Transcranial Direct Current Stimulation of the Motor Cortex in Essential Tremor: A Randomized Controlled Pilot Study

Principal investigator

Rechdi Ahdab, MD, PHD

Neurology Division, Lebanese American University Medical Center Risk Hospital, Beirut, Lebanon

Co-investigators

Naji Riachi, MD

Neurology Division, Lebanese American University Medical Center Risk Hospital, Beirut, Lebanon

Joumana Freiha, MD

Neurology Division, Lebanese American University Medical Center Risk Hospital, Beirut, Lebanon

Romy Zgheib, MD

Neurology Division, Lebanese American University Medical Center Risk Hospital, Beirut, Lebanon

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I. Introduction

Essential tremor (ET) is a common progressive neurological disorder and is the most common movement disorder. Worldwide , up to 5% of the population suffer from this disorder with an increased incidence with advanced age (Agarwal and Biagioni 2018). Although essential tremor is considered as a benign disorder, studies have shown that quality of life in patients with ET is affected. Patients reported that the tremor interfered with their activities of daily living (Louis and Machado 2015) , as well as, causing them anxiety and embarrassment (Chandran and Pal 2013).

The 2017 Movement society concusses statement includes the following criteria for the clinical diagnosis of essential tremor (Bhatia et al. 2018):

1. Isolated tremor syndrome of bilateral upper limb action tremor.
2. At least 3 years history of tremor.
3. With or without tremor in other locations (head, voice and lower limbs).
4. Absence of other neurological signs such as dystonia, ataxia and Parkinsonism.

The treatment possibilities currently available for patients with ET are scarce and were mostly discovered incidentally. The limitations of existing therapeutic options is partly attributable to the absence of an established clear-cut mechanism of ET seeing as neurotransmitter deficits, microscopic pathologies, and the genetic defects that cause ET have yet to be identified (Deuschl et al. 2011).

At present, patients with ET can be prescribed either pharmacological or non-pharmacological treatments. The options available have been approved for the treatment of ET; however it is important to note that many of the studies conducted to determine the efficacy of these remedies were based on small sample sizes and performed over a brief observation period (Schneider and Deuschl 2015).

1. **Pharmacological Treatment:** The medications available include Propranolol or Primidone as first line therapy as well as Benzodiazepines (Alprazolam), Topiramate or Gabapentin as second line treatments. The major downside to the available pharmacological remedies is that most of the patients may not tolerate the adverse events associated with these medications. Moreover , the available treatments have limited effectiveness and possess various contraindications that ultimately limit their use (Schneider and Deuschl 2015) (Hedera et al. 2013) (Zesiewicz et al. 2011).

2. **Non-pharmacological Treatment:** Surgical interventions are reserved for severe refractory cases of ET as they are rather invasive. Considering the predictable postoperative morbidity (Sadeghi and Ondo 2010) and major side effects experienced by patients limit their optimal use (Zesiewicz et al. 2013). These include Deep Brain Stimulation, Thalamotomy, Gamma Knife Thalamotomy and MRI-guided focused ultrasound. The adverse effects of these modalities may be unpredictable due to equipment malfunction and may include weakness, seizures, cognitive defects and others. (Zesiewicz et al. 2013)

The proposed mechanism that underlies ET, the central oscillating network, is mainly composed of the olivocerebellar system, thalamus and motor cortex (Raethjen and Deuschl 2012). The thalamocortical projections originates in the lower brainstem, passes through the thalamus and projects to the motor cortex. An interruption in the projections between the thalamus and the motor cortex limits the ability of the cortex to reorganize and restore ET (Chalah et al. 2015). In addition, unilateral subdural motor cortex stimulation was able to reduce contralateral hand tremor in two of the three studied patients with ET (Moro et al. 2011). Chalah et al described a case of 76 year old female with essential tremor that disappeared following a cortico-subcortical prerolandic stroke despite complete motor recovery (Chalah et al. 2015). These finding highlight the role of the motor cortex in ET production and possible therapeutic role of transcranial direct current stimulation.

