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Looking beyond the face area: lesion network mapping of prosopagnosia

Alexander L. Cohen,[1,2,3] Louis Soussand,[2] Sherryse L. Corrow,[4] Olivier Martinaud,[5] Jason J.S. Barton[6] and Michael D. Fox[2,7,8]

Damage to the right fusiform face area can disrupt the ability to recognize faces, a classic example of how damage to a specialized brain region can disrupt a specialized brain function. However, similar symptoms can arise from damage to other brain regions, and face recognition is now thought to depend on a distributed brain network. The extent of this network and which regions are critical for facial recognition remains unclear. Here, we derive this network empirically based on lesion locations causing clinically significant impairments in facial recognition. Cases of acquired prosopagnosia were identified through a systematic literature search and lesion locations were mapped to a common brain atlas. The network of brain regions connected to each lesion location was identified using resting state functional connectivity from healthy participants (n = 1000), a technique termed lesion network mapping. Lesion networks were overlapped to identify connections common to lesions causing prosopagnosia. Reproducibility was assessed using split-half replication. Specificity was assessed through comparison with non-specific control lesions (n = 135) and with control lesions associated with symptoms other than prosopagnosia (n = 155). Finally, we tested whether our facial recognition network derived from clinically evident cases of prosopagnosia could predict subclinical facial agnosia in an independent lesion cohort (n = 31). Our systematic literature search identified 44 lesions causing prosopagnosia, only 29 of which intersected the right fusiform face area. However, all 44 lesion locations fell within a single brain network defined by connectivity to the right fusiform face area. Less consistent connectivity was found to other face-selective regions. Surprisingly, all 44 lesion locations were also functionally connected, through negative correlation, with regions in the left frontal cortex. This connectivity pattern was highly reproducible and specific to lesions causing prosopagnosia. Positive connectivity to the right fusiform face area and negative connectivity to left frontal regions were independent predictors of prosopagnosia and predicted subclinical facial agnosia in an independent lesion cohort. We conclude that lesions causing prosopagnosia localize to a single functionally connected brain network defined by connectivity to the right fusiform face area and to left frontal regions. Implications of these findings for models of facial recognition deficits are discussed.

1 Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
2 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
3 Computational Radiology Laboratory, Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
4 Department of Psychology, Bethel University, St. Paul, MN, USA
5 Department of Neurology Neuropsychology and Imaging of Human Memory, Caen-Normandy University, PSL Research University, EPHE, INSERM, Caen University Hospital, Caen, France
6 Departments of Medicine (Neurology), Ophthalmology and Visual Sciences, Psychology, University of British Columbia, Canada
7 Athinoula A. Martinos Centre for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, USA
8 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Correspondence to: Alexander Li Cohen, MD, PhD
Department of Neurology
Boston Children's Hospital
300 Longwood Avenue

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Boston, MA 02115, USA
E-mail: alexander.cohen2@childrens.harvard.edu

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Abbreviation: FFA = fusiform face area

Introduction

Face recognition is a highly developed skill supported by specialized brain regions, most notably the right fusiform face area (FFA) (Bruce and Young, 1986; Haxby *et al.*, 1994, 2000; Kanwisher *et al.*, 1997). Damage to this region can impair face recognition, a syndrome termed prosopagnosia, and has become a classic example of how damage to a specialized brain region can disrupt a specific function (Bodamer, 1947; Hecaen and Angelergues, 1962). However, lesions sparing the right FFA, and the left FFA, can still disrupt this important ability (Mattson *et al.*, 2000; Barton, 2008; Steeves *et al.*, 2009). Similarly, face recognition can be disrupted in conditions without obvious FFA pathology such as developmental prosopagnosia and autism spectrum disorder (Kennerknecht *et al.*, 2008; Dimitriou *et al.*, 2015; Barton and Corrow, 2016*a*). These observations and others have led to the conclusion that face recognition involves a network of brain regions that go well beyond the FFA, and identifying this network has been the subject of intense study utilizing a number of imaging techniques (Fairhall and Ishai, 2007; Ishai, 2008; Li *et al.*, 2009; Cohen Kadosh *et al.*, 2011; Davies-Thompson and Andrews, 2011, 2012; Dima *et al.*, 2011; Dinkelacker *et al.*, 2011; Herrington *et al.*, 2011; Nagy *et al.*, 2012; Rossion *et al.*, 2012; Pyles *et al.*, 2013; Matsuyoshi *et al.*, 2015; He *et al.*, 2015; Wang *et al.*, 2016; Rosenthal *et al.*, 2017; Kale *et al.*, 2019).

