Chapter IV. Lesions and neurological examination of visual function

To find out how something works, it is often useful to try to take it apart, examine its function upon removing individual components and then try putting it back together. Trying to figure out how the brain works by examining behavioral manifestations after restricted lesions has been an important approach in Neuroscience since the very beginnings (Finger 2000).

Of course, this is easier said than done. First, different components of the system may interact with one another, such that removing one of them could lead to indirect functional consequences. Second, there could be a significant amount of redundancy, such that another component could take over, thereby shadowing the actual use of the removed piece. Third and equally important, it is not always easy to remove parts of the system (the brain) in a clean way, without affecting multiple other parts in the process.

In spite of these and other challenges to be discussed below, much has been learnt about the function of the visual object recognition circuitry through the study of lesions in animal models as well as in humans.

4.1. Some tools to study the functional role of brain areas in animal models

Several tools are in use to examine the effect of removing or silencing a given brain area including lesion studies, cooling experiments, pharmacological intervention, imaging combined with specific cell ablation and molecular tools such as gene knock-outs. Each of these techniques has its own advantages and limitations.

Below, we will focus on several studies that involve lesions. Cooling is based on the notion that neuronal activity decreases quite sharply when the temperature of the brain or a given brain region is lowered. Cooling devices can be implanted in the brain and lower the local temperature by several degrees. Cooling can completely silence activity in the region surrounding the electrode. In contrast to lesions, cooling is a transient and reversible procedure so that the same animal can be studied behaviorally before, during and after the effects of cooling.

Pharmacological intervention can also be used to silence brain regions. The most well-known type of chemical intervention is perhaps general anesthesia where the entire brain is affected. There is also the possibility of injecting neuronal inhibitors to affect activity in local circuits. Pharmacological silencing procedures are often also reversible and the silencing effects disappear when the drugs wash out.
In a few heroic studies, investigators have used high-resolution imaging tools to identify specific cell types and then ablated those cells one-by-one to examine the behavioral consequences.

The last several decades have seen the development of powerful molecular biology tools to silence specific genes through knock-outs and knock-ins. This has been traditionally the domain of mice work and it remains difficult, though not necessarily impossible, to use these techniques in primate research. More recently, primate researchers have turned their attention to virus injection techniques that could achieve high molecular specificity without having to incur in the time and cost of developing knock-outs in primates.

Arguably, one of the most widely used tools to study function in the brain has been the behavioral examination of subjects with lesions. In animal models, investigators may remove specific brain areas to examine the behavioral deficits. This has led to the understanding that primates with lesions to the superior colliculus are still capable of visual object recognition whereas animals with complete lesions of primary visual cortex are not. Posterior studies examined the function of different parts of visual cortex through lesions. For example, lesions to the MT area (also known as V5) lead to severe impairment in discriminating motion direction (reviewed in (Born & Bradley 2005)) whereas lesions to inferior temporal cortex lead to object recognition deficits (Dean 1976, Gross 1994, Holmes & Gross 1984). Lesion studies in animals often provide highly valuable information but are not always easy to interpret. First, it is difficult to make anatomically-precise lesions. Second, behavioral assessment may not be trivial. Unless the animal shows a clear impairment in batteries of more or less well-defined tasks, important deficits could be missed. Finally, by definition, lesions defined by anatomical landmarks include multiple cell types and multiple different connections including inputs and fibers of passage. As a very coarse analogy, imagine removing the entire state of Massachusetts from the US map. There would be severe deficits but some may not be obvious to spot, some may not be unique to Massachusetts, some may require clear insights about where to look.

A number of distinctions need to be made while reading studies involving lesions and silencing. First, as noted above, many of the current techniques involve silencing (or removing) large amounts of tissue. Therefore, an often-encountered discussion in the literature concerns the separation of local effects from "fibers of passage" effects. Imagine that axons going from area A to area C happen to pass by nearby area B. A lesion to area B may also cut through the A-C axons. The subsequent behavioral effects may not be due to the function of area B but to the function of areas A or C. Another distinction to be made concerns immediate versus long-term effects. The brain has a remarkable degree of plasticity. Over time, it is possible that the behavioral effects of lesions to a given brain area are overcome or changed through compensatory changes in other brain areas and connections. One obvious such potential compensatory mechanism is the presence of a "copy" of the same brain area in the other hemisphere. Many (but not all) parts of cerebral cortex exist in both hemispheres.
The effects of unilateral lesions can be masked by activity in the other hemisphere (unless specific precautions are taken in the experimental design; see e.g. (Tomita et al 1999)).