Transcranial direct current stimulation (tDCS) has been used to treat a wide range of psychiatric and neurological disorders such as depression (Boggio et al. 2008), migraine (Antal et al. 2011), stroke (Schlaug et al. 2008) and Parkinson's disease (Benninger et al. 2010). tDCS is a type of non-invasive brain stimulation technique proven efficacious in modulating human cortical function by producing prolonged but reversible shifts in cortical excitability (Priori et al. 1998). This technique has the potential to be an ideal treatment option for essential tremor.

One of the most accepted effects of tDCS is its ability to modify neuronal membrane polarity depending on the polarity used (Nitsche and Paulus 2001). In other words, when the anode is placed over the motor cortical area, tDCS increases cortical excitability both during and following the stimulation. Whereas cathodal stimulation decreases cortical excitability. The

duration of tDCS effect depends on the duration and intensity of the stimulation (A. and W. 2000; Priori et al. 1998).
Most tDCS studies have adopted similar stimulation techniques. A pair of sponges (25-35cm^2) soaked in normal saline solution are placed over the stimulation site. The tDCS electrodes, made of metal or conductive rubber, are then wrapped in a perforated sponge pocket. Constant current of 1–2 mA is then delivered to the patient's scalp through anodal and cathodal electrodes with a ramp up and ramp down period of 30s at the start and end of the session (Zhao et al. 2017). Sham-controlled studies are easier with tDCS, because subjects rarely experience sensations related to the treatment. Ramping for 10 seconds at the beginning and end of tDCS, combined with a stimulation duration of 30 seconds in the sham condition, results in similar sensory experiences which make real tDCS and sham tDCS difficult to distinguish (Gandiga et al. 2006).

Importantly, tDCS has been shown to be safe in a number of trials (Brunoni et al. 2011). Worldwide, no major side effects have been reported in thousands of known human subjects (Nitsche et al. 2009). There is also individual data on patients who received over 100 sessions of tDCS for treatment of schizophrenia and depression that states that no adverse effects arose from cumulative exposure (Bikson et al. 2016). However, minor side effects such as sensation of itching under the electrodes, mild skin erythema and headaches have been reported but these are rarely disturbing and resolve after stimulation is halted (Brunoni et al. 2011).

Our primary goal is to evaluate the effects of cathodal tDCS of the motor cortex in essential tremor patients, particularly its effect on tremor amplitude, and quality of life. Should tDCS prove effective, this would be a breakthrough in the treatment of this condition, given its excellent safety profile, simplicity and affordability.

II. Study objectives

Primary objectives

The primary objective of the study is to assess the effect of cathodal tDCS stimulation of the motor cortex on tremor amplitude

Secondary objectives:

The secondary objectives are to:

- Assess change from baseline tremor on clinical rating scale
- Assess change in quality of life

III. Study outcomes

Primary outcome:

Change in tremor amplitude using an accelerometer pre and post cathodal tDCS of the motor cortex.

Secondary outcome:

Measure change in baseline tremor and effect on quality of life using the TETRAS scale

IV. Study methodology / design

Study design

A randomized, sham-controlled, double blind and crossover study.
It will be carried at LAUMC-RH, Beirut, Lebanon over the course of 2 years.

Study setting

Lebanese American University Medical Center Risk Hospital (LAUMC-RH), Beirut, Lebanon

Participants

We will recruit 40 Patients diagnosed with essential tremor based on the 2017 movement society criteria (Bhatia et al. 2018)

Inclusion Criteria	Exclusion Criteria
· Patients who fulfil the 2017 Movement society concusses statement criteria for essential tremor · Age 18 and above	· Isolated focal tremor (voice, head) · Orthostatic tremor with a frequency of more than 12 Hz · Task and position specific tremor · Sudden onset and stepwise deterioration of tremor · History of substance abuse or dependence in the past

