004, Sligte et al, 2011). It should be noted that this study measured the working memory performance with a visual 2-back working memory task. Thus, present results are in line to confirm the role of the right DLPFC on visual working memory, based on which dampening the right DLPFC leads to the performance deterioration in some aspects of cognitive functions such as the visual working memory.

To distinguish the role of the right and left DLPFC in visual working memory, our results suggest that the involvement of the left prefrontal area in visual working memory depends on the verbal encoding of visual stimuli (Smith and Jonides, 1997), whereas the stimuli used in this study were unfamiliar and unmeaning images, thus so difficult to use in verbal encoding with. Therefore, with respect to more dominant role of the right prefrontal on image-based visual working memory than the left DLPFC (Hong et al, 2000), we may assume that the disruption of the right DLPFC function in left anodal/right cathodal stimulation impaired the accuracy by interfering in processing of visual stimuli in working memory performance.

On the other hand, methodological consideration should be entertained. Our study, however differs with previous studies in a several ways. The stimulation intensity in our study was 2 mA, while the previous studies used 1-2 mA. This consideration is important that stimulation intensity is a critical parameter, in which Boggio et al (2006) showed that 2 mA versus 1 mA current stimulation over the left DLPFC can enhance the working memory in patients with Parkinson's Disease. In addition, we tested the working memory performance before and after the stimulation, whereas others (Fregni et al, 2005; Ohn et al, 2008; Boggio et al, 2008; Jvadi and Walsh, 2011) tested this during the online stimulation. Some evidences suggest that stimulation of the brain areas during the task accomplishment have different effect in comparison with offline stimulation (Nitsche &Paulus, 2001). Moreover, the duration of stimulation in this study was 20 min, which was higher than other studies. We applied bilateral stimulation, in which Ohn et al (2008) confirmed that longer stimulation was enhanced working memory performance. Although, some other studies (Fregni et al, 2005; Ohn et al, 2008; Javadi & Walsh, 2011; Mulquiney et al, 2011; Javadi& Cheng, 2011) used unilateral stimulation of the left DLPFC, It has been shown that electrode positioning affects the flow of the current and so likely the stimulated brain area (Im et al, 2008; Nitsche M, Paulus, 2000). However, considering Marshal et al (2005) study in which they used the bilateral intermittent stimulation of the lateral prefrontal cortex, it should be noted that this type of electrode positioning impairs the response selection-related processing. Taken together, it seems that the bilateral stimulation of DLPFC in present study was responsible for the impairment of accuracy and exerted declining effects on working memory. This observation is important as it might indicate that the bilateral stimulation can affect brain in a different way compared to unilateral stimulation. Therefore, it seems likely that other unilateral or bilateral electrode position-

ing lead to a significant improvement in the working memory accuracy.

With regard to the speed of working memory, bilateral stimulation of DLPFC results in slowing the speed in working memory (Marshal et al, 2005). Discrepancy in our finding with others' results may be due to the task type and current. We examined the 2-back working memory task, whereas they tested Sternberg's working memory task. In addition, we applied the constant current, while they used an intermittent stimulation during the experiment. In another study, Left anodal stimulation of the DLPFC enhanced the speed of the performance in working memory task (Mulquiney et al, 2011) whereas, some other works (Fregni et al, 2005; Ohn et al, 2008; Javadi and Walsh, 2011; Jvadi & Cheng, 2011) showed that the anodal stimulation of the left DLPFC did not alter the speed of working memory performance. In the present study, the bilateral stimulation effect on speed was in line with the two later reports. Thus, we can acclaim that type of electrode positioning may meaningfully affect the operations in working memory.

With respect to tDCS, in future studies it may also be advantageous to investigate the role of the right DLPFC in working memory performance with other electrode positioning. In the previous brain stimulation studies, little attention is paid to the role of the right DLPFC in working memory performance. While the right DLPFC is shown to be involved in an extended range of working memory dimentions (Zimmer, 2008; Paulesu et al, 1993; Salmon, 1996). Moreover, it should be noted that there is little definite evidence explaining whether the effect of tDCS in working memory is indeed via modulation of the DLPFC excitability and if yes, under what possible mechanism(s)? Further studies should proceed to investigate the functional differences between the right and left DLPFC in visual working memory.

In summary, our study indicated that tDCS effect on working memory performance, is dependent to the electrode positioning, and Bilateral stimulation of DLPFC have negative effect on the accuracy of performance upon a working memory task.

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Restoring Motor Functions in Paralyzed Limbs through Intraspinal Multielectrode Microstimulation Using Fuzzy Logic Control and Lag Compensator

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Functional Electrical Stimulation,
Intraspinal Microstimulation,
Fuzzy Logic Control,
Motor Function.

ABSTRACT

In this paper, a control strategy is proposed for control of ankle movement on animals using intraspinal microstimulation (ISMS). The proposed method is based on fuzzy logic control. Fuzzy logic control is a methodology of intelligent control that mimics human decision-making process. This type of control method can be very useful for the complex uncertain systems that their mathematical model is unknown. To increase the stability and speed of the system's response and reduce the steady-state error, we combine the FLC with a lead (lag) compensator. The experiments are conducted on five rats. Microelectrodes are implanted into the spinal cord to provide selective stimulation of plantarflexor and dorsiflexor. The results show that motor functions can be restored using ISMS. Despite the complexity of the spinal neuronal networks and simplicity of the proposed control strategy, our results show that the proposed strategy can provide acceptable tracking control with fast convergence.

1. Introduction

Functional electrical stimulation (FES) is a potentially useful technique to restore motor functions in individuals with spinal cord injury, head injury, stroke, and multiple sclerosis (Agarwal et al., 2003; Hardin et al., 2007). Currently, FES systems utilize peripheral nerve stimulation or direct muscle stimulation to restore motor functions. Though some advances have been achieved by traditional FES systems, there are still unsolved problems. The challenge of peripheral nerve stimulation or direct muscle stimulation is the physiological recruitment order of motor units (Tai & Jiang, 1994) and the muscle fatigue. Larger motor units are activated physiologically after smaller ones have been recruited according to the "size principle" (Fang & Mortimer, 1991; Karu, Durfee, & Durfee, 1995). However, in conventional FES, larger motor units are excited before smaller ones. This type of "reverse recruitment" order and synchronized activation result in poor force gradation and rapid muscle fatigue for electrically activated muscles (Fang & Mortimer, 1991; Karu et al., 1995).

To overcome the difficulties of the traditional FES systems (nerve or direct muscle stimulation), intraspinal microstimulation (ISMS) has been recently proposed as a means to activate the paralyzed skeletal muscle through electrical stimulation of the lumbo-sacral portion of the spinal cord (Pikov, 2008). The spinal cord contains neuronal circuitry called motor neuron pools. All of the motor neurons in a motor neuron pool innervate a single muscle, and all motor neurons that innervate a particular muscle are contained in the same motor neuron pool. Each individual muscle fiber in a muscle is innervated by one, and only one, motor neuron. However, a single

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motor neuron can innervate many muscle fibers. Therefore, different groups of muscles could potentially be selectively activated by implanting microelectrodes into different motor-pools.

It has been demonstrated that ISMS has several advantages over peripheral nerve or direct muscle stimulation (Tai, Booth, Robinson, de Groat & Roppolo, 1999; Tai, Booth, Robinson, de Groat & Roppolo, 2000; Mushahwar & Horch, 2000). It was shown that graded muscle contraction in individual muscle or muscle groups could be generated by electrically stimulating motor neurons in the lumbo-sacral of spinal cord (Bamford, Putman, & Mushahwar, 2005). The gradual force recruitment characteristics of ISMS have been attributed to its ability to activate motor neurons in a near normal physiological order based on their size (Fang & Mortimer, 1991). It was demonstrated that intramuscular stimulation is characterized by rapid muscle fatigue and that ISMS is able to elicit prolonged and stable force generation (Lau, Guevremont, & Mushahwar, 2007).

Although ISMS is expected to have several advantages over peripheral nerve or direct muscle stimulation, several challenging problems remain to be solved. An important issue is the selective stimulation of the hind limb muscles. Mushahwar and Horch (2000) demonstrated that the selective activation of muscle groups can be achieved through ISMS. They showed that the selective activation of quadriceps, tibialis anterior or triceps surae/plantaris muscles occurs when the target muscle's motor pool is directly stimulated. However, increasing the stimulation intensity to increase the force level and the ranges of motion causes the spread of current to adjacent motor pools and the activation of the other motor pools.

To solve this problem, we have already demonstrated that the selective activation of the muscle can be enhanced by delivering the stimulation signal through the electrodes at multiple locations within a given motor activation pool (Roshani & Erfanian, 2012). Mushahwar and Horch (1997) showed that fatigue is essentially eliminated by interleaved stimulation when the stimuli are delivered through two separate electrodes simultaneously in an interleaved manner. Moreover, they demonstrated that the values of mean and standard deviation of force increase during simultaneous stimulation through two electrodes compared to the sum of the forces generated by stimulation through each electrode alone.

Tai et al. (2000) used three different electrode combinations (single electrode only, electrode pairs and three electrodes) for evaluating the effects of multielectrode ISMS. They showed that the isometric torque evoked by ISMS with a three electrode combination could be enhanced or suppressed when compared with that evoked by single or paired electrode stimulation. Lemay, Galagan, Hogan, and Bizzi (2001) evaluated the responses produced by coactivation of two spinal sites in frog. They found that for multielectrode stimulation, the forces under coactivation were the scaled vectorial summation of the individual responses.

All these studies demonstrated the several benefits of the ISMS through a distributed set of electrodes implanted in a given motor activation pool including finer control of force generation, selective activation, and fatigue resistance. Another important challenge to the restoration of paralyzed motor function through the use of ISMS is the control strategy for generation of appropriate electrical stimulation patterns. In previous work (Asadi & Erfanian, 2012), we developed a robust control strategy for movement control via ISMS using a single electrode implanted in each motor pool within the spinal cord. In the current study, we develop a control strategy for control of ankle movement using ISMS via two microelectrodes implanted in motor pool of each muscle. A major problem to control of such systems is the highly nonlinear and time-varying properties that are exposed to strong influence of internal and external disturbances. Moreover, developing an accurate model of such systems is totally impractical. One simple approach to deal with such systems is fuzzy logic control (FLC). Fuzzy control provides a formal methodology for representing, manipulating, and implementing a human's heuristic knowledge about how to control a system. In this paper, we use FLC for control of movement using ISMS.

2. Methods

2.1. Controller Design

2.1.1. Structure of Controller

The configuration of the proposed control strategy is schematically depicted in Fig. 1. For each neuro-muscle-joint complex an independent controller is designed. Each controller has two outputs (i.e., stimulation signal) which are delivered to the spinal cord via two microelectrodes implanted in the motor pool of the muscle. The objective of the controllers is to generate stimulation signals to force the joint angle to track a desired trajectory in the presence of system uncertainties, time-delay, and disturbances.

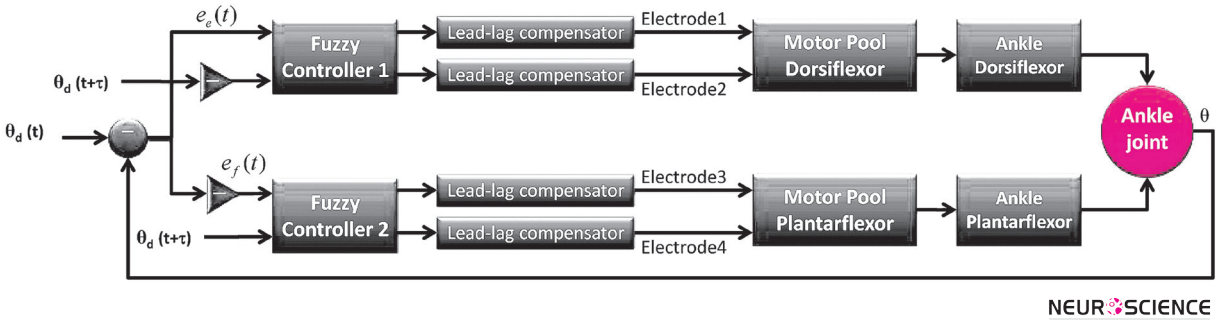

Figure 1. Block diagram of the proposed fuzzy logic control for control of the ankle movement using multielectrode intraspinal microstimulation (ISMS).

2.1.2. Fuzzy Logic Controller

The fuzzy controller has four main components (Fig. 2): fuzzy rules, fuzzification, fuzzy implication, and defuzzification (Kovacic & Bogdan, 2006).The fuzzification interface simply modifies the inputs so that they can be interpreted and compared to the rules in the rule-base. The conversion of a numerical value of x into a corresponding linguistic value by associating a membership function is called fuzzification. In the proposed FLC, inputs are the normalized error signal and the future value of the normalized desired trajectory. The fuzzy rule base is the central component of a fuzzy controller and it holds the knowledge in the form of a set of rules. The rule base includes a set of "if…then…" rules. Each rule describes a relationship between the input fuzzy sets and the output fuzzy sets. The inference engine evaluates which control rules are relevant at the current time and then decides what the input to the plant should be. In this paper, we use mamdani implication (Kovacic & Bogdan, 2006) to determine the influence produced by the antecedent part of the fuzzy rule on the consequent part of the rule. The defuzzification interface converts the conclusions reached by the inference mechanism into the inputs to the plant. In the proposed FLC, fuzzy sets consist of negative big (NB), negative small (NS), zero (Z), positive small (PS), positive medium (PM), and positive big (PB).

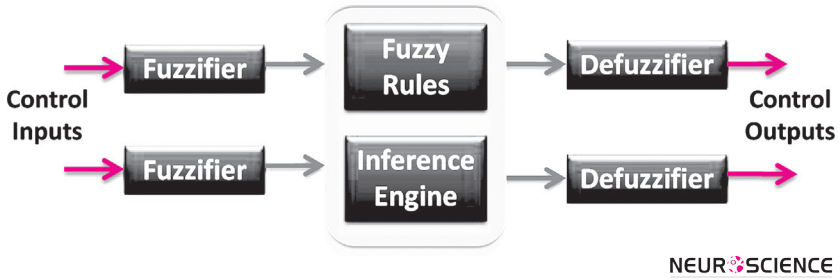

Figure 2. Structure of the fuzzy logic control (FLC).

Using the pre-defined fuzzy rule base (Table I), mamdani implication, singleton and Gaussian membership functions, sum–min aggregation, and the center of area (COA) defuzzification, the output of FLC can be defined as

$$u_{FLC}(x_k, y_k) = \frac{\sum_i u_i . \mu_u(x_k, y_k, u_i)}{\sum_i \mu_u(x_k, y_k, u_i)} \quad (1)$$

where

$$\mu_u(x_k, y_k, u) = \sum \min_{i=1}^{r} \left[\mu_{R_{pq}}(x_k, y_k), \mu_{P_m}(u) \right] \quad (2)$$

where $u_{FLC}(x_k, y_k)$ represents the crisp value of the fuzzy controller output, u_i is a discrete element of an output fuzzy set and $\mu_u(x_k, y_k, u_i)$ is its membership function, R_{pq} and P_m are antecedent and consequent parts of the fuzzy rule, respectively, denotes a number of fuzzy rules activated by x_k and y_k and $\mu_u(x_k, y_k, u_i)$.

2.1.3. Lead (lag) Compensator

The purpose of lag compensator is to, improve the transient response characteristics by increasing the phase margin of the system, and reduce the steady-state error

by increasing only the low-frequency gain. The lead compensator increases the bandwidth by increasing the gain crossover frequency to realize a faster transient response. The lead or lag compensator is described by a transfer function

$$G_f(s) = K_f \frac{T_f s + 1}{T_M s + 1} \quad (3)$$

where K_f is the gain coefficient, T_f is the lead-time constant and T_M is the desired time constant.

If $T_f \leq T_M$ transfer function (3) will be a lead compensator and if $T_f \leq T_M$ it will be a lag compensator. Depending on desired response any combination of lead and lag compensator can be used (Kovacic & Bogdan, 2006).

