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REVIEW

Indirect structural disconnection-symptom mapping

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Abstract
In vivo tracking of white matter fibres catalysed a modern perspective on the pivotal role of brain connectome disruption in neuropsychological deficits. However, the examination of white matter integrity in neurological patients by diffusion-weighted magnetic resonance imaging bears conceptual limitations and is not widely applicable, as it requires imaging-compatible patients and resources beyond the capabilities of many researchers. The indirect estimation of structural disconnection offers an elegant and economical alternative. For this approach, a patient's structural lesion information and normative connectome data are combined to estimate different measures of lesion-induced structural disconnection. Using one of several toolboxes, this method is relatively easy to implement and is even available to scientists without expertise in fibre tracking analyses. Nevertheless, the anatomo-behavioural statistical mapping of structural brain disconnection requires analysis steps that are not covered by these toolboxes. In this paper, we first review the current state of indirect lesion disconnection estimation, the different existing measures, and the available software. Second, we aim to fill the remaining methodological gap in statistical disconnection-symptom mapping by providing an overview and guide to disconnection data and the statistical mapping of their relationship to behavioural measurements using either univariate or multivariate statistical modelling. To assist in the practical implementation of statistical analyses, we have included software tutorials and analysis scripts.

Keywords Lesion-symptom mapping · Inference · Connectome · Diffusion tensor imaging · White matter · Statistics

Lesion-disconnection-deficit mapping

The study of brain damage underlying cognitive deficits can give us unique insights into the functional anatomy of the brain. Lesion-symptom mapping (Bates et al. 2003; Rorden and Karnath 2004) has long been the most popular method in this line of research. This approach assesses brain damage using structural imaging, which allows focal damage to be identified and associated with behavioural measures. Topographic lesion-symptom mapping results are most often referenced to grey matter atlases. Hence, studies typically focus on the contribution of grey matter damage to cognitive pathology. The role of white matter damage and the resulting structural disconnection between spared functional areas have often been ignored until recently, largely due to the lack of methods to examine white matter in vivo aside from invasive approaches such as intra-operative stimulation (Thiebaut de Schotten et al. 2005). This limits our ability to understand the anatomical basis of cognitive deficits in neurological disease, as well as the neural correlates of recovery and brain plasticity after stroke (Catani and Ffytche 2005; Grefkes and Ward 2014; Kuceyeski et al. 2014). However, the advent of methods for the non-invasive in vivo reconstruction of white matter tracts from diffusion-weighted imaging (DWI) data has enabled researchers to overcome this obstacle (Catani et al. 2002). DWI has become an important tool in cognitive neuropsychology and neurology, as it allows researchers to infer areas of reduced white matter integrity in neurological patients (Buch et al. 2016; Gleichgerrcht et al. 2017; He et al. 2007; Ivanova et al. 2016; Lunven et al. 2015; Umarova et al. 2014; Urbanski et al. 2008; Yourganov et al. 2016). However, the in vivo examination of white matter by diffusion imaging bears limitations. First, it requires MR-compatible patients and resources and expertise often beyond the capabilities of researchers.

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Second, although fibres, in principle, can be tracked with high reproducibility in stroke patients (Borich et al. 2012), the validity of fibers tracked through affected areas is unclear due to the potential impacts of pathology on the diffusion MRI signal. Diffusion MRI measures obtained from scans of pathological patients also reflect the joint contributions of the lesion, the patient's individual anatomy, and data/reconstruction quality. This can make it difficult to disambiguate the direct effects of the lesion on specific structures from other sources of variation.

The interpretation of focal lesion-symptom mapping results by reference to white matter data collected from normative subjects has emerged as an economical and practical alternative to direct estimation of white matter measures in patients (e.g., Bird et al. 2006; Corbetta et al. 2015; Karnath et al. 2009; Mirman et al. 2015; Thiebaut de Schotten et al. 2014). This has been facilitated by the public availability of white matter atlases that delineate the spatial positions and/or trajectories of canonical fibre pathways (e.g. Thiebaut de Schotten et al. 2011; Wakana et al. 2004; Yeh et al. 2018; Zhang et al. 2010). However, the strategy of first applying traditional lesion-symptom mapping and then leveraging white matter atlases to inform the interpretation of statistically significant results has important limitations. Due to the spatially distributed nature of white matter tracts, spatially distant lesions can damage and/or disconnect the same fibre bundle (Fig. 1). In traditional univariate analyses, this can lead to a limitation that is often referred to as the "partial injury problem" (Rorden et al. 2009; see Sperber et al. 2019 for an illustration), which arises when partial damage of larger neural correlates—such as a large region, network or fibre bundle—can induce a deficit. The statistical power, i.e. the probability of obtaining statistically significant results in the neural correlates of a behavioural function, is then decreased. One possible outcome is false negatives, such that a statistical analysis may fail to identify the neural correlates of a function in part or whole. This problem is likely to be most relevant in scenarios where the symptom under investigation can result from damage to long association and projection fibres. These often extend over different arterial territories and therefore areas that are unlikely to be lesioned together in a single patient. While a data representation on structural disconnections does not fully eliminate the partial injury problem, it has the potential to drastically decrease it whenever disconnection underlies a deficit. Further, the architecture of white matter fibre pathways is spatially compact and often overlapping. Hence, even small white matter lesions can induce severe fibre tract disconnection, which voxel-wise structural lesion data may not well represent. This may even lead to samples for which voxel-wise lesion-symptom mapping is not feasible due to low overlap of small lesions, i.e. a lack of shared pathological features on which a statistical comparison can be based. On the other hand, a representation by disconnection metrics may provide the variance required for statistical analysis, even when the structural lesions do not overlap. Further, in scenarios where white matter disconnection is a plausible source for a deficit, measures that aim to model the lesion-induced disconnection are conceptually appealing, and they might provide a higher predictive value for a cognitive deficit (Griffis et al. 2019; Hope et al. 2016; Siegel et al. 2016) and, therefore, may enable anatomical analyses that are more sensitive to the mechanism underlying the deficit.

