**Utilizing Transcranial Direct Current Stimulation to Enhance Laparoscopic Technical Skills Training: A Randomized Controlled Trial**

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**IRB Summary**

1. **Title:** Utilizing Transcranial Direct Current Stimulation and Gaze Training to Enhance Laparoscopic Technical Skills Training

## 2. Purpose of the Study

To test the influences of transcranial direct current stimulation (tDCS) and gaze training (GT) on the acquisition of laparoscopic surgical skills. For this purpose, we will compare variants of tDCS and GT in experiments 1 and 2, respectively, and then compare the optimal variants from each of these in experiment 3 in a crossed design with a follow up test of retention. These questions will be evaluated using the validated Fundamentals of Laparoscopic Surgery (FLS) modules 1 and 5, with the overall goal of developing a surgical training curriculum that achieves expert level skill in an expedited timeframe. This research provides a novel approach to general surgery training that has the potential to reduce the amount of time and repetitions required to achieve expert laparoscopic skills.

## 3. Background & Significance:

Developing expert performance requires assessment of the thought processes underlying performance and continued refinement of skills in order to obtain automaticity and intuition. Therefore, developing expert surgical skill is a process likely to take longer than the length of residency, thereby diminishing the quality of care delivered to patients.

The proposed study will implement novel neuroscience techniques of transcranial direct current stimulation and gaze training to determine if they have the capacity to accelerate technical surgical skill learning in order to achieve competency and expertise in an earlier timeframe. tDCS is a non-invasive brain stimulation technique that delivers constant, low current stimulation via electrodes placed on the scalp to modify cortical excitability in an area of interest. When applied to the motor cortex, promising data indicates that tDCS-induced changes lead to expedited recovery in stroke patients as well as enhanced learning in healthy individuals.

Studies of skill performance have demonstrated that eye movement patterns can be optimized to improve subsequent motor movements. Therefore, gaze training encourages novices to adopt the more efficient gaze patterns of experts while performing a specific task such as laparoscopic surgery. These techniques have never been applied in the training of surgical residents making this project an innovative approach to enhance skill development.

**4.Design & Procedures**

**Experiment 1**: Determine if tDCS can accelerate the learning of laparoscopic skills.

In this experiment, we will compare behavioral learning curves from FLS modules 1 in three cohorts who undergo either active tDCS to the bilateral motor cortex (bilateral configuration), active tDCS to the supplementary motor cortex (SMA configuration), or sham tDCS (half in each configuration). This will be tested in groups of 20 participants who train on FLS module 1 for 40-minutes in 3 sessions that occur within 1-3 weeks. We hypothesize that both active bilateral and SMA tDCS will lead to faster skill acquisition as measured by trials required to gain proficient completion scores (calculated as time plus errors), relative to sham.

We hypothesize that both bilateral and vertex tDCS will lead to faster skill acquisition, with bilateral greater than vertex as measured by trials required to gain proficient module completion scores, relative to the group of participants who practice without active tDCS.

**Experiment 2**: Determine if gaze training can accelerate the learning of laparoscopic skills.

In this experiment we will first establish expert gaze patterns in the Fundamentals of Laparoscopic Surgery modules 1 and 5 by testing a total of 9 participants, including attending surgeons, senior residents, and novices trained to proficiency. We will then compare behavioral learning curves from non-expert participants without gaze training against those trained using both explicit (by reviewing the expert gaze pattern) and implicit gaze (by using a visual mask during the training, leading the participant to follow the expert gaze) derived from the expert gaze patterns. This will be tested in 3 groups of 20 participants, who train for 40-minutes in each of 6 sessions that occur within 3 weeks.

We hypothesize that both explicit and implicit gaze training will lead to faster skill acquisition with implicit greater than explicit. These training sessions will be measured by trials required to gain proficient module completion scores relative to the group of participants who practice without any gaze training.