These studies have established that there are a core set of regions in occipital and temporal lobes that demonstrate face-selective activity, including the FFA, the occipital face area, and the superior temporal sulcus as well as an extended set of regions with a lesser degree of face-selectivity including the amygdala, inferior frontal gyrus, intraparietal sulcus, precuneus, and superior colliculus (Haxby *et al.*, 2000; Ishai, 2008). However, exactly which regions are critical for facial recognition, remains uncertain (Davies-Thompson and Andrews, 2011; Rossion *et al.*, 2012). Similarly, it remains unclear why lesions to some face-selective locations, but not others, lead to prosopagnosia.

Recently, it has been become possible to map neurological symptoms to brain networks based on lesion locations that cause the symptom and a map of human brain connectivity (Boes *et al.*, 2015; Fox, 2018). This technique, termed lesion network mapping, uses connectivity data from a large normative database to identify the network of regions functionally connected to each lesion location. Commonalities across different lesion locations causing the same symptom can then be identified. The technique has been validated for 2D approximations of 3D lesions, such as those available in published case reports, making it an ideal technique for studying rare lesion-induced neurological syndromes like prosopagnosia (Boes *et al.*, 2015; Darby *et al.*, 2017*b*). This technique has been previously applied to lesion-induced hallucinations, delusions, movement disorders, criminality, and a variety of other symptoms (Boes *et al.*, 2015; Fischer *et al.*, 2016; Laganiere *et al.*, 2016, Darby *et al.*, 2017*a*, *b*; Fasano *et al.*, 2017; Joutsa *et al.*, 2018*a*). Further, lesion network mapping results have shown promise as treatment targets for therapeutic brain stimulation (Joutsa *et al.*, 2018*b*). Here, we use this technique to test whether lesion locations causing prosopagnosia fall within a common brain network, and to identify the critical nodes of this network.

Materials and methods

Patient cases from the literature

We identified patients with acquired prosopagnosia via a PubMed search for 'prosopagnosia AND stroke'. Inclusion criteria included: (i) a deficit in facial recognition of sufficient severity that it came to clinical attention; (ii) the deficit was attributed by the authors to a focal brain lesion; and (iii) published images of the brain lesion that were of sufficient quality to allow transfer of the lesion's location onto a standardized brain atlas. Forty-four subjects across 19 studies met these criteria (Supplementary Table 1 and Supplementary Fig. 1). Given the rarity of reported cases of acquired prosopagnosia with included imaging, all discovered cases were used to maximize power.

For 32 patients, '2D lesion masks' derived from published figures were traced by hand (by A.C.) onto the MNI152 sixth generation atlas (2 mm resolution) included with FSL v5.0 (Jenkinson *et al.*, 2012) using 3DSlicer v4 (Fedorov *et al.*, 2012). In cases where the published image showed multiple 2D slices, all slices were traced and combined into a single lesion mask. For 12 patients, volumetric '3D lesion masks' were traced from volumetric imaging data (by S.C.) onto the same MNI152 sixth generation atlas. As in prior work (Boes *et al.*, 2015; Darby *et al.*, 2017*b*), we tested whether 2D lesion masks provide an adequate approximation of 3D lesion location by generating a 2D lesion mask through the centre of each of our 12 3D lesions and comparing the resulting lesion networks. Lesion networks based on 2D slices were nearly identical to lesion networks based on the full 3D lesion masks, with a median spatial correlation of 0.98 (Supplementary Fig. 2).

Overlap of prosopagnosia lesions with an *a priori* right fusiform face area

To generate an unbiased *a priori* region of interest in the right FFA, we performed a meta-analysis of task-functional MRI studies using the online Neurosynth repository (Yarkoni *et al.*, 2011) and the search term 'face' (n = 720). The resulting map was thresholded at $Z > 10$ and clustered using Nilearn's connected_regions function (Abraham *et al.*, 2014) to generate a single peak cluster in an *a priori* right FFA (centred at MNI: 42, −50, −19). This region of interest is consistent with recent individual studies using face localizer tasks (Davies-Thompson and Andrews, 2012; Rossion *et al.*, 2012). Each prosopagnosia lesion mask was tested for voxelwise intersection with this *a priori* right FFA region of interest.