4.2. Some tools to study the functional role of brain areas in humans

Due to ethical reasons, most of the techniques mentioned above cannot be used in studies in human subjects. There are, however, a wide variety of neurological conditions that provide interesting and important insights about functional neuroanatomy of the human brain. These cases typically come from a variety of neurological conditions, accidents and wounds.

Bullets and wounds inflicted by other weapons have provided several insights about function in visual cortex. Carbon monoxide poisoning as well as certain viral infection such as encephalitis often produce severe deficits, particularly in the temporal lobe, often leading to severe visual deficits. Bumps, partial asphyxia during first weeks of life, tumors and hydrocephalus have also been documented to produce visual deficits.

An important advantage of human neurological studies over animal studies is the accessibility of subjective behavioral reports. In some cases, specific visual deficits after lesioning or silencing experiments in animal models may be hard to detect due to the limited nature of the behavioral assessment paradigms. Behavioral evaluation is often easier in human patients. Yet, it is always important to design the experiments carefully. Even remarkable behavioral deficits could be missed in human patients. Consider, for example, the case of split-brain patients. These are patients with pharmacologically-resistant epilepsy who undergo severance of the corpus callosum fibers as treatment for epilepsy. For a long time, it was assumed that there was nothing wrong with these subjects. It was not until Roger Sperry designed careful experiments based on his scientific understanding of the neuroanatomy of the visual system that some of the deficits became apparent (Sperry 1982). Sperry knew that the right visual hemifield maps onto the left hemisphere in visual cortex and vice versa. Here it is important to distinguish between the right and left eyes and the right and left visual hemifields. The right and left visual hemifields are defined by the position of the fixation point. Most of the information from the right hemifield reaches both the left and right eyes and vice versa. By designing an experiment where visual information about an object reached only the right hemisphere (information from the left hemifield), Sperry and colleagues showed that the main language hemisphere (typically left) did not have access to the visual information after the callosotomy treatment.

The study of “natural lesions” in human patients encounters other challenges. Depending on the exact nature of the “natural lesion”, many studies may be unique and hard to reproduce. There are plenty of single case studies. These studies may be very interesting and highly informative. Yet, without
reproducibility it is not always easy to follow up or investigate the deficits in higher detail as can be done in studies in animal models. Additionally, “natural lesions” do not necessarily respect any “boundaries” established by anatomical, cytoarchitectonic, neurophysiological or animal lesion studies. Therefore, many neurological lesions encompass large parts of cortex and multiple regions that are functionally distinct. This sometimes makes it challenging to interpret the findings due to multiple effects, indirect effects and non-specific lesion effects. Another difficulty in human lesion studies is that it is not always easy to localize the lesion or brain abnormality. Magnetic resonance imaging can only detect certain types of relatively large-scale brain transformations but more subtle effects may well be missed.

4.3. V1 lesions

The beginning of studies of human primary visual cortex can be attributed to the careful examination of bullet trajectories during and after World War I. Both Holmes and Riddoch described clear and delimited visual field deficits contralateral to the lesion (Holmes 1918, Riddoch 1917). Shape, color and, to a lesser extent, motion discrimination also, were typically completely absent within the scotoma, the specific visual field region that maps onto the damaged part of visual cortex. Similar effects are often encountered through vascular damage, tumors and trauma studies. Several studies in macaque monkeys have shown that the animals are essentially blind after complete lesions of V1.

It is worth mentioning that there was a considerable degree of excitement in the vision community a few years ago with the description of a phenomenon called “Blindsight” (Weiskrantz 1996, Zeki & ffytche 1998). As the name suggests, the observation was that some subjects with profound lesions to occipital cortex were still capable of certain visual behavior within the scotoma. Several possibilities were proposed to account for these observations including anatomical routes that bypass V1 and the presence of small intact islands in V1 in spite of the lesions. Although the phenomenon was quite clearly demonstrated the range of visual behaviors was rather limited. Subjects could detect motion (this was also observed in the initial study by Riddoch in 1917), subjects could discriminate day from night and other coarse visually-elicited behavior. Yet, in all cases, their capacity for fine visual discrimination was lost.

