Video Article

Performing Behavioral Tasks in Subjects with Intracranial Electrodes

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URL: https://www.jove.com/video/51947
DOI: doi:10.3791/51947

Keywords: Behavior, Issue 92, Cognitive neuroscience, Epilepsy, Stereo-electroencephalography, Subdural grids, Behavioral method, Electrophysiology

Date Published: 10/2/2014

Citation: Johnson, M.A., Thompson, S., Gonzalez-Martinez, J., Park, H.J., Bulacio, J., Najm, I., Kahn, K., Kerr, M., Sarma, S.V., Gale, J.T. Performing Behavioral Tasks in Subjects with Intracranial Electrodes. *J. Vis. Exp.* (92), e51947, doi:10.3791/51947 (2014).

Abstract

Patients having stereo-electroencephalography (SEEG) electrode, subdural grid or depth electrode implants have a multitude of electrodes implanted in different areas of their brain for the localization of their seizure focus and eloquent areas. After implantation, the patient must remain in the hospital until the pathological area of brain is found and possibly resected. During this time, these patients offer a unique opportunity to the research community because any number of behavioral paradigms can be performed to uncover the neural correlates that guide behavior. Here we present a method for recording brain activity from intracranial implants as subjects perform a behavioral task designed to assess decision-making and reward encoding. All electrophysiological data from the intracranial electrodes are recorded during the behavioral task, allowing for the examination of the many brain areas involved in a single function at time scales relevant to behavior. Moreover, and unlike animal studies, human patients can learn a wide variety of behavioral tasks quickly, allowing for the ability to perform more than one task in the same subject or for performing controls. Despite the many advantages of this technique for understanding human brain function, there are also methodological limitations that we discuss, including environmental factors, analgesic effects, time constraints and recordings from diseased tissue. This method may be easily implemented by any institution that performs intracranial assessments; providing the opportunity to directly examine human brain function during behavior.

Video Link

The video component of this article can be found at https://www.jove.com/video/51947/

Introduction

Epilepsy is one of the most common brain disorders, characterized by chronically recurrent seizures resulting from excessive electrical discharges from groups of neurons. Epilepsy affects about 50 million people worldwide and approximately 40% of all individuals with epilepsy have intractable seizures that cannot completely be controlled by medical therapy[1]. Surgery may result in seizure free status if the brain areas responsible for the generation of seizures (the epileptogenic zone - EZ) are localized and surgically removed or disconnected. In order to define the anatomical location of the EZ and its proximity with possible cortical and subcortical eloquent areas, an array of non-invasive tools are available: analysis of seizure semiology, video-scalp electroencephalographic recordings (ictal and interictal recordings), neuropsychological testing, magnetoencephalography (MEG) and MRI[2]. When the noninvasive data is insufficient to precisely define the location of the hypothetical EZ, when there is the suspicion of early involvement of eloquent cortical and subcortical areas or when there is the possibility for multi-focal seizures, chronic invasive monitoring may be required[3,4].

Methods of chronic invasive monitoring for defining the location and boundaries of an EZ may include subdural grids and strips, with electrodes placed on the brain's surface, and stereo-electroencephalography (SEEG), when multiple depth electrodes are placed in the brain in a three-dimensional fashion. Subdural intracranial recordings were initially reported in 1939 when Penfield and colleagues used epidural single contact electrodes in a patient with an old left temporal-parietal fracture and whose pneumoencephalography disclosed diffuse cerebral atrophy[5]. Subsequently, the use of subdural grid arrays became more popular after multiple publications during the 1980's demonstrated their safety and efficacy[6]. The SEEG method was developed and popularized in France by Jean Tailarach and Jean Bancaud during the 50's and has been mostly used in France and Italy as the method of choice for invasive mapping in refractory focal epilepsy[7-9].

