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LETTER TO THE EDITOR

Reply: Lesion network mapping: where do we go from here?

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In a letter to the editor, Dr Aaron Boes (2020) commented on our study (Salvalaggio *et al.*, 2020) in which we compared different structural and functional MRI methods to predict behavioural deficits in a large cohort of subacute stroke patients (Corbetta *et al.*, 2015). Specifically, we used lesion symptom mapping, i.e. the behavioural prediction based on lesion location and volume, as a baseline for three methods measuring brain network(s) disconnection. Two methods assessed disconnection 'indirectly' using the lesion to generate maps of altered connectivity based on healthy control datasets (7 T 'Human Connectome Project' datasets: http://www.humanconnectome.org/study/hcp-young-adult/; Vu *et al.*, 2015). We computed structural disconnection of white matter pathways (SDC) and functional disconnection of brain networks (FDC), or lesion network mapping (Boes *et al.*, 2015). The third method measured patterns of altered functional connectivity directly based on the temporal correlation of the spontaneous blood oxygen level-dependent (BOLD) signal. Our results showed comparably high behavioural prediction for lesion, SDC, and functional connectivity, but a weak prediction for FDC. We concluded that FDC might be used to localize abnormal networks, but its low sensitivity to the severity of behavioural deficits implies that it cannot predict behaviour or recovery of function, nor be a substitute for direct functional MRI functional connectivity.

We want to thank Dr Boes for his interest and for highlighting the relevance of our analysis to the quantitative evaluation of lesion network mapping, a method proposed for the evaluation of network dysfunction in neurological and psychiatric disorders (Fox, 2018). Dr Boes reminded us that the method, originally designed to identify cortical network dysfunction caused by small subcortical lesions (Boes *et al.*, 2015), may not be suited for large cortico-subcortical strokes that encompass grey and white matter and that represent most patients in Salvalaggio *et al.* (2020).

The white matter BOLD signal is about a quarter of the amplitude of the grey matter signal, which in principle leads to weaker temporal correlation maps at the cortical level, the procedure used in lesion network mapping. However, recent studies have shown topographic-specific cortical networks derived from BOLD signals derived from specific regions of the white matter (Peer *et al.*, 2017; Huang *et al.*, 2018; Li *et al.*, 2019).

We agree that the mixture of grey and white matter damage in large lesions is essential for the low accuracy of behavioural predictions derived from FDC maps. In the article, we qualitatively discussed this issue by contrasting lesions that cause visual field versus motor deficits. In the former case, the most predictive lesions damaged the lateral occipital cortex. Correspondingly, FDC showed a beautiful map of the Visual network that was strongly predictive of

