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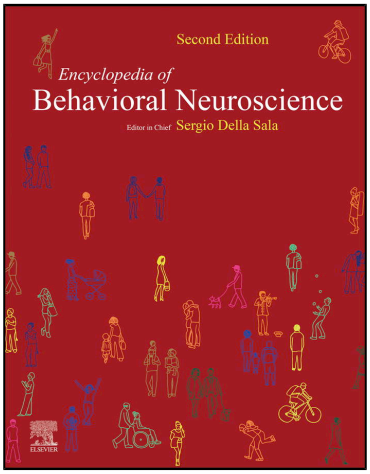

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From Forkel, S.J., 2021. Lesion-Symptom Mapping: From Single Cases to the Human Disconnectome. In: Della Sala, S. (Ed.), Encyclopedia of Behavioral Neuroscience, vol. 1. Elsevier, pp. 142–154. https://dx.doi.org/10.1016/B978-0-12-819641-0.00056-6.
ISBN: 9780128196410
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Lesion-Symptom Mapping: From Single Cases to the Human Disconnectome

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Glossary

Disconnectome Clinical-neuroanatomical correlation methods based on the study of the disruption of the white matter connectome by lesions.

Metabolic disconnection Brain regions are structurally connected to work together through co-activation, inhibition or disinhibition. These processes can be interrupted functionally without an evident lesion on conventional structural imaging, which is considered as metabolic disconnection.

Pseudonormalization A dynamic signal change seen in the subacute stage of the ischemic stroke where the diffusion signal appears in the range of healthy tissue masking an underlying lesion.

Structural negative MRI scan Magnetic resonance imaging (MRI) structural scans do not reveal a lesion despite clinical symptoms of patients suggesting the presence of a brain lesion.

Voxel-based lesion-symptom mapping Clinical-neuroanatomical differential methods that associate lesioned voxels and psychometric assessments.

The famous cases of neuroscience, including Henry Gustave Molaison (patient 'H.M'), Phineas Gage, and Louis Victor Leborgne (patient 'Tan'), have critically shaped initial theories about the functioning of the brain and remain highly influential today to the field of human brain mapping. Understanding the functions of the brain and how they came to be associated with specific brain areas and networks has been a vivid field of study since. This association was primarily based on the observation of single patients that allowed principle functions such as perception (Ungerleider and Mishkin, 1982), emotion (Adolphs et al., 2005), memory (Corkin, 2013), attention (Posner et al., 1982), and verbal communication (Lichtheim, 1885) to be identified, localized and subsequently fractionated into more specific cognitive subprocesses. The clinical-anatomical association method based on lesion-symptom mapping is one of the oldest means to study the brain's structure-function relationship. The earliest reports of the use of lesion mapping methods were based on patients presenting with behavioral peculiarities or a loss of function following a lesion to the brain (e.g., traumatic brain injury, stroke). Behavioral changes were associated with structural damage to a surface area of the brain or a specific brain region (e.g., Broca, 1861; Wernicke, 1874; Sperry 1961; Luria 1966). For centuries, such single cases were carefully described, and together they form the origins of modern neurosciences and neurology (Finger, 1994; Damasio and Damasio, 1989). While these studies greatly enhanced our understanding of the anatomical-functional division of the brain surface (Glasser et al., 2016; Yarkoni et al., 2011), they did not comprehensively map the entire brain and its functions. This is in part due to methodological limitations (e.g., availability of neuroimaging, limited case numbers), conceptual limitations (e.g., localizationism) and the fact that natural lesions (e.g., strokes, tumors) are not homogeneously distributed across the brain (Mah et al., 2014). These limitations are further aggravated by a significant degree of inter-individual variability in the architecture of the brain and location of function (e.g., Uylings et al., 2005; Caulo et al., 2007; Leonard et al., 1998; Eichert et al., 2021; Basso et al., 1985, Vigneau et al., 2006, Forkel et al., 2020b). With the advent of neuroimaging techniques, it became feasible to systematically study

Encyclopedia of Behavioral Neuroscience, Second Edition, 2021, 142–154

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lesions and their behavioral impacts in a large number of patients. Applying neuroimaging methods to lesion studies revealed novel insights. These insights ranged from mapping lesion characteristics, over more segregated functional differentiation to elucidating the relationship between brain disconnections and dysfunctions (Thiebaut de Schotten et al., 2020).

With a conceptual shift in the field toward brain networks rather than areas and increasing sophistication of imaging contrasts, recent lesion methods utilize multiple imaging contrasts (e.g., structural, perfusion, diffusion) and complex statistical approaches (e.g., machine learning). The study of the famous cases has closely mirrored this trajectory in cases where the data was still available. While early imaging studies mapped the cortical extent of their lesions (Signoret et al., 1984; Harlow, 1848, 1868), recent studies have demonstrated the subcortical damage associated with these lesions (Dronkers et al., 2007; Corkin et al., 1997; Ratiu et al., 2004) and mapped the disconnection of the underlying white matter network (Van Horn et al., 2012; Thiebaut de Schotten et al., 2015). While this re-evaluation using novel imaging techniques partially confirms previously reported findings on these datasets, they highlight the extent of damage beyond the lesion that has been underrepresented in our quest to map the structure and function of the brain using clinical data. This article will provide an overview of univariate and multivariate lesion-symptom approaches from a conceptual and practical perspective and highlight some exciting new avenues to explore lesion-symptom studies.

Univariate Lesion-Symptom Analysis

Lesion Identification and Delineation

Patients with brain lesions offer a unique window of opportunity to understand the functioning of the brain. With the availability of neuroimaging methods, this window was greatly expanded to repeatedly study the living human brain and large numbers of patients. Computer tomography (CT) and structural magnetic resonance imaging (MRI) are commonly used for lesion delineation and provide an estimate of lesion location, size, and extent to both cortical and subcortical regions. Identifying lesions and delineating them on either of these modalities poses challenges depending on the cause of the lesion (e.g., head trauma, tumor, stroke), the lesion complexity (e.g., penumbra), the delay between imaging and insult (e.g., acute vs. chronic lesions, pseudonormalization), imaging parameters (e.g., data quality, imaging sequences), and means of delineation (e.g., manual vs. automatic). While some of these challenges can be mitigated, others are less easily controlled for.

