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Commentary

Rethinking voxel-wise lesion-deficit analysis: A new challenge for computational neuropsychology

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This commentary refers to the recent study published in *Brain* entitled 'Human brain lesion-deficit inference re-mapped', by Mah et al. (http://dx.doi.org/10.1093/brain/awu164).

Over the two past decades, large-scale neuropsychological studies have permitted to gain considerable insights into the anatomical architecture of complex neurocognitive systems. A part of this advance in knowledge has often been associated with the development of sophisticated and powerful lesion data analysis techniques, such as voxel-based lesion-symptom mapping (Bates et al., 2003; Damasio & Frank, 1992). Such analyses are becoming increasingly used by neuroscientists (having regard to the tends of published papers using lesion-deficit mapping in journals with a broad audience such as *Brain*, *Cortex*, or *Cerebral Cortex*), mainly because they enable in principle to minimize or override a number of methodological shortcomings inherent to the classical lesion method (e.g., region-of-interest analysis necessitating prior knowledge or assumptions, low number of patients, inhomogeneous spatial distribution of lesions). However, one should not lose sight of the fact that voxel-wise lesion-deficit analysis suffers from a number of weaknesses often discussed (see for instance Rorden & Karnath, 2004) but not further addressed. From a methodological standpoint, it is therefore time to tackle the existing gaps in the technique in order to improve the validity of the resulting brain-behavioural inferences. In this context, the study of (Mah, Husain, Rees, & Nachev, 2014) is timely and convincingly demonstrates the necessity to refine the way in which neuroscientists process lesion data.

The fundamental problem in voxelwise lesion-deficit analyses is related to the statistical approach used. Schematically, a one-tailed statistical test (parametric or non-parametric) is performed to compare the behavioural performance of patients having a given voxel damaged versus the behavioural performance of patients not having that voxel damaged. This procedure is repeated for each voxel taken into account in the analyses, allowing to generate probabilistic maps of brain–behaviour relationships. The condition of application of this 'mass-univariate' approach (each statistical test is performed independently across voxels) should be that the spatial distribution of lesions is random (i.e., all voxels have the same probability to be affected by the lesion) and, importantly, that damage to a particular voxel is fully independent to damage to other voxels. However, as highlighted by Mah, Husain, et al. (2014), but also previously by Husain and Nachev (2007) or others (e.g., Bartolomeo, 2011), this is not the case; lesion distributions are anatomically constrained for biological reasons. This is true for ischemic strokes which typically damage brain structures sculpting the sylvian fissure (brain territories mainly supplied by the middle cerebral artery which are especially vulnerable to ischemia), but also for other neuropsychological conditions such as, for instance, diffuse low-grade glioma which preferentially invalidate the posterior medial frontal cortex and the fronto-

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insular regions (Duffau & Capelle, 2004). As a result, this raises the issue of how consider, from a statistical standpoint, a lesioned voxel given that a collection of contiguous voxels (sometimes very distant at the anatomical scale because of the typically large size of lesions) may be also affected by the same lesion and that in a stereotyped manner across patients. Yet these collaterally damaged voxels are likely to not share any relations with the process of interest, potentially affecting the spatial validity of brain-behaviour statistical maps (i.e., displacement of brain–behavioural loci). Traditional approaches to lesion mapping do not deal with the problem of the non-independence of voxels.

In their work, Mah and colleagues have studied 'the impact of high-dimensional lesion pattern inhomogeneities on lesion mapping' using a huge structural imaging dataset from a cohort de 581 ischemic stroke patients. Specifically, the authors have sought to assess whether stereotyped patterns of brain damage can insidiously displace the spatial locations of significant lesion-symptom relations. Lesions were mapped using a newly fully-automated procedure (see Mah, Jager, Kennard, Husain, & Nachev, 2014). The results of this modelling study are quite impressive and should not be overlooked. Through an innovative approach based on machine learning, the authors succeeded in quantifying and modelling the spatial biases (in terms of magnitude and direction) due to the intrinsic multivariate nature of lesion distributions. The results are displayed in the form of a three-dimensional vector plot and show that mislocalization seems to be tightly related to the spatial structure of the neurovascular system.

