Chapter VI. Part 3. Beyond neurophysiological correlations: electrical stimulation of visual cortex

As often stated, correlations do not imply causation[1]. This simple logical statement is often ignored, leading to much confusion in misinterpreting cause and effect in Neuroscience and many other domains. There are plenty of examples of this type of misinterpretation in the news. For example, the following statements can easily be misinterpreted to imply causality: "Smoking is correlated with alcoholism"; "Girls who watch soap operas are more likely to show eating disorders"; ""Finns who speak the language of their Nordic neighbors are up to 25 percent less likely to fall ill than those who do not". The medical community is not immune to this fallacy. Consider the following statement: "The majority of children with autism are diagnosed between the ages of 18 months and three years old. That's also the same period of time when children receive a large number of immunizations. People see the correlation between receiving immunizations and the diagnosis of autism, and assume that that means that the immunizations cause autism." The correlation between the age of immunization and the appearance of autism syndromes does not imply any causal relationship between the two. Of course, it does not disprove any causal relationship between the two either.

As discussed in the previous chapters, it is essential to study the activity of individual neurons along visual cortex to examine the mechanisms underlying visual recognition. Yet, neurophysiological recordings provide correlations between neuronal responses and visual stimuli, or between neuronal responses and visually evoked behavior. Moving beyond these correlations to causal effects is not a trivial matter. One approach to bring us a step closer towards understanding the relationship between neural activity in specific brain circuits and visual perception is to examine the effects of electrical stimulation[2].

6.7. Early efforts in electrical stimulation of the human brain

William Penfield (1891-1976) was one of the key figures in the invasive study of the human brain through his work with epileptic patients (Penfield and Jasper, 1954). As a neurosurgeon, he realized that he had direct access to the inner workings of the human brain through his neurosurgical approach to epilepsy. He studied subjects at the behavioral level after brain resections and he was one of the pioneers in performing neurophysiological recordings from

[1] Non Causa Pro Causa

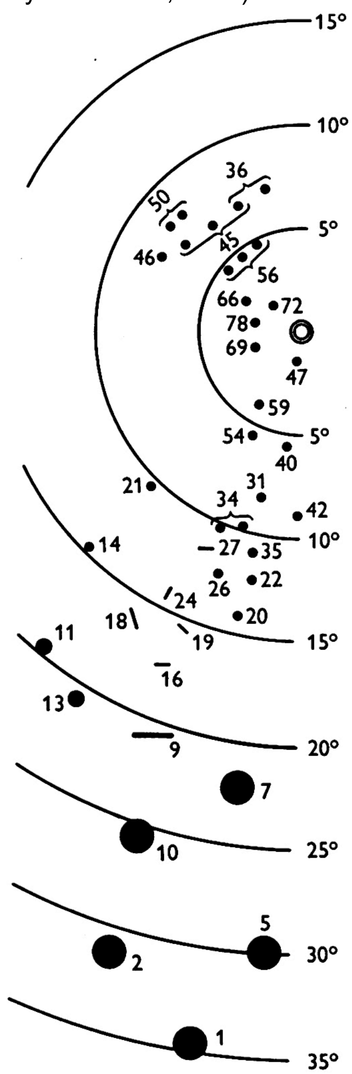
[2] To be clear, electrical stimulation studies do *not* prove causality. They establish yet another correlation (between external activation of a specific circuit X and a certain percept Y or a certain behavior Z). This additional correlation may support the notion that activity in X can lead to Y or Z but it is not a mathematical demonstration of causality at all.

intracranial electrodes in the human brain. Additionally, he extensively studied the behavioral effects of electrical stimulation (Penfield and Perot, 1963).

He provided many examples of the effects of electrical stimulation in different parts of the human brain in his summary reported in (Penfield and Jasper, 1954; Penfield and Perot, 1963). He worked with patient with pharmacologically intractable epilepsy, specifically in cases where he was going to resect part of the epileptogenic tissue as part of treatment for epilepsy. Before resecting human brain tissue, he used electrodes placed subdurally to perform electrical stimulation while the subject was awake in the operating room. This is a standard procedure that is used routinely in hospitals throughout the world (e.g. (Penfield, 1958; Dobelle and Mladejovsky, 1974; Blanke et al., 2002; Coleshill et al., 2004; Tellez-Zenteno et al., 2006; Anderson and Lenz, 2009; Desmurget et al., 2009; Murphey et al., 2009; Parvizi et al., 2012; Suthana et al., 2012; Lozano and Lipsman, 2013)). Because there are no pain receptors in the brain, this is not a painful procedure. It is important in these cases to work with subjects who are awake to be able to map cognitive function before resection. In particular, neurologists and neurosurgeons are concerned about language functions, which often reside close to epileptogenic areas. The goal is to treat the epileptic seizures without affecting any other cognitive operation.

