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Investigating the Function of Deep Cortical Structures Using Stereotactic Electroencephalography: Lessons from the Anterior Cingulate Cortex

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Abstract:	<p>Stereotactic Electroencephalography (SEEG) is a technique used to localize seizure foci in patients with medically intractable epilepsy. This procedure involves the chronic placement of multiple depth electrodes into regions of the brain typically inaccessible via subdural grid electrode placement. SEEG thus provides a unique opportunity to investigate brain function. In this paper we demonstrate how SEEG can be used to investigate the role of the dorsal anterior cingulate cortex (dACC) in cognitive control. We include a description of the SEEG procedure, demonstrating the surgical placement of the electrodes. We describe the components and process required to record local field potential (LFP) data from consenting subjects while they are engaged in a behavioral task. In the example provided, subjects play a cognitive interference task, and we demonstrate how signals are recorded and analyzed from electrodes in the dorsal anterior cingulate cortex, an area intimately involved in decision-making. We conclude with further suggestions of ways in which this method can be used for</p>

	investigating human cognitive processes.
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September 30th, 2014

Allison Diamond
Associate Editor – Life Sciences
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1 Alewife Center, Suite 200
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Dear Ms. Diamond,

We are pleased to submit our manuscript entitled “Investigating the Function of Deep Cortical and Subcortical Structures Using Stereotactic Electroencephalography: Lessons from the Anterior Cingulate Cortex” to be considered for publication in the Journal of Visualized Experiments (JoVE). We believe that JoVE’s unique multimedia format is perfect for this study as it combines a surgical technique with task-based human subject research in order to obtain local field potential data (LFP) from specific neuronal regions. Basic science studies that use single neuron or LFP recordings in their analysis frequently have minimal detail regarding the surgical techniques used to place the electrodes properly. On the other hand, clinically focused surgical research demonstrating new or updated techniques will frequently include patient outcomes and complication rates but rarely include any data that can be used to investigate neuronal function. Thus, we believe this manuscript, if published in JoVE’s multimedial format, has the potential to fill this significant gap in the literature.

In this paper, we describe how the implantation of stereotactic electroencephalography (SEEG) electrodes into patients with medically refractory epilepsy can be used to investigate cognitive function in regions of the brain that have traditionally been difficult to access for neuroscientists. We include a description of the SEEG procedure, the components and process required to record LFP data from subjects while they are engaged in a behavioral task and demonstrate how signals are recorded and analyzed from electrodes in the dorsal anterior cingulate cortex, an area intimately involved in decision-making.

Drs. Sheth, McKhann and Feldstein contributed to the patient selection and surgical procedures portion of the manuscript. All other authors contributed to the writing, data preparation and manipulation and review of the manuscript. Drs. Sheth, McGovern and Ms. Ratneswaran were involved in the conception of the manuscript. The material in this manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language. We thank you in advance for consideration and review of our work.

Sincerely,

Robert McGovern
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TITLE:

Investigating the Function of Deep Cortical and Subcortical Structures Using Stereotactic Electroencephalography: Lessons from the Anterior Cingulate Cortex

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SHORT ABSTRACT:

Stereotactic Electroencephalography (SEEG) is an operative technique used in epilepsy surgery to help localize seizure foci. It also affords a unique opportunity to investigate brain function. Here we describe how SEEG can be used to investigate cognitive processes in human subjects.

LONG ABSTRACT:

Stereotactic Electroencephalography (SEEG) is a technique used to localize seizure foci in patients with medically intractable epilepsy. This procedure involves the chronic placement of multiple depth electrodes into regions of the brain typically inaccessible via subdural grid electrode placement. SEEG thus provides a unique opportunity to investigate brain function. In this paper we demonstrate how SEEG can be used to investigate the role of the dorsal anterior cingulate cortex (dACC) in cognitive control. We include a description of the SEEG procedure, demonstrating the surgical placement of the electrodes. We describe the components and process required to record local field potential (LFP) data from consenting subjects while they are engaged in a behavioral task. In the example provided, subjects play a cognitive interference task, and we demonstrate how signals are recorded and analyzed from electrodes in the dorsal anterior cingulate cortex, an area intimately involved in decision-making. We conclude with further suggestions of ways in which this method can be used for investigating human cognitive processes.

INTRODUCTION:

Epilepsy, a common neurological disorder characterized by multiple recurrent seizures over time, accounts for 1% of the worldwide burden of diseases¹. Anti-epileptic medications fail to control seizures in 20-30% of patients^{2,3}. In these medically intractable patients, epilepsy surgery is often indicated^{4,5}. The decision to proceed with surgery requires locating the seizure focus, a prerequisite to formulating a surgical plan. Initially, non-invasive techniques are used to lateralize and localize the seizure focus. Electroencephalography (EEG), for example, measures cortical electrical activity recorded from electrodes placed on the scalp and can often provide sufficient information about the location of the seizure focus. In addition, magnetic resonance imaging (MRI) can demonstrate discrete lesions, such as hippocampal sclerosis, the classic pathology seen in the most common form of medically intractable epilepsy, mesial temporal lobe epilepsy (MTLE).

Frequently, however, the noninvasive workup is unable to identify a seizure focus. In these cases, invasive electrocorticography (ECoG) with intracerebral electrodes is required to localize the focus and guide further surgical treatment⁶. ECoG is a neurophysiological technique used to measure electrical activity using electrodes placed in direct contact with the brain. Grids or strips of surface (subdural) electrodes are placed over the surface of the brain, a process that requires a craniotomy (removal of a bone flap) and large opening of the dura. These surface electrodes can be placed over the putative area(s) of seizure onset. The distal ends of the electrodes are tunneled through small openings in the skin and connected to the recording equipment in the epilepsy monitoring unit (EMU). In the EMU, the patient is monitored for clinical seizure activity through continuous video and ECoG recordings. This technique is useful for collecting long-term (days to weeks) recordings of ictal and interictal electrical discharges over relatively large areas of the cortical surface. While these intracranial recordings are invaluable clinically for investigating seizure foci and propagation, they also provide us with the opportunity to investigate cognitive function and neurophysiology in humans undergoing specifically designed behavioral tasks.