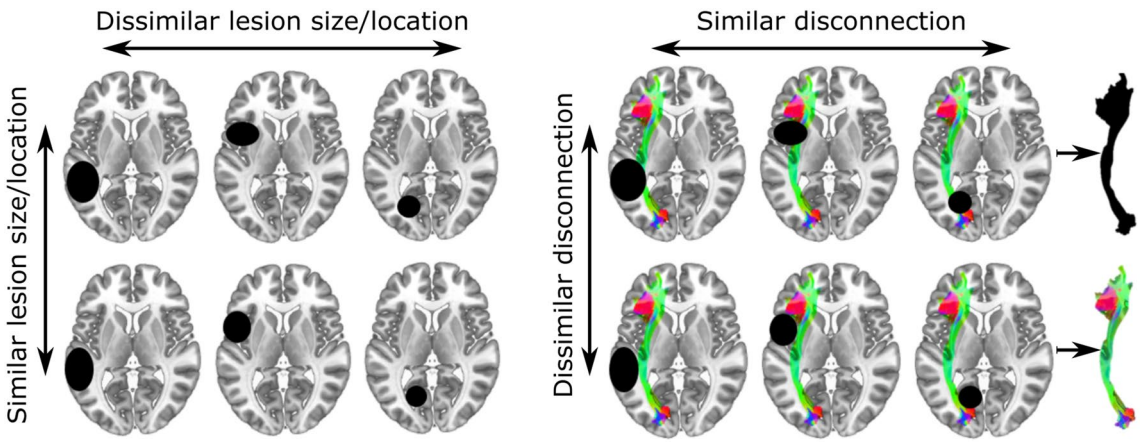

Fig. 1 Voxel-wise versus disconnection-wise representation of structural brain pathology. Illustration of how a voxel-wise data representation may fail to represent structural disconnection. The issues in mapping the behavioural effects of small lesions are also illustrated here. Small lesions that rarely overlap (left panels) provide only little anatomical variance that can be utilised by statistical models. However, the disconnection-wise representation (right panels) may provide features with the variance needed for statistical modelling.

Indirect structural disconnection-symptom mapping

The considerations discussed above have led to increased interest in indirect structural disconnection mapping, an approach that infers structural disconnection for an individual patient by integrating spatial lesion data with prior anatomical information provided by normative white matter data. This method involves embedding the patient's lesion mask into normative connectome data obtained from healthy individuals to model the expected impact of a lesion on the typical white matter connectome. It includes several measures that attempt to represent the disconnectome, i.e. the disruption of the network architecture of the brain, after a brain lesion (Fig. 2). With these measures, one can address the issues related to the inference of disconnection in traditional lesion-symptom mapping. The critical aspect of this approach constitutes an inversion of the sequence in the standard methodological pipeline: in the first step, structural disconnection estimates are obtained for each patient and, in the second step, the relation between the estimated disconnection measures and behavioural/cognitive/clinical variables is statistically assessed in a group analysis. This strategy often employs probabilistic fibre tract atlases to enable a so-called tract-wise or hodological approach where estimates of disconnection are obtained for canonical white matter fibre tracts such as the corticospinal tract or the superior longitudinal fasciculus (Rudrauf et al. 2008; Thiebaut de Schotten et al. 2014). Other approaches, however, aim to model the whole-brain region-to-region "disconnectome" using normative streamline tractography datasets to compute the disconnection between pairs of grey matter regions (Foulon et al. 2018; Griffis et al. 2021; Kuceyeski et al. 2013). In this case, the network can be represented as a graph with nodes for grey matter regions and edges quantifying the extent of disconnection between grey matter regions. This approach can be further expanded using the estimated disconnectome to compute graph-theoretic connectivity measures, such as changes in the shortest path length between brain regions (Griffis et al. 2021), region-wise connectivity changes (Kuceyeski et al. 2013), or global network metrics (Bassett and Bullmore 2009).

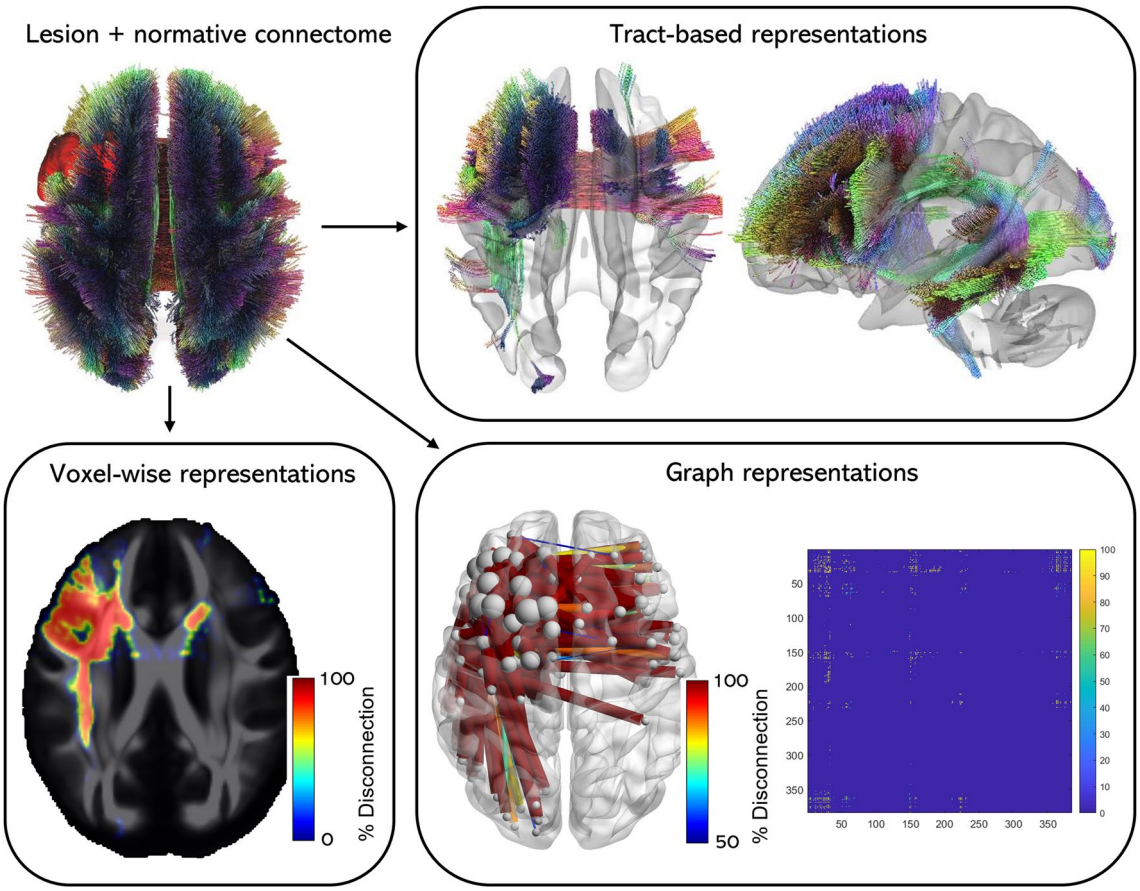

Fig. 2 Types of indirect lesion disconnection data

Toolboxes to assess indirect structural disconnection

Several toolboxes have been developed to facilitate the modelling of structural disconnection in patients with brain lesions. Here, we will discuss three prominent toolboxes: the Lesion Quantification Toolkit (LQT; Griffis et al. 2021), the Brain Connectivity and Behavior Toolkit (BCBtoolkit; Foulon et al. 2018), and the Network Modification tool (NeMo; Kuceyeski et al. 2013). Each of these toolboxes requires a set of patient lesion masks registered to the MNI template space and sampled to the same voxel resolution as the reference connectomic data. Therefore, lesion data must be preprocessed before being embedded into the normative reference datasets. To estimate region-level disconnection or a whole-brain disconnectome, the user may either provide a grey matter parcellation or select an atlas implemented in the toolbox. Critically, these toolboxes differ in several ways: they have different software dependencies, employ different reference datasets, use different strategies to model and quantify white matter disconnection, and produce different measurements as outputs. As a user, it is essential to be aware of these differences to make informed decisions about which toolbox and output measurement are best suited for the research project at hand. In what follows, we will give a comprehensive overview of the three toolkits and point towards the most important distinctions. A full overview on the available indirect disconnection measures is provided in Table 1, and Fig. 3 visualises a selection of disconnection data for an example lesion.

