

## SHORT INTERVAL PERIODIC TRANSCRANIAL DIRECT CURRENT STIMULATIONS INDUCED LONG-TERM REMISSION OF SYMPTOMS IN A PATIENT WITH POST-STROKE DEPRESSION

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### ABSTRACT

**Objective:** We present report of a patient with PSD who had long-term mood improvement upon receiving periodic tDCS sessions with short inter-sessions intervals following relapse of symptoms at 3 weeks after improvement due to stimulations with long inter-sessions intervals.

**Background:** tDCS has been shown to be effective in the management of patients with post-stroke depression, but with high relapse rate.

**Materials and Methods:** A 60 years old patient presented with moderate PSD, having BDI score of 25. She received anodal tDCS to the left dorsolateral prefrontal cortex using two different application protocols. Initially, a stimulation session of 2mA intensity for 20 minutes was given every working day for two weeks. After 3 weeks, she then received 7 sessions of periodic stimulations of 2mA intensity for 13 minutes each with 20 minutes inter-sessions interval. BDI score was taken before the intervention, immediately after, and at 3 weeks and 6 months post-intervention.

**Results:** Immediately following the last session of the initial protocol of stimulation, the BDI score reduced from 25 to 7. However, the symptoms relapsed at 3 weeks post intervention to initial the BDI score of 25. There was no change in the BDI score immediately after follow-up with short interval periodic stimulations. Nonetheless, the BDI score improved to 18 at three weeks and later to 7 at six months post-intervention.

**Conclusions:** Series of periodic tDCS with short-intersession intervals may be more effective in inducing long-term mood improvement in patients with post-stroke depression.

**Key words:** Transcranial direct current stimulation, Post-stroke depression, Non-invasive brain stimulation, Major depression, Long-term potentiation

## INTRODUCTION

Stroke is a cerebrovascular accident that majorly presents with motor impairments as well as other non-motor affectations. Post-stroke depression (PSD) is one of the debilitating non motor sequel of stroke that causes cognitive deficits, poor recovery in activities of daily living, long hospitalizations and high mortality in about 40% of patients with acute stroke [1]. Pharmacological intervention for PSD have

often presents mixed findings [2] and also limited by contraindications, pharmacokinetic interactions and severe adverse effects, particularly in older individuals [3]. Thus, Non-invasive brain stimulation (NIBS) has emerged as an alternative or adjunct non pharmacological treatment.

Transcranial direct current stimulation (tDCS) is a cheap and safe technique of NIBS that involve the administration of a

relatively weak direct current from a battery powered stimulator through two electrodes, cathode and anode, to the brain [4]. Anodal stimulation enhances sub-threshold excitability, while cathodal stimulation suppresses it [5,6]. Anodal stimulation to the left dorsolateral prefrontal cortex (DLPFC) has been shown to improve depression symptoms in patients with major depression [7-11] and also in those with PSD [12-14]. tDCS is believed to exert its antidepressant effect by reversing the hypoactivity in the left DLPFC as observed in patients with depression [15]. However, the protocols of tDCS in most studies on major depression and PSD are either single session or periodical stimulations with an interval of 24 hours that would normally produce remission of symptoms that

lasts for few weeks. Additionally, most of those studies don't have adequate follow ups.

tDCS elicits long-lasting after effect depending on the protocol employed [16]. The long-term increase of excitability following tDCS was shown to be due to N-methyl-d-aspartate (NMDA) receptor dependent long-term potentiation (LTP) [17]. It occurs in two stages, early LTP (e-LTP) and late LTP (l-LTP). e-LTP is defined as increase in excitability lasting for about 1 hour as a result of  $Ca^{2+}$ /calmodulin-dependent kinases activation (CaMKs) [18], while l-LTP is the excitability enhancement lasting for more than 3 hours due to sustained activity of CaMKs and subsequent activation of transcription factors, gene expression and protein synthesis to accomplish

