Frontal and Parietal Contributions to Proprioception and Motor Skill Learning

NCT05739994

Study Protocol

June 1, 2023

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Support Provided by:
National Institute of Neurological Disorders and Stroke (NINDS)

1.0 Background & Rationale

Motor learning is defined as the process that occurs in the brain aimed at developing new movements with practice until they can be performed automatically (Schimdt & Wrisberg 2008). Motor skill improvement is best noted by a change in the speed-accuracy function, meaning execution of motor patterns occurring more accurately at different speed ranges (Kantak et al., 2017; Reis et al., 2009). Learning motor skills necessitates the interaction of several high-level cognitive processes with low-level sensorimotor mechanisms (Krakauer & Mazzoni, 2011). A complex neuroanatomical architecture supports the learning and retention of motor skills, which includes increased activation in the frontoparietal cortices like dorsolateral prefrontal cortex (DLPFC), primary motor cortex, and posterior parietal cortex (PPC), and subcortical structures like the cerebellum and basal ganglia, which show increased activation during the later stage of short-term motor learning (Floyer-Lea & Matthews, 2005; Halsband & Lange, 2006).

Motor skill learning involves not only changes in the motor system, but also depends on sensory systems. One of the sensory modalities critically important for motor skill is position sense or proprioception. It is the ability of an individual to integrate sensory inputs from the muscles and joints to determine the positions and movements of body segments in space (Han et al., 2016). The proprioceptive information about the hand's position is taken into consideration by the motor system as feedback which is required for smooth and skilled movement execution (Bossom, 1974; Jeannerod, 1988). Many studies have shown that an enhancement in proprioception results in improvements in motor learning/decline in motor deficits or vice versa, although the neural basis of such interactions is unclear. In addition to acting as an interface between the sensory and motor cortex, posterior parietal cortex (PPC) is thought to play a role in processing higher-level proprioceptive information (Amaral, 2013). Stroke research has revealed the critical involvement of PPC, specifically supramarginal gyrus (SMG) in processing the sense of position (Findlater et al., 2016). A study by Ben-Shabat et al., 2015, found a key role of SMG in proprioception. They suggested that in patients with stroke, decrease in proprioception might be associated with decrease in right SMG function which might be due to SMG's role in motor control and spatial processing (Ben-Shabat et al., 2015). However, it is unclear how SMG modulates proprioceptive functioning to affect motor skill learning.

Research has also found an indirect connection between DLPFC and proprioception. Stagg et al., (2013) applied anodal tDCS over left DLPFC and found an enhanced functional connectivity between sensorimotor cortex and DLPFC. They further suggested that the enhanced activity in the DLPFC might be linked to enhanced proprioception. Beck et al., (2019) also found an increased activity in the sensorimotor cortex possibly through the fronto-striato-thalamic pathways after applying anodal tDCS over DLPFC suggesting that DLPFC might be involved in enhancing proprioception in healthy individuals. They proposed that DLPFC can be used as a potential target in neurorehabilitation in patients with motor deficits (Beck et al., 2019).

The sensorimotor network associated with proprioception and motor skill learning is not fully understood, and the functional role of activity in high-level areas such as DLPFC and SMG is particularly unclear. With greater knowledge of these processes in the healthy brain, it may one day be possible to develop rehabilitation strategies that target a patient's unique mix of sensory and motor deficits.

2.0 Objective(s)

The aim of the present study is to test role of activity in SMG and DLPFC in proprioception and motor skill learning. A robust way to identify whether a brain region plays a role in a behavior is to temporarily modulate its excitability in healthy people using non-invasive brain stimulation

(Cohen et al., 1997; Reis et al., 2008). This is commonly done in research with a short sequence of low-intensity transcranial magnetic stimulation (TMS), also known as repetitive TMS (rTMS). A small, temporary reduction in cortical excitability can be achieved through continuous theta burst stimulation (cTBS), a low intensity patterned form of rTMS that is delivered over 40 seconds, with excitability effects lasting up to an hour (Huang et al., 2005). rTMS is used clinically to treat conditions such as depression and is considered very low risk provided the generally accepted screening criteria are met. In the research setting, this technique is widely used not only in healthy adults (as in this study) but also in children and people with concussion, stroke, Parkinson's disease, and more (Rossi et al. 2021).

