

COVER INFO

Official Title: Cognitive Control Functions of the Human Thalamus

Brief Title: Cognitive Control Functions of the Human Thalamus

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PROTOCOL SUMMARY

This study is a Basic Experimental Studies with Humans investigation designed to examine the mechanisms underlying cognitive control, with a particular emphasis on the role of the thalamus in cognitive flexibility.

Participant: The study will enroll both healthy adults and individuals with stroke, including participants with focal thalamic lesions as well as comparison participants with cortical lesions that do not directly involve the thalamus.

Intervention: All participants will complete a computerized cognitive flexibility task while neural activity is recorded using either functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). The task requires participants to learn and adapt stimulus-response associations and to modify their responses when task contingencies change, allowing assessment of cognitive flexibility and adaptive behavior under changing environmental demands.

Study procedures: There are 3 types of testing procedures, (cognitive behavioral testing, EEG, and MRI,) that investigators will describe in detail below. The types of procedures involved vary from participant to participant, depending on what kind of data investigators need and which procedure subjects agree to participate. The subject may participate in all testing procedures, (MRI, EEG, and behavioral,) two or three. The subject is also free to decline any of the testing procedures, equivalent to not participating in the research study. For each procedure, the testing time will never exceed 3 hours, so the maximum time commitment for the subject will be 9 hrs. For each subject, no more than two testing procedures will occur within 24 hours. When two testing procedures occur within the same 24-hour period, the time between the two testing procedures will be whatever is most convenient for the subject. The time between testing procedures that do not occur within the same 24-hour period will be whatever is most convenient for the subject, (this could mean weeks or months depending on the subject.) The specific procedure(s) the subject agrees to participate in will be checked on the consent form. The order which a subject will participate in these three types of procedures will also vary from subject to subject, which depends on the subject's schedule and the availability of the research facilities.

Behavioral cognitive task: The type of cognitive task that will be administered aimed at measuring subject's ability to monitor internal goals and intentions, maintain and manipulate information in working memory, select task-relevant information, inhibit distractions, and organize action plans to accomplish these goals. These tasks involve the presentation of visual or auditory stimuli through a computer system, and the subjects must pay attention to the presented stimuli and make button press responses. Their eye movements may be monitored by a non-invasive eye-tracking device placed 1 to 2 feet in front of the participants. The eye-tracking device passively records the subject's eye gaze direction and no part of the device will be touching the subject, therefore, there will be no negative impact on the subject's comfort. The testing time for this procedure will be 1 to 3hrs.

EEG: In this procedure, subjects will have EEG recorded while concurrently monitoring behavior. Subjects are asked to sit in a testing room and have conventional EEG electrodes placed on their scalp with conducting paste. The experiments involve the presentation of images on a computer monitor, sounds through speakers or headphones. The tasks may be changed flexibly as required by our behavioral testing of the tasks (i.e., is this task too easy for subjects? Too hard? These are questions investigators can only answer once investigators begin piloting the task behaviorally), however the task will always be asking subjects to manipulate the simple or complex stimuli in mind and respond to the participants in a brief period of time. The task will get at our questions about cognitive control by engaging brain regions involved in memorizing stimuli, attending to stimuli, ignoring stimuli, and preparing responses. These are components of cognitive control that are of interest for this project. The subject is asked to respond to certain stimuli by pressing a button. All stimuli are presented at a comfortable level. Similar to the cognitive behavioral procedure, a non-invasive eye tracking device may record subject's eye movements during EEG recording. This eye-tracking device is non-invasive and no parts of the device will cause any discomfort or interfere with the EEG recording. An EEG recording session typically takes 1 to 3hrs. The subject is given breaks every 5- 10 minutes, but may request a break or stop the experiment at any time. After the testing, investigators will remove the electrodes, and provide shampoo and towels for subjects to wash off the EEG conducting paste. Investigators will provide a hairdryer.

3T fMRI: Before participants enter the magnet room, participants will be screened for contradictions (i.e., metal implant). If the subject also wears glasses that contain metal to correct their visual acuity to 20/40 or better, investigators will have the subject use plastic, MR-compatible glasses provided by the MRI center. If the subject knows their prescription it will expedite the process of finding lenses suitable for the participants. If not,

a few minutes will be allocated to trying on the best fitting pair to approximate the vision required to view the screen within the MRI, which is positioned close to subjects' face. Brain anatomical MRI scans are collected. Brain anatomical MRI scans are collected to determine the location of brain structures. In MRI studies, subjects who have history of brain MRIs will be acclimated to the MRI environment in a mock scanner. This is performed at a dedicated setup at MRRF in PBDB. For comfort, foam pads are placed around the subject's head to limit head movement during the scan. A MRI scanning session takes about 40 - 60 minutes and the subject is given breaks every 5-10 minutes. The subject may request a break or stop the experiment at any time.

Outcome measure of task conditions: The primary objective is to characterize the behavioral outcome that support cognitive flexibility. Behavioral performance during task performance will be compared across groups to identify the specific contribution of the thalamus to cognitive control. The primary behavioral outcome measures are extradimensional shift (EDS) accuracy, intradimensional shift (IDS) accuracy, and stay accuracy, which quantify participants' ability to shift between task rules, maintain relevant task sets, and adapt behavior in response to changing task demands. These measures will be analyzed from behavioral data collected during fMRI neuroimaging and electrophysiological data to investigate the neural circuits supporting cognitive flexibility.

STATISTICAL PROCEDURE

For all analysis, which purpose is to quantify the task effects of set-switching, will be performed using a within-subjects design. This allows each participant to be their own control. The biggest threat to a within-subjects design is the exposure of each participant to all conditions. We will minimize this confound by counterbalancing the order of exposure for each of the task conditions. We will further maximize rigor through random assignment the order of EEG and fMRI sessions. Thus, we will first calculate the mean accuracy of each set shifting (cognitive flexibility) task conditions (EDS, IDS, Stay), and reaction time within each subject, then quantify individual subject differences using standard deviation. The mean accuracy across subjects/participants will also be reported.

Power analysis: for all experiments, we determined sample size based on the smallest effect size we estimated from our preliminary data. Given $N=96$, we will have 80% power to detect the smallest effect size ($d = 0.28$) from our pilot preliminary analysis.