ECoG using subdural grid electrodes has been used to investigate various aspects of cortical function, including sensory and language processing. As one of many examples, Bouchard *et al* demonstrated the temporal coordination of the oral musculature in the formation of syllables for spoken language in the ventral sensorimotor cortex, a region identified as the human speech sensorimotor cortex⁷. Furthermore, ECoG with subdural grid placement has also been utilized to study the mechanisms by which humans are able to attend to a particular voice within a crowd: the so-called 'cocktail party effect'^{8,9}. ECoG recordings demonstrated that there are two distinct neuronal bands that dynamically track speech streams, both low frequency phase and high-gamma amplitude fluctuations, and that there are distinct processing sites - one 'modulation' site that tracks both speakers, and one 'selection' site that tracks the attended talker⁵.

Another emerging application of ECoG with subdural electrode placement is the potential for use with Brain Computer Interfaces (BCIs), which "decode" neuronal activity in order to drive an external output. This technology has the potential of allowing patients with severe brain or spinal cord injuries to communicate with the world and manipulate prostheses^{10,11}.

While subdural grid placement has contributed greatly to our understanding of superficial cortical areas and is useful in identifying cortical epileptogenic foci, this technique does require a craniotomy and its attendant risks, and is generally limited to studying the outer surface of the brain. Stereotactic electroencephalography (SEEG) is a technique that enables the assessment of deep epileptogenic foci¹². With a long history of use in France and Italy, it is also increasingly being used in the US¹³. SEEG involves the placement of multiple electrodes (typically 10-16) deep within the substance of the brain through small (few mm) twist drill burr holes. Advantages of SEEG over subdural grid placement include its less invasive nature, the ease of examining bilateral hemispheres when required, and the ability to generate three-dimensional maps of seizure propagation. Furthermore, these electrodes enable the identification of deep epileptogenic foci that were previously difficult to identify with surface electrodes. This procedure also provides the opportunity to investigate the neurophysiology and function of deep cortical structures, such as the limbic system, the mesoparietal cortex, the mesotemporal cortex, and the orbitofrontal cortex, all of which were previously difficult to directly investigate in humans.

This paper demonstrates how SEEG can be utilized to investigate cognitive function in the dorsal anterior cingulate cortex (dACC). The dACC is a widely investigated brain region, but it is also one of the most poorly understood. Considered a significant region for human cognition, it is likely that the dACC is central to the dynamic neural processing of decisions in the context of continuously changing demands imposed by the environment¹⁴. Studies in both primates^{15,16} and humans¹⁷ suggest that the dACC integrates potential risks and rewards of a given action, especially in situations of multiple simultaneous conflicting demands¹⁸⁻²¹, and modulates these decisions in the context of previous actions and their outcomes^{14,22,23}.

The Multi- Source Interference Task (MSIT), a Stroop-like behavioral task, is frequently used to investigate conflict processing in the dACC. The MSIT task activates the dACC by recruiting neurons involved in multiple domains of processing regulated by the dACC^{24,25}. This task specifically activates the dACC by testing features of decision-making, target detection, novelty detection, error detection, response selection, and stimulus/response competition. In addition, the MSIT task introduces multiple dimensions of cognitive interference, which are utilized in this study to investigate dACC neural responses to simultaneous conflicting stimuli using SEEG.

PROTOCOL:

Ensure that each patient is reviewed for suitability for the research study, and appropriate patients must be consented for participation in the study according to local IRB procedures.

1. Patient Selection for SEEG and Research

1.1) Patient Selection for SEEG

Note: Epilepsy patients must be clinically assessed by a multidisciplinary team consisting of epileptologists, neuropsychologists and neurosurgeons.

1.1.1) Ensure that the patient has medically refractory focal epilepsy, defined as failure to respond to at least 2 adequate trials of anti-epileptic medications.

1.1.2) Ensure that non-invasive techniques have failed to localize the epileptogenic foci.

1.1.3) Confirm with multidisciplinary team that patient is not suitable for investigation only with subdural grid electrodes.

1.1.4) Confirm with multidisciplinary team that there is clinical suspicion of a deep seizure onset zone.

1.2) Patient selection for research task

1.2.1) Ensure that subject is between the ages of 13 and 65 years.

1.2.2) Obtain consent or assent (together with parental consent if below the age of 18 years) from the patient.

1.2.3) Ensure that subjects are able to attend to the task and cooperate with the testing.

2. Preparation and Implantation Technique

2.1) Preparation

2.1.1) Perform a volumetric T2 and contrast enhanced volumetric T1 MRI preoperatively and transfer the images to the stereotactic navigation software, according to manufacturer's protocol.

2.1.2) Plan the depth electrode targets based on the MRI and clinical suspicion of seizure foci.

Note: The examples provided are based on the BrainLab navigation software and are thus specific to this system. However, any stereotactic navigation software can be used to plan depth electrode trajectories and placement.

2.1.3) Define the anatomical region of interest as the target point within the "Stereotactic Planning" function in the stereotactic navigation software.

2.1.3.1) For example, use dACC as the target of interest. To define its trajectory, press "New Trajectory," then press "target" and click on the dACC. Center the target in the middle of dACC by examining dACC in all 3 planes (axial, coronal and sagittal) and clicking on the middle of dACC in each plane.

2.1.4) Define the entry point on the scalp within the "Stereotactic Planning" function in the stereotactic navigation software.

2.1.4.1) For example, choose a point on the scalp that appears to be the shortest path to the dACC. Press “entry” and choose the point on the scalp to make the entry point.

2.1.5) Click and drag the “target” and “entry” points to modify the defined trajectory to avoid cortical and subcortical vascular structures as well as any potential eloquent cerebral regions.

2.1.6) Repeat for all planned depth electrode targets (Figure 1).

2.1.7) Admit the patient on the morning of the surgery, bring to the operating room, and induce under general anesthesia^{26,27}.

2.1.8) Attach a Cosman-Roberts-Wells (CRW) stereotactic headframe to the patient’s head with skull screws.

2.1.9) Obtain a volumetric CT with the headframe in place.

2.1.10) Load the volumetric CT and MRI images into the stereotactic navigation software via the “Load and Import” function.

2.1.11) Click on the “Localization” function within the stereotactic navigation software.