2.2. Experimental Setup

2.2.1. Animal Preparation

Five male adult Wistar rats (350-400 g) were used in this study. Five sessions of experiment were performed (each session on a rat). The rats were anesthetized with intraperitoneal injection of urethane (1.65 g/kg). Then a partial laminectomy was performed to expose the T12-L2 segments and the dura mater over these laminas was opened longitudinally. The rats were placed in a stereotaxic frame (SR-6R, Narishige Group Product) which allowed hindlimbs to move freely (Fig. 3). All surgical procedures and experimental protocols were approved by the local ethics committee.

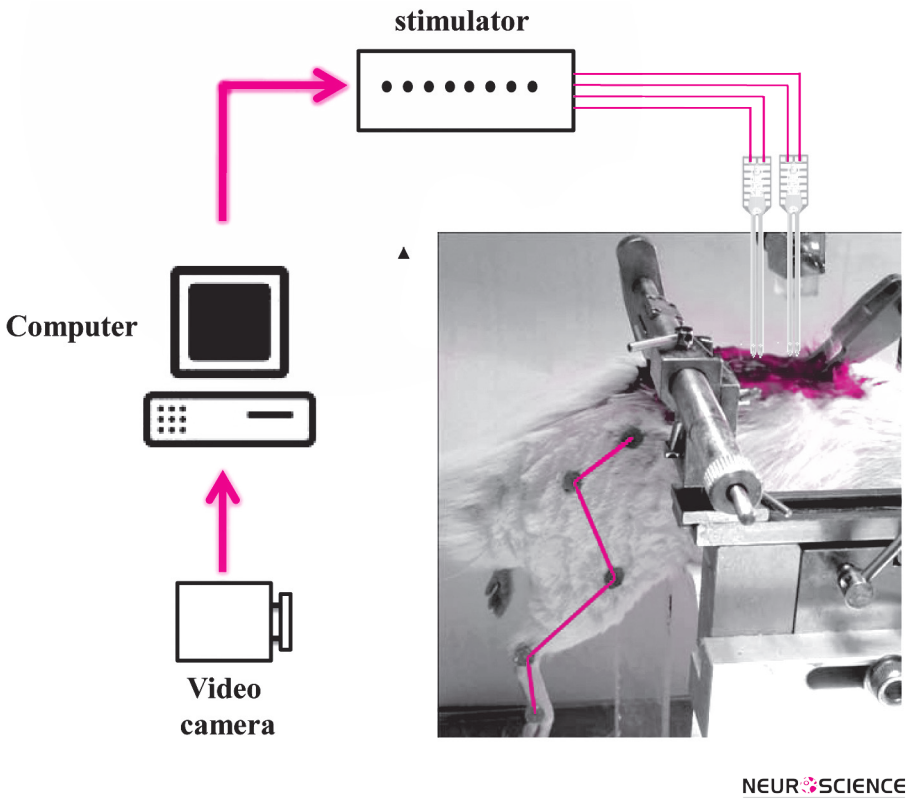

Figure 3. Schematic of the experimental setup for closed-loop control of the knee movement using ISMS.

2.2.2. Data Acquisition and Stimulation Electrode

To measure the joint angles, colored markers were attached to each link. A webcam was focused to capture the location of the markers during limb movements elicited by ISMS. We used NI Vision development module in LabVIEW to estimate the joint angles.

An eight-channel computer based stimulator (STG4008 -1.6mA Multi Channel Systems MCS GmbH) was used to stimulate the spinal cord. The stimulator can generate charge balanced, biphasic current pulses. The amplitude, pulse width, and frequency of the stimulation signal can be varied online using custom software package written in LabVIEW. Stimulus pulses were delivered through a

custom-made multi-electrode array implanted in the ventral horn of the L1 spinal segment. The multi-electrode array was made of tungsten electrodes (127 µm in diameter, A-M Systems, WA) with fixed inter-electrode spacing of 300 µm. The stimulating electrode was mounted in a Narishige micromanipulator which controlled its three-dimensional position in the lumbo-sacral portion of the spinal cord.

2.2.3. Experimental Procedure

Multielectrode array was positioned at the locations within the ventral horn where selective stimulation of the dorsiflexor (plantar flexor) muscle could be obtained by each electrode. To determine the best electrode position for selective muscle stimulation, the electrode array was vertically advanced through the spinal cord in 50 µm steps, dorsoventrally, and then, the electrode was withdrawn and moved 100 µm mediolaterally and/or rostrocaudally to an adjacent location where the testing was repeated. At each stop along the electrode track, biphasic pulses with 80-µs duration, 60-µA amplitude, and 50-Hz frequency were delivered to the spinal cord through the microelectrode to identify the effective positions for selective dorsiflexion (plantar flexion). The positions that produced the highest movement range on the ankle joint and the least effect on the other joints were selected. Two electrodes were implanted in each motor pool of the muscle with 300-µm spacing.

In the current study, pulse amplitude (PA) modulation at a constant frequency (50 Hz) and constant pulse width (PW) was used to stimulate the spinal cord. The proposed control strategy was implemented with LabVIEW. The period for control updates was 20 ms. The interleave time between two electrodes implanted into a motor pool was set to zero (i.e., no stimulus interleave time).

3. Results

In this section, the performance of the proposed control strategy is evaluated. For this purpose, the controller is first applied on a mathematical model of musculoskeletal system. Then, the results of experiments on rats are presented.

We use the root-mean-square (RMS) error and normalized RMS (NRMS) as the performance indices to measure the tracking accuracy as

$$\mathrm{RMS} = \sqrt{\frac{1}{T}\sum_{t=1}^{T}\left(\theta(t)-\theta_d(t)\right)^2} \qquad (4)$$

$$\mathrm{NRMS}(\%) = \frac{1}{\left(\theta_d^{\max}-\theta_d^{\min}\right)}\sqrt{\frac{1}{T}\sum_{t=1}^{T}\left(\theta(t)-\theta_d(t)\right)^2}\times 100 \qquad (5)$$

where θ and θ_d are the measured and desired joint angle, respectively.

3.1. Simulation Studies

A model of musculoskeletal system which was presented in (Abbas & Chizeck, 1995) is used here to simulate ankle joint movement. The model consists of two pairs of agonist-antagonist muscles (i.e., two flexors and two extensors) acting around the joint. The model of electrically stimulated muscle that is used in this study includes a 50-ms time-delay, nonlinear recruitment, linear dynamics and multiplicative nonlinear torque-angle and torque-velocity scaling factors. To consider the processing time, stimulator delay, and video frame capture time, a 100 ms delay is also considered. The virtual joint consists of a single skeletal segment in a swing pendulum configuration with one degree-of-freedom. The skeletal segment is acted upon by an agonist–antagonist pair of electrically stimulated muscles. The set of parameters for muscle and skeletal model are taken from (Abbas & Chizeck, 1995). The parameters of the compensator were selected as follows:

$$K_f = 1, \quad T_f == 0.25, \quad T_M = 0.1.$$

The value of was set to 150 ms (i.e., the total system delay). The future value of desired trajectory was normalized to values between -1 and 1. The error signals used for extensor and flexor controllers were calculated by

$$\begin{bmatrix} e_e \\ e_f \end{bmatrix} = \begin{bmatrix} +1 \\ -1 \end{bmatrix}\left[\theta - \theta_d\right]$$

where e_e and e_f are the error signals for controllers of the flexor and extensor, respectively; θ is the measured joint angle, and θ_d is the reference trajectory.

Fig. 4(a) shows the result of the FLC of the simulated ankle joint angle using only error signal ($e(t)$) as the input of the controller and without using compensator. The result shows that the tracking error is 8.3° (20.8%). The results of the control of simulated ankle joint using FLC with both $e(t)$ and $\theta(t+\tau)$ as the inputs of the controller is shown in Fig. 4(b). The RMS (NRMS) tracking error is 4.4° (11.0%). The results of tracking control using the proposed FLC (Fig. 1) is shown in Fig. 4(c) [RMS error

2.0° (5.0%)]. The results show that the tracking performance is improved by the proposed FLC. An interesting observation is the fast convergence of the controller. The generated joint angle converges to its desired trajectory in less than 0.5 s. Figure 4 shows that there is a low level of co-activation at the low activation levels. The level of agonist–antagonist co-activation tends to decrease as the muscle activation increases.

Effects of External Disturbance: To evaluate the ability of proposed control strategy to external disturbance rejection, a 20 Nm constant torque (which is about 20% of maximum generated torque during disturbance-free trial) was added to the torque generated by the muscles. Fig. 5 shows the result of tracking performance during applying the disturbance. It is observed that an acceptable disturbance rejection is achieved using the proposed

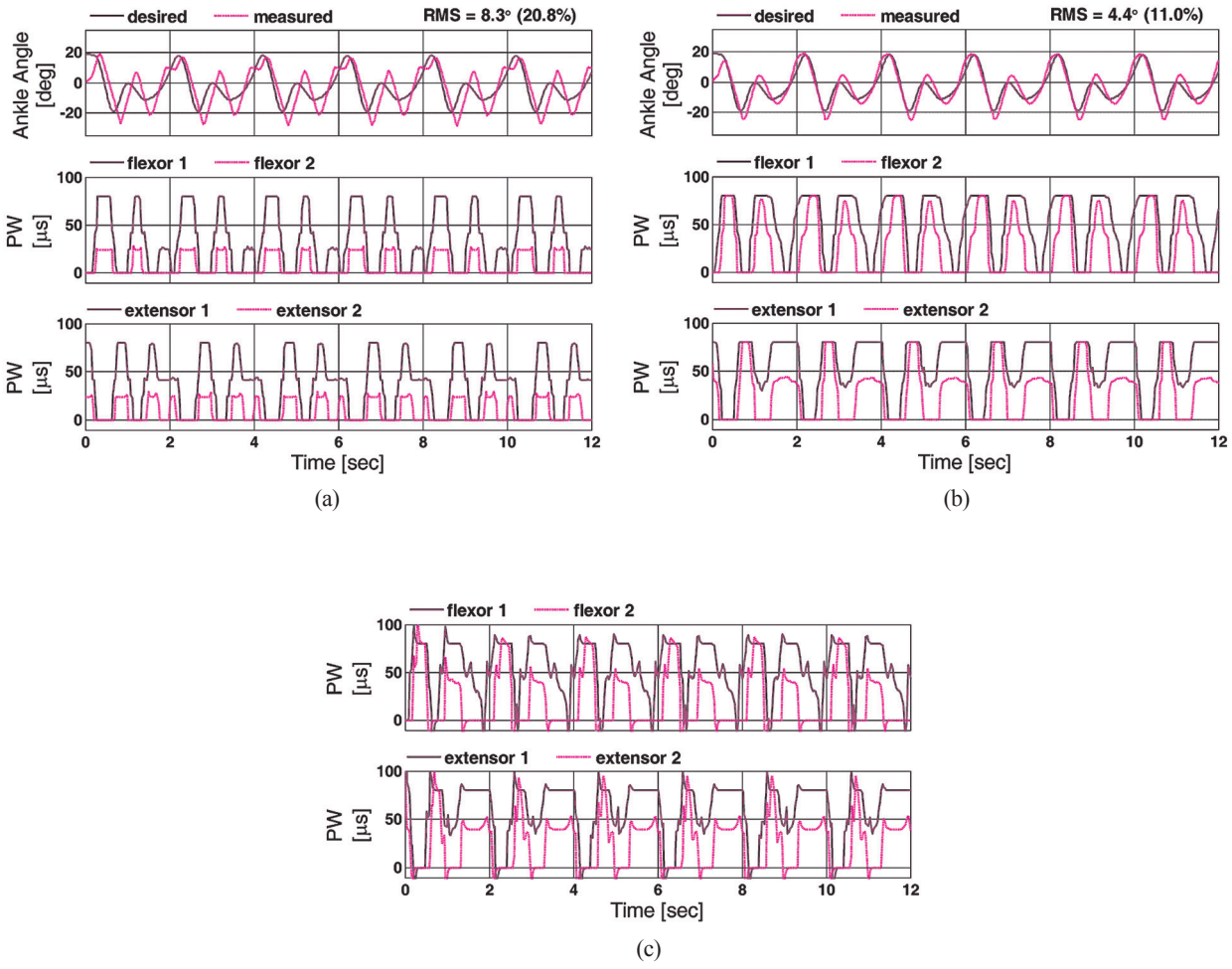

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Figure 4. Simulation results of joint movement control using fuzzy logic control. (a) Using FLC with only error signal as the input (b) Using FLC with both error signal and feature value of the desired trajectory as the inputs of the controller (c) Using FLC (both error signal and feature value of the desired trajectory as the inputs of the controller) combined with the lead-lag compensator.

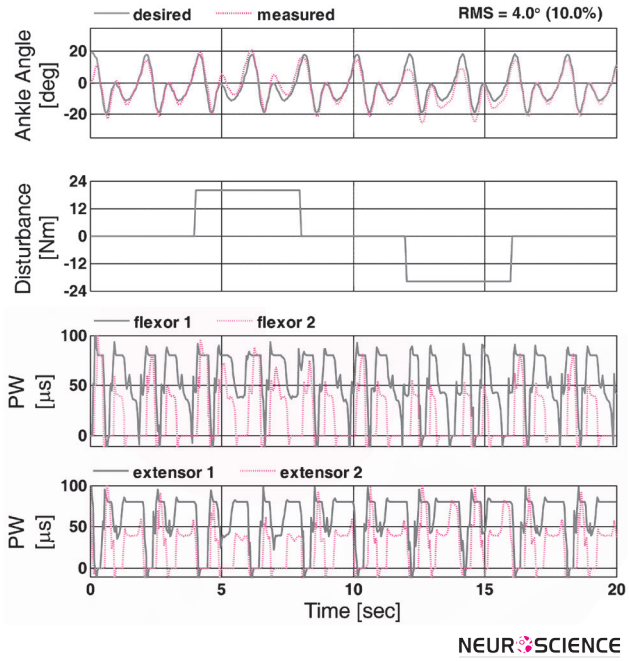

Figure 5. Simulation results of an external disturbance rejection using the proposed FLC. A constant torque in amount of 20 Nm (which is approximately 20% of the peak generated torque during the disturbance-free trial) was added to and subtracted from the net torque generated by the muscles for a duration of 4s. The bottom plot shows the control outputs (i.e., stimulation signals).

FLC. The tracking error obtained during disturbance is 4.0° (10.0%). Positive torque causes joint extension and negative torque causes joint flexion. It is observed that during positive disturbance, the flexor stimulation signals were increased and the extensor stimulation signals were decreased to compensate for the effects of disturbance.

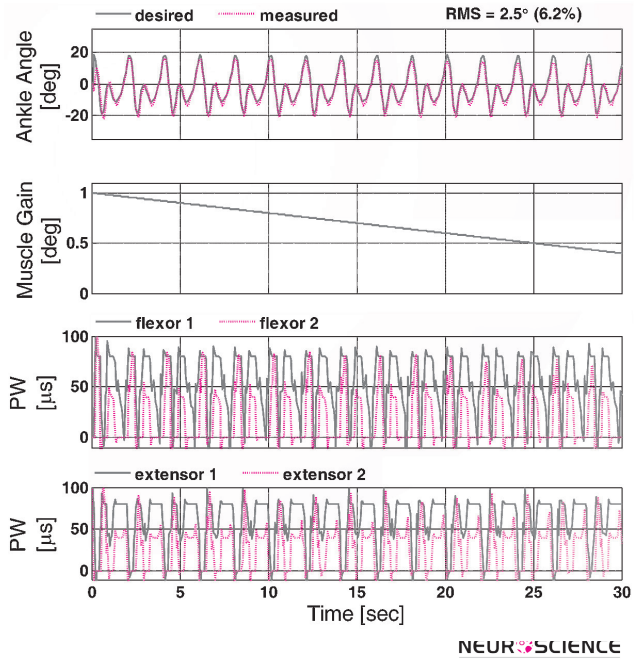

Figure 6. Simulation result of fatigue compensation obtained by the proposed FLC. The effects of muscle fatigue were simulated by exponentially decreasing the muscle input gains during the course of the simulation.