In separate groups of subjects, we will use a 40-second sequence of rTMS called continuous theta burst stimulation (cTBS) over SMG, DLPFC, or sham (control), before the subject performs tasks known to involve proprioception and either a short or longer sequence of motor skill learning (a maze tracing task). If cTBS over SMG or DLPFC has an impact on task performance for that group (in comparison to the sham, or control group), it suggests activity in that brain region is important for the affected aspect of task performance.

This project has two objectives:

- Objective 1. To explore the role of DLPFC and SMG in proprioception.
- Objective 2. To assess the role of DLPFC and SMG on motor skill learning and proprioceptive changes at two different time scales.

Because cTBS is intended to be disruptive, it is possible that the sham group will have the best performance in one or more outcome measures. It is also possible that some aspects of performance will be better in the SMG or DLPFC group due to complexities of the neural networks supporting these behaviors. However, it is not the goal of the study to determine which intervention yields the “best” task performance, it is simply to determine the details of how the DLPFC and SMG groups differ from each other and from the sham group.

3.0 Outcome Measures/Endpoints

Outcome measures will be assessed during the main (experimental) session, which takes place on a single day. Proprioceptive outcome measures will be assessed 3 times, and motor outcome measures 4 times, on this day (Fig. 1).

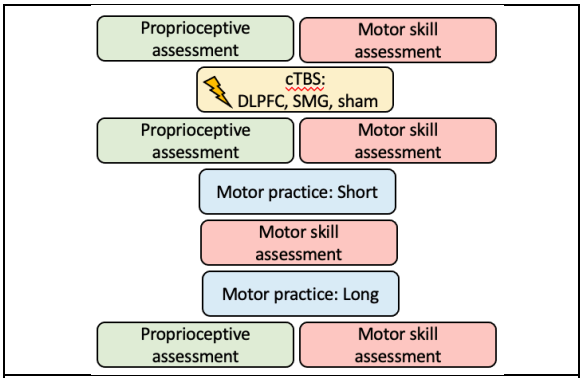


Fig. 1. Session design of the main (experimental) session, which takes place on a single day. Proprioception and motor skill will be assessed at multiple time points.

Outcome Measure 1: Proprioception. This will be quantified from a psychometric function, based on a sequence of trials in which the participant estimates their hand position. From the psychometric function we will extract proprioceptive bias (50% point) and sensitivity (distance between 25% and 75% points on the function).

Outcome Measure 2: Motor skill. This will be quantified from the speed-accuracy function, based on the person’s in-track accuracy when tracing the maze at three different speeds. Shifts in the speed accuracy function (better accuracy at any of the movement speeds) indicates motor skill learning.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Between the ages of 18-45 years old. Aging has been shown to affect the morphology of sensory and motor nerves, conduction velocities of nerves, and number of motor neurons in the spinal cord; to avoid these confounding factors we will only examine younger-to middle-aged adults.
- Right-handed. There are differences in cortical function and corticospinal projections such that testing the right arm of a right-handed individual is not necessarily equivalent to testing the left arm of a left-handed individual. To eliminate this confound, we will only test right-handed individuals.
- Covid has been found to have neurological effects in some people, but mostly the effects on sensorimotor control and neurophysiology are unknown. We will only include individuals who report being free of Covid symptoms in week preceding testing.