The most widely used imaging modality in stroke patients, for example, is CT owing to its ability to quickly determine the presence of a hemorrhagic lesion and inform individualized treatment pathways. While its fast availability and low risk make CT a very feasible technique in the clinical routine (e.g., Mazzocchi and Vignolo, 1979; Naeser and Hayward, 1978), its low spatial resolution and reduced sensitivity to early ischemic changes have progressively favored the use of MRI for research studies (Wall et al., 1982). For most MRI contrasts the time of acquisition is important as the images can be subject to pseudonormalization. Pseudonormalization is a process that may temporarily hide the lesion before the signal attenuates again to pathological levels (Warach et al., 1995). While pseudonormalization is not relevant in chronic stages of lesions, it might pose a challange for acute imaging studies when patients are scanned at variable time points, which could result in a different estimation of the lesion volume. The differential appearance of lesioned tissue on different imaging contrasts can, however, be used as an advantage to delineate lesions when co-registering the images and use them as a cross-reference to guide delineation. Different lesions may benefit from different sequences due to their individual pathologies and mechanisms, causing cortical damage and disconnections to local and remote networks (**Fig. 1**).

The clinical usability of imaging contrasts varies in their sensitivity to lesion onset, their resolution, and how long it takes to acquire the image. Using stroke as an example, the highest sensitivity and specificity to an acute occlusion of a vessel is provided by a diffusion-weighted scan where the lesion can become visible within seconds to minutes of its occurrence. Diffusion images, however, suffer from low anatomical resolution (classically around 2–2.5 mm) compared to a T1-weighted scan (classically 0.8–1 mm) and pseudonormalization effects occur within the first days. In a clinical setting, a T2-weighted scan may be favored owing to its pathological sensitivity and fast acquisition time (~2 min). Ideally, the perfect contrast would have the sensitivity of diffusion-weighted scans with the resolution of a T1-weighted scan and the fast acquisition of a T2-weighted scan. In a research setting, it is possible – albeit tedious for the patients – to obtain all of these sequences to satisfy all needs equally. However, despite many groups collecting multiple data types, they are often investigated in isolation rather than within a multidimensional framework. While some exciting efforts are underway to improve our acquisitions and contrasts (e.g., Wiesinger et al., 2016; Ljungberg et al., 2020; Chen et al., 2019), it will likely be several years before these advances will be implemented in a clinical routine.

In both the research and clinical setting, the best practice for lesion mapping is manual lesion delineation - especially when working with acute clinical data. Lesion delineation tends to be time-consuming based on a myriad of variables. Manual delineation is time intensive as it depends on the anatomical expertize of the tracer especially when comorbidities and previous lesions are present. Automatic methods, on the other hand, are also time-consuming due to their high computational demands and the need to correct the delineations manually afterwards. Several methods are available to automatize or semi-automatize lesion delineation using a range of sequences (Pustina et al., 2016; Ito et al., 2019; de Haan et al., 2015; Seghier et al., 2008; Mah et al., 2014; Jha et al., 2020).

Group-Level Lesion Studies and Voxel-Based Lesion-Symptom Mapping (VLSM)

For any group-level lesion analysis, a prerequisite is to have all individual data in the same standard space. To compare the lesions drawn in the patients' native space, they have to be processed before further analysis can commence. The lesion

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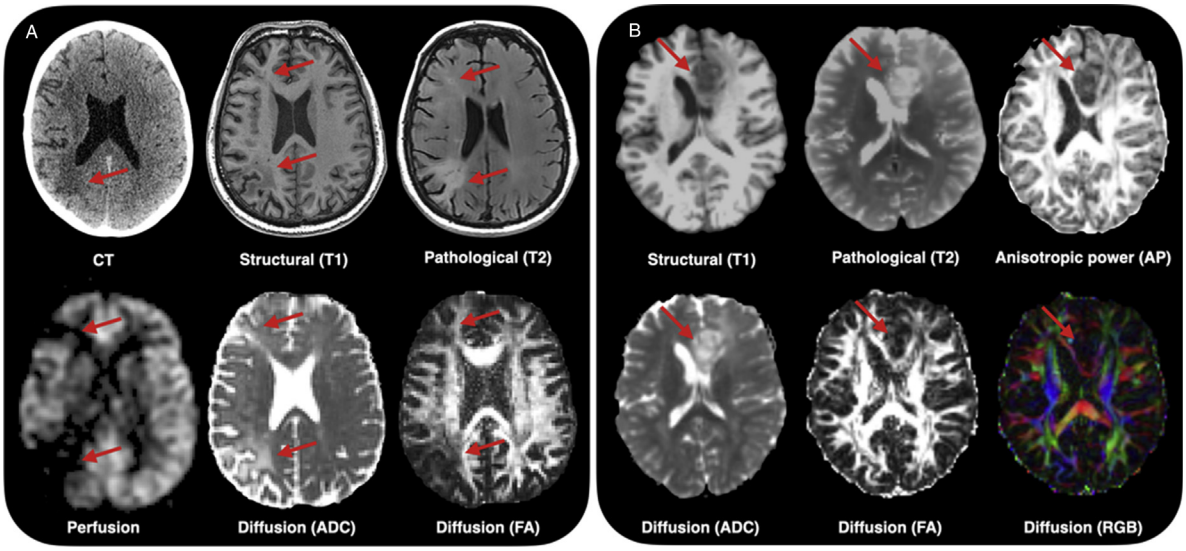

