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Computer-controlled electrical stimulation for quantitative mapping of human cortical function

Technical note

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Cortical mapping with electrical stimulation (ES) in neurosurgical patients typically involves the manually controlled delivery of suprathreshold electrical current to a discrete area of the brain. Limited numbers of trials and imprecise current delivery methods increase the variability of the behavioral response and make it difficult to collect quantitative mapping data, which is especially important in research studies of human cortical function.

To overcome these limitations, the authors developed a method for computer-controlled delivery of defined electrical current to implanted intracranial electrodes. They demonstrate that stimulation can be time locked to a behavioral task to rapidly and systematically measure the detection threshold for ES in human visual cortex over many trials.

Computer-controlled ES is well suited for the systematic and quantitative study of the function of virtually any region of cerebral cortex. It may be especially useful for studying human cortical regions that are not well characterized and for verifying the presence of stimulation-evoked percepts that are difficult to objectively confirm.
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Key Words • computer-controlled electrical stimulation • cortical electrical stimulation • psychophysics

Cortical ES mapping is a well-established technique for studying the function of discrete areas of cerebral cortex in awake and cooperative patients in both intraoperative and extraoperative neurosurgical settings.[3,7,8,10,12,13] The technique typically employs a manually controlled device, such as the widely used Ojemann Cortical Stimulator (Integra Neurosciences), to deliver pulses of current to discrete regions of cortex until an observable response is elicited or the patient reports a percept.[12] The response elicited by ES at each cortical site is usually described in qualitative terms, and only a few trials of stimulation are typically performed at each site to confirm that the response is reproducible. In addition to its well-established value as a clinical tool for surgical planning, stimulation mapping is also valuable as a neuroscience research tool.[6] However, the use of small numbers of trials and manually delivered currents limit the data that can be collected to qualitative descriptions of responses.

It is desirable, then, to generate quantitative, as well as qualitative, measures of responses to ES so that this technique can be used to more precisely study cortical function, particularly for research purposes. To efficiently collect quantifiable responses to stimulation across multiple trials, it is critical to deliver precise amounts of current at specific time points across repeated trials. This can be accomplished through the use of intelligent automation such as a computer-controlled apparatus for stimulation. In spite of the clear potential value of computer-controlled cortical ES, our review of the literature uncovered only 2 studies that note the use of computers to control the delivery of electrical current to intracranial electrodes in human patients,[5,15] and in both studies the methods for computer-controlled stimulation were not described. Here we describe the methods we have developed for mapping cortical function using CCCES.

Abbreviations used in this paper: CCCES = computer-controlled cortical electrical stimulation; DAI = data acquisition interface; EEG = electroencephalography; 2-AFC = 2-alternative forced-choice.

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We demonstrate that CCCES can be time locked to a behavioral task to rapidly and systematically measure the detection threshold for ES in the human visual cortex, and we discuss the potential value of CCCES in human brain mapping.

Methods

Computer-Controlled ES Apparatus

Figure 1 shows a schematic illustration of the computer and stimulator apparatus. Both the delivery of CCCES to the patient and the collection of related behavioral data are conducted using custom software running on a Macintosh G5 computer (Apple, Inc.) with 2 DAIs (ITC-18, Instrutech). The software is programmed to allow the experimenter to select from a wide range of behavioral parameters (for example, poststimulation response interval and intertrial interval) and ES parameters (for example, current amplitude, pulse duration, train duration, and pulse frequency). Computer-generated waveforms are converted to an analog signal via a DAI and then relayed to a linear biphasic stimulus isolator (BAK BS-I, BAK Electronics). The stimulus isolator converts the voltage waveform into an optically isolated current waveform that is delivered to a standard clinical subdural electrode (AdTech) implanted on the patient's cerebral cortex. The computer simultaneously sends a command to release a gating mechanism that serves as a safety interface between the stimulus isolator and patient. This patient safety interface is designed with a current limiter such that even when the gate releases, a maximum of 10 mA may be delivered and a voltage limiter that limits the output to < 100 V. A signal from the patient safety interface is also sent to a DAI interface to record the current level actually delivered to the patient. Quantitative behavioral responses to stimulation (typically button presses with a standard universal serial bus mouse) also relay through a separate second DAI. Stimulus pulses and patient responses are recorded as time-stamped events. The software provides a dynamically updated online display of behavioral data and records data for real-time monitoring and offline analysis. An oscilloscope receives feeds from both the computer and the patient safety interface to verify the integrity of the setup online. We used the setup to deliver monopolar stimulation with a reference grounding pad providing the return path, but it could easily be modified to deliver bipolar stimulation. Because the delivery of electrical current is under computer control and monitoring, current delivery is highly precise, rapidly delivered, and can be time locked to computer generated stimuli (for example, a tone or visual image) or patient behavior.