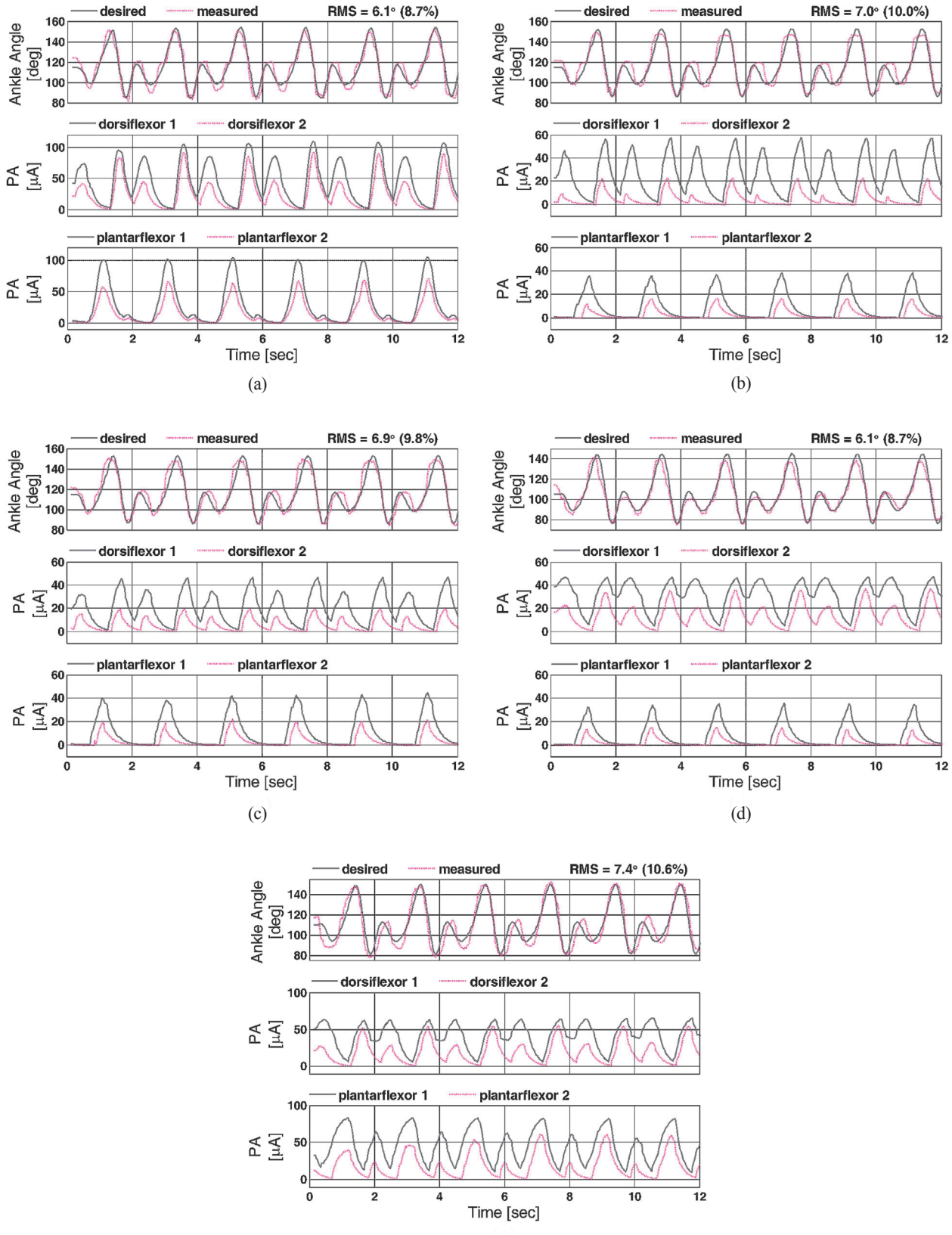

Figure 7. Typical results of controlling plantarflexion and dorsiflexion using the proposed FLC on five rats. (a) Rat 1 (b) Rat 2 (c) Rat 3 (c) Rat 4 (d) Rat 5. The bottom plots show the stimulation signals delivered through four electrodes (dorsiflexor 1, dorsiflexor 2, plantarflexor 1, plantarflexor 2).

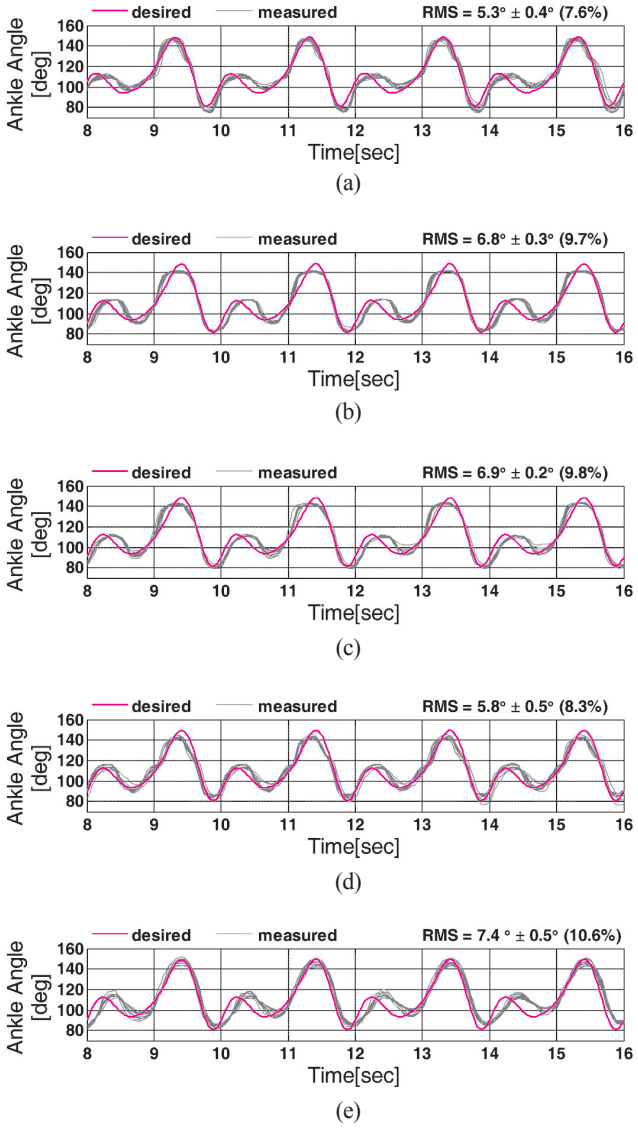

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Figure 8. Results of the ankle movement control using the proposed FLC during ten trials of experiment on five rats.

Table 1. Fuzzy rule base

$\Theta(t+\tau)$ \ e		BN	SN	Z	SP	BP
BN	Out1	Z	Z	Z	Z	Z
	Out2	Z	Z	Z	Z	Z
SN	Out1	M	Z	Z	Z	Z
	Out2	Z	Z	Z	Z	Z
Z	Out1	B	M	Z	Z	Z
	Out2	Z	Z	Z	Z	Z
SP	Out1	B	B	S	Z	Z
	Out2	M	Z	Z	Z	Z
BP	Out1	B	B	B	M	Z
	Out2	B	M	Z	Z	Z

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Table 2. Average Root-Mean-Square tracking error obtained during ten experimental trials using proposed control strategy for different rats.

Trial	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5
1	6.1°	7.0°	6.9°	6.1°	7.4°
2	5.5°	6.8°	6.8°	6.9°	8.1°
3	5.6°	6.7°	7.0°	5.6°	7.7°
4	5.3°	6.8°	7.1°	5.4°	7.1°
5	5.2°	6.8°	6.7°	5.2°	7.2°
6	5.3°	6.1°	6.8°	5.6°	8.5°
7	5.1°	6.4°	7.0°	5.8°	7.1°
8	5.3°	7.0°	6.8°	5.8°	6.9°
9	4.7°	7.2°	6.5°	5.5°	7.0°
10	5.1°	6.8°	7.0°	5.8°	7.2°
Mean±STD	5.3°±0.4°	6.8°±0.3°	6.9°±0.2°	5.8°±0.5°	7.4°±0.5°
NRMS	7.6%	9.7%	9.8%	8.3%	10.6%

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Effects of Muscle Fatigue: In FES applications, muscle fatigue can cause degradation of system performance. To evaluate the ability of the controller to account for muscle fatigue, the effects of muscle fatigue were simulated by a linear decrease in the agonist's (antagonist's) input gain to 40% of its original value over 30 s. Fig. 6 shows the result of fatigue compensation using the proposed controller [RMS error 2.5° (6.2%)]. It is observed that, during prolonged stimulation, the levels of the stimulation signals were increased to compensate the effects of muscle fatigue.

3.2. Experimental Evaluation

In this section, the performance of employing the proposed control strategy on animals is presented. The experiments were conducted on five rats. The parameters of the compensator (i.e. and) were chosen heuristically to achieve the best controller performance during experimental studies as follows:

k_f=1, T_f== 0.05, T_M= 0.2.

To implement the proposed fuzzy logic controller, it is necessary to estimate the time-delay (i.e.,). To estimate the time-delay, a 1.5-s long sequence of pulses with constant width and constant amplitude was delivered to the motor pools and time delay was estimated experimentally. The results showed that there was approximately a 200 ms time-delay in response.

Examples of the ankle joint angle trajectories obtained with the proposed FLC during one experimental trial for five rats are shown in Fig. 7. The results show that a good tracking performance with fast convergence is achieved. The RMS errors obtained during the first trial of experiment are 6.1° (8.7%), 7.0° (10.0%), 6.9° (9.8%), 6.1° (8.7%), and 7.4° (10.6%) for rat1, rat2, rat3, rat4, and rat5, respectively. Almost the same results were obtained in all experimental trials on all rats. The control signals (i.e., stimulation signal) show that there is antagonist co-activation during ankle movement. At the low levels of activation, both muscles are engaged. The activity of antagonist (agonist) decreases as agonist (antagonist) ac-

tivity increases. At the peak angles, there is no overlap between the agonist and antagonist muscles.

Table 2 summarizes the tracking errors obtained during 10 experimental trials for each rat. The average of tracking error over 10 experimental trials is 5.3°±0.4° (7.5%), 6.8°±0.3° (9.7%), 6.9°±0.2° (9.8%), 5.8°±0.5° (8.3%), and 7.4°±0.5° (10.6%), for rat1, rat2, rat3, rat4, and rat5, respectively. Standard deviation of the tracking errors is less than 0.5° that indicates the repeatability of the control performance over the different experimental trails and different rats.

Fig. 8 shows joint angle trajectories obtained using the proposed FLC during ten trials of experiment on five rats. The results clearly indicate that the controller is robust during different experimental trials.

4. Discussion

In this paper, we proposed a control strategy for control of ankle movement using multielectrode ISMS. The controller is based on the combination of fuzzy logic control with a lead (lag) compensator. The results indicate that motor functions can be restored through ISMS. The average of tracking error over the five rats is 6.4°±0.8° (9.2%). One important issue in the design of control strategy is time-delay. There is a significant time-delay in neuromuscular system response with respect to stimulation signal. The existence of the time-delays may be the source of instability and may degrade the performance of the closed-loop system. In this paper, we designed the fuzzy rules based on the future value of the desired trajectory to compensate the effect of the time-delay. For this purpose, a constant time-delay was considered. Nevertheless, the time-delay in neuromuscular system is time-varying. The time-varying delay needs a deeper analysis since its presence may induce complex behaviors. Moreover, in this study, we employed the proposed control strategy for control of the ankle joint during short period of stimulation. Future work will focus on the extension of this strategy to cope with uncertain time-varying time-delay for multi-joint control and control of locomotion using ISMS.

In this work, two microelectrodes were implanted into motor pool of each muscle and the fuzzy rule base was designed such that the stimulus was delivered first through one electrode. If the tracking error is still high and the future value of the desired trajectory is big, then the second electrode will be recruited. During multielectrode ISMS, electrical stimulation induced by a microelectrode can be made sufficiently focal so that only a small group of motoneurons will be activated. Designing a control strategy to activate motor units in the same muscle by focally stimulating several small groups of motoneurons asynchronously within the same motor pool is a challenging problem in ISMS control.

In this work, the parameters of the compensator were chosen heuristically to achieve the best controller performance. Optimal estimation of the parameters and stability analysis of the closed-loop system remain the key issues in fuzzy logic control of spinal cord.

Acknowledgement

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Evaluation of the Endothelial Cell Antibodies in Serum and Perilymphatic Fluid of Cochlear Implanted Children with Sensorineural Hearing Loss

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ABSTRACT

Introduction: Serum Anti endothelial Cell Antibodies (AECAs) play a prominent role in idiopathic Sensorineural Hearing Loss (SNHL) in that they induce vascular damage (immune mediated).The of the current study is To compare AECAs in serum and perilymphatic fluid of idiopathic SNHL children (<15y) undergoing cochlear implant surgery.

Methods: This was a cross sectional study performed in the cochlear implant ward in Rasoul Akram hospital, Tehran, Iran (2008 -2010) on 99 SNHL children undergoing cochlear implant surgery. The data collected from47 idiopathic and 52 non-idiopathic SNHL cases. AECAs were measured by indirect immuno fluorescence assay and compared in sera and perilymphatic fluids between the two groups. P-value<0.05 was considered significant.

Results: Idiopathic SNHL was diagnosed in 47.5% of cases. Positive AECA results in serum and perilymphatic fluid were 10% and 12%, respectively. Although AECA results in perilymphatic fluids were different between idiopathic and non-Idiopathic SNHL patients (PV<0.05), AECAs in serum showed no significant difference between the two (PV=0.1). No significant difference was detected between the mean age of idiopathic and non-idiopathic SNHL patients with positive AECAs in serum and perilymphatic fluids (PV=0.2; PV=0.2).

Discussion: Idiopathic SNHL was diagnosed in 47.5 % of studied cases. Idiopathic SNHL has a poor out come in children. In cases with idiopathic SNHL, finding AECAs in perilymphatic fluids are more valuable than in the serum. We suggest that serum and perilymphatic fluids testing for AECAs would be helpful in management of idiopathic SNHL cases.

Specific immunosuppressive treatments for selected cases suffering from Idiopathic SNHL (only in those older than 5) might be successful in disease management. However, this theory should first be validated by randomized clinical trials.

1. Introduction

The incidence of unilateral hearing loss in children is approximately 0.1 %. In 7.5% of cases unilateral deafness is diagnosed accidentally, usually between the age of 7 and 10 (Olusanya & Okolo,2006). Neither children nor their parents could precisely determine the time of its onset, especially when it is not accompanied by other symptoms, such as dizziness or tinnitus (Walch et al., 2009). The etiology of most of these cases remains unknown (Adams, 2002). Risk factors for hearing loss in neonates have been explained by some authors (Martínez-Cruz , Poblano & Fernández-Carroc-

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era,2008; Kountakis,2002). Idiopathic sudden sensorineural hearing loss and its prognostic factors have also been discussed in many references (Cadoni et al.,1996; Vasama & Linthicum,2000 ; Merchant , Adams & Nadol,2005). AECAs are of prognostic importance in these diseases and can be considered as a useful clinical tool to differentiate patients with idiopathic hearing loss(Vasama & Linthicum,2000; Merchant et al.,2005).

Autoimmune hearing loss is a plausible explanation for a certain percentage of the group categorized as the idiopathic type. SNHL in children can be caused by autoimmune disorders localized to the inner ear or secondary to systemic immune diseases (Merchant et al., 2005; Cadoni et al., 2003).

Cadoni et al. (2003) investigated the presence of AECAs and its role in causing striavascularis damage in immune-mediated sensorineural deafness.

