Protocol

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Memory Modulation using Electrical Brain Stimulation in Patients with Epilepsy

Specific Aim

To investigate whether stimulation of medial temporal structures influences spatial memory function. The proposed research project aims to identify stimulation regions and parameters that may enhance memory performance during a cognitive task that requires medial temporal lobe engagement.

Background

The medial temporal lobe (MTL) is composed of the hippocampus proper (CA fields 1, 2, and 3; dentate gyrus (DG); and subiculum) and adjacent cortices (parahippocampal (PHC), entorhinal (ERC), perirhinal (PRC)). These areas are critical for the formation of declarative memory, or the memory of facts and previously experienced events (Scoville and Milner, 1957; Squire et al., 2004). The ability to learn associations between distinct items within an event is central to forming episodic memories, and requires the processing of the context in which the memories are formed (Eichenbaum, 2004). The context, which may include a spatial component, assists in the binding of the events into a stable representation, or memory (Burgess et al. 2002; Holscher 2003).

The facilitative effect of electrical brain stimulation on memory has been demonstrated in animal and human studies. Rats receiving stimulation from depth electrodes implanted in the lateral hypothalamus performed better on a subsequent memory task than animals who did not receive stimulation (Redolar-Ripoll et al., 2002; Soriano-Mas et al., 2005). Furthermore, researchers have shown that electrical stimulation of the hippocampus in rats with fornix lesions improves spatial memory (Turnbull et al., 1994). In humans, thalamic stimulation has been associated with enhancement of declarative memory performance (Fields et al., 2003; Johnson and Ojemann, 2000) and researchers have further found that electrical stimulation can produce hippocampal long-term potentiation, acetylcholine release, and induce hippocampal theta activity, all associated with declarative memory function (Ehret et al., 2001; Feuerstein and Seeger, 1997; Pastalkova et al., 2006; Vertes, 2005; Williams and Givens, 2003). Thus, preliminary evidence suggests that electrical stimulation can affect memory and these stimulation effects may apply to humans.

General Methods

We will include pharmacologically intractable temporal lobe epilepsy patients who have depth electrodes implanted for clinical evaluation. Electrode placements are determined based on clinical criteria. Patients provide informed consent and all experimental sessions last approximately 30 min and conform to the Medical Institutional Review Board and Human Subjects Protections Committee at UCLA.

Stimulation: Testing will take place during diagnostic monitoring with implanted depth electrodes. Stimulation parameters of up to 3.0V, 450 ms pulse width and 130 Hz, appear to be safe and well tolerated in patients with temporal lobe epilepsy with depth electrodes in the temporal lobe (Boon et al., 2007). Electrodes are usually implanted orthogonally in the temporal lobe and can thus sample various medial temporal lobe (MTL) structures. Stimulation contacts will be selected on the basis of location within the MTL circuits (i.e., one within the right or left hippocampus, entorhinal and parahippocampal cortices). Note that it may not be possible to test all contacts or all experimental paradigms in each patient; thus a larger sample of participants is required. Electrodes are .059 cm^2 in surface area and have 3 or 5 mm spacing between contacts and the total number of contacts can be up to 8 per electrode (Ad-tech Medial Instruments). Our stimulation uses current regulated, charge-balanced, biphasic rectangular pulses set below the afterdischarge threshold. Current delivered ranged from 0.5–2mA in previous patients. Impedance is measured before each experiment and the frequency, shape,

and width of the pulse will be verified using an oscilloscope. The impedance measured has been between 1-9kΩ. Stimulation used has been between 2.5-10.1μC/cm^2 per phase, well below the safe maximum used for chronic (30 μC/cm^2 per ph) and acute (57 μC/cm^2 per ph) stimulation (Agnew & McCreery, 1990; Gordon et al., 1990). We will also have an attending neurologist present during all stimulation sessions (Dr. John Stern), who will monitor the patient at bedside and view their EEG data on-line.

Electrode Localization: Prior to implantation with depth electrodes, patients are scanned with a Siemens Trio head-only 3 Tesla scanner. High in-plane resolution structural images with a matrix size of 512 x 512 (spin echo, TR = 5200 ms, TE = 105 ms, 19 slices, contiguous; voxel size: 0.391 x 0.391 x 3 mm) are acquired in the oblique coronal plane perpendicular to the long axis of the hippocampus. Patients also receive a 3-T whole brain T1 weighted MP-RAGE GRE scan (TR=1800 msec, TE=2.93 sec, voxel size= .9 x .9 x .8mm) as part of depth-placement planning. Patients are then implanted with depth-electrodes for surgical monitoring. Following implantation with depth-electrodes, subjects received a Spiral CT scan (1 sec rotation, high-quality (HQ) mode, helical pitch 1.5, 1 mm slice collimation, and a 0.5 mm reconstruction interval to localize electrodes. CTs are registered to the high-resolution MRI and to the whole brain MRI using a 3-way registration in BrainLab sterotactic and localization software (www.brainlab.com; Gumprecht et al., 1999; Schlaier et al., 2004; Ekstrom et al., 2008). Electrodes are visualized on a flat map created by unfolding the gray matter.