2.1.12) Localize the CRW headframe by clicking on all of the images defined by the stereotactic navigation software as containing the headframe and then pushing the “Assign localizer” button.

2.1.13) Click on the “AC/PC Localization” function within the stereotactic navigation software.

2.1.14) Identify the anterior and posterior commissures based on their anatomical location.

2.1.15) Designate the anterior and posterior commissures via the “Set AC/PC system” function within the stereotactic navigation software.

2.1.16) Click on the “Image Fusion” function within the stereotactic navigation software.

2.1.17) Merge the CT images with the MRI images in the stereotactic navigation software^{28,29}. Click on the paired volumetric CT and MRI images underneath the “Fusion” tab and then click “Auto Fusion”.

Note: This places the MRI within the stereotactic frame coordinates.

2.1.18) Click on the “Stereotactic Planning” function within the stereotactic navigation software and confirm the planned trajectories from steps 2.1.2-2.1.6.

2.1.19) Choose the volumetric CT as the stereotactic reference under the “Stereotactic Functions” tab.

2.1.20) Click the “print” icon in the vertical column of icons to print the final stereotactic coordinates for each depth electrode trajectory^{30,31}.

2.2) Implantation technique

2.2.1) Return the patient to the operating room following the CT scan.

2.2.2) Prepare and drape the surgical field using routine sterile methods^{32,33}.

2.2.3) Ensure that a fluoroscope is in the operating room and draped along with the rest of the surgical field.

2.2.4) Using the printed stereotactic coordinates from step 2.1.20, set the coordinates for the first depth electrode on the headframe.

Note: The stereotactic coordinates are given in 3 planes: lateral (x), vertical (y) and anterior-posterior (z). For example, the printed coordinates for a target in the right dACC are +48.2 mm A-P, 6.6 mm Lateral and +2.2 mm Vertical. The headframe is then set to those coordinates accordingly.

2.2.5) Extend the guideblock down to the skin and mark the location of the burr hole on the scalp with a marking pen. Fix the guideblock in place based on the stereotactic coordinates and as such, no landmarks are necessary to mark the incision.

2.2.6) Inject 2-3 mL of 0.5% bupivacaine in a 1:100,000 dilution of epinephrine into the marked incision.

2.2.7) Make a nick in the scalp with a scalpel down to the skull into the marked incision.

2.2.8) Cauterize the dermis and deep tissue using monopolar cautery directed with a coated obturator in order to minimize any bleeding from vessels in the skin or subcutaneous tissue.

2.2.9) Drill a burr hole using a 2.1 mm twist drill bit in the middle of the incision.

2.2.10) Open the dura with a rigid obturator probe. Screw an anchor bolt into the skull. Place a pre-measured stylet probe through the anchor bolt to make a track for the electrode.

2.2.11) Carefully advance the electrode to the pre-calculated depth. Tighten the anchor bolt cap down to secure the electrode.

2.2.12) Repeat this process for all of the depth electrodes.

2.2.13) Place the fluoroscope underneath and surrounding the patient's head in both AP and lateral planes to obtain fluoroscopic images to ensure adequate placement trajectories of all electrodes.

2.2.14) Connect the electrodes to the clinical EEG system to verify appropriate impedances.

2.2.15) Wake the patient from anesthesia and transport to the recovery room, and subsequently to the EMU.

2.2.16) In the EMU, monitor the patient via closed circuit monitoring for clinical seizures and via ECoG for electrographic evidence of seizures.

3. Behavioral Task and Data Acquisition

3.1) Behavioral task

3.1.1) Open behavioral software on computer devoted solely to running the behavioral software.

Note: The instructions provided are based on MonkeyLogic, a MATLAB toolbox designed for the presentation and execution of temporally precise psychophysical tasks^{34,35} and are thus specific to that behavioral software platform. This program is run on Matlab version 2010a and requires the "Data Acquisition Toolbox." However, any behavioral software platform capable of presenting visual stimuli and recording electrophysiological data could be used.

3.1.2) Set the conditions file designed to run the MSIT task to include all four trial types of equal frequency.

Note: The MSIT task consists of presenting the subject with a cue of three numbers between 0 and 3, where two of the numbers, the 'distractors', are the same and one number, the 'target', is different.

3.1.2.1) Instruct the subject to identify the 'target' by pressing the corresponding button on a button box. If '1' is the target, the left button is the correct choice. If '2', the middle button, and if '3', the right button. '0' does not correspond to a possible button (Figure 2).

3.1.3) Press the "Set conditions" button and choose the desired conditions file set in the prior step.

Note: There are two types of cognitive interference that induce conflict during the decision making process. Flanker interference trials occur when the distractors are possible (1, 2, or 3, rather than 0) button choices (e.g., 121), while spatial interference trials occur when the target number's spatial location differs from the response location (e.g. 200, in which the middle button is the correct response, despite the fact that the target number is in the left position). There are four trial types based on the presence or absence of these two interference types.

3.1.4) Test the behavioral display monitor by clicking “Test” in the display box. The display monitor should show the test visual stimulus for 2-3 seconds.

3.1.5) Connect the subject interface device (button box) to the analog inputs on the data acquisition board on the computer devoted to recording the electrophysiological data via three standard BNC cables.

3.1.6) Connect the button box to a power source.

3.1.7) Connect the data acquisition board to the 512-channel neural signal processor via a ribbon cable split into 9 ribbons. 8 of the ribbons are connected to ports 0-7 on the digital I/O portion of the data acquisition board while the 9th ribbon is connected to port 0 on the digital PFI portion of the data acquisition board.

Note: The ribbons send 8-bit digital markers (ports 0-7, digital I/O) and a strobe pulse (port 0, digital PFI), to the neural signal processor.

3.1.8) Set the desired sampling rate in the neural signal processor software.

3.1.8.1) In this example, set the desired sampling rate to 50,000 samples per second, alias and down-sample online to 1000 samples per second. Adjust the sample rate to fit the specific goals of the task. Sub-millisecond precision timing requires an extremely high sampling rate.

3.1.9) Connect the amplifier to the neural signal processor via fiber optic cable.

3.1.10) Connect the neural signal processor to the data streamer and the optical PCI card in the neural data acquisition computer via fiber optic cable.

