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## Transcranial Direct Current Stimulation and EEG Alpha power in elderly undergoing elective on-pump CABG: Design of a pilot exploratory proof-of-concept trial

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### Abstract:

**Background:** Cognitive decline is age-related, although some clinical situations and comorbidities may raise and worsen the condition. Transcranial Direct Current Stimulation (tDCS), a neuromodulation technique which uses low electrical currents, has previously been used to enhance cognition in healthy elderly. Previous studies point that tDCS raises neuroplasticity markers such as EEG-alpha power. Postoperative cognitive decline (POCD) is a common complication of on-pump coronary artery bypass graft (CABG) surgery, leading to increased postoperative morbidity and mortality. There is no effective treatment to avoid POCD and the tDCS, through raising EEG-Alpha power, may offer better preoperative patient conditions to lower POCD incidence. Once tDCS has never been used in this population before, this is a proof-of-concept design to determine if 10 sessions of tDCS treatment increase EEG-alpha power as compared to sham tDCS in elderly at risk of POCD undergoing elective CABG surgery.

**Methods:** The proposed study design describes a randomized, sham-controlled, double-blinded, single center trial. In total, 40 patients are to be equally divided in blocks of 4 patients and randomized with concealed allocation. Study arms: 1) anodal stimulation or 2) sham stimulation. The primary outcome is the mean EEG-alpha power (difference in tDCS group as compared to sham tDCS). The secondary outcomes include the measurements of cognitive performance before intervention, after intervention and postoperatively, as indexed by The Cambridge Neuropsychological Test Automated Battery (CANTAB) (higher score signals cognitive enhancement and lower score cognitive decline).

**Conclusion:** This study is a considerable step before a larger randomized double-blind clinical trial, which provides the information needed for clinical use. This design sheds light on the mechanisms underlying POCD related to EEG-Alpha power and establish the role of tDCS as a tool to enhance cognitive reserve

**Keywords:** Transcranial direct current stimulation (tDCS), cognitive aging, cognitive reserve, neuronal plasticity, alpha rhythm, coronary artery bypass, postoperative complications/prevention and control, neuropsychological tests.

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### INTRODUCTION

Cognitive decline is age-related, although some clinical situations and comorbidities may raise and worsen this condition. Older patients require more effort to accomplish tasks that were easier when they were younger mainly due to complex changes in functional

#### Abbreviations

CABG: Coronary Artery Bypass Graft  
CNS: Central Nervous System  
CANTAB: Cambridge Neuropsychological Test Automated Battery  
EEG: Electroencephalogram  
NIBS: Non-invasive brain stimulation  
POCD: Postoperative cognitive decline  
tDCS: transcranial Direct Current Stimulation

activation patterns on frontoparietal regions. Previous studies applied transcranial Direct Current Stimulation (tDCS) on healthy elderly producing improvement on frontoparietal networks engaged in working memory, combined with working memory training, benefiting from improved motor function, proper name recall and decision-making (Jones 2015, Martin 2014). Long lasting treatment benefits are observed after a month or even a year. The tDCS helped maintain practice gains over time and enhanced transfer task performance (Jones 2015).

Transcranial Electrical Stimulation (tDCS) is a type of Non-invasive Brain Stimulation (NIBS) (Brunoni 2011). tDCS is a portable, relatively affordable, safe and well tolerated device with transient few mild adverse effects such as headaches, itching sensation under electrode placement, and skin redness (Boggio 2008). Applying electrical current over specific brain regions can polarize cortical tissue, modifying neuronal excitability while shifting membrane resting potentials (Bindman 1964). Anodal electrical stimulation shifts neural membrane potentials toward greater depolarization, increasing neural firing rates, and hence increased cortical excitability (Ulam 2015). Thus, responsivity of the targeted brain regions to afferent input or efferent demand is modified (Boggio 2008).

Anodal tDCS above the postero-parietal cortex changes electrical activity on electroencephalogram (EEG), increasing alpha and beta power during and after stimulation (Mangia 2014), specially alpha (Spitoni 2013). The hypothesis from the data above indicates neuroplastic effects promoted by weak depolarization/hyperpolarization which enhances conductivity of connected neural networks (Keeser 2011) between interand intra-cerebral cortexes (Mangia 2014).

