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How is electrical stimulation of the brain experienced, and how can we tell? Selected considerations on sensorimotor function and speech.

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Abstract

Electrical stimulation of the nervous system is a powerful tool for localizing and examining the function of numerous brain regions. The use of electrical stimulation in the operating room also has proven an effective means of identifying eloquent cortex for surgeons to avoid during resection of pathologic tissue. Delivered to motor regions of the cerebral cortex, electrical stimulation can evoke a variety of first-order effects, including observable movements or an urge to move, or somatosensory, visual, or auditory percepts. In still other regions the subject may be oblivious to the stimulation. Often overlooked, however, is whether the subject is aware of the stimulation, and if so, how the stimulation is experienced by the subject. In this review of how electrical stimulation has been used to study selected aspects of sensorimotor and language function, we raise questions that future studies might address concerning the subjects' second-order experiences of intention and agency regarding evoked movements, of the naturalness of evoked sensory percepts, and of other qualia that might be evoked in the absence of an overt first-order experience.

Keywords

cerebral cortex; electrical stimulation; intracortical microstimulation; perception; sensation

“There is no reason to suppose that one part of the brain is excitable and another not. The question is, how the stimulation manifests itself.”

D. Ferrier

1886 2nd version of Functions of the Brain (Ferrier, 1886)

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Introduction

Electrical stimulation of the nervous system has proven to be a powerful tool for probing the function of different brain areas. Clinically, electrical stimulation has become a critical tool for identification of the eloquent cortex to be avoided in resecting a tumor or epileptogenic zone. First-order responses—such as a movement of the subject's body or the subject's verbal description of a sensation, percept, or more complex phenomenon (e.g. déjà vu) can inform our understanding of the regional function of the brain, but a variety of second-order questions often remain unaddressed. Here we initially examine second-order questions stemming from stimulation of the sensorimotor cortex. For example, when a movement is evoked is the subject aware that a movement occurred, and does the subject feel he/she was the voluntary agent that produced the movement? How natural is the sensation evoked by stimulation of the primary somatosensory cortex? We then go on to consider what the subject might experience when electrical stimulation appears to evoke no effect at all. Is the subject even aware that stimulation occurred? Consideration of issues such as these may not only deepen our understanding of how the stimulated cortex itself functions and interacts with other parts of the brain, but also inform our development of neuroprosthetic devices that will use stimulation—electrical or optogenetic—to write information into the nervous system. In focusing on these selected issues, we will not consider many other phenomena that can be elicited by electrical stimulation, such as visual hallucinations (Blanke, Landis, & Seeck, 2000; Jonas et al., 2014; Megevand et al., 2014; Vignal, Chauvel, & Halgren, 2000), emotions (Meletti et al., 2006), or out of body experiences (Blanke, Ortigue, Landis, & Seeck, 2002). We hope, however, that the nature of the questions we raise here will provide examples that can be adapted for use in investigation of those more complex phenomena.

Electrical Stimulation and Functional Localization in the Brain – A Brief Sketch

Late in the 18th century, Galvani demonstrated electrical stimulation could elicit muscle contractions (Galvani, 1791), though electrical stimulation was not immediately employed for further study of nervous system function. At that time, the entire nervous system was thought to be a single, syncytial, protoplasmic reticulum, precluding the notion that different functions might be localized in different regions of the brain. Our understanding began to change, however, when Broca causally attributed difficulty with language production to lesions in the left frontal lobe (Broca, 1861, 1863, 1866). Shortly thereafter Hughlings Jackson, having observed the progressive spread of certain epileptic seizures on one side of the body, hypothesized a neural center in which movements of the face, arm, and leg were represented systematically in different locations (Jackson, 1958; G. K. York, 3rd & Steinberg, 2011; G. K. York & Steinberg, 1994). Hughlings Jackson's hypothesis was promptly confirmed by Hitzig and Fritsch, who applied electrical stimulation to the frontal lobe of dogs and found specific, reproducible movements of the face, neck, forelimb, and hindlimb could be evoked from different sites (Fritsch & Hitzig, 1870). Moreover, Hitzig and Fritsch recognized that other investigators, having assumed the brain to be a single electrically-excitabile reticulum in which stimulation anywhere should have the same effect,

had failed to evoke movements because they had stimulated only under the “posterolateral wall” where no motor centers actually exist. Hitzig and Fritsch thus not only demonstrated the brain was electrically excitable, but also the region of cerebral cortex from which muscle contractions could be excited was limited to a specific region, i.e. localized.

As the reticular theory gave way to the neuron doctrine—that individual, separate cells, i.e. neurons, comprise the nervous system—electrical stimulation played an increasing role in attributing specific functions to different regions. Ferrier, for example, used electrical stimulation to identify different regions subserving movement; and based on orienting movements of the eyes or pinnae, that other regions were related to vision or hearing (Ferrier, 1886). As captured in his statement quoted in the epigraph above, before long the question became not whether the brain was electrically excitable, but rather how the effects of electrical stimulation in different regions could be observed. Decades of research since have shown that electrical stimulation of specific regions of the brain can elicit not only different movements, but also various sensations, perceptions, urges, or other experiences.