**Experiment 3:** Compare tDCS and gaze training in a crossed design to evaluate learning and retention.

In this experiment, we will utilize the most effective active tDCS condition from experiment 1 and the most effective Gaze Training condition from experiment 2 in a crossed design to evaluate learning and retention. In this crossed design, four groups of 20 participants that receive either: active tDCS and gaze training, active tDCS with no gaze training, gaze training with sham tDCS, or just sham tDCS. In each case,

participants will partake in 3-6 sessions of 40-minutes over 1-3 weeks, training on FLS modules 1 and 5, and will also participate in a follow-up FLS assessment 4 to 6 weeks after the completion of training to evaluate the retention of trained skills. We hypothesize that applying tDCS and gaze training will result in additive improvement on learning curves, and will lead to greater retention of trained skills at the follow up assessment, compared to either condition alone or to the sham group.

## 5. Selection of Subjects

Inclusion/Exclusion criteria were chosen to allow us to meet our study aims while following safety protocols that have been well-defined in prior studies.

tDCS portion
Inclusion Criteria:
1) Age ≥18 years, healthy male and female
2) Negative urine pregnancy test for female participants
3) Willing and able to provide informed consent
4) Able to follow study procedures

Exclusion Criteria:
1) Indwelling metallic implants
2) Neurological or psychiatric medical history
3) Drug or alcohol abuse
4) Current or prior brain tumor
5) Current or prior seizures
6) Neuroactive medications
7) Current pregnancy
8) Damage, rash, or skin lesion in area of electrode placement
9) Blindness
10) Inability to read and/or understand English

Gaze training portion
Inclusion Criteria:
1) Age ≥18 years, healthy male and female
2) Willing and able to provide informed consent
3) Able to follow study procedures

Exclusion Criteria:
1) Blindness
2) Inability to read and/or understand English

## 6. Subject Recruitment and Compensation

We propose to enroll 249 healthy subjects consisting of Duke medical students, undergrads, surgical residents, and surgical attendings.  We anticipate that 40 of the recruited participants will not complete the protocol, with 209 completing the full study.  A sample size of 249 was carefully selected. This study includes three separate aims requiring new subjects for each due to the improvement in technical skill from repetition alone. Therefore, the same subjects cannot be utilized in the tDCS portion of the study as well as the gaze training or cross design study.

Prior tDCS studies have enrolled less than 20 subjects per group. For example, Reis et al 2009, which we are using as a model design, used 12 participants per group. Typical gaze training studies within surgery have had very small enrollment numbers of 5-10. Putting this together, we aimed for a cohort of 20 subjects for each intervention. The tDCS portion of the study evaluating bilateral stimulation, SMA stimulation, versus sham will require a total of 60 subjects with 20 in each study arm. As for gaze training, we need 9 subjects to help determine the expert gaze pattern. Again, 60 subjects will be required for 20 in each study arm when examining explicit, implicit, and sham gaze training. Both of these studies lead to our large cross design with four separate study arms. Therefore, a total of 80 subjects will be required for completion of Aim 3. Based on our prior experience with longitudinal designs, we accounted for attrition of about 40 subjects, resulting in a total study sample of 249.

These numbers are sufficient to obtain accurate pilot data in tDCS and gaze training in order to further direct our research going forward. The sample sizes utilized will be larger than most in published surgical education literature, which will emphasize our ability to complete thorough and novel research here at a large undergraduate and medical campus.

Participants will be recruited mostly via email to the Duke Undergraduate pre-health students and the Duke University School of Medicine general surgery interest group. Attending surgeons will also be invited to participate via email as well as in person through study staff. The Interdisciplinary Behavioral Research Center (IBRC) will also circulate the study to individuals registered in its databased, according to IBRC established standards, in order to access a wider array of potential novice participants. Participants will be enrolled once they sign the approved informed consent form, at which point they will complete a questionnaire evaluating inclusion and exclusion criteria and demographics. The Duke University campus includes this large pool of possible subjects which is optimal for recruiting participants with varying exposure to surgical technical skill.  Recruitment materials and the information covered by the questionnaire are provided in separate document.