3.2) Data acquisition

3.2.1) Use the research rig for EMU electrophysiology containing a 512-channel neural signal processor for processing and filtering digitized, pre-amplified electrical signals from the depth electrodes.

Note: While there are 512 channels for processing, in practice, there are never more than 15-20 electrodes placed for clinical purposes. Therefore, we recommend recording from as many electrodes as feasible as data size and spatial resolution is never an issue.

3.2.2) Transport the rig to the patient’s room, place the behavioral monitor in front of the patient on a portable table and connect to the behavioral control computer running the behavioral software using a standard DVI cable.

3.2.3) Place the recording rig behind or to the side of the patient’s bed in order to remain as unobtrusive as possible.

3.2.4) Connect the research system to the splitter box that separates the research recording from the clinical system.

3.2.5) Control recording parameters and instantiation using the neural signal processor software^{34,35}.

Note: This system enables sub-millisecond control over behavioral events^{34,35}. Synchronization between neural and behavioral data can be accomplished with either analog pulses coding for task events or digital markers. Both signals can be sent from either the digital or analog outputs on the data acquisition board to the analog or digital inputs on the neural signal processor.

3.2.6) Hand the patient the subject interface device (button box) and give task instructions.

3.2.7) Click "Run" to run the task.

3.2.8) Allow the patient to complete 2 blocks of 150 trials each.

4. Data Analysis

4.1) Open software package that allows for visualization of electrophysiological data.

Note: The instructions provided below are specific to Matlab version 2010a but any software that allows for visualization and manipulation of electrophysiological data can be used.

4.2) Open .edf file containing raw electrophysiological data from the trial session.

4.3) Visualize SEEG signal from the session to ensure there is no visible artifact such as epileptiform discharges or movement artifact (Figure 3A).

4.4) Overlay the timing pulses from the behavioral task onto the raw LFP trace (Figure 3B) to illustrate how analog pulses can delineate trial structure.

4.5) Using the timing pulses, align the SEEG trace to cue presentation for each trial (Figure 3C).

4.6) Remove outliers (>4 standard deviations) and artifact traces (Figure 3D).

4.7) Save all aligned trials in a matrix for further analyses (20 trials shown stacked in Figure 3E).

4.8) Average LFP activity across trials to reduce effect of noise, artifact, or EEG activity not related to the presented stimuli, and to increase the signal of interest (Figure 3F).

4.9) Create the raw, trial-averaged spectrogram using multi-tapered spectral analysis³⁶⁻³⁸.

Note: Time-frequency analysis can be used in order to investigate the specific spectro-temporal dynamics across single or multiple trials. This method enables the investigation of neuronal oscillations at different frequencies over time.

4.10) Pad the signal from each trial with zeroes to the next largest power of 2 to avoid edge effects.

4.11) Apply a 800 ms sliding window with 5 leading tapers and a time-bandwidth product of 9 every 10 ms through the duration of the signal to create the spectrogram (Figure 4A).

4.12) Multiply the log of the spectrogram by 10 and normalize to display higher frequency information.

Note: Spectrograms can be normalized by a theoretical frequency distribution (i.e. each frequency value raised to the negative 2nd power)(Figure 4B), the mean spectrum of some baseline activity (Figure 4C), or by dividing by the mean and subtracting the standard deviation of the values in each frequency band (Figure 4D). This procedure allows for the examination of specific frequency bands in both raw and normalized forms over time for changes specific to the task. For example, high gamma band activation (70-150 Hz), which is shown in Figure 3E, is thought to reflect local excitatory activity of the local neuronal population surrounding the electrode^{39,40}.

REPRESENTATIVE RESULTS:

Once a patient is selected for SEEG electrode placement, he/she undergoes a volumetric T2 and T1 contrast enhanced MRI. SEEG electrode trajectories are then planned using stereotactic navigation of the volumetric MRI sequences (Figure 1). This technique allows for the collection of local field potentials from structures deep within the cortex such as dorsal anterior cingulate cortex (light orange trajectory, Figure 1) that would not be possible with typical surface electrode placement. Post-operatively in the EMU, the patient performs the Multi-Source Interference Task (Figure 2), designed to activate dACC neurons. After an adequate number of trials, the local field potential data from the SEEG electrodes in dACC are preprocessed in order to align the LFP data to cue presentation for subsequent meaningful analysis (Figure 3). In addition, once aligned, the LFP data can be averaged to examine changes in the averaged electrophysiological response between trial types (Figure 3F). Subsequently, multi-taper spectrograms are made to investigate changes in frequency bands over time (Figure 4). As scalp EEG studies have implicated different frequency bands in the activity seen in dACC, time-frequency analysis is an important method to link the electrophysiological changes in dACC with behavior.

Figure 1. Planned SEEG electrode trajectories using stereotactic navigation of volumetric T1 contrast enhanced MRI. Top left panel. Top down view of three-dimensionally reconstructed face with superimposed planned SEEG electrode trajectories. Top right, bottom left, and bottom right panels. Axial, sagittal and coronal views of planned SEEG electrode trajectories superimposed onto patient's MRI. Orange electrode trajectories represent implantation into the anterior cingulate cortex bilaterally.

Figure 2. The Multi-Source Interference Task. Initially, the subject fixates on a cross in the middle of the screen prior to the cue being shown. The cue is then presented and the subject must identify the “target” number, which is the one number different from the other two numbers presented. The subject indicates the choice with a button push: left button if the target is “1”, middle if “2” and right if “3.” In this example, if the subject presses the middle button, he/she is shown the number “2” in green, indicating he/she made the correct choice. If he/she chooses either of the other buttons, “2” is shown in red, indicating an incorrect choice. Subjects also undergo trials in which they do not receive valenced feedback about their choice, in which case the “2” is shown in blue regardless of whether the choice is correct or not.

Figure 3. Preprocessing SEEG data. A. All data recorded from a single channel in the dACC. B. A minute-long recording from anterior cingulate cortex with overlaid timing pulses for the behavioral task. C. Data for each trial aligned on the cue presentation. D. Data for each trial aligned on the cue presentation with outliers and artifact traces removed. E. LFP from 20 trials aligned on cue presentation and stacked. F. Averaged LFP aligned on cue presentation from a medial prefrontal electrode. Dotted lines represent the onset of the fixation point. Dashed lines represent the cue onset. Dash-dotted lines represent the average response time.