The principle of SEEG is based on anatomo-electro-clinical correlations, which takes as its main principle the 3-dimensional spatial-temporal organization of the epileptic discharge within the brain in correlation with seizure semiology. The implantation strategy is individualized, with electrode placement based on a preimplantation hypothesis that takes into consideration the primary organization of the epileptiform activity and the hypothetical epileptic network involved in the propagation of seizures. According to several European and recent North American reports, SEEG methodology enables precise recordings from deep cortical and subcortical structures, multiple noncontiguous lobes, and bilateral explorations while avoiding the need for large craniotomies[10-15]. Afterwards, postoperative images are taken to obtain the exact anatomical position of the implanted electrodes. Subsequently, a monitoring period starts in which patients remain in the hospital for a period of 1 to 4 weeks in order to record interictal and ictal activities from the implanted electrodes. This monitoring period is an opportune time for studying brain function using event-related SEEG analysis, as there is no added risk and the patient typically views the research study as a welcome reprieve from the mundane monitoring period. The recordings garnered from intracranial electrodes are not only vital to improved evaluation and care of epilepsy patients, but additionally provide the exceptional opportunity to study human brain activity during behavioral paradigms.

Several researchers have already realized the opportunity to study invasive recordings from epilepsy patients. Hill *et al.* reported on the methodology for recording electrocorticographic (ECoG) signals from patients for functional cortical mapping[16]. ECoG recordings have also provided insight to motor-language coupling[17]. Patients with implanted depth electrodes have performed navigational tasks to study brain oscillations in memory, learning[18] and movement[19]. Depth electrode recordings were also used to study paradigms with otherwise unattainable temporal resolution such as hippocampal evoked activity[20], neural activity in the default-mode network[21], and the temporal course of emotional processing[22]. Hudry et al studied patients with temporal lobe epilepsy who had SEEG electrodes implanted into their amygdala for short-term olfactory stimuli matching[23]. Another group has studied simple limb movements such as hand flexion or unilateral movement of the hand or foot in healthy brain sites from epileptic patients with implanted SEEG[24,25].

The studies described above are a small sampling of a very diverse collection of relevant literature. There exists an insurmountable potential to learn and understand how the human brain works using a combination of behavioral tasks and intracranial recordings. While there are other methods for achieving this goal, intracranial recordings possess several benefits including high temporal and spatial resolution as well as access to deeper structures. The authors aim to describe the general methodology for recording from patients with intracranial electrodes during behavioral tasks. However, there are several deterrents and barriers to successfully completing clinical research in patients receiving care. Limitations, confounding effects, and significance of this research will also be identified and explored.

Protocol

All tasks were performed according to an approved protocol submitted to the Institutional Review Board (IRB) of the Cleveland Clinic Foundation. An informed consent process was conducted with each patient prior to all research activities. In this example, a subject that meets study criterion that has had stereo-electroencephalography (SEEG) electrodes implanted for seizure is chosen. The project was discussed with the subject and they have consented to participate.

1. Patient Enrollment

1. Evaluate patients with refractory epilepsy in consideration for intracranial electrode implantation. If the patient is a good candidate for the invasive surgery, analyze the patient's MRI, PET and MEG along with the seizure pathology in order to optimize placement of the electrodes. A clinical team carries out all evaluations and no decisions are made for research purposes. .
2. Identify eligible patients for the study subsequent to evaluation for implantation and verify the patients per the approved IRB protocol based on the inclusion/exclusion criteria.
   NOTE: It is in the best interest of the patient to include subjects with an aura in the inclusion criteria. Patients with auras are able to notify the researchers that they are about to have a seizure; giving the researchers and patient time to take the necessary precautions (pressing the seizure alarm to notify the clinical staff and pulling all equipment out of the way). However, if subjects are recruited that do not have an aura, ensure that the patient input devices can be readily removed from the patient area and that the staff is aware of the research equipment and protocol.
3. Obtain informed consent prior to any research activities in accordance with the IRB. During the informed consent, explain the research, emphasizing that participation is strictly voluntary and will in no way impact the patients clinical care. In most cases there is no direct benefit to the patient and their willingness to participate is altruistic.
4. Maintain respect for the patient's rights and privacy at all times. Remind the patients that their information will remain anonymous and confidential and they may cease participation in the study at any time under no consequence.
5. Have the patient sign and date the informed consent if he or she understands and agrees to participate in the study. Leave one copy is left with the patient to review; should they have any questions or concerns encourage the patients to contact the PI.