Fig. 1 Lesion appearance on multi-modal clinical imaging contrasts exemplified for one acute stroke (A) and one tumor patient (B). Panel A shows an example of neuroimaging scans to investigate an ischemic stroke lesion on computer tomography (CT) scan vs. MRI-based structural (T1-weighted and FLAIR T2-weighted), perfusion and diffusion sequences. Panel B shows the structural (T1-weighted and T2-weighted) and diffusion sequences for a tumor patient. In both these clinical cases of different pathological origin, the lesion extent, location and characteristics appear differently due to the sensitivity of the imaging. *Arrows* indicate lesions.

delineation (manual or automatic) will provide a three-dimensional reconstruction of the lesion in the native space, which is binarized, so every voxel is assigned either 0 or 1 to indicate healthy and lesioned tissue. In order to compare lesions between patients, the binarized lesion reconstructions are normalized to a common standard space (e.g., Rorden and Brett, 2001; Avants et al., 2011; Klein et al., 2009). Several approaches have been proposed to optimize this step as spatial normalization tools can be affected by the presence of a lesion (or any signal abnormality for that matter; Ripollés et al., 2012). The cost function approach weights the normalization toward brain tissues (e.g., gray matter, white matter and corticospinal fluid) rather than non-brain tissue (i.e., lesions; Brett et al., 2001). This method should be used with bilateral lesions or if the aim is to normalize without skull information. Another method, known as enantiomorphic normalization, uses the reconstructed lesion mask and replaces this area with the healthy tissue of the symmetrically contralateral hemisphere (Nachev et al., 2008). Normalization pipelines can also benefit from using a dedicated brain extraction tool optimized for pathological brains (Lutkenhoff et al., 2014).

These binarized and normalized lesion reconstructions can then be used as input files to associate the lesioned area with a loss of function. Three methods are commonly used to form this relationship: lesion overlay, lesion subtraction, and voxel-based lesion-symptom mapping. Lesion overlay is used for single group studies where a patient group is defined based on homogeneous neuropsychological and clinical deficits (e.g., aphasia) and their lesions are overlapped to identify the brain region most commonly damaged in this group (e.g., Arévalo et al., 2012; Dragoy et al., 2017; Ivanova et al., 2016; Baldo et al., 2012a; Hope et al., 2018; Puglisi et al., 2019, **Fig. 2**A). When a control group is available, meaning a group of patients with lesions but without a given deficit of interest, a common approach is a subtraction study. In these circumstances, a lesion overlay map for each group is calculated and subtracted from each other to identify the selective voxels associated with deficits in one group but not the other (**Fig. 2**B; e.g., Dronkers et al., 1996; Thiebaut de Schotten et al., 2014; Besharati et al., 2014).

While both these approaches are powerful and informative to relate dichotomized clinical symptoms (i.e., deficits present or not) to critical areas of the brain and lesions thereof, lesions are not confined to functionally neat areas and usually cause an array of symptoms. To capture this complexity better, a more formal statistical analysis has been proposed. Multiple algorithms are currently available to perform statistical lesion-deficit analysis, including voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003), non-parametric mapping (NPM; Rorden, Karnath and Bonilha, 2007a), and Anatomo-Clinical Overlapping Maps (AnaCOM; Kinkingnehun et al., 2007). All these software packages differ concerning their required input data (e.g., binary vs. continuous scores), statistical analysis (i.e., parametric vs. non-parametric), underlying assumptions on voxel independence (e.g., single voxel analysis vs. clusters of voxels), and their need for specific study designs (e.g., number and demographics of groups). Despite these differences, all lesion-deficit approaches need to fulfill prerequisites, including accurate and precise anatomical delineation of the lesions, utilizing assessments with diagnostic sensitivity to the cognitive processes of interest (e.g., continuous or categorical data), and reliable statistical methods to associate lesion characteristics with cognitive and behavioral deficits (Medina et al., 2010).

The advent of voxel-based lesion-symptom mapping (VLSM) nearly two decades ago (Bates et al., 2003, **Fig. 2**C) revolutionized the field by bringing mass-univariate statistical analysis to lesion-symptom mapping and ignited a new era of clinical-anatomical

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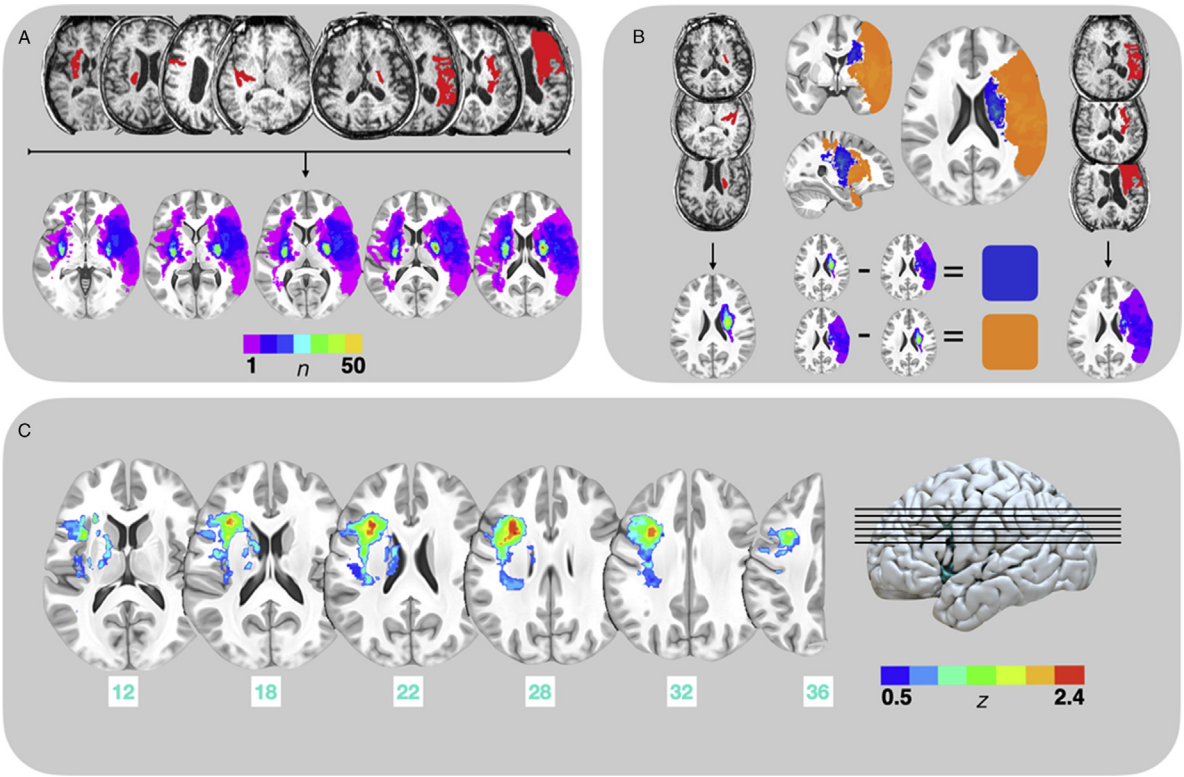

