Journal of Neuroscience Methods 304 (2018) 162–167

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Modular auditory decision-making behavioral task designed for intraoperative use in humans

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ARTICLE INFO

Keywords:
Intraoperative
Behavioral paradigm
Matlab
PsychToolbox
Arduino

ABSTRACT

Background: Neurosurgical interventions that require active patient feedback, such as deep brain stimulation surgery, create an opportunity to conduct cognitive or behavioral experiments during the acquisition of invasive neurophysiology. Optimal design and implementation of intraoperative behavioral experiments require consideration of stimulus presentation, time and surgical constraints. We describe the use of a modular, inexpensive system that implements a decision-making paradigm, designed to overcome challenges associated with the operative environment.
New method: We have created an auditory, two-alternative forced choice (2AFC) task for intraoperative use. Behavioral responses were acquired using an Arduino based single-hand held joystick controller equipped with a 3-axis accelerometer, and two button presses, capable of sampling at 2 kHz. We include designs for all task relevant code, 3D printed components, and Arduino pin-out diagram.
Results: We demonstrate feasibility both in and out of the operating room with behavioral results represented by three healthy control subjects and two Parkinson's disease subjects undergoing deep brain stimulator implantation. Psychometric assessment of performance indicated that the subjects could detect, interpret and respond accurately to the task stimuli using the joystick controller. We also demonstrate, using intraoperative neurophysiology recorded during the task, that the behavioral system described here allows us to examine neural correlates of human behavior.
Comparison with existing methods: For low cost and minimal effort, any clinical neural recording system can be adapted for intraoperative behavioral testing with our experimental setup.
Conclusion: Our system will enable clinicians and basic scientists to conduct intraoperative awake and behaving electrophysiologic studies in humans.

1. Introduction

Understanding how the brain uses sensory stimuli to make and act upon a decision is a fundamental goal in neuroscience (Glimcher, 2014; Glimcher, 2003; Gold and Shadlen, 2007; Newsome et al., 1989). Classically, decision-making has been studied in the context of sensory-motor discrimination paradigms. Experimental paradigms that include the acquisition of neural activity at the level of individual action potentials, or spikes, are superior to other measures of brain activity, like fMRI, because spikes allow a higher spatiotemporal resolution readout of basic brain function (Buzsaki et al., 2012; Buzsaki and Mizuseki, 2014; Cisek and Kalaska, 2010). While substantial knowledge has been obtained from spike recordings performed in animal models and such models remain critically important for neuroscience (Cisek and Kalaska, 2010; Newsome et al., 1989), the ultimate goal for neuroscientists is to understand the *human* brain (Insel et al., 2013; Yuste and Bargmann, 2017). While such opportunities are rare, in vivo electrophysiology in human subjects is often performed during select neurosurgical treatments, including tissue resection, epileptic foci mapping, and deep brain stimulation (DBS). During these procedures, most patients are kept awake to assess their cognitive function in real time, which allows for brief behavioral paradigms while clinicians record from neural structures.

In the work that follows, we describe an open-source intraoperative paradigm and as proof of concept, present behavioral and neural data acquired during awake brain surgery. DBS lead implantation surgery is an optimal experimental setting for combining electrophysiological recordings and intraoperative behavioral testing because

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https://doi.org/10.1016/j.jneumeth.2018.05.004
Received 20 January 2018; Received in revised form 4 May 2018; Accepted 5 May 2018
Available online 07 May 2018
0165-0270/

microelectrode recordings (MER) are often used by clinicians to map deep brain structures. Furthermore, because DBS is most often used to treat Parkinson's disease (PD), there are a limited number of brains targets: subthalamic nucleus (STN) or the internal globus pallidus (GPi), and regions within the stereotactic trajectory, like the substantia nigra pars reticulata (SNr), that can be recorded from. This feature of DBS allows for large scale sampling of neuronal activity from the same brain region across patients. Much of what is known about human deep brain structure physiology has been elucidated through intraoperative neural recordings in this manner. For example, the notable finding that STN (DBS target for PD) neurons with movement-related receptive fields are almost entirely localized to the dorsal-rostral portion of their subnuclei was determined using intraoperative recordings (Abosch et al., 2002). Despite the high impact such research can have, human spike data is rarely incorporated into an experimental paradigm due to the challenges inherent to intraoperative research. Here, we seek to lower the barriers to carrying out intraoperative behavioral paradigms by providing a framework designed to take advantage of common potential targets for intraoperative recordings and to overcome challenges in the intraoperative setting.