He used numbers to identify each of the electrodes and locations that he stimulated and asked the subject to report his sensations upon electrical stimulation. In Penfield's 1963 summary, he relates the observations upon electrical stimulation in multiple parts of cortex in one patient. The first time he stimulated electrode "5", the patient did not reply. Upon a second stimulation pulse in the same location, the patient said "Something". The fourth time, he reported "People's voices talking". Penfield switched to electrode "7". The first pulse in electrode "7" elicited the following response: "Like footsteps walking – on the radio". Upon third stimulation pulse in electrode "7", the subject explained "it was like being in a dance hall, like standing in the doorway – in a gymnasium – like at the Lenwood High school." Twenty minutes later, Penfield moved back to electrode "5" and the subject reported "People's voices". Here I relate some of the observations *verbatim* to illustrate the exciting opportunities in terms of the questions that we can ask by obtaining direct verbal reports from stimulating human cortex. At the same time, the example illustrates how challenging it is to interpret the output of these fascinating but anecdotal reports. What exactly was being stimulated? How many neurons? What type of neurons? What locations? How did the answer to these questions depend on the pulse duration and intensity? How do the conclusions depend on the behavioral output? What did the subject exactly "feel"? There may be a rich experience lost in translation. What exactly is "Something"? Or "People's voices talking". To what extent is repeating stimulation a comparable experience? In some cases, repeated stimulation yielded similar reports. Sometimes it didn't. How much electrode to cortex shift was there in between repetitions? To what extent is the subjective report influenced by the environment (surgery, doctors, etc)? How can we map

Figure 9.1: Position of phosphenes in the visual field elicited by electrical stimulation in human occipital cortex. The center circle indicates the fovea and the numbers are used to identify the electrodes through which electrical stimulation pulses were delivered. The symbols coarsely denote the size and shape of the elicited phosphenes. Reproduced from (Brindley and Lewin, 1968).



these fascinating reports upon electrical stimulation to our understanding of the functions of cortex?

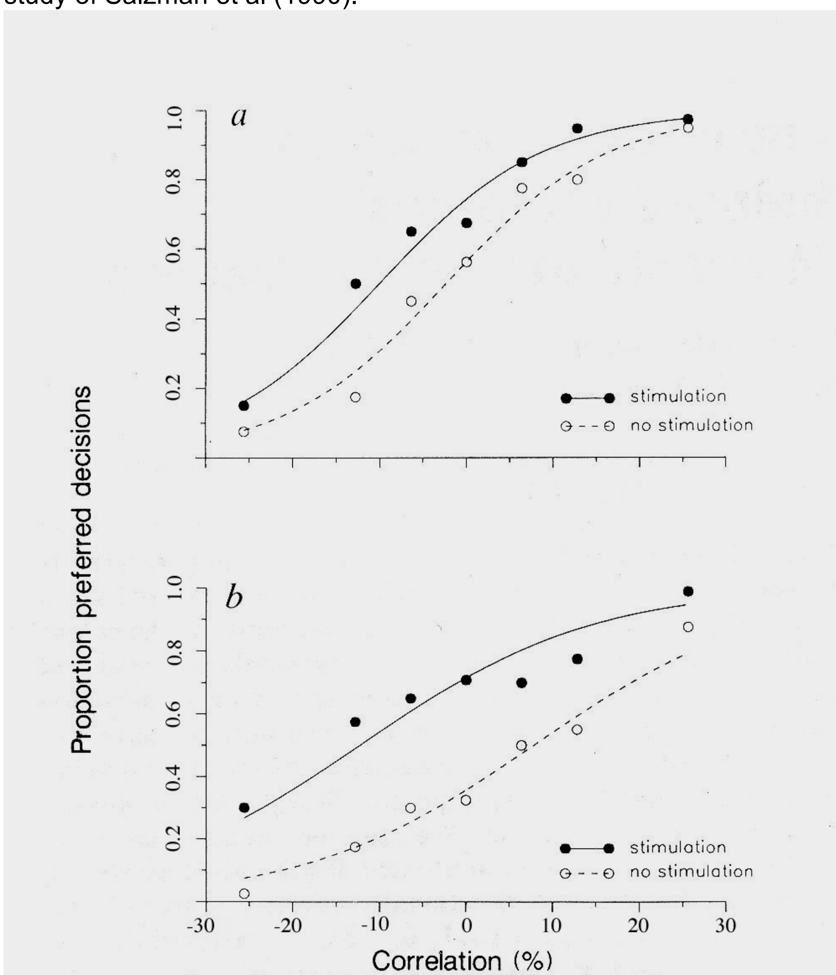
In some cases, electrodes are placed in parts of visual cortex. Particularly when electrodes are placed in early occipital cortex, several investigators have demonstrated that it is possible to elicit perceptual light flashes denominated "phosphenes" (Brindley and Lewin, 1968; Brindley and Donaldson, 1972). Consistent with the retinotopic organization of early visual cortical areas, the location in the visual field of these phosphenes depends on the exact area of stimulation (**Figure 9.1**).

