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Mapping functional brain organization: rethinking lesion symptom mapping and advanced neuroimaging methods in the understanding of human cognition

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1. INTRODUCTION

The current understanding of the functional architecture of the human brain is rooted in lesion symptom mapping studies linking lesion location to patients' cognitive impairments. Most introductory lectures in cognitive neuroscience at least briefly mention famous case studies such as Phineas Gage or Monsieur Leborgne to demonstrate how analyses of behavioural deficits in brain-damaged patients have shaped theories about human cognition. However, the bulk of data presented in cognitive neuroscience lectures comes from functional brain imaging or brain stimulation studies in healthy individuals, with the contribution of modern lesion symptom mapping work frequently overlooked. This gives an impression that lesion symptom mapping approaches are either relics from the past or tools nowadays used mainly by clinical neuropsychologists.

Lesion-symptom mapping was pioneered in the 19th century by anatomists such as Broca and Wernicke who based their discoveries on the detailed behavioural and cognitive examination of individual patients followed by subsequent post-mortem brain dissections. This approach remained largely unchanged for the best part of a century and lesion symptom mapping in 20th century still mainly reported data derived from examining relatively small groups of patients and coarse anatomical localisation of brain lesions. However, over the past thirty years, the introduction of non-invasive neuroimaging techniques together with the development of advanced computational and statistical approaches on the one hand have significantly revolutionized the lesion-symptom mapping approach in patients, whilst on the other hand, have expanded the exploration of brain-behaviour relationships through the study of healthy individuals. This has gradually resulted in questions being raised as to what extent lesion mapping is still relevant to our understanding of the functional architecture of human cognition (see also Adolphs, 2016; Rorden & Karnath, 2004).

Perhaps the use of lesion data to infer brain organization is now outdated and no longer needed in the era of advanced neuroimaging techniques and computational methods. Why investigate idiosyncratic individual patients or groups of difficult to recruit patients when it is possible to study easily large cohorts of healthy brains with a precision much greater than with lesion-symptom mapping? The aim of this special issue is to address these questions through a comprehensive critical review of modern lesion-symptom mapping methods, by providing examples of their ongoing role in mapping functional brain organization and by contrasting neuropsychological patient studies with alternative methods based on technical advances in neuroimaging healthy brains and studies using animal models. This special issue will also take a look at whether improving lesion symptom mapping methods based on mass-univariate statistical approaches as well as more recently popularized methods utilizing multivariate decoding, track-wise lesion symptom mapping and diffusion tractography could potentially reshape lesion symptom mapping and increase its relevance to modern cognitive neuroscience. In this editorial, we highlight some of the themes that emerged through the submitted papers (7 reviews and 13 original research reports) which we divide here accordingly into four sections: i) Lesion symptom mapping methods and applications; ii) Methodological advances in lesion symptom mapping; iii) Mapping white matter disconnections; and iv) Human brain mapping: beyond lesion-deficit analysis.

2. Lesion-symptom mapping methods and applications

The key advantage of lesion-symptom mapping approaches is the ability to infer directly the function of a discrete brain region based on observed cognitive deficits. Since the pioneering work by Broca and Wernicke, lesion symptom mapping methods have gradually evolved and single case studies based on post-mortem dissections have been replaced initially by lesion overlap/lesion subtraction methods and more recently by voxel-based statistical analyses linking neuroimaging and behavioural data in large groups of neuropsychological patients (Rorden & Karnath, 2004). The first paper in this special issue (de Haan & Karnath, 2017) presents a comprehensive overview of widely used lesion symptom mapping methods together with practical guidelines for conducting lesion-symptom mapping studies starting with the selection of patients, visualization and demarcation of brain damage, the choice of appropriate statistical analysis tools and ending with the interpretation of results. The authors discuss the pros and cons of different approaches and emphasize the importance of careful planning, pinpointing for example the weight of lesion visualization and lesion delineation methods in subsequent interpretation of findings. This excellent practical guide is succeeded by a critical review of factors affecting the validity of currently used voxel-based lesion-symptom mapping (VLSM) approaches (e.g., Bates, et al., 2003; Rorden, Karnath, & Bonilha, 2007) as well as methods for testing the validity of conclusions derived from lesion symptom mapping (Sperber & Karnath, 2017). The discussed issue of the validity of lesion-symptom mapping is of particular interest not only from the point of view of reported inconsistencies between different lesion studies but also in facilitating comparisons between lesion-symptom mapping and functional brain imaging as well as brain stimulation studies in healthy individuals.