The network modification (NeMo) toolbox

The Network Modification tool (Kuceyeski et al. 2013; https://kuceyeski-wcm-web.s3.us-east-1.amazonaws.com/upload.html) is a stand-alone web application relying on a set of 420 healthy adult DWI scans from the 7T Human Connectome Project (HCP). The reference streamline tractography can be estimated based on the user's preferences using either a deterministic or a probabilistic tracking algorithm, employing the SD_STREAM or iFOD2 and ACT functions in MRtrix3 (Tournier et al. 2019; https://mrtrix.readthedocs.io/en/latest/). While probabilistic tracking—unlike deterministic tracking—mitigates the risk of error-propagation, it is more sensitive to non-dominant fibre orientation, which might increase false positives in the generated connectomes (Behrens et al. 2007).

It should be emphasized that all tractography approaches are limited in reconstructing the true density of the underlying fibre bundles. They estimate voxel-wise orientation peaks assuming that most fibres included in this voxel run in parallel to this orientation, resulting in a "most likely trajectory" through the data (Jones et al. 2013). This very nature of streamline propagation can introduce several biases to the tractogram, compromising the quantification of connection strengths based on streamline densities. To control for these biases, NeMo allows the user to apply the extended spherical-deconvolution informed filtering of tractograms (SIFT2; Smith et al. 2015) approach included in MRtrix3, which weighs streamlines automatically to improve the biological accuracy of reconstructed streamlines. As demonstrated by Smith et al. 2013, this approach can, e.g., correct for overfitting in long bundles, where tractography algorithms tend to fit higher numbers of streamline reconstructions as they find a greater volume from which to seed.

The NeMo tool generates graph representations of whole-brain disconnection based on either a custom atlas, which needs to be uploaded along with the normalised lesion map or one of the readily available atlases included with the tool. The tool co-registers the provided lesion masks and grey matter atlas to the tractography of each subject in the reference dataset. To quantify the primary output measure—a change of connectivity (ChaCo) score for every single region in the parcellation—NeMo determines the proportion of streamlines intersected by lesioned voxels among all streamlines connecting to a given atlas region. It repeats this procedure for every atlas region and

Table 1 Overview of indirect disconnection measures available in the NeMo, BCB and LQT tools

Toolbox	Reference Connectome data	Disconnection measure	Data structure	Description
NeMo	420 7 T DWI scans from the HCP	ChaCoConn	Symmetric 2D matrix	Pair-wise regional
		ChacoVol	1D vector	Region-wise
BCB	7 T tractography from 10 + HCP subjects	Disconnectome Map	3D image	Voxel-wise & probabilistic
	Probabilistic atlas of 68 WM pathways	Tractotron disconnection probability	1D vector	Tract-wise & probabilistic
		Tractotron affectation proportion	1D vector	Tract-wise lesion overlap
LQT	70 canonical WM tracts in the HCP-842 streamline tractography	Tract disconnection	1D vector	Tract-wise
		Disconnection map	3D image	Voxel-wise
		Parcel disconnection	Symmetric 2D matrix	Pair-wise regional
		Δ Shortest structural path length	Symmetric 2D matrix	Graph-theoretical

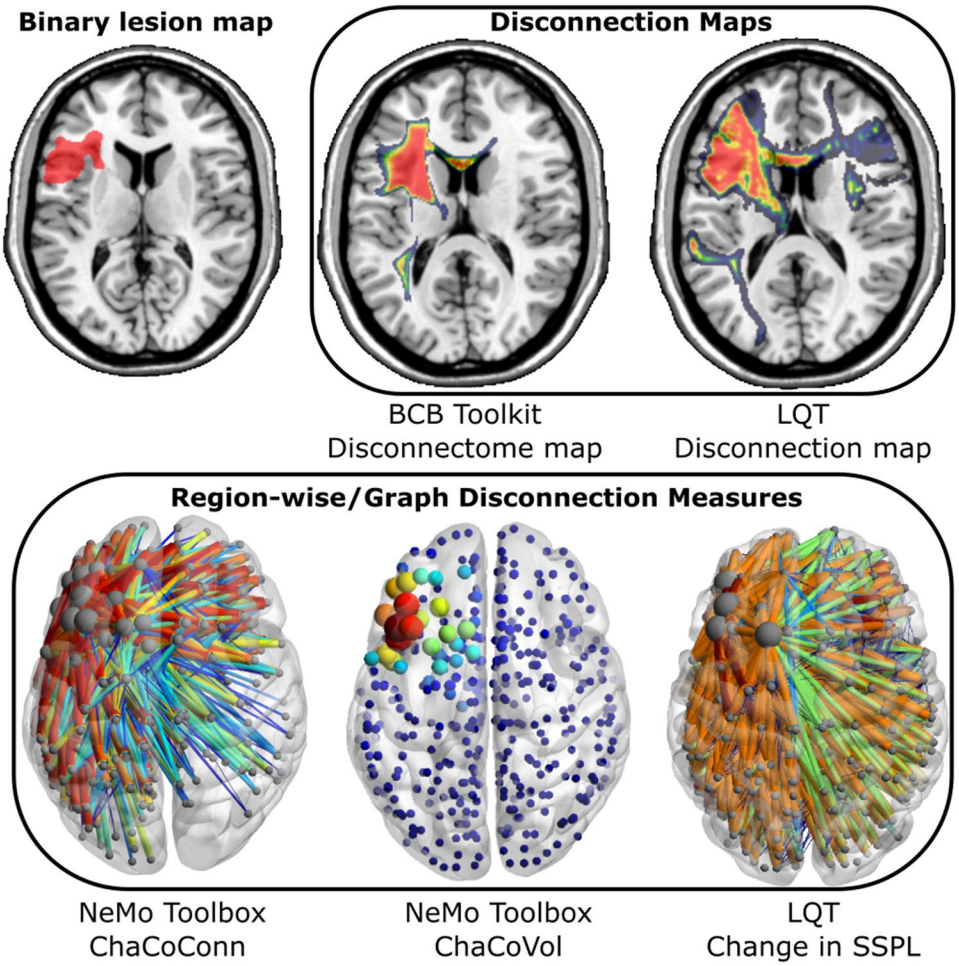

Fig. 3 Example indirect disconnection data for a single lesion. An example of all toolbox outputs for the lesion is provided in the online materials on Mendeley data

every reference connectome, yielding a total of 420 disconnection vectors, of which mean, and standard deviation are derived.