Ferrier’s words are still relevant today as we continue to use electrical stimulation to probe the specific functions of different regions of the brain. Here, we review electrical stimulation of the cerebral cortex quite broadly, from classical to modern studies, from prefrontal to primary visual areas, from Faradic stimulation of the cortical surface to single pulse intracortical microstimulation. But rather than attempting to be exhaustive and comprehensive, we focus selectively on issues that raise questions yet to be answered and consider how these issues might be approached.

A Curated History of Electrical Stimulation in the Motor Cortex

Evoking movements of the body was the easiest first step in demonstrating the electrical excitability of the cerebral cortex. In retrospect, we can recognize that this occurred because i) the descending cortical projection to the ventral horn of the spinal cord in carnivores, primates, and humans arises largely from a relatively circumscribed region of cortex, ii) body movements obvious to the investigator can be evoked in animal subjects that cannot respond verbally, and iii) movements can be evoked when the animal is anesthetized. Subjects could be sedated or awake, and investigators could change the locus, amplitude, frequency, or duration of the stimulation to evoke visible movements of different parts of the body.

Ferrier extended the results of Hitzig and Fritsch to other species, demonstrating that electrical stimulation in a region of the frontal lobe of macaques, dogs, jackals, cats, rabbits, guinea pigs, and rats consistently evoked muscle contractions that moved different parts of the contralateral body (Ferrier, 1886). Subsequently, more detailed studies employing increasingly sophisticated methods of electrical stimulation provided accumulating evidence that within the movement-producing region of the cortex, different parts of the body were represented in a consistent sequence. In old world primates, apes, and humans—where this region becomes progressively expanded just anterior to the central sulcus (Rolandic fissure)—movements of the face were evoked laterally, movements of the leg and foot medially, and

movements of the arm and hand in between (Foerster, 1936a, 1936b; A. S. F. Leyton & C. S. Sherrington, 1917; Woolsey, Erickson, & Gilson, 1979; Woolsey et al., 1952).

A noteworthy difference between studies in experimental animals and those in human subjects emerged in these studies of motor cortex, a difference that continues today. Individual animal subjects could be studied more extensively than individual human subjects. In studies of chimpanzees, orang-utans (sic), and gorillas, Leyton and Sherrington, for example, reported the movements evoked by electrical stimulation at as many as 109 systematically explored points in the left precentral gyrus of an individual animal (A. S. F. Leyton & C. S. Sherrington, 1917, count from their Fig 1B). In contrast, Penfield and Boldrey reported a total of 414 points¹ from which precentral stimulation evoked body movements (not including turning of the eyes and/or head) in 126 patients undergoing neurosurgical procedures, an average of 3.3 precentral points per subject (Penfield & Boldrey, 1937). In a single case selected from the Penfield archive for a large number, 13 precentral points had been stimulated (Schieber, 2001, Fig. 2)². The illustration of the motor homunculus thus constitutes an amalgamation of observations from many individual subjects, each of whom contributed only a small number of data points. Such summary maps from human studies have tended to gloss over the complex details evident in more extensive and systematic mapping performed in individual animal subjects, and in some cases human summary maps may have interpolated information derived from animal studies (Scharff, 1940).

Through the mid-20th century, electrical stimulation of the cerebral cortex was delivered through ball electrodes applied to the exposed surface (Marshall, Woolsey, & Bard, 1941). In the second half of the 20th century, however, sharpened needle-like electrodes, insulated except at the tip, were inserted through the pia-arachnoid mater and into the cortical gray matter to enable investigators to record the extracellular activity of single neurons (Evarts, 1964; Mountcastle, Davies, & Berman, 1957). Soon thereafter, Asanuma and colleagues developed the use of such “microelectrodes” to deliver electrical stimulation within the cortical gray matter, referring to their technique as “intracortical microstimulation” or “ICMS” (Stoney, Thompson, & Asanuma, 1968). Movements now could be evoked with microamperes of current, rather than the milliamperes required with surface electrodes. Early findings using this technique suggested the topographic organization of motor cortex extended down to microscopic efferent zones where threshold ICMS (i.e. stimulation using the minimum current required to produce a detectable response) elicited excitation of a single muscle (Asanuma & Rosen, 1972). Motor cortex then could be viewed as a “complex mosaic” of efferent zones for different muscles, with each muscle receiving cortical input from multiple separate zones. Subsequent studies have shown, however, that single motor units in different muscles can be excited from overlapping territories (Andersen, Hagan, Phillips, & Powell, 1975) and averaging EMG triggered on single pulses of ICMS often

¹We have totaled the number of precentral points at which responses were reported of the tongue, mouth, jaw, eyelid, face, swallow, fingers, hand/arm/shoulder, and trunk/legs. This total may be an overestimate, however. For example, a movement recorded as “closure of the fingers and thumb, slight wrist flexion” might have been counted both under fingers and under hand/arm/shoulder.