Many studies established the non-specific auto antibodies vs. the inner ear, such as anti endothelial cell antibodies(Cvorović , Deric , Probst & Hegemann,2008; Xenellis & Karapatsas,2006; Solares , Hughes & Tuohy,2003; Naumann , Hempel & Schorn,2001; Ceylan et al.,2007; Agrup & Luxon,2006).

The appearance of antiendothelial cell antibody is related to poor outcome in hearing loss. AECAs detection could be helpful in the selection of particular patients with sensorineural hearing loss for specific immunosuppressive treatments(Plontke et al.,2005; Banerjee & Parnes,2005; Westerlaken , Stokroos , Dhooge , Wit & Albers,2003; Tucci , Farmer , Kitch & Witsell,2002; Fowler & Boppana,2006).

SNHL due to various etiologies is common in Iranian children (Verbeeck et al.,2008; Foulon, Naessens , Foulon , Casteels & Gordts,2008). Cochlear implant surgery is needed for some cases (Noorbakhsh et al., 2008; Noorbakhsh , Memari , Farhadi & Tabatabaei,2008 ; Noorbakhsh et al., 2006; Noorbakhsh, Farhadi & Tabatabae,2008; Noorbakhsh, Farhadi & Tabatabaei,2005; Noorbakhsh, Siadati & Farhadi,2006).

Serum AECA might play some role in idiopathic SNHL in that they induce vascular damage (immune mediated).

Aim of study: To compare AECA in serum and perilymphatic fluid of idiopathic SNHL children (<15y) undergoing cochlear implant surgery. The outcome suggests possible clinical relevance for assessment of AECA in serum and perilymphatic fluid of children with suspected ISNHL and clinical significance.

2. Methods

This was a cross sectional study performed in the cochlear implant ward in Rasoul Akram hospital, Tehran, Iran (2008 -2010).This study was approved by the Ethical Committee in the ENT and head &Neck surgery Research Center affiliated by Tehran University of Medical Sciences. The parents (or patients) signed the consent letter.

Initially, a questionnaire was completed by an authorized physician for each case. Audio logic screenings (Auditory Brainstem Response, Evoked Otto-acoustic Emissions and Pure Tone Audiometry) appropriate for patients` age were performed in all cases. 99 children undergoing cochlear implant surgery entered the trial. All cases were candidates for cochlear implant surgery due to severe SNHL (>95db).They were between 2.5-12 years old with a mean age of 5.22.6±1.7years old. 61% of the patients were male and 39% were female. 47 idiopathic and 52 non-idiopathic SNHL cases were diagnosed by specialists based on AAO (American academy of Otolaryngology) criteria for distinguishing the type of SNHL (idiopathic and non- idiopathic). Blood samples (2 ml) were taken, then centrifuged and transferred to our research laboratory. Perilymphatic fluids were taken by ENT specialist during surgery in operation room. All samples were kept frozen at -80°C until usage. We looked for AECAs (IgG) in sera and perilymphatic fluids by indirect fluorescent antibody test (KMI diagnostics, USA). The results were calculated qualitatively as suggested by the AECAs manufacturer. AECAs were measured and compared in sera and perilymphatic fluids between the two groups.

In order to minimize the false-positive interferences with AECAs, titers of rheumatoid factors (RFs) and antinuclear antibodies (ANAs) were measured in serum samples. All patients with positive RFs and ANAs (5 Idiopathic cases and 3 non-idiopathic) were excluded.

Statistical analysis: Student t-test was used to determine differences between the means of all continuous variables. Chi-square values were calculated for all categorical variables. P value less than 0.05 was con-

sidered significant. All analysis was conducted using SPSS version 11.5.

3. Results

Idiopathic type of SNHL was diagnosed in 47.5% (n= 47) of cases, and non-idiopathic type in 52.5% (n=52). Known causes of SNHL include familial 16%, infectious causes 14%, convulsion 13.3%, mental retardation 4.5%,Trauma 1.5%, prematurity1.5%, hypoxic ischemic 6.5% and fetal radiation 3%.

There was no meaningful difference between the age of patients and idiopathic and non-idiopathic types of SNHL (Mean age 5.6±1.4 vs. 5±1.9 years; P-value =0.2).

Serologic results: Positive AECAs were detected in 10% of serum samples and 12% of perilymphatic fluids in SNHL cases.

AECAs detection in perilymphatic fluids showed different results between idiopathic and non-idiopathic types of SNHL (P-value=0.04) (Table1, Fig.1).

However, positive AECAs in serum was not significantly different between the two types of SNHL (P-value=0.1) (Table2, Fig.2).

The mean age of cases with positive AECAs in serum and perilymphatic fluid had no significant difference between idiopathic and non-idiopathic type of SNHL (P-value=0.2, P-value=0.2).

Table 1. Comparison between positive perilymphatic AECAs in the two types of SNHL

Total	Idiopathic		Perilymphatic AECA
	Negative	Positive	
12	3	9	Positive
87	49	38	Negative
99	52	47	Total

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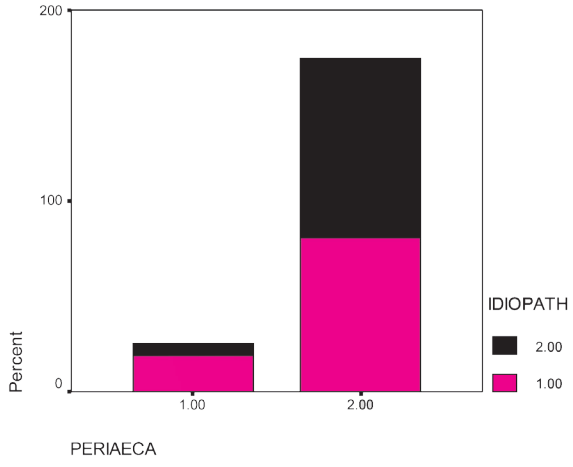
Table 2. Comparison between serum AECAs results in the two types of SNHL

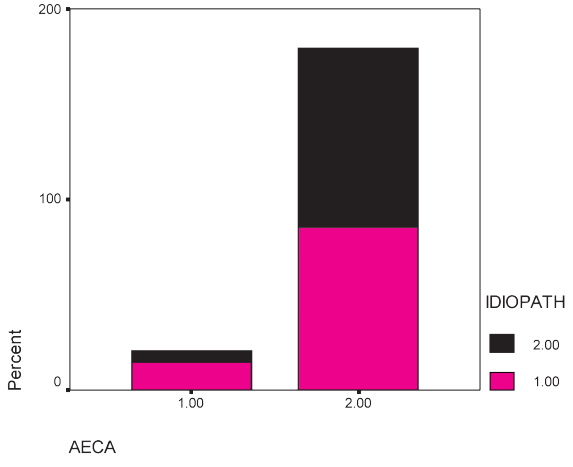
Total	Negative	Positive	
10	3	7	AEC
89	49	40	A
99	52	47	Total

NEUROSCIENCE



NEUROSCIENCE

Figure 1. Positive perilymphatic AECA in the two types of SNHL



NEUROSCIENCE

Figure 2. Positive serum AECA in the two types of SNHL

4. Discussion

In this study, Idiopathic SNHL was diagnosed in 47.5% of children undergoing cochlear implant surgery. At least one etiologic factor was recognized for profound SNHL in 52.5% (n= 52) of cases (age: 2.5-12 years old).

Familial SNHL (16%), infectious causes (14%) and convulsive disorders (13.3%) were the 3 most common causes. Incidence of idiopathic type of SNHL in our study was very close to that reported by other studies (38.7%)(Olusanya & Okolo,2006; Walch et al.2009; Adams,2002; Martínez-Cruz et al., 2008).

Idiopathic hearing loss basically means hearing loss without any perceivable reason. A more likely scenario would be that the person's hearing loss actually takes place over a few hours(Cadoni et al.,2003; Cvorović et al.,2008; Xenellis et al.,2006).

Positive AECAs were observed in serum of 10% (10/99) of cases between 3.5-5.5 years old, without any meaningful differences between idiopathic and non-idiopathic cases (P-value=0.1).

This number is much lower than the 54% reported by Cadonni et al.(2003) in adult cases suffering from SNHL.6The results of a previous study in our center determined that there is no difference between cases with SNHL and normal controls in regard to positive serum AECAs (14.5% vs. 21%, P-value=0.36), but cases with positive serum AECAs were older than those with negative results (mean=50 vs. 32 months, P-value=0.047). But in this study, no such difference was observed (P-value=0.2).

Cadoni et al. (2003) investigated the presence of AECAs and their role in causing damage to the striavascularis in immune-mediated sensorineural deafness. Cvorovićet al. (2008) reported a prognostic model for predicting hearing recovery in patients with idiopathic sudden sensorineural hearing loss. Xenelliset al.(2006) described prognostic factors for idiopathic sudden sensorineural hearing loss .The appearance of endothelial cell antibody is related to the poor outcome of hearing loss (Solares , Hughes & Tuohy ,2003; Naumann , Hempel & Schorn,2001; Ceylan et al.,2007; Agrup & Luxon,2006; Chen , Emmerling , Ilgner & Westhofen,2005).

Positive AECAs in older idiopathic SNHL cases (> 5years old) could define the clinical associations of AECAs with immune-mediated inner-ear disorders. Probably, AECAs play a prominent role in causing damage to the striavascularis after infancy in immune-mediated SNHL. Production of serum AECAs would act as a marker of disease activity. The association between AECAs and endothelial injury in the course of these diseases prompted us to develop assays for said antibodies in clinical practice.

Positive AECAs in perilymphatic fluid was reported in 12% of cases (3.5 -5.7 years old) and more frequently in idiopathic type of SNHL (P-value=0.04). No significant difference was observed between positive and negative results in regard to the age of patients (P-value= 0.3).

Cvorovićet al.(2008) reported that the appearance of AECAs is related to poor outcome and recovery of the adults. Prognostic factors for Idiopathic SNHL in adults have been reported by many authors(Cvorović et al,.2008; ; Xenellis et al.,2006; Solares et al.,2003; Naumann et al.,2001; Ceylan et al.,2007). Multiple potential mechanisms can result in immune-mediated inner ear disease in children. All previous studies, but for one, were carried out in adults (Herr & Marzo, 2005).

Many authors recommendsystemic or intra tympanic steroids as a treatment for immune-mediated SNHL in adults (Agrup & Luxon,2006; Chen , Emmerling , Ilgner & Westhofen n,2005; Herr & Marzo,2005 ; Gouveris , Selivanova & Mann,2005; Plontke et al.,2005; Banerjee & ParnesL, 2005).

Westerlaken et al. (2003) and Tucci et al. (2002) even treated the Idiopathic SNHL cases with a combination of steroids and antiviral drugs.

Not enough studies have been performed previously on the correlation between infections and AECAs in children. These studies were mostly done in adults rather than children, especially the Idiopathic SNHL cases.

The most important limitation of the study is the small study sample especially in younger patients (<2 years). To determine the clinical outcome and possible clinical relevance of AECA assessment in serum and perilymphatic fluid of children with suspected Idiopathic SNHL, follow up studies are recommended.

Conclusion: Idiopathic SNHL was diagnosed in 47.5 % of studied cases. Idiopathic SNHL has a poor outcome in children. In cases with idiopathic SNHL, finding AECAs in perilymphatic fluids are more valuable

than in the serum. We suggest that serum and perilymphatic fluids testing for AECAs would be helpful in management of idiopathic SNHL cases.

Specific immunosuppressive treatments for selected cases suffering from idiopathic SNHL (only in those older than 5) might be successful in disease management; however this theory should first be validated by randomized clinical trials.

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Ethical Considerations

Ethical Committee in the ENT and head &Neck Research Center inTehran University of Medical Scienceshas reviewed and approved the Waiver of Authorization for use of protected health information (PHI) for research purposes for the following study.

Principal Investigator: DrSamilehNoorbakhsh MD; Professor in Pediatric Infectious Diseases; Research Center of Pediatric Infectious Diseases, Tehran University of Medical Sciences.

Title: Searching the Antiendothelial cell antibody (AECA) in perilymphatic fluid and serum of cochlear implanted children"

Date of Approval: May 2007

The following PHI for which use or access is requested has been determined to be necessary for the conduct of the study by the ENT &CPID Research centers.

[Insert the patient information to be used or disclosed, or attach documentation of the information.]

In approving this Waiver of Authorization, the ENT &CPID Research centers have made the following determinations:

1. The use or disclosure of PHI involves no more than minimal risk.

• Granting of waiver will not adversely affect privacy rights and welfare of the individuals whose records will be used.

• The project could not practicably be conducted without a waiver.

• The project could not practicably be conducted without use of PHI.

• The privacy risks are reasonable relative to the anticipated benefits of research.

• An adequate plan to protect identifiers from improper use and disclosure is included in the research proposal.

• An adequate plan to destroy the identifiers at the earliest opportunity, or justification for retaining identifiers, is included in the research proposal.

• the project plan includes written assurances that PHI will not be re-used or disclosed for other purposes.

• whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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Comparing the Anticonvulsant Effects of Low Frequency Stimulation of Different Brain Sites on the Amygdala Kindling Acquisition in Rats

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ABSTRACT

Low frequency stimulation (LFS) is a potential alternative therapy for epilepsy. However, it seems that the anticonvulsant effects of LFS depend on its target sites in the brain. Thus, the present study was designed to compare the anticonvulsant effects of LFS administered to amygdala, piriform cortex and substantia nigra on amygdala kindling acquisition. In control group, rats were kindled in a chronic manner (one stimulation per 24 h). In other experimental groups, animals received low-frequency stimulation (8 packages at 100 s intervals, each package contained 200 monophasic square-wave pulses, 0.1 ms pulse duration at 1 Hz andAD threshold intensity) in amygdala, piriform cortex or substantia nigra 60 seconds after the kindling stimulation, the AD duration and daily seizure stages were recorded. The obtained results showed that administration of LFS in all three regions reduced electrical and behavioral parameters of the kindling procedure. However LFS has a stronger inhibitory effect on kindling development when applied in substantia nigra compared to the amygdala and piriform cortex which reinforce the view that the substantia nigra mediates a crucial role in amygdala-kindled seizures. LFS had also greater inhibitory effects when applied to the amygdala compared to piriform cortex. Thus, it may be suggested that antiepileptogenic effect of LFS depends on its target site and different brain areas exert different inhibitory effects on kindling acquisition according to the seizure focus.

1. Introduction

Epilepsyis known as a common neurological disorder affecting about one percent of the world's population(Zhang, Franklin, & Murray, 1993).The most common epileptic syndrome in adults is temporal lobe epilepsy (TLE) and one of the most commonly used animal models of TLE seizures, is the kindling model of epilepsy(French et al., 1993). Kindling is defined as a chronic model in which the repeated application of electrical stimulation, with a depth electrode in particular brain sites, induces permanently enhanced seizure susceptibility and other enduring brain alterations that are similar to those occurring in human TLE(Sato, Racine, & McIntyre, 1990). Among brain sites, the amygdala is one of the most sensitive areas for induction of kindled seizures(Mohapel, Dufresne, Kelly, & McIntyre, 1996).

Unfortunately many epileptic patients are resistant to current therapies and there is a need to find new, effective and safe alternative therapies. One of the potential alternative therapies for epilepsy is deep brain stimulation(Kile, Tian, & Durand, 2010). Low frequency stimulation(LFS) as a form of deep brain stimulation

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is thought to inhibit the activity by increasing the threshold for the firing of neuronal action potentials through more complex mechanisms(Albensi, Ata, Schmidt, Waterman, & Janigro, 2004; Schrader et al., 2006). Moreover, LFS requires fewer pulses per second compared to other forms of deep brain stimulation therapies, thereby lowering the required current injection and minimizing the potential for the stimulation-induced damage of the target tissue(Kile et al., 2010). LFS is reported to be an antiepileptic and antiepileptogenic electrical stimulation(Ghorbani, Mohammad-Zadeh, Mirnajafi-Zadeh, & Fathollahi, 2007). Application of LFS as an inhibitory factor on kindling acquisition was first reported in 1980s by Gaito(Gaito, 1980; Gaito, Nobrega, & Gaito, 1980). Nowadays, LFS has been determined as an alternative to the brain surgery for refractory epilepsy, due to its titratability, reversibility and low risk of complications(Li & Mogul, 2007). However, it seems that the effects of LFS on amygdala kindled seizures depend on its target sites.