2. Behavior System Set-up

1. Before bringing the equipment into the room, ensure that there is sufficient space in the patient's room, as well as access to the necessary outlets (2).
2. Check that all equipment and wires are ready to expedite the set up. The behavioral system includes an FDA approved robotic arm (which allows the subject to control a cursor during the task), a laptop computer to control the behavioral program, a monitor for presenting the task stimuli, and a data acquisition system to store the electrophysiological and behavioral data.
   NOTE: Make necessary modifications to meet specific needs of one's research. For instance, use a button box for the patient interface instead of the robotic arm.
3. If the patient is not presently positioned in a manner suitable to complete the task, assist the patient to a reclining chair (or bed) with arms, should they have a seizure.
   NOTE: It is a good idea to discuss the study design, equipment, etc. with all the members of the monitoring unit to inform them of what is going on, how the group will be interacting with the patients, and any possible issues that may arise.
4. When the patient is ready, bring the behavioral system into the room and begin booting up the behavioral system and robotic arm.
5. Connect the digital event marker output from the behavioral computer to the DC channels of the electrophysiological acquisition system in order to time lock the recorded SEEG signals with behavioral event markers.

NOTE: At this center there is a separate electrophysiological acquisition system designated for research purposes, which does not interfere with the clinical acquisition system. However, it is possible to use the clinical acquisition system by working with the appropriate personnel. All efforts should be made not to disrupt the clinical acquisition.

6. Calibrate the robotic arm and position it such that the range of motion is comfortable for the patient. If using another interface device, ensure that the equipment is operating correctly and is positioned comfortably for the subject to use.
7. While using the robotic arm, ensure that the emergency stop buttons are easily accessible by the researchers throughout the behavioral task. In the event of a seizure, the emergency stop button is pressed and the equipment is pulled away from the patient so that they do not harm themselves. In addition, we do not use the velcro straps that come with the robot system to facilitate removal from the patient in case a seizure occurs.
NOTE: In this example, the parallel port of the behavior rig is connected to the digital input port of the acquisition system using a parallel port cable. Additional analog signals such as the x & y position of the robotic arm are recorded simultaneously.

3. Behavioral Task

1. Explain the task to the patient following the completion of the rig set up and calibration of the interface device.
2. Use a behavioral task similar to the children's card game of "war". Ask the patient to make wagers as to whether their card is greater than the computer's card. The choice of the wager is based on the patients' perception of the relative value of their card. Simplify the task for subsequent analysis, by only using cards of one suit and limiting the deck to the 2, 4, 6, 8, and 10 numbered cards.
3. Show a fixation cue on the screen for 350 msec. Ensure the patient holds the cursor over the fixation mark to initiate the task.
4. Show the stimulus for 1,000 msec. Allow the patient to see their card with the computer's card next to it face down.
5. Following the cards disappearance, show a go-cue (<5,000 msec) displaying two options, asking the patient to bet either $5 or $20, based on their card. Ask the patient to place the bet by moving the cursor using the robotic arm, over their chosen wager. Randomize the wager position from trial to trial to ensure no bias based on position.
6. After the wager has been selected, notice a 250 - 500 msec delay (blank screen), followed by the revelation of the computer's card (1,000 - 1,250 msec). Observe the outcome (1,000 msec), whether the trial was a win, lose, or draw and how much was won or lost.
7. Allow the patient to practice until they are confident in their performance and have no questions.

4. Data Acquisition

1. Record the data when the patient is ready and verify that the settings on the research (or clinical) acquisition system are appropriately selected.
2. Turn off the room lights and TV to keep the background noise to a minimum during the recording. Additionally, ask the patient to refrain from behaviors such as tapping their foot, talking or shaking their legs.
3. Begin the task and record the patient performing the task. Ask the subject to perform the task for 30 min. The sampling rate of the robotic arm system is 1 KHz, and that of SEEG recording system is 2 KHz.
NOTE: This duration may be different for other paradigms.

5. Data Analysis

1. First, de-identify the recorded SEEG data to ensure that the patient's information remains confidential and that his/her data is submitted anonymously.
2. Obtain the coordinates of the electrode locations from the postoperative CT and preoperative MRI.
3. Align the neurophysiological recordings with the digital timestamps of interests from the behavioral task.
4. Apply signal analysis methods to analyze the event dependent brain activity modulation.
NOTE: In this study, power spectral density (PSD) of the event related SEEG signals was calculated using Chronux multitaper toolbox[26,27]. Each trial data was aligned with respect to the relevant event (time zero), and the calculated PSD was normalized in each frequency bin with respect to the baseline PSD.