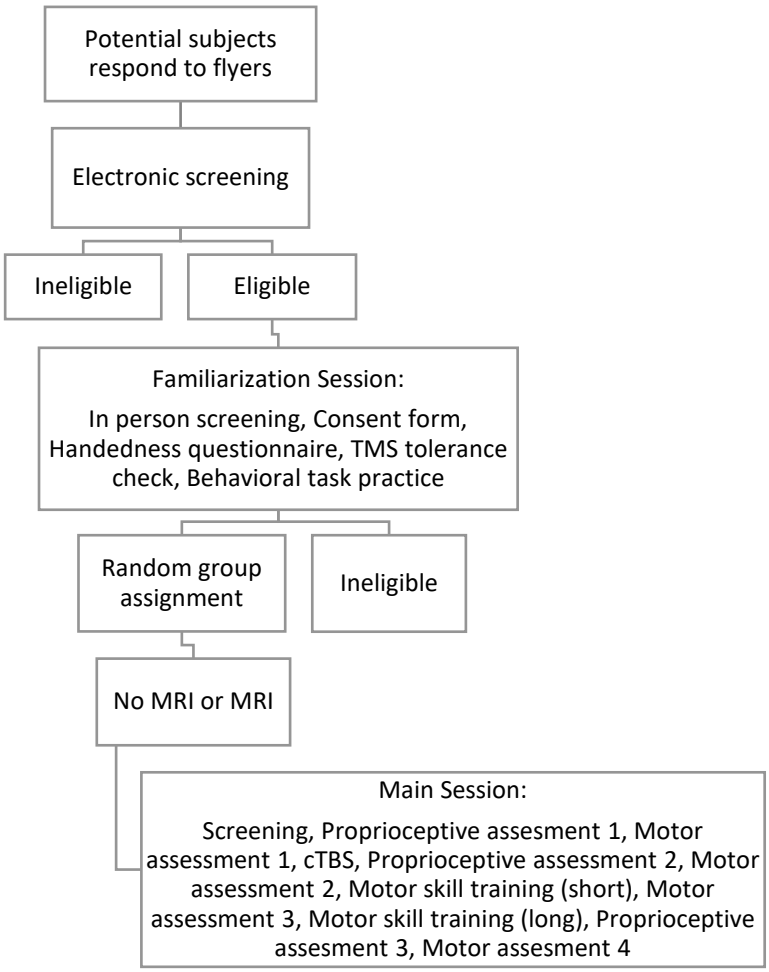
4.2 Exclusion Criteria

- Any past or present history of neurological disorders, heart or respiratory disease, hypertension, brain injury, spinal cord surgery, or metal implants in the head.
- Orthopedic or pain conditions.
- Pregnant or think they might be pregnant.
- Lack of normal vision or corrected-to-normal vision with contacts or glasses.
- Subjects will also be excluded if they currently suffer from frequent severe headaches, glaucoma, heart or respiratory disease, hypertension, psychiatric conditions, or learning or attention conditions.
- They will also be excluded for current or past: visual, hearing, or balance impairments; stroke, seizure/epilepsy (including family history), or severe head trauma; fainting; or diabetes.
- Subjects will be excluded for metal implants in the head other than titanium; cochlear implants; implanted neurostimulator; cardiac pacemaker; intracardiac lines; or a medication infusion device.
- Because TMS does not penetrate deeply into the head, we cannot test subjects whose hair does not permit contact between the TMS coil and the scalp. We will therefore exclude subjects with dreadlocks, weaves, or hair extensions.
- To protect the data from extraneous peripheral influences, we will also exclude subjects who have had serious injury to the bones, joints, or muscles of either hand or arm, and have not fully recovered. For the purpose of this study, "fully recovered" means they no longer notice any pain, weakness, or loss of sensation in the injured area, and have no mobility limitations.
- Taking medications or drugs that are known to affect cortical excitability and possibly seizure risk in an rTMS study. These medications/drugs are (Rossi et al., 2009): imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocaine, (MDMA, ecstasy), phencyclidine (PCP, angel's dust), ketamine, gamma-hydroxybutyrate (GHB), theophylline, mianserin, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, reboxetine, venlafaxine, duloxetine, bupropion, mirtazapine, fluphenazine, pimozide, haloperidol, olanzapine, quetiapine, aripiprazole, ziprasidone, risperidone, chloroquine, mefloquine, imipenem, penicillin, ampicillin, cephalosporins, metronidazole, isoniazid,

levofloxacin, cyclosporin, chlorambucil, vincristine, methotrexate, cytosine arabinoside, BCNU, lithium, anticholinergics, antihistamines, sympathomimetics.

- Claustrophobic, or are unable to remain still for long periods of time; or use an intra-uterine device (IUD) who's MR compatibility has not been established.
- People who have a BMI over 30 will be excluded as it may be uncomfortable or impossible to lay in the MRI scanner.
- Potential subjects will be invited to reschedule if they would otherwise be eligible (according to the initial screening), but the day of testing have drunk more than 3 units of alcohol or taken other recreational drugs in the 24 hour period prior to testing; have had more than 3 cups of coffee in the last hour; are sleep deprived (<4 hours sleep the previous night); or have participated in another brain stimulation experiment the same day.
- In addition, we will invite subjects to reschedule if they have any of the common Covid symptoms within the last week.
- After giving their consent, participants may be excluded during or after the familiarization session if they are unable to perform the reaching task or follow instructions, or if their TMS stimulation parameters cannot be reliably determined by the experimenter, or if TMS is not well tolerated.