Electrophysiological recordings: For each patient, the threshold for eliciting an after-discharge (ADG), or absence of any ADG, was determined immediately prior to behavioral testing. The presence of ADGs is determined by a specialized clinical neurologist who is present at every study. Each navigation trial lasts approximately 10-15 seconds. This time is variable because the patient is freely navigating and can take a variable amount of time for each store destination. No test is administered within at least 2 hours of a seizure. Thus far, no seizures have occurred within 24 hours prior to testing. We also visually inspect the electrophysiological data and eliminate trials with ADGs. Also, after-discharges can vary from brief events lasting a second or two at the site of stimulation to events, which propagate widely and last many seconds when stimulation is too strong. Our experience in testing thresholds with small increments has always resulted in the former pattern, one which is unlikely to have lasting effects on performance, and which has only occurred during testing on one occasion. We also analyze EEG data from the testing sessions on- and off-line using matlab software. The presence of epileptiform discharges occurring in the region of macroelectrode contacts are determined by visual inspection of both ictal and interictal periods. Ictal periods are previously determined on the basis of either (1) alteration of the clinical status of the patient, frequently coinciding with habitual seizures, or (2) a sustained electrographic pattern similar to that seen in (1) but without frank clinical manifestations (i.e. bland or subclinical seizures). At least 15 minutes of interictal EEG is also reviewed, typically consisting of baseline recordings prior to the onset of seizures during video-EEG telemetry.

Experimental Presentation and Apparatus: PyEPL will be used to present virtual reality stimuli and to record navigational routes and keypress reaction times. Matlab will be used to present visual stimuli for the face recognition paradigm. Keypress reaction times will also be recorded using matlab. All stimuli are presented using a Macintosh laptop computer. For memory testing we will choose stimulation settings that are 'subliminal', that are below ADG threshold and that do not produce any obvious or reported effects. Thus, patients will be masked to stimulation condition and we can compare the performance when the stimulation is on versus off. Stimulation will be delivered during encoding and/or retrieval phases, as appropriate for specific tasks. As it is unlikely that tasks can be examined at each of the five selected electrode contacts due to excessive patient burden, the testing protocol will ensure adequate sampling of contacts and tasks across subjects. Although the general principles of MTL memory engagement are well articulated, determining the precise paradigms to best reveal possible

modulatory effects of stimulation effects requires considerable effort. Based on the scant information available from the literature, we have to consider that either facilitative or disruptive effects might be found and the nature of the effect may depend on combinations of the foregoing factors. Thus, we need to rigorously evaluate different paradigms over which we can exert precise experimental control. The candidate paradigms to be investigated in this project are outlined below, together with the specific hypotheses relevant to each. Each hypothesis is framed in a positive direction – i.e., that simulation is likely to enhance performance on MTL-sensitive tasks.

Experimental Design: Spatial Navigation. The yellow cab task was developed by Kahana and colleagues and was used in several electrophysiological recording and fMRI studies to examine spatial navigation and memory phenomena (Ekstrom et al., 2007; Ekstrom et al., 2003; Ekstrom et al., 2005; Suthana et al., 2009). Subjects play a taxi driver computer game in which they explore a virtual town, searching for and locating passengers or objects and delivering them to fixed target locations. Unit recording in various medial temporal sites during the yellow cab task revealed a significant increase in response (spike rates) in over 40% of cells as a function of the location in the virtual town, the objects viewed, and passenger goal. Furthermore, somewhat different effects were observed during encoding (greater population of responsive neurons) and associative retrieval (increased broadband power) phases of the study, suggesting that there may be an opportunity to observe differential effects of stimulation during these processes. As with the foregoing memory paradigms, our hypothesis is that performance on recollection components of the virtual navigation task will be enhanced with MTL stimulation during learning. Patients will navigate to stores within in a city during alternating blocks of navigation and control tasks. Every other trial will be stimulated and order will be counterbalanced across patients.

During the three control conditions patients will complete two tasks. The first will consist of a direction pressing task where patients will see an arrow pointing left or right randomly and are instructed to press the corresponding button as quickly as possible. There will also be a perceptual control task, which will consist of matching stores below to a target store presented above the screen. Again, order of stimulated trials will be counterbalanced across patients. We will also measure whether stimulation has differential effects on navigation learning during allocentric (viewpoint independent) vs. egocentric training, indicates the former is associated with greater activity in hippocampus and requires increased integration over trials for subjects to form a map of the environment (Suthana et al., 2009).

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