Fig. 2 Univariate lesion mapping. Schematic diagram of lesion overlay (A), two group lesion subtraction analysis (B), and voxel-based lesion-symptom mapping (C). For overlay heat maps, all lesions in the same space are combined to show the areas most commonly lesioned in one group. Subtraction analysis uses the overlay from two different groups – one with and one without a symptom – and calculates the difference between them. Voxel-based lesion-symptom mapping calculates a statistical association between lesioned voxels and neuropsychological test scores (phonemic fluency used here). Open data courtesy of ATLAS, Liew et al. (2018).

correlation studies. As a result, VLSM has become the standard method for large-scale lesion-symptom mapping studies. To run a VLSM analysis, binarized lesion reconstructions are provided to a software (e.g., NPM, VLSM, ANACOM) alongside the corresponding behavioral scores. Both the imaging data and the behavioral data should have been obtained at a similar point in time to minimize confounding variables with the exception of predicting recovery when the acute imaging can be used to predict chronic behavior and long-term recovery. The behavioral data is usually organized so that the higher the score the better the behavior, i.e., less impairment, and the cohort has to be of sufficient size (Shahid et al., 2017; Forkel and Catani, 2018a,b; Lorca-Puls et al., 2018). To ensure adequate coverage to draw meaningful statistical inferences, data is conventionally thresholded to only include voxels affected by a minimum of 10% of patients (Kimberg et al., 2007). VLSM runs a differential statistical analysis (classically a *t*-test or Brunner-Menzel test) on each voxel within the lesion mask to determine its contribution to an observed deficit (Baldo et al., 2012b). Given the multitude of tests run across voxels, these results are usually corrected for multiple comparisons (Mirman et al., 2018). VLSM has been the method of choice and has found broad application in clinical populations which provided unique insights to clinical-anatomical correlations (for review see Baldo et al., 2020). The most significant advantage of using lesion-symptom methods lies in the fact that they identify critical areas for a given function and by doing so complement findings obtained from functional imaging in healthy controls. As such, lesion-symptom methods offer a unique possibility to study the impact of lesions on the brain.

Using Atlases to Map Lesion Impact

To link the lesions to anatomical labels and further expand the information obtained from lesion-symptom methods, they can be combined with atlases obtained from a group of healthy controls to estimate the degree of damage to a given brain region or white matter pathway (**Fig. 3**). Nowadays, there is a plethora of atlases available that can be used for this purpose. Cortical probabilistic atlases take into account some degree of interindividual variability and are available for surface anatomical features such as gyri and sulci (e.g., Hammers et al., 2003; Shattuck et al., 2008; Caspers et al., 2013), histological features (Zilles et al., 1997), functional connectivity patterns (e.g., Joliot et al., 2015; Salehi et al., 2020), or surface-based multimodal MRI acquisitions (Glasser et al., 2016). While each atlas has its own advantages and limitations the choice of the atlas depends on the available data and research

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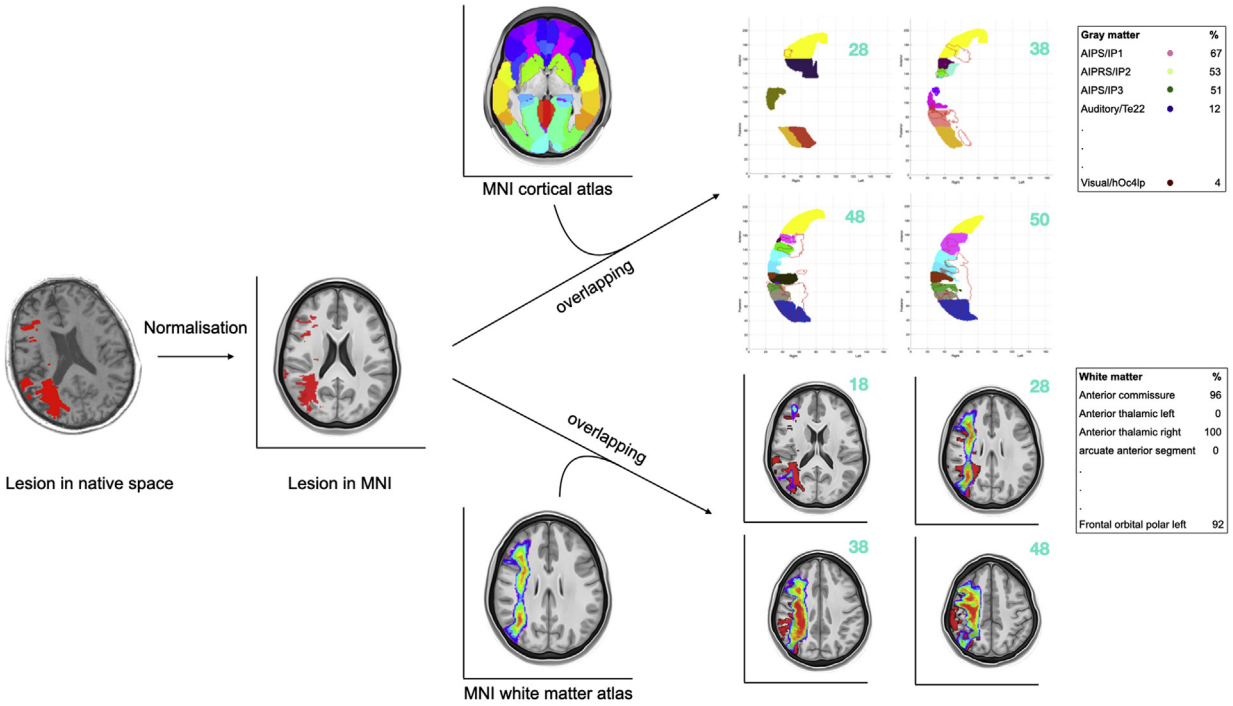