Stimulation of inappropriate brain structures may result in no effect on or even aggravation of evoked seizures(Wu, Zhu-Ge, et al., 2008). In most of the previous studies the LFS was applied at the kindling focus. However LFS at other target sites can also produce inhibitory effects against kindling seizures.Many studies showed that application of LFS at the kindling focus,such as amygdala (Ghotbedin, Janahmadi, et al, 2012; Velisek, Veliskova, & Stanton, 2002; Wu, Xu, et al., 2008) and piriform cortex (Ghorbani et al., 2007; Yang et al., 2006)results in a significant increase of seizure threshold and suppression of behavioral seizures. However, the brain areas which are important in epileptic seizure spreading may also be considered as the possible targets of LFS application site. Among these area piriform cortex and substantia nigra have important role on amygdala kindled seizures (Ghorbani et al., 2007; Jahanshahi, Mirnajafi-Zadeh, Javan, Mohammad-Zadeh, & Rohani, 2009; Mohammad-Zadeh et al., 2009; Sadegh et al., 2007; Shi, Luo, Woodward, & Chang, 2006; Velisek, Veliskova, & Moshe, 2002; Yang et al., 2006).Thus, the present study was designed to compare the anticonvulsant effects of low frequency stimulation administered to different brain sites on the amygdala kindled seizures in male rats. Amygdala, piriform cortex and substantia nigra were considered as the target sites for the LFS application.

2. Methods

2.1. Animals

Male Wistar rats (weighing 250-300 g, provided by the Kerman Neuroscience Research Center) were caged individually and maintained under constant temperature (23 ± 1 °C) and 12-h light–dark cycle (light on at 07:00). They had free access to standard food and water. All experimental protocols and treatments were approved by Ethical Committee of the Kerman Neuroscience Research Center (EC/KNRC/89-4) that was completely coinciding with the "NIH Guide for the Care and Use of Laboratory Animals".

2.2. Surgical Procedure

Under ketamine (100mg/kg) and xylazine (10mg/kg) anesthesia, rats were mounted in a stereotaxic apparatus and bipolar stimulating and monopolar recording electrodes (twisted into tripolar configuration) were implanted into the right basolateral amygdala (-2.5 mm posterior and 4.8 mm lateral from bregma and 8.5 mm below skull) according to atlas of Paxinos and Watson (Paxinos & Watson, 2007). Two other groups of animals were also subjected to an implantation of a bipolar electrode into the piriform cortex (-0.8mm posterior and 4.9mm lateral from bregma and 8.8 mm below skull), or substantia nigra (-4.8 mm posterior and 1.6 mm lateral from bregma and 8.2 mm below skull) of the same hemisphere (Paxinos & Watson, 2007). In the amygdala group, the same electrodes were used for delivering kindling and low-frequency stimulations. Electrodes (teflon-coated, 125 μm in diameter; A.M. system Inc., USA) were insulated except for 0.5 mm at their tips. Another electrode was connected to the skull screws and placed above the left cortical surface as earth electrode. The pins attached to the electrodes were inserted to a socket which was embedded in the skull with dental cement.

2.3. Kindling and LFS

Following at least 7 days post-surgical recovery, the afterdischarge (AD) threshold was determined by application of 1 ms monophasic square wave of 60 Hz at the train duration of 2 s. The stimulating current was initially delivered at 25 μA and was increased in increments of 25 μA at 5 min intervals until at least 5 s of ADs was recorded. This intensity was considered as AD threshold and used for daily stimulation.

Rats were subjected to one kindling stimulation/day. Stimulation of the amygdala was applied by a stimulus

isolator (A365; WPI, USA) and electroencephalograms (EEGs) at the amygdala were amplified with an amplifier (DAM80; WPI, USA) and recorded by means of data acquisition (D3108; ScienceBeam Co., Iran) and the biochart software (v 1.53; ScienceBeam Co., Iran). The seizure severity was classified according to Racine scores (1972) as follows: (1) facial movement; (2) head nodding; (3) unilateral forelimb clonus; (4) bilateral forelimb clonus and rearing; and (5) rearing and falling. AD duration (ADD) was also measured and expressed as the increased percentage relative to the first day of stimulation. Kindling stimulations were continued until animals showed a stage 5 seizure for the first time. 60 sec after termination of the kindling stimulation, eight packages of LFS was daily administered at 100 sec intervals. Each LFS package contained 200 monophasic square-wave pulses, 0.1 ms pulse duration at 1 Hz and AD threshold intensity at the end of experiments, the position of electrodes was histologically verified and only animals with correct electrode implantation in the stimulated sites were included in the statistical analysis.

2.4. Experimental Design

In this experiment, rats were divided into four groups. In control group the animals were subjected to daily kindling stimulations. In amygdala-LFS, piriform-LFS and substantia nigra-LFS (SN-LFS) groups, daily LFS was applied after each amygdala kindling stimulation at the amygdala, piriform cortex and SN respectively.

2.5. Statistical Analysis

Data were expressed as the mean±SEM and accompanied by the number of observations. Two-way analysis of variance (ANOVA) was used to compare the changes in the increased percentage of ADD and one-way ANOVA was used to compare the number of stimulation days to achieve different seizure stages in different groups. The significant differences were evaluated further by a Tukey post-test. The changes in behavioral seizure scores were analyzed in the same manner by using the nonparametric Kruskal–Wallis and Mann–Whitney U test. A p-value of less than 0.05 was considered as statistically significant difference.

3. Results

The obtained results showed no significant differences in the mean seizure stage of animals in different groups after the first stimulation (0.77±0.27 in control group, 0.5±0.22 in amygdala-LFS group and 0 in piriform-LFS and SN-LFS groups). In addition, there were not any significant difference in the duration and threshold of ADs between different experimental groups.

LFS application induced a significant reduction in the behavioral seizure stages in different groups. This reduction was seen only in 2nd and 3rd days of kindling procedure in the piriform-LFS group. However amygdala-LFS and SN-LFS groups showed significant lower

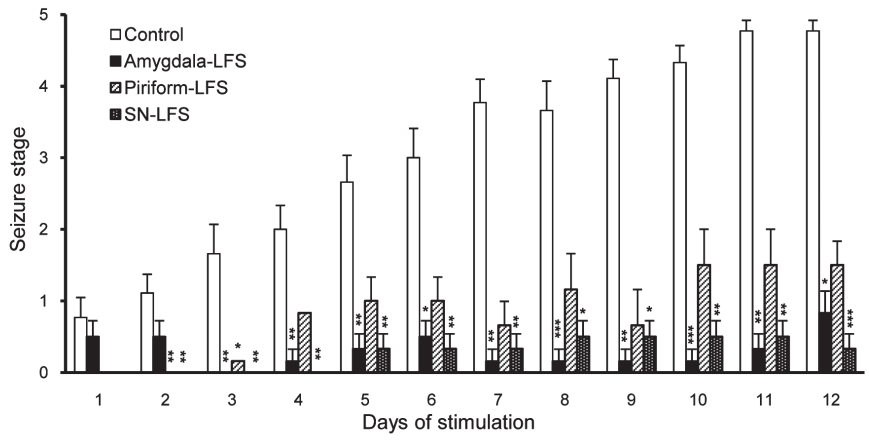

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Figure 1. The effects of LFS administration in different brain sites on seizure stage during kindling stimulations of the amygdala. Values are mean±SEM (n=6). * p<0.05, ** p<0.01 and *** p<0.001 in comparison with the control.

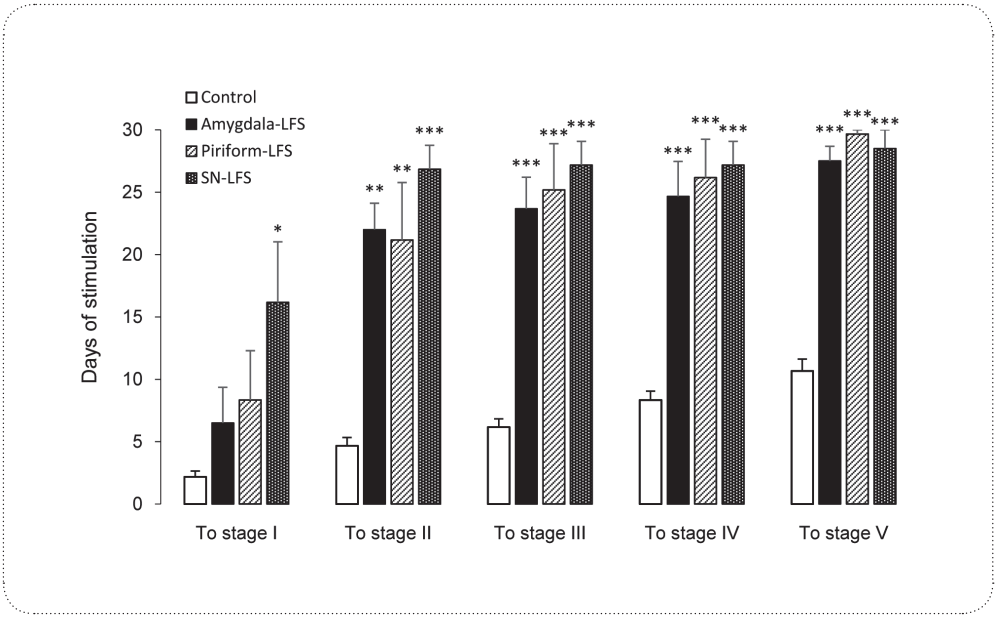

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Figure 2. The effects of LFS administration in different brain sites on the number of stimulations required to achieve different seizure stages. Values are mean±SEM (n=6). * p<0.05, ** p<0.01 and *** p<0.001 in comparison with the control.

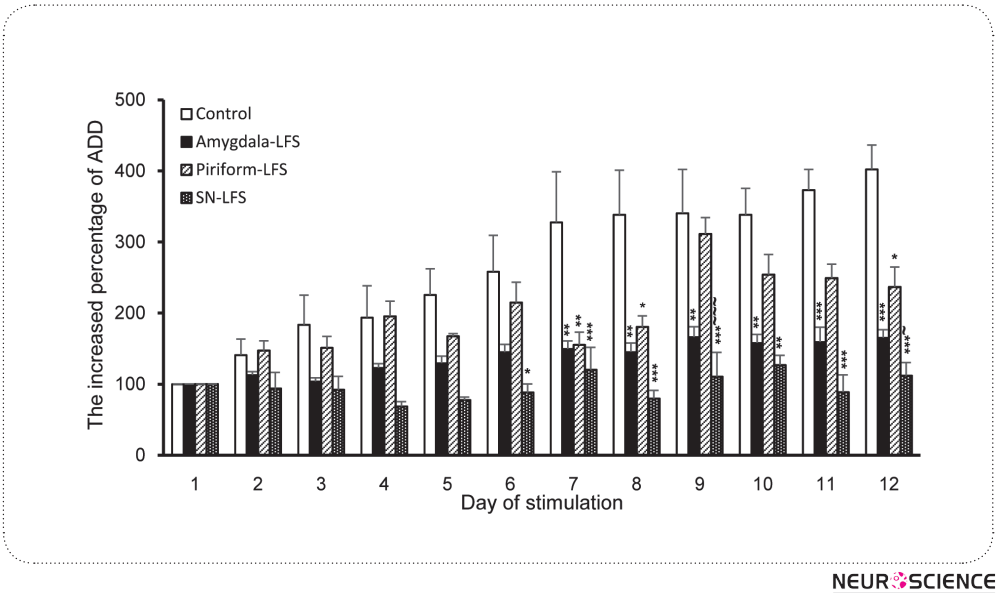

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Figure 3. The effects of LFS administration in different brain sites on the daily increased percentage of afterdischarge duration (ADD) upon daily stimulation of the amygdala. Values are mean±SEM (n=6). * p<0.05, ** p<0.01 and *** p<0.001 in comparison with the control. ~ p<0.05 and ~~~ p<0.001 compared to the piriform-LFS.

seizure stages in comparison with the control group until the 12th day of the kindling procedure (Fig. 1). For a better comparison, the number of stimulations needed to reach different seizure stages, have been also shown in Fig. 2. As the figure shows, the number of electrical stimulations necessary to reach stages 2 to 5 was significantly increased in all LFS -administered groups compared to the control group ($F(3,20)= 12.08$, $P<0.001$ for stage 2; $F(3,20)= 15.35$, $P<0.001$ for stage 3; $F(3,20)= 16.19$, $P<0.001$ for stage 4 and $F(3,20)= 72.53$, $P<0.001$

for stage 5). Only SN-LFS group showed higher required days of stimulation to reach stage one seizure in comparison with the control group.

In addition, LFS application in all brain areas prevented the increase percentage of ADD during first 12 days of the kindling stimulations ($F(44, 286) = 4.097$, $P<0.001$) (Fig. 3). As the Fig.3 shows, LFS application had a preventing effect on progression of ADD following the kindling stimulations. The daily application of LFS at amygdala reduced the increased percentage of ADD from day 7 to 12 of the kindling procedure significantly. The SN-LFS group showed a significant reduction in the increased percentage of ADD compared to the control group in 6th to 12th day of stimulations. This reduction in piriform-LFS group was just at the 12th day of the kindling procedure compared to the control group.

LFS had stronger antiepileptogenic effect when applied in the substantia nigra compared to amygdala and piriform cortex. ATukey post-hoc test showed that there was a significant difference between the ADD parameter of SN-LFS group compared to the piriform-LFS group on days 9 ($P<0.001$) and 12 ($P<0.05$) of the kindling procedure.

4. Discussion

The results of the present study indicated that administration of LFS either in the kindling focus or other target sites can retard amygdala kindled seizures acquisition. All LFS administered groups showed significant lower daily seizure stages compared to control group from the 2nd day of the kindling procedure. However in the case of the piriform-LFS group the difference was significant only in the 2ndand 3rdday. Moreover, all the LFS administered groups required more stimulation days to achieve different seizure stages. In addition, LFS prevented the increased percentage of ADD in all LFS administered groups.

Our obtained results from the amygdala-LFS group are in line with previous studies. Application of LFS to the amygdala as the kindling focus can provoke a dramatic elevation in the local AD threshold. The mechanism of anticonvulsant actions of LFS is unknown, however, the mechanisms involved in long-term depression or depotentiation may have a role in reducing the excitability and elevating the AD threshold (Albensi et al., 2004; Cheong, Yun, Mook-Jung, Kang, & Jung, 2002; Kemp & Bashir, 2001). Moreover, LFS administration could result in changing of some receptors involved in the expression of the seizures. The possible alterations in receptor binding may be associated with suppressed excitability, reduced recruitment, and elevated AD thresholds during kindling acquisition (Ackermann, Finch, Babb, & Engel, 1984). Recently, it has also been shown that application of LFS in amygdala as the kindling focus preserves the electrophysiological properties of the rat hippocampal CA1 pyramidal neurons from the destructive effects of amygdala kindling and provided further support for the use of LFS as a very beneficial alternative treatment method for epilepsy (Ghotbedin et al., 2012).

The piriform cortex has strong connections to limbic structures, including the amygdala, hippocampus, and entorhinal cortex. It has a significant modulating effect on seizures (Loscher & Ebert, 1996) and during initial phase of kindling in each brain regions, piriform cortex is the first to show the epileptic activity (Ebert & Loscher, 1995). This structure is critically involved in generation and propagation of epileptic discharges that induced by electrical stimulation of other brain sites (Loscher & Ebert, 1996). Therefore it could be considered as a suitable candidate to interfere with kindling procedure by LFS administration. The results of our study are in line with the previous studies which showed that the administration of LFS in the piriform cortex can retard the progression of seizure stage and reduce AD duration induced by amygdaloid kindling in rats (Ghorbani et al., 2007; Yang et al., 2006; Zhu-Ge et al., 2007). However, it is of interest that in previous studies the LFS administration to the piriform cortex had greater inhibitory effect than what we observed in the present research. Although it is very difficult to compare the inhibitory action of LFS in various studies, the difference in LFS pattern could be the main reason for the difference between their results and ours.