The role of alpha waves on cognition and working memory was discussed by Zaehle and Cols (2010). Upper frequency alpha amplitude is associated with inhibition of non-essential activity which may facilitate performance on the task (Bazanov 2014). Alpha power increases during early childhood and declines from 50 to 60 years, not due to age per se, but related to aging neurological disorders or cognitive impairments in any age. Experiments with electrical stimulation to artificially enhance alpha power also improved cognitive performance, thus the upregulation of neural oscillations might potentially reduce age- and disease-related performance deterioration (Zaehle 2010).

Elderly undergoing surgery are at risk of postoperative cognitive decline (POCD), a common condition which may affect cognitive complex abilities such as verbal learning, working memory, processing speed and attention shifting (Deiner 2009). Diagnosis of a

decline in performance has been detected in at least 30% of all patients over age 60 on discharge (Wang 2014). Previous studies using computer based psychometric tests such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) have diagnosed 52% of patients with POCD related to other surgical procedures (Tan 2015). CANTAB can test specific cognitive domains most affected in POCD, including memory and attention. The patient will get a score for the tasks accomplished, and a lower score after surgery compared with preoperative score concludes the diagnosis of POCD.

POCD is the most common significant neurological complication in cardiac surgery (Tan 2013). This impairment is transient in most of the cases but can persist over three months after surgery in about 10% of patients, or even lead to significant cognitive impairment in a few subjects after six years of follow up (Rundshagen 2014). POCD is related to higher mortality, earlier retirement and greater utilization of social financial assistance (Steinmetz 2009). Elderly subjected to risk factors such as coronary atherosclerosis, pre-existing subclinical dementia, alcohol abuse and low educational level are at higher risk of POCD (Rundshagen 2014).

Although underlying etiologic mechanisms are not understood as a whole, some hypotheses suggest possible brain injury caused by immune response, inflammatory activity, hypoxia, hypoperfusion, microvascular obstruction, anesthetic agents with toxic effects on the Central Nervous System (CNS), and even genetic polymorphisms (Rundshagen 2014). Patients with pathological cognitive aging and low cognitive reserve have a limited capacity to compensate for neurological insults and are more likely to develop dementia, thus the ability to enhance synaptic plasticity might be an important component in the pathophysiology of POCD (Whalley 2004).

Applying meticulous surgical and anesthesiological techniques and adopting neuroprotection methods to a clinical optimized patient can reduce the risk of POCD to a minimum (Rundshagen 2014). However, previous study applied a multimodal postoperative rehabilitation program, and despite intervention, the incidence of POCD reached 32%, with 18% of patients experiencing over 50% decline in Mini-mental scores (Bitsch 2006). After cardiac surgery, the incidence of POCD can reach as high as 80% (Wang 2014).

There is no effective treatment to avoid POCD and the tDCS, through raising EEG-Alpha power, may offer better preoperative patient conditions to lower POCD incidence. Therapeutic use of tDCS needs evidence for broad use in clinical field, thus special attention on

methodological issues is required in order to obtain valid results. (Brunoni 2011)

Considering that tDCS long-lasting effects might be related to synapse plasticity (Zahele 2010), and that tDCS can improve cognitive impairment in some populations (Salehinejad 2015), since there are no previous studies that use tDCS to enhance cognitive reserve in patients with high risk of POCD, the present study will be a pilot exploratory proof-of-concept trial, using a small sample size, focused on elucidating mechanisms, establishing safety for using tDCS on this specific population and maintaining internal validity.

## STUDY AIM

The main objective of this study is to assess whether the mean EEG-Alpha power in the tDCS group is higher than the sham group, signaling neuroplasticity. Secondary hypothesis evaluates the clinical effect of tDCS through task performance indexed by CANTAB as a tool to enhance cognitive function (higher score after intervention) to prevent POCD in elderly undergoing elective on-pump CABG (no significant change between pre- and postoperative score).

