REVIEW ARTICLE

FRONTIERS IN MEDICINE

# Mapping Symptoms to Brain Networks with the Human Connectome

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THE STUDY OF FOCAL BRAIN LESIONS HAS TRADITIONALLY BEEN USED TO map neurologic symptoms to specific regions; however, many neurologic and psychiatric symptoms correspond more closely to networks of connected regions. A new resource termed the human connectome, derived from functional neuroimaging of thousands of healthy persons, provides a map of these brain connections. With the use of the connectome, lesions in different locations that cause the same symptom can be linked to common networks in ways not previously possible. This approach, termed lesion network mapping, is being applied to lesions associated with a variety of neuropsychiatric symptoms, including hallucinations, delusions, abnormal movements, pain, coma, and cognitive or social dysfunction (see the interactive graphic, available with the full text of this article at NEJM.org). Connectome localizations may expose new treatment targets for patients with complex neurologic and psychiatric symptoms. To appreciate this new approach to symptom localization, it is helpful to understand the evolution of classic lesion localization, functional imaging, the human brain connectome, and the analytic method of lesion network mapping.

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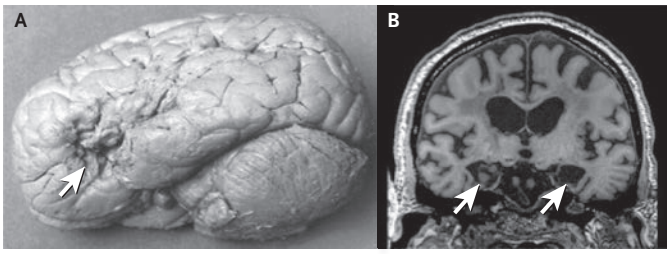
N Engl J Med 2018;379:2237-45.
DOI: 10.1056/NEJMra1706158


## LESION ANALYSIS

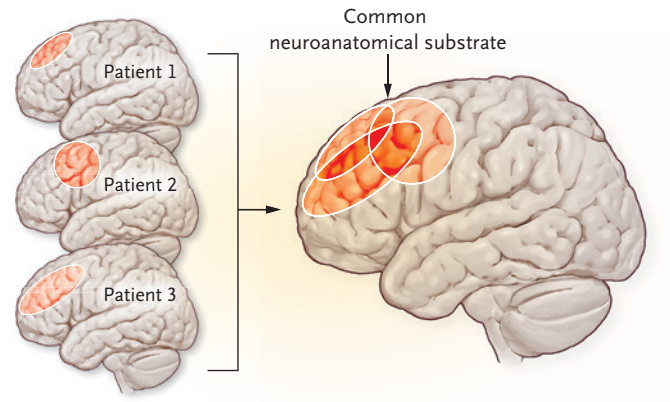
Single-lesion analysis has been the foundation of clinical neurology and the basis for localization of most neurologic symptoms and behaviors.[1-5] The traditional neurologic approach to localization of brain function has been by the identification of focal areas of damage — for example, from stroke — that correspond to a symptom or sign, such as paralysis. Complex behaviors traditionally associated with frontal-lobe damage, such as apathy, aggression, or social disinhibition, have also been studied in this manner. This type of analysis allows for causal inferences between neuroanatomical structures and human behaviors.[1-4]

*An illustrated glossary and an interactive graphic are available at NEJM.org*

The earliest lesion studies that were based on autopsy material were more correlative than they were causal, because the symptom and the observed lesion were separated by many years. With the advent of computed tomography (CT) and magnetic resonance imaging (MRI), causal relationships could be inferred as a result of the temporal correspondence between a new symptom and a new lesion detected with imaging.[1-4] Exemplary and historically significant neurologic cases with focal brain damage include those of Louis Victor Leborgne ("Tan"), whose left frontal lesion established this region as essential to speech production (Fig. 1A)[6]; Henry Molaison ("H.M."), whose medial temporal lesions gave insight into the essential role of this region in memory (Fig. 1B)[7]; and Phineas Gage, whose frontal-lobe damage provided information on frontal brain regions and social behavior.[8] When lesions that caused the same symptom in many different