Figure 4. Spectral analysis. A. Raw trial-averaged multi-taper spectrogram aligned on cue. B. The same spectrogram in A normalized by $1/f^2$. C. The same spectrogram in A normalized by the mean spectrum from 500 milliseconds before the cue. D. The same spectrogram in A normalized by frequency band. E. Mean high gamma band power for normalized and unnormalized spectra. In all plots, dotted lines represent the onset of the fixation point, dashed lines represent the cue onset, and dash-dotted lines represent the average response time. Colored bars indicate the high gamma bands used in E.

DISCUSSION:

In this paper SEEG was used to investigate the activity of local neuronal populations within the dACC during a decision-making task in humans. Previous work has investigated the activity of individual neurons in the dACC using intraoperative microelectrode recordings¹⁴ and demonstrated that dACC activity is modulated by previous activity. Microelectrode studies enable the investigation of the spiking activity of individual neurons. SEEG measures LFPs, which are related to the summated synaptic potentials across a large population of neurons. SEEG therefore allows the opportunity to simultaneously investigate population neuronal activity from several brain regions.

When using a clinical technique such as SEEG to investigate scientific questions, it is critical to first ensure that the operative and research plans are aligned. The clinical problem to be solved involves determining the patient’s seizure onset zone and will always take precedence. Because the operative plan is dictated by clinical need, it will not always be possible to investigate the same research problem with every case. Thus, we have developed a series of tasks designed to answer separate scientific questions that can be adapted to the patient’s operative plan depending on the regions being interrogated with electrodes.

In this study, SEEG LFP data was utilized to investigate cognitive control over goal directed behavior in the dorsal anterior cingulate cortex, a deep cortical structure in the medial prefrontal region that is difficult to investigate in humans. LFP data acquisition can be carried out with many different systems. A crucial aspect to consider is the sampling rate as this must be high enough to acquire the signals in which the researcher is interested. In general, the sampling rate should be four times higher than the highest frequency band being examined. For example, if the researcher is interested in looking at evoked potentials (<50 Hz), the sampling rate need only be around 200 samples/s. However, if the scientific question involves examining high gamma activity (60-200 Hz), the sampling rate should be at least 500 samples/s. Additionally, the system should be able to record enough electrodes as are implanted, and hardware filters on the data acquisition system should not exclude frequency bands of interest. For example, many systems do not record direct current signals. If the researcher is interested in studying very slow signals, he/she should use a recording system with an appropriately low high-pass hardware filter. During the data analysis stage, it is important to remove trials with very large or fast transients and remove channels or trials that exhibit epileptiform activity as normal physiology is very difficult to study in the presence of epileptiform activity.

The role of the dACC in error prediction^{23,41}, processing reward motivated action¹⁵ and in behavioral adaptation in the context of competing demands¹⁸⁻²¹, conflicting responses⁴² and previous activity^{14,22,23}, is well established. However, a unified and integrative theory for the specific neural mechanisms by which the dACC modulates cognitive control is still subject to conjecture due to a lack of empirical evidence from human studies investigating these domains simultaneously^{43,44}. SEEG provides the opportunity to investigate neural activity in the human dACC and therefore contribute to an integrated understanding of dACC function.

SEEG affords the opportunity to investigate other cortical areas which may be difficult to access with surface electrodes, such as the orbitofrontal cortex (OFC), whose involvement in the emotional and reward-based aspects of decision-making has been explored in studies using single unit recordings in macaque monkeys⁴⁵ and connectivity studies in humans using diffusion-weighted imaging tractography⁴⁶. While these studies have contributed to the theory of OFC function in human decision-making⁴⁷, there is a scarcity of literature in humans studying OFC function specifically⁴⁸. SEEG provides the opportunity to address this knowledge gap. Furthermore, SEEG can be used to demonstrate the function of different regions of the limbic system, a collection of deep cortical and subcortical structures involved in processing emotion, pain, fear and negative affect. One such SEEG study investigating the response of the limbic system to expressive faces has demonstrated that the hippocampus and amygdala contain specific neuronal populations that distinguish happy from fearful faces, while amygdala neuronal populations appear to track the subjective judgment of these emotional faces⁴⁹. Dysfunction in these regions is believed to be implicated in anxiety disorders⁵⁰ including obsessive-compulsive disorder⁵¹, and SEEG studies provide the opportunity to understand the affected neural pathways and pathophysiology of these disorders in more detail.

Furthermore, SEEG can be utilized to investigate the precuneus, a site that is often targeted during SEEG epilepsy investigations, but rarely covered with subdural grid implants. The

function of this region of the postero-medial parietal lobe is poorly understood, primarily because of its anatomical location deep within the interhemispheric fissure. Functional imaging studies have shown that the precuneus is active in the 'default mode' or conscious resting state⁵², in self processing⁵³⁻⁵⁵, and in episodic memory processing, including for autobiographical memories^{56,57}. However, since these findings are based on limited studies in non-human primates and humans, our understanding of the neurocognitive importance of this region is still in its infancy⁵⁸. With SEEG, we now have the potential to investigate neuronal activity within the precuneus in awake humans, which may provide novel insight into the function of this brain region.

As with any technique, SEEG has limitations in both its acquisition and use. As a clinical technique, it is necessarily limited by both patient selection and the clinical nature of the patient's epilepsy. While researchers can design a number of tasks to work around this limitation, the anatomical regions studied will always be limited by the operative plan. In addition, as previously mentioned, SEEG record local field potentials, which represent the summed synaptic potentials of many neurons. Thus, this technique does not have the spatial resolution of single neuron recording techniques and cannot provide data on spiking activity or action potential waveforms. As such, when designing tasks to investigate scientific questions, it is important to ensure that LFP data can answer the question of interest.

In this paper, SEEG was utilized to investigate deep cortical and subcortical structures that were previously difficult to study in awake human subjects. These studies have the potential to enhance our understanding of human cognitive processes. As SEEG is increasingly incorporated as a tool within the armamentarium of epilepsy programs, the opportunity of neuroscientists to harness its potential to study the human brain will grow significantly.

