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LETTER TO THE EDITOR

Reply: Capgras syndrome: neuroanatomical assessment of brain MRI findings in an adolescent patient

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Sir,

We would like to thank Ferguson *et al.* 2017 for their interesting letter regarding a 16-year-old male patient with a 1-year prodrome of progressive social isolation, agitation, and delusional beliefs who developed the delusion that his parents had been replaced by imposters (Capgras syndrome). Work-up revealed a small area of gliosis in the left frontal periventricular white matter of indeterminate age. This lesion location appeared to have a different connectivity profile from the 16 lesions included in our recent publication (Darby *et al.*, 2017), raising the possibility of an alternate neuroanatomical substrate for delusional misidentifications.

This case highlights an increasingly common clinical conundrum: is an abnormality identified on MRI causally related to the patient's symptoms or an incidental finding (Vernooij *et al.*, 2007; Morris *et al.*, 2009; Gupta *et al.*, 2016)? Answering this question is particularly difficult for symptoms such as Capgras delusion, which can be due to lesions in multiple different brain locations (Darby *et al.*, 2017), but can also be due to primary psychiatric disease (Kirov *et al.*, 1994; Salvatore *et al.*, 2014). In fact, psychiatric disease is a much more common cause of Capgras delusion than focal brain lesions (Förstl *et al.*, 1991).

Motivated by the case of Ferguson *et al.*, we performed additional analyses to determine whether lesion network mapping could help determine the probability that a brain lesion is causally associated with a patient's symptom. We identified new cases of delusional misidentifications with brain lesions that failed to meet inclusion criteria for our initial publication. These cases were divided into two groups based on the clinical probability that the lesion caused the delusional misidentification and compared to the network topography in our previous paper (Darby *et al.*, 2017).

Materials and methods

Case selection

Lesions identified using our initial search criteria (Darby *et al.*, 2017), but excluded from our original analysis were analysed. Of these excluded lesions, we identified a high probability group and a low probability group based on the clinical likelihood that the lesion caused the delusion. The high probability group included four cases with no history of neuropsychiatric symptoms, acute onset of delusional misidentifications without other psychotic symptoms, and symptom onset within 3 months of a focal brain lesion (Box *et al.*, 1999; Feinberg *et al.*, 1999; Moreira *et al.*, 2010; Pignat *et al.*, 2013). The only difference between this high probability group and our original cohort was lesion aetiology (stroke versus trauma/

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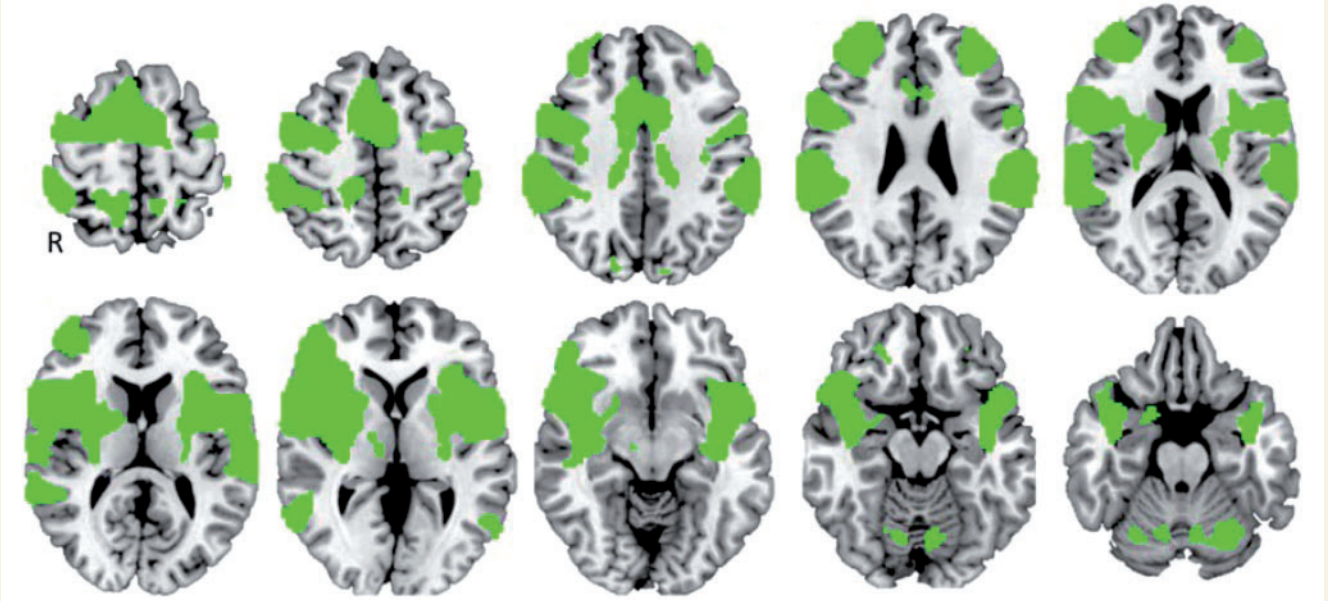