	· Comorbid medical conditions and medications capable of producing or enhancing tremors · History of neurological disorders, brain tumors, brain surgery or abnormal neurological examination · Epileptic disorders · Cardiac pacemakers · Metallic hardware in the head or scalp (surgical clips) · Eczema or skin abrasion at the intended site of stimulation · Currently pregnant or plan for pregnancy in the next 6 months · Patients with prior experience with tDCS · Major psychosocial problems or medical problems rendering informed consent impossible

Study Population:

The minimum sample size required for the study was obtained using the Chow et al. method. A difference of 30% in the accelerometer score will be considered significant. The minimal sample size needed per sequence is 17, so a total of 36 samples. In order to account for any possible dropout from the study we plan to enroll a total of 40 participants for the study. They will be randomly assigned to either one of the two arms (cathodal tDCS versus sham tDCS) as per study methodology discussed below.

Recruitment and randomization

Patients who had visited or will visit LAUMC-RH with a diagnosis of ET on their records would be contacted and those interested in participating in the trial would be randomly assigned into either (1) cathodal tDCS or (2) sham tDCS.

One researcher who will not be blinded to group assignment will perform cathodal tDCS or sham tDCS. However, another researcher who will assess the outcome measures will be blinded to group assignment. The third blinded researcher will collect the demographic data

and assess adverse events. All participants will be blinded to the order in which the cathodal/sham conditions will be given.

V. Study procedure

Initial visit:

The first visit is an inclusion visit, where the examining physician takes a comprehensive history, performs a neurological exam, and verifies the inclusion/exclusion criteria. The physician will explain the protocol to the patient and provide him/her with information regarding the consent form, and the other questionnaires to be filled. The patient will be called within the following days to check if he/she agrees to participate in the research and therefore plan for the stimulation session.

tDCS sessions:

Prior to starting the first tDCS session, the patient will be asked to fill his/her first TRG essential tremor assessment (TETRAS) scale which includes an activity of daily living subscale and a performance subscale (Elble et al. 2012).

The physician will then quantitatively analyze the tremor on the most affected side using an accelerometer. Two measures are obtained with the accelerometer: the tremor frequency and amplitude. Sensors are fixed on the skin at a given landmark (index finger) (Grimaldi and Manto 2010). The tremor will be assessed in two different positions: (1) at rest and (2) postural.

Subsequently TMS of the motor cortex contralateral to the hand used above will be performed with a figure-of-eight coil (70 mm) on a Magstim machine. To determine the optimal site of stimulation (hotspot), the coil will be moved around the primary motor cortex (M1) eliciting the largest MEP motor-evoked potentials (MEPs) from the first dorsal interosseous (FDI) of the hand tested above.

Finally, cathodal tDCS will be administered through a pair of conductive rubber electrodes covered by saline soaked sponges (35 cm^2). The current will be delivered continuously at 2 mA for 30 min through a battery-driven constant-current stimulator. The cathode will be positioned on the area representing the primary motor cortex and the anode over the contralateral supraorbital area.

tDCS stimulation (cathodal and sham) will be done daily for 5 consecutive days during weeks 1 and 5. Each stimulation session will last 30 minutes. tDCS will be performed while the patient is at rest, without any concurrent cognitive or motor task. The two tDCS sessions will be separated by a 23 day washout period.

Post tDCS/Clinical evaluation

Patient will be asked to fill out their TETRAS at days 1 and 5 of each tDCS session (cathodal and sham), and days 12 and 19 after each tDCS session (cathodal and sham). Please refer to figure 1.

Accelerometer assessment of the tremor will be performed at days 1 and 5 of each tDCS stimulation session (cathodal and sham).