C Overlap in Lesion Location across Patients with the Same Symptom




D Different Lesion Locations across Patients with the Same Symptom

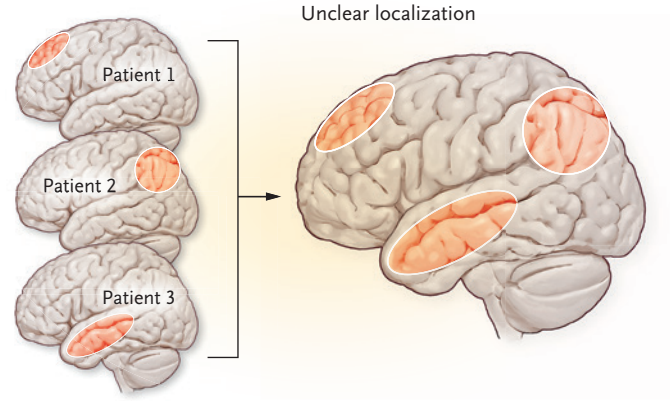



**Figure 1. Symptom Localization from Focal Brain Lesions.**

Shown are index cases in which focal brain lesions (arrows) caused impairment in language (in Patient Tan)[6] (Panel A) or memory (in Patient H.M.)[7] (Panel B). Overlap in lesion location across patients with the same symptom (Patient 1 through Patient 3) can identify a common neuroanatomical substrate (arrow) (Panel C). In practice, lesions that cause the same symptom often occur in different locations, so localization remains unclear (Panel D).

patients overlapped in one brain region, the causal link between that region and the resulting symptom was strengthened (Fig. 1C). Methodologic and statistical improvements, including comparison with lesion locations that did not cause a particular symptom, enhanced the usefulness of lesion analysis.[3,9-11]

Over time, it became apparent that lesion-based localization is sometimes flawed because similar symptoms can result from lesions in different brain locations (Fig. 1D). For example, most lesions that disrupt language are located outside the left frontal cortex,[6,10] most lesions that disrupt memory are located outside the hippocampus,[12] and lesions that disrupt social behavior are frequently outside the frontal cortex.[13] Even when the locations of lesions overlap between patients with the same symptom, the site of overlap may not conform to conventional ideas about the function of that part of the brain. For example, brain-stem lesions that cause visual hallucinations overlap in the midbrain and medial thalamus, but these locations have no clear role in vision or visual imagery.[14] The relationship between symptoms and lesion location is therefore not straightforward.

Lesion-based localization is also limited by the fact that many complex symptoms occur in patients without overt brain lesions. Common neurobehavioral and psychiatric conditions, such as delirium, amnesia, autism, and schizophrenia, occur in patients with no obvious brain lesions. Animal models only imprecisely replicate these disorders, which leaves discrete localization of most neuropsychiatric symptoms and disorders uncertain.

## FUNCTIONAL NEUROIMAGING

Functional neuroimaging can detect regional changes in brain metabolism, blood flow, blood oxygenation, water diffusion, and electrical activity.[15,16] Because these physiological changes can be identified in regions that appear anatomically intact, neuroimaging can localize symptoms in patients who have no structural brain lesions. Functional neuroimaging has been particularly useful in the analysis of psychiatric symptoms, such as auditory hallucinations, anxiety, and depression, in which changes in the activity of certain regions may direct attention to potential treatment targets for these symptoms.[15,17,18]

Functional neuroimaging can also show networks of interacting brain regions with the use of tools that measure brain connectivity.[16-22] Two