Pair-wise regional disconnection can be computed in a similar fashion, where only streamlines that directly connect two atlas regions are considered. In this case, results are entered into a symmetrical $N \times N$ matrix, where N is the number of atlas regions, and mean and standard deviation across the reference sample can be obtained. In summary, the NeMo tool is particularly suited for graph-theoretical measures as a way of compressing network information to atlas-derived grey matter regions and their structural connections. Furthermore, it provides some control over the determination of reference connectomes and captures the variability within the reference sample as it reports the standard deviation of each metric across the reference connectome sample.

The lesion quantification toolkit (LQT)

The LQT runs in a Matlab environment and can be used either by a graphical user interface or by a Matlab script. Example scripts for batch-processing and single-subject processing are provided in the current distribution. Its repertoire includes tract-based (i.e., hodological), voxel-wise, and region-wise/graph representations of white matter disconnection. For all outputs, the LQT refers to an expert-vetted tractography atlas delineated from DWI data obtained from a set of 842 healthy HCP participants (Yeh et al. 2018). For tract-based analyses, it includes delineations of 70 canonical white matter tracts. The basic principle for estimating disconnection involves embedding each patient's topographical lesion map in the tractography atlas and estimating the severity of disconnection expected at the tract, region or voxel level. Disconnection severity is estimated as the proportion of disconnected streamlines assigned to a given tract, connecting a given region pair, or traversing a given voxel. Thus, similar to the NeMo tool, the LQT provides a proportional metric of disconnection severity based on the disruption of a streamline. However, in contrast to the NeMo tool, the LQT does not attempt to account for individual variability within the reference group but instead operates on the assumption that the large-sample tractography atlas represents a stable,

population-based description of the features of the normative structural connectome.

Apart from that, the LQT is the only tool that attempts to estimate how the effects of region-wise disconnections propagate throughout the connectome. Specifically, it estimates the increases in shortest structural path length (SSPL) that are expected between pairs of grey matter regions by comparing the shortest path length in the spared connectome to those in the healthy normative connectome. The SSPL defines the topological distance between pairs of grey matter regions and corresponds to the minimal number of connections that establish a structural connection between a given region pair. Hence, if two regions share a direct structural connection, they have an SSPL of 1, but if they are connected only indirectly via a series of direct connections to other regions, they have an SSPL > 1. For a given lesion and grey matter parcellation, the toolbox calculates the increase in SSPL with the brain lesion relative to the healthy connectome. Specifically, it determines a binary matrix defining all direct region-to-region connections spared by the lesion and determines the shortest path lengths. The same procedure is applied to a binarised matrix of direct region-to-region connections defined by the template that resembles the brain's healthy state, and the resulting path length matrices are subtracted. It has been shown that SSPL scales with the strength of functional coupling (Goni et al. 2014), highlighting its potential as a direct predictor of functional connectivity. Consistent with this expectation, both direct disconnections and SSPL increases have been linked to disrupted functional connections in stroke patients (Griffis et al. 2020). Brain lesions may disrupt direct connections but spare indirect pathways, urging the brain to use other less efficient routes to re-establish functional pathways (Kuceyeski et al. 2016). Thus, metrics that represent large-scale structural connectivity changes, such as the change in SSPL, may be useful as biomarkers to predict recovery after brain injury (e.g., Del Gaizo et al. 2017; Umarova et al. 2017; Wilmskoetter et al. 2021).

The brain connectivity and behavior toolkit (BCB toolkit)

Lastly, the BCB toolkit runs as a graphical user interface on the Linux or OSX system and can generate two different tract disconnection estimates and 3D voxel-wise disconnection maps. While, by default, it refers to a set of ten healthy control subjects, the reference set can be boosted by including readily available tractography data from 178 subjects from the 7T HCP (freely available for download at toolkit.bcblab.com). Like in the NeMo tool, disconnection induced by a given lesion is estimated separately for each reference tractography. Specifically, the software uses pre-computed tractograms in standard space and filters the streamlines that intersect the lesion mask to determine a single-subject 3D disconnection map. Next, the overlap of disconnection maps across the sample is determined per voxel. Thus, each voxel within the 3D disconnection map represents the likelihood of this voxel containing disconnected streamlines. Note that this requires a different interpretation than the LQT voxel-wise disconnection map, where each voxel represents the proportion of streamlines affected by the lesion.

For the estimation of hodological, tract-based disconnection, BCB toolkit refers to a probabilistic atlas containing tractography reconstructions of 68 white matter pathways obtained from 47 healthy participants (Rojkova et al. 2016). Each voxel of the atlas represents the proportional overlap of streamlines assigned to a particular tract in the atlas reference set. In other words, each voxel in the atlas contains the proportion of reference subjects that has this voxel assigned to a particular tract. Tract affectation probability is determined by iteratively embedding the lesion map in the probabilistic representation of each individual tract. Among the group of tract voxels that overlap with the lesion map, only the one with the maximal streamline overlap, i.e., the voxel with the highest probability for a particular tract, is reported. This represents the probability that a lesion affects a particular tract as defined by the atlas. Note that this metric, while integrating information about the variance in the atlas reference set, can only provide conclusions of the type "tract X is likely disconnected or not". A threshold of 50% is commonly introduced as a decision boundary (Foulon et al. 2018), although the user may select another value. Alternatively, a proportion metric is calculated, which, in contrast to the approaches applied by NeMo and LQT, quantifies the mere percentage of voxels assigned to a given anatomical fibre tract that overlaps with the lesion. We note that the biological plausibility of volumetric lesion-tract overlap measures has been subject to debate, with some authors arguing that such measures are likely to underestimate the impact of small lesions that nonetheless bisect a tract (Griffis et al. 2021; Hope et al. 2016). Nonetheless, volumetric lesion-tract overlap measures are commonly used in the research literature, and more dedicated comparisons are necessary to fully clarify the strengths and weaknesses of different approaches to measuring lesion-induced disconnections.

Toolboxes—Summary and conclusion

The three toolboxes are user-friendly and can be used with preprocessed high-quality connectome data from healthy controls taken from public databases such as the Human Connectome Project. With their help, a scientist can perform the first step in structural disconnection-symptom mapping without specialised MR imaging sequences acquired in patients and without expertise in DTI data processing. The only requirement is a binary map of the structural

lesion and the behavioural measure. However, with the indirect disconnectome data at hand, a scientist encounters the next obstacle. While anatomo-behavioural inference is not conceptually different in indirect disconnectome data and binary lesion data, the indirect disconnectome data can differ from binary lesion data in several aspects, including structure, type, and file format. Therefore, commonly used lesion mapping software might be limited or even unable to process the indirect disconnectome data. In the remaining chapters, we want to provide an overview and guide on those aspects of indirect disconnection-symptom mapping that are not covered by the toolboxes. The focus will be the statistical analysis of disconnectome data, the different data structures, and the interpretation of results. Moreover, we provide readers with an introduction to the prerequisites for indirect disconnection-symptom mapping.