Fig. 3 Schematic diagram showing a lesion analysis pipeline from a binarized lesion reconstruction, to normalization to Montreal Neurological Institute (MNI) standard space and overlapping the lesion with a gray (top panel) and white matter (lower panel) atlases. For visualization the Julich gray matter atlas and the probability (i.e., accounting for interindividual variability) spherical deconvolution white matter atlas from Rojkova et al. (2016) (http://www.bcblab.com/BCB/Atlas_of_Human_Brain_Connections.html) were used. The results are the brain maps alongside the list of areas and tracts affected by the lesion and the percentages of overlap. Courtesy of Lia Talozzi and Michel Thiebaut de Schotten.

question (Messé, 2020). The percentage of overlap between a lesion and cortical region can help to estimate if the damage encapsulates the entire region or a part of it and assess what percentage of damage may be clinically relevant (**Fig. 3**, top panel). Similar considerations should be applied to white matter atlases. Current atlases defined a range of tracts that can be reliably identified (Mori et al., 2005; Lawes et al., 2008; Catani and Thiebaut de Schotten, 2008; Mori et al., 2009; Thiebaut de Schotten et al., 2011; Rojkova et al., 2016) with some recent atlases identifying additional intralobar connections and U-shaped fibers (Catani et al., 2012, 2017; Guevara et al., 2012, 2020; Shastin et al., under review) To estimate the percentage of overlap between lesions and tracts as a proxy for severity of disconnection the lesion reconstructions can be mapped onto an atlas obtained from a group of healthy controls (Thiebaut de Schotten et al., 2014; Rojkova et al., 2016; Dell'Acqua et al., 2015; https://megatrackatlas.org/lesion; **Fig. 3**, lower panel).

These lesion mapping methods are descriptive in nature in the case of lesion overlays or are statistically comparing two groups (patients with and without the symptom of interest) to compute a test statistic to associate structure and function. There are, however, some limitations to this approach, for example, the assumption that each voxel is independent of its neighbor. When considering the brain's vasculature, lesions seem to not be randomly distributed (Mah et al., 2014). Recent approaches hence consider multiple voxels at once or lesion clusters instead of one voxel at a time to determine the relationship between structural damage and function.

Novel Approaches to Lesion-Symptom Mapping

Similar to the revolution that VLSM brought to the field of brain structure and function mapping, currently evolving methods might just ignite the next fundamental shift in our methodological approaches. This second wave was triggered by the systematic finding that lesions may not be randomly distributed across the brain but follow the underlying vasculature (Mah et al., 2014). In parallel to this discovery, the development of multivariate lesion behavior mapping (MLBM) methods dramatically changed the field. Among these novel developments are advances that apply Bayesian statistics to lesions (Sundarensen et al., 2019; Pacella et al., 2019), utilize graph theory for modeling brain connectivity (Toba et al., 2017), make use of multivariate decoding techniques (Nachev 2015; Xu et al., 2018), and combine computational modeling with lesion mapping to identify neural signatures of cognitive models (Gläscher et al., 2019). With this branch of lesion-symptom mapping still being in its infancy, there will inevitably be many more exciting technical developments and relevant clinical findings in the years to come.

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Multivariate Lesion Analysis by Support Vector Regression-Based Lesion-Symptom Mapping (SVR-LSM)

Multivariate lesion-symptom methods are considered to be superior to univariate methods as they account for non-independence between voxels and map the impact on wider brain networks (Smith et al., 2013; Zhang et al., 2014; Toba et al., 2017; Pustina et al., 2018; Garcea et al., 2019; Xu et al., 2018). Another advantage of multivariate analysis lies in the reduced number of tests to be run as voxels are considered as non-independent clusters and as such an uneven distribution of lesions is methodologically acceptable. Due to these improvements, the field is moving toward multivariate lesion-symptom mapping approaches (e.g., SVR-LSM, SCCAN; Zhang et al., 2014; DeMarco and Turkeltraub, 2018; Pustina et al., 2018). Multivariate lesion-symptom mapping using support vector regression treat each voxel as independent variable and a measured behavior as the dependent variable. For each voxel, a beta value is outputted that indicates the strength of the relationship between this voxel and a predicted behavior. Given the use of a regression model, this method allows to account for nuisance variables and apply corrections to the data (e.g., lesion volume). Permutation testing is applied to the data as a means to perform multiple corrections and to make the beta values interpretable by estimating the feature weights that could be expected with random data. Multivariate lesion analyses are hence capable of identifying complex dependencies due to accounting for multiple voxels simultaneously, and therefore can mitigate some of the limitations of univariate lesion mapping, although they cannot overcome them all (for discussion see Sperber, 2020). Future studies will have to rigorously compare the two approaches and evaluate their clinical applications as many of the arguments in favor of multivariate methods so far have been discussed on theoretical grounds without having been put to a clinical test (Sperber et al., 2019; Ivanova et al., 2020).