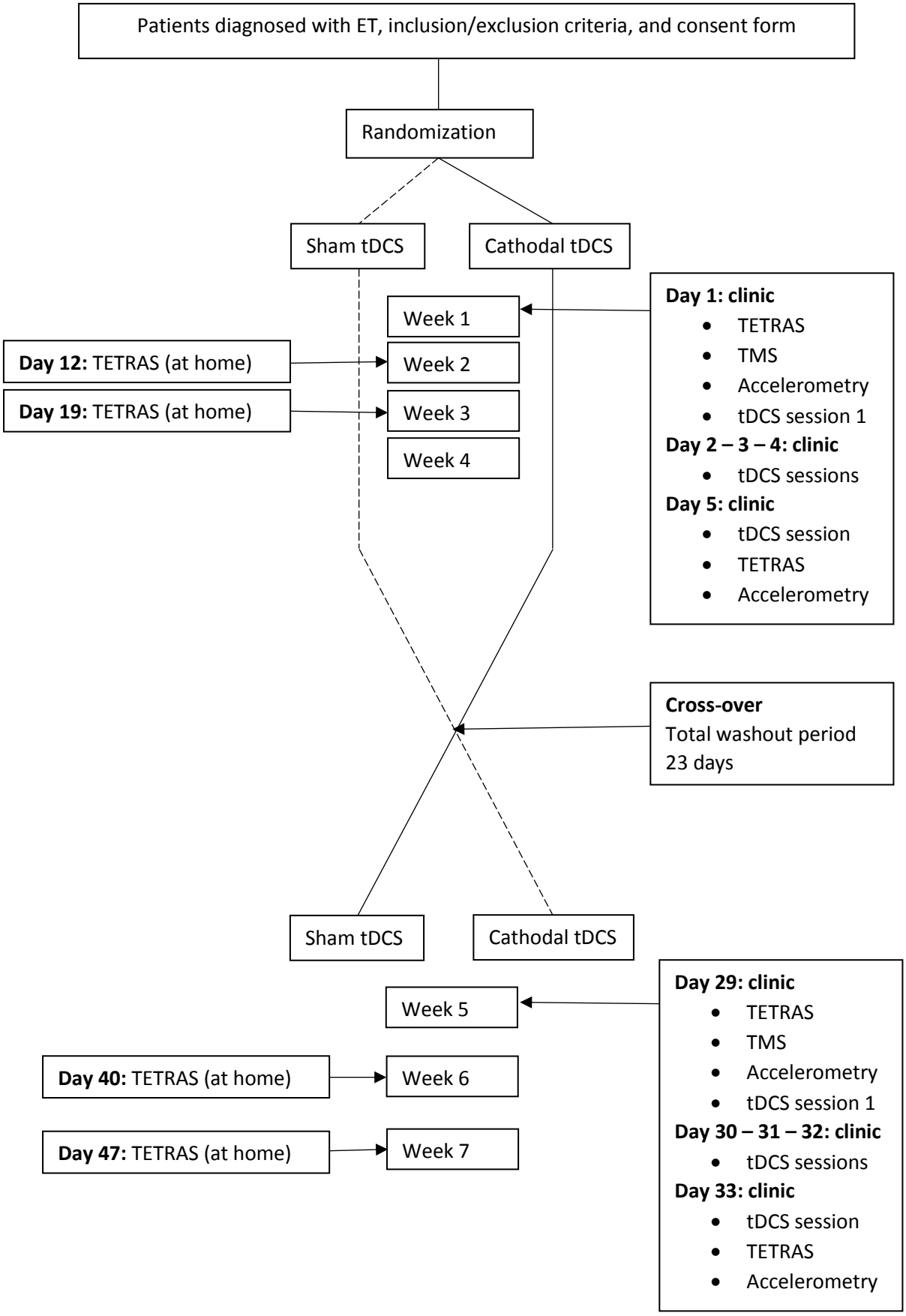

Figure 1: Study design and procedure

VI. Statistical Analysis

The analysis will be conducted using the R statistical package. Demographic data will be summarized using frequencies, means, standard deviations and confidence intervals. The change in the TETRAS and Accelerometer scores will be assessed using Wilcoxon paired test at different time points (illustrated in figure 1) and the correlation between thee TETRAS and Accelerometer scores will be tested using the Pearson method.