6.8. Electrical stimulation in primate visual cortex

A number of investigators have used electrical stimulation through microwires in the macaque monkey visual cortex. One of he seminal studies involved electrical stimulation of the MT area (also known as area V5) (Salzman et al., 1990). MT receives direct (magnocellular) input from area V1. Neurons in this area are selective for motion direction within the receptive field. A typical stimulus used to drive these neurons is a display consisting of many dots moving in random directions. A given percentage of the dots is set to move coherently in one direction. Depending on the percentage of coherent motion, the stimulus can elicit a strong motion percept. A typical sigmoid psychometric curve can be plotted (both for humans as well as monkeys) showing the proportion of trials in which the subject reports that the dots are moving in one direction as a function of the degree of correlation of the dots in the display. If 100% of the dots move coherently in one direction, subjects report movement in that direction in all the trials. If 0% of the dots move coherently (all dots are moving randomly), then subjects report random movement in one direction or the other.

Newsome's team trained monkeys to report their percept while recording the activity of neurons in area MT. Recording from a neuron in area MT, the investigators would start the experiment by mapping the preferred direction of motion. In a typical experiment, a fixation spot comes up, monkeys are required to fixate, the visual stimulus is displayed for one second, the stimulus disappears and the monkey needs to indicate (e.g. by making a saccade) the direction in which the dots were moving in a two-alternative forced choice paradigm. The direction of motion would be aligned to the neuron's preferred direction so that the dots could be coherently moving in the preferred direction or in the anti-preferred direction. As in other parts of neocortex, there is a topographical arrangement of neuronal preferences in area MT. In other words, nearby neurons in MT typically have similar movement direction preferences. This is presumably important in terms of understanding the effects of electrical stimulation.

Figure 9.2: Results of an electrical stimulation experiment in area MT of the macaque monkey. The plots show the behavioral psychometric function in discriminating the neuron's preferred motion direction in the presence (filed circles) or absence (empty circles) of electrical stimulation (see text for details). The plot is reproduced from the study of Salzman et al (1990).



Based on the neurophysiological recordings, the investigators asked whether electrical stimulation through the same microwire would bias the monkey's visually evoked behavior in the motion discrimination task and whether this bias would be consistent with the neurophysiological preferences. To answer this question, they applied 10 μA biphasic square pulses with 200 Hz frequency and 0.2 msec duration. Electrical stimulation was applied in the center of regions where there was a cluster of neurons within ~150 μm with similar motion preferences. Monkeys were rewarded on correct responses. The results of such experiments are illustrated in **Figure 9.2**. In the absence of microstimulation (empty circles), monkeys showed an approximately sigmoid curve. Monkeys reported the preferred direction of motion in >80% of the trials when the dots had 30% correlation in the preferred direction and they reported the anti-preferred direction of motion in >80% of the trials when the dots had 30% correlation in the anti-preferred direction. In the 0% correlation condition, monkeys reported one or the other direction with close to 50% performance (the monkeys had some inherent bias to report one or the other direction, showing departures from 50% in the 0% correlation condition). Remarkably, upon applying electrical stimulation (filled circles) there was a clear shift of the psychometric curve. Monkeys reported movement in the preferred direction more often (~15%) than in the absence of electrical stimulation. This was a very important finding because it showed convincing and clear evidence that the neurophysiological recordings revealed a signal that could translate into behavioral decisions upon electrical stimulation of the relevant neuronal circuits.