²Penfield stimulated relatively few points on the precentral gyrus because of the known tendency for stimulation there to evoke seizures. In his procedures, the Rolandic fissure typically was identified by stimulating multiple points along its posterior aspect in primary somatosensory cortex, and then stimulating only a few selected spots anteriorly to confirm that this was motor cortex (personal communication to MHS from William Feindel).

facilitates multiple muscles from the fingers to the shoulder (Park, Belhaj-Saif, & Cheney, 2004). Extensive use of ICMS in animals thus has not increased the resolution of topographic organization in the primary motor cortex (Donoghue, Leibovic, & Sanes, 1992; Gould, Cusick, Pons, & Kaas, 1986) beyond demonstrating a central core of more intense outputs to distal forearm and hand musculature surrounded by a “horseshoe” of more intense output to proximal muscles in the macaque upper extremity representation (Kwan, MacKay, Murphy, & Wong, 1978; Park, Belhaj-Saif, Gordon, & Cheney, 2001).

The trains of ICMS pulses used in the latter 20th century to evoke minimal, twitch movements typically lasted 30–40 ms. In more recent studies using train durations of 500 ms, complex movements of the entire upper extremity were evoked (Graziano, Aflalo, & Cooke, 2005; Graziano, Taylor, & Moore, 2002). These long trains of ICMS delivered at a given intracortical site drive the extremity to a consistent posture whatever its starting configuration, with different postures produced by stimulating different sites in both the primary motor cortex and the premotor cortex. Studies of the EMG activity driven by such long-train ICMS show different tonic levels of EMG activity are produced in different muscles from the shoulder to the hand, with different combinations of tonic levels being produced by stimulation at different cortical sites (Griffin, Hudson, Belhaj-Saif, & Cheney, 2011). Overall, electrical stimulation has proven to be a useful tool for mapping what muscle contractions or movements can be evoked from specific cortical locations, defining both the extent and limitations of somatopic organization in the motor cortex.

We now know many primary motor cortex neurons receive afferent input from both cutaneous and deep mechanoreceptors (Fetz, Finocchio, Baker, & Soso, 1980; Lemon, Hanby, & Porter, 1976; Lemon & Porter, 1976; Murphy, Kwan, MacKay, & Wong, 1978; Rosen & Asanuma, 1972), raising a question that has received scant attention in studies employing motor cortex stimulation: What does the subject feel? Indeed, of the 822 sites at which Penfield and Boldrey evoked a somatosensory percept, 330 were precentral, i.e. in the motor cortex (Penfield & Boldrey, 1937). At other sites anterior to the Rolandic fissure (though more frequently posterior to it), Penfield’s patients reported the sensation that a particular body part had moved although no movement could be observed. Stimulation in the supplementary motor area also has evoked a sense that movement had occurred in the absence of visible movement (Fried et al., 1991).

But many important questions remain open. Does surface stimulation or ICMS of the motor cortex at currents subthreshold for evoking movement or muscle contraction routinely evoke a somatosensory percept? If so, how closely does the perceived movement correspond to the movement actually evoked with suprathreshold stimulation? And when movement is evoked by electrical stimulation, does the subject feel which body part has moved, in what direction, and to what extent? If the evoked movement is low in amplitude, or if only muscle twitches are evoked, does the subject feel it? And if so, does the subject have the experience that the movement was voluntary or involuntarily?

Voluntary movement, agency, and intention

We normally feel the vast majority of movements our own body makes are made of our own volition. You yourself are making those movements intentionally. Although jerking your hand away from a hot object actually begins as a flexion withdrawal reflex at the spinal level, you nevertheless feel you were the agent who pulled your hand back. In contrast, when a physician taps your knee with a hammer and your foot kicks out due to a stretch reflex at the spinal level, you have the sense that although your body moved you were not the agent of that movement. To you, such a movement of your own body seems involuntary.

Involuntary movements occur commonly in a number of neurological disorders, generally referred to as “movement disorders.” Although many of the movements made by patients with such movement disorders are natural and voluntary, these patients also make a variety of involuntary movements described as tremor (e.g. in Essential Tremor or Parkinson’s Disease), myoclonus (e.g. Action Myoclonus), athetosis (e.g. Spasmodic Torticollis), chorea (e.g. Huntington’s Disease), or tics (e.g. Tourette’s Syndrome). Such patients do not feel they themselves are the agent of these movements, although clearly their own body is moving. Such neurologic diseases seem to result in the production of movements dissociated from the sense of voluntary intent.

Normally self-initiated voluntary movements are preceded by electrophysiological activity in the brain. In particular, beginning about 1 second before a normal, prompt voluntary movement, electroencephalography (EEG) electrodes systematically detect a slow potential shift at the vertex, commonly referred to as the “Bereitschaftspotential” or “readiness potential” (Deecke, Scheid, & Kornhuber, 1969; Shibasaki & Hallett, 2006). Detecting the Bereitschaftspotential requires averaging EEG activity over multiple instances of the movement all aligned at the moment of movement onset. When involuntary movements with prompt onset—jerks, myoclonus, or tics—are used as triggers for aligning EEG activity, however, no Bereitschaftspotential is present (Brown & Thompson, 2001), indicating the neurophysiological processes initiating such movements differ from those initiating normal, voluntary movements.