DISCLOSURES:

The authors have no conflict of interest to disclose.

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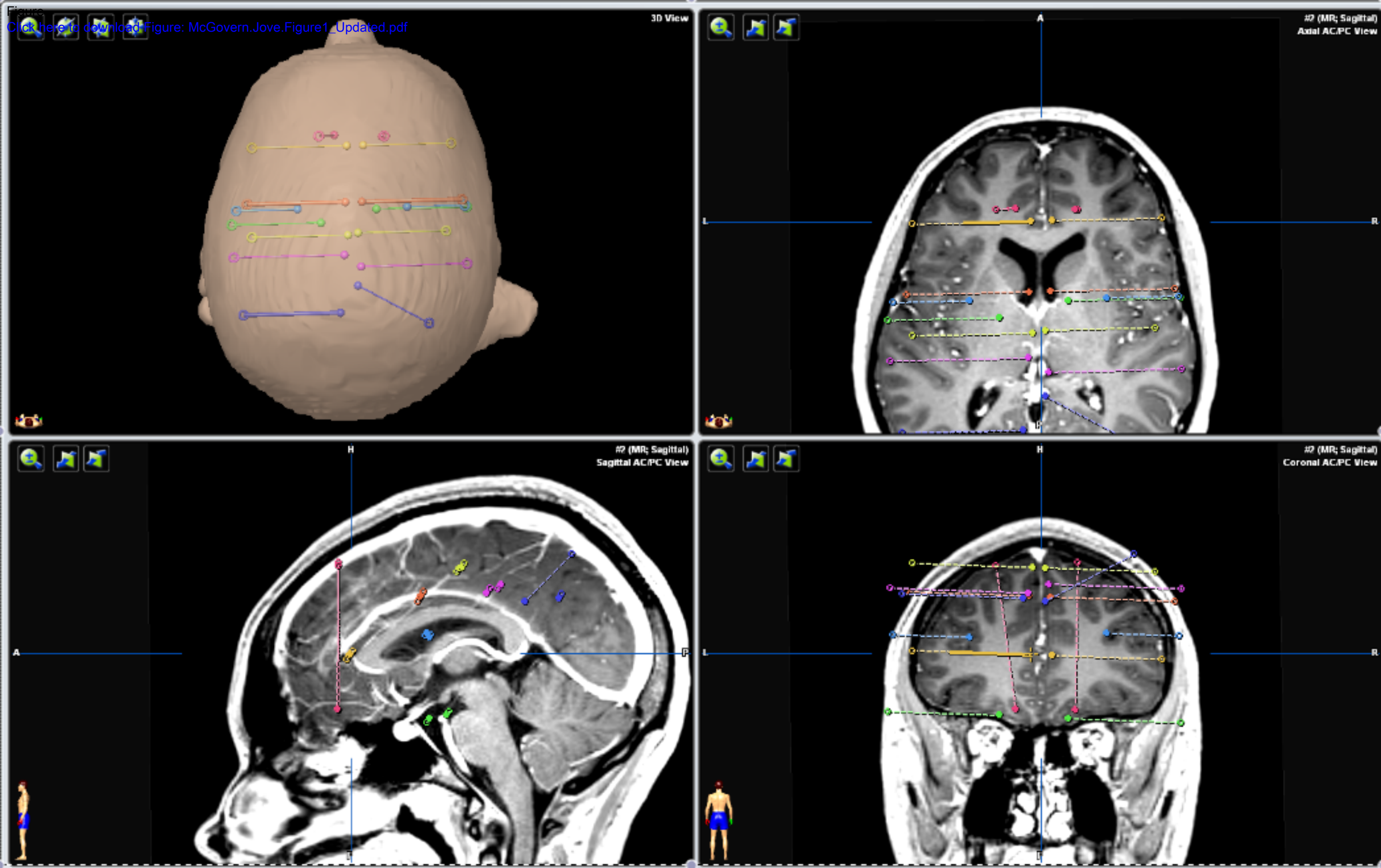
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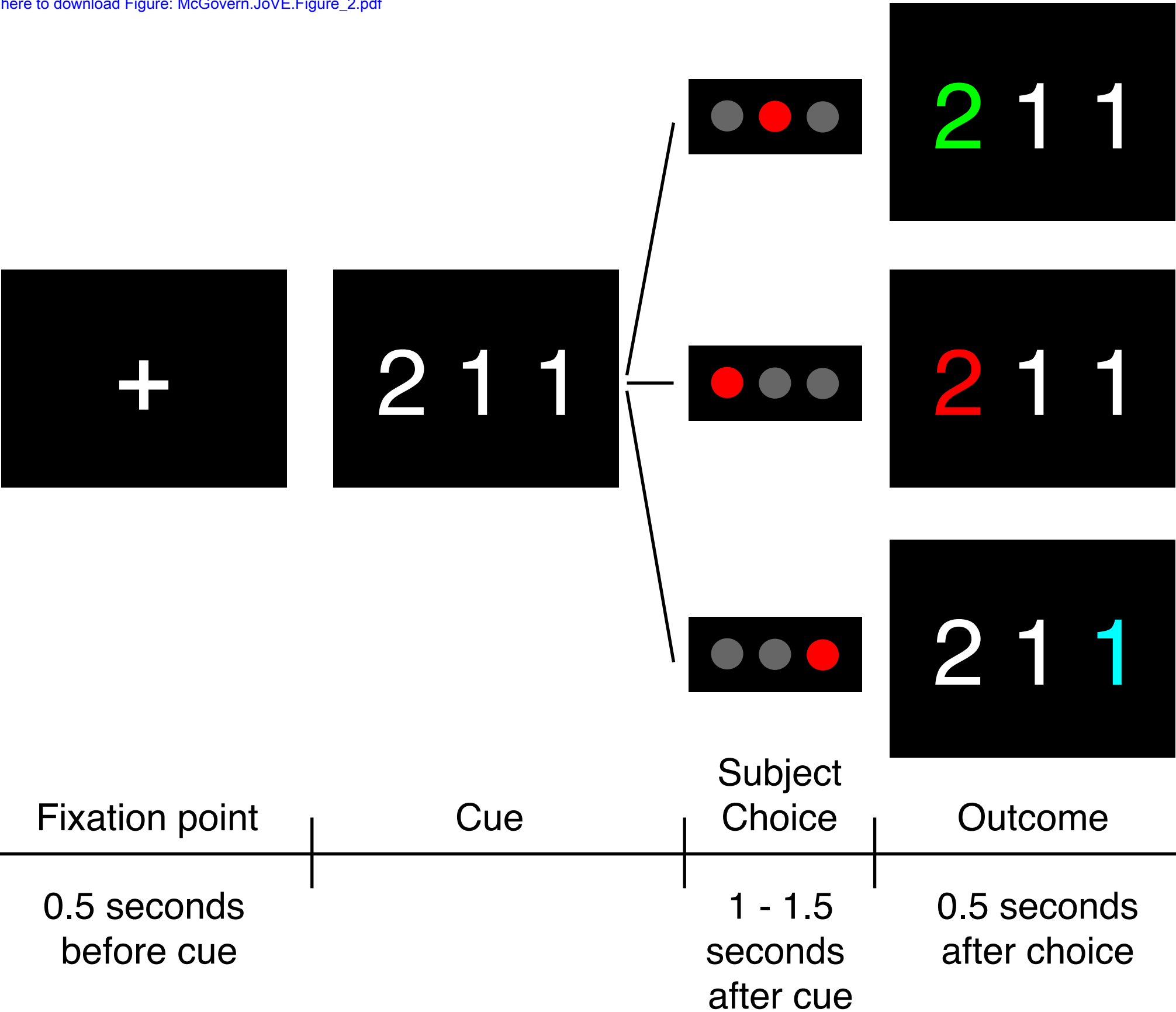