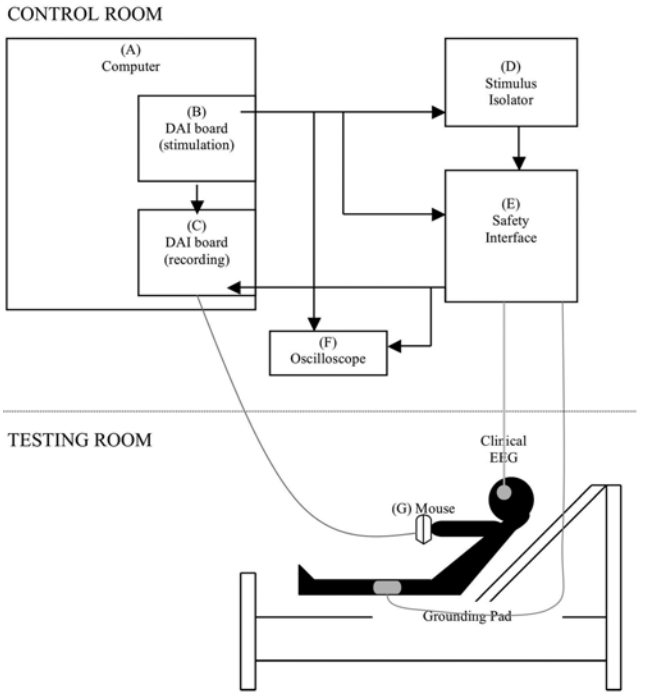

FIG. 1. Schematic illustration of the computer and stimulator apparatus: the computer with online display of acquired behavioral data and controls for stimulation and behavioral task parameters (A); DAIs within the computer, guided by custom software, that regulate the delivery of ES to the patient and collect the behavioral responses (B and C); linear stimulus isolator that functions as a source of optically isolated current delivered to the implanted electrodes (D); custom patient safety interface that prevents inadvertent delivery of current to the brain (E); oscilloscope used to verify the integrity of the setup (F); and standard universal serial bus mouse used to record patient responses as left or right mouse clicks (G).

Sample Application: Measuring Stimulation Thresholds in the Visual Cortex

To demonstrate the utility of these methods, we describe their use to quantitatively measure the electrical current threshold for producing percepts with stimulation of a patient's visual cortex. This patient underwent inpatient video EEG monitoring with surgically implanted intracranial subdural electrodes as part of a preoperative evaluation for epilepsy surgery. The patient had intact visual fields and normal visual acuity. The institutional review board at Baylor College of Medicine approved all experimental procedures. Implanted electrodes were localized using AFNI (Analysis of Functional NeuroImages) software, which allowed preimplantation T1-weighted anatomical and functional MR imaging data to be fused with a postimplantation CT scan. Electrical stimulation was delivered at an electrode positioned on visually responsive cortex (determined by a preoperative functional MR image) in the ventral temporal lobe (see black dot in Fig. 2C), at a site subsequently determined to be outside the patient's epileptic zone. During the experiment, the patient was seated comfortably in a hospital bed in a dark room. A blindfold was placed over the patient's eyes, and the patient was instructed to keep his eyes oriented directly forward during the experiment. Clinical EEG activity was continuously monitored for after-discharge potentials related to stimulation, as well as for spontaneous seizures.