Lesion network mapping

Our 44 traced lesions were used as individual seeds in a resting state functional connectivity analysis using data collected from 1000 healthy adult control subjects ranging in age from 18–35 years (Yeo *et al.*, 2011; Holmes *et al.*, 2015). A functional connectivity map for each lesion was determined by: (i) calculating the correlation between each lesion location's average time course and the time course of every other brain voxel using resting state data from each individual normal control (Boes *et al.*, 2015; Darby *et al.*, 2017*b*); (ii) applying a Fisher's z transformation, z = arctanh(r), to each of the 1000 functional connectivity correlation maps to normalize the distribution of values; and then (iii) calculating a T-map for each lesion, with a T-score value for each individual voxel representing the statistical relationship of each voxel to the lesion location. Each lesion's T-map was thresholded at $T > \pm 9$ [voxelwise familywise error (FWE) corrected at $P < 10^{-11}$] to create a binarized map of regions functionally connected to each patient's lesion location. This threshold is somewhat arbitrary and is more conservative than many prior papers from our lab (Boes *et al.*, 2015; Fischer *et al.*, 2016; Laganiere *et al.*, 2016, Darby *et al.*, 2017*a*, *b*; Fasano *et al.*, 2017; Joutsa *et al.*, 2018*a*). It was chosen to maximize specificity while maintaining 100% sensitivity of connectivity to at least one brain region. Use of alternative thresholds (e.g. $T > \pm 7$) did not alter the present results, and all statistical analyses described below used continuous connectivity values that did not depend on this threshold. Binarized maps were overlapped to create a group map indicating the number of patients with lesions functionally connected to each individual voxel.

Split-half replication

As each lesion was traced by a single observer (A.C. or S.C.), we assessed the internal reliability of our lesion network mapping results by randomly dividing our dataset into two subsets of 22 patients. We repeated the above lesion network mapping on each subset. Regions of interest were derived from each subset by identifying volumes of at least 250 mm^3 present in at least 21 of the 22 binarized lesion network maps. Functional connectivity between each region of interest from Subset 1 and each lesion location in Subset 2 (and vice versa) was computed using our normative connectome dataset and significance was assessed using a two-tailed *t*-test.

Replication without global signal regression

Our normative connectome used for lesion network mapping was processed using global signal regression, a useful manoeuvre for eliminating noise but one that can complicate interpretation of negative correlations (Murphy and Fox, 2017; Li *et al.*, 2019). To ensure our results were independent of this processing step, we repeated our lesion network mapping using a 100-subject normative connectome generated without using global signal regression, similar to prior work (Boes *et al.*, 2015). Resting state data were processed using the aCompCor strategy as implemented in the Conn Toolbox (www.nitrc.org/projects/conn) (Behzadi *et al.*, 2007; Whitfield-Gabrieli and Nieto-Castanon, 2012), which includes regression of noise variables derived from motion, CSF, and white matter, but not the global signal. All settings for preprocessing and regression were kept as default/recommended.

Comparison with control lesions

We compared our acquired prosopagnosia lesion network mapping results to lesion networks derived from two independent datasets of control lesions. The first control dataset included 135 3D lesion volumes from consecutive stroke patients, part of the Washington University Stroke Project (Corbetta *et al.*, 2015). The second control dataset included 155 2D lesion masks associated with other neuropsychiatric syndromes previously investigated by our lab including aphasia, auditory hallucinations, Capgras syndrome, central post-stroke pain, criminality, freezing of gait, hemichorea, post-stroke delusions, and peduncular hallucinosis (Boes *et al.*, 2015; Laganiere *et al.*, 2016, Darby *et al.*, 2017*a*, *b*; Fasano *et al.*, 2017). These control cohorts were not explicitly tested for face recognition deficits, but the presence of any possible prosopagnosia in these cohorts should bias us against identifying group differences. Two-sample *t*-tests were carried out on the unthresholded lesion network maps via non-parametric permutation testing (FSL PALM v.alpha109) using 2000 permutations, tail approximation (Winkler *et al.*, 2014), and a conservative voxelwise FWE rate corrected P-value < 0.001. Non-parametric permutation testing and voxelwise statistics were chosen because they are resilient to false positives seen with some common cluster-based approaches (Eklund *et al.*, 2016).

Regions of interest sensitive and specific to acquired prosopagnosia

To generate regions of interest for use in further analyses, we first identified voxels functionally connected to at least 42 of 44 lesion locations causing prosopagnosia (95% sensitive). We then masked this result with our map of voxels significantly more connected to prosopagnosia lesions than either of our control cohorts. This conjunction analysis identifies connections that are both sensitive and specific to lesion locations causing prosopagnosia. A clustering algorithm (Nilearn's connected_regions function) (Abraham *et al.*, 2014) identified regions of interest containing at least 250 mm^3 and at least one voxel connected to all 44 of the prosopagnosia lesion locations. This analysis identified a single positively correlated region of interest in the

presumed location of the right FFA, hereafter referred to as the identified right FFA to distinguish it from the *a priori* FFA described above, and four negatively correlated regions of interest in the left frontal cortex. Given the similar location and connectivity profile of the four left frontal regions of interest, they were combined into a single region of interest to simplify subsequent analyses. Results are unchanged if these regions of interest are considered separately.