As far as we know, this is the first study which assessed the inhibitory effects of LFS application to the SN. However, previous studies showed that high-frequency electrical stimulation of the substantia nigra completely blocks amygdaloid-kindled seizures in nearly a half of experimental animals (Shi et al., 2006). There are also several lines of other evidences which have indicated that the substantia nigra is critically involved in epileptic seizures. Lesions of substantia nigra appear to suppress kindling (Shin, Silver, Bonhaus, & McNamara, 1987) and electrical stimulation of the substantia nigra within a wide range of frequencies attenuates cortical epileptiform activity (Boda & Szente, 1992; Sabatino, Gravante, Ferraro, Savatteri, & La Grutta, 1988) and blocks kindling induced seizures (Velisek, Veliskova, & Moshe, 2002). Previous electrophysiological work also revealed

that substantia nigra neurons can led subthalamic nucleus and hippocampus neurons in synchronized firing during amygdala-kindled seizures (Shi et al., 2006) reinforcing the view that the substantia nigra mediates a crucial role in amygdala-kindled seizures.

In the present study there was a significant difference in antiepileptogenic effect of LFS when applied in different experimental groups. It has a stronger inhibitory effect on kindling development when applied in substantia nigra compared to the amygdala and piriform cortex. On the other hand, LFS had also greater inhibitory effect on percentage increase of the ADD when applied to the amygdala compared to piriform cortex. Considering the fact that piriform cortex is more sensitive to kindled seizures than amygdala (Loscher & Ebert, 1996), the decreasing effect of LFS on seizure activity may be more difficult when applied in the piriform cortex than that of amygdala. In contrast, administration of LFS to the substantia nigra significantly decreased both behavioral and electrophysiological parameters of seizures. SN-LFS group was the only group which significantly increased the required number of stimulations to reach seizure stage one. The increased percentage of ADD was significantly lower from the 6th day the kindling procedure. In addition, SN-LFS group showed significant lower ADD parameter on the 9th and 12th day of the kindling procedure in comparison with the piriform-LFS group. Our results introduce the substantia nigra as a suitable brain region for LFS anticonvulsant action. However, further studies are required to confirm these findings and also determine the role of substantia nigra in mediating the anticonvulsant action of LFS.

In conclusion, the inhibitory effects of LFS on kindled seizures depend on the target site for LFS administration. In this study, we observed that administration of LFS to the substantia nigra produced somehow stronger anticonvulsant effects compared to the kindling focus (amygdala) and piriform cortex. However, beside the target site for LFS application, there are many other factors which must be taken into consideration when using brain stimulation as a therapeutic approach.

Acknowledgement

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Commentary : Non-Invasive Brain Stimulation for Enhancement of Corticospinal Excitability and Motor Performance

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ABSTRACT

During the past 20 years, non-invasive brain stimulation has become an emerging field in clinical neuroscience due to its capability to transiently modulate corticospinal excitability, motor and cognitive functions. Whereas transcranial magnetic stimulation has been used extensively since more than two decades ago as a potential "neuromodulator", transcranial current stimulation (tCS) has more recently gathered increased scientific interests. The primary aim of this narrative review is to describe characteristics of different tCS paradigms. tCS is an umbrella term for a number of brain modulating paradigms such as transcranial direct current stimulation (tDCS), transcranial alternative current stimulation (tACS), and transcranial random noise stimulation (tRNS). Their efficacy is dependent on two current parameters: intensity and length of application. Unlike tACS and tRNS, tDCS is polarity dependent.These techniques could be used as stand-alone techniques or can be used to prime the effects of other movement trainings.

The review also summarises safety issues, the mechanisms of tDCS-induced neuroplasticity, limitations of current state of knowledge in the literature, tool that could be used to understand brain plasticity effects in motor regions and tool that could be used to understand motor learning effects.

1. Lifelong Brain Plasticity

The old concept that the brain structures become unalterable after childhood has been deserted based on the evidence that all areas of the brain remain plastic in adulthood and during physiological ageing, with even some evidence for neurogenesis (Bütefisch 2004). This capacity of a neural system to acquire or improve skills, and to adapt to new environments through a learning process has been labelled "neuroplasticity" (Rakic 2002; Overman Carmichael 2013; Zagrebelsky Korte 2013). Neuroplasticity refers to the ability of the nervous system to change its structure and function, as part of the processes that underlie learning and memory, to adapt to environmental changes, and to recover function after brain lesions. In recent years, new techniques have been developed for the understanding and induction of human neuroplasticity. An important contribution has come from the introduction of non-invasive brain stimulation (NIBS) (Wassermann et al. 2008; Kuo et al. 2013; Marcos 2013). The development of NIBS techniques to induce neuroplasticity constitutes a major breakthrough in our ability to study how changes in brain states account for behavioural changes such as motor performance.

2. Non-Invasive Brain Stimulation

Several NIBS strategies aimed at modifying corticomotor excitability have emerged in recent years. These

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include transcranial magnetic stimulation (TMS), repetitive TMS (rTMS) (Pascual-Leone et al. 1994) which activates axons via short-pulsed stimulation and leads to new action potentials; and transcranial current stimulation (tCS) (Paulus 2011), which uses ultra-low intensity current, to manipulate the membrane potential of neurons and modulate spontaneous firing rates, but is insufficient on its own to discharge resting neurons or axons. tCS is an umbrella term for a number of brain modulating paradigms such as transcranial direct current stimulation (tDCS) (Nitsche et al. 2007; Kuo et al. 2013) transcranial alternative current stimulation (tACS) (Antal et al. 2008) and transcranial random noise stimulation (tRNS) (Terney et al. 2008) (Figure 1).

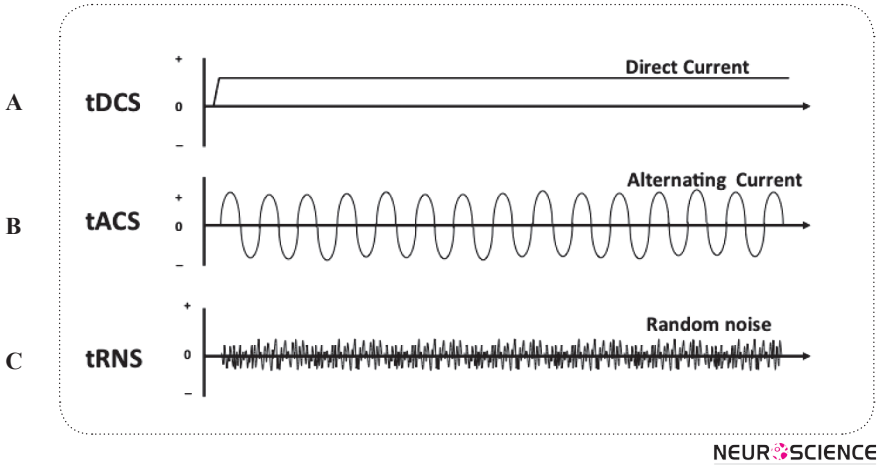

Figure 1. tCS paradigms. tDCS: transcranial direct current stimulation; tACS: transcranial alternative current stimulation; tRNS: transcranial random noise stimulation.

Compared to TMS, tCS (Figure 1A) has a number of advantages. tCS has no or minimal side effects such as itching and burning sensations and it can be applied by an inexpensive battery-operated device which is very simple to operate (Jeffery et al. 2007; Bolognini et al. 2009), even by patients. tCS has a very long history in the literature with tDCS the most studied paradigm (Paulus 2011).

Transcranial Direct Current Stimulation

tDCS has been receiving increased interest in recent years as a tool for modulating cortical excitability and motor performance in a range of clinical settings and experimental conditions. tDCS involves application of weak, direct current (1-2 mA) to the scalp via sponge-based rectangular pads (nominally 25-35 cm2) (Webster et al. 2006). This produces a sub-sensory level of electrical stimulation, which remains imperceptible by most people during its application. In a small percentage of participants it may cause minimal discomfort with a mild tingling sensation, which usually disappears after a few seconds (Nitsche et al. 2003). Skin burn is another side effect of tDCS, which should be avoided. A minor flaw in application of the technique such as small electrode size can easily result in skin burns.

The applied current modifies the transmembrane neuronal potential and thus influences the level of excitability (Nitsche et al. 2008). The nature of these modulations depends on tDCS polarity, which may increase or decrease corticospinal excitability (CSE) (Nitsche et al. 2003). Anodal tDCS (a-tDCS), application of anode over cortical target area (i.e. primary motor cortex), increases CSE and Cathodal tDCS (c-tDCS), application of cathode over cortical target area, decreases CSE. In both cases the reference electrode could be placed on the opposite supraorbital area (Figure 2). This is just one of the most applicable type of montages.

The respective changes evolve during tDCS, remain for up to 1 hour after it ceases (Nitsche Paulus 2001; Nitsche et al. 2003). These effects are probably intracortical. This was evidenced by increase in the size of TMS-induced MEPs and no changes in transcranial electrical stimulation (TES)-induced MEPs which are indicators of spinal changes (Nitsche Paulus 2000; Nitsche Paulus 2001; Nitsche et al. 2003). tDCS can be used as a stand-alone paradigm or as an add-on paradigm to prime the effects of motor training (Hummel et al. 2005; Hesse et al. 2007).

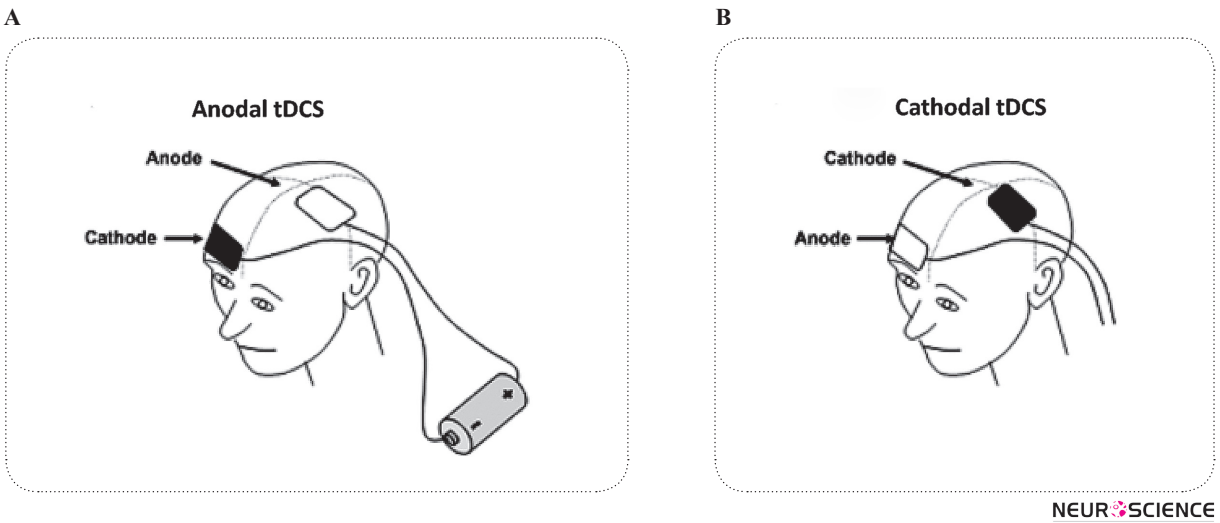

Figure 2. Anodal (A) and cathodal-tDCS (B) of primary motor cortex.

Effects of Motor Cortex Stimulation on Motor Skill Learning

Precise motor performance is essential to almost everything we do, from typing, to driving, to playing sports. Having a motor skill implies a level of performance in a given task that is only achievable through practice and motor learning. Motor learning is always associated with enhancement of M1 corticospinal excitability (Pascual-Leone et al. 1999; Muellbacher et al. 2002), which refers to both practice-related expansions in cortical representation area(s) of the involved muscles and increases in its strength of activations (Poldrack 2000). This increase is caused by recruitment of additional cortical units, which is evidenced by increase in size of TMS induced MEPS (Poldrack 2000). NIBS techniques facilitate motor skill learning by increasing the corticospinal excitability. Evidence from recent studies suggests links between a-tDCS induced corticospinal excitability, skill learning (Boggio et al. 2006; Galea Celnik 2009; Hunter et al. 2009; Reis et al. 2009) Bastani Jaberzadeh 2012 and motor performance (Nitsche et al. 2003; Hummel et al. 2010). Therefore, understanding of the interaction between modulations of corticospinal excitability and motor learning is critical for clinical approaches. A growing number of studies have shown added effects of a-tDCS for improvement of motor learning in healthy adults (Nitsche et al. 2003; Fregni et al. 2005; Hummel et al. 2005; Fregni et al. 2006; Hummel Cohen 2006; Fregni Pascual-Leone 2007; Matsuo et al. 2011). Within-session performance improvements (online effects) occur in the minutes of a single training session and continue over days and weeks of repeated training sessions (offline effects) (Reis et al. 2009). This improvement can be retained to varying degrees over weeks to months after the completion of training (long-term retention) (Savion-Lemieux Penhune 2005).

Priming the Effects of Motor Training Paradigms

Literature indicates that, there has been an effort to prime training strategies after brain lesions such as constraint-induced movement therapy, bilateral arm training, mirror and randomised training schedules or robotic-based approaches (Cauraugh Kim 2003; Wittenberg et al. 2003; Luft et al. 2004; Summers et al. 2007; Cramer 2008; Lo et al. 2009; Tanaka et al. 2010). Additionally, new technical approaches have been proposed to facilitate the beneficial effects of training on motor skill learning in the setting of rehabilitation interventions like somatosensory stimulation (Conforto et al. 2007) and non-invasive brain stimulation techniques, such as transcranial tDCS. Within the past two decades these techniques have been used to explore possible causal relations between activity in specific brain areas and particular behaviours (Hallett 2000; Nitsche et al. 2008). Improved understanding of the involvement of a brain region in a type of behaviour was followed by attempts to modulate activity in specific cortical areas with the goal to enhance motor performance (Hummel et al. 2005; Hummel Cohen 2006; Webster et al. 2006; Fregni Pascual-Leone 2007; Reis et al. 2008; Tanaka et al. 2011). Research studies in patients suffering from chronic stroke showed that a-tDCS on M1 of the affected hemisphere can beneficially influence motor performance of the paretic hand (Fregni et al. 2005; Hummel et al. 2005) (Hummel et al. 2006; O'Shea et al. 2013). Similar effects are also reported in the subacute stage of the post stroke patients (Kim et al. 2009). Refer to review by Gomez Palacio Schjetnan (2013) and Bastani and Ja-

berzadeh (2012) for further details (Bastani Jaberzadeh 2012; Gomez Palacio Schjetnan et al. 2013).

The Effects of Electrode Size and Electrode Montage

One important parameter in tDCS is electrode montage. In fact one of the reasons for the lack of significant effects for early tDCS studies (before the 90s) is electrode montage that result in lack of significant current being applied over the targeted cortical areas (Murphy et al. 2009). Nitsche and Paulus showed that tDCS-induced cortical excitability depends on the location of the electrodes (Nitsche Paulus 2000). During tDCS, electrodes are placed and secured to the scalp over the desired areas and current are delivered to the underlying cortical tissue. The direction of current flow determines the effects on the underlying tissue. Anodal tDCS, using the anodal electrode over M1 and the cathodal electrode over the contralateral supra orbital area, enhances cortical excitability, which increases the amplitude of motor evoked potentials (MEPs). On the other hand, cathodal tDCS, with the cathodal electrode over M1, shows the opposite effect (Nitsche Paulus 2000). Similar results were obtained in a modelling study (Wagner et al. 2007).