We used an experimental design that anchors a patient's sensory experience of CCCES to performance

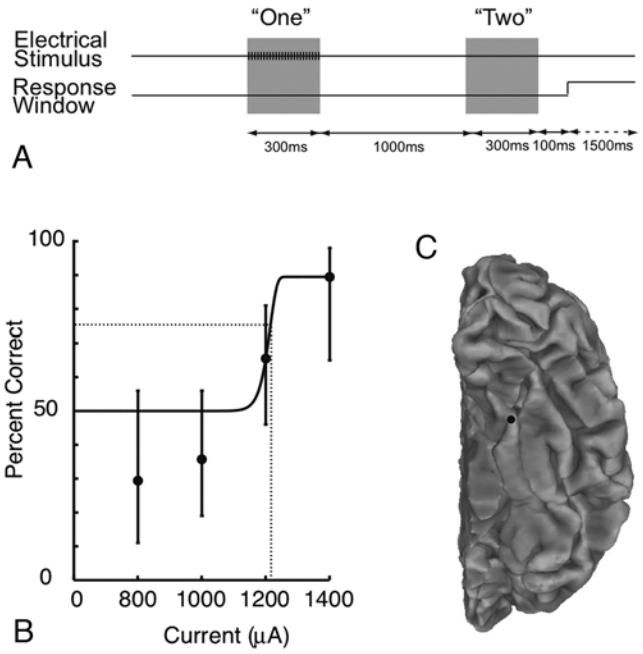

FIG. 2. A: The 2-AFC detection task. The electrical stimulus was delivered during Period One or Period Two. Epochs were demarcated by the words "One" and "Two." The patient indicated which interval contained the stimulation by pushing 1 of 2 buttons. B: Graph showing the sigmoid function between percentage of correct responses in detecting ES (for example, performance on the 2-AFC task) and current intensity for an electrode on the ventral temporal lobe. For a saturating behavioral function, 82% correct detections corresponded with the detection threshold. Here, performance does not saturate, and therefore a threshold of 1214 μA (shown where the *dotted lines* converge) corresponds with a lower percentage of correct detections (75% correct). Each data point represents the average performance for at least 15 stimulation trials. *Error bars* represent 95% binomial CIs. C: *Black dot* indicates an electrode position at a site in the ventral temporal lobe. This site was determined to be visually responsive on a preoperative functional MR image obtained in this individual.

on a 2-alternative forced-choice (2-AFC) detection task, a classic psychophysical method (Fig. 2A). The forced-choice design replaces unverifiable qualitative patient reports of the effects of ES with a rigorous measure of detection of stimulation across multiple trials and with a range of current levels. Each individual trial was composed of a 2-AFC task that included two distinct 300-msec intervals typically separated by a period of 1000 msec and followed by a 100 msec "too-fast" response period. This was followed by a 1500-msec intertrial interval. The purpose of the too-fast period was to discourage guesses that were not based on the ES, which, if delivered in the second interval, would take longer to inform a motor response. In each trial, the patient would hear 2 intervals marked by the words "one" and "two." In every trial, only 1 of the 2 intervals was randomly paired with the delivery of a short train of ES. The patient's task was to attend to the 2 intervals and then to indicate the interval in which a percept was detected by pressing 1 of 2 buttons during the subsequent response period. The custom software recorded the patient's behavioral response and generated feedback on each trial to indicate correct or incorrect identification of the interval that coincided with stimulation. In this "forced choice" design, the patient was instructed to respond with his best guess on every trial, even on trials in which the current level was low and nothing was detected.

Our custom software used an adaptive procedure, QUEST (Quick, Unbiased and Efficient Statistical Tree), to rapidly determine behavioral threshold. The QUEST algorithm was used to select currents from among the discrete log scale current levels described below that were normally distributed around threshold.[9] Figure 2B shows these data plotted as a psychometric curve, with the current amplitude of ES delivered in the x axis and the percentage of correct detections on the y axis, where 50% corresponds to guessing. The patient's ability to detect CCCES increased from chance level at 800 μA to saturating performance at 1400 μA. The detection threshold (75% correct) was measured at 1214 μA (range 1173–1391 μA, 95% CI by bootstrap). Collection of these data took < 10 minutes.