Representative Results

In these results we present the analysis of the SEEG data from the limbic system captured in one subject playing the War Task. We can demonstrate that various aspects of the War Task evoke significant gamma-band (40 - 150 Hz) modulation in the limbic system (**Figure 1**). As seen, in the visual cortex, the presentation of an object on the screen results in a fast latency (~200 msec) wide band response regardless of the task contingency. In addition, there appears to be differences in the duration of the response during the reward period and a potential difference between the power of the evoked response for unrewarded trials as compared to rewarded trials. In contrast, the inferior frontal gyrus is only modulated in trials that result in reward. This modulation was longer in latency (~500 msec), suggesting a period when the reward information was being processed. The reward related responsiveness is consistent with the function of this part of the cortex, as it is thought that the inferior frontal gyrus is involved in decision making and reward evaluation [28].

In this analysis, we chose to examine the frequency content of the electrophysiological data in the gamma band range, as it is thought that this band of activity represents cognitive processing[29]. However, there are a large variety of analysis techniques that can be employed to local field data relative to behavioral tasks, such as the frequency content in other bands, evoked activity, or network based analysis. In addition, offline statistical analysis will delineate the statistical significance with respect to the behavioral tasks.

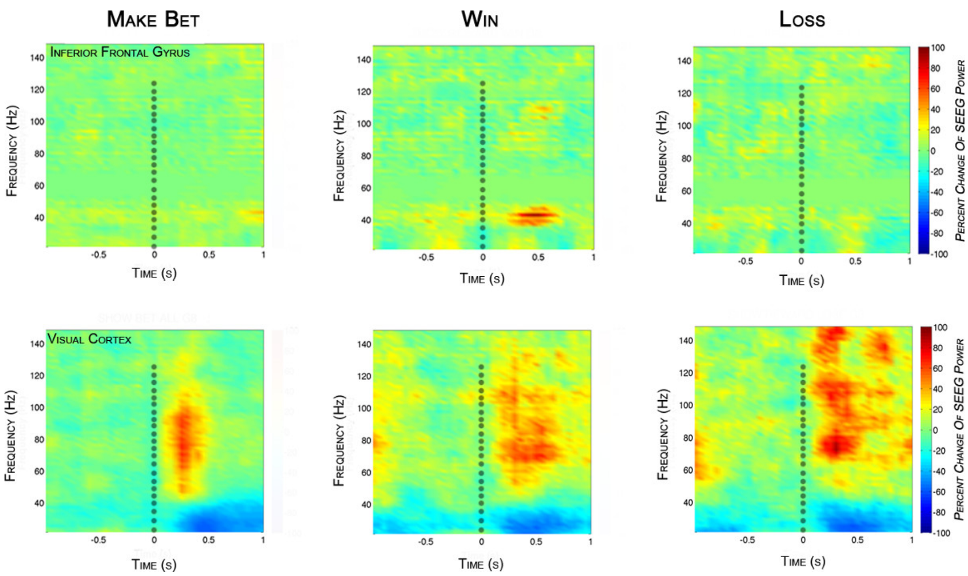

Figure 1. **Power spectrum of activity relative to three different epochs (t = 0) in the War Task.** The first row depicts the activity of the inferior frontal gyrus and the second row depicts the activity of the visual cortex, (x-axis: time relative to epoch, y-axis: frequency and color represents z-score relative to baseline). The time zeros of the graphs in each column represents the appearance of bet options (left column), the appearance of positive reward (middle column), and the appearance of negative reward (right column). The color scales are the percent changes of the recorded signal power in each frequency band with respect to the baseline. Please click here to view a larger version of this figure.

Discussion

Here we have presented a method for performing intracranial electrophysiological studies in humans as they engage in a behavioral task. This methodology and its simple permutations are important for studying human movement and cognition. While there inherently exists advantages and disadvantages to any technique, recording from intracranial electrodes has advantages over other electrophysiological and imaging techniques. Two of the major advantages are the ability to collect high quality data with better control and design of behavioral tasks.