Challenges in indirect lesion-disconnection-deficit mapping

Voxel-based lesion-symptom mapping probably owes its popularity to its relative simplicity. We can map functional brain anatomy solely with a structural image that depicts brain damage and a behavioural measure. This is also true for indirect disconnection-symptom mapping. In general, one could view the creation of an indirect disconnectome merely as an additional step in the common method pipeline in lesion-symptom mapping. Many methodological concepts in lesion-symptom mapping can be transferred to indirect disconnection-symptom mapping and have been elaborated on in several guides and reviews (e.g. de Haan and Karnath 2018; Pustina and Mirman (in press); Rorden and Karnath 2004; Sperber and Karnath 2018). However, not all concepts can be directly transferred, others are still up for discussion in lesion-symptom mapping, and new challenges arise.

Prerequisite—assessment of the structural lesion

Before the disconnectome of a patient can be estimated indirectly, a binary lesion map is required. This map indicates voxels in the brain that are structurally (and presumably functionally) compromised due to a lesion. The identification of such voxels is no trivial issue. Which imaging modality is suited depends on the aetiology of brain damage. While high-resolution MR imaging is often ideal, MR or CT imaging obtained within a clinical routine can be used as well (Rorden et al. 2012). The lesioned area has to be delineated on the image, which can be done manually (e.g. with MRIcron [https://www.nitrc.org/projects/mricron] or ITK-Snap [http://www.itksnap.org]) or (semi-) automatically (e.g. de Haan et al. 2015; Griffis et al. 2016; Pustina et al. 2016; for a comparison, see Ito et al. 2019). The next step is spatial normalisation, i.e. the process of warping the lesion map into a common brain template space. This ensures that the lesions of all patients are spatially comparable and, of major relevance to indirect disconnection mapping, also spatially aligned with the healthy subjects' reference connectome data. All three toolboxes operate in the Montreal Neurological Institute (MNI) brain template space, which is also the brain space of most normalisation templates. An additional challenge in normalising diseased brains is distortions induced by the lesioned tissue. Hence, images of lesioned brains are commonly normalised with special algorithms that account for the lesioned area (Brett et al. 2001; Nachev et al. 2008) and which are also provided in the BCB Toolkit (Foulon et al. 2018).

For both imaging and behavioural testing, the choice of aetiology is important. The question of the optimal aetiology for lesion-symptom mapping is highly controversial. While some scientists take strong positions for or against certain aetiologies, arguably, all neurological diseases come with certain limitations and no optimal aetiology exists. Acute stroke patients are difficult to test, and structural brain imaging can be distorted due to temporary swelling or might fail to capture non-intact brain areas due to extra-lesional malperfusion (Hillis et al. 2001) or fogging effects (O'Brien et al. 2004). Any pathology that existed or progressed over a longer period, including chronic stroke, tumours or chronic inflammation, can trigger plastic (e.g., compensatory) changes in functional brain anatomy (Cargnelutti et al. 2020; Wang et al. 2010; Ward and Cohen 2004) which limits our ability to infer normal, healthy functional brain anatomy. For pathologies such as slow-growing tumours, adaptive plasticity may mitigate the cognitive and behavioural impact that would be expected from acute-onset lesions to the same location (Anderson et al. 1990; Desmurget et al. 2006). In addition, structural brain anatomy is subject to atrophy even years after stroke (Seghier et al. 2014) which may hinder lesion delineation or normalisation (Sperber and Karnath 2018). The identification of non-intact brain areas is limited in tumours, as the border of a tumour—if it can be objectively identified at all—does not necessarily represent the border between intact and non-intact tissue (Karnath and Steinbach 2011). In the end, a researcher should be aware of such limitations and, if adequate, discuss results in their context.

Similarities in mapping lesions and indirect disconnection

The binary map of structural damage, i.e. the lesion map, and the indirect disconnection data share many features that guide the statistical analysis. Depending on the featurisation of the lesion map, i.e. if structural damage is represented on the level of voxels, regions or computational components

(see Kasties et al. 2021), the lesion data range from several dozen to over one million features (i.e. data points). Likewise, indirect disconnection data range from a few dozen features with a tract-wise representation up to over a million with a three-dimensional, voxel-wise representation. In the end, any data featurisation requires large-scale methods to infer the role of individual imaging features in behavioural pathology. The common univariate and multivariate approaches used in lesion-symptom mapping can also be applied to disconnection data with some adaptations.

In general, anatomo-behavioural inference in such high-dimensional data is challenging. The localisation of brain lesions is highly systematic and, in the example of ischemic stroke, follows the vasculature (Zhao et al. 2020). Therefore, anatomical pathology correlates between features (Sperber 2020), meaning that many brain regions are often typically damaged or spared in unison, and the informational content of the data is often drastically lower-dimensional than the original high-dimensional data space (Calesella et al. 2021; Kasties et al. 2021; Salvalaggio et al. 2020). Further, it was shown that this systematic localisation of lesions induces a spatial mislocalisation of topographical lesion-symptom mapping results (Mah et al. 2014), and, given that lesions also systematically affect fibre tracts, this should not be different for disconnection-symptom mapping. Yet, there is another limitation imposed by the anatomy of lesions. Not all brain areas are equally affected by lesions, and the variance in the anatomical data differs across features. The statistical power of univariate tests can be critically low for features from brain areas that are rarely lesioned (Kimberg et al. 2007), and small sub-samples of patients with an uncommon lesion location could drive statistical results (Gajardo-Vidal et al. 2018). Therefore, voxels that are rarely or never affected are commonly excluded from the statistical analysis in lesion-symptom mapping (Sperber and Karnath 2017). The same should be considered in disconnection-symptom mapping. Some tracts or region-to-region connections might be rarely or never affected in a given patient sample. Moreover, disconnection data add another layer to this issue. First, region-to-region connectivity matrices provide measures for every pair of regions, while not all brain regions are directly connected and, hence, only a proportion of all connections are biologically plausible (see Zhang et al. 2014a). Therefore, many features are per se zero in all patients. Second, some imaging features might maximally indicate only faint disconnection, and the variance of the anatomical data might be in the range from zero to low values. While such faint disconnection is not necessarily meaningless, one should ideally consciously decide to include or exclude such features.

What is specific to disconnection-symptom mapping?

A few differences exist between the structure of lesion maps and disconnection data that are relevant to the statistical analysis. First, lesion maps are most often binary and indicate for each voxel if a lesion is present ('1') or not present ('0'). On the other hand, indirect disconnection data are most often continuous, like, for example, continuous proportions or probabilities between 0 and 1, or integer numbers. This is particularly important for univariate analyses, where continuous independent data prevent the direct transfer of statistical methods from voxel-based lesion-symptom mapping to disconnection-symptom mapping. For example, group comparisons, such as *t*-tests or χ^2-tests, which are popular for lesion-symptom mapping, can be used with the binary lesion status as an independent grouping variable, but not equivalently with a continuous independent variable.