Electrical stimulation of the brain also is capable of dissociating voluntary intention from the actual production of movement. Penfield and Boldrey found that surface stimulation of the precentral gyrus occasionally evoked a “desire to move” a particular body part although no movement occurred (Penfield & Boldrey, 1937, Fig. 20). Stimulation in the supplementary motor area likewise has evoked an “urge” to perform a movement, or a sense of anticipation that a movement was about to occur, with no actual movement associated (Fried et al., 1991). When stimulation intensity was increased at such locations, however, the movement evoked was not always the movement for which the subject had expressed an urge, involving instead a more proximal part of the same limb, or even a different extremity. Another study in which electrical stimulation was delivered to the inferior parietal lobe via temporarily-implanted electrocorticography (ECoG) electrode grids also described that at low stimulation amplitudes participants reported an urge or desire to move (Desmurget et al., 2009). As the stimulation amplitude was increased, the participants experienced “illusory movements,” describing that their mouth, hand, foot, or chest had moved, although no actual

movements were detected by observers or by electromyographic (EMG) recordings. In contrast, when the same investigators delivered electrical stimulation to the premotor cortex, actual movements of different body parts were evoked, but here the subjects were unaware the movements had occurred and denied any intent or desire to make such movements. In other words, the participant was not the agent of these evoked movements.

Future work can provide opportunities to address these issues more systematically over a wider variety of cortical areas: When electrical stimulation evokes an observable movement, the subject could be asked whether he/she was the voluntary agent of the movement, “Did you move your thumb just then, or did I [the investigator] cause it to move?” When stimulation is subthreshold for evoking observable movement and the subject experiences only an “urge,” “desire,” “anticipation,” or “intention” to move, the subject could be asked, “If that movement had occurred, would it have been you making the movement, or me [the investigator] causing it?” Whatever the response to this question, the subject also could be asked, “If you felt an urge/desire/anticipation/intention to make that movement, why didn’t you go ahead and do it?” And in followup, “Was the urge/desire/anticipation/intention not strong enough for you to make the movement, or did you think you were expected to remain passive?” And if stimulation at such sites is increased to the point of evoking an observable movement, how closely does that movement correspond to the movement for which the subject experienced the urge/desire/anticipation/intention at lower intensity? If a movement is then evoked, the subject again could be asked, “Did you make that movement, or did I [the investigator] cause it to happen?” Moreover, in conjunction with all these questions, recordings of EEG or ECoG signals at the vertex could be used to examine whether any of the subjects’ verbal descriptions are associated with a slow potential shift at the vertex resembling the Bereitschaftspotential (recognizing the difficulties of detecting such a slow potential, as doing so requires averaging over multiple trials which may be contaminated by stimulation artifacts).

Is electrical stimulation perceived as artificial or natural?

Although intracellular stimulation might be capable of reproducing natural time series of action potentials in individual neurons (Mainen & Sejnowski, 1995), the extracellular electrical stimulation used to study awake animal and human subjects inevitably drives simultaneous action potentials in dozens to thousands of neurons (Andersen et al., 1975; Histed, Bonin, & Reid, 2009; Stoney et al., 1968). Such populations of neurons do not normally discharge action potentials synchronously. To what extent, then, is electrical stimulation perceived as natural?

Surface stimulation of the primary somatosensory cortex in awake humans evokes sensations that, while localized to a somatotopically specific region of the skin, are not particularly natural. When evoked with milliamperes of current at the cortical surface, where Brodmann’s area 2 is exposed on the crown of the postcentral gyrus, these sensations typically are described by the subject with words such as “tingling” (Penfield & Rasmussen, 1950; Roux, Djidjeli, & Durand, 2018). Tingling is a word commonly used to describe the cutaneous sensations experienced when a nerve that has been ischemic is re-perfused and “wakes up,” a sensation distinct from normal cutaneous sensations. Although animal studies

have shown that neurons in area 2 respond to natural stimulation of both cutaneous and deep mechanoreceptors (Iwamura & Tanaka, 1978; Iwamura, Tanaka, Sakamoto, & Hikosaka, 1985), only occasionally does surface electrical stimulation of area 2 in humans evoke a perception of a body part having moved (Penfield & Boldrey, 1937; Roux et al., 2018). The sensations evoked by surface stimulation of human area 2 thus are experienced largely as artificial.

ICMS may provide sensations perceived as being closer to a natural experience. Mechanical vibration on the skin of a fingertip at frequencies between 50 and 200 Hz is described by humans as a vibration or fluttering sensation. Rhesus monkeys have been trained to report whether the second of two such mechanical vibrations is higher or lower in frequency than the first. When ICMS—delivered through an electrode that recorded quickly adapting units in area 3b—was substituted for the second mechanical vibration, monkeys were able to report whether the ICMS was higher or lower in frequency than the preceding mechanical stimulation as accurately as if the second stimulation had been mechanical (Romo, Hernandez, Zainos, & Salinas, 1998). Similarly, Rhesus monkeys have been trained to report whether the pressure delivered by mechanical indentation of the skin on one fingertip is greater or less than the pressure delivered on another. When ICMS in area 3b or 1 was delivered at different current amplitudes in place of the second mechanical indentation, monkeys reported higher currents as being comparable to more pressure (Tabot et al., 2013). At certain sites in the primary somatosensory cortex, the perceived frequency of ICMS accurately emulates that of mechanical vibration on the skin, and current amplitude emulates the intensity of mechanical pressure.