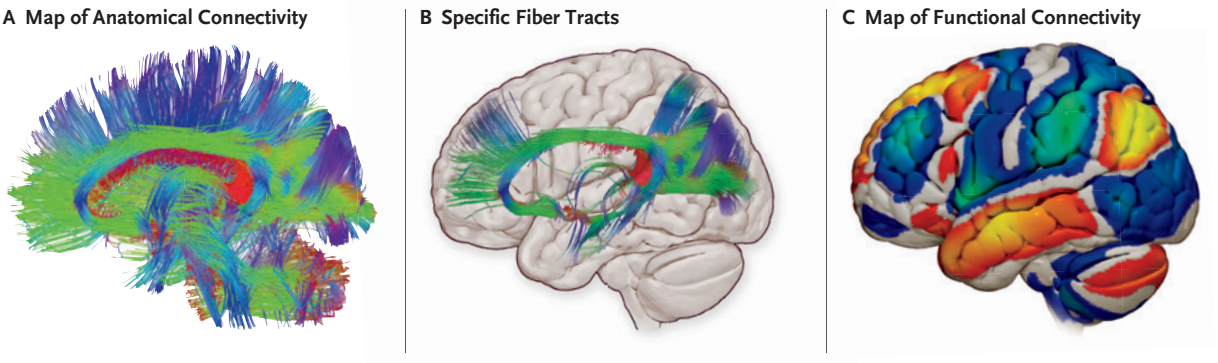



**Figure 2. The Human Brain Connectome.**

Current human brain maps of anatomical connectivity (Panel A) can be used to isolate specific fiber tracts, such as those passing through the posterior cingulate (Panel B). Maps of functional connectivity can be used to identify brain regions with spontaneous activity that is positively correlated (yellow or red) or negatively correlated (blue or green) with any other region, such as the posterior cingulate (Panel C).

types of connectivity have been explored. Anatomical connectivity is derived from MRI sequences that are sensitive to water diffusion (Fig. 2A).[22] Because water moves more freely along white-matter fiber bundles than across them, it is possible to reconstruct white-matter pathways and identify fibers that pass between regions (Fig. 2B). These reconstructed fiber diagrams correspond reasonably well to postmortem human studies and anatomical tracing studies in nonhuman primates.[5,22] Functional connectivity is derived from MRI sequences that are sensitive to spontaneous fluctuations in blood oxygenation, an indirect marker of neuronal activity (Fig. 2C).[16] These spontaneous fluctuations occur in all brain regions. When the spontaneous activity in two regions is positively or negatively correlated, the regions are said to be functionally connected.

Regions that are anatomically connected tend to also be functionally connected; however, functional connectivity provides a different map than anatomical connectivity because it reflects the influence of more extensive polysynaptic connections and linked functional relationships between brain regions.[16,20] With both types of brain-connectivity techniques, complex symptoms that transcend localization to single brain regions can be mapped to larger distributed brain networks.[15,20,23]

Functional neuroimaging has limitations[15,23] Patients often move while the image is being acquired, which compromises the quality of imaging data. Patients with severe symptoms may be agitated or confused, which can make image acquisition difficult. Furthermore, findings from different neuroimaging methods are often inconsistent. The same symptom may be correlated with atrophy in one region, reduced metabolism in another, and connectivity between unanticipated additional regions, depending on the imaging technique. Imaging findings can also change over time in relation to treatment, disease duration, and disease severity.

Functional neuroimaging can identify correlates of symptoms but not necessarily causes of symptoms.[2] For example, a neuroimaging correlate may be the result of compensation for a symptom rather than its cause, and treatment that is aimed at suppressing the activity of a region could make the symptom worse. Or if regional brain activity is correlated with but not causally related to a symptom, targeting the region may have no effect. These ambiguities make it difficult to translate functional-neuroimaging correlates directly to treatment targets.

Owing to the difficulties of interpreting functional-neuroimaging findings, some investigators have advocated a return to traditional symptom localization with the use of brain lesions because of the causal inferences they provide.[2,4] However, the limitations of lesion analysis have become apparent as experience has been gained with functional neuroimaging and visual-

ization of brain networks.[17,20,24,25] If a complex behavior requires integrated function of multiple connected brain regions, lesions in any of these regions can disrupt behavior and lead to similar symptoms. For example, complex problem solving requires coordinated function of frontal and parietal regions, and lesions in either location degrade performance.[26,27] Similarly, damage to the connection between regions can cause complex "disconnection" syndromes, while the cortical regions required for the behavior remain intact. This has long been appreciated in the syndrome of alexia without agraphia, in which damage to the connection between visual and language areas disrupts the ability to read while leaving the ability to write intact, but in which there is no damage to language areas of the cortex.[19,28]

Neurologic symptoms can also result from physiological changes in anatomically intact brain regions that are distant from but connected to the lesion, a phenomenon termed diaschisis.[24,25] For example, lesions in the brain stem may cause visual hallucinations through remote effects on the extrastriate visual cortex.[14,24]

These indirect and remote physiological effects have been found after many types of brain lesions, particularly acute ones, and may be a common cause of lesion-induced symptoms that were previously difficult to understand.[20,24,29] Although the role of brain connectivity, disconnection, and diaschisis in the production of neurologic symptoms has been known for more than a century,[19,20,24,25,28] a frontier in neurology is the search for newer tools to incorporate these factors into symptom localization.