## METHODS

### Population

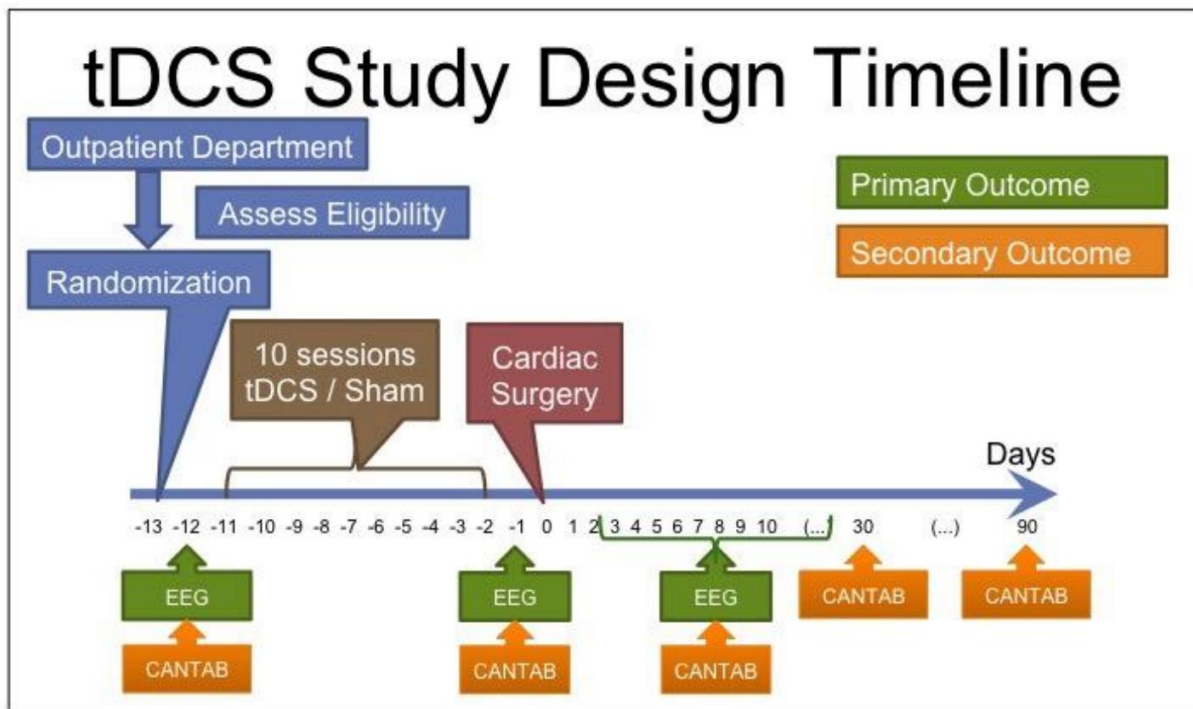
Inclusion criteria are patients over 70 years old, right handed in Edinburgh handedness test, with less than 8 years of schooling and undergoing at least two grafts elective on-pump CABG. On the other hand exclusion criteria are other neurological conditions, use of CNS medications, altered baseline EEG and contraindications for tDCS, as skin lesions or irritations on scalp. A sample of 40 subjects is selected during outpatient presurgical medical visit. After the CABG indication by the surgeon, study eligible patients are explained the risks of surgery and POCD, and are invited to be randomly assigned to undergo 10 sessions of tDCS treatment 15 days before surgery or the sham treatment. After obtaining informed consent, subjects are randomized using online computer generated sequences for block randomization of 4 patients, 1:1 ratio between active and control. The study doctor, patient, EEG technician, CANTAB technician, and tDCS technician are under blinding. Group allocation and randomly generated tDCS access codes are maintained in a password protected database to be revealed only in case of emergency.

## Intervention

Our stimulation protocols mirror those used by Park et al (2014) for enhancement of working memory and cognitive function in healthy subjects over 65 years old, following recommendations for good tDCS quality (Schestatsky 2013). All subjects are to undergo 10 sessions with same device independent of group assignment. The active group are to receive 2mA anodal stimulation for 20 minutes, with 5 x 7 cm<sup>2</sup> electrodes housed in saline-soaked sponges on the scalp over the dorsolateral prefrontal motor cortex. In the sham group, the same stimulation is applied for 30 seconds, ramping up and down at the beginning and end of stimulation to give the participant a physical sense of stimulation associated with current change (Jones 2015). Protocols are initiated through a custom device interface requiring a unique access code after which a confirmatory screen prompt appears indicating success. Each code-associated stimulation protocol are to be pre-programmed onto the device to ensure blinding. All patients are to undergo EEG before and after tDCS/sham sessions, as well as 48 to 72 hours after surgery or later, as soon as clinical conditions allow a complete evaluation. Initial EEG diagnoses preexisting neurological disease and establish baseline EEG-Alpha power. After the intervention, EEG-Alpha power is re-evaluated to measure the initial effect of tDCS. Postoperative EEG evaluation assesses permanence of initial effect. If postoperative patient evaluation identifies delirium the evaluation is postponed until better clinical conditions. Those whose postoperative clinical conditions does not allow EEG evaluation during hospitalization are excluded. Cognitive performance is appraised by a computer based psychometric test (Cambridge Neuropsychological Test Automated Battery or CANTAB) immediately after each EEG sessions as well as 30 and 90 days after surgery (Picture 1). The patient will be asked to accomplish some activities displayed on a touchscreen device, following voice instructions. The program will offer some tasks to evaluate memory by paired associates learning, graded naming test or verbal recognition memory. Attention can also be tested through reaction time, choice reaction time, simple reaction time and attention switching task. This test is validated in elderly and highly intuitive. Each test offers a score that can be compared along time and among the groups. A higher score after the intervention signalizes cognitive enhancement and a lower score after the surgery makes the diagnosis of postoperative cognitive decline (POCD).