Potential participants will be asked to come to the SEAL simulation lab, located on the 5th floor of the Mary Duke Biddle Trent Semans Center for Health Education.  Here, they will be provided a full description of the study, asked to read and sign the consent form, and undergo a qualifying interview. The reviewed information will be obtained from the subject via face-to-face interview and will be restricted to answers to questions intended to determine whether subjects meet entry criteria. All information obtained during this review will be handled confidentially. Subjects will participate voluntarily and will be compensated $15/hour (3 sessions in Aim 1) and $10/hour (6 sessions in Aim 2) for their time.

**7. Consent Process**

Section 14 question have been completed on the e-IRB submission form.

Written Informed Consent will be obtained from each subject prior to enrollment into the study.  Separate consent forms have been developed for tDCS, gaze training, and the identification of expert gaze pattern. A fourth consent will be developed later for the cross-design study in a way that will keep subjects blinded.  However, this will require outcomes from Experiments 1 and 2 above first.  All potential subjects will be informed as to the purpose of the study and the potential risks and benefits known, reasonably predicted, or expected.  Once a subject has been consented, the screening process will begin. Verification consists of a detailed interview with the participant to obtain a neurologic and psychiatric history of illness as well as surgical exposure and experience. The Investigator will retain the original copy of the Informed Consent Form signed by the patient, a duplicate will be provided to the patient. Only the consent form approved by the IRB will be used.

**8. Subject's Capacity to Give Legally Effective Consent**

Potential subjects who do not have the capacity to give legally effective consent will not be included in this study.

**9. Study Interventions**

9.1. Fundamentals of Laparoscopic Surgery procedure

To evaluate expert performance and the effectiveness of each training intervention, this study will utilize a portion of the Fundamental Laparoscopic Skills (FLS) curriculum. FLS is a curriculum that targets basic laparoscopic skills required for success in the variety of operations that are performed with the minimally invasive technique. The FLS curriculum has been validated as translatable to the operating room, and completion is required by The American Board of Surgery to be eligible for certification.  FLS consists of five pre-defined skill modules with timed assessments. The current study will utilize only FLS module 1 (module 1 for Aim 1, both modules for Aim 2 and Aim 3) which are performed on the standard laparoscopic box trainer. Based on the average times for completion as well as the average number of repetitions required to achieve proficiency, both of these skills are developed over a prolonged time period making them ideal training models for this study.

FLS module 1 is the Peg Transfer task in which two Maryland dissectors are used to move 6 objects from the subject's left side of the pegboard to the right and back.  The transfer between hands must be done in the air without assistance from the pegs.  Time penalties are incurred if the object is dropped outside the field of view.  Timing stops upon release of the last object.

In the current study pending the Aim, these two modules will be used as both the assessment benchmarks and as the training tasks. As illustrated in **Table 1**, each participant will perform four 20-minute training sessions on the tasks over one to three weeks while

receiving their group-specific augmentation. If the participant is in Experiment 3, an additional follow up session will be scheduled approximately 4-6 weeks after the end of the main training procedure to evaluate retention of learned skills.

| Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|---------|---------|---------|---------|---------|---------|
| 90 minutes | 60 minutes | 60 minutes | 60 minutes | 60 minutes | 60 minutes |
| Introduction<br>Screening<br>Consent<br>Videos<br>Acclimation<br>Pretest<br>Task A – 20min<br>Break 5 min<br>Task B – 20 min | Acclimation<br>Task A – 20min<br>Break 5 min<br>Task B – 20 min | Acclimation<br>Task A – 20min<br>Break 5 min<br>Task B – 20 min | Acclimation<br>Task A – 20min<br>Break 5 min<br>Task B – 20 min | Acclimation<br>Task A – 20min<br>Break 5 min<br>Task B – 20 min | Acclimation<br>Task A – 20min<br>Break 5 min<br>Task B – 20 min<br>Posttest |

**Table 1**: Experimental protocol and activities. Tasks A and B correspond to the FLS module 1, which will be counterbalanced over participants and sessions pending Aim. All 3-6 visits will occur within 1-3 weeks, again pending Aim. An additional follow up visit (not shown here) will occur at approximately 4-6 weeks for participants in Exp 3.