Intracranial electrode recordings have a number of advantages over other methods used to measure brain activity during behavioral tasks. Namely, a vast majority of studies have been conducted using imaging techniques such as fMRI and PET, which offer the advantage of high spatial coverage but limited temporal resolution (on the order of 1 - 1.5 sec). As such, these studies grossly estimate brain function as a change in activity relative to baseline states and cannot provide realistic estimates of dynamic processing relative to specific components of behavior. MEG studies, on the other hand, have better temporal resolution (<1 msec) but the spatial coverage is restricted to cortical targets and can be confounded by signals generated deep within the brain. Single and multi unit studies have been successful at providing insight into brain function, as they provide high temporal resolution. However, the limitation of conventional single and multi unit studies relates to the placement of electrodes directly into the brain area of interest, limiting spatial coverage to a small volume of tissue. Hence, these studies tend to focus on one part (or nucleus) of the brain and fail to examine how interconnected brain nuclei communicate to control behavior[30]. In contrast, intracranial electrodes provide high temporal resolution (1 msec) and wide spatial coverage (up to 200 electrode positions), allowing the researcher to examine information processing across multiple structures of the brain simultaneously at time scales capable of discerning specific components of behavior.

In addition to the data quality, there are also advantages to the design of behavioral studies that can be conducted in these subjects. In contrast to animal studies, the cognitive ability of human patients allows for brief training periods on complex tasks, leading to fast data acquisition and larger sample sizes. Secondly, the neural activity gained from these studies is related to human behavior, eliminating the need to account for species variations in either neural processing or behavior. Finally, because the subjects are in the monitoring area for extended periods and there is no substantial risk in conducting these studies, it is possible to collect many trials in a given task and to perform more than one task in the same patient. This advantage is of particular importance because it improves statistical power and allows for the execution of control trials. With other techniques used in human studies, time (*i.e.,* single/multi unit recordings in the operating room) and cost (*i.e.,* fMRI or MEG) restraints lead to small data collection periods, which limit the ability to make strong inferences or to account for alternative explanations for an observed effect. In contrast, studies conducted in animal models allow for long recording periods but are typically limited to one type of behavior due to constraints of behavioral training. Moreover, patients can also provide feedback, either positive or negative, on the task and how to potentially improve the patient experience in the future.

While there are multiple advantages to this type of research, there are some disadvantages as well. As these patients are confined to their room while they are being monitored after surgery, the behavioral task must adapt to the constraints of the room, which may include location of outlets, background noise from appliances in the room, or interruptions from clinical personnel. Observations should be made during the recordings so that any unexpected artifacts may be accounted for. With respect to the data collected, the brain areas targeted are determined solely by the surgical team in an effort to locate the EZ, therefore researchers need to understand they may not always collect data from their ideal target or from brain areas that are not affected by disease. Another drawback is the potential for confounding effects of any analgesics or medications that the patient may be taking at the time they are performing the behavioral task. Without controls to account for these confounds, there is no way to determine how medications will affect the patient's ability to perform the task; although in some cases, the effects of analgesics or medications may be the focus of the study.

Other issues with this technique include patient safety and integrity of clinic electrophysiological data. namely every effort should be made to guard against injury to the patient during the experimental task. For instance, in this study, we chose to have the patients in a chair while they performed the behavioral task. The chairs we used are a normal furnishing in our epilepsy seizure monitoring rooms and are designed to reduce patient injury during seizure events. Often the patient is already in the chair before we start the experiment and requests to remain in the chair after the experiment is completed. With regard to protecting clinical data, connections to the acquisition system should be made without disrupting data acquisition for clinical purposes. We accomplish this through the use of a second acquisition system for collecting research data in our subjects that is independent of the clinical acquisition system. However, this may cause synchronization errors between the behavioral presentation system and the clinical acquisition system, which can be corrected for in advance, if forethought is given to the hardware requirements needed to connect the behavioral system to the acquisition system. Finally, the research team must be flexible to accommodate the patient's medical needs, especially with respect to scheduling around the clinical staff.

Directly correlating human brain activity to behavior is an important opportunity to advance the understanding of brain function and dysfunction. The data obtained through intracranial recordings has a number of advantages over other invasive and noninvasive techniques, but does not render these other techniques invalid or obsolete. In fact, the combination of intracranial recordings and data collected noninvasively or in an animal model is complimentary and only strengthens the ability to understand the mechanisms of information processing and behavioral control. While human electrophysiological experiments are filled with obstacles and require a great deal of patience, these techniques have the ability to yield novel and exciting information with regard to human behavior.

Disclosures

The authors have no conflicts to disclose.

Acknowledgements

This work was supported by EFRI-MC3: # 1137237 awarded to S.V.S. and J.T.G.

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