5.0 Study Design



6.0 Enrollment/Randomization

Potential subjects will initiate contact with the research staff in response to the recruitment flyers. The subject will be given information about what the experiment entails and will be asked questions to make sure they meet the inclusion/exclusion criteria. If they are interested in participating and meet the inclusion/exclusion criteria, then they will be scheduled for their first session (familiarization session) which will take place in the Sensorimotor Neurophysiology Laboratory, 1025 E. 7th St., PH 079, Bloomington IN, 47405.

At the familiarization session, before any experimental procedures occur, a research team member will explain the procedures in more detail and go through the consent form with the subject. The subject will then have the opportunity to ask any questions and read the informed consent before signing. After the familiarization session, if the subject was not bothered by TMS and wants to continue, random group assignment will occur, following a block randomization table. There will be 3 groups that differ in cTBS intervention and amount of motor skill practice. Subjects will have a 67% chance of receiving cTBS, and a 33% chance of receiving sham cTBS (details below).

7.0 Study Procedures

All procedures are conducted for research purposes only. The study will be comprised of a familiarization session, an anatomical MRI brain scan session (except for those assigned to a sham group) and one experimental session. Subjects will be offered the option to combine their familiarization session and MRI scan or MRI scan and experimental session in the same day for a total of 2 lab visits or on separate days for a total of 3 lab visits. (Table 1). All study procedures will take place in the Sensorimotor Neurophysiology Lab, SPH 079 and the MRI scan will take place in the Imaging Research Facility in the Psychology building.

Table 1. Study structure. TMS = transcranial magnetic stimulation, cTBS = continuous theta burst stimulation, MRI = Magnetic Resonance Imaging. TMS is applied over motor cortex. cTBS is applied over DLPFC or SMG.

Session	Procedures	Proceed to next session if…
Familiarization	TMS, motor skill task, proprioception assessment	Subject comfortable with TMS, can follow task instructions, and wants to continue
MRI anatomical scan	Anatomical scan of the brain – dependent on group assignment	Subject wants to continue
Main Session	TMS, cTBS, proprioception and motor skill assessments, motor skill practice.	End of experiment

The familiarization session involves transcranial magnetic stimulation (TMS) over the motor cortex, a motor skill task that involves a series of tracing movements with the right arm, and a position sense task that involves a series of judgements about the location of their right-hand position. First, subjects will fill out a TMS screening form. Upon confirming eligibility, subjects will sit in a comfortable chair while a non-invasive brain stimulation device (the TMS coil) is held over their head. We will deliver brief magnetic stimuli over the motor cortex that evoke a small twitch in their hand muscles. Subjects will wear a pair of goggles that enable accurate positioning of the TMS coil relative to the

head (Brainsight Neuronavigation system) and have stick-on sensors on their hand to measure their muscle activity upon stimulation. This will take approximately 20 minutes.

For the motor skill task and the position sense task, they will sit in a comfortable chair and view the task display in a mirror while grasping a robotic manipulandum handle (BKIN) in their right hand (Fig. 2). During the motor skill task, they will guide a cursor representing hand position through the displayed maze. The hand feedback will be given using a visual cursor (10 mm diameter white circle). This design is similar to Mirdamadi and Block (2020) with six straight line segments connected in abrupt corners (Fig. 2, left). Subjects will move the cursor into a red square at the start of the trial. The square will turn green after 1s, and the maze track will appear with another green square at the end it. The participants will be instructed to reach the second target at the end of the track by moving the white cursor within the track as accurately as possible. The trial ends when the cursor enters the second target at the end of the maze. Feedback will be given about their movement time (too fast, too slow, good speed) and accuracy with points. The desired speed range will change during the speed-accuracy tradeoff assessment. The maze will be performed over three movement times (MT) ranges to assess the speed-accuracy tradeoff in three blocks of trials (MT 1:-600 – 850 ms; MT 2: 850 – 1100 ms; MT 3: 1100 – 1400 ms). 10 trials will be performed in each MT range and the block order will be randomized. The maze tracing will be standardized meaning the same maze will be used for all the trials between subjects.