In a similar vein, a more recent example of electrical stimulation was performed by Afraz and colleagues in inferior temporal cortex (Afraz et al., 2006). The experiment closely followed the Newsome study in area MT. Because neurons in ITC are more interested in complex visual shapes than motion direction, the investigators compared faces against other shapes[3]. They presented faces and other non-face images embedded in noise. The noise level changed from 100% (pure noise stimulus) to 20%. The visual signal changed from -80% (20% noise and 80% non-face image), through 0% (100% noise) to +80% (20% noise and 80% face signal). As shown in other studies, the ITC neurons in this study showed visually selective responses (Chapter 7); the investigator here focused on sites that revealed consistent enhanced responses to faces within an area of approximately ± 150 μm. The investigators applied electrical stimulation in those regions and evaluated the extent to which the monkeys reported seeing faces or not for stimuli with levels of noise. On average, the investigators were able to elicit a ~10% change in the behavior in the direction of increasing the number of times that the monkeys reported seeing faces (even in cases where information about faces was minimal due to the

[3] The choice of faces as one of the two stimuli may have been an important methodological point. First, it is possible that it is easier for monkeys to recognize 2d renderings of faces. Second, perhaps there is a stronger topography for faces than other shapes.

noise). Furthermore, the behavioral effects elicited by electrical stimulation were correlated with the degree of selectivity of the neurons (stimulation of more selective sites led to stronger behavioral biases).

6.9. More electrical stimulation in human cortex

Following up on the seminal studies of Penfield, several other investigators used electrical stimulation in epileptic patients to map function in human cortex. In one of these studies, Gloor et al (Gloor et al., 1982) compiled a large list of subjective experiences elicited after stimulation of the temporal lobe. He described visual illusions, elementary visual hallucinations (phosphenes), and complex visual hallucinations[4]. Complex visual hallucinations could be elicited in 5 subjects. In another study, Bartolomei et al stimulated rhinal cortices, the amygdala and hippocampus. Among others, the main effects were déjà vu and memory reminiscences (Bartolomei et al., 2004).

A recent elegant study by Murphey and colleagues further examined the relationship between electrical stimulation, neurophysiological recordings and functional imaging measurements (Murphey et al., 2009). They examined an area that responded to colors, more specifically, to the blue color, according to both functional imaging measurements and field potential recordings. They subsequently used a psychophysical task to ask whether subjects could determine the time of electrical stimulation. Subjects reported perceiving blue upon electrical stimulation.

As discussed in the previous chapter, several studies have shown that electrodes around the fusiform gyrus in the human brain show responses that are selective to complex shapes. Many of these electrodes are strongly activated by faces. Several studies have shown that applying electrical stimulation through these electrodes distorts or impairs ability to perceive faces (McCarthy et al., 1999; Parvizi et al., 2012).

6.10. Many open questions about electrical stimulation

A number of questions remain open and are the subject of intense investigation. The exact biophysical effects elicited by electrical stimulation are not fully understood (Tehovnik, 1996). The behavioral effects elicited by electrical stimulation in MT could be the result of MT signals being transmitted to other areas. The distinction between direct and indirect effects of electrical stimulation is not trivial.

The number and type of neurons stimulated in this procedure is not well defined. It is clear that electrical stimulation elicited by this technique affects large

[4] In addition to these effects, Gloor et al describe a large number of other experiences including fear, thirst, familiarity and others.

numbers of neurons in the vicinity of the electrode (many more neurons than what the electrode is recording from). Because of limited time and the difficulty inherent in these experiments, the dependence of the behavioral effects on the intensity of stimulation, pulse type, type of electrodes, etc. has not yet been thoroughly described.

Depending on the stimulation parameters, different numbers of neurons could be recruited. Depending on the exact position of the electrode and the topography of the area under study, the effects could be different. If electrical stimulation affects 10,000 neurons, 5,100 of which prefer movement to the right and 4,900 of which prefer movement to the left, the end result could be due to the differential activation of those 200 neurons. More specific stimulation conditions could lead to larger behavioral effects.

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