In sum, all lesion-symptom methods discussed so far have shed light on our understanding of brain functions and their underlying cortical anatomy. The methods applied to lesion-symptom mapping have become increasingly sophisticated and statistically complex over the past two decades. A fundamental limitation to all these methods is, however, that they are constrained to voxels within a lesion mask. Lesion symptom methods, therefore, require a precise anatomical lesion delineation and are blind to the cascade of changes occurring remotely. As such, lesion-symptom mapping results are driven primarily by areas of overlay where statistical power is higher, which is amplified in small patient samples (Bates et al., 2003; Kimberg et al., 2007; Medina et al., 2010; Rorden et al., 2007a,b; Rorden et al., 2009; Rudrauf et al., 2008). To study the impact of a lesion beyond the immediate tissue damage, other methods have been developed recently to make "hidden lesions" visible and map the disruption of local and remote white matter networks.

Lesion Mapping Beyond the Lesion Mask

Metabolic Lesion Mapping

In the presence of brain pathologies, structural MRI is traditionally used for lesion delineation and provides an estimate of the lesion location, its size, and its extent to cortical and subcortical regions. These anatomical observations can be complemented by functional MRI sequences that shed light on the deterioration of brain functional networks and their reorganization (Corbetta et al., 2005).

Despite significant achievements and advances with neuroimaging, clinicians are accustomed to seeing patients with cognitive deficits indicative of brain lesions yet with no visible evidence on the MRI scan. There might be several reasons as to why this incongruent presentation might occur. While cognitive impairments may be caused by other underlying conditions in some patients (e.g., toxins, infections *etc.*), in others our conventional imaging tools may be insufficient to detect damaged tissues. The brain might appear structurally intact, but some of its function may have been compromised when brain regions are not working effectively together anymore. Hence, the absence of a structural lesion on conventional MRI does not preclude the presence of a functional disconnection. Reliable neuroimaging methods are therefore crucial to aid diagnostics, inform treatment pathways and improve quality of life for patients. Despite the best efforts to improve our methods to study structural and functional disconnections in patients, we still lack advanced imaging tools to identify "hidden damage" (Thiebaut de Schotten and Foulon, 2018). Thus, it becomes clear that new neuroimaging strategies are required to improve diagnosis, treatment and, subsequently, patients' quality of life.

One way to visualize hidden lesions is to map perfusion and metabolic deficits in clinical cohorts (Metter, 1991; Prabhakaran et al., 2007; Crinion et al., 2013; Jha et al., 2020). The advantages of metabolic-disconnection mapping over classical lesion-symptom mapping are that perfusion and cerebral glucose metabolism can be extracted as graded deviations while lesion maps are extracted as binary masks. The metabolic gradient includes hypofunction and hyperfunction that reflect deterioration and reorganization of the brain and might improve clinical-anatomical correlations. In addition, patients with structural MRI negative scans, meaning that no lesion was visible, often exhibit metabolic lesions. The spatial distribution of metabolic lesions tends to be more uniformly distributed across the brain as compared to structural lesions. In stroke, lesions tend to adhere to the vasculature of the brain and form clusters of lesioned neighboring voxels (Mah et al. 2014). Hence, these results suggest that metabolic imaging might be helpful to map symptoms comprehensively.

These metabolic-symptom maps can be generated through voxel-wize mass-univariate inference between the metabolic lesions and neuropsychological assessments. By doing so, most functions are associated with both positive and negative metabolic activity across the brain. Contrary to classical lesion-symptom mapping, which points toward the most commonly

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damaged and critical area, metabolic approaches may reveal the underlying extended network affected by a lesion. These networks resemble results from functional imaging in healthy controls for the same cognitive domains (Forkel and Thiebaut de Schotten, 2020).

Given the broad clinical impact of this method to show "hidden lesions," this approach should be extended. Rather than relying on a radioactive tracer, it could be extended to a non-invasive sequence (e.g., diffusion-perfusion mismatch, Hillis et al., 2005). Combining metabolic lesion mapping with multimodal imaging will significantly move forward our understanding of structural-functional lesion relations. For instance, extending this line of investigation from its current focus on gray matter to benefit also from white matter tractography might allow one to partially decipher the structural mechanisms behind metabolic changes as identified (Jha et al., 2020). In addition, metabolic imaging offers continuous measure of a lesion which is a great advantage as it increases statistical power and might allow for grading of a lesion (e.g., core, penumbra, edema). Taken together, this approach feeds the quest for mapping the function of the brain, understanding its functioning and pathology while having the potential to critically improve clinical diagnosis and treatment.

White Matter Lesion Mapping—The Human Disconnectome

The lesion-symptom mapping and metabolic disconnection methods discussed so far have greatly advanced clinical-anatomical correlations of structure and function and have informed clinical diagnostics. When mapping lesions in the white matter, however, they are limited in their scope to map the damage to individual pathways or the structural disconnection between brain regions (Forkel and Catani, 2018a,b). To study the impact of lesions on individual white matter pathways and disconnections of networks, white matter tractography is calculated from the diffusion-weighted imaging MRI (DWI). Recent research has proven that tractography is a sensitive method in clinical populations to associate damage to white matter connections to functional deficits (Forkel et al., 2020b; Thiebaut de Schotten et al., 2020). In the clinical setting, tractography correlations are most commonly reported in neurological and neurosurgical cohorts (Forkel et al., 2020b), where they are often combined with classical lesion-symptom mapping methods (Forkel et al., 2014; Forkel and Catani, 2018a,b; Puglisi et al., 2019) or functional disconnection analysis (e.g., Turken and Dronkers, 2011; Griffis et al., 2019; Corradi-Dell'Acqua et al., 2020; Salvaggio et al., 2020). Combining tractography with clinical methods such as direct cortical stimulation (e.g., Kinoshita et al., 2015; Kemerdere et al., 2016; Puglisi et al., 2019), deep brain stimulation (e.g., Akram et al., 2017; Akram et al., 2018), cortico-cortical evoked potentials (e.g., Tertel et al., 2011; Silverstein et al., 2020; Nakae et al., 2020), or transcortical magnetic stimulation (e.g., Cazzoli and Chechlacz, 2017; Ille et al., 2018; Mirchandani et al., 2020; Giampiccolo et al., 2020) will positively impact on the role tractography can play for precision medicine.