alteration of synaptic strength [19,20]. Number of stimulation sessions and the intervals between them are the two critical factors determining the elicitation of either of these types of LTP. In brain slices, whereas for induction of e-LTP a single stimulation session is sufficient, for l-LTP generation two or more stimulation sessions within a critical time window of about 30 minutes after the first stimulation are usually necessary [20]. Similarly, Monte-Silva et al. [21] induced l-LTP like excitability enhancements in the primary motor cortex of healthy subjects by giving two sessions of spaced tDCS with short interval of 3 or 20 minutes between them which was present for more than 24 hours after tDCS. In contrast, the after-effects were abolished when a wide interval of 3 or 24 hours was used.

We believed that, in order to elicit long-term remission of symptoms in patients with PSD and, probably major depression, spaced stimulations within the after effect period of each other (<30 minutes) should be given. Therefore, we present report of a patient with PSD who had long-term mood improvement upon receiving periodic tDCS sessions with short inter-sessions intervals following relapse of symptoms at 3 weeks after improvement due to periodic stimulations with wide inter-sessions intervals.

## **MATERIALS AND METHODS**

The research was conducted at the Physiotherapy department of Federal Medical Center, Nguru, Yobe State, Nigeria. The patient was treated as part of routine clinical practice which the local

ethical did not adjudge it necessary to grant approval. However, verbal informed consent was obtained from the patient to participate in the study and for the study to be disseminated.

### **Case presentation**

The patient was a 60 years old woman who presented to the accident and emergency unit of Federal Medical Center, Nguru, with complaint of recurrent weakness of the right side of the body, slurring of speech, blurring of vision and headache. A diagnosis of left hemispheric cerebrovascular accident was made and the patient was put on antihypertensives and referred to Physiotherapy department. On examinations, the patient presented with Brunnstrom Recovery Stage (BRS) of 4,4,5 on both right hand, upper limb, and lower limb.

She received treatment in the form of proprioceptive neuromuscular facilitation and task oriented training which yielded result as she started performing her basic and instrumental activities of daily living independently. However, 4 months post the diagnosis, the patient started complaining of recurrent episodes of spontaneous crying and anxiety. A Psychiatrist diagnosed her as having post-stroke depression using Mini-International Neuropsychiatry Interview for Diagnostic and Statistical Manual Fourth Edition, and Beck depression inventory (BDI) with a score of 25 (see Table 1 and Figure 3).

Insert Table 1 about here

Insert Figure 3 about here

### **Intervention**

The patient received anodal tDCS. The anode electrode

was placed on the left dorsolateral prefrontal cortex, while the cathode was placed on the contralateral supraorbital region. The site of the stimulation was determined using 10-20 international EEG system of electrode placement. She was first given periodic stimulation protocol with long inter-sessions intervals, consisting of 2mA stimulation for 20 minutes every working day for 2 weeks. BDI score was taken before the first session and immediately after the last session. There was remission of symptoms initially but had relapse at 3 weeks post intervention. She then received 7 stimulation sessions with short inter-sessions interval, consisting of 2mA stimulation for 13 minutes with interval of just 20 minutes between successive sessions (see Table 2). BDI score was taken before the

intervention, immediately after, and at 3 weeks and 6 months post intervention. Insert Table 2 about here

## RESULTS

The instrument used in this study was BDI which is a reliable scale [22] consisting of 21 questions with each one having four possible responses arranged in a likert scale of 0-3. The highest possible score is 63 showing extreme depression, and the least score is 0 suggesting normal score. The interpretation of the total score is as follows: 1-10 (Normal mood swinging), 11-16 (mild mood disturbance), 17-20 (borderline clinical depression), 21-30 (moderate depression), 31-40 (severe depression) and over 40 (extreme depression). Immediately following the last session of the long inter-session interval periodic stimulation, the BDI score

reduced from 25 to 7. However, the symptoms relapsed at 3 weeks post intervention to initial BDI score of 25 (see figure 1). There was no change in the BDI score immediately after follow-up with short-intersession periodic stimulations. Nonetheless, the BDI score improved to 18 at three weeks and later to 7 at six months post-intervention (See figure 2). Insert Figure 1 and 2 about here