The profound deficits after V1 lesions in both animals and humans, combined with the challenges in examining visual behavior in animals led several prominent investigators to argue that V1 (also known as area 17) is not only necessary but also sufficient for visual perception. In an interesting historical overview, Gross cites several striking demonstrations of this narrow-minded and wrong scientific perception (Gross 1994):
“In human subjects there is no evidence that any area of the cortex other than the visual area 17 is important in the primary capacity to see patterns. . . . Whenever the question has been tested in animals the story has been the same. (Morgan and Stellar, 1950)"
“. . . visual habits are dependent upon the striate cortex and upon no other part of the cerebral cortex. (Lashley, 1950)"
“. . . image formation and recognition is all in area 17 and is entirely intrinsic. . . . the connections of area 17 are minimal. (Krieg, 1975)"

4.4. Lesions in inferior temporal cortex

We jump now from primary visual cortex all the way to inferior temporal cortex. One of the earliest demonstrations that V1 could not be the entire story was the study of the so-called Kluver-Bucy syndrome (Kluver & Bucy 1939). After bilateral removal of the temporal lobe in macaque monkeys, the original reports included a variety of behavioral effects including loss of visual discrimination (but also increased tameness, hyper sexuality and altered eating habits).

The work of Kluver-Bucy was subsequently refined by making more precise lesions restricted to inferior temporal cortex (Dean 1976, Holmes & Gross 1984, Mishkin 1954, Mishkin & Pribram 1954). Bilateral removal of inferior temporal cortex (ITC) leads to impairment in learning visual discriminations as well as deficits in retaining information about visual discriminations that was learnt before the lesions. The severity of the deficit is typically correlated with task difficulty. In other words, monkeys can still perform "easy" visual discrimination tasks after bilateral ITC lesions. The deficits are long lasting. These observations apply to objects, visual patterns, object size, color, etc. Deficits in recognizing forms defined by motion or luminance have also been described (Britten et al 1992). The behavioral deficits are restricted to the visual domain and do not affect discrimination based on tactile, olfactory or auditory inputs. None of the "psychic blindness" or other social effects described originally by Kluver and Bucy were apparent after bilateral ITC lesions. This emphasizes the importance of restricted lesions to properly interpret the behavioral deficits.

In the same way that the Kluver-Bucy syndrome could be fractionated by more detailed and circumscribed lesions, it is quite likely that future more specific lesions within ITC will further fractionate the object recognition deficits prevalent after bilateral ITC ablation. Indeed, hints of this type of specificity are apparent in recent elegant work combining pharmacology, optogenetic manipulation, neural recordings and behavior in monkeys (Afraz et al 2015). The authors focused on an area of inferior temporal cortex with an abundance of neurons that respond preferentially to faces compared to other objects (a theme that we will return to when we examine the neurophysiological properties of neurons in ITC). To the extent that the activity of those neurons is instrumental in tasks that depend on understanding face shapes, the authors hypothesized that local regions would disrupt behavioral performance in those tasks. To evaluate this hypothesis, they trained monkeys in a gender discrimination task. Once the animals were trained, they inactivated small local parts of IT cortex. This inactivation was performed
using either optogenetic manipulation\(^1\) or pharmacological intervention\(^2\). Suppressing local neural activity led to a small but significant impairment in gender discrimination performance in the monkeys. These behavioral effects were reversible: when light was not shown or the effects of the drug were washed out, performance returned to normal levels. The effects were also specific: inactivation of other regions not responding to faces did not lead to such behavioral impairments.

4.5. **Dissociation between “vision for action” and “vision for shape”**

Two main pathways of information processing emerge from V1. These are usually referred to as the dorsal / where / action pathway and the ventral / what / object pathway (Felleman & Van Essen 1991, Haxby et al 1991, Mishkin 1982). The dorsal pathways are particularly involved in the spatial localization of objects within their environment and detecting object movement. The ventral pathways is particularly involved in object shape and color discriminations. Although these are often referred to as parallel independent pathways, there are multiple interconnections that bridge across these two systems. In the next lecture, we will discuss neurophysiological investigations along the ventral visual cortex.

A remarkable patient with a lesion largely restricted to the temporal lobe was described by Goodale and Milner (Goodale & Milner 1992). This subject had severe impairment in object shape recognition. Yet, in spite of her inability to recognize objects, she showed a rather remarkable ability to interact with many objects. She showed an appropriate reach response towards objects that she could not describe. She also showed correct behavioral performance in visuomotor tasks. Goodale and Milner proposed that the dorsal pathway is particularly engaged in “vision for action”, the immediate use of visual information to carry out specific visually guided behaviors. In contrast with this action mode, they proposed that awareness about an object requires activity in the ventral stream and the temporal lobe in particular.