Comparison of lesion to *a priori* face-selective regions of interest

Regions of interest were defined for the core face-selective regions from the Neurosynth 'face' meta-analyses of task-functional MRI studies (n = 720) as was done for the *a priori* right FFA above (Yarkoni *et al.*, 2011). Bilateral FFA, occipital face areas (OFA), and amygdala regions were obtained as clusters of voxels with a $Z > 10$ using Nilearn's connected_regions function to find contiguous regions containing at least 50 mm^3 (Abraham *et al.*, 2014). Defining regions of interest for the bilateral superior temporal sulcus (STS) and the right inferior frontal gyrus (IFG) required reducing the statistical threshold to $Z > 4.5$, corresponding to a false discovery rate (FDR) corrected P-value of < 0.00001. To examine the relative sensitivity of the known face-selective regions for connectivity to lesions associated with acquired prosopagnosia, we used the lesion network mapping approach above to determine the proportion of lesions with a maximal $T > \pm 9$ (voxelwise FWE corrected at $P < 10^{-11}$) within each *a priori* region of interest. We also calculated the pairwise average correlation between each *a priori* face-selective region of interest and each lesion in our prosopagnosia cohort and our two control cohorts. These correlation values were used to compute a two-way (group × region of interest) ANOVA for unequal group sizes using type III sum of squares with the 'car' package in R to identify significant interaction effects. *Post hoc* one-way ANOVAs were also carried out, across group for each region of interest, to determine the relative specificity of lesion region of interest correlations across the three groups (Fox and Weisberg, 2019).

Logistic regression to determine independent prediction

We then performed a binomial logistic regression relating group (prosopagnosia versus control) to the independent variables of lesion-to-identified region of interest correlation for our 44 prosopagnosia lesions and 135 control stroke lesions using the Statsmodels python package (Seabold and Perktold, 2010). The optimal model included connectivity with the identified right FFA region of interest, connectivity with the left frontal region(s) of interest (ROI), and an interaction term (Case ~ ROI A + ROI B + ROI A:ROI B). McFadden pseudo R^2 and odds ratios were computed to define the amount of variance explained by each model and the predictive power of each independent variable.

Validation in an independent dataset of subclinical facial agnosia

By definition, the set of voxels positively correlated with the identified right FFA and negatively correlated with our left frontal region(s) of interest define a brain network that encompasses our original lesion locations causing prosopagnosia. We tested whether intersection of lesion location with this network would predict subclinical facial agnosia in an independent dataset. 3D lesion masks were obtained from 31 patients with posterior cerebral artery strokes and no clinically obvious visual agnosia who underwent detailed neuropsychological assessment (Martinaud *et al.*, 2012). In addition to standardized tests of vision and cognition, patients underwent a 2-h battery of assessments combining four experimental paradigms designed to assess visual recognition of a chosen visual category: picture detection within an array, Cambridge Memory Tests of visual recall, old/new discrimination, and a timed reading test for alexia. Multiple visual categories of stimuli were tested using each of these testing paradigms including houses, faces, sunglasses, phones, words, flowers, scenes, horses, houses, cars, guns, and tools. These experimental paradigms were also administered to 41 healthy control subjects who did not statistically differ in terms of age, educational level, or sex. For each of the 31 patients, performance on each test was converted to a z-score based on the mean and the standard deviation (SD) of the control sample (complete data tables are available in the supporting information for Martinaud *et al.*, 2012). Performance was considered abnormal when the z-score was $\leqslant -2$. This identified 11 patients with subclinical facial agnosia, identified as Patients 10, 12, 19, 20–22, 25–27, 30 and 31 in Martinaud *et al.*, (2012) with the remaining patients demonstrating similar face processing ability to control subjects (n = 20). Patients with and without subclinical facial agnosia also had a variety of combinations of subclinical object agnosias, with few patients having a pure agnosia for any particular visual category. Of note, no patients endorsed visual processing deficits prior to assessment. A two-sample t-test was performed to compare the intersection of lesion location with our prosopagnosia network for patients with (n = 11) versus without (n = 20) subclinical facial agnosia. To ensure this result was not driven by lesion size, we performed a binomial logistic regression relating facial agnosia to the independent variables of lesion volume and overlap with our prosopagnosia network.