Even though ICMS in the primary somatosensory cortex can be compared accurately with mechanical stimulation of the skin, ICMS is not necessarily experienced as entirely natural. Two recent reports describe sensations evoked by ICMS delivered via microelectrode arrays implanted presumably in area 1 of individual human subjects with tetraplegia resulting from spinal cord injury. One subject experienced ICMS trains delivered through single electrodes as focal sensations on the hand, forearm, or upper arm, which he described variously as: squeeze, tap, vibration, blowing, pinch, press, goosebumps, or movement in different directions (Armenta Salas et al., 2018). In the other subject, ICMS trains were experienced as most often as “pressure” at different, somatotopically organized sites on the palmar skin at the bases of the four fingers (Flesher et al., 2016). As shown previously using ICMS in macaque areas 1 and 3b (Tabot et al., 2013), this human participant was able to discriminate ICMS trains of different amplitudes. But when asked to rate the perceived sensation on a 5-point scale from “totally natural” to “totally unnatural,” the participant rated the sensations as “3, possibly natural” for 93% of the ICMS trains.

Interestingly, though not providing entirely natural sensations, electrical stimulation of primary somatosensory cortex nevertheless can provide some degree of embodiment—the experience that something artificial is part of one’s self—as assessed using the rubber hand illusion (Botvinick & Cohen, 1998). The rubber hand illusion typically is produced by having human participants watch a rubber (mannequin) hand as it is brushed synchronously with their own hand, which is hidden from view. Gradually, the participant comes to experience the brushing of the rubber hand as if it is occurring on their natural hand. The

experimenter then stops brushing the natural hand, and the participant feels his/her own hand being brushed as the experimenter continues to brush only the observed rubber hand. When electrical stimulation through ECoG electrodes over the hand region of primary somatosensory cortex was delivered instead of brushing the natural hand, human participants still experienced the illusion, reporting that it was their own hand they saw being brushed after the brushing of the natural hand was stopped and only the electrical stimulation in somatosensory cortex continued (Collins et al., 2017). But if the electrical stimulation was delivered either asynchronously or to a different area of primary somatosensory cortex, the participants did not report such ownership. Surface electrical stimulation of primary somatosensory cortex thus can substitute for natural somatic sensation to evoke this multisensory illusion of hand ownership.

What happens when “no effect” is detected while delivering electrical stimulation?

Electrical stimulation of the primary somatosensory cortex, like that of the primary visual or auditory cortices, evokes sensory percepts even though the subject is not engaged in any particular behavior. The subject feels, sees, or hears something and thereby knows stimulation has occurred. But in areas further removed from the primary sensory and motor fields, Penfield and his colleagues found surface stimulation of large expanses of human frontal, parietal, and temporal cortex produced no identifiable effect: the patient was “oblivious” to the fact that stimulation had been delivered (Penfield & Rasmussen, 1950, page 234). However, Penfield’s patients typically were resting passively during intraoperative stimulation. As expressed in the opening quotation from Ferrier, electrical stimulation presumably can excite neurons anywhere in the nervous system. Observing the effects of electrical stimulation in many areas of the cerebral cortex may require that the brain be actively engaged in a behavior that relies specifically on the stimulated cortical area (Histed, Ni, & Maunsell, 2013).

Indeed, Penfield recognized that if the patient was speaking, stimulation in language-related areas often caused the patient to stop speaking until the stimulation ended. Such “speech arrest” is perhaps the best-known example of electrical stimulation being delivered as the brain is engaged in a specific behavior. Penfield evoked speech arrest most often when stimulating the inferior precentral gyrus, “...between the representation of ‘throat movement’ below and ‘upper face’ above....” (p. 93). Given that lip movement was associated in one-fifth of the instances, one might infer that stimulation that evoked speech arrest often drove tonic contraction of articulatory muscles and thereby prevented the phasic articulatory movements of speech, not unlike the tonic contractions of limb muscles evoked by long-train ICMS that ‘hijack’ the limb and drive it to a fixed position (Griffin, Hudson, Belhaj-Saif, & Cheney, 2011).

Penfield also described other failures of speech production that he termed “aphasic arrest,” most often evoked from the inferior frontal lobe anterior to the precentral gyrus, from the inferior parietal lobule, or from the middle temporal region. The subject might be unable to name an object during the stimulation, sometimes still being able to say, “This is a _____.”

The subject might be able to count forward, but not count backward. This approach continues to be used in human neurosurgery to identify cortical areas involved in language function, with the goal of avoiding resection of cortex that might leave the patient aphasic. To achieve this goal, electrical stimulation is delivered as the patient performs various language tasks (Rofes et al., 2018). While electrical stimulation is delivered along the Sylvian fissure, such language tasks might include picture naming (Herbet, Moritz-Gasser, Lemaitre, Almairac, & Duffau, 2018), counting, and word repetition (Boatman, Lesser, & Gordon, 1995), or judging whether a word is abstract or concrete (Orena, Caldiroli, Acerbi, Barazzetta, & Papagno, 2018). Stimulation then might cause errors. The patient might not “hear” the cue; might add, delete, or substitute phonemes; might repeat a previous target word; might produce slurred or distorted speech; might delay speech output; or might produce no speech at all (speech arrest) (Leonard et al., 2018, Figure 2 in Leonard, Cai, Babiak, Ren, & Chang, 2016). Because these patients can hear themselves, they presumably are aware they have made these errors as a result of the stimulation (although this point is rarely addressed), and may be able to report, “I know what it is but can’t think of the word for it.” But if the patient had not been actively engaged in an appropriate task, neither the patient nor the examiner might have known that electrical stimulation had been delivered.

