Session VII: Frontal/Executive Breakout

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1. Target Function and Population

With a stated goal of using stimulation to explore frontal lobe functions, the group decided to prioritize ecological validity as a criterion when selecting an experimental task. Because both clinical and healthy elderly populations complain frequently of problems with prospective memory, the group targeted prospective memory as an appropriate construct to explore.

Although prospective memory is a common complaint in elderly populations, the group discussed healthy undergraduates as potential participants due to both the frequency with which they have been studied in past stimulation experiments and the ease with which a homogenous population can be obtained. Dr. Elaine Wencil suggested possible ethical concerns about stimulation in nonclinical populations and Dr. Pascual-Leone was concerned that qualitative differences in neural networks between young and elderly populations suggest the possibility that stimulation might benefit the elderly but worsen prospective memory in young participants. Ultimately, the group settled on healthy participants older than age 65.

2. Overall Design

The group settled on an experimental protocol that begins with participants being given a "regimen" of pills to take for one week. They would be given electronic pill dispensers to monitor compliance. After one week they would be brought to a lab and asked to complete a series of prospective memory tasks in a hospital cafeteria as a baseline. They would subsequently receive stimulation while they completed the same cafeteria tasks. Stimulation would target areas previously implicated in prospective memory: Brodmann's area 10, right dorsolateral prefrontal cortex or left dorsolateral prefronatal cortex. Participants would later be retested on the cafeteria tasks after stimulation and asked to comply with the pill regimen again in the week after stimulation. The follow-up adherence task is designed to determine if acute effects of stimulation during lab-based prospective memory training generalize to more long lasting effects on medication adherence. Participants would also be given neuropsychological tests of prospective memory before and after stimulation.

3. Stimulation Protocol

With real-world applicability and clinical utility as guiding principles, the group decided that using transcranial direct current stimulation (tDCS) would be more appropriate than transcranial magnetic stimulation (TMS) because of the relative advantages of tDCS in terms of both portability and affordability. There was also general agreement that in exploratory studies in which the exact location of the primary target area may be poorly specified, the relative lack of focality of tDCS, compared to TMS, could be advantageous.

There was considerable discussion about whether to stimulate before or during the training task. The group felt that stimulation during task performance would likely show larger effects, and that stimulation should be augmented by some form of learning task, based on prior research on enhancing motor function.

Due to practice effects of the cafeteria task, multiple training/stimulation sessions did not seem feasible. However, the group did discuss the ethics of multiple session stimulation in exploratory research. While some members felt that there was little difference between multiple sessions of stimulation and repeated behavioral interventions that change brain physiology, others expressed concern that there is little data on the effects of repeated stimulation, which is cause for concern given studies showing that 5 days of TMS in normal subjects has lasting effects on voxel-based morphometry changes in gray matter thickness. The group decided that an exploratory study should begin with a single session to demonstrate an effect prior to moving to multiple sessions to extend or increase effects in clinical populations. The uncertainty about cumulative effects of repeated stimulation further emphasized the need for basic parametric studies.

There was some debate about stimulation strength. Although some researchers felt that slowly increased stimulation up to 2.5 mA cannot be distinguished from sham, others felt that stimulation could be differentiated from sham at 2.0 mA. Ultimately 1.5 mA was chosen for this reason. The time period of stimulation was not specified but times of both one hour and 20 minutes were suggested.

The merits of active control sites compared to sham were also discussed. Although using active controls increases a study's power to detect an effect, Dr. Hicks said that NIH study sections and other grant distributing organizations prefer the use of sham controls in stimulation proposals, so the group decided that some participant groups would be partially sham controlled.

Throughout the symposium, there was considerable debate about the placement of the reference electrode in tDCS experiments. Because the reference electrode can also have active effects, it was suggested to use larger reference electrodes to disburse such effects, if cephalic sites were chosen. There was also discussion of the merits, confounding effects, and safety of using extracephalic locations for the reference electrodes. Ultimately, smaller stimulating electrodes were preferred to increase resolution and reference electrode location was not determined.

In order to gain a more clear understanding of stimulation effects, a final design element in which a portion of the participants from each of the 6 stimulation groups (anodal and Cathodal for each of the three sites) would receive perfusion MRI to examine tDCS stimulation effects during a prospective memory activation task.

During the discussion of the proposal, it was suggested that the proportion of participants who can tell sham from stimulation with tDCS increases with the strength of stimulation. Electrode cream was suggested as a way to hide the tingling effects experienced by participants in tDCS experiments. It was also emphasized that 100% of participants who have received TMS can tell stimulation from sham and that the ability to use sham was an advantage of tDCS.

4. Other Issues

In discussing what task might have the most ecological validity in an exploration of prospective memory, the group expanded its discussion to examine some of the core issues that might be relevant to stimulation studies across fields. The need to obtain a reliable physiological measure of the effects of stimulation was emphasized. In the absence of such measures, researchers must apply what they know about the neural connectivity of the primary stimulation site to secondary sites and to test hypotheses about the affects of stimulation on the functions of those secondary areas.

In addition to the need for physiological studies of unintended or secondary effects of stimulation, there was a general group consensus about the need for parametric studies that might provide some guidance about more basic issues, such as the effects of altering the strength of stimulation, period of stimulation, or number of stimulation sessions and to what extent such effects vary for various target sites.