Statistical analysis

As detailed above, we took multiple steps to ensure the reproducibility and generalizability of these methods. To summarize, we: (i) varied the thresholds of our lesion network mapping approach to confirm stability of our localization; (ii) assessed the validity of using 2D versus 3D lesion samples; (iii) performed a split-half replication to assess the consistency of our results; (iv) used a non-parametric/permutation-based approach to perform statistical tests on volumetric images; (v) used FWE rather than FDR correction where appropriate; (vi) computed McFadden pseudo R^2 for our logistic regressions; and (vii) used a single software package for each type of analysis in accordance with existing best practice recommendations (Poldrack *et al.*, 2017). These choices reduce but do not eliminate the risk of false positives (Eklund *et al.*, 2016; Poldrack *et al.*, 2017).

Data availability

Data are available from the corresponding authors upon request.

Results

Lesions causing prosopagnosia vary in location but localize to a single brain network

A systematic literature review identified 19 studies describing 44 cases of acquired prosopagnosia with sufficient information to create a representative lesion mask (Fig. 1). The mean age at time of injury was 39 years (SD = 19), with a male predominance (32M:12F) (Supplementary Table 1). No single brain region was lesioned in all cases of prosopagnosia. Lesions from 29 of the 44 cases intersected an *a priori* right FFA, identified from the Neurosynth database (Fig. 2A and B), but 15 did not (Fig. 2C and D). The network of brain regions functionally connected to each lesion location was computed and commonalities were identified (Fig. 3A–C). All 44 lesion locations were functionally connected to a region intersecting our *a priori* right FFA, hereafter referred to as the identified right FFA. Of note, the peak of this identified FFA (MNI coordinates: 42, −48, −19) fell in the centre of our *a priori* FFA (MNI coordinates 42, −50, −19) (Fig. 3C). A subgroup analysis of the 15 subjects whose lesions did not overlap the *a priori* right FFA generated a nearly identical pattern of connectivity, again with a peak within the centre of our *a priori* right FFA (Fig. 3D). Split-half replication analysis showed near perfect reproducibility of peak overlap across cohorts (Fig. 4).

In addition to positive functional connectivity to the identified right FFA, lesion locations causing prosopagnosia were also negatively correlated with several left frontal areas, including anterior prefrontal/frontopolar cortex (APFC: −32, 60, 14), anterior cingulate cortex (ACC: −5, 29, 37),

