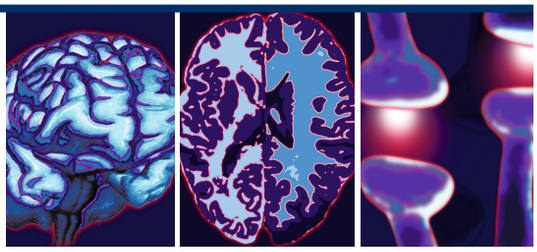
EDITORIAL



From known to unknown; old to new: can lesion studies inform psychiatry about mental illness in the 21st century?

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"With the integration of 21st century technologies, including imaging, biochemistry and genetics, human lesion studies can provide powerful tools to elucidate psychiatric illnesses."

"There are but two ways at coming at the knowledge of a Machine, either to be taught the whole contrivance by the Maker, or to take it to pieces, and to examine each Piece by itself, and as it stands in relation to the rest."

– Niels Stensen, *Discours de Monsieur Stenon sur l'anatomie du cerveau* (1669)

One hundred and sixty three years ago an explosion propelled an iron spike through the frontal lobe of a railroad worker named Phineas Gage. Miraculously, he survived. In reporting the case, John Harlow described the behavioral changes that occurred after the accident and speculated on the functions of the frontal lobes [1]. This marked a milestone as one of the first human 'lesion' (from the Latin word for injury) studies of the brain and behavior.

Ever since, lesion studies in neuroscience have traditionally been defined as experiments that examine the effects of accidental or intentional brain injury in humans or animals to determine the normal function of the injured area. The logic of these studies is that if people or animals exhibit a behavioral deficit after injury, the brain area affected must be necessary to perform that behavioral function. The lesion method has been historically important and led to fundamental neuroscientific insights, for example, the findings of Broca and Wernicke on the neuroanatomy of language [2].

Since the development of noninvasive brain imaging in the mid-to-late 20th century and the advent of systems neuroscience and molecular neurobiology the use of lesion studies has waned. In fact,

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one can ask if lesion studies have become anachronistic – a relic of the past, such as pneumoencephalography, which has been supplanted by superior technologies [3]. In addition, it can be argued that mental disorders, such as schizophrenia, depression and anxiety disorders, entail disturbances in neural circuits that are distributed across multiple anatomic regions and, therefore, are not amenable to lesion studies [4]. However, despite these developments, we suggest that the lesion method continues to be a powerful mode of inquiry, including for psychiatric disorders.

Redefining lesion studies

The fundamental difference between lesion studies and nonlesion studies is the direction of inquiry; nonlesion studies attempt to move from the unknown to the known, while lesion studies attempt to move from the known to the unknown. For example, if your car does not start, a nonlesion approach would be to compare it to other cars that work in an attempt to move from the unknown (why does my car not start?) to the known (the salient difference between the cars that explains why mine does not start). Lesion studies, by contrast, start with a known (the spark plugs are missing in my car) and attempt to determine the unknown (will this affect the ability of the car to start?) to learn about the function of spark plugs. We propose redefining the lesion method as follows: 'a scientific experiment in which subjects with a defined and identified abnormal anatomical, genetic or biochemical variant not usually found in healthy subjects are observed in an attempt to determine the normal function of the variant in healthy subjects'.

Functional MRI & human lesion studies in psychiatry

As an example of how lesion studies can be used to research mental disorders, we will discuss how human lesion studies can be used to address the weaknesses of functional MRI (fMRI) studies in psychiatric patients. fMRI is currently a popular imaging technique to investigate mental disorders and human behavior. Thousands of papers have been published using fMRI to investigate psychiatric disorders. However, weaknesses of fMRI include potential under- and over-inclusiveness of findings and difficulty interpreting interactions between brain structures [3]. Human lesion studies address these problems in the following ways [3].

fMRI detects regional changes in the blood-oxygen-level-dependent signal when a subject performs a task or a symptom is provoked, which is usually interpreted as changes in activation of a brain region [5]. However, fMRI is subject to the problem of overinclusiveness; only a subset of the brain areas that are activated during fMRI while performing a certain task or exhibiting a behavior actually mediate this behavior. To determine which brain areas are necessary to perform a behavior or experience a symptom, a lesion study is required.