## THE HUMAN BRAIN CONNECTOME

Large-scale functional-neuroimaging efforts, such as the Human Connectome Project, have resulted in normative maps of anatomical and functional brain connectivity that surpass previously available models of brain structure and function.[21,22] These maps are generated with the use of special MRI scanners, cohorts of thousands of persons, and advanced processing algorithms. The result is a detailed wiring diagram of the human brain that is referred to as the human connectome (Fig. 2). Analogous to the human genome, the human connectome provides a resource on which neuropsychiatric symptoms can be mapped. Connectivity data from symptomatic patients can be compared with this normative database to identify correlates of complex symptoms.[15,20,23] This resource is also valuable in linking lesion locations that cause similar symptoms to a common network, not just to a single site, which could help make sense of previously vexing disorders.

## COMBINING LESION ANALYSIS WITH THE HUMAN CONNECTOME

The human connectome can be used to determine whether lesions that are at different sites but that cause similar symptoms are located within the same brain network (Fig. 3). This is an advance over traditional lesion analysis, because the same symptom is often caused by lesions in different locations as a result of the aforementioned connectivity, disconnection, and diaschisis.[19,20,24,25,28] The combination of lesion location and its locus in a connected network is also an advance over functional neuroimaging, because this approach requires only a static image that localizes the lesion and that can be overlaid on the connectome, rather than requiring specialized scanning in a particular patient.

An example that shows the concept of the connectome in lesion analysis is the seemingly mundane problem of paralysis. Destructive lesions in the brain stem, midbrain, pons, or cerebral cortex can all cause paralysis of the limbs on the opposite side. These lesions fail to overlap in a single brain region, but all intersect the corticospinal tract, an anatomical connection that can be visualized with the connectome. The degree to which a lesion intersects the corticospinal tract correlates with motor impairment.[30] Similar localization to white-matter tracts rather than to specific regions of the cortex has been shown for spatial neglect,[31] aphasia,[32,33] and the Gerstmann syndrome (agraphia, dyscalculia, right–left confusion, and finger agnosia).[34] Lesions that cause the greatest number of symptoms occur at the intersection of large white-matter pathways[10] and at hubs that are functionally connected to large numbers of other brain regions.[35]

However, these examples require some a priori knowledge of which anatomical or functional