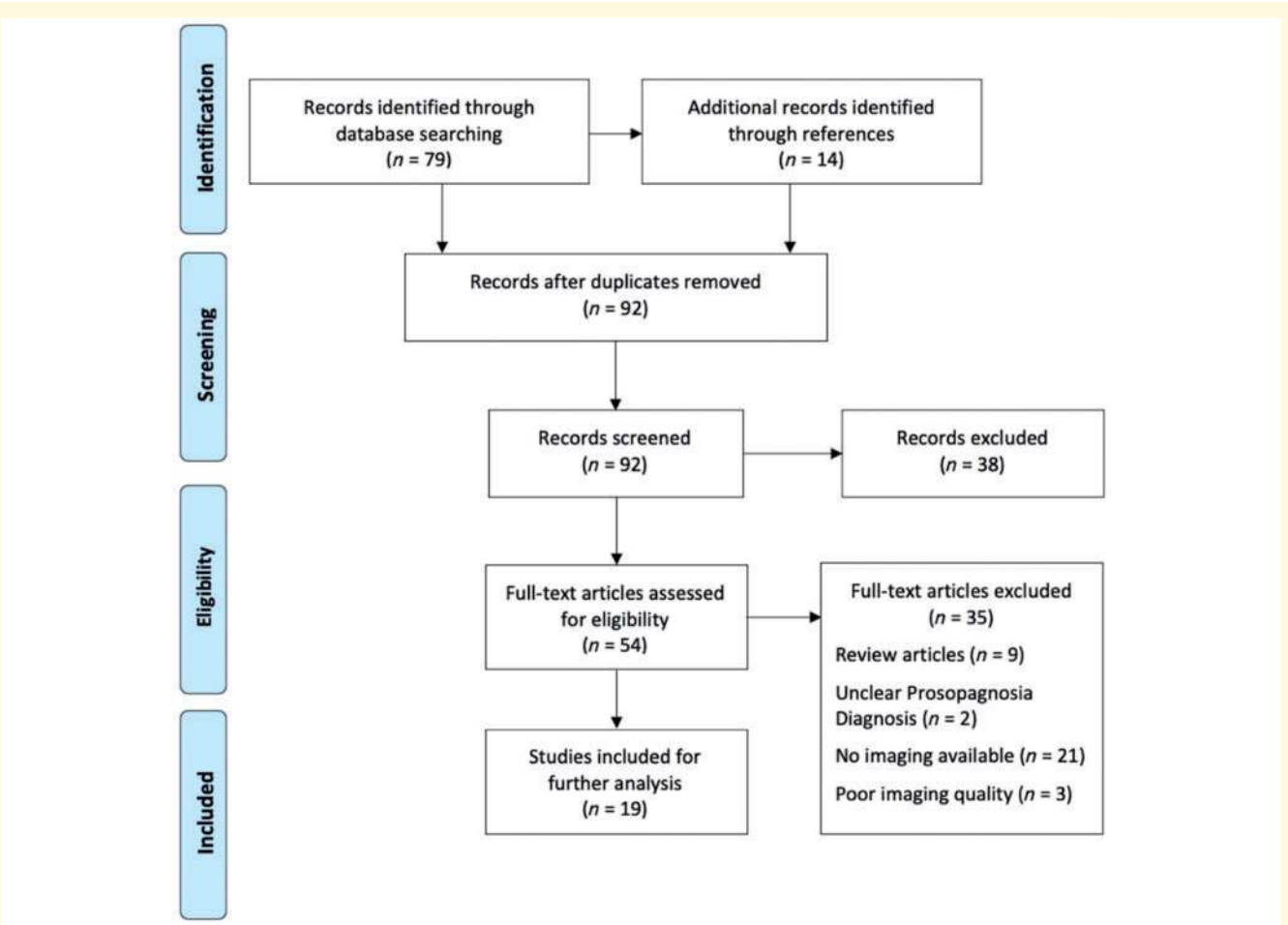

Figure 1 PRISMA flow chart identifying possible lesion locations causing acquired prosopagnosia. We identified patients with acquired prosopagnosia via a PubMed search for 'prosopagnosia AND stroke' and by collecting articles referred to by that initial set of papers. Inclusion criteria included description of acquired prosopagnosia from a focal brain lesion and published images of the brain lesion of sufficient quality to allow transfer of the lesion's location onto a standardized brain atlas. Forty-four subjects across 19 studies met these criteria.

