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TRANSCRANIAL DIRECT CURRENT STIMULATION AND STROKE RECOVERY: OPPORTUNITIES AND CHALLENGES

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ABSTRACT

Objectives:
Transcranial direct current stimulation (tDCS) is one type of neuromodulation, which is an emerging technology that holds promise for the future studies on therapeutic and diagnosis applications in treatment of neurological and psychiatric diseases. However, 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. This article reviews the tDCS as tools of neuromodulation for stroke and discusses the opportunities and challenges available for clinicians and researchers interested in advancing neuromodulation therapy. The aim of this review is to highlight the usefulness of tDCS and to generate an interest that will lead to appropriate studies that assess the true clinical value of tDCS for brain diseases in developing countries. **Methods:** Literature review was done on PubMed from 2016 on neuromodulation in under-developed countries (UDCs) by non-invasive brain stimulation methods, using the key words "stroke", "rehabilitation", and "tDCS". **Results:** We first identified articles and websites, of which were further selected for extensive analysis mainly based on clinical relevance, study quality and reliability, and date of publication. **Conclusion:** Despite the promising results obtained with tDCS in basic and clinical neuroscience, further progress has been impeded by a lack of clarity to use in mostly UDCs.

INTRODUCTION

During stroke, an interruption to all or part of the brain's blood supply, with the subsequent deprivation of oxygen and glucose to the affected area, causes the rapid loss of brain function through the destruction of neuronal function and the initiation of an ischemic cascade that seriously damages or kills neurons1. Strokes are classified as an ischemic (caused by embolism, thrombosis or systemic hypoperfusion) approximately 80% and hemorrhagic (intracerebral, subarachnoid, subdural or epidural in type) strokes[1, 2]. The main symptoms associated with stroke are weakness in facial, speech and a loss in visual field and paralysis in the arm or leg. These symptoms may last only a few hours and disappear completely within 24 hours, as with TIAs, but even under these circumstances, immediate medical assistance should be sought, as this will help minimise damage to the brain and help prevent progression to larger, more serious episodes of stroke[2]. Stroke can result in lasting neurological damage or may even cause death unless it is diagnosed and treated promptly. When the stroke is severe, the patient often faces a prolonged stay in hospital and, following their discharge and depending on the severity of the consequences, constant care. This care is either provided by a family member or, in the most severe cases, by a nursing home. Stroke disease not only affects health-related quality of life (HRQOL) of patients but it can also increase their hospital length of stay (HLoS)[3, 4]. HLoS will even be more increased if patients are suffering with stroke combined with diabetes mellitus and hypertension[5].

Stroke treatment and rehabilitation

It is vital that the individual who has suffered a stroke receives medical attention as rapidly as possible, as this increases the likelihood of making a full or partial recovery, and can even save lives. Rehabilitation can help an individual to regain as much independence as possible, allowing the patient to relearn lost skills, learn new skills and discover ways to manage any permanent disabilities. Rehabilitation treatments include physiotherapy, occupational therapy, speech and language therapy, and vision correction[9] (Figure 1, Table 1). Neuro-rehabilitation after stroke is extremely essential. The local rehab is spending a lot of money on infrastructure and physical, hearing, and speech therapy. The facilities provided by the rehab program to stroke victims are still not up to the mark in UDCs. If stroke is treated in an effective and modern way, long-term disability and lives can be saved. Given the extensive health technologies available, it is often difficult for UDCs to decide which emerging technologies are best suited for their own needs with their current resources.

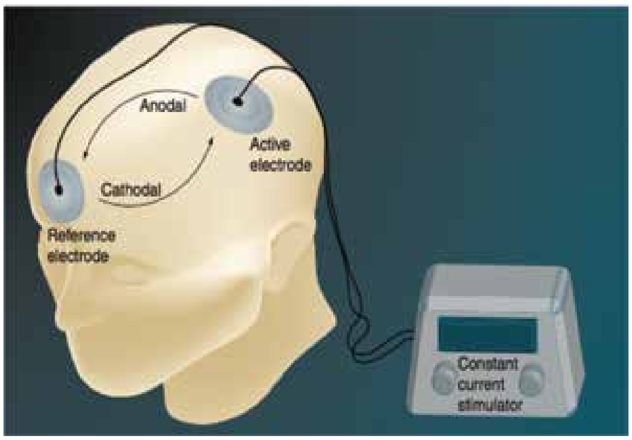

Figure 1: Transcrinal direct current stimulation set up equipment.

Brain stimulation by direct current is a new method that holds promise for the future study and treatment of brain diseases. Major advances in this emerging field have been made relatively quickly, from new stimulation protocols for research to their application for the neurological disorder such as Parkinson's disease, Alzheimer disease and pain [6-8]. But there is a serious question among UDCs 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.