The spatial focality (targeting) of tDCS is considered pivotal for efficacy and safety in many biomedical applications. Focality is limited, in part, by the electrode size used. Traditional tDCS designs include two sponge-based electrodes, saturated with saline and connected to the stimulator via conductive rubber electrodes. The electrode on the target area is called active electrode and the one, which is usually placed on the contralateral supraorbital area, is called indifferent electrode. Decreasing active electrode size can improve spatial focality which may enhance cortico-plasticity (Bastani Jaberzadeh 2013). Indeed, by using smaller active electrodes we may avoid some inhibitory effects from stimulation of nearby cortical areas that might be functionally connected to M1 (Bastani Jaberzadeh 2013). Literature also indicates that, there are other methods that have been utilised to improve stimulation focality. Array electrodes and tripolar-electrodes configuration are among such examples (Datta et al. 2008). On the other hand, any decrease in electrode size, increases current density (Nitsche et al. 2007; Datta et al. 2008), which increases concerns related to safety issues such as skin irritation.

Inter hemispheric competition (rivalry model) and intra-hemispheric cortico-cortical connections (functional connectivity model) provide a number of tDCS strategies which could be used to promote M1 excitability and enhance motor performance (Nitsche et al. 2003; Boggio et al. 2006; Vines et al. 2006; Vines et al. 2008; Lindenberg et al. 2013). Interhemispheric rivalry assumes that any increase in motor performance may arise from excitation of contralateral cortex and inhibition from the ipsilateral cortex. Hence, motor performance might be facilitated by upregulating the excitability of the contralateral motor cortex through anodal tDCS or by downregulating the excitability of the ipsilateral motor cortex through cathodal tDCS (Nitsche et al. 2003; Boggio et al. 2006; Vines et al. 2006; Vines et al. 2008; Lindenberg et al. 2013). This is the basis for dual stimulation technique. The concept of functional connectivity is viewed as central for understanding the organized behaviour of anatomic regions in the brain during their activity (Kirimoto et al. 2011). This organization is thought to be based on the interaction between different and differently specialized cortical sites. For example, motor association cortex has inhibitory effects on M1 (Kirimoto et al. 2011) while premotor cortex facilitates M1 by reducing short-interval intracortical inhibition (Boros et al. 2008). Although these previous neurophysiological and modelling studies provided important insights regarding the optimal location for electrode placement it is critical to systematically test for different montages with different electrode sizes.

tDCS Safety

Safety of brain stimulation depends on the strength of current, the size of the electrodes and the duration of the stimulation (Nitsche et al. 2003; Iyer et al. 2005). In an MRI study, it was found that tDCS protocols, which are known to result in cortical excitability changes persisting for an hour post-stimulation, did not induce brain edema or alterations of the blood–brain barrier or cerebral tissue (Nitsche et al. 2004). The only main published safety study of DC stimulation, evaluated 103 subjects, (Iyer et al. 2005) found no adverse effects on cognitive and psychomotor measures, nor EEG changes during or after 20 min of treatment. In a double-blind, sham-controlled study (Gandiga et al. 2006) it has been shown that comparing tDCS and sham stimulation of the motor cortex elicited minimal discomfort and difference in the duration of tingling sensations. This study concluded that there have been no differences in self-rated attention or fatigue, or investigators could not distinguish real tDCS from sham.

Mechanisms of tDCS-Induced Neuroplasticity

Weak tDCS with a homogenous DC field at intensities of around 1 mA induces long-lasting changes in

the brain. tDCS can be used to manipulate brain excitability via membrane polarisation: cathodal stimulation hyperpolarises, while anodal stimulation depolarises the resting membrane (Bindman et al. 1964; Nitsche et al. 2003). The induced after-effects of tDCS depend on N-methyl-d-aspartate (NMDA) receptor efficacy changes (Liebetanz et al. 2002). There is also evidence for both GABAergic (Nitsche et al. 2004) and dopaminergic modulation of tDCS-induced effects (Nitsche et al. 2006). Relevant mechanisms underlying these after-effects include synaptic long-term potentiation (LTP) and long term depression (LTD) (Cooke Bliss 2006).

Intracortical inhibition and facilitation were prominently modulated by tDCS (Nitsche et al. 2005). For the short-lasting after-effects (7 min tDCS), inhibition was diminished and facilitation increased by anodal tDCS, whereas the effect of cathodal tDCS was the reverse. This result fits well with the fact that the after-effects of tDCS as well as intracortical inhibition and facilitation are at least partly controlled by NMDA receptor activity (Ziemann et al. 1998; Nitsche et al. 2003). Essentially, the results are identical for the long-lasting after-effects (9 or 13 min tDCS) (Nitsche et al. 2005).

A variety of other parameters influence tDCS effects. Co-application of neuropharmacologically active drugs may most impressively prolong or even reverse stimulation effects (Nitsche et al. 2003; Kuo et al. 2008). For example, administration of the NMDA antagonists decreased while GABA antagonists increased the tDCS effects (Nitsche et al. 2004). These findings provide evidence for involvement of these receptors in induced changes.

Other tCS Paradigms

Transcranial Alternating Current Stimulation (tACS)

tACS (Figure 1B) is another brain stimulation approach which involves application of alternating current through the skull over the target cortex of the brain (Antal et al. 2008). In this paradigm sinusoidally applied transcranial alternating current allows manipulation of intrinsic cortical oscillations with externally applied electrical frequencies. Of course, any combination of any frequency is possible. Motor learning under an implicit motor learning paradigm (Nitsche et al. 2003) was however better with 250 than with 140 Hz.

Transcranial Random Noise Stimulation (tRNS)

This paradigm (Figure 1C) is a form of tACS applied at random frequencies between 0.1 and 640 Hz, which can lead to an increase in performance of implicit motor or perceptual learning tasks (Terney et al. 2008; Ambrus et al. 2011; Fertonani et al. 2011; Saiote et al. 2013). Its effects on cortical excitability have also been shown to depend on the frequency range used for stimulation: high-frequency tRNS (101–640 Hz) increases cortical excitability whereas low-frequency tRNS (0.1–100 Hz) does not induce significant alterations (Terney et al. 2008).

A consistent CSE increase lasting at least 60 minutes, was induced by 10 minutes of tRNS (Terney et al. 2008). This effect may either be attributed to the repeated opening of NA channels or to a higher sensitivity of neuronal networks to field modulation than the average single neuron threshold (Francis et al. 2003).

Advantages of this technique compared to tDCS include it's insensitivity to electrode polarity and further reduction of skin sensations under the electrodes during stimulation. It is also easier to blind than tDCS (Ambrus et al. 2010).

Limitations of Current State of Knowledge

Although a considerable body of research has demonstrated the effects of tDCS paradigms in humans on cortical excitability and motor performance, there are considerable limitations with the studies that have been done to date.

1. While the neural substrates of motor skill learning involve functional changes in a distributed network that includes the primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), somotosensory cortex (S1), dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), cerebellum, thalamic nuclei, and the striatum (Bo et al. 2008; Shadmehr Krakauer 2008; Doyon et al. 2009; Seidler 2010), most tDCS studies carried out so far have focused on efforts to only modulate activity within M1. The impact of cortical functional connectivity on motor learning and motor performance has not been fully understood yet.

2. Minimal research has investigated whether the effect of tDCS depends on what motor training paradigm is associated with.

3. Different paradigms of tCS (tDCS, tACS and tRNS) have developed in isolation from each other and no comparative studies have looked at whether or one or more of these plasticity paradigms have greater or lesser effects than the others.

4. Of particular relevance to neurorehabilitation is the finding of increased tDCS after effects with repetitive stimulation over days (Reis et al. 2009). Thus, the most efficient training protocols may turn out to be daily repetitions, further optimised with repetitive tDCS applications. Thus far little attention has been directed to the importance of daily repetition of tDCS sessions, number and interval between sessions.

5. Only a few studies have actually attempted to understand the mechanisms through which these paradigms change cortical activity (Nitsche et al. 2003; Stagg et al. 2011; Stagg Nitsche 2011). However, scientific rigor of double-blinded, randomised controlled trials was not carefully followed.

These limitations substantially inhibit the translation of the findings of this basic research into clinical applications. Where clinical applications have been developed, the choice of tCS paradigm and parameters has been rather idiosyncratic as opposed to being driven by knowledge of the effects of these stimulation parameters on brain function. Clearly, improving our knowledge of optimal tCS parameters and mechanisms would markedly enhance our capacity to develop effective clinical interventions.

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Commentary:
Treatment of Neurological and Psychiatric Disorders with Deep Brain Stimulation; Raising Hopes and Future Challenges

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ABSTRACT

The technology of Neural Stimulation in recent years has become the focus of the research and treatment, although it has been around for many years. The potential use of stimulating the brain and nerves ranges from the spinal cord stimulation to the implantations of cochlear and bionic eyes with a large discrepancy between the clinical readiness for these various uses.

Electrical high-frequency Deep Brain Stimulation (DBS) was developed as an alternative option to treat a few neurological disorders. However, with advancing in surgical procedures, technologies and safeties, the applications of DBS are expanding not only for therapeutic purposes but also for research. Although the exact mechanisms of action/s are not fully understood, the outcome of the ongoing research and clinical trials are promising. DBS has been used to treat the essential tremor since 1997, Parkinson's disease (PD) since 2002 and dystonia since 2003. It has also been used to treat various disorders, including major depression. The therapeutic effect of DBS in PD is well established but for other diseases such as epilepsy the outcomes are unclear and ambiguous. This article is a succinct review of the literature, focusing on PD, epilepsy and Obsessive Compulsive Disorder (OCD).

Introduction

Perhaps the ancient Romans and Greeks were the first to document the affect of the electrical pulses on nervous system. Torpedo nobiliana from the family of Torpedinidae was named by Romans (Rossi, 2003) for its ability to cause torpor. The same species was named by Greek narke for narcotizing its prey (Debru, 2006).

Claudius physician; Scribonius Largus, 47 AD., treated headache with the live ray. The same method was later on used for hemorrhoids, gout, depression, and epilepsy (Rossi, 2003). Although Avicenna (980-1037 AD.) had mentioned (Sharafkandi, 1997) the brain is not homogenous as it was thought to be but the breakthrough came by the observation and the subsequent experiment made by German neurologist Edward Hitzig 1864 who was assisted by an anatomist Fritsch, applying an electrical pulse to the exposed cerebral cortex of a dog without anaesthesia (Fritsch & Hitzig, 1992). Soon after the new era of brain stimulation has started with Cincinnati, Bartholow 1874 applying electrical current to a terminal patient whose scalp and cranium had eroded by basal cell carcinoma (Bartholow, 1982). these experiments went well, eliciting contralateral movements. A current DBS device has generally a quadripolar electrode inserted into the brain. The aligned extensions run behind the ear with an internal pulse generator implanted either on top of or deep to the pectoralis fascia. The current technology is advancing on daily basis and beyond imagination. The cochlear implant is already in use and some advances in

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bionic eyes have been made. Potentially DBS devices can be programmed through remote access by telephone or via internet as it is the case with the cardiac pacemakers (Schwalb & Hamani, 2008).

Parkinson's Disease

PD is the most common form of progressive neurodegenerative disease of the central nervous system (CNS). Approximately 10 million people are diagnosed by PD worldwide and that does not reflect the millions of cases that go undetected (De Lau & Breteler, 2006). Men are one and half times more likely to have PD than women. As many factors contribute to prevalence and incidence of PD, including gender, age, diagnostic criteria and medical facilities, therefore, the comparison of PD prevalence and incidence in different parts of the world has become very difficult (Friedman JH, et al., 2007) (Friedman & Friedman, 1993). The early symptoms of PD are motor-related that slows down the movement (bradykinesia), causes the resting tremor, muscular rigidity, shuffling, and flexed posture which are resulted from the death of dopaminergic neurons of the Substantia Nigra pars compacta (SNpc), a region of the midbrain with the appearance of the intracellular inclusions known as Lewy bodies (Vale, 2008). In the later stage of PD and sometimes during the early stage, a variety of non-motor-symptoms, including autonomic, sensory, sleep, cognitive, and psychiatric disturbances and also dementia may arise (Friedman & Friedman, 2001) (Alves, Wentzel-Larsen, & Larsen, 2004). The principle of neural stimulation is to restore the physiological function/s of the nerves or muscles by targeted and controlled delivery of electrical stimulation to the affected areas (Castrioto, 2011). Deep Brain Stimulation (DBS) has been used on the patients in the later stage of PD that pharmacological treatments offer them little to nothing and it has certainly improved locomotive ability and to some extent cognitions in patients with PD without dementia (Krack, 2003) (Liang, 2006).

In DBS electrical stimulation pulses are continuously applied to specific brain regions at high frequency by chronically implanted electrodes. These electrodes with lead extensions and a pulse generator are implanted surgically (Krack, 2003). A transdermal programming device is also used to allow different therapeutic options. Subthalamic nucleus (STN) and the globus pallidus internus (GPi), are thought to be over-activated in PD and they are the main target of DBS (Limousin, 1995). However, the ventralis intermedius nucleus of the thalamus is sometimes targeted, but STN is the most common target of DBS. While the mechanism of DBS is not fully understood, it appears to be due to modulation of neuronal activities, overriding the abnormal patterns in the basal ganglia, replacing them with less disturbing patterns (Limousin, 1995).

DBS has provided an alternative treatment for sever PD. It is widely used and known to greatly improve the symptoms of PD, including pain relief and cognitive deficit to some extent, but not dementia associated with PD.

Epilepsy

Epilepsy is a diverse set of chronic neurological disorders associated with recurrent seizures (Chang & Lowenstein, 2003). Epileptic seizure must be repeated at least twice or one single seizure with brain alterations which could increase the chance of future seizure (Fisher, 2005).

Excessive, abnormal or hypersynchronous neuronal activity in the brain causes epileptic seizure (Fisher, 2005). Over 50 million people worldwide have epilepsy, predominantly in developing countries (Brodie, Elder & Kwan 2009) (Holmes, Thomas, Browne & Gregory, 2008). About 70% of the epileptic seizures can be controlled with medication for the other 30%, medication offers little to nothing. Surgery or DBS therefore, may be considered (Cascino, 1994).

Electrical stimulation of the vagus nerve (VNS) is performed in the treatment of refractory epilepsy patients who are not suitable for surgery, and medications offer them no benefit.

The mechanism of action (MoA) of VNS in treatment of seizure suppression is not clear. Vagal afferent synapses use excitatory neurotransmitters, inhibitory neurotransmitter, acetylcholine and a variety of neuropeptides. Majority of vagal afferent synapses are received by Nucleus Tractus Solitarius (NTS). The NTS projects to other brainstem nuclei, including the LC and raphe magnus, and thus modulates norepinephrine and serotonin release, respectively. These neurotransmitters have ultimately effects the limbic, reticular, and autonomic centers of both cerebral hemispheres (Zabara, 1985). Hypothetically, afferent vagal synapses attenuate seizure activity through neurotransmitter modulation (Miller, 1992). An implanted device administrates electrical pulses at the cervical level of the neck. Intracranial and brainstem structures along the anatomical pathway from point of stimulation towards the cortex play a key func-

tional role in VNS's MoA; including the locus coeruleus, thalamus, NTS and limbic structures (Vonck, Herdt, Sprengers, & Ben-Menachem, 2012).

Obsessive Compulsive Disorder

OCD is an anxiety disorder, the disorder of the brain and behavior, characterized by disturbing thoughts, uneasiness, fear, apprehension and worries that lead to repetitive behaviors to reduce the associated anxiety; or by a combination of such obsessions and compulsions. The repetitive behavior includes excessive washing or cleaning, checking, hoarding and preoccupation with sexual, violent or religious thoughts. Notwithstanding, daily life routines, religious rituals and practices and repetitive learning activities are not compulsions. It seems that OCD caused by abnormalities of the cortico-striato-thalamocortical (CSTC) circuit involving the ventral-mesial pre-frontal cortex (PFC), dorsal anterior cingulate cortex, orbitofrontal cortex (OFC) and their associated basal ganglia and thalamus connections (Lyons, 2011). OCD has a prevalence of 2% worldwide in which approximately 20-40% of those affected, have persistent symptoms, leading to chronic functional impairment (Mian, Campos, Sheth, & Eskandar, 2010). The current treatments (including selective serotonin reuptake inhibitors, cognitive behaviour therapy and ablative surgery) are effective, however, approximately 10% of the patients do not respond to these treatments. These patients are good candidates for DBS and they may benefit from it (Huff, 2010).