In the absence of diffusion data from an individual patient, the lesion mask, as obtained from any imaging contrast, can be applied to an atlas generated from healthy tractography reconstructions. Several software platforms are available to automatically calculate the percentage of damage to a pathway or network (e.g., BCBtoolkit, Foulon et al., 2018; Dell'Acqua et al., 2015; megatrack, Stones, 2019). As with the atlases discussed earlier, these two methods differ slightly in their approach. Megatrack provides access to white matter dissections from two diffusion datasets optimized for diffusion tensor imaging (DTI) or high angular resolution diffusion imaging (HARDI). Users can query subjects based on specific demographics (i.e., age, gender, handedness) and view averaged density maps for the white matter tracts available within each atlas (Howells et al., 2020). Statistical metrics (e.g., fractional anisotropy) for the averaged tracts are also generated. By contrast, the BCBtoolkit offers two tools, tractotron and disconnection maps, to study the impact of lesions. Tractotron was mentioned previously as it provides a percentage for the lesion-tract overlay, based on an atlas of white matter pathways. Disconnectome maps, on the other hand, use the lesion from a patient as a region of interest to map the white matter connections passing through this region based on the tractography of a cohort of healthy controls. To obtain white matter disconnection maps, the tractogram (whole brain white matter connections) is reconstructed from a set of healthy controls (Rojkova et al., 2016) and the normalized lesions from patients are introduced to this dataset (Foulon et al., 2018, **Fig. 4**). Patients' lesions in the standard space are registered to the native space of each control dataset using affine and diffeomorphic deformations (Klein et al., 2009; Avants et al., 2011) and subsequently used as a region of interest for the tractography dissections in Trackvis (www.trackvis.org). Tractography reconstructions based on the lesions are then transformed into visitation maps (Thiebaut de Schotten et al., 2011), binarized and brought to standard space. Finally, a percentage overlap map is produced by summing up the normalized visitation map of each healthy participant in every voxel of the standard space. In the resulting disconnectome map, the value in each voxel, therefore, takes into account the interindividual variability of tract reconstructions in the healthy population. It indicates a probability of disconnection between 0% and 100% for any given lesion (Thiebaut de Schotten et al., 2015).

Current advances are aiming to go beyond mapping the structural disconnections caused by lesions by also using this novel method to map cognitive functions and the disruption thereof along the whole brain white matter network (Thiebaut de Schotten et al., 2020). By combining meta-analytic analysis from functional imaging data in healthy controls and white matter analysis based on the lesion disconnectome method the first functional white matter atlas has recently been proposed (Thiebaut de Schotten et al., 2020). This new atlas summarizes 590 cognitive functions mapped onto the white matter. This important work highlights several new findings. For example, this functional white matter atlas identified most functions are distributed in a network rather than a single brain region and that most white matter tracts mediate several functions. These exciting developments highlight the importance of brain connections and pave the way to study their disconnections in large clinical populations to add a missing puzzle piece to our map of the human brain.

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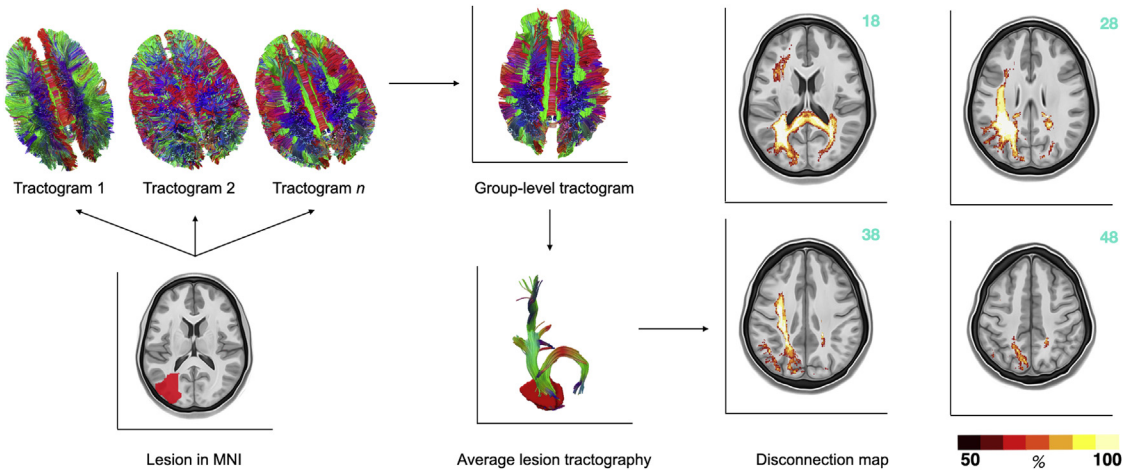

Fig. 4 Schematic diagram showing the human disconnectome approach to mapping the impact of lesions to white matter networks beyond the lesion mask.

Discussion

For centuries, lesion-symptom mapping methods have provided a window into the functioning of the brain, sparked novel theories about localization of function and have started an entire field of human brain mapping. This group of methods is among the most exciting techniques we have available in clinical neurosciences and has repeatedly had a tremendous impact on our fundamental understanding of the brain. This journey has started with the famous cases in neuroscience and evolved into a set of statistical methods that have fundamentally reshaped our clinical-anatomical study designs. The last two decades have seen the most significant advances in this long tradition, and as a result, many new promising findings will await clinical validation in the future (e.g., Forkel et al., 2020a; Toba et al., 2020).