## DISCUSSION

To date, there is no standard protocol of application of tDCS for the management of PSD and major depression. For the first time, this study has successfully reported the improvement of mood after several sessions of tDCS with short inter-session intervals delivered in the same day. Prior to that, the patient has received a

session of tDCS applied every working day for two weeks, with improvement that lasted for just three weeks. We believed that, series of tDCS given within the after-effect period of each other might have led to activation of gene transcription and protein synthesis that caused long-term synaptic strengthening at the left DLPFC [19] and thus, the long-term improvement of symptoms. This has been shown previously in a study by Monte-Silva et al. [21] on healthy subjects that two sessions of tDCS, with the second stimulation given not later than 30 minutes after the first, induced excitation change that lasted for more than 24 hours compared to when wide interval of 3 or 24 hours was used. Studies on learning and memory have already shown that low number of repetitions with short intervals in-between

them are better in the long-term memory formation compared to high number of repetitions with long intervals in-between them are better in the long-term memory formation [23-25].

All the seven sessions in this study were given in the same day, but there was no immediate improvement of symptoms after the last session. In fact, there were some residual symptoms even at 3 weeks post intervention. However, after that period, the symptoms improved significantly and remained in remission since then. This may be attributed to the fact that gene transcription does not occur immediately as it takes some hours to commence [20].

Furthermore, since LTP is the molecular mechanism behind learning and memory, the phenomenon that memory consolidation takes place during deep sleep

[26,27] might have contributed to the slow but progressive improvement of the symptoms. In contrast to the short-interval periodic tDCS, wide-interval stimulation resulted in immediate improvement after the last session but only lasted for three weeks. This may not be unrelated to the fact that widely spaced stimulation activates CaMKs through increase in post-synaptic calcium concentration [17, 28]. These enzymes maintains their activity through autophosphorylation for some time as the calcium gets depleted through the process of synaptic homeostasis [29] and thus, the short-term mood improvement following the tDCS.

## CONCLUSION

Series of periodic tDCS with short-intersession intervals may be more effective in inducing long-



term mood improvement in patients with depression. However, this study is just a report of a single case. More studies are needed, possibly, randomized controlled trials to further explore these findings. If confirmed, this protocol will totally eliminate the need for combining tDCS with antidepressants as State.

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Table 1. Patient Characteristics

Characteristics	
Gender	Female
Age	60
Side affected	Right
Time since stroke	4 months
Handedness	Right
Comorbidities	Hypertension, Depression
BDI Score	25

BDI=Beck Depression Index (score of 25 indicates moderate depression)

Table 2. Intervention

Intervention	Parameters	Frequency
Long interval periodic tDCS	2mA for 20 minutes	Every working day for 2 weeks
Short interval periodic tDCS	2mA for 13 minutes	Every twenty minutes, 7 repetitions