The target of stimulation is currently STN and the anterior limb of the internal capsule, the ventral capsule/striatum (VC/VS) and inferior thalamic peduncle (ITP) are also the sites of interest in future studies (Lyons, 2011). There are advantages/disadvantages with each site that required more studies and trials. Stimulation of the STN may reduce surgical complications as this is a common procedure in the treatment of Parkinson's disease and it has been well established (Mian, Campos, Sheth, & Eskandar, 2010). On the other hand, the stimulation of VC/VS requires lower stimulation energies, thus allowing a longer battery life, reducing any side-effects caused by surgery. The outcome of this treatment is promising, in two different studies, four out of six patients had significant reduction in Y-BOCS scores (Yale-Brown Obsessive Compulsive Scale), but more thorough investigation and clinical trials should be carried out to determine the efficacy and the safety of the treatment (Goodman et al., 2010) (Mayberg, Lozano, Voon, McNeely, & Seminowicz, 2005).

Other Brain Disorders

Some other brain disorders may benefit from DBS such as; Tourette syndrome (also called Tourette's syndrome, Tourette's disorder, Gilles de la Tourette syndrome, GTS or just Tourette's or TS) which is an inherited neuropsychiatric disorder with onset in childhood. This neuropsychiatric disorder is characterized by multiple physical (motor) tics and at least one vocal (phonic) tic. However, as the procedure is invasive and Tourette's is more common in pediatric populations, therefore, it is only recommended for treatment-refractory cases (Malone DA, & Pandya MM 2006). There have also been some successful clinical trials of DBS for patients with Lesch-Nyhan syndrome in France, Switzerland and Japan (Cif et al 2007). Other disorders such as Phantom limb pain, severe depression, sever pain/s and perhaps the most predominant neurodegenerative disease Alzheimer's could benefit from DBS (Hardenacke et al. 2012).

Future Challenges Facing DBS

We still have a long way ahead as lots of clinical trial has not been finished or published yet. The so called neuromodulatory therapies for brain disorders have raised more questions than hopes and answers. Some of these therapies such as spinal cord stimulation for pain relief and PD, cochlear implant and severe depression have been well established and some others such as; Attention deficit-hyperactivity disorder and Alzheimer's have not. The science of neuromodulatory therapies itself has yet to be established. Although neuroanatomy and neurophysiology has advanced very well, the best target for treating a disorder yet to be determined. There are technical and clinical questions that yet to be addressed such as; what are the most effective parameters for stimulatory frequencies and rates and which patients will most benefit and the duration of the stimulation (Schwalb & Hamani 2008). The long term side effects of DBS have not been clearly identified. The legal and ethical responsibilities also should be addressed and need to be regulated.

Conclusion

The implantable neuromodulatory devices have been very beneficial to patients and their therapeutic usages are rapidly expanding. Their efficacy and potential in the treatment and management of brain disorders have been validated by numerous clinical cases and trials (Schwalb & Hamani 2008). The knowledge and experiences have been gained has leveraged DBS into the other area of medicine, psychology and nutrition. The accurate regula-

tion of neurotransmission and downstream neurochemical cascades via both invasive, DBS, and non-invasive such as trans cranial magnetic stimulation proved to be a serious challenge ahead. Variety methods of stimulations are facilitated by these devices of which they have the ability to target highly specific foci in the CNS. This can be in the form of both inhibitory and/or excitatory action (Schwalb & Hamani 2008).

DBS has emerged to a new therapeutic level with the aid of functional imaging with MRI or positron emission tomography. The advances in surgical procedures have decreased infections and surgical complications. Nevertheless, it is an invasive procedure and the risk of surgical complications, particularly in vulnerable patients do exist. DBS today is considered an alternative therapy for not only psychiatric disorder but also as a potential therapy for non-psychiatric disorder such as hypertension, obesity, and eating disorders. Autonomic changes have been reported in patients with chronic pain receiving periaqueductal/periventricular grey (PAG/PVG) (Schwalb & Hamani 2008). DBS has created a new field in which specialized physicians and nurses need to be trained and the field continues to expand.

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Commentary:
Repetitive Transcranial Magnetic Stimulation (rTMS) in the Management of Alcohol Dependence and other Substance Abuse Disorders – Emerging Data and Clinical Relevance

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) has been used widely in various psychiatric disorders like depression and schizophrenia. There have been some reports of its usefulness in alcohol dependence and substance use disorders. The present paper reviews the studies done using rTMS in substance use disorders including alcohol and nicotine dependence. Various studies done have been reviewed including the proposed mechanisms of action are outlined with the future research needs and need for further clinical data

Introduction

Substance abuse is a major health problem worldwide and has been linked to several neuropsychiatric disorders, gastrointestinal diseases, cancer, cardiovascular diseases, fetal alcohol syndrome, pre-term birth complications and diabetes mellitus (Chesher et al., 2011). Genetic, biological and environmental factors could all together influence the development of alcohol and substance abuse (Tarter, 2002). Substance abuse disorders are often difficult to treat and relapse rates are high, even when successful detoxification is followed by pharmacotherapeutic or psychotherapeutic interventions (Garner, 2009).

Critical Aspects of Drug and Alcohol Dependence

A recent important paper on the neurobiology of alcohol dependence (Koob, 2011) describes an Addiction Cycle in alcohol dependent patients, which consists of three phases, namely the binge/intoxication phase, the withdrawal/negative affect phase and the preoccupation/anticipation phase. Further, before becoming dependent, this cycle is usually repeated multiple times. Although other neurotransmitter systems can be involved as well, the dopaminergic system is the key player in all these phases (Kalsi et al., 2009). Alcohol addicted patients display a deregulated dopaminergic system, which results in stronger alcohol orientation and loss in interest for natural rewards. Because of this malfunctioning dopa-

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minergic system alcoholic patients encounter difficulties in learning new reward associated stimuli and they lack motivation to seek new rewarding stimuli (Heinz et al., 2009). Once 'addiction' is established, the cycle is characterized by impulsivity and compulsivity (Koob & Volkow 2010).

Main Cognitive Targets For Therapeutic Interventions In Drug And Alcohol Dependence

Impulsivity is characterized by non planned reactions to external and internal stimuli and it is associated with positive reinforcement (Zhang et al. 2012). The underlying neurobiology of impulsivity in alcohol dependency is complex (Potenza and Taylor, 2009). The prefrontal cortical network, and in particular the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC) play an important role in inhibitory control mechanisms when patients are confronted with addictive substances (Bechara 2005; Schoenbaum et al., 2009). Increasing the activity of the PFC and thus cognitive control could decrease automatic impulses and therefore reduce substance abuse behavior (Houben et al., 2011). Next to the deregulation of the dopaminergic system, the hypothalamus-pituitary-adrenal (HPA) axis is dysfunctional (Koob & Volkow 2010, Sinha et al., 2011).

Recently, neuromodulation techniques, such as transcranial magnetic stimulation (TMS) have been applied to substance abuse and alcohol dependent patients (Barr et al., 2008). However, to date no clear guidelines in alcohol addiction are at hand to determine when such interventions can be applied. Therefore, the purpose of this review is to critically evaluate the efficacy of TMS in the treatment of alcohol dependence and other substance abuse disorders.

Method of Conducting this Review

We conducted a broad search on electronic databases such as PubMed and the Cochrane Library. We used PubMed search terms were alcohol dependence, craving, addiction, cocaine abuse, nicotine dependence and transcranial magnetic stimulation. Only articles written in English were taken into account. Systematic reviews and meta-analysis were also analysed and relevant articles were chosen for this study.

Repetitive Transcranial Magnetic Stimulation (Rtms) in The Treatment of Alcohol Dependence

rTMS can alter cortical excitability, and hence induce changes in neuronal circuits (Fitzgerald et al., 2009, Cho & Strafella, 2009). rTMS is also able to influence the HPA-axis (Baeken et al., 2011). With this technique, the DLPFC is the preferred stimulation place for the rTMS application in alcohol dependency (Bechara, 2005, Mishra et al., 2010). rTMS has the capacity to modulate decision-making in healthy individuals and it is hypothesized that this neuromodulation technique can change impulsivity in addicted individuals (Fecteau et al., 2010).

In a recent study authors (Heremans et al., 2012) stimulated thirty-six recently detoxified alcohol-dependent patients with one sham-controlled high-frequency (HF)-rTMS session delivered on the right DLPFC. Alcohol craving was evaluated and measured with the Obsessive Compulsive Drinking Scale (OCDS). Immediate effects were registered in the lab setting without cue exposure, while long-term effects were evaluated in patients' natural environment. The lack of effect in subjective craving measurements was explained by the absence of cue reactivity and because not all alcoholic patients do experience craving when confronted with alcohol cues (Ooteman et al., 2006).

In a case report, a 48-year-old woman with a treatment-resistant alcohol dependence problem was stimulated with low-frequency (LF)-rTMS during an active drinking period (De Ridder et al., 2011). The frontal cortex was stimulated with a double cone coil. A double cone coil is able to modulate both dorsal and subcallosal ACC, both important in craving. The patient was stimulated during 5 weeks. During the treatment craving measurements were suppressed and remained so until three months after stimulation. Authors (Mishra et al., 2010) have performed a sham-controlled study with ten daily sessions of HF-rTMS on the right DLPFC in forty-five alcohol-dependent patients. Craving was evaluated before the first and after the last stimulation session with the Alcohol Craving Questionnaire (ACQ-NOW). Real rTMS was significantly superior in decreasing craving measurements compared to sham stimulation. Craving measurements were evaluated until 4 weeks after stimulation. After four weeks however, there were no significant differences between the active and the sham group, which might imply that the effects are waning after a couple of weeks.

Höppner et al. (2011) stimulated nineteen detoxified alcohol-dependent female patients at the left DLPFC during 10 days with HF-rTMS in a sham-controlled design. Although no differences were found in craving measurements with the OCDS, they found an alteration in the attentional blink (AB) paradigm. According to the authors this alteration in the AB could be a physiological parable for craving reduction. However, patients did not acknowledge a decrease in subjective craving. Research on rTMS in alcohol dependence is still relatively scarce and over the different studies there is a considerable variability in methodology. Therefore it is difficult to draw firm conclusions. Stimulation parameters, such as frequency, % of motor threshold, train duration, inter-train interval and laterality of stimulation differ significantly among studies. Until now, there are no fixed stimulation protocols in alcohol addiction. Research on the effect of rTMS on impulsivity is inconclusive and as to which hemisphere needs to be stimulated remains to be determined. The use of multiple sessions may prove to be more effective in decreasing craving. We suggest the evaluation of multiple rTMS sessions in larger, randomized, sham controlled population samples. Studies should also be done to evaluate whether patients need stimulation with high or low frequency.

Repetitive Transcranial Magnetic Stimulation in other Substance Abuse Disorders

Recently, Camprodon and colleagues (2007) examined rTMS as a potential treatment for the cravings experienced by cocaine-dependent individuals. In this randomized cross-over design, two sessions of 10 Hz rTMS was administered to the right and left DLPFC at 90% RMT. Visual analogue scales were administered to obtain level of cocaine cravings 10 minutes before, immediately, and 4 hours following rTMS treatment. RTMS applied to the right, but not the left DLPFC, was found to decrease subjects' level of cravings for cocaine with these differences existing between baseline and immediately after rTMS session, and baseline and 4 hours post rTMS session.

Moreover, as rTMS applied to the DLPFC has been shown to induce DA release in the subcortical structures and the caudate nucleus (Strafella et al., 2001), these findings provide a possible mechanism through which the cravings associated with chronic use of cocaine are reduced (Goldstein and Volkow, 2002).

Although several treatments including buproprion, varenicline, nicotine nicotine chewing gum, nicotine skin patch, nicotine nasal spray and lozenges and psychosocial as well as behavior therapy, are proven to be approximately double to triple the rate of smoking cessation (Siu and Tyndale, 2007), an effective treatment is still needed to target the altered neurotransmission resulting from chronic nicotine dependence. In this regard, rTMS applied to frontal regions has been shown to increase the release of DA in rats (Keck et al., 2000) and in humans (Strafella et al., 2001) associated with enhanced GABA-B receptor activity (Daskalakis et al., 2006). Repetitive TMS applied to the DLPFC, therefore, shows promise as an effective treatment in nicotine dependence. The Eichammer group (Hoffmann et al., 2003) were the first to examine the efficacy of rTMS as a potential treatment in nicotine dependence. In the first pilot double-blind cross-over study, 11 smoking dependent individuals who hoped to stop smoking were administered either active or sham rTMS over the left DLPFC at 90% of RMT. In the individuals who received active high-frequency rTMS over the DLPFC reported significantly reduced levels in smoking cravings 30 minutes following the treatment as compared to those who received sham stimulation. These findings, therefore, motivated further examination of rTMS' potential in the treatment of nicotine dependence in smokers with aims to reduce not only the level of cravings but also smoking consumption. In the second double-blind cross-over design study, 14 individuals who wished to stop smoking were administered 2 active, and 2 placebo-control sham rTMS in a randomized order for 4 consecutive days. High-frequency (20 Hz) rTMS was applied to the left DLPFC at an intensity of 90% RMT, and smoking cravings were measured at baseline and 30 minutes after the rTMS session using a 100-point visual analogue scale. During this 6 hour time period, the number of cigarettes smoked following rTMS applied to the left DLPFC was significantly decreased, with no change in the level of cravings. Treatment with high-frequency rTMS was, therefore, found to reduce the level of cravings for cigarettes in the pilot study, although this finding was not replicated in the second study. A similar out patient study stimulating the DLPFC with HF-rTMS has also shown to attenuate nicotine craving (Amiaz et al., 2009).

Limitations of Studies and Future Directions

Repetitive TMS has been shown to induce cortical changes in preclinical and clinical investigations through its effects on neurotransmission (Daslakis et al., 2006). The treatment studies that examined the efficacy of rTMS in the treatment of cocaine and nicotine dependence in are the first in this field. Although the reviewed work represents promise in the use of rTMS in the treatment of substance abuse, certain limitations must be ad-

Table 1. Summary of major studies of rTMS in Substance Abuse and Alcohol Dependence

STUDY DETAILS	METHODS	RESULTS
Alcohol Dependence		
Bechara 2005	DLPFC 10 sessions HF-rTMS	Decreased craving
Mishra et al., 2010 Hoppner et al., 2011 Heremans et al., 2012	DLPFC 10 sessions HF-rTMS	Decreased carving Attenuates Attentional Blink
Substance Abuse		
Camprodon et al., 2007	Cocaine dependence HF DLPFC stimulation	Decreased cocaine craving
Hoffman et al., 2003 Amiaz et al., 2009	Nicotine dependence HF DLPFC stimulation	Attenuates nicotine craving

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dressed. First, the use of larger sample sizes in the examination of rTMS as a potential treatment in persons with substance abuse with aims to reduce the level of cravings and consumption would strengthen this preliminary evidence with increased statistical power. Second, the studies reviewed here are limited to the short-term effects of rTMS on the level of cravings and consumption, and fail to examine the efficacy of rTMS' long-term effects and its potential to achieve abstinence. In addition, preclinical studies using animal models to examine the efficacy of rTMS in the treatment of substance abuse represents an area that needs to be further explored.

Conclusions

Transcranial magnetic stimulation has provided a safe and non-invasive method to evaluate the neurophysiology of the human cortex. Moreover, TMS has shown promise in the diagnosis of several patient populations, including SUDs. Although, this research remains in its infancy, TMS paradigms have demonstrated alterations in cortical excitation in chronic cocaine, nicotine, and alcohol users. Moreover, rTMS has been reported to modulate neurotransmission, and early studies suggest that it may be a promising treatment for a number of substance abuse disorders.

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