LETTER TO THE EDITOR

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

R. Ryan Darby¹,²,³ and Michael D. Fox¹,²,⁴

¹ Berenson-Allen Center for Non-Invasive Brain Stimulation and Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
² Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
³ Department of Neurology, McLean Psychiatric Hospital, Harvard Medical School, Belmont, MA, USA
⁴ Athinoula A. Martinos Centre for Biomedical Imaging, Charlestown, MA, USA

Correspondence to: Ryan Darby
Berenson-Allen Center for Noninvasive Brain Stimulation
Beth Israel Deaconess Medical Center
330 Brookline Ave, Kirstein Building KS 158
Boston, MA 02215, USA
E-mail: rdarby@bidmc.harvard.edu

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of progressive social isolation, agitation, and delusional beliefs who developed the delusion that his parents had been replaced by imposters (Capgras syndrome).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/
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).

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
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.
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).

**Funding**

This work was supported by funding from the Sidney R. Baer, Jr. Foundation (R.D., M.F.), the NIH (K23NS083741 to M.F.), The Alzheimer’s Association (R.D.), the BrightFocus Foundation (R.D.), and the American Brain Foundation (M.F.)

**References**