A second limitation of fMRI is potential underinclusiveness [3]. fMRI studies that detect changes in activation with performance of a task or experience of a symptom fail to detect brain areas that do not change activation. However, some brain areas could be essential for performance of the task or experience of the symptom, but are constituently active and, thus, are not detected. There is accumulating evidence that certain brain networks, for example, the 'default' network, are active when subjects are not performing external tasks, which is important to understand behavior, memory and brain disorders [6]. Human lesion studies can detect which brain areas essential to the performance of a behavior or experience of a symptom that are not detected by fMRI. The importance of networks composed of interacting brain structures is, of course, not new, having been proposed by Luria, the father of neuropsychology, in his 'functional network theory'. Luria stressed the need for lesion studies to deconstruct these functional networks [7].

Human lesion studies can also address the problem of the interpretation of interactions of brain areas found to be activated or deactivated on fMRI. Brain areas do not act in isolation and it is difficult to determine the effects of activation or deactivation of one brain structure on other brain structures. If two connected brain areas are activated by a task or symptom provocation, is the activation of one area driving the other? Is one area active because it is trying to suppress the other? These questions are not easily answered by fMRI, but can be addressed with human lesion studies in which the differential effects of lesions in the two areas can be examined. As an example, we analyzed the effects of brain lesions on the subsequent development of post-traumatic stress disorder to elucidate the relative roles of the ventromedial prefrontal cortex and the amygdala [8].

Genetics & lesion studies

Human lesion studies can also complement knowledge gained from nonlesion genetic studies. Genome-wide association studies are commonly used to identify the genetic basis of complex disorders, such as mental illnesses. So far, these studies have accounted for a very small fraction of the known heritability of mental disorders [9]. Genome-wide association studies are designed to be able to detect the effects of multiple genes on the development of complex disorders, however, they are based on the assumption that the gene variants associated with the disorder are homogenous in the patient group [10]. This is likely to be an invalid assumption for many mental illnesses. An alternative approach to identify genes associated with mental illness is to find patients with a known genetic defect that results in psychiatric symptoms and identify the responsible gene(s). For example, velocardiofacial syndrome or DiGeorge Syndrome, is a neurodevelopmental disorder caused by a deletion of approximately 3 million base pairs near chromosome 22q11.2. It is associated with the development of psychosis, suggesting that disruption of a gene or genes on chromosome 22q11.2 can result in psychosis [11].

Biochemical lesion studies

Parkinson's disease is a classic biochemical lesion study. This idiopathic degeneration of dopamine neurons in the substantia nigra pars compacta results in a deficiency in dopamine neurotransmission, with resultant motor, and often, psychiatric symptoms. This condition can be mimicked by the biochemical lesion inflicted by MPTP administration. Similar biochemical lesion models have been utilized in depression with serotonin depletion [12].

Criticisms of the use of human lesion studies in psychiatry

Some of the limitations of human lesion studies to study mental disorders are surmountable, while others are inherent to the lesion method. Lesion studies have been rightly criticized for relying on single case studies of unusual patients, reducing generalizability and the ability to subject hypotheses to statistical tests. To address this criticism, human lesion studies should adopt many of the research standards used in other types of clinical research: sufficient sample sizes, the use of control groups, *a priori* hypotheses and statistical methods to test hypotheses.

Of course, we cannot ethically induce permanent lesions in humans and so we are limited to opportunistic or reversible neuroanatomic, biochemical and genetic lesions. Techniques for reversible neuroanatomic lesions, such as transcranial magnetic stimulation and deep-brain stimulation, continue to develop and can be used to target an increasing number of brain areas.

Damage to the brain is not random, for example, strokes tend to occur in watershed areas of perfusion. Thus, it can be difficult to ascertain sufficient patients with damage to a particular brain area of interest without involvement of subsequent areas. Mutations do not act in isolation either; a mutation in a single gene can affect other gene products. These problems can be partially addressed statistically [13]. Another criticism is that complex behavior, personality, and emotion have a large premorbid variability, therefore it can be difficult to distinguish the changes that are due to the lesion from pre-existing characteristics. This problem can be addressed by using outside informants. There are also some situations in which subjects can be tested before and after a lesion (e.g., patients undergoing brain surgery and presymptomatic mutation carriers).

Conclusion

Psychiatric disorders are complex and multidetermined. Human lesion studies, which determine the effects of removing a single element from a biological system, can simplify the problem and, thus, provide unique insights on complex psychiatric disorders. With the integration of 21st century technologies, including imaging, biochemistry and genetics, human lesion studies can provide powerful tools to elucidate psychiatric illnesses.

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