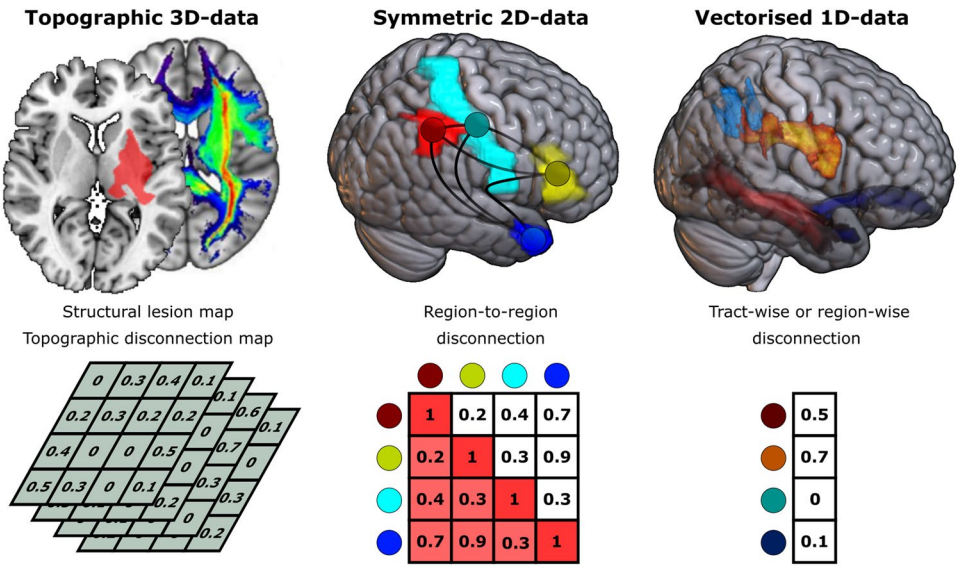

Fig. 4 Structure of indirect disconnection data

Second, the data format and structure of disconnection data vary (Fig. 4). Lesion maps are three-dimensional matrices that are usually stored in a brain imaging data format, such as NIFTI (.nii), and topographical 3D disconnection maps have the same data format. Other disconnection data are either one- or two-dimensional matrices and can be stored in data container formats. Region-to-region disconnection data are symmetric two-dimensional matrices or graphs with redundant features above and below the diagonal. As the connectivity of a region with itself is, so far, not conceptually included in indirect disconnection-symptom mapping, the diagonal of these matrices contain meaningless features. In the end, however, all data are nothing but numbers within matrices, and these can be used in all kinds of statistical models to investigate the relationship between the disconnection measures and any clinical or behavioural measure.

Univariate statistical mapping

Statistical parametric mapping (Friston et al. 1994) is a popular methodological framework for the analysis of brain imaging data and provided the foundation for voxel-wise statistical lesion-symptom mapping (Bates et al. 2003). With this method, brain-behaviour inference with imaging data that were normalised to a common brain space is astonishingly simple. Each imaging feature—e.g., each voxel—is assessed with an independent statistical test for the relation between the imaging feature (e.g. a voxel's 0/1 lesion status) and the behavioural variable. The resulting test statistic is then back-projected into the brain space, and clusters of significant results are interpreted as a deficit's neural correlates. Statistical parametric mapping originally focussed on the use of general linear models (Friston et al. 1994), which are highly flexible and can be adapted to different data structures. However, statistical parametric mapping is even more flexible in the sense that almost any kind of statistical test can be used, including parametric and non-parametric tests (Rorden et al. 2007), tests for continuous or binary data, and so on. In the context of brain-behaviour inference, this analysis strategy has often been termed a 'mass-univariate' approach, referring to the massively repeated use of univariate statistical tests. Note the generally heterogeneous use of the term 'univariate'. In the statistics literature, it usually refers to statistics that model a single dependent variable (here: a deficit, e.g. an aphasia score). In brain-behaviour inference, it instead indicates a test that models only one independent variable (here: an imaging feature, e.g. the lesioned/non-lesioned status of a voxel), at a time, thereby contrasting multivariate lesion-symptom mapping methods that model multiple imaging features at once.

The repeated use of statistical tests inflates false positives. With a large number of statistical tests performed at a common α-level of $p = 0.05$, many tests will reject the null hypothesis and wrongfully indicate a statistically significant association between brain pathology and the deficit even in the absence of any true positive effects. This can be countered with a correction for multiple comparisons, which is not trivial in brain-behaviour inference. Some algorithms assume the independence of statistical tests, which, as discussed below, is not appropriate. The two correction strategies are family-wise error rate (FWER) correction, which aims to reduce the probability of obtaining at least one false positive to the originally chosen α-level, and false detection rate (FDR), which controls the proportion of false positives among all positive tests. For FWER, popular algorithms such as Bonferroni correction can drastically reduce statistical power in mass-univariate analyses (Karnath et al. 2018). Monte Carlo simulation-based permutation statistics provide an approximately exact but computationally more demanding alternative (Mirman et al. 2018; Nichols and Holmes 2002). This correction provides a balanced trade-off between the prevention of false positives and false negatives and is often seen as a gold standard for multiple comparison correction in lesion-symptom mapping (Karnath et al. 2018). For FDR correction, algorithms for dependent data exist (Benjamini and Yekutieli 2001) and can easily be applied to a set of uncorrected p values.

The univariate framework is simple, flexible, and easily transferred to disconnection-symptom mapping. A univariate statistical test can be applied to a feature from a voxel, a connection between two regions, or a fibre tract. The BCB Toolkit (Foulon et al. 2018) already includes AnaCOM2 (Kinkingnéhun et al. 2007), which allows the univariate statistical analysis of disconnectome data with a few conceptual variations compared to the approach described above. With most disconnection data being continuous, general linear models can be used to test continuous behavioural variables and logistic regression for binary behavioural variables. Mass-univariate analyses are also widely accessible, as they are implemented in many statistical tools, such as SPM or FSL. However, univariate analyses have limitations in mapping functions from brain pathology. First, statistical power depends on the variance in the imaging feature and can be low for many features (Kimberg et al. 2007). If the neural correlates of a deficit span across voxels that are only rarely affected by lesions, univariate methods are unlikely to correctly identify them. Second, univariate statistical tests are independent and, therefore, neither able to fully represent the functional dependence of brain areas (also referred to as the "partial injury problem", see Rorden et al. 2009; Sperber et al. 2019), i.e. that multiple anatomical features together—a large area or network—are the neural correlate of a function, nor to represent the dependence of the pathological status between features, i.e. the systematic anatomy of brain damage (Mah et al. 2014; Sperber 2020). These

limitations can lead to both over-or underestimations of the neural correlates of a function.

Multivariate (statistical) mapping

While the methodological concept of most univariate anatomo-behavioural analyses can be traced back to the framework outlined above, multivariate analyses are conceptually far more heterogeneous. The unifying factor is that, in contrast to univariate statistical mapping, multivariate analyses model the anatomical information from multiple or all available features at once. Besides this, multivariate mapping approaches can differ markedly, ranging from descriptive analyses to statistical permutation-based feature-wise inference. A likely reason for this pluralism of methods is the challenge of feature-wise inference in multivariate models. A discrepancy exists between inference and prediction with multivariate models (Bzdok et al. 2020; Coveney et al. 2016; Hebart and Baker 2018), and while model training is essential to both, anatomo-behavioural inference requires an additional step that is nontrivial and often even controversial (Coveney et al. 2016; Hebart and Baker 2018).