The methods we currently have available are complementary to each other and are continually increasing in their sophistication with the aim to map the structure and function of the brain fully. Future research still has many questions to answer, and we are only at the cusp of being able to capture the complexity of the data we are working with. Among these exciting challenges, the following three should be highlighted. The first challenge is inter-individual variability that is consistently highlighted by patients who do not match predictions based on average models of the structure and the function of the brain. By accounting for interindividual variability, "atypical" patients might be captured by lesion-symptom models. Accounting for variability will lead to better predictions on the resilience to brain lesions, and differential recovery slopes after brain damage might be better foreseen. Lesion mapping methods rely on the presence of a lesion and it is always difficult – if not impossible – to infer the preinsult anatomy and location of function in stroke patients which are the most commonly studied patient group. This challenge may be progressively elevated by systematically studying neurosurgical patients (e.g., brain tumor and epilepsy) which offer a unique possibility to study the brain before and after the occurrence of a surgical lesion or capitalising on exciting new population-wide databases, such as the UK Biobank. The third challenge will be to combine multimodal imaging data and be able to draw reliable conclusions from it. The current imaging modalities tap into the anatomy of the brain at different temporal and spatial resolutions and measure across an anatomical spectrum from micro-to macroscale. For example, diffusion tractography is sensitive to white matter underneath the cortical ribbon (**Fig. 5**B), functional imaging measures blood flow changes within the gray matter (**Fig. 5**C), electrocortical and transcortical magnetic methods such as EEG and TMS are skull-based (**Fig. 5**D), while invasive methods such as direct cortical stimulations record directly from the cortical surface and subcortical resection cavities (**Fig. 5**E). Combining all these signals in one brain model is computationally and conceptually challenging. Multimodal brain mapping studies, however, are already pushing the boundaries to combine multimodal imaging in lesion mapping methods (e.g., Lerch et al., 2017; Pustina et al., 2017; Howard et al., 2019; Mollink et al., 2019).

While some groups are working on the processing of the data, others are still improving the way we acquire data. One of the most promising features of these novel methodological advances is that we will be able to improve the patient experience during scanning by using structural and functional scans with a minimum amplitude of acoustic noise (Wiesinger et al., 2016; Ljungberg et al., 2021). Providing a more pleasant experience to the patients will result in better quality data (e.g., fewer motion artifacts) but also open up new avenues for experimental study designs as novel functional paradigms might be possible if the scanner environment is silent. Taken together, we will likely reshape our current structural and functional brain maps when using these novel tools and cement the use of neuroimaging as a clinically useful method to determine imaging biomarkers and facilitate precision medicine.

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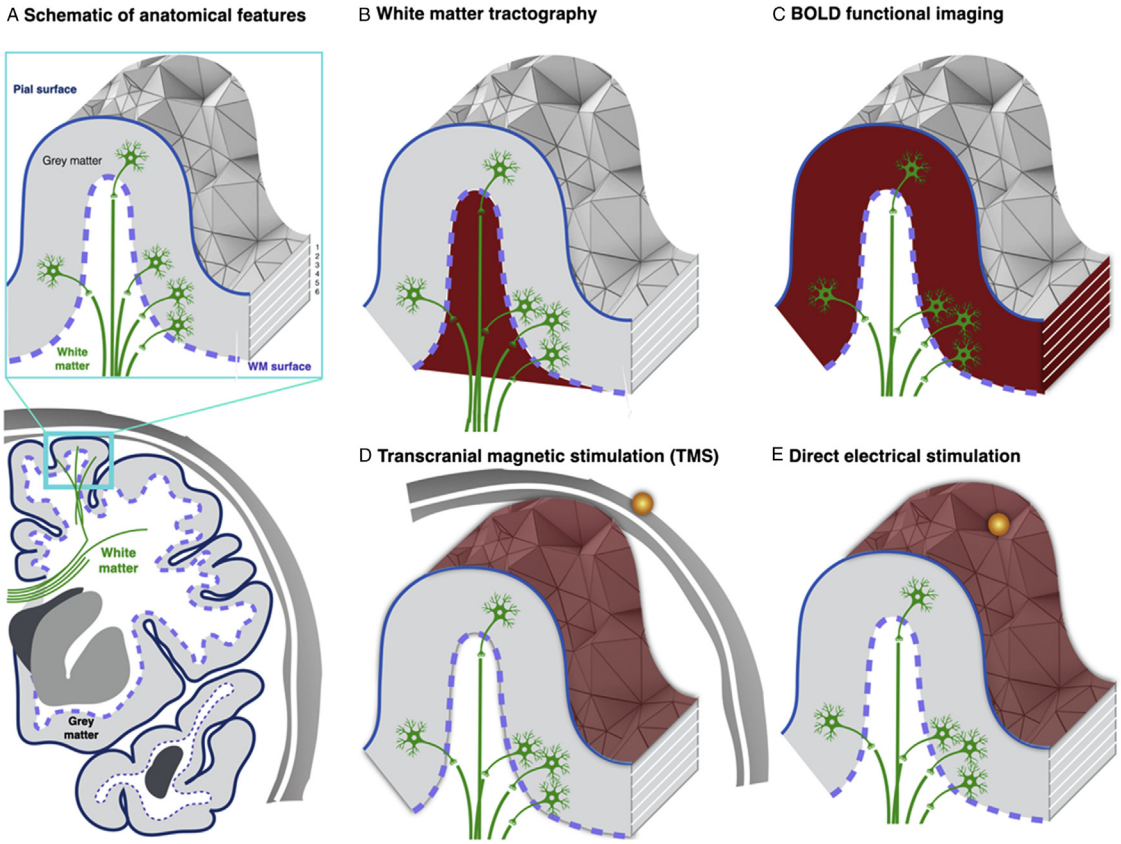

Fig. 5 Schematic diagrams of anatomical scales and the layers that different methods are sensitive to. This figure highlights that each imaging modality is tapping into a different feature of the brain's anatomy (e.g., white matter, cortex, cortical surface). Panel D and E show TMS applied to the skull and direct cortical stimulation where a probe (indicated by an *orange ball*) is placed directly on the cortical surface.

Acknowledgments

Funding for this work was provided by the European Union's Horizon 2020 research and innovation program (grant agreement No. 818521). I am grateful to Henrietta Howells, Lia Talozzi, Maria Ivanova, Carolina Tammurello and Patrick Friedrich for their input and discussions.

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