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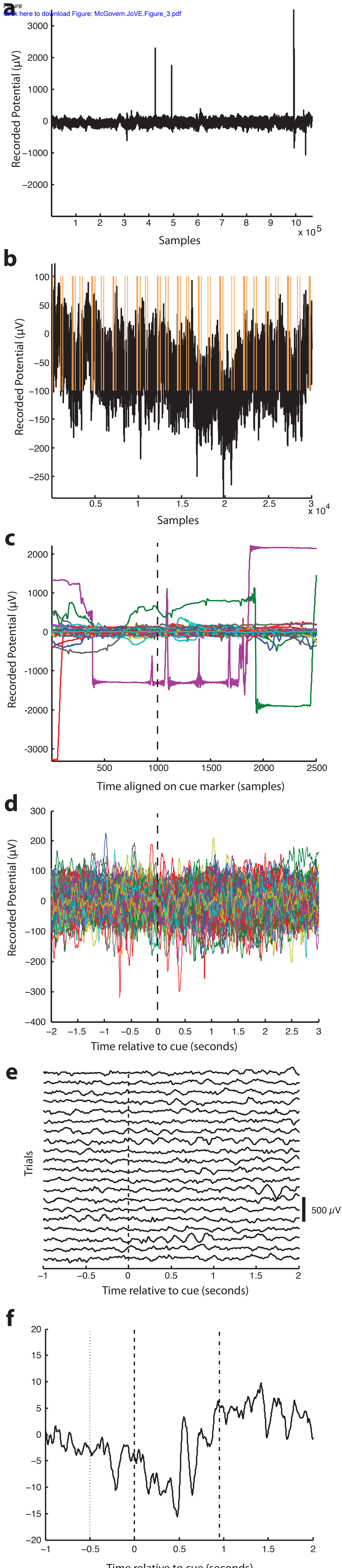
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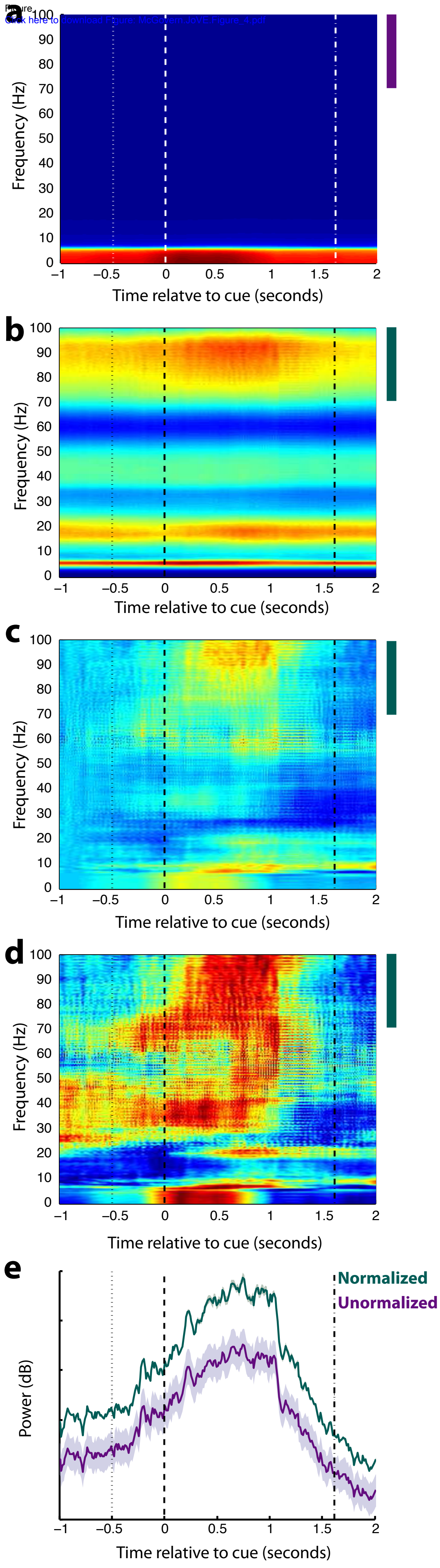
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Column1