Prior to the start of FLS activities, each participant will begin by watching two videos demonstrating how to correctly complete FLS modules 1 and 5 (links below). After watching these videos, participants will be instructed by the experimenter on how to use the device and will have the opportunity to practice 2-4 trials to become familiar with the equipment before starting the experiments. In order to carry out quantitative assessment of the training interventions, video will be recorded directly from the box trainer video screen (showing only the tools and the FLS objects). This video will be coded to document the number of repetitions, completion times, and FLS scores for each task.

Data collected from these FLS modules will provide the core dependent variables in our analyses. This will include the number of repetitions and completion times for each of the tasks performed during the sessions. Progress through each of the training sessions and over multiple training sessions will be recorded in the form of behavioral learning curves. Completion times will be based upon official FLS scoring utilizing video coding for most accurate data.

FLS video modules:
https://www.youtube.com/watch?v=gAQPXHWqdXQ

9.2. Transcranial Direct Current Stimulation (tDCS) Procedure (Experiment 1)

Transcranial direct current stimulation is a noninvasive neuromodulatory technique that delivers constant, low-intensity, direct current to cortical areas via electrodes placed on the scalp. Over the past 10 years, numerous studies have shown that this approach can be used

to facilitate or inhibit spontaneous neuronal activity and there are a growing number of studies that have demonstrated tDCS can enhance motor learning in healthy individuals as well as speed recovery in clinical populations.  Further, the ease with which tDCS can be implemented and tolerated, paired with the lasting changes in cortical excitability it induces, gives this approach powerful potential to facilitate surgical skill learning.

Participants in this study will be randomly assigned to receive one of four tDCS conditions (2 electrode configurations, each with active or sham) administered using the Soterix 1x1 clinical trial device. All individual tDCS stimulations will take place in 20-minute blocks, with a 5-minute break between each block. Current will be delivered through saline-soaked sponges (3 cm x 5 cm) that will be re-wetted with saline when needed during the experiment and in the breaks between blocks to prevent skin irritation and increase impedance.

There will be two active tDCS conditions:

1. Bilateral configuration tDCS, with anode over the left motor cortex, and cathode over the right motor cortex, corresponding to C3 and C4 10-20 EEG sites, respectively;

2. Supplemental motor area (SMA) configuration tDCS, with anode over the SMA (3 cm anterior to the vertex), and cathode over midline prefrontal cortex (Fpz).

The two sham tDCS conditions will utilize the same two electrode configurations (50% of each across participants). In both active and sham conditions, the current will be initially increased in a ramp-like fashion over 30 seconds until reaching 2 mA. During the active conditions, the current will be maintained for 20 minutes, while in the sham condition it will be turned off after 30 s. This initial current ramp-up allows us to reproduce the perceived sensations on the skin (tingling, fade) induced by the active tDCS and thus, create an effective placebo condition.


9.3. Expert Gaze Tracking Procedure (Experiment 2a)

Gaze tracking is an approach by which movement of the pupils is measured to infer where people are looking.  In the current study this will be achieved by wearing the Mobile Eye head-mounted tracking system from Argus Science.  This wearable device tracks the pupil as well as the scene at 30 Hz.  This data is then analyzed via the ETAnalysis software on a connected laptop.  This software is able to produce discrete gaze points, gaze patterns, heat maps, and peek maps.  These patterns and maps can then be exported to a secure server and reproduced for viewing by study staff and subjects in particular for explicit training described below.