Figure 1 Predicted 'delusional misidentification map'. Regions where lesions would be predicted to cause delusional misidentifications due to positive connectivity with the right ventral frontal cortex and negative connectivity with the left retrosplenial cortex. MNI *z* coordinates (from *left* to *right*, *top* to *bottom*): 61, 52, 38, 27, 16, 13, 3, −10, −15, −22.

oedema). The low probability group included four cases with a history of psychiatric symptoms and unclear temporal relationship between the lesion and the delusional misidentification (Lewis, 1987; Hospital, 2007; Turkiewicz *et al.*, 2009). The case of Ferguson *et al.* was included in this group.

Predictive map

We generated a map of brain regions where strokes would be predicted to result in delusional misidentifications. To generate this map, we created a 4 mm radius spherical region of interest centred at peak region of positive connectivity (right ventral frontal cortex, MNI coordinates $x = 54$, $y = 14$, $z = 10$) and negative connectivity (left retrosplenial cortex, MNI coordinates $x = 6$, $y = 56$, $z = 12$) from our prior study of lesion-induced delusional misidentifications (Darby *et al.*, 2017). Functional connectivity maps for each region of interest were generated and combined to identify voxels both positively correlated with the right ventral frontal cortex and anti-correlated with the left retrosplenial cortex at a threshold of $t > 4.25$, $P < 0.00005$ uncorrected (Fig. 1). Based on our original report (Darby *et al.*, 2017), lesion locations causing delusional misidentifications should fall within this 'delusional misidentification network'.

Neuroimaging analysis

Each lesion was traced onto a standardized brain template and compared with the above delusional misidentification network to identify areas of overlap. To test this relationship quantitatively, we determined the strength of connectivity between each lesion location and our seed regions of interest in the ventral frontal cortex and retrosplenial cortex (Darby *et al.*, 2017). Resulting *r*-values were converted to a normal distribution using Fischer's *r* to *z* transform and averaged across our high probability and low probability cohorts. We tested for significant differences from zero and significant differences between cohorts using a two-tailed *t*-test. All statistics were performed using STATA (College Station, TX, version 14.0). Of note, the current analyses utilized a larger normative connectome dataset ($n = 1000$ subjects) (Yeo *et al.*, 2011), which included the 98 subjects from the connectome dataset from our original publication (Darby *et al.*, 2017).

Results

Regions where lesions predicted to cause delusional misidentifications

The distribution of voxels within our 'delusional misidentification network' is shown Fig. 1 and available upon request. As expected, this network overlaps the lesion locations from our original cohort of 17 causal lesions (Fig. 2A).

The lesion presented by Ferguson *et al.* did not fall within the regions predicted to result in delusional misidentifications (Fig. 2B, left). There was no significant connectivity between the brain lesion and either the right ventral frontal cortex ($r = -0.01$), or the left retrosplenial cortex ($r = 0.0009$).

Causal versus non-causal brain lesions

The group of low probability lesions showed little overlap with our delusional misidentification network (Fig. 2B), while the high probability lesions showed similar overlap to our original cohort (Fig. 2C). Consistent with our