Following the first two papers introducing the concept of lesion symptom and voxel-wise statistical analysis methods, the next three studies included in this special issue present examples of the application of the VLSM methods to isolate neural substrates of verbal working memory tasks (Ivanova, et al., 2018), spatial perseveration (Kaufmann, et al., 2018) and single-word versus sentence-level reading and writing (Baldo, et al., 2018). In VLSM analysis, for each voxel, patients are separated into two groups according to the presence or absence of a lesion and subsequently a statistical map is produced in which each voxel is assigned the value of the statistical test assessing the behavioural performance of the two groups (Bates, et al., 2003; Rorden, et al., 2007). While VLSM methods are used to examine the association between cognitive deficits and discrete lesion location and therefore are the most relevant for mapping functional brain organization, a different approach based on categorically grouping patients based on a common lesion location, or the presence or absence of a lesion within a particular region of interest is often used by cognitive neuropsychologists to decompose different cognitive components associated with heterogeneous neurological syndromes e.g., unilateral neglect (see for example Saj, Verdon, Hauert, & Vuilleumier, 2018 in this special issue).

Although lesion symptom mapping has been traditionally used as a method of progressing our understanding of human cognition (human brain mapping) and the neuroanatomy of neurological disorders following brain damage, the lesion-symptom mapping methods have been also used to validate specific neuropsychological tests for the assessment of discrete cognitive functions (e.g., executive function by the Cognitive Estimation Test; see Cipolotti, et al., 2017 in this special issue), in decomposing cognitive mechanisms underlying distinct deficits in performance of specific behavioural tasks (e.g. figure drawing Chechlacz, et al., 2014; trial making test Varjacic, Mantini, Demeyere, & Gillebert, 2018 in this special issue) and to assess the prospects of recovery following brain damage (e.g., recovery of language function following stroke; Crinion, Holland, Copland, Thompson, & Hillis, 2013; Forkel & Catani, 2018 in this special issue). It is worth noting here that the issue of the validity of tests used for assessment of specific cognitive functions and consistency of cognitive assessment (eloquently illustrated here by Cipolotti, et al., 2017 and Ivanova, et al., 2018) is critical in lesion-symptom mapping as inappropriate use of clinical tools and/or scoring methods as well as use of non-specific shallow tests might result in erroneous findings (for further commentary see also other included here papers; de Haan & Karnath, 2017; Sperber & Karnath, 2017; Varjacic, et al., 2018).

3. Methodological advances in lesion symptom mapping

The key step in the development of modern lesion symptom mapping was the introduction of the mass-univariate voxel-wise statistical analysis methods such as VLSM (Bates, et al., 2003; Rorden, et al., 2007) but this approach is not without certain limitations. While the two review papers opening this special issue (de Haan & Karnath, 2017; Sperber & Karnath, 2017) provide an overview of how erroneous application of voxel-wise lesion methods and ignoring its limitations could easily lead to spurious and heterogeneous findings, three empirical papers that follow (Gajardo-Vidal, et al., 2018; Lorca-Puls, et al., 2018; Mirman, et al., 2017) not only provide relevant examples but also suggest potential improvements. The first of these papers is a cautionary tale, which based on bootstrap methods, convincingly demonstrates the effect of sample size on reproducibility of lesion symptom mapping, and how the reported findings might vary despite the analysis methods and behavioural assessments being held constant between studies (Lorca-Puls, et al., 2018). Another issue greatly affecting validity of results is the accurate application of correction for multiple comparisons. In their paper Mirman et al (2017) not only comprehensively discuss this issue but also present a viable solution in the form of the novel continuous permutation-based FWER (voxel-level family-wise error rate) correction method. The last of the three empirical papers provides compelling evidence as to how false negative results in lesion symptom mapping might arise when particular cognitive functions are sub-served by widely-distributed neural networks and thus the same cognitive deficits might be caused by damage to different brain regions (Gajardo-Vidal, et al., 2018). Furthermore, Gajardo-Vidal and colleagues not only suggest a potential solution to overcome this limitation based on the interactive mass-univariate approach, but also advocate the necessity of supplementing findings from the univariate analysis by mapping white matter disconnections and/or the use of multivariate approaches (Gajardo-Vidal, et al., 2018).

Indeed, in the last few years, the effectiveness and validity of the mass-univariate approaches to human brain mapping has been increasingly criticized, and many recent studies strongly promote the use of multivariate decoding and computational modelling of data (Herbet, Lafargue, & Duffau, 2015; Karnath & Smith, 2014; Mah, Husain, Rees, & Nachev, 2014, 2015; Nachev, 2015; Smith, Clithero, Rorden, & Karnath, 2013). While some of the commentaries and original work published to date only point to the limitations of univariate approaches in lesion mapping analysis arising from complex architecture of neural networks i.e., cognitive functions being sub-served by widely distributed networks interconnected by white matter pathways (e.g., Gajardo-Vidal, et al., 2018; Herbet, et al., 2015; Karnath & Smith, 2014; Smith, et al., 2013), others argue that the problem lies not in the complex functional architecture of the brain but in the complex structural architecture of lesions (e.g., Mah, et al., 2014, 2015; Nachev, 2015). The later point of view is thoroughly and elegantly elucidated here by Xu, Jha and Nachev (2017). The two following empirical papers propose different approaches to multivariate inference in lesion symptom mapping. One utilizes an inference approach based on game theory (Multi-perturbation Shapley value Analysis, MSA) to decompose functional contributions from multi-lesion patterns (Malherbe, et al., 2017) and the other presents a multivariate optimization technique, a sparse canonical correlation analysis for neuroimaging (SCCAN) to overcome lesion-symptom mapping limitations and the heterogeneity of findings arising from functional dependency on single versus multiple areas, lesion patterns following vascular rather than functional territories, as well as differences in sample size and used thresholding mechanisms (Pustina, Avants, Faseyitan, Medaglia, & Coslett, 2017).