Many of the multivariate mapping approaches that were established in lesion-symptom mapping can be grouped with respect to central methodological aspects. A first common strategy takes advantage of metrics that assess the contribution of each feature to the model. Most often, these are feature weights, such as the β-parameters in a regression, which can be computed for some linear regression approaches, or, under specific conditions, approximated in non-linear support vector regression (Zhang et al. 2014b). A feature weight alone, however, is not informative if we want to infer if the feature considerably (or significantly) contributed to a model. This information can be derived by different computationally demanding permutation approaches that either investigate feature weights under the null condition to infer feature-wise p values (Salvalaggio et al. 2020; Zhang et al. 2014b) or compute confidence intervals for each feature weight (Griffis et al. 2019; Kuceyeski et al. 2016; McIntosh and Lobaugh 2004). Some pitfalls exist with this approach. First, model hyper-parameters (i.e. parameters that need to be set before the model can be trained) are commonly selected to optimise prediction accuracy, which, counter-intuitively, can decrease the stability of features across subsamples, also termed feature reproducibility (Rasmussen et al. 2012). However, instability in feature estimation is problematic when we use the expression of features and their relationship to each other for inference. In other words, if a feature varies greatly depending on the characteristics of an empirical sample, it might not be a good measure to infer knowledge about the entire population. Therefore, the optimisation of model hyper-parameters might take into account prediction accuracy and the reproducibility of feature weight across (sub)samples (Zhang et al. 2014b). However, hyper-parameters that provide a decent trade-off between both variables cannot be identified by a single maximisation procedure and, so far, have been chosen manually according to partially subjective criteria (e.g. Wiesen et al. 2019; Zhang et al. 2014b). Second, the inclusion of all features into the model—even features that bear no informative value for the target variable—can decrease the model performance in regards to both prediction accuracy and feature weight reproducibility due to over-fitting to such features. Hence, it is difficult to evaluate the overall performance of the model. Third, although only one single model underlies the procedure, the statistical inference might be performed for each feature separately, which again inflates false positives and requires a correction for multiple comparisons (Sperber et al. 2019), which is, however, not the case for all approaches (McIntosh and Lobaugh 2004).

A second common strategy for multivariate inference is to train and optimise only a single model without feature-wise statistical inference (e.g. Ivanova et al. 2021; Mah et al. 2014; Pustina et al. 2018). For this approach, the optimised model ideally chooses a sparse feature space. In other words, the algorithm first selects a small subset of all features that are considered informative, e.g. by the lasso method (Tibshirani 1996) or penalised matrix decomposition (Witten et al. 2009), and then trains the model. This procedure does not include any statistical inference, but the model's prediction performance can be statistically evaluated against the null hypothesis (Pustina et al. 2018), i.e., one can statistically test if the model predicts the behavioural variable better than chance. The subset of features selected by the algorithm is then considered as the neural correlates of the behavioural deficit. However, the optimisation and training of a model and the valid estimation of its predictive performance are not trivial (Arlot and Celisse 2010; Varoquaux et al. 2017) and require complex scripting.

The available methods in multivariate lesion-symptom mapping can be transferred to structural disconnection data (e.g. Garcea et al. 2020; Griffis et al. 2019; Rosenzopf et al. 2022; Salvalaggio et al. 2020; Wiesen et al. 2020; Yourganov et al. 2016). However, out-of-the-box solutions that apply to any kind of connectome data are currently lacking. For example, available multivariate lesion-symptom mapping software might have been written to read and process three-dimensional binary lesion data, which requires several adaptations to process two-dimensional continuous disconnection data that contain redundant features. Therefore, we recommend multivariate analyses for users that are familiar with a programming language, such as Matlab or Python, and who have some basic knowledge about data modelling.

In general, multivariate modelling requires modelling decisions and the automatisation of optimisation procedures,

and we share the opinion of other authors that programming skills are essential here (Bzdok and Yeo 2017) if only to adapt publicly available scripts to your data. In addition, many researchers still do not publish software and analysis scripts, so some methods remain difficult to replicate and partially untraceable. A few methods stand out in the lesion-symptom mapping field as analysis scripts are publicly available and documented, and the methods were validated with synthetic data. This includes support vector regression-based lesion-symptom mapping (DeMarco and Turkeltaub 2018; Ivanova et al. 2021; Sperber et al. 2019; Zhang et al. 2014b) and sparse canonical correlation analysis for neuroimaging data (Pustina et al. 2018). Further, several other regression methods that are suited for datasets for which the number of input features surpasses the number of observations has been implemented and evaluated, including partial least squares regression (Ivanova et al. 2021).

Some multivariate methods can be computationally demanding, but most of them are feasible with a decent desktop computer. Although the assumption exists that multivariate models require sample sizes that are by far larger than the sample sizes common to neuropsychology (Mah et al. 2014), typical sample sizes seem to be sufficient (Pustina et al. 2018; Sperber et al. 2019), and multivariate analysis is not even necessarily inferior to univariate analysis even in small samples (Pustina et al. 2018). However, this does not mean that multivariate inference is precise in small samples, but rather that all approaches are limited with small sample sizes (Ivanova et al. 2021). Besides, certain cross-validation procedures that are often used for the training of multivariate models require training and validation sub-samples, each of which should be sufficiently large on its own. Currently, it is still up for discussion if there is an optimal approach to multivariate anatomo-behavioural inference—if it is not situation-specific at all—and what we gain from the use of multivariate methods. Multivariate inference is commonly assumed to be more sensitive (Hebart and Baker 2018), and indeed, the sensitivity seems to be increased in mapping complex neural correlates by accounting for the functional dependence between features (Mah et al. 2014; Zhang et al. 2014a, b; Pustina et al. 2018; Sperber, 2020), i.e. that multiple features together constitute the neural correlates of a function. Thereby, multivariate methods are thought to overcome the partial injury problem. On the other hand, there is no consensus if limitations due to lesion anatomy (see Sect. Similarities in mapping lesions and indirect disconnection) are specific to univariate inference (Mah et al. 2014; Nachev 2015) or a general limitation of any inference (Ivanova et al. 2021; Sperber et al. 2019; Sperber 2020). So far, simulations on synthetic data found that multivariate methods are sometimes superior to univariate methods, but not under all conditions and in all regards (Ivanova et al. 2021; Pustina et al. 2018; Sperber et al. 2019; Zhang et al. 2014b), and theoretical objections against a general superiority of multivariate methods exist (Coveney et al. 2016; Sperber 2020).

Further, the computation of voxel-wise respectively feature-wise statistical power (Kimberg et al. 2007) that has been found to identify as a potentially limiting factor in univariate analyses cannot be transferred to multivariate methods. The question remains how much multivariate methods are affected by features that rarely indicate a pathological status and if such features can under- or over-proportionally and undesirably affect the results in multivariate analyses. Given the complexity and multitude of multivariate models, we are unable to make any strong predictions. However, we deem it likely that any feature that is only rarely affected and, thereby, only provides limited variance, might be inadequately incorporated into any model. Therefore, we believe that similar issues with statistical power might exist for multivariate methods.