tDCS= Transcranial Direct Current Stimulation

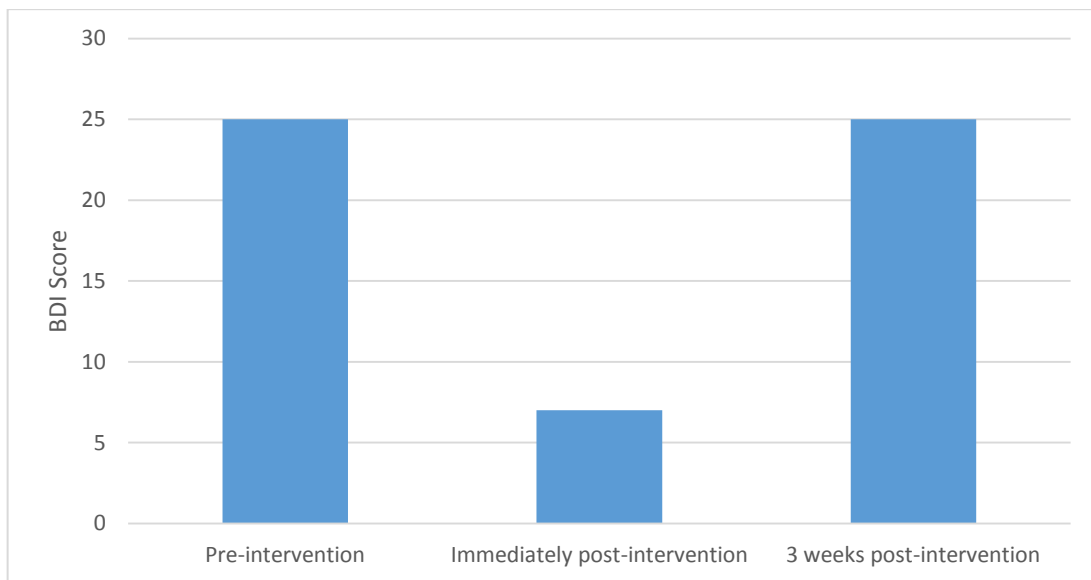


Figure 1. Bar graph of BDI score prior to and following long interval periodic tDCS

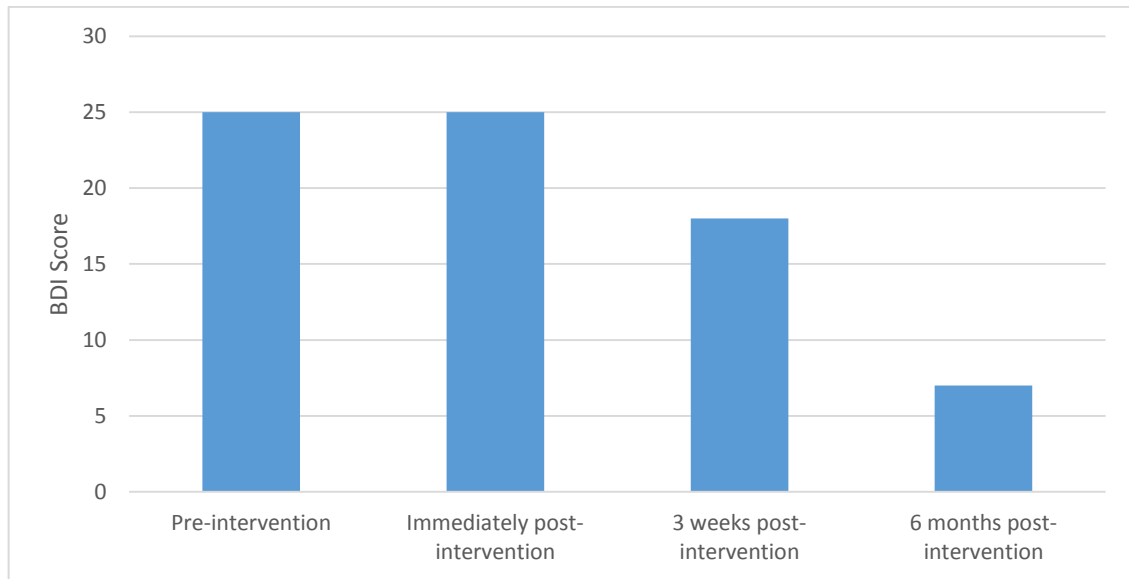


Figure 2. Bar graph of BDI score prior to and following short interval periodic tDCS

Short Interval Periodic Transcranial Direct Current Stimulations Induced Long-Term Remission of Symptoms in a Patient With Post-Stroke Depression

