Supplemental Online Materials

Direct electrical stimulation evidence for a dorsal motor area with control of the larynx

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Participant Details

Case History. AJ had a history, going back to his teenage years, of right hemi-cranial "migraines". A prior MRI scan (2014), intended to evaluate the pineal gland for a possible endocrine deficiency, had revealed an asymptomatic, low-grade glial neoplasm in the right frontal lobe, undercutting the superior and middle frontal gyri. The lesion was followed over the course of the following years to evaluate changes in size and characteristics. Because of clear interval growth of the lesion the patient was consulted for surgery in 2017. As the posterior aspect of the tumor encroached on the anterior margin of the motor cortex in the right frontal lobe, it was suggested that further growth was likely to limit a complete resection. On that basis, the patient elected to move forward with image-guided resective surgery with intraoperative awake mapping. AJ was 27 (in 2017) at the time at which he was consulted for surgery.

Prior to surgery, the patient was referred for pre-operative functional magnetic resonance imaging (fMRI) and cognitive testing as part of a larger prospective study of cognitive brain mapping in neurosurgical patients; for details on testing and functional imaging, and the corresponding dataset see [1].

Neurosurgical Intervention and Intraoperative Methods

Because of the proximity of the lesion to motor cortex (Figure 1B) the surgery for removal of the tumor was carried out using an asleep-awake-asleep procedure for language and motor mapping [2-4], following an established protocol at the University of Rochester Medical Center (for prior studies using this protocol, see [5,6]; for an overview, see [1]). Given the location of AJ's tumor, the patient was positioned on the operating table on his left side. AJ's head was secured by a Mayfield head-holder, at an angle facilitating both the surgery and the patient's ability to see a small monitor directly in his line of sight. Following a right frontal-parietal craniotomy and exposure of the cortical surface (right frontal lobe, parietal and superior temporal cortex), AJ was titrated off of general anesthesia to participate in awake intraoperative mapping. Once awake, AJ took part in an intraoperative picture-naming task (Fig 1a) that was paired on roughly half of the trials (see below for details) with direct electrical stimulation. The patient's responses were captured by a directional microphone, projected and amplified by a speaker system for the purposes of the clinical team, and recorded for offline analysis. The clinical purpose of the awake task was to provide the neurosurgical team with real-time causal evidence of the borders of eloquent (language and motor) cortical areas, thus identifying tissue to be spared during resection (particularly at the posterior margin of the tumor which was believed to be adjacent to primary motor cortex). Direct electrical stimulation was delivered with a bipolar Ojemann stimulator (Nicolet) at an amplitude around 3.5 mA throughout the task (determined based on after-discharge thresholds), and with a variable duration of stimulation on the surface of the brain (at the attending surgeon's discretion) ranging between 1530 and 3370ms (mean = 2304; SD = 485ms). Nine carbon tipped surface electrodes were arranged along the superior (three electrodes) middle (three electrodes) and inferior frontal gyri (three electrodes). The purpose of the surface EEG was purely clinical: to monitor after-discharges during direct electrical stimulation, allowing for delivery of stimulation at an amplitude just below the after-discharge threshold.

Registration of Intraoperative Stimulation Sites to Pre-operative MRI

The location for each site of intraoperative direct electrical stimulation was acquired in real time using the Brainlab system for cranial navigation, and StrongView™ software for data acquisition and time-stamping. Those coordinates were subsequently analyzed offline by projecting them into native T1 anatomical space, and subsequently to Talairach space. A 3mm radius sphere was defined around each stimulation coordinate to represent each stimulation event (for details and precedent, see [5,7,8]).

Scoring of Intraoperative Performance

During the intraoperative mapping procedure Patient AJ was presented with stimuli that combined reading and picture naming (Figure 1). Stimuli consisted of a leading written phrase ("Here is a") and a line drawing of a variable object (e.g., bench). 64 different stimuli were presented for a total of 70 trials (6 stimuli were presented twice). A new stimulus was presented every 6310 milliseconds (controlled with StrongView). Response time and video analyses were conducted offline. At the time of analysis, scoring of audio files (by author JRB) was blinded to trial identity (e.g., stimulation versus no stimulation). Supporting video related to this article can be found at: https://youtu.be/AotZG22KvEs

Supplemental Analyses of Intraoperative Data

As noted in the text, the principal analyses were based on 63 trials. One concern that may be raised is that response times and performance may be altered for trials that immediately follow a stimulation-induced error. To address this, we carried out a more stringent analysis in which we reduced the number of analyzed trials from 63 to 53, by excluding any trial that followed an overt error that had been induced by stimulation, regardless of whether the excluded trial was correct or incorrect (this implied removal of one trial paired with stimulation to the dLMC resulting in transient speech arrest). For this more stringent analysis there were 32 trials paired with stimulation and 21 without stimulation. Importantly, the effect of stimulation on the likelihood of error (11/32 vs. 0/21; $\chi 2 = 7.139$; $p < .001$) remained.

We then repeated all core analyses over this reduced set of 53 trials; all core findings remained. Errors were more likely after stimulation to the dLMC compared to surrounding structures (10/10 vs. 1/22; $\chi 2 = 23.70$; $p < .001$). On 5 of the trials paired with dLMC stimulation, the patient was able to produce a correct response once the stimulator broke contact with surface of the brain (i.e., a “transient laryngeal speech arrest”). The average response time for those 5 trials was 2931ms (SD = 661ms), which was longer than the mean of the 21 accurate response times for trials associated with stimulation to surrounding structures (Response Time = 938.9ms, SD = 229ms; Welch Two Sample t-test, $t = 6.645$, $p<.005$). Again, there was no difference in response time for trials without stimulation (n = 21; 1078ms, SD = 439ms) compared to trials with stimulation to structures adjacent to, but non-overlapping with, dorsal laryngeal motor cortex (Welch Two Sample t-test, $t = 1.29$, $p=.21$).

Quantification and Statistical Analysis

In addition to the details provided above, R software was used for all statistical analyses reported in this manuscript.

Data and Software Availability

All MRI data are deposited on FigShare, and scripts and materials are available through the open science platform for neuropsychological research, www.openbrainproject.org, and request by contacting BZ Mahon (bmahon@andrew.cmu.edu). The supplementary video related to this article can be found at: https://youtu.be/AotZG22KvEs

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