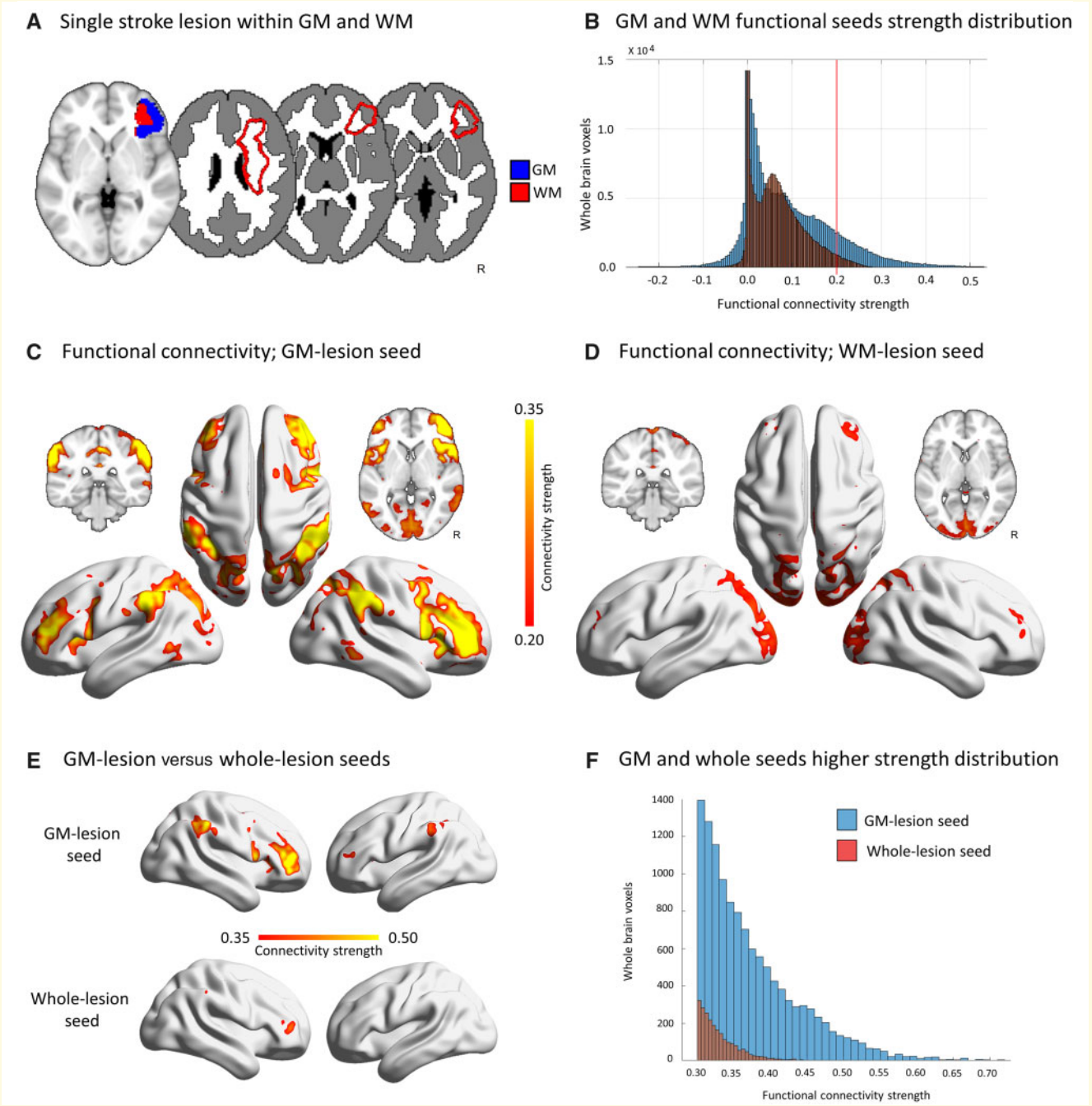

Figure 1 Indirect functional connectivity maps estimated using grey and white matter regions lesioned by a single stroke as seeds. Indirect functional maps were computed from a set of healthy controls (see Salvalaggio *et al.*, 2020 for details). (**A**) Stroke lesion segmentation (red) overlapping with grey matter (grey mask) and white matter (white mask). The Harvard cortical and subcortical template was used to compute tissue-lesion seed regions of interest, which were subsequently used to compute mean functional connectivity maps. (**B**) Whole brain mean functional connectivity strength (Pearson's correlation) for each tissue regions of interest shows a different distribution pattern: stronger values (e.g. >0.20) are more frequent in the grey matter seed map compared to the white matter seed map (distributions of 0 values are truncated to improve visualization). (**C**) Spatial grey matter seed mean functional connectivity map. (**D**) Spatial white matter seed mean functional connectivity map. (**E**) Visual comparison between spatial grey matter seed functional connectivity map and mean functional connectivity computed using the whole stroke lesion as seed region of interest (i.e. averaging grey and white matter signals). Clusters showing higher connectivity strength (>0.30) in the grey matter seed map are not represented in the whole-seed map. (**F**) Distribution of the higher connectivity strength values (>0.30) separately for grey matter seed and whole-seed network maps. GM = grey matter; WM = white matter.