Gaze tracking will be initiated by recruiting a sample of 9 participants, including three attending surgeons, three surgical residents, and three novices in order to deduce the expert eye movement patterns specifically for FLS task 1.  Each of the three cohorts will train to proficiency on each of the tasks as defined by FLS guidelines (average of 48 seconds for task 1).  Participants will be allowed to practice as much as needed in order to achieve this level of proficiency.  However, they will not be asked to practice more than 10 hours.  We hypothesize

that attending surgeons and senior residents will achieve proficiency quickly while novices will require the average amount of repetitions to reach proficiency (57 repetitions on task 1). Once proficiency standards are met, each subject will undergo testing with gaze tracking.

Testing will take place in a 20-minute session in which they will complete the single FLS task repeatedly for 20-minutes. Gaze position will be calibrated using the Argus ET Mobile device before the gaze will be tracked for the duration of the active 20-minute session. This procedure will yield continuous information about the position of the pupils in relation to the scene in front of them for all repetitions completed.

Video recording of the performance will be coded as described above to collect number of repetitions, completion times, and FLS scores for each task. The subject, regardless of initial cohort, with the fastest time and best FLS score will be deemed the expert gaze pattern, and that pattern will be used in the following experiments to help train novices more efficiently.

## 9.4. Gaze Training Procedure (Experiment 2b)

Surgical novices will participate in the gaze training procedures. These individuals will be randomly assigned into implicit learning, explicit learning, or control training groups.

The *explicit training group* will review the expert gaze pattern videos for both FLS tasks with a member of the study staff. Together they will discuss where the expert gaze focuses throughout the tasks. The subject will then complete a 45-minute training session consisting of 20-minutes of FLS task 1, a 5-minute break, and 20-minutes of FLS task 5. The subject will complete as many repetitions of the task as time allows. Between training sessions, the study staff will process the subjects' gaze patterns from the prior session. The subject along with a member of the study team will review the expert gaze pattern as well as the subject's previous performance before starting each subsequent training session.

The *implicit training group* will complete the same regimen as described above. However, they will not receive explicit instructions on the expert gaze pattern. Instead, they will perform the FLS tasks with a contrast mask superimposed on the video screen. This mask will be derived from the expert gaze pattern obtained in Stage 1 and will consist of a moving opacity occlusion that allows for transparent viewing of 1-degree of visual angle around the fixation points, while masking the rest of the screen with an 80% contrast mask. The transparent area of interest will progress through the task until completed by the subject. Participants will complete as many repetitions as possible during 20-minutes of training on one of the tasks, followed by a 5-minute break, then another 20 minutes on the other task. Task order will be counterbalanced across participants and all 6 training sessions

The *control group* will perform the same tasks, 20-minutes each, without review of gaze pattern or implicit mapping.

All subjects will complete a total of six 60-minute training sessions over a 3-week period.

## 9.5. Combination of tDCS and GT (Experiment 3)

Experiment 3 will include the tDCS and GT approaches described above in a 2 by 2 crossed design with four cohorts: active tDCS and gaze training, active tDCS without gaze training, gaze training with sham tDCS or just sham tDCS. For each of the interventions, the most effective parameter will be chosen (implicit or explicit for gaze training, and bilateral or vertex tDCS), based on the results from the two previous experiments.

This protocol will unfold in the same manner, and under the same schedule as described for Experiments 1 and 2, except that participants will be exposed to different combinations of interventions and will be asked to return for a 4-6 week follow up visit in which they only perform the FLS modules without intervention (no tDCS or GT).

In regard to the interventions outlined here, Dr. Morgan Cox, the General Surgery Research Fellow in charge of all enrollment and participation, has all necessary training for tDCS and eye tracker technology to ensure these are used safely and administered according to proper procedures.

## 10. Risk/Benefit Assessment
There are no more than minimal medical or psychological risks associated with this research.
### 10.1. Gaze Training
There are no known significant adverse effects of gaze training. The only anticipated adverse event is the potential for discomfort from the wearable gaze tracking equipment. Participants will be asked to report any discomfort immediately to the study staff and proper steps will be taken to adjust or pad the headset with gauze to relieve discomfort.