While the study of Mah, Husain, et al. (2014) has the merit of pinpointing a weighty limitation in the inferences carried out by voxel-wise lesion-deficit analyses, an aspect not addressed by their work (which is downstream of the problem identified by the authors) is related to the potential impact of white-matter fibre disconnection in the spatial validity of the lesion-deficit maps. The importance of this largely neglected is substantial for the very reason that lesion centres are almost all located on the spatial course of associative pathways (purely cortical focal damages are extremely rare); and current knowledge gained from anatomic dissection and tractography reconstruction studies shows that associative connectivity is highly organized into multiple subnetworks. For instance, the inferior fronto-occipital fasciculus is a large-scale and complex pathway interconnecting almost all prefrontal areas to occipital, temporal and superior parietal regions (Caverzasi, Papinutto, Amirbekian, Berger, & Henry, 2014; Martino, Brogna, Robles, Vergani, & Duffau, 2010; Sarubbo, De Benedictis, Maldonado, Basso, & Duffau, 2013). This ventral connectivity is at least composed of two layers (the superficial and the deep one), differentially involved in semantic processing (modality-specific *vs* amodal semantic processes) (Duffau, Herbet, & Moritz-Gasser, 2013; Moritz-Gasser, Herbet, & Duffau, 2013) or even in mentalizing (Herbet, Lafargue, Moritz-Gasser, Bonnetblanc, & Duffau, 2014) – as evidenced by data from axonal mapping in awake surgery. As a result, depending of which subnetwork is disrupted, a 'similar' lesion may lead to different clinical signs due to widespread disruption of functional connectivity between specific cortical nodes.

While at present we do not known exactly the weight that should be given to dis-connective damage in the occurrence of functional disturbances in lesion mapping studies, a few recent studies has nonetheless brought important clues in this respect, by demonstrating that the behavioural counterpart of disconnection is at the very least significant. Typically, these studies have mixed conventional voxelwise and supplemental tractwise lesion-deficit analyses [based, in the latter case, on fine-grained tractography-based white matter fibre atlas (Catani & Thiebaut de Schotten, 2008; Thiebaut de Schotten et al., 2011)]. Even if not still perfect, such a dual-strategy (see Rudrauf, Mehta, and Grabowski (2008) for the first interesting attempt) has enabled to gain major insights into the functional anatomy of associative connectivity. For instance, Thiebaut de Schotten et al. (2014) have shown that the most reliable predictor of chronic spatial neglect was a disconnection of the layer II of the right superior longitudinal fasciculus (see also Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Thiebaut de Schotten et al., 2008). In the same vein, Herbet, Lafargue, Bonnetblanc, et al. (2014) has provided evidence that the degree of disconnection of the right perisylvian white matter network (including the arcuate and the lateral superior longitudinal fasciculus) and the right cingulum was respectively associated with a decrease in low-level, face-based and high-level, inference-based mentalizing performance – laying the foundation for a dual-stream model of mentalizing processes. The findings from these studies, but also from other in different domains such as emotion recognition (Philippi, Mehta, Grabowski, & Adolphs, 2009) or language (Almairac, Herbet, Moritz-Gasser, de Champfleur, & Duffau, 2014; Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013), should prompt researchers to reflect more deeply on how combining voxel-wise and tract-wise statistics *in the same analysis* in order to fairly gauge the contribution of white-matter damage in the emergence of neuropsychological impairments (Bartolomeo, 2012). This endeavour is nothing less than challenging because of the very nature of the mechanisms involved. Damage to white matter connectivity leads to a hodological (non-localized) functional disruption (Catani & Ffytche, 2005; Catani & Mesulam, 2008a; Catani et al., 2012) (i.e., disruption of the inter-regional communication between two or several cortical nodes). Typically, vascular lesions spread over large territories, generally affecting both white matter and cortex. In this context, clinical symptoms due to associative disconnection may be mistakenly attributed to cortical structures which are collaterally damaged, but not involved in the function of interest (Bartolomeo, 2011). This problem is exacerbated by the fact that functional impairments are theoretically reproducible after disconnection of any parts of a given associative pathway (Bartolomeo, 2012) – a well-known fact in awake surgery for glioma (i.e., stimulating white matter fibres at any locations of the same fasciculus results in the same neuropsychological stimulation). This is precisely for these reasons that lesion-induced behavioural variance related to disconnection can induce considerable spatial distortions in the location of significant brain–behavioural relationships, because not only of the internal structures of lesions (Mah, Husain, et al., 2014) but for the reason of long-range disconnective breakdown – not taken into account in conventional voxelwise analyses that remains in essence purely *topological*. Following Geshwind (1965) and Mesulam (1998),