Discussion

Computer Control Permitting Rapid, Precise, and Systematic Delivery of Multiple Trials of ES

The traditional methods for cortical ES mapping of human brain function involve delivering a few trials of manually controlled stimulation at suprathreshold levels to each cortical area of interest. While these methods can be effective in providing a qualitative description of local cortical function when stimulation elicits an observable response or stops an ongoing behavior, the small number of trials does not allow for reliable quantitative measurement of the responses to stimulation. The methods for CCCES that we have described allow the rapid delivery of multiple stimulation trials, which provide statistical power for measurements of behavioral detection of ES (Fig. 2B). A computer-controlled system is much more efficient than manual delivery of multiple trials of stimulation.

Computer-controlled stimulation also allows more precise delivery of electrical current across trials. Manipulation of current delivery by hand, particularly of temporal factors such as pulse duration or intertrial intervals, is more likely to introduce variability. Stimulation studies in trained monkeys[17] and humans[14] suggest that small variations in stimulation parameters can affect the behavioral response to stimulation, which can result in inconsistent effects of stimulation of a cortical region. Furthermore, the systematic delivery of different current levels by CCCES makes it possible to characterize behavioral consequences of stimulation parametrically. Randomization or interleaving of stimuli prevents the patient from anticipating the intensity of a percept after repeated stimulation trials, which can lead to inaccuracy of a measured threshold for detection due to increased sensitivity, adaptation, or over-learning of a particular current level.[1,16] Finally, with computer control, ES and behavioral parameters can be dynamically manipulated based on behavioral responses to result in more efficient collection of relevant data.

Computer-Controlled Stimulation Precisely Synchronized to Behavioral Task

Electrical stimulation mapping in patients undergoing neurosurgical procedures is often performed with a yes/no or free-response paradigm, rather than specific coupling to a behavioral task. For example, when somatomotor, somatosensory, or visual cortices are mapped with ES in the clinical setting, the patient is typically asked to indicate if he/she experienced anything during stimulation (yes/no) or to report anything that is experienced such as a readily apparent muscular contraction, somatic sensation, or visual phosphene (free response). In contrast, when language-related cortical areas are mapped, ES is delivered to a focal region of cortex while the patient performs a behaviorally relevant task (such as counting or naming). This classical clinical method for language mapping works well because the precise timing of ES is nonessential, because long pulse trains are required to overtly disrupt language function, and temporally precise delivery of current is unnecessary. Research studies of other human cortical functions, however, may require more precise time locking to behavioral tasks than can be achieved manually. For example, studies of the organization and function of human sensory cortex may require careful synchronization between ES and a computer-generated sensory stimulus (such as a tone or a visual image), as demonstrated in monkey experiments, which reveal that activation of neurons in higher visual areas can systematically bias perception.[2,4] The computer-controlled stimulation techniques we have described can be adapted to a wide variety of behavioral tasks performed in conjunction with ES in a manner that can be useful for studying various higher cortical functions.

Conclusions

While full understanding of the practical utility of systematic CCCES for human brain mapping will require further study, our experience demonstrates that this technique is safe and efficient when used in awake and cooperative human patients with implanted intracranial electrodes. The techniques we have described are adapted from those used in microstimulation studies in nonhuman primates, and the scientific utility of these methods has been well validated.[2,4,11] We believe that CCCES can safely add significantly to brain mapping studies in neurosurgical patients by enabling investigators to rapidly collect objective and quantifiable data across multiple trials with precise time locking to a behavioral task. These methods are useful for verifying the presence of complex percepts that are difficult for the examiner to objectively confirm and can be applied to functional mapping of essentially any area of cortex including extra-eloquent regions with functions that are not yet well defined.

Disclosure

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The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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