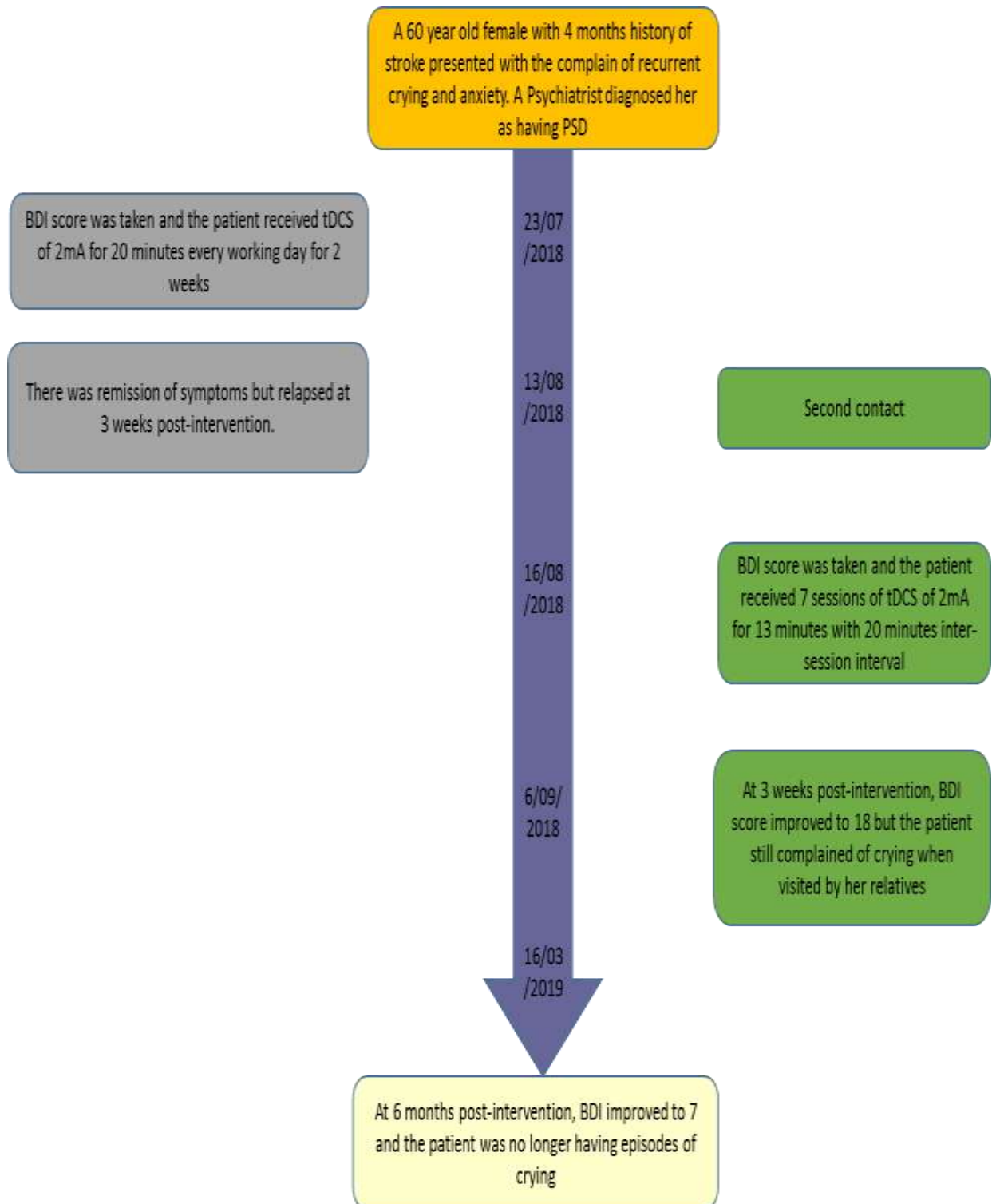


Figure 3. Experimental Flow Chart



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