## Data Analysis

A sample size of 40 patients is required, accounting for 20% dropouts, 80% power and alpha error of 0.05. Data



**Fig. 1.** The patient comes to the outpatient department for medical consultation when he/she is invited to participate, evaluated eligibility, obtained informed consent and included in the study. The patient is randomized to receive 10 sessions of tDCS or sham tDCS before cardiac surgery. The EEG is performed before sessions, after sessions and after surgery. Psychometric test (CANTAB) is applied before sessions, after sessions, after surgery in-hospital, 30 days and 90 days after surgery.

is evaluated using two-tailed tests, with a statistical significance level of 0.05. The EEG-Alpha power mean is evaluated as a continuous variable, after testing for normality, with unpaired t-test. If data shows a non-normal distribution, non-parametric tests (Mann Whitney) are considered. A steering committee monitors data and statistical analysis. Baseline score, age and educational level are confounders that must be adjusted during the analysis.

## DISCUSSION

The EEG waves are an important surrogate endpoint for the effects of tDCS according to previous studies (Schestatsky 2013). The EEG performed after surgery offers a new parameter for EEG-Alpha power, which has never been evaluated systematically in this population. The EEG is a method to evaluate the timing of neuronal activity more accurately. Although other methods such as functional magnetic resonance imaging (fMRI) can offer better spatial resolution (Schestatsky 2013) this method is not feasible in perioperative context. Furthermore, fMRI reflects how hard the brain works, while the EEG-Alpha power reflects how efficiently the brain works, evaluating effective cognition (Bazanov 2014). Ardolino et al. (2005) investigated EEG modifications after tDCS in healthy right-handed patients, applying tDCS 1.5 mA

during 10 minutes and performing EEG after 20 minutes. The mean alpha power was higher in the tDCS group as compared to sham. However, their study failed to reach statistical significance because it was underpowered which might suggest that their results were due to false negatives (Ardolino 2005). Spitoni et al. (2013) evaluated the effect of tDCS over spontaneous brain rhythms in 15 healthy subjects and observed that EEG-Alpha power was enhanced after anodal tDCS, which reinforces the EEG-Alpha power as a good marker of tDCS effect.

Previous studies evaluated cognitive decline by several instruments, such as questionnaires, or measuring the time to perform specific tasks, but these methods lack precision and are subject to low interrater reliability (Deiner 2009). Computer based neuropsychological tests display a precise and consistent way of measuring cognition in specific domains, with less chance of manipulation or examiner bias. Nevertheless, we cannot avoid the inherent ability of learning and the patient may improve the scores not only due to the intervention (Deiner 2009). Thus randomization and blinding are essential to confirm the effect of the tDCS treatment in cognitive enhancement. External generalizability is an inherent limitation of a pilot study. Given that, to the present time, there is limited evidence to support that tDCS increases neuroplasticity markers

(as EEG-Alpha waves) in this specific population (patients over 70 years old undergoing elective on-pump CABG with at least 2 grafts planned), the scope of this trial is to provide initial results which are essential to design further studies to determine effectiveness in a broader population.

## CONCLUSION

As the number of cardiac surgeries performed in the elderly increases, so does the impact of POCD. Efforts should be directed towards finding means of preventing this entity. tDCS has the potential to improve cognitive function, however no reliable markers of its efficacy have been found in this population. EEG-Alpha power represents an attractive surrogate endpoint for tDCS efficacy due to its ease of measurement, cost, and demonstrated correlation with cognitive performance. The proposed study sheds light on the mechanisms underlying POCD and evaluates the utility of EEG-Alpha power in this context. This represents a considerable step towards a larger randomized double blind clinical trial, which could establish the role of tDCS as a tool to prevent POCD in these patients.

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## Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest

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