For some neurosurgical procedures, including DBS, the skull is typically fixed in position with a rigid stereotactic frame. This factor warrants special consideration regarding how stimuli are delivered as well as how behavioral responses are collected. Visual stimuli are commonly used for behavioral tasks (Calkins and Iacono, 2000; Kamienkowski et al., 2012; Kunimatsu et al., 2016; Rashbass, 1961; Sereno and Holzman, 1995; Tehovnik et al., 2000). But in the setting of a stereotactic surgery, visual tasks depend on the use of computer monitors extended within the subject's angled and restricted field of view. In addition, subjects often have trouble visualizing the computer monitor even when optimally placed for many reasons − including poor vision and inability to keep their eyes open. The delivery of auditory stimuli, in contrast, is less obstructed and requires less vigilant engagement to ensure stimuli are perceived.

On the behavioral side, in human studies, responses are often recorded using key presses (Kraemer et al., 2017), and many classic non-human primate electrophysiologic studies track saccades (Hikosaka and Wurtz, 1983). However, both methods have limitations for use in the operating room. To address some of the constraints associated with frame-based procedures, as well as the limited physical capacity of subjects undergoing surgery, we incorporated a single-hand-held controller interface. For example, in the context of DBS implantation surgery, the upper limb contralateral to the side of the brain being operated on must remain unconstrained for kinesthetic testing. This frees one hand to interact with a controller. A directional thumb movement is convenient for reporting decisions because moving a joystick with one's thumb is not physically taxing, and different trajectories can carry different meanings.

With these challenges and opportunities in mind, we have developed an auditory pitch discrimination task dependent on use of a single-handed controller that has been optimized for use in the operating room. We present behavioral data from control and intraoperative subjects to demonstrate that our task has been designed for use in and out of the operating room. We also demonstrate, using neurophysiology intraoperatively recorded during the task, that the hardware configuration and behavioral paradigm described here allows us to examine neural correlates of human behavior.

2. Materials & methods

2.1. Subjects

All materials and protocol design were approved by the University of Colorado School of Medicine Colorado Multiple Institutional Review Board (COMIRB). Three students (male, 25–32) completed the task under non-surgical conditions, serving as controls. Two adult patients (female, 63; male 77) undergoing deep brain stimulation (DBS) implantation of the subthalamic nucleus (STN) for Parkinson's disease were voluntarily enrolled at the University of Colorado Anschutz Medical Campus. The female patient participated in two separate sessions, which took place during the left and right hemisphere DBS implantation. The male patient participated for a single session during right hemisphere DBS implantation.

Table 1
Order List.

Component	Estimated price ($)
Wii controller (Nunchuck/Wiichuck) PID: 342	12.50
Nunchucky (Wii Nunchuck breakout adapter) PID: 345	3.00
Arduino Uno R3 (Atmega328–assembled) PID: 50	24.95
9 VDC 1000 mA regulated switching power adapter – UL listed PID: 63	6.95
Tiny breadboard PID: 65	4.00
Total	51.40

Populated cart is available via Adafruit Wish List – https://www.adafruit.com/wishlists/437225.

2.2. Hardware design

Necessary hardware components included a PC (Windows 10, Intel iCore7, 16GB RAM), display monitor (23-inch LCD monitor, 144 Hz refresh rate), headphones (JBL in-ear 3.5 mm stereo), controller (Adafruit Wiichuck), Arduino UNO board, 3D printed controller attachment, and 3D printed Arduino UNO board housing. The controller-Arduino interface is the only component requiring assembly; refer to Table 1 for information on necessary parts and for complete pinout diagram (see Fig. 1). The Wiichuck, a one-handed controller capable of acquiring joystick, button press, and 3-axis accelerometer data, is well suited for this setting. The commercially available Wiichuck controller was assembled with an Arduino board to permit communication between the controller and computer system. Although the thumb-stick allows subjects the freedom to indicate a range of directional responses, we altered the functionality of the Wiichuck by affixing 3D printed lateral borders to restrict movement to two perpendicular axes (see 3D file in supplemental information), a modification that resulted in more stereotyped movement paths. In the context of our task and intraoperative patient population, this addition was important to achieving optimal levels of performance.

2.3. Software implementation

Two free software packages compatible with Windows, Mac, and Linux operating systems were used in this paradigm's design: 1) the Arduino integrated development environment (IDE) version 1.8.5 was used to program the physical Arduino board to allow controller input to be recorded by the operating system, 2) PsychToolbox (PTB) version 3.0.14, an add-on to Matlab (Mathworks, 2017b) was used to design, control, and record all features of the behavioral paradigm (Fig. 1). Commercial software necessary to implement our paradigm include Matlab (Mathworks, 2017b) and the Matlab add-on module 'MATLAB Support Package for Arduino Hardware' version 17.2.0.

It is possible that unforeseen complications will arise when our paradigm is used with computers running operating systems (e.g., MacOS) or versions of software different from those stated above.

2.4. Task design

Our intraoperative task is variation of paradigms used in animal model decision-making research (Felsen and Mainen, 2008; Lintz and Felsen, 2016). We chose to investigate decision-making because there are several reasons humans are optimal subjects for this type of