During the position sense task, the participant's hand will be passively moved by the robotic manipulandum to two different positions. Participants will be asked to report whether the second position is closer to their body than the first position. An adaptive staircase algorithm is used to determine the test positions with a 0.5 cm step size. There will be 82 trials in total each time and the test will be standardized across participants.

The motor skill and position sense assessments will take approximately 30 minutes. If subjects are comfortable with all procedures and can follow task instructions, they will be assigned to a group. This group assignment will decide whether they need an anatomical brain scan.

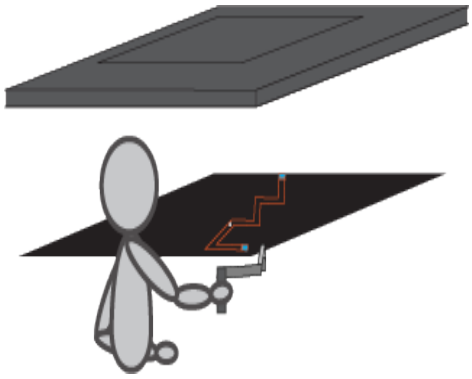


Figure 2. Setup for behavioral procedures. Participant holds handle of robotic manipulandum with right hand and makes arm movements to targets presented in visual display (motor skill task) or judges where handle is moved in relation to a target (position sense task).

The MRI scan of the brain, if needed, will involve a 20-minute visit to the IU Imaging Research Facility (IRF) at 1101 E 10th St, Bloomington IN (PY 159). The participant will complete a safety screening questionnaire. Then they will be asked to lay in the scanner bed and remain still for the scan, which takes 6 minutes.

The main session will take about two hours. The subjects' MRI scans will be uploaded in the Brainsight neuronavigation system in the lab (Rogue Research), which will be used for accurate positioning of the TMS coil for cTBS delivery. MRI-guided TMS is widely used in the field for targeting brain structures outside of primary motor cortex with TMS (Caulfield et al.,2022; Nieminen et al., 2022). The main session includes all the same elements as the familiarization session (TMS, proprioceptive assessment, motor skill task), plus cTBS. After the first motor skill assessment and proprioception assessment (Fig. 1), we will deliver single pulses of magnetic stimuli over the motor cortex and determine the resting motor threshold (RMT) as the lowest TMS intensity that elicits a muscle twitch of at least 50 microvolts at least 10 times out of 20 (Rossini et al., 2015). We will then deliver cTBS in the standard pattern (600 pulses over 40 seconds, at an intensity of 70% of RMT). For non-sham groups the coil will be positioned over DLPFC or SMG, as determined by the Brainsight neuronavigation system. For sham groups, the coil will be tilted 90 degrees so the magnetic field is not directed into the head; they hear the clicking noises but no current is induced in the brain (Rossi et al., 2009). Then, subjects will perform second pair of assessment tasks. This will be followed by practice of the maze tracing task for about 20 minutes, with a motor skill assessment partway through. Practice of the maze task will occur at a single MT range (MT 2). The session will conclude with the third pair of assessment tasks.

8.0 Study Calendar

	Familiarization Session	MRI session if needed	Main Session
	First visit	Second visit	Second or third visit
STUDY PROCEDURES			
In person screen, Consent and Handedness questionnaire	X		
TMS tolerance check	X		
Practice Behavioral tasks	X		
Random group assignment	X		
In person Screening		X	X
cTBS			X
Position sense assessment task			X
Motor skill assessment task			X

	Familiarization Session	MRI session if needed	Main Session
	First visit	Second visit	Second or third visit
Motor skill practice			X

9.0 Reportable Events

Outcome and Adverse Event Data including: seizure induction (rare), syncope (epiphenomenon); transient headache, neck pain, toothache, paresthesia, hearing changes; lightheadedness; and nausea (Rossi et al., 2009).
Expected adverse events that will be reported in annual reviews:

1. Slight discomfort lasting less than a second on the scalp near the TMS coil.
2. Twitching of the face and jaw due to the magnetic pulse, which may be unpleasant but usually not painful.
3. Transient headache, neck pain, toothache, paresthesia, hearing changes.
4. Lightheadedness or nausea

Exceptional adverse events that will be reported immediately:

1. Seizure. The appearance of a seizure during application of TMS with stimulation parameters regarded as safe cannot be excluded, therefore we defined appearance of a seizure as an exceptional adverse event.
2. Syncope.