4.6. **Dorsal stream lesions in the human brain**

Several other visual deficits due to cortical lesions have been described in humans. In general, the types of deficits associated with lesions along the dorsal visual stream are quite distinct from those associated with lesions along the ventral visual stream.

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1 Optogenetics constitutes a fancy and transformative recent technique to specifically manipulate neural activity. Briefly, neurons are genetically modified, by injecting a virus in the case of this study, to express a light-sensitive ion channel, which will inhibit neural activity in this case. Upon shining light, the genetically modified neurons are silenced.

2 The authors injected muscimol, which is a potent GABA channel agonist and inhibits neural activity. Muscimol is the main psychoactive component of many mushroom drugs.
Lesions along the dorsal stream can lead to akinetopsia, neglect, hemineglect, optic ataxia and simultanagnosia. *Akinetopsia* refers to the specific inability to discriminate visual motion (Zeki 1991). This has been described as a visual sensation similar to that evoked by stroboscopic lights in a discotheque. The subject can see isolated snapshots but not the movement trajectory. Both neglect and hemineglect have been discussed as attentional disorders. Hemineglect is defined as the inability to attend to a visual hemifield (Bisiach & Luzzatti 1978, Driver & Mattingley 1998, Farah et al 1990). For example, a subject may eat from only the right half of the plate, or may copy only one half of a drawing. *Simultanagnosia* is the inability to see more than one or two objects in a scene. We can argue that in all of these conditions, object shape recognition remains intact.

### 4.7. Lesions leading to shape recognition deficits

Along the ventral visual stream, lesions around area V4 lead to *achromatopsia*, a specific inability to recognize colors (Zeki 1990). Note that this condition is distinct and dissociable from retinal color blindness.

Lesions in higher areas of the temporal lobe can lead to a variety of intriguing forms of agnosias. Several studies have reported category-specific agnosias (Warrington & Mc Carthy 1983, Warrington & Mc. Carthy 1987, Warrington & McCarthy 1994). For example, some studies report a larger deficit in recognizing “living things”. Other studies describe inability to recognize animals, or tools, words, landmarks.

The human lesion studies are at the same time fascinating and frustrating. They are fascinating because they point to remarkable and sometimes specific deficits in visual shape recognition. At the same time, these studies often involve a single subject and the lesions are necessarily not well circumscribed to make definite conclusions. Shape recognition agnosias have been subdivided into a number of groups depending on whether they are thought to be mostly visual, whether the deficits also involve language and whether the deficits affect object manipulation or recognition through other sensory modalities. One of these variants is called “aperceptive visual agnosia”. The subject cannot name, copy or match simple shapes while his/her visual acuity, color recognition and motion perception remain largely intact. These deficits are typically associated with bilateral damage to extrastriate visual areas. Another variant is called “associate visual agnosia”. This label is assigned to cases where copying a drawing and matching complex shapes remain intact but drawing from memory and object identification are significantly impaired (Heilman & Valenstein 1993, Warrington & Mc. Carthy 1987).

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3 Agosia (greek): lack of knowledge.
A specific form of agnosia has received particular attention in the literature. Prosopagnosia\(^4\) refers to the specific inability to visually recognize faces with intact ability to identify other objects and shapes (Benton & Wav Allen 1972, Damasio et al 1990). Face agnosia is very rare and typically occurs after brain damage caused by strokes in the right posterior cerebral artery (although some authors have described a congenital form of prosopagnosia (Behrmann & Avidan 2005)). The fusiform and lingual gyri are typically affected. The extreme nature of prosopagnosia was emphasized by Oliver Sacks narrative about “The man who mistook his wife for a hat” (Sacks 1998). Subjects are often able to recognize people based on their voices, clothes, gait and other characteristics but not from photographs of the face. The extent to which the effects should be described as face-specific has been debated and some authors argue that the impairment in face recognition can be better described as a general difficulty in identifying exemplars from a class with many similar stimuli and the degree of expertise with those stimuli (Gauthier et al 1999).

### 4.8. References


Dean P. 1976. Effects of inferotemporal lesions on the behavior of monkeys. *Psychological Bulletin* 83: 41-71


\(^4\) Proso (greek): face


Kluver H, Bucy PC. 1939. Preliminary analysis of the functions of the temporal lobes in monkeys. *Archives of Neurology and Psychiatry* **42**: 979-1000