Other studies have revealed additional situations in which electrical stimulation can affect an ongoing behavior. ICMS delivered in areas participating in various forms of visual perception, for example, have been shown to bias that particular perception if the subject is actively engaged in an appropriate task. A recent study using ECoG electrodes temporarily implanted over human visual cortical areas, for example, showed that although stimulation of V1, V2, or V3 in the occipital lobe evoked visual percepts, stimulation of the fusiform face area on the inferior aspect of the occipitotemporal junction did not (Murphey, Maunsell, Beauchamp, & Yoshor, 2009). Although no percept was evoked by stimulating this face area in humans, ICMS in the inferior temporal lobe face patches of macaques biased the monkeys to categorize noisy visual images as “faces” instead of “non-faces” (Afraz, Kiani, & Esteky, 2006). Other instances have been described in which ICMS biased visual perception while monkeys were performing behaviors that specifically engaged the visual motion sensitivity of the medial temporal (MT) area (Celebrini & Newsome, 1995; Murasugi, Salzman, & Newsome, 1993) or the object shape sensitivity of neurons in the anterior intraparietal (AIP) area (Verhoef, Vogels, & Janssen, 2015). When engaged in such tasks, does the subject know when perception has been altered by electrical stimulation? And if electrical stimulation was delivered when the subject was not engaged in the task, would the subject know the stimulation had occurred?

Beyond biasing perceptual decisions, ICMS in other areas can alter other, specific behaviors. Biomimetic multichannel ICMS delivered in the CA1 field of the hippocampus based on responses to visual stimuli recorded in the CA3 field can prolong working memory in a delayed match to sample task (Deadwyler et al., 2017). ICMS delivered in a negative-valence subzone of the pre-genual anterior cingulate cortex increases the likelihood of avoidance decisions in an approach/avoidance task (Amemori & Graybiel, 2012). In such cortical areas as well, we can ask whether the subject knows when behavior has been altered by electrical stimulation, and whether the subject would be aware of stimulation when not engaged in the area-appropriate behavior.

To approach these issues, some studies have trained monkeys to detect and respond to the electrical stimulation *per se*. Monkeys have been trained over many trials to respond to electrical stimulation of the cortex by pressing a lever either to obtain a food reward or to avoid a shock delivered to the hindlimb or tail (Doty, 1965). Such trained responses could be obtained by stimulating sites in either the prefrontal cortex or the superior parietal lobule; however, effective currents (0.05 to 0.7 mA) typically were within an order of magnitude of the current needed to evoke an observable movement of the body, head, or eyes (0.2 to 1.0 mA). Note these lever-press responses conditioned on electrical stimulation of the prefrontal or superior parietal cortex required the subject to detect the electrical stimulation, but not to distinguish stimulation at different closely spaced sites.

Monkeys also have been trained to distinguish ICMS delivered through different electrodes in the premotor cortex. In macaques, ICMS delivered in the premotor cortex with sufficient amplitude and duration is known to elicit movements (Gentilucci et al., 1988; Graziano et al., 2005; Graziano et al., 2002; Rizzolatti et al., 1988; Weinrich & Wise, 1982). But a recent study showed that ICMS in the premotor cortex too low in amplitude and too short in duration to drive movements or muscle contractions may nevertheless have been experienced by the subject (Mazurek & Schieber, 2017). Monkeys previously trained to perform four different movements instructed with visual cues subsequently were trained to perform the same movements instructed with low-amplitude ICMS delivered through four different electrodes in premotor cortex. Moreover, after the assignments of particular electrodes to instruct particular movements had been shuffled, the monkeys relearned the new electrode-movement assignments, indicating the monkeys' performance of a given movement was not simply driven by the stimulation at a particular electrode. The monkeys thus appeared to have had different experiences upon stimulation at the different electrodes in premotor cortex, which they learned to associate with performing particular movements voluntarily to receive rewards³.

Although monkeys may be able to detect sufficient electrical stimulation anywhere in the cerebral cortex, whether stimulation at different closely spaced electrodes can be distinguished in any given association area remains to be determined. Moreover, in areas where stimuli at different electrodes can be distinguished, how many different stimuli—at different electrodes, of different frequency, at different intensity—can be distinguished reliably? A similar paradigm in which the subject reports different experiences by performing different movements could be useful in addressing these questions in association areas, not only in non-human primates and other species, but in humans as well. Although humans can be asked to report with language, not all experiences are available to even the human language system, as is evident from phenomena such as blindsight (Weiskrantz, 1996) and visuomotor dissociation (Goodale, Jakobson, & Keillor, 1994; Goodale & Milner, 1992).

³The association of ICMS at a given electrode with a particular movement may have been made through Hebbian learning, such that the monkeys eventually performed the correct movements subconsciously (Lebedev & Ossadchi, 2018). Even in such case, however, the Hebbian process may have led to the formation of distinguishable qualia specifying which movement to perform.

