Challenges in Recruitment for the Study of Noninvasive Brain Stimulation in Stroke: Lessons from Deep Brain Stimulation

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Objective: Noninvasive brain stimulation (NIBS) can augment functional recovery following stroke; however, the technique lacks regulatory approval. Low enrollment in NIBS clinical trials is a key roadblock. Here, we pursued evidence to support the prevailing opinion that enrollment in trials of NIBS is even lower than enrollment in trials of invasive, deep brain stimulation (DBS). *Methods:* We compared 2 clinical trials in stroke conducted within a single urban hospital system, one employing NIBS and the other using DBS, (1) to identify specific criteria that generate low enrollment rates for NIBS and (2) to devise strategies to increase recruitment with guidance from DBS. *Results:* Notably, we found that enrollment in the NIBS case study was 5 times lower (2.8%) than the DBS trial (14.5%) ($\chi^2 = 20.815$, $P < .0001$). Although the number of candidates who met the inclusion criteria was not different ($\chi^2 = .04$, $P < .841$), exclusion rates differed significantly between the 2 studies ($\chi^2 = 21.354$, $P < .0001$). Beyond lack of interest, higher exclusion rates in the NIBS study were largely due to exclusion criteria that were not present in the DBS study, including restrictions for recurrent strokes, seizures, and medications. *Conclusions:* Based on our findings, we conclude and suggest that by (1) establishing criteria specific to each NIBS modality, (2) adjusting exclusion criteria based on guidance from DBS, and (3) including patients with common contraindications based on a probability of risk, we may increase enrollment and hence significantly impact the feasibility and generalizability of NIBS paradigms,

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particularly in stroke. **Key Words:** tDCS—rehabilitation—TMS—DBS—clinical trial—patient recruitment.

Introduction

Noninvasive brain stimulation (NIBS) has become a popular method to augment plasticity expressed during recovery in patients with stroke.[1-4] NIBS is able to safely modulate such cortical plasticity through currents applied over targeted regions of the brain[5-7] and has been proven to be particularly advantageous for rehabilitation because it is relatively inexpensive and easy to administer.[8] However, despite decade-long investigations,[1,6,9-14] no NIBS modality is clinically approved for stroke rehabilitation.

A primary roadblock to clinical approval is the lack of demonstrated efficacy in pivotal large-scale phase III clinical trials. Understandably, a crucial reason for this is that evidence describing the efficacy of NIBS has been mixed, with reports citing inconsistent responses.[15-19] Further, while large-scale trials would be needed to generate class A or level I quality of evidence, currently, NIBS studies suffer from limited patient enrollment.[19,20] For example, in 2014, Anjos et al[21] reported that only 4.7% of screened patients were enrolled (enrollment rate) in their NIBS clinical trial for stroke rehabilitation. In addition, we have noted that, in general, percent enrollment in NIBS trials in stroke over the past decade has varied from 5% to 45% and the number of patients enrolled is typically between 5 and 50.[12,21-35] Thus, while large sample sizes would help account for inherent patient variability in stroke and allow for stratified patient subset analysis, to date, this has yet to be fully realized.

Given the reported challenge of patient recruitment for clinical trials in stroke,[36-39] it is not surprising that enrollment rates for the study of NIBS in stroke are alarmingly low. However, when compared to other invasive stimulation modalities, an even more surprising paradox is revealed. Specifically, enrollment for the study of NIBS in stroke is even lower than that across trials of invasive stimulation, such as deep brain stimulation (DBS) for movement disorders.[28,29,34,40] For example, current work suggests an average enrollment rate of 40%-91% for DBS trials with 70-200 patients per trial.[40-44] This difference between recruitment in stimulation modalities is staggering because NIBS is by definition nonsurgical, safer, and simpler than invasive stimulation and stroke is a more prevalent cause of disability. Therefore, besides concerns for approval, this paradox raises serious ethical concerns regarding the clinical utility of NIBS for stroke. In particular, given this paradox, we pose the question: are there possible reasons for poor enrollment for studies of NIBS in stroke in comparison to invasive modalities, such as DBS?

Aims

To address this question directly, here, our primary aim was to examine the paradox of patient enrollment and to answer whether NIBS is indeed more restrictive than DBS in the same neurological population of stroke. We also aimed to evaluate whether inclusion/exclusion criteria create lower enrollment rates for NIBS in comparison to DBS.

To address our aims, we chose to compare enrollment rates and rationale for patient exclusion between 2 clinical trials being conducted at the Cleveland Clinic: (1) a NIBS trial aimed at facilitating rehabilitative outcomes of the paretic upper limb and (2) a DBS trial for poststroke thalamic pain. We chose to compare only these 2 trials for several reasons. Our primary goal was to compare enrollment of NIBS to a DBS trial utilizing the same patient population of stroke, but we could not identify any active clinical trials using DBS to facilitate rehabilitative outcomes of the paretic upper limb in stroke (as indicated by clinicaltrials.gov). Second, institutional policies could affect recruitment rates; therefore, by utilizing ongoing, rather than retrospective, clinical trials at the same center, we aimed to ensure a comparable demographic pool and recruitment efforts.

By using such a unique comparison, we sought to address whether in trying to ensure safety we have become so restrictive that we limit the generalizability of NIBS in stroke. In a much broader sense, we aimed to learn strategies to recruit patients for testing the effects of NIBS with guidance from DBS.

Methods

Case Study 1: NIBS for Stroke Rehabilitation

The NIBS study involved a single-center, randomized pilot clinical trial design, where patients were assigned to receive transcranial direct current stimulation (tDCS) or sham tDCS. While tDCS was applied during rehabilitation of the paretic upper limb with the intent of augmenting therapeutic benefit, transcranial magnetic stimulation (TMS) was utilized for evaluating plasticity (NCT01539096). Details of this trial are provided in Plow et al.[17] This trial was chosen because it represents the most common indication for use of NIBS in stroke, affecting rehabilitative outcomes of the paretic upper limb. Inclusion and exclusion criteria were based on published recommendations for TMS,[45] tDCS,[18] and magnetic resonance imaging (MRI)[46] (Table 1).