Region Name	Number of Studies
World	1120
Africa	4
Central America	4
East Asia	174
Japan	7
Europe	292
Middle East	42
North America	502
Canada	118
Mexico	2
United States	401
North Asia	18
Pacifica	17
South America	35
South Asia	12
Southeast Asia	37

Table 1: Stroke rehabilitation program around the world. Data derived from clinical trial registry

Transcranial direct current stimulation (tDCS)

tDCS is a noninvasive brain stimulation method, which is easy to administer, noninvasive inexpensive and painless. In tDCS, low voltage currents are applied on the scalp by two spongy electrodes, anode and cathode soaked in saline. A current generator sends low intensity electric current and polarize membrane potential in the stimulated area. It induces polarity-dependent (anodal electrode increase excitability and cathode decrease excitability) alterations of cortical excitability. A constant current stimulator and surface electrodes soaked in normal saline are required for tDCS. The former is the source of steady flow of 0-4 mA direct current and it continually monitors the resistance in the system.

A previous study demonstrated that current density up to 25 mA/cm2 did not damage brain tissue and the protocols where 1-2 mA current is administered fall within these limits [10]. Previous studies have argued that in spite of a fraction of the direct current being shunted through the scalp, tDCS carries enough currents to the underlying cortex, sufficient for neuronal excitability shifts [11]. Another study has also reported change in measures of cerebral blood flow in brain regions that are subjected to transcranial anodal direct current thereby proving that transcranially administered direct currents can affect tissue excitability as well as regional blood flow as an indirect indicator of change in regional tissue excitability [12].

tDCS and stroke

tDCS is being used in the rehabilitation for stroke in different parts of the world (Figures 2, 3 and Table 2). Different authors have reported different results but overall outcome is positive [13-33]. Patients sufferingfrom chronic, chronic right hemispheric, occipital, post-stroke nonfluent aphasia, left hemisphere, post-stroke dysphagia, subcortical, upper limb and sub-acute stroke showed improvement (Table 3). For instance, few studies conducted with post-stroke chronic aphasia and stroke patients did not demonstrate improvement of conditions of patients using tDCS [31-33]. Authors, year of study, and total number of subjects studied are shown in the table 3. The difference in response to tDCS can be attributed to severity of neurological disorders and differences in areas of the brain that were subjected to stimulation by tDCS [34]. However, overall tDCS application enables researchers to modulate cognitive (35) and emotional processing [36].

Figure 2: Stroke rehabilitation program around the world. Data derived from clinical trial registry.

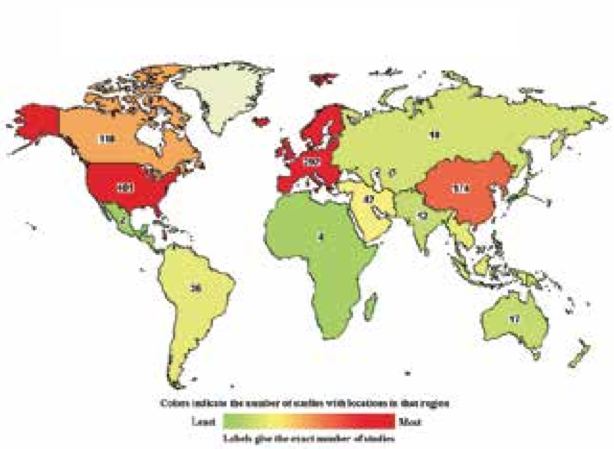

Figure 2: Stroke rehabilitation program around the world. Data derived from clinical trial registry.

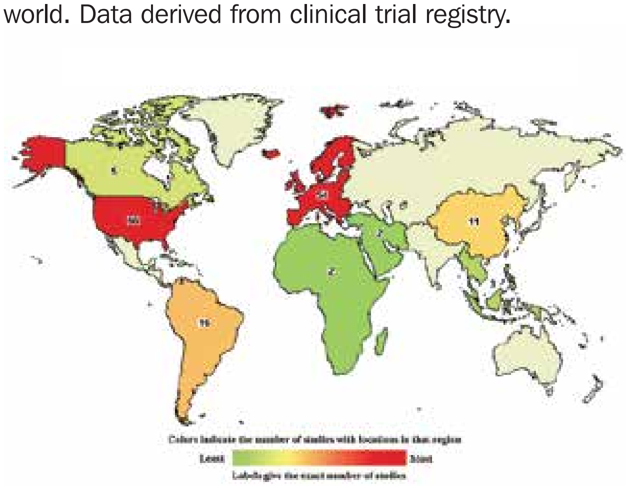

Figure 3: Transcranial direct current stimulation and stroke rehabilitation program around the world. Data derived from clinical trial registry.

Region Name	Number of Studies
World	157
Africa	2
East Asia	11
Europe	54
Middle East	2
North America	61
Canada	5
United States	56
South America	15
Southeast Asia	3

Table 2: Transcrinal direct current stimulation and stroke rehabilitation program around the world. Data derived from clinical trial registry

Economic effects of stroke

Economically, stroke has a huge effect, with almost 5% of the medical costs of industrialised countries given to the disease. Although in real terms morbidity is relatively low, the long-term impairments left behind are hugely detrimental both in terms of hospital and other care sector costs. In the past, the greatest prevalence of stroke has been in the developed countries, but a change in this pattern may be expected as more and more countries adopt a more westernised way of life. The overall rate stroke incidence in low and middle income countries exceed that than of high-income countries, by about 20% (37). It is estimated that there will be 23 million first ever strokes and 7.8 million stroke deaths in 2030[38]. Stein et al. [39]

Demonstrated that rapid urbanization with low physical activities and increasing habits of smoking can increase rate of cardiovascular and stroke diseases in developing countries. An unseen cost in stroke is the effect it has on those caring informally for the survivors. In real terms, the costs to the Canadian economy are $2.7 billion a year, with an average of $27,500 being spent, per stroke, on acute care. In total, 3,000,000 days are spent by Canadian stroke sufferers in hospital per year, which again is a severe drain on the economy [2]. In the United Kingdom, it is estimated that economic costs of stroke from a societal perspective totals around £9 billion a year [40].