Effects depend on the manner in which electrical stimulation is delivered

Techniques for electrical stimulation of the brain have evolved considerably over the last two centuries. Whereas Hitzig and Fritsch used Galvanic stimulation (a surge of direct current delivered by closing a switch from a battery), Ferrier used Faradic stimulation (repeating pulses of complex waveform delivered through an induction coil), and Penfield used a thyratron⁴ or a Rahm stimulator (Rahm & Scarff, 1943). These forms of stimulation were based on the voltage at the electrodes (constant-voltage stimulators), while modern stimulators deliver constant-current, bipolar pulses lasting a controlled number of microseconds. Stimulation classically was delivered through ball electrodes resting on the surface of the brain. Though similar electrodes are still in use intraoperatively, electrodes now may be implanted arrays of ECoG discs 2 mm in diameter, ECoG microwires, 800 μ m diameter depth electrodes implanted deep in the cortex for stereo EEG (sEEG), or intracortical microelectrodes.

The effect evoked by electrical stimulation delivered at a given locus depends to a considerable extent on the manner in which stimulation is delivered. In monkey primary motor cortex, for example, single pulses of ICMS delivered at long intervals (e.g. 100 ms) are generally insufficient to evoke any activity in quiescent muscles. If the monkey is actively contracting muscles, however, the same single ICMS pulses can produce facilitation or suppression of specific motoneuron pools detected by averaging hundreds of segments of continuously recorded EMG activity all aligned at the delivery time of hundreds of individual ICMS pulses. As the current amplitude of such single pulses increased from 10 to 40 μ A, the magnitude of such stimulus-triggered facilitation increases in a given muscle, and additional muscles show facilitation (Widener & Cheney, 1997). Increasing the current increases the radius at which not only neuron somata are discharged by ICMS pulses, but also axons of passage (Histed et al., 2009). Nevertheless, to elicit contraction of quiescent muscles requires repetitive trains of ~10 ICMS pulses delivered at short intervals (e.g. 3 to 10 ms), which allow for trans-synaptic recruitment of neurons not directly activated by the ICMS pulses (Gustafsson & Jankowska, 1976; Jankowska, Padel, & Tanaka, 1975). Such short trains elicit muscle contractions sufficient to produce visible twitch movement of various body parts. Again, as the current amplitude of the train is increased from 10 to 40 μ A, the EMG activity of a given muscle increases and additional muscles are affected, producing more overt twitch movements (Donoghue et al., 1992; Widener & Cheney, 1997). And finally, if the train duration is increased from ~30 ms to 500 ms, complex movements of the entire extremity—from the shoulder to the fingers—can be evoked (Graziano et al., 2002; Griffin et al., 2011). Surface stimulation of human primary motor cortex as performed by Penfield generally elicited twitches not unlike the short trains of ICMS used in monkeys. But interestingly, intraoperative surface stimulation at currents near threshold for evoking twitch movements from human primary motor cortex can evoke after-discharges that occasionally progress to seizure activity. Surface stimulation of primary motor cortex in awake macaques likewise can evoke after-discharge (Doty, 1965). This tendency to evoke after-discharge and seizures using surface stimulation, not seen with ICMS in the primary

⁴A gas-filled electron tube that provides a high-power switch and controlled rectifier, able to handle larger currents than a vacuum tube.

motor cortex of awake monkeys, limits the range of current amplitudes and train durations that can be explored in primary motor cortex of awake humans. We are unaware of studies in which ICMS has been applied in human primary motor cortex. Future studies might find that ICMS can evoke motor responses with less tendency to evoke after-discharges or seizure activity than surface, ECoG, or stereo EEG stimulation.

Primary motor cortex is not the only area in which the effect varies depending on how electrical stimulation is delivered. In the primary somatosensory cortex, surface stimulation produces tingling paraesthesias whereas ICMS produces more naturalistic sensations. Intracortical stimulation of primary visual cortex in awake humans can produce phosphenes of highly saturated color, but as the stimulus intensity is increased humans report phosphenes of yellow, white, or gray (Schmidt et al., 1996). Presumably, as larger volumes of primary visual cortex are activated, the experience reported averages across an increasing variety of color blobs. Similarly, whereas ICMS at lower currents in macaque area MT can bias the perceived direction of visual motion, ICMS at higher currents up to 80 μ A impairs direction discrimination (Murasugi et al., 1993), presumably the result of activating neurons with a wider variety of preferred directions. The evoked experience averages across all directions and the actual direction of visual motion can no longer be identified accurately.

We speculate that such “averaging out” may be responsible in part for deficits of normal function produced by electrical stimulation⁵, such as anomia. Put in a vastly oversimplified manner, electrical stimulation does not selectively evoke a specific word representation, but rather evokes the representation of many words at the same time, amongst which the subject is unable to choose accurately, resulting in particular types of errors depending on the function of the local cortex (semantic, lexical, paraphasic), or even rendering the subject unable to come up with any word (“This is a _____”).