All exceptional adverse events will be reported to the IRB immediately by the PI. Subjects will be excluded for seizure induction and syncope. However, the subject will make the decision for continuation for the other transient discomforts.

In addition to the IRB's minimal requirements, we will report adverse events including: date, time, description of the adverse event, and treatment or handling of the event. We will also provide a summary of cumulative adverse events annually.

10.0 Data Safety Monitoring

The PI will be responsible for data and safety monitoring. The study team will meet at least monthly to discuss any difficulties with carrying out the experimental protocol and to review the data. Dr. Block will always be available in person or by phone when data collections are occurring. Notes recording the date of each meeting and the results of the safety review will be kept in the Block lab's Teams channel for this project.

11.0 Study Withdrawal/Discontinuation

The participant will contact the study personnel by phone or e- mail and inform us that he or she is withdrawing. There are no risks to participant by withdrawing early. If an exceptional adverse event occurs, we will withdraw the subject immediately. For minor, expected adverse events, withdrawal will be discussed with the subject. We would also withdraw the subject if they are unable to follow the instructions for the motor skill task or position sense task. If a subject meets exclusion criteria temporarily on their familiarization session and/or first experimental session (e.g., did not get more than 4 hours of sleep the night before, drank too much coffee, etc), we will simply reschedule the session. However, if they temporarily meet the exclusion criteria on their second experimental session, they will be excluded. If the subject develops a medical condition such that they no longer pass the TMS screening questionnaire and the situation is not temporary, we will withdraw the subject. Participants may also be excluded if we are unable to make the TMS measurements. This happens on rare occasions

when we can't identify a good motor hotspot to deliver the stimuli. In any case, we would pay any withdrawn participant for the amount of time they have spent participating.

12.0 Statistical Considerations

Based on a prior study performed in the lab with a similar paradigm using cTBS (Mirdamadi & Block, 2021), we predict an effect size *f* of at least 0.14 to detect a significant interaction in the planned mixed measures ANOVA between stimulation type (DLPFC, SMG, sham), motor training duration (short, long) and timepoint on the proprioception function and motor skill function. Power analysis indicates we need 24 subjects in each group to have 0.8 power to detect this effect (alpha 0.05).

13.0 Statistical Data Management

Primary data will be collected via direct data capture from measurement instrument and stored electronically in the lab's Teams storage. The storage location will be backed up automatically every day.

14.0 Privacy/Confidentiality Issues

No one will be in the room with the subject except the investigator(s) when the consent process begins. The experimenter will review each section of the ICS with the subject in person, in the lab, at the beginning of the first session. The risk of loss of confidentiality will be minimized by storing identifying information only in two places, both secured to the best of our ability: (1) Printed identifying information consists of the signed consent form and in-person screening forms. Both will be kept in the subject's folder in a locked file cabinet in our lab (PH 079), which is also locked when we're not in there. (2) Electronic identifying information exists in a password-protected spreadsheet of subject names and contact information, with the numerical code that will be associated with the experimental data. The spreadsheet is kept on a secure network drive on the IU Teams server, accessible only to the investigators. If subjects respond to the initial screening questions over e-mail, we will delete this e-mail after determining eligibility. The text of the initial screening e-mail tells the subject we are happy to ask the screening questions by phone, so they know they have the option of not writing personal information in an e-mail. All the information we ask in the initial screening is replicated on the in-person screening form, which subjects fill out when they come to the lab, and this form is used to officially determine eligibility, so there is no need to retain the initial e-mail. To protect the subject's confidentiality, we will only e-mail the subject from an IU e-mail account (ending in indiana.edu or iu.edu). There will be no other electronic or paper identifying information, as all experimental data we collect (through software or a paper data sheet during the experiment) will only have the numerical code assigned to the subject.

Individual data will be associated with a numerical code rather than the subject's name or birthdate. Printed data (forms) will be stored in the subject's folder in the Laboratory in a locked file cabinet in a locked room. Electronic data will be stored on a secure drive on the SPH server. An electronic document containing the numerical codes with identifiable subject information such as name and contact information will be password protected and kept on a secure drive on the SPH server, accessible only by the investigators. Data analysis and publication will not include any identifying information.

15.0 Follow-up and Record Retention

This study will take up to 3 years. We will retain paper and electronic data for 3 years after the study is completed and then destroy them: paper documents will be shredded, and electronic data will be deleted and overwritten.

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