4. Mapping white matter disconnections

To a large extent various cognitive functions rely on widely distributed neuronal networks sub-served by long association and commissural white matter pathways (Makris, et al., 2005; Petrides & Pandya, 2006; Schmahmann & Pandya, 2006). Therefore, not surprisingly, development of diffusion tractography methods enabling the non-invasive mapping of white matter pathways in the living human brain (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Le Bihan, et al., 2001; Mori & van Zijl, 2002), recent popularization of the concept of the disconnection syndrome (Catani & Ffytche, 2005; Catani & Mesulam, 2008), and finally the introduction of track-wise lesion deficit analysis methods allowing the capture of the interaction between white matter damage and observed cognitive deficits (Foulon, et al., 2018; Thiebaut de Schotten, et al., 2014) have had a substantial impact on the field of the lesion-symptom mapping. The concept of disconnection syndrome is predominantly used to describe disorders of higher cognitive function resulting from a breakdown of associative connections between cortical areas due to white matter lesions (Catani & Ffytche, 2005; Catani & Mesulam, 2008; see also Kleinschmidt & Vuilleumier, 2013 for a critical commentary on the recent resurgence of the term disconnection syndrome). Thus, in practical terms, mapping of the white matter damage in neuropsychological patients on the one hand can expand the understanding of the critical lesions underlying observed behavioural deficits and on the other hand has also the potential to increase the understanding of the organization of the neural networks sub-serving specific cognitive functions. Four papers included in this special issue provide excellent examples of the application of either diffusion tractography or tract-wise lesion deficit analysis in mapping predictors of heterogeneous deficits in visual neglect (Toba, et al., 2017), aphasia recovery (Forkel & Catani, 2018) as well as white matter pathways underlying verbal working memory (Ivanova, et al., 2018) and face-based mentalizing (Nakajima, Yordanova, Duffau, & Herbet, 2018).

5. Human brain mapping: beyond lesion-deficit analysis.

It could be argued that the development of new neuroimaging techniques such as fMRI (functional magnetic resonance imaging), diffusion imaging, EEG (electroencephalography), MEG (magnetoencephalography), TMS (transcranial magnetic stimulation) and tES (transcranial electrical stimulation) and associated statistical and image processing methods have not only opened up the prospect of linking discrete cognitive functions to specific brain regions and neuronal networks, but perhaps also of stimulated the improvement of lesion-symptom mapping approaches, in particular by introducing more stringent voxel-wise statistical analysis methods, the use of new imaging modalities for lesion visualization as well as modern image processing tools and most recently new computational and multi-variate data processing approaches as illustrated by several papers compiled in this special issue.

Different neuroimaging techniques come with a set of specific advantages as well as limitations (e.g., Coltheart, 2006; Hari, Levanen, & Raij, 2000; Henson, 2005; Pascual-Leone, Walsh, & Rothwell, 2000; Paulus, 2011) and the use of each of them separately to infer functional brain organization and human cognition so far has failed to provide a complete picture. Therefore, not surprisingly multimodal approaches and combining evidence obtained through different methods are increasingly gaining popularity among basic cognitive neuroscientists interested in functional brain mapping as well as neuropsychologists and neurologists striving to understand the neuroanatomy of cognitive disorders. Three papers included in this special issue touch on the use of other modalities to infer human cognition and the converging evidence arising from lesion-symptom mapping and functional brain imaging or brain stimulation studies in healthy individuals, as well as discuss potential causes of discrepancies in findings derived based on different techniques (Petitet, O'Reilly, & O'Shea, 2017; Pleger & Timmann, 2018; Varjacic, et al., 2018).

Last but not least Bell and Bultidue (2017) make an excellent contribution to this special issue by presenting a compelling case for combining lessons from animal models with findings from human studies, as a way to fully elucidate neural mechanisms underlying human cognition as well as to further the understanding of the effects triggered by brain stimulation and pharmacological interventions (Bell & Bultitude, 2017).

6. Conclusions

It was our intention that this special issue would uphold lesion symptom mapping as a research tool not without limitations, but nevertheless, deserving its place among more recent neuroimaging and brain stimulation techniques, and thus worthy of consideration by modern cognitive neuroscientists. Furthermore, we hope that this special issue will stimulate new research taking full advantage of methodological developments based on computational modelling and multivariate decoding to better capture the multi-dimensionality of brain networks, lesions and behavioural data (Corbetta, Siegel, & Shulman, 2018; Herbet, et al., 2015; Mah, et al., 2015; Nachev, 2015).

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