Averaging out might contribute as well to the observation that awake human subjects are oblivious to surface stimulation in much of the higher order association cortices (Penfield & Rasmussen, 1950). Future studies investigating how electrical stimulation manifests itself in these areas may require not only the subject be engaged actively in a specific, area-appropriate behavior, but also require the stimulation be limited to a relatively small region of cortex using a technique such as ICMS.

Conversely we note that electrical stimulation even in regions with “known” functions, often fails to have any detectable effect. For example, although stimulation of the posterior inferior frontal gyrus can produce anomia, no more than 15% of stimulations in this region do produce anomia (Sanai, Mirzadeh, & Berger, 2008). We speculate that this may reflect the distributed network nature of information processing in the brain. Unless a given locus is a unique and critical node in the network underlying performance of a given task, electrical stimulation at that locus will not impair performance of that task so long as the necessary processing can continue to flow through other nodes of the network. Affecting performance then may require simultaneous stimulation at multiple loci, none of which impairs

⁵Indeed, repetitive trains of transcranial magnetic stimulation (rTMS) now are used routinely to produce transient “virtual lesions” (Pascual-Leone, Walsh, & Rothwell, 2000; Ziemann, 2010).

performance when stimulated alone. Such coordinated stimulation at multiple selected sites awaits future investigation.

Conclusions and Moving Forward

Electrical stimulation has proven a useful tool for activating intact neural circuits to localize and investigate function in numerous areas of the nervous system. Whether electrical stimulation produces an observable response is inherently tied both to the behavioral task being studied and the methodological details of the stimulation being delivered. Technological advances both for localization of epileptogenic foci and for neuroprosthetic applications currently are providing opportunities for increasingly refined electrical stimulation in a widening variety of brain regions in both experimental animals and humans. In Table 1 we have summarized some questions that clinicians might ask study participants to investigate second-order aspects of the experiences evoked by electrical stimulation in sensorimotor cortex. These examples might be adapted as appropriate for studying other regions of the brain. And in Table 2 we suggest paradigms for investigating the participants' experiences when no first-order effect is evoked. Although the limitations on participant time and effort and on stimulation intensity are well known, the progressively increasing time periods during which ECoG arrays, stereo-EEG electrodes, and microelectrode arrays can remain implanted may provide the opportunity to employ such paradigms. As the manner in which stimulation is delivered continues to change with technological progress, incorporating tasks that probe progressively more sophisticated aspects of behavior will be equally important. Combinations of stimulation technology and behavioral tasks carefully chosen to suit the areas of interest will continue to enhance our understanding of brain function, and how we can influence that function beneficially.

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Table 1.**Questions regarding second-order sensorimotor experiences**

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1. Somatic sensation in the motor cortex evoked by stimulation subthreshold for movement:
 - Do you feel anything on or in your body when I stimulate here? Can you describe the feeling?
 - Was it on your skin? If so, where on your skin?
 - Was it a movement of your body? If so, movement of what part in what direction and how far?
 - Was it a sensation inside your chest or stomach?
 - How would you rate the naturalness of the sensation from 10 (completely natural) to 0 (completely unnatural)?
 - When the stimulation is increased to evoke a movement, how does that movement compare to the sensation evoked by lower intensity stimulation?
 2. When a movement is evoked:
 - Do you know that part of your body just moved?
 - What part?
 - In what direction?
 - How would you rate the naturalness of the movement from 10 (completely natural) to 0 (completely unnatural)?
 - Did you make that movement, or did I [the investigator] cause it?
 3. Intention and agency evoked by stimulation subthreshold for evoking movement per se:
 - Did you feel an urge, desire, or intention to move or a feeling that you were about to make a movement?
 - If so, of what part of your body and in what direction?
 - If you wanted to, why did you not make that movement?
 - If you had made the movement, would it have been you making the movement or me [the investigator] causing the movement?
 - If I [the investigator] increase the intensity of stimulation, does that movement occur, or a different movement?
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Table 2.

Paradigms for “no-effect” loci

1. Does the subject have any reproducible, perhaps subliminal qualium?
Deliver a cue (e.g. the word “now”) at irregular intervals. Deliver stimulation with the cue on 50% of the trials and no stimulation on 50%, selected randomly. Ask the subject to respond (forced choice) after each cue, “Yes, something happened” or “No, nothing happened.” “Yes” responses on significantly more than 50% of the trials indicate that the subject experienced some qualium from the stimulation. As an alternative for language-based responses, the same paradigm could be performed with the subject responding by pressing one button for “Yes” and another for “No.”
2. Can the subject distinguish stimulation at different “no-effect” loci?
If the subject experiences qualia at more than one no-effect locus, then one locus can be labeled “A,” another “B,” etc. Different loci can be stimulated in a randomized sequence at irregular intervals with or without a cue (e.g. “Now”) and the subject asked to respond in each trial (forced choice) with “A” or “B” either verbally or by pressing two different buttons.
3. Repeat testing at “no-effect” loci
If no-effect was obtained at the current locus, but an effect was obtained at the preceding locus, the effect obtained at the preceding locus may have affected the result at the no-effect locus. Consider returning or waiting a sufficient duration and then re-testing the no-effect locus.
4. Multiple “no-effect” loci
Consider stimulating multiple “no-effect” loci either simultaneously or in rapid sequences to determine whether an effect can be evoked.