Interpretation of results

In the statistical analysis of anatomo-behavioural data, a researcher can investigate the relation between several dozen up to more than a million imaging features and a behavioural variable. This complexity is also reflected in the results, which can comprise a large number of relevant features. How can one make sense of the complex results in large-scale statistical mapping? In voxel-wise lesion-symptom mapping, a solution is to interpret clusters of significant voxels by reference to a brain atlas (de Haan and Karnath 2018), which allows assigning many thousand relevant voxels to a few brain areas. However, the data formats in disconnection-symptom mapping require other solutions.

The interpretation of tract-wise results should be relatively simple. Only well-known fibre tracts are included in the atlases, and their number is manageable. The publications that introduced the underlying brain atlases provide more information on the fibres, and a large body of literature covers the anatomy and function of the most relevant long association fibres. However, we advise caution. A striking heterogeneity exists in the definition and nomenclature of fibre tracts (Mandonnet et al. 2018) and, therefore, the comparison of results between atlases and studies can be difficult.

Several strategies for the interpretation of results from graph representations are available. With clear hypotheses, a researcher can focus on the connectivity of specific regions. With an exploratory approach, and if results are limited to only a few relevant inter-regional disconnections, no additional interpretation steps are required. The interpretation is more difficult with a larger number of relevant disconnections. The mere enumeration of 40 connections may be informative but is unlikely to provide a memorable and

holistic understanding of a deficit's disconnectome. With feature-wise statistical significance values, it is possible to focus on a smaller set of disconnections with peak statistical values, similar to voxel-based lesion-symptom mapping studies that often focus on statistical cluster peaks (e.g. Pustina et al. 2018). A categorisation of connections by anatomical or functional criteria may be helpful, for example into categories such as intra- versus inter-hemispheric, cortico-cortical versus projection fibres, or within versus between functional networks (e.g. Griffis et al. 2019). A graphical representation by node-and-edge plots suits to visually convey the results and also possibly suggests a graph-theoretical approach to describe the disconnectome (Farahani et al. 2019; Sporns et al. 2007; van den Heuvel and Sporns 2013).

The use of graph-theoretical summary metrics can circumvent difficulties in the interpretation of a large set of relevant features. Global network measures derived from these node-and-edge representations can summarise the properties of networks, e.g. overall network efficiency or network integrity, in simple numbers (Rubinov and Sporns 2010; Bassett and Bullmore 2009). These metrics have previously captured network alterations in neuropathology (Bassett and Bullmore 2009) and have proven to be useful markers of treatment response after stroke (Bonilha et al. 2016). While radically simplifying statistical modelling problems by compressing many network features into one variable, this approach does not allow any anatomical interpretations. In other words, the effects on behavioural markers cannot be pinpointed to particular anatomical regions or tracts but rather to the overall state of the network.

If the aim is to maintain some anatomical information, we can resort to region-wise summary metrics that model the local influence or hub-like properties of any given network node, such as the region-wise ChaCo score in the NeMo toolbox, which summarises all disconnections of a region (Kuceyeski et al. 2013). However, this comes with the downside that it might obscure situations in which only a few out of many connections of a region are relevant for a deficit. For example, if a hypothetical deficit results specifically due to the disruption of a connection between regions A and B, but not by any other disconnection, then a region-level disconnection sum may obscure this effect because it implicitly assumes that the deficit is not attributable to any specific connection or subset of connections but rather to the total number of connections affected.

Topographical results can be used for the visually appealing illustration of a deficit's white matter disconnectome. Popular visualisation tools for imaging data allow the three- or two-dimensional presentation of the results. The description of clusters of significant voxels by their position can deepen the interpretation of results, which is attractive for the differentiation of the role of the two hemispheres and callosal fibres. However, maybe aside from small and very focal results, the topographic statistical results do not allow us to precisely determine the role of specific fibres or regions in a deficit. This is because fibres associated with many region-to-region connections may coexist within a voxel, and so a significant effect of disconnection at a given voxel cannot be used to infer the implicated connection or fibre tract directly.

Perspective and limitations

We provided an introduction and methodological guide on the fields of indirect structural disconnection estimation in patients with focal brain lesions and statistical methodology for disconnection-based brain mapping. Both fields are wide and, at least in parts, relatively recent and still subject to regular innovations or critical evaluations. Therefore, we are not able to provide a permanently valid and fully comprehensive overview of these topics. We highlighted several measures of indirect structural disconnection and discussed some of their conceptual advantages and limitations. Yet, an extensive comparison of methods is so far lacking and we do not see any substantial limitations to any of the discussed methods of indirect disconnection estimation. Therefore, methods can be selected based on personal preference and their conceptual adequacy to answer your scientific questions. For example, if you hypothesize that disconnection of a cortical region should be relevant for a deficit, a region-based indirect disconnection measure is preferable over tract-wise or topographic disconnection measures. Moreover, we are optimistic that forthcoming innovations in fibre tracking will also quickly transfer to indirect disconnection measures and open up conceptually new or biologically more elaborated measures. Similarly, the presented information on statistical methodology focussed on a few well-established approaches that were, to some degree, evaluated for their use in lesion-symptom mapping. Our overview is not comprehensive and omits lesser popular, but also promising approaches such as Bayesian modelling (e.g., Achilles et al. 2017) or evolutionary algorithms (Li et al. 2021). Further, although previous evaluations of statistical methods focussed on voxel-wise structural lesion mapping, we are confident that the known advantages and disadvantages of the discussed methods largely transfer from structural lesion mapping to disconnection mapping. However, as addressed in our article, we believe that open questions on lesion-symptom mapping in general remain. Especially multivariate mapping is relatively recent and its advantages are still debated. Even though some empirical evaluations exist, we are unsure if any of the methods discussed in this article is generally optimal for all data types and deficits, and it might even be the case that a generally optimal algorithm does not exist at all. Therefore, we refrain from claiming any gold standards for statistical mapping. Instead, at the current point, we believe that the

well-informed use of any of the mentioned methods can be justified.

From theory to praxis

In this article, we provide readers with a theoretical overview of those methodological aspects of indirect disconnection-symptom mapping that are not covered by recent toolboxes. With the article at hand, a researcher should have sufficient background to understand basic concepts and plan the disconnection-wise analysis of neuropsychological data with structural imaging and behaviour. Nevertheless, a gap between the present article's general theoretical overview and the hands-on practical analysis remains. We intend to close this gap with a collection of tutorials in the supplementary and online materials at Mendeley Data (https://data.mendeley.com/datasets/hdzptzz8r5/2). This includes custom analysis scripts for univariate and multivariate analyses, guides on the use of statistic tools with disconnection data, software recommendations, and more.

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Data availability This review paper is accompanied by a collection of Matlab scripts available at Mendeley Data (https://data.mendeley.com/datasets/hdzptzz8r5/2). For more information, see the analysis tutorials in the online supplementary.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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