VII. Data Management

The study records will be kept as confidential as possible. We will protect carefully the information about the patient. What we learn from samples will be described only in a way that does not identify the patient. To protect the patients' privacy, samples will be linked to a secret code. Names will only be recorded on the informed consent form. We will keep the secret code in a locked and carefully protected file, with access only granted to the principal investigator of the study and authorized personnel. The records will be monitored and may be audited without violating confidentiality. Published data resulting from the study will not mention the names of the people who participated in this study. The data will be published in peer-reviewed journals. Following the study, the data will be safely stored and kept for quality assurance.

VIII. Adverse Event Reporting

The minor adverse events reported in association with use of tDCS (sensation of itching under the electrodes, mild skin erythema and headaches) will be provided the necessary short-term medical care by the investigator. They usually resolve spontaneously after stimulation is halted.

IX. Patients' withdrawal:

No available conditions in the study protocol can trigger the patient's withdrawal. However, the patient can withdraw consent, at any point during the study, without any consequences.

X. Quality assurance, monitoring & safety

No external committees will be overseeing the study. No interim analysis will be done. To prevent skin irritation, sponge electrodes will be soaked in saline water.

The investigator is responsible/in charge of recording and reporting all the adverse events and serious adverse events (SAEs) that might happen throughout the entire research protocol, from the time of taking consent, and throughout the whole period required to monitor the participants. SAEs will be recorded on a comprehensive form provided for this purpose. This form will be completed, printed, dated, signed, and the principal investigator will be promptly notified. Moreover, regardless of the time of onset following the protocol, all SAEs suspected to be the result of the research protocol should be reported to the investigator unless other reasonable explanation exists. All the other adverse events (AEs) will be reported only on the medical file of each patient, including the date of onset, characteristics, intensity, and duration, etiologies, taken actions, treatments, and resolutions if any. There are no specific safety measures related to this research and no important safety data to be collected.

XI. Dissemination of Results and Publication policy

The data will be published in peer-reviewed journals. If the results show a significant improvement in essential tremor patients, further studies will be designed to study the optimal maintenance tDCS dose and the long term effect of tDCS.

XII. References

- A., Nitsche M. and W., Paulus (2000), 'Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation', *The Journal of Physiology,* 527 (3), 633-39.
- Agarwal, S. and Biagioni, M. C. (2018), 'Tremor, Essential', *StatPearls* (Treasure Island (FL): StatPearls Publishing.
- Anonymous '90.(2007) OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, http://www.hhs.gov/ohrp/policy/advevntguid.html.'.
- Antal, A., et al. (2011), 'Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine', *Cephalalgia,* 31 (7), 820-8.
- Benninger, D. H., et al. (2010), 'Transcranial direct current stimulation for the treatment of Parkinson's disease', *J Neurol Neurosurg Psychiatry,* 81 (10), 1105-11.
- Bhatia, K. P., et al. (2018), 'Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society', 33 (1), 75-87.