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Materials

Trigger I/O cable

BNC cables for analog pulses

Power strip with surge protection and battery backup

National instruments multifunctional daq data acquisition box NI PCIe-6382 DAQ cards

Custom made button box - human interface device

Xltek 128 channel clinical intracranial EEG monitoring system EMU128FS

Subject monitor and associated cables for visual stimulus presentation

Personal computer running behavioral software with DAQ cards installed

Mains cable for monitor

Monkey Logic software which runs on Matlab 2010A

MATLAB 2010a software with data acquisition toolbox

sEEG electrodes AD TECH or PMT

Cabrio connectors

Tucker Davis Technologies Amplifier

Tucker Davis Technologies processor

TuckerDavis Technologies data streamer

Fiber optics cables to connect TDT systems

ribbon cable and snap serial connector for digital markers

personal computer for running TDT RPvdsEx and OpenEx software

middle atlantics server cabinet with casters

Tucker Davis Technologies splitter box to split clinical and research recordings

Researcher monitor with requisite cables

button box power source - 5 volts, 2 amperes

TDT optical interface PCI card

Company	Catalog Number
Natus Medical Inc.	5029
Tripp Lite	SMART500RT1U UPC
National Instruments	PCIe-6382 w/ BNC 2090A
Natus Medical Inc.	002047c
Dell	U2212HMc
Superlogics	SL-2U-PD-Q87SLQ-BA
Mathworks	
AD TECH	2102-##-101
PMT	2125-##-01
Tucker Davs Technologies	PZ5
Tucker Davs Technologies	RZ2
Tucker Davs Technologies	RS4
Tucker Davs Technologies	F05
Superlogics	SL-2U-PD-Q87SLQ-BA
Middle Atlantic Products	PTRK-21
Tucker Davs Technologies	
Dell	U2212HMc
Tucker Davs Technologies	P05

Comments/ Description

PS2 to BNC cable

Can be ordered from most electronics stores.

Power source and backup

PCI cards for behavioral control interface

Any human interface device with three buttons may be used. Alternatively, 3 keyboard buttons may be

Clinical recording system

Most Monitors are adequate here.

Computer for recording neural data

Usually comes with the monitor, can be purchased at any electronics store.

Free from MonkeyLogic website

Matlab software

Platinum tip, diameter (0.89 mm, 1 mm, 1.1 mm), uninsulated length 2.3 mm; The ## in the catalog num

The ## in the catalog number indicates the number of contacts on the electrode (08, 10, 12, or 16)

preamplifier for neural data

Neural signal processor for neural data

Data streamer and storage

Fiber optic cables for connecting Tucker Davis Technologies' products.

Can be ordered from most electronics stores.

computer for behavioral control

Server case to house all of the research items

This splitter box is a semi-custom device. Researchers should consult the attending neurologists about

Most Monitors are adequate here.

Can be purchased at any electronics store.

used.

number indicates the number of contacts on the electrode (08, 10, 12, or 16)

splitting the research and clinical recordings in a way that doesn't interfere with clinical care.



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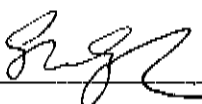
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We thank the reviewers for their careful and helpful comments and set out below the changes we have made to the manuscript in response. These changes are also tracked in the Microsoft Word document.

Reviewer's comments	Authors' response
<u>Major concerns: No major concerns except the figure 1 that is a little bit confusing because all electrodes are superimposed: it seems that some electrodes are implanted in the thalamus or the lateral boarder of the brainstem for example (yellow and green one) which is not the case . It would be nice to have also a view of the electrodes implanted in the anterior cingulate gyrus.</u>	<u>We have modified Figure 1 such that all three planes are demonstrating the anterior cingulate electrodes. Unfortunately, since the electrodes are all in different planes, some of them will appear to be in different planes no matter which cuts we choose.</u>
<u>L 130: at least one of the first paper describing the original methodology should be mentioned to be fair: Talairach J, Bancaud J: Stereotaxic approach to epilepsy. Methodology of anatomo-functional stereotaxic investigations. Progr Neurol Surg 5:297-354, 1973.</u>	<u>Although a search of Medline did not reveal this reference, we have added a similar reference from those authors. Thank you.</u>
<u>L138: I will add the following sentence : SEEG has been used for 4 decades mainly in France and Italy, and for that reason it is more common in Europe.</u>	<u>This has been added.</u>
<u>I 140 : burholes should be replaced by twist drill</u>	<u>This has been changed.</u>
<u>L141 i will add : « the ease of examining bilateral hemispheres, but only when required and not on a systematic basis"</u>	<u>This has been changed.</u>
<u>L181 : Ensure that the patient suffers from focal epilepsy</u>	<u>This has been changed.</u>

<u>L186 : SEEG is not indicated only when grids are not indicated ; in centers using SEEG, all patients requiring depth recordings are explored using SEEG, even if a superficial cortical focus is suspected</u>	<u>The language has been changed.</u>
<u>L526 : LFPs originate from excitatory and inhibitory post synaptic membrane potentials</u>	<u>This has been changed.</u>
<u>L530 : i do not understand what « SEEG Ecog data » means ? do you mean SEEG data ?</u>	<u>Ecog has been removed.</u>
<u>L541 : i am not sure that the orbito cortex is deeply located (as opposed to insula or cingulate cortex), it is at the surface but not easily reached from the convexity</u>	<u>Language changed.</u>
<u>1) It may be useful for the reader to have more information about the electrodes used in the procedure. For instance, are the electrodes from FHC or Medtronic? What is the electrode material? What is the general impedance of the electrodes and the tip diameter and un-insulated length?</u>	<u>We have added those details to the materials section of the paper. Thank you.</u>
<u>2) Although the processor has 512 channels, does the authors suggest an ideal number of depth electrodes that can be (should be) simultaneously recorded from when considering spatial/temporal resolution and technical/data size feasibility and management? As a related question, what is the safest/closest distance that one depth electrode can be from another using the stereotactic navigation software and</u>	<u>The number of electrodes is determined by the clinical status of the patient in terms of potential seizure foci. In practice, there are never more than 15-20 electrodes placed so spatial/temporal resolution and data size management is never an issue. Placed an additional note at line 401 for clarity. In general, the head frame and navigation software claim an accuracy within 1-2 mm but in practice, each electrode is probably at least 1-1.5 cm away from the nearest electrode.</u>

<u>considering surgical considerations, e.g., hemorrhage?</u>	
<u>3) The last page of the manuscript (page 26) is incomplete and the sentence on page 25 starting with "This splitter box is a semi-custom device" is also incomplete.</u>	<u>This may be a function of the Excel table being large in landscape format and going on to the next few pages.</u>