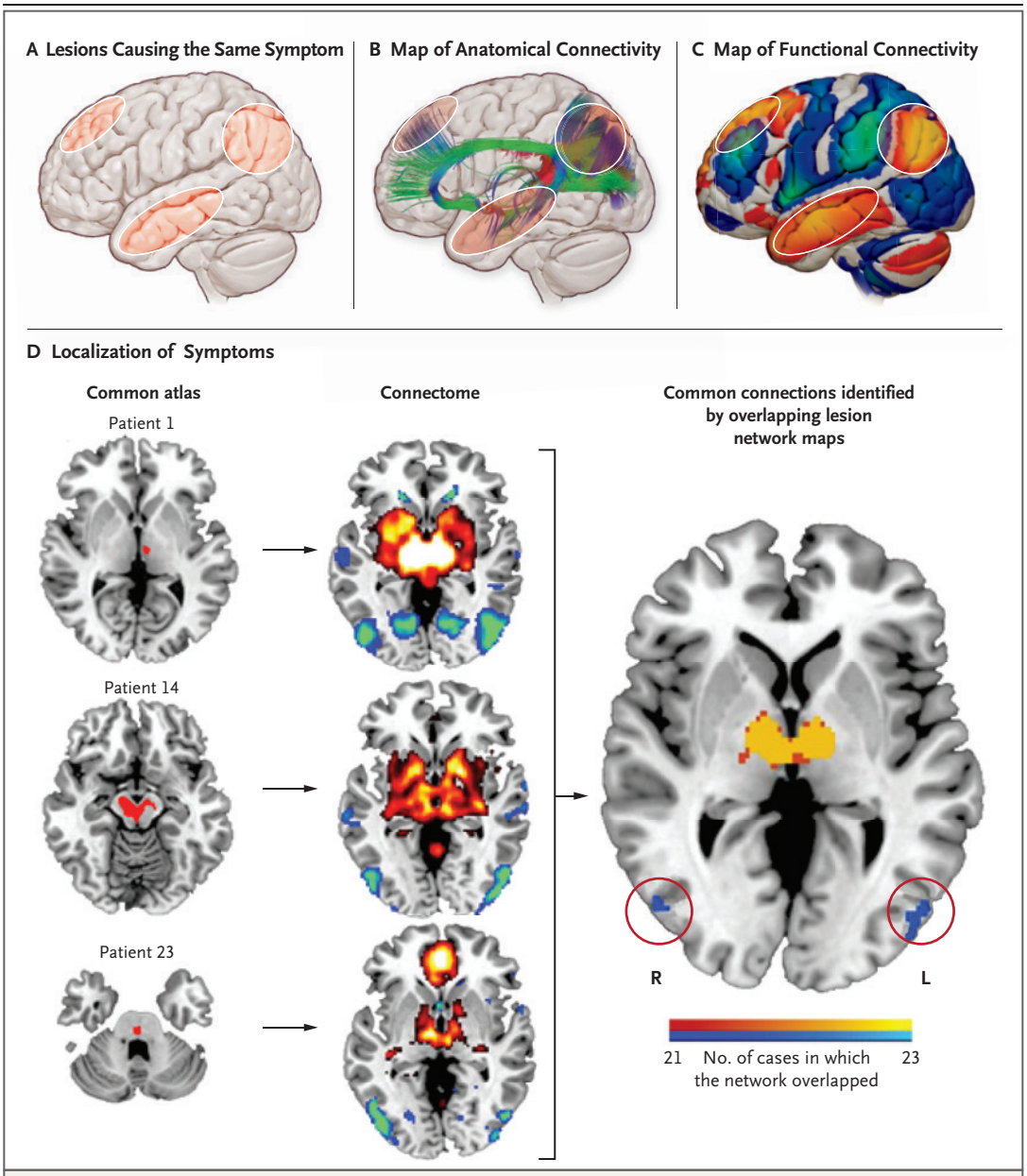



**Figure 3. Using the Human Brain Connectome to Localize Symptoms from Focal Brain Lesions.**

Lesions that cause the same symptom but occur in different brain locations (Panel A) can be overlaid on a map of anatomical connectivity (Panel B) or functional connectivity (Panel C) to determine whether they are part of the same connected brain network. With lesion network mapping, lesion locations from different patients that cause the same symptom are traced on a common atlas (Panel D, left column). Functional connectivity between each lesion location and the rest of the brain is computed with the use of the connectome (Panel D, middle column). Lesion network maps can then be overlapped to identify common connections (Panel D, right column). In this example, lesion locations that cause visual hallucinations are functionally connected to a part of the brain involved in visual imagery (red circles). Panel D is modified with permission from Boes et al.[14]