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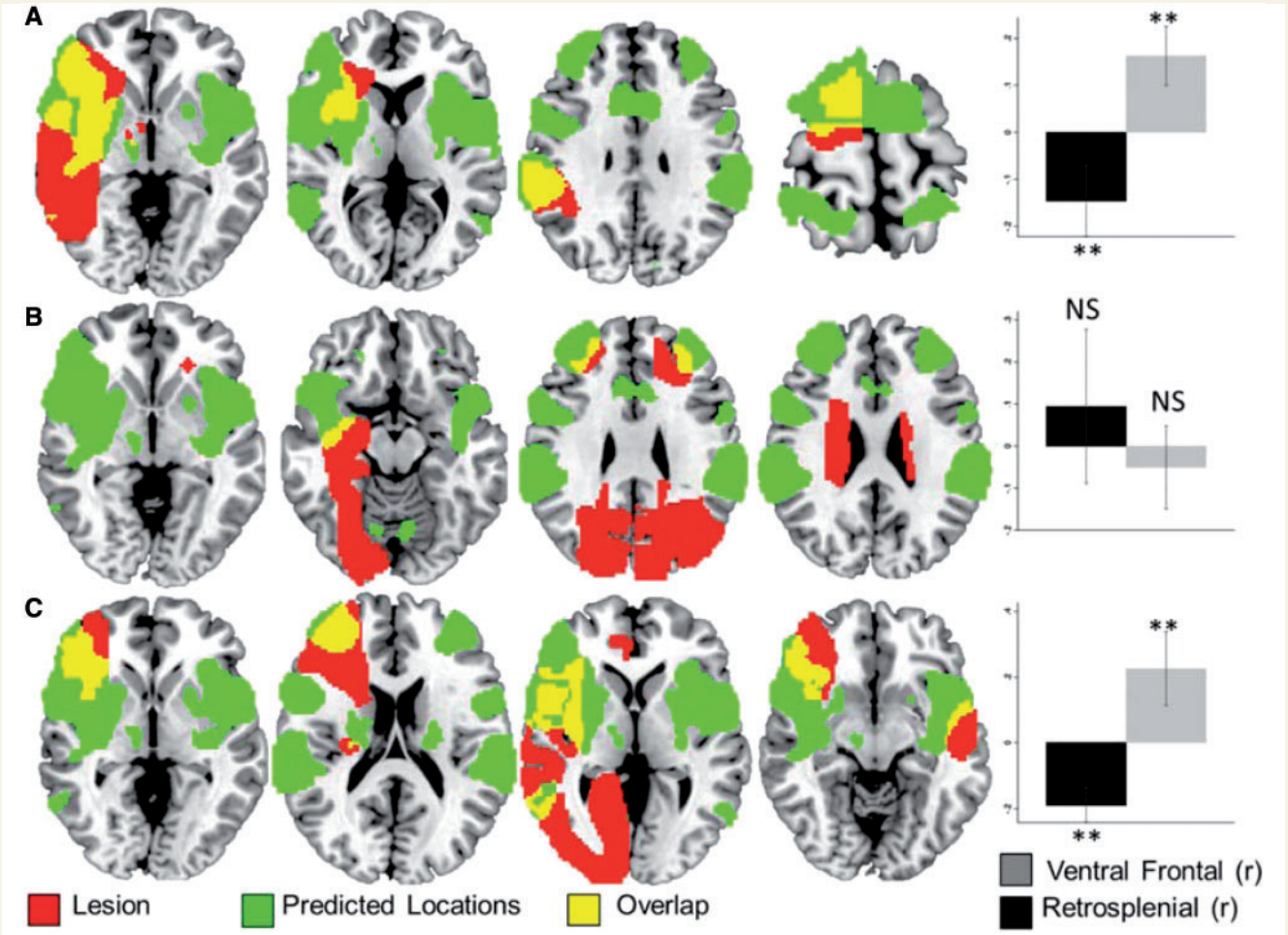

Figure 2 High probability causal lesions occur in predicted locations in delusional misidentification patients. On the *left*, lesions in patients with delusional misidentifications from our original cohort (**A**), four new low probability causal lesions (**B**, including Ferguson *et al.* to far left), and four high probability causal lesions (**C**). On the right, lesions from our original cohort (**A**) and new high probability causal lesions (**C**) are significantly connected to the right ventral frontal cortex and retrosplenial cortex, while low probability lesions are not significantly connected to these regions (**B**). $^{**}P < 0.05$. NS = not significant.

hypothesis, high probability lesions were positively correlated with the right ventral frontal cortex ($r = 0.22$, $P < 0.05$) and negatively correlated with the left retrosplenial cortex ($r = -0.19$, $P < 0.005$), while low probability lesions were not. Further, there was a significant difference in connectivity between the high and low probability cohorts ($P < 0.05$ for both comparisons).

Discussion

The case presented by Ferguson *et al.* highlights a common challenge in clinical neurology: how does one determine whether a brain lesion is causing a neuropsychiatric symptom when lesions causing that symptom can occur in different locations? Here, we provide evidence that lesion network mapping can help assess the probability that a given lesion is causing a delusional misidentification.

It is not possible to exclude the interpretation offered by Ferguson *et al.* that their case implicates a separate neuroanatomical substrate linking lesion location to delusional misidentification. However, given the patient's preceding psychiatric symptoms, uncertain temporal relationship to the lesion, high prevalence of delusional misidentifications in psychiatric compared to lesion-based disease, and present lesion network mapping results, we suggest that the most parsimonious explanation is that the lesion is not causally related to the patient's delusion.

A limitation of our analysis is that the relationship between lesion location and symptoms in persons with psychiatric disease might be different than the relationship in normal persons. Our analysis uses normative connectome data and connectivity differences have been reported across numerous psychiatric diseases (Fox and Greicius, 2010). Thus, caution should be advised when using our method in patients with pre-existing neurological or psychiatric diseases.

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In conclusion, we provide evidence that lesion network mapping can help determine the probability that a lesion identified on clinical MRI is causing a specific neuropsychiatric symptom. We hope that providing the voxel-wise topography of our delusional misidentification network (Fig. 1) will prove useful to other clinicians facing similar clinical conundrums to Ferguson *et al.* (2017).

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