### 10.2. tDCS
Since the development of tDCS in the 1960's, thousands of subjects have participated in studies and received tDCS without any substantial adverse effects. There has been no evidence of neuronal damage induced by tDCS: Nitsche and Paulus (2001) and Nitsche et al. (2003) found no elevation of neurone-specific enolase (sensitive marker of neuronal damage). McCreery et al. (1990) demonstrated that current densities below 25mA/cm$^2$ do not induce brain tissue damage even by applying high-frequency stimulation over several hours. In our protocol, we stimulate with a maximum current density of approximately 0.03 mA/cm$^2$, a thousand fold below this limit. Duration of stimulation is an additional factor contributing to potential tissue damage, which has been detected at a minimum total charge of 216 C/cm$^2$ (Yuen et al.,1981). This protocol exposes subjects to maximum total charges of 0.02 C/cm$^2$, which is far below the established safety threshold.

Within these parameter ranges tDCS has been shown to be a safe and tolerable minimally invasive technique. Nonetheless, commonly observed adverse effects of tDCS are skin irritation that may occur at the site of the tDCS electrodes, including reddening of the skin and itching under the electrode sites while the current is on. To minimize chemical reactions at

the electrode-skin interface, non-metallic, conductive rubber electrodes, covered completely with saline-soaked sponges will be used, as recommended by Nitsche and Paulus, 2000.

In order to reduce these minimal risks, the impedance of the tDCS system will be continuously monitored on a visible LED display throughout all training sessions.  In addition, the stimulator device has an automatic shut-off switch that shuts off current when impedances exceed the safety guidelines.

Electrode positioning with good skin contact will be ensured by the experimenter and the sponges will be re-wetted during breaks and as needed.

Our group has extensive experience administering tDCS, as well as other more invasive forms of neuromodulation.  These activities are described in Duke SOM IRB protocols; Pro00065334 "Using TMS to increase executive function in older adults", Pro00064107 "PAS in Healthy Subjects", and Pro00069059 "TMS_INS".

A member of the research team will be present at all times to monitor patient safety, and standard procedure will be followed whenever an adverse event is recorded.  Dr. Ranjan Sudan, General Surgery Vice-chair of Research and Director of SEAL, will be available as study doctor for the duration of this protocol.

## 10.3 Reproductive Risks

All female subjects of child-bearing age will undergo a urine pregnancy test.  If positive, that individual will be excluded from the study.

## 10.4 Benefits

Subjects have the ability to benefit from participating in this study due the exposure to laparoscopic surgical skills and the FLS curriculum.  They will gain repetitions on FLS tasks that are required to be board certified in surgery.  Pending the subjects' career goals, this could have a positive impact on their future.

## 11. Costs to the Subject

There will be no charge to subjects for any of the tests, procedures, or professional services related to this study.

## 12. Data Analysis & Statistical Considerations

Members of the research team including Drs. Appelbaum, Cox and Beynel will perform data analysis.  Statistical tests will be performed to evaluate learning attributable to the active tDCS and gaze training interventions.  Dependent variables in these analyses will be completion times and error rates in the FLS task drills.  These performance measures will be tested using a combination of analysis of covariance and growth curve modeling. In all cases, active interventions (e.g. bilateral or SMA tDCS) will be compared to matched control

conditions (e.g. sham tDCS) to provide a principled reference to evaluate selective learning resulting from the interventions.  Moderator variables such as testing schedule, age, and gender will be considered.

## 13. Data & Safety Monitoring

The subjects will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The subject's wellbeing will be continuously monitored by the experimenter, and the Principal Investigator will report all serious adverse events in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's standard operating procedures.

The study monitor will be the PI, Dr. Greg Appelbaum. Dr. Appelbaum will ensure the quality of the study and establish that all operations are complying with the investigational plan and IRB regulations. In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), and all reportable AEs will be submitted per the DUHS IRB policies. Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators and a single facility in which the study is being conducted.

Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, that accurate, complete, and current records are maintained, that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol, investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. He will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met.


## 14. Privacy, Data Storage & Confidentiality

Section 12 of the e-IRB submission form has been completed.