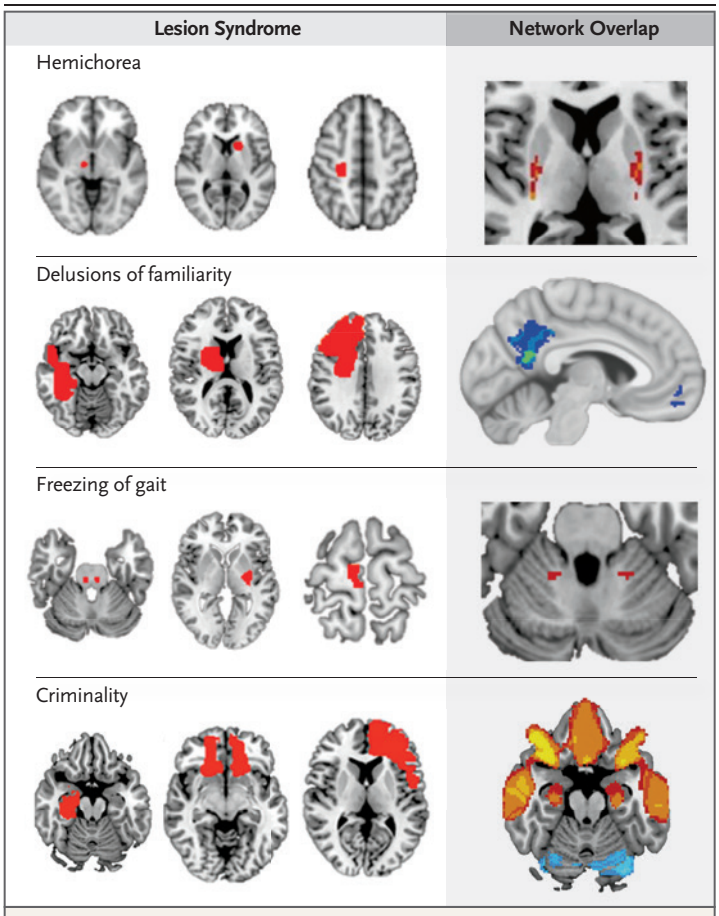



**Figure 4. Lesion Network Mapping of Neuropsychiatric Symptoms with Unknown Localization.**

Many symptoms are caused by lesions in different locations (three examples for each symptom are shown in red). However, more than 90% of lesion locations that cause the same symptom are functionally connected to the same brain regions (right column). Lesion locations that cause hemichorea are connected to the posterolateral putamen, a region implicated in motor control. Lesion locations that cause delusions of familiarity are connected to the retrosplenial cortex, a region activated by familiar stimuli. Lesion locations that cause freezing of gait are connected to the dorsal medial cerebellum, a region activated by locomotion tasks. Lesion locations that are associated with criminality are connected to the orbitofrontal cortex, a region activated by moral decision making.

connections are important for which symptom. For most neuropsychiatric symptoms, this information is unknown. Instead, a form of reverse analysis, referred to as lesion network mapping, can be conducted.[14] This approach begins with the determination of the locations of lesions by means of routine clinical imaging (MRI or CT) in the patient with a symptom under study; the results are then traced onto a standard brain atlas (Fig. 3D). Connectome data that are coregistered to the atlas are then used to identify a network that is connected to each lesion location (Fig. 3E). Although anatomical connectomes can be used for this purpose,[5,11] most studies have used functional connectomes in order to incorporate the widest possible network that is connected polysynaptically rather than in a simpler point-to-point manner.[13,14,36-43]

Network maps that are derived from lesions in different patients with the same or similar symptoms are then overlapped or compared statistically to identify connections common to these symptoms (Fig. 3F). In the case of visual hallucinations, for example, lesion locations are functionally connected (and negatively correlated) with the extrastriate visual cortex,[14] a region involved in visual imagery.

Lesion network mapping has been applied to a variety of other neuropsychiatric symptoms, many of which have eluded localization with traditional lesion analysis (Fig. 4). These include auditory hallucinations,[14] aphasia,[14] pain,[14] hemichorea,[37] parkinsonism,[42] impaired decision making,[36] delusions of familiarity,[38] freezing of gait,[39] criminality,[13] coma,[40] and disorders of volition and agency.[41,43] In each case, lesions in different locations that cause the same symptom are part of a single brain network, defined by their functional connectivity. These results of lesion network mapping are reproducible across independent groups of patients with lesions that cause the same symptom[13,37,38,44] and are specific when compared with lesions that cause different symptoms.[13,14,37-40]

For some symptoms, lesion locations show connections to more than one region or network that may need to be affected simultaneously to produce the symptom. For example, lesions that cause delusions of familiarity (e.g., the Capgras syndrome) are connected to both the retrosplenial cortex, which is implicated in familiarity detection, and the right ventral frontal cortex, which is implicated in belief evaluation.[38] This dual pattern of connectivity may help explain how a single lesion can disrupt two functions and result in complex and unusual symptoms.[38] Lesion locations that are associated with criminality have also been tentatively connected to two distinct brain networks.[13]