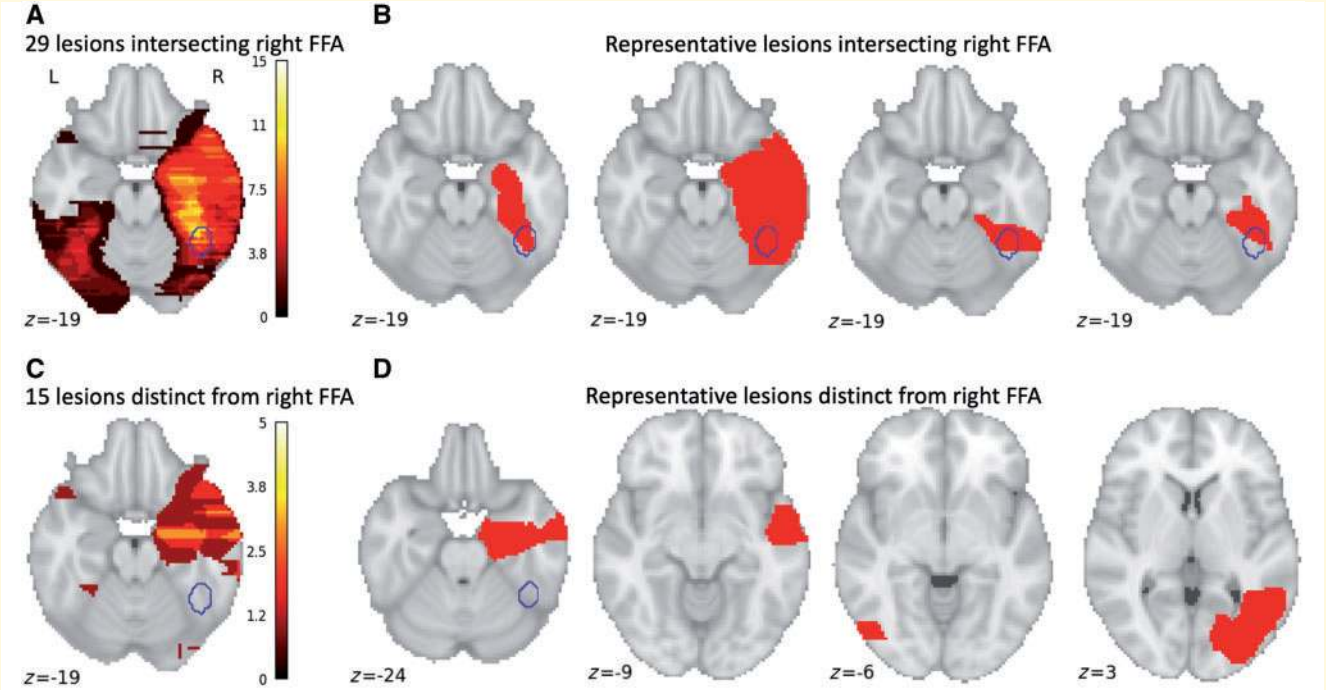

Figure 2 Lesions causing acquired prosopagnosia varied in location. Lesions from 44 patients with acquired prosopagnosia were identified from a systematic literature search or from cases seen by the authors and traced onto a common brain atlas (MNI sixth generation atlas). Twenty-nine lesions intersected an *a priori* right FFA (**A**), as shown by four representative lesions (**B**). Fifteen lesions did not intersect an *a priori* right FFA (**C**), demonstrated by four representative lesions (**D**). In all images, lesion locations are shown in red while the *a priori* right FFA region is shown as a blue outline.

middle frontal gyrus (MFG: −30, 37, 45), and superior frontal gyrus (SFG: −20, 12, 67) (Fig. 4A). These negatively correlated regions were also highly reproducible, i.e. all lesion network overlap regions identified in one-half of the lesions showed significant connectivity to the lesion locations in the other half and vice versa (Fig. 4B and D). These four frontal regions were also identified using solely the 15 regions that did not overlap the *a priori* right FFA (Supplementary Fig. 3). Finally, these negatively correlated regions were present independent of our connectome processing strategy and independent of global signal regression (Supplementary Fig. 4A and B). As expected, the exclusion of global signal regression from the preprocessing pipeline increased the magnitude of positive correlations and decreased the magnitude of negative correlations; however, the regions identified above are still clearly present and remain significantly negatively correlated with the lesion cohort. In other words, the negative correlations observed were not 'introduced' by the global signal regression procedure and were still present in data with more conservative artefact regression strategies (Supplementary Fig. 4C and D).

Connectivity to the identified right FFA and left frontal cortex is specific to lesions causing prosopagnosia

This connectivity pattern for lesion locations causing prosopagnosia (Fig. 5A) was highly specific compared to 135 sequentially acquired stroke lesions (Corbetta *et al.*, 2015) (Fig. 5B) or 155 lesions causing other specific neuropsychiatric syndromes (Boes *et al.*, 2015; Laganiere *et al.*, 2016; Darby *et al.*, 2017*a*, *b*; Fasano *et al.*, 2017) (Fig. 5C). Conjunction analysis revealed the identified right FFA and four left frontal regions (APFC, ACC, MFG and SFG) as both sensitive and specific for acquired prosopagnosia (Fig. 5D). Interestingly these four frontal regions all localize to a previously described frontoparietal control network (Vincent *et al.*, 2008; Smith *et al.*, 2009; Yeo *et al.*, 2011) (Fig. 6).

Connectivity to the identified right FFA and left frontal cortex are independent predictors of prosopagnosia

A binomial logistic regression model predicting prosopagnosia based on connectivity between lesions and the identified right FFA and left frontal regions of interest was highly significant (χ^2 = 90, P < 0.05) and explained 51.5% of the variance (McFadden pseudo R^2). Both positive connectivity to the identified right FFA (odds ratio 14.058, P = 0.006) and negative connectivity to our left frontal regions (odds ratio 16.129, P < 0.001) were independent predictors of prosopagnosia compared to control lesions.