behaviour (R^2 = 0.38; Fig. 2 in Salvalaggio *et al.*). In the latter case, motor deficits were most severe for lesions affecting the white matter's corona radiata. Correspondingly, motor FDC maps were less specific and accounted for less behavioural variability (R^2 = 0.12; Fig. 3 in Salvalaggio *et al.*). Moreover, lesion maps for language involving even more extensive white and grey matter perisylvian regions yielded FDC maps with no predictive value for the severity of deficit (R^2 = 0.06; Fig. 6 in Salvalaggio *et al.*).

We are currently investigating this issue quantitatively. Figure 1A shows a single stroke lesion that encompasses the grey matter of the right frontal cortex and the underlying white matter extending to the periventricular region. The two subregions can be segmented, and each subregion used as a region of interest for a whole brain functional connectivity analysis in healthy controls. Interestingly, the distribution of Fisher *z*-correlation values is significantly higher from grey matter than white matter region of interest (Fig. 1B). These differences are more pronounced when considering higher functional connectivity values (e.g. Pearson's correlation values >0.2). These regions of high correlation are those estimated as more functionally disconnected in lesion network mapping. Possibly more reliable functional connectivity values from white matter regions of interest will be derived when centring the regions of interest on recently identified white matter functional systems (Peer *et al.*, 2017). Inspection of the whole-brain functional connectivity maps shows more robust networks for grey matter regions of interest, and even diverging networks for grey and white matter regions of interest (Fig. 1C and D). Critically, we obtain more significant maps and distribution of inter-regional functional connectivity scores with higher means and standard deviation when the region of interest includes only damaged grey matter voxels compared to the whole lesioned region as in the standard lesion network mapping approach (Fig. 1E and F). This loss of strength and variability inevitably affects behavioural prediction.

These preliminary results are consistent with Dr Boes' and our suggestion that mixing BOLD signals from white and grey matter, or different cortical networks, may weaken the resulting functional connectivity maps. However, it remains to be seen whether these effects will also solve the low spatial variability or dimensionality of FDC maps, which further weakens these maps' ability to predict the variability of behavioural scores.

Note, however, that low dimensionality is a not *a priori* a negative feature of FDC maps. Multivariate machine learning methods suffer from the well-known 'curse of dimensionality' when applied to relatively small samples. Low dimensionality prevents overfitting and promotes out-of-sample generalization, a prerequisite for any clinical application. Low dimensionality *per se* does not seem to be the problem, as FDC-based models predicted from 0 to 52% of the variance (for different domains) using the same (small) number of input components (Salvalaggio *et al.*, 2020). Nevertheless, the FDC method generates maps with low spatial variability for many networks, which implies small between-patient variability and low predictive accuracy.

Dr Boes also suggested different strategies to improve lesion network mapping. His idea of describing lesions based on the parcellated white matter or cortical connectomes may yield more specific lesion network mapping solving the issue of network signal mixing.

More generally, the methodology for indirectly assessing disconnection (structural or functional) is likely not optimal. As noted in another commentary to our paper (Umarova and Thomalla, 2020), the results are susceptible to even slight changes in parameter settings. Other concerns raised include different sample sizes and flexible threshold selection applied to the maps (Sperber and Dadashi, 2020).

Finally, we suggest that even though lesion network mapping, and indirect methods for assessing structural-functional disconnection, are motivated by the objective difficulty of measuring functional MRI and diffusion imaging in acute neurological or psychiatric patients, or rare patient groups, we believe it possible to set up protocols that capture this information as part of routine clinical scans. Automated pipelines can then derive high-quality maps of functional or structural disconnection (Griffis *et al.*, 2020). We believe that direct measures of structural and functional disconnection are possible and should become part of clinical practice. This effort will be especially valuable to guide novel interventions for post-stroke behavioural deficits.

Data availability

The data that support the illustrative example in Fig. 1 are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

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