## LIMITATIONS OF LESION NETWORK MAPPING

When lesions that cause a symptom in different persons overlap in a single brain region, we infer that the region plays a causal role in symptom formation.[2,4] When lesions overlap in a single brain network, we can infer the same about the network. However, this causal inference does not necessarily extend to the region at the center of the network, which, despite its critical role in defining the network, may or may not be critical for producing the symptom. For example, subcortical lesions that cause visual hallucinations fall within a single network, defined by functional connectivity to an essential component of the network, the extrastriate visual cortex (Fig. 3).[14] Functional connectivity with the extrastriate visual cortex thus defines the network of regions that, when damaged by a lesion, can cause visual hallucinations. However, the extrastriate visual cortex is associated with lesion-induced visual hallucinations only on the basis of patterns of brain connectivity. Whether regional associations that are derived from lesion network mapping are stronger, weaker, or complementary to associations from functional neuroimaging remains to be determined.

The relevance of lesion network mapping for patients with symptoms who have no associated destructive brain lesions also remains uncertain, but there have been provocative findings.[37,43] For example, lesion locations that cause hallucinations are connected to regions that are hyperactive in patients with schizophrenia, in which there are no consistent brain lesions, who have hallucinations.[14,15] However, the clinical features of hallucinations differ between patients with schizophrenia and those with focal brain lesions, and patients with schizophrenia have functional-neuroimaging abnormalities that extend well beyond the implicated networks.[15] Whether lesion network mapping can identify brain regions that are associated with specific symptoms independent of the cause of the symptom is an area of investigation.[14,37,39]

Finally, lesion network mapping focuses on the spatial component of lesion-induced symptoms, but the temporal component may be equally important. Lesion-induced symptoms change over time as the brain responds to injury, which results in a dynamic process of compensation and recovery.[20]

## CLINICAL APPLICATIONS OF LESION NETWORK MAPPING

Lesion network mapping is anticipated to identify new symptom-based treatment targets. As a measure of face validity of network mapping to identify treatment targets, some of these targets align with those previously derived through other methods that have led to effective treatment. For example, the extrastriate visual cortex has been targeted with transcranial magnetic stimulation (TMS), a tool to noninvasively alter brain activity, to reduce visual hallucinations[45]; the supplementary motor area, part of the lesion network associated with hemichorea, has been targeted with TMS for relief of chorea in Huntington's disease[46]; and the leg area of motor cortex, part of the gait network, has been targeted with TMS for relief of freezing of gait in Parkinson's disease.[47] Whether new therapeutic targets for symptoms such as delusions or criminality will prove useful are testable hypotheses. It also remains unknown whether these targets will be more useful for patients with brain lesions or, as in the above-mentioned TMS trials, for patients with similar symptoms but without overt structural brain damage.

Therapeutic targets may also be identified through network mapping of lesion locations that alleviate or prevent symptoms. For example, network mapping of spontaneous lesions that relieved tremor identified a therapeutic target in the thalamus that has been effective for tremor relief.[48] Brain stimulation sites can also be incorporated into this type of analysis in order to identify connections that are common to stimulation sites that provide therapeutic benefit. This approach has identified previously unappreciated connections that predict response to deep-brain stimulation in Parkinson's disease,[49] predict response to TMS in depression,[50] and link stimulation sites in different locations that are effective for the same symptom.[51]

## FUTURE DIRECTIONS

Connectome atlases based on hundreds of thousands of persons,[52] higher-resolution imaging

A video interview with Dr. Fox is available at NEJM.org

methods,[53] and propagation of electrical stimulation along neural networks are all being developed. The integration of results from different connectomes, including connectomes based on data acquired during the performance of various tasks, may prove more informative than analyses based on a single connectome. Connectome data sets could be sex-matched and age-matched to each patient to create more accurate analyses of complex behaviors on an individual basis. As maps of the human brain connectome improve, so should their value as a resource for mapping complex neurologic and neuropsychiatric symptoms.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Aaron Boes, Ryan Darby, and Alvaro Pascual-Leone for helpful comments on an earlier version of the manuscript.

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