- Bikson, M., et al. (2016), 'Safety of transcranial Direct Current Stimulation: Evidence Based Update 2016', *Brain Stimul,* 9 (5), 641-61.
- Blomstedt, P., et al. (2007), 'Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up', *Br J Neurosurg,* 21 (5), 504-9.
- Boggio, P. S., et al. (2008), 'A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression', *Int J Neuropsychopharmacol,* 11 (2), 249-54.
- Brunoni, A. R., et al. (2011), 'A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation', *Int J Neuropsychopharmacol,* 14 (8), 1133-45.
- Chalah, M. A., et al. (2015), 'Permanent reversal of essential tremor following a frontal lobe stroke', *J Neurol Sci,* 354 (1-2), 133-4.
- Chandran, V. and Pal, P. K. (2013), 'Quality of life and its determinants in essential tremor', *Parkinsonism Relat Disord,* 19 (1), 62-5.
- Deuschl, G., et al. (2011), 'Treatment of patients with essential tremor', *Lancet Neurol,* 10 (2), 148-61.
- Elaimy, A. L., et al. (2010), 'Gamma knife radiosurgery for movement disorders: a concise review of the literature', *World J Surg Oncol,* 8, 61.
- Elble, R., et al. (2012), 'Reliability of a new scale for essential tremor', *Mov Disord,* 27 (12), 1567-9.
- Gandiga, Prateek C, Hummel, Friedhelm C, and Cohen, Leonardo G (2006), 'Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation', *Clinical Neurophysiology,* 117 (4), 845-50.
- Gironell, A., et al. (1999), 'A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor', *Arch Neurol,* 56 (4), 475-80.
- Grimaldi, G. and Manto, M. (2010), 'Neurological Tremor: Sensors, Signal Processing and Emerging Applications', *Sensors (Basel),* 10 (2), 1399-422.
- Gunal, D. I., et al. (2000), 'New alternative agents in essential tremor therapy: double-blind placebo-controlled study of alprazolam and acetazolamide', *Neurol Sci,* 21 (5), 315-7.
- Hedera, P., Cibulčík, F., and Davis, T. L. (2013), 'Pharmacotherapy of Essential Tremor', *J Cent Nerv Syst Dis,* 5, 43-55.
- Louis, E. D. (2016), 'Treatment of Medically Refractory Essential Tremor', *N Engl J Med,* 375 (8), 792-3.
- Louis, E. D. and Machado, D. G. (2015), 'Tremor-Related Quality of Life: A Comparison of Essential Tremor vs. Parkinson's Disease Patients', *Parkinsonism Relat Disord,* 21 (7), 729-35.

- Moro, E., et al. (2011), 'Unilateral subdural motor cortex stimulation improves essential tremor but not Parkinson's disease', *Brain,* 134 (Pt 7), 2096-105.
- Nazzaro, J. M., Pahwa, R., and Lyons, K. E. (2012), 'Long-term benefits in quality of life after unilateral thalamic deep brain stimulation for essential tremor', *J Neurosurg,* 117 (1), 156-61.
- Nitsche, M. A. and Paulus, W. (2001), 'Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans', *Neurology,* 57 (10), 1899-901.
- Nitsche, M. A., et al. (2009), 'Treatment of depression with transcranial direct current stimulation (tDCS): a review', *Exp Neurol,* 219 (1), 14-9.
- Ondo, W., et al. (2000), 'Gabapentin for essential tremor: a multiple-dose, double-blind, placebo-controlled trial', *Mov Disord,* 15 (4), 678-82.
- Priori, A., et al. (1998), 'Polarization of the human motor cortex through the scalp', *Neuroreport,* 9 (10), 2257-60.
- Raethjen, Jan and Deuschl, Günther (2012), 'The oscillating central network of Essential tremor', *Clinical Neurophysiology,* 123 (1), 61-64.
- Sadeghi, R. and Ondo, W. G. (2010), 'Pharmacological management of essential tremor', *Drugs,* 70 (17), 2215-28.
- Schlaug, G., Renga, V., and Nair, D. (2008), 'Transcranial direct current stimulation in stroke recovery', *Arch Neurol,* 65 (12), 1571-6.
- Schneider, S. A. and Deuschl, G. (2015), 'Medical and surgical treatment of tremors', *Neurol Clin,* 33 (1), 57-75.
- Witjas, T., et al. (2016), 'Essential tremor: Update of therapeutic strategies (medical treatment and gamma knife thalamotomy)', *Rev Neurol (Paris),* 172 (8-9), 408-15.
- Zesiewicz, T. A., et al. (2013), 'Update on treatment of essential tremor', *Curr Treat Options Neurol,* 15 (4), 410-23.
- Zesiewicz, T. A., et al. (2011), 'Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology', *Neurology,* 77 (19), 1752-5.
- Zhao, H., et al. (2017), 'Modulation of Brain Activity with Noninvasive Transcranial Direct Current Stimulation (tDCS): Clinical Applications and Safety Concerns', *Front Psychol,* 8.