No.	Author	Year	No. of Subjects	Disease investigated	Result
1	Sunwoo H[23]	2013	10	chronic right hemispheric stroke	improved
2	Olma MC[24]	2013	12	occipital stroke	improved
3	Polanowska KE[25]	2013	24	post-stroke nonfluent aphasia	improved
4	Volpato C[19]	2013	8	post-stroke chronic aphasia	not improved
5	Fiori V[26]	2013	7	left hemisphere stroke	improved
6	Shigematsu T[27]	2013	20	post-stroke dysphagia	improved
7	Yang EJ[28]	2012	16	post-stroke dysphagia	improved
8	Lindenberg R[29]	2012	10	chronic stroke	improved
9	Zimerman M[30]	2012	12	subcortical stroke	improved
10	Lefebvre S[31]	2012	18	chronic stroke	improved
11	Giacobbe V[32]	2013	12	chronic stroke	improved
12	O'Shea J[33]	2014	13	chronic stroke	improved
13	Lefebvre S[34]	2014	19	chronic hemiparetic stroke	improved
14	Fusco A[35]	2013	9	subacute stroke	improved
15	Rossi C[18]	2013	50	acute stroke	not improved
16	Danzl MM[36]	2013	10	chronic stroke	improved
17	Ochi M[37]	2013	18	chronic stroke	improved
18	Jeon SY[38]	2012	32	verbal working memory and naming	improved
19	Ang KK[39]	2012	5	upper limb stroke	improved
20	Peruzzotti-Jametti L[40]	2013	15	chronic stroke	improved
21	Elsner B[41]	2013	54	stroke	not improved

Table 3: Using transcranial direct current stimulation for stroke rehabilitation

In the region of South Asia, which includes developing countries like Pakistan, Sri Lanka, India, and Bangladesh, prevalence of stroke is high. In India and Pakistan alone, 152-262 cases per 100,000 and 250 cases per 100,000 population, respectively are reported annually. These countries in addition to a limited acute stroke care, including thrombolysis and stroke units and inadequate public awareness, physician training, research facilities are lacking prevention strategies at the Government level (41).

Despite major advances in the scientific understanding and management of stroke globally; South Asian countries are still suffering from stroke and its consequences. Implementation of tDCS in the treatment/management of stroke in the South Asia will not only be useful for stroke patients but also reduce burden of the governments for spending a lot of money on stroke management.

Technical limitation of tDCS in experimental settings

In comparison to transcranial magnetic stimulation (TMS), the major limitation of tDCS is that it is not focal and “strong” enough to map cortical functions precisely. But in comparison to TMS, tDCS requires inexpensive hardware and the procedure is simple. The most important component is a current generator, which is capable of delivering a constant electrical current flow of up to 2 mA. In principal, the building of such a battery-driven device should not be a complicated task for an experienced electronic engineer. Furthermore, it cannot produce temporally focused effects like TMS. On the other hand, applying tDCS is simple. Blinding of subjects and investigators is easier thereby allowing the conduct of more robust double-blind and sham-controlled trials. Further studies, particularly in humans are required to understand and verify tDCS actions on brain tissue, its mechanisms, and the associated behavioral and cognitive effects.

CONCLUSIONS

Stroke is a leading cause of death and neurological disability in adults, inflicting a heavy burden on affected individuals and their families. It has serious consequences for the global economy and predictions are gloomy [42]. There is still high rate of mortality or dependence where access to new technologies and expert facilities is available, making it imperative that new treatments and technologies are discovered and exploited in the battle against stroke. Another main focus must be easing the burden on the career, making rehabilitative methods high priority. The ultimate goal would, of course, be total rehabilitation of the patient, this allowing their return to work and a decent quality of life. tDCS has an important role to play in the fight against stroke and its consequences, whether as a prognostic technique, or as a rehabilitative method [12].

tDCS is becoming popular among developed countries for the treatment of patients suffering from stroke and depression. This technique has neurobiological effects and is relatively easy to use, safe, and cheaper. It will not only equip hospitals with the latest technique but also reduce cost of treatment of stroke.

Declaration of Interests

The authors declare that they have no competing interests.

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Author's contribution:
Murtaza G: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review
Hussain F: Study concept and design, data collection, data analysis, manuscript writing, manuscript review
Iqbal M: Study concept and design, data collection, data analysis, manuscript writing, manuscript review
Shahid Bashir: Study concept and design, data collection, data analysis, manuscript writing, manuscript review