

## LETTER TO THE EDITOR

### Reply: Heterogeneous neuroimaging findings, damage propagation and connectivity: an integrative view

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Sir,

We thank Cauda *et al.* (2019) for their letter discussing the implications of our recent paper in which we showed that seemingly heterogeneous neuroimaging findings are reproducible to common brain networks (Darby *et al.*, 2018a). The authors propose a generalized ‘pathoconnectivity model’ for understanding brain diseases. They suggest three implications of their model, which we respond to below.

We agree with Cauda *et al.* (2019) that network localization matches symptoms, not underlying pathology. We investigated neuroimaging studies of patients with the same clinical dementia syndromes, but not necessarily the same underlying neuropathological diagnosis. For instance, patients with behavioral variant frontotemporal dementia can have either tau or TDP-43 pathology, and patients with corticobasal syndrome can have either tau or Alzheimer’s pathology, yet these different pathologies result in similar clinical symptoms and localize to the same brain network. Second, we found common network localization for delusions in patients with brain lesions and Alzheimer’s disease (Darby *et al.*, 2018a), and for disordered free will perception in patients with brain lesions and psychiatric diseases like catatonia, non-epileptic

seizures, and conversion disorder (Darby *et al.*, 2018b). These results and others support the idea that neuropsychiatric symptoms localize to common brain networks regardless of the underlying pathology or diagnosis.

We also agree that there is a hierarchical structure to brain-behavior relationships matching the structure of the human connectome. Prior studies have suggested that simple neurological symptoms localize to specific brain regions, while more complex symptoms localize to brain networks (Siegel *et al.*, 2016). Similarly, we found previously that lesions causing delusions localized to one brain network, but lesions causing a specific and complex type of delusion (delusional misidentifications) were also part of a second brain network related to the content of the delusion, suggesting an internetwork localization (Darby *et al.*, 2017). Finally, prior studies have related consciousness to global changes across the entire brain/connectome (Chennu *et al.*, 2017). This prior work supports the hypothesis that different symptoms may localize to different levels of brain organization (i.e. regional, subnetwork, network, internetwork, and global levels).

However, we disagree with Cauda *et al.* (2019) that the reasons for network localization in focal brain lesions and neurodegenerative disorders are different. It is true that

some mechanisms proposed to account for network localization in neurodegenerative disease may not apply to network localization of focal brain lesions, such as prion-like spread of misfolded proteins (Seeley *et al.*, 2009; Zhou *et al.*, 2012). However, most mechanisms proposed to account for network localization of focal brain lesions could apply to network localization of neurodegenerative disease, such as diaschisis (Carrera and Tononi, 2014; Fox, 2018). Heterogeneity of lesion locations across different patients with the same symptom may be analogous to the heterogeneity of neurodegenerative ‘epicentres’ across different patients with similar symptoms, which may be analogous to heterogeneous neuroimaging findings across different studies of that symptom. This possibility is supported by our finding that lesions and dementia studies investigating the same clinical symptom (delusions) had the same network localization (Darby *et al.*, 2018a). As such, while we agree that different mechanisms ‘may’ underlie network localization of lesions and neurodegenerative disease, a common mechanism is also possible, and this convergence could have important implications for understanding brain disease in general.

In summary, we thank the authors for discussing how our paper on network localization of heterogeneous neuroimaging findings contributes to a broader theory on understanding brain behavior relationships. We agree with the authors that (i) network localization is not disease specific, and can be used to localize common symptoms across different neurological and psychiatric diseases; and (ii) specific symptoms may localize to different levels of the connectome, based on the complexity of the cognitive processes involved. Whether the mechanisms underlying network localization of focal brain lesions, neurodegenerative epicenters, and heterogeneous neuroimaging findings are the same or different requires further work.

## Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this work.

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## Competing interests

The authors report no competing interests.

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