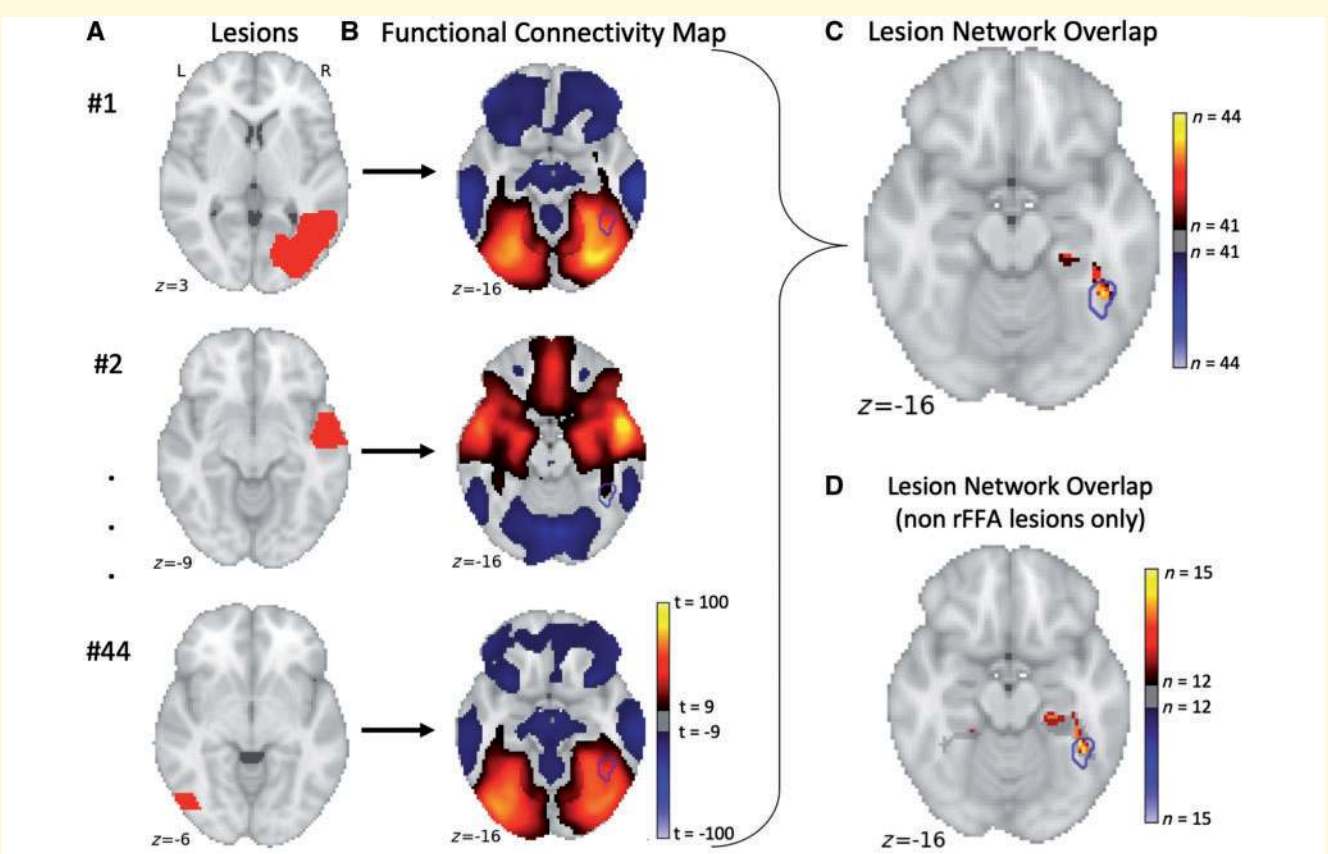

Figure 3 Lesion network mapping identified consistent regions connected to all lesions causing acquired prosopagnosia. Lesions were traced onto a standardized MNI brain template (**A**). Brain regions functionally connected to each lesion location were then obtained using a large resting state functional connectivity database (**B**). Overlap of thresholded functional connectivity maps ($t > 9$) from each lesion identified brain regions connected to the greatest number of lesion locations (**C**). Of note, consistent connectivity to the right FFA was still observed from lesion locations that did not intersect the right FFA (**D**). In all images, the *a priori* right FFA region is shown as a blue outline.

Face-selective regions of interest demonstrate variable connectivity to lesions causing prosopagnosia

Lesions causing prosopagnosia also demonstrated differential connectivity to *a priori* regions with known face-selective activity from the Neurosynth database. Consistent with the lesion network mapping results above, the *a priori* right FFA was indeed the only region significantly correlated ($T > \pm 9$, voxelwise FWE corrected at $P < 10^{-11}$) with 100% of acquired prosopagnosia lesions, although the left FFA, bilateral OFA, and right STS were also connected to >50% of lesions (Fig. 7). A two-way ANOVA across all face-selective *a priori* regions of interest revealed a strong group × region of interest interaction between lesions causing prosopagnosia and our two control cohorts ($F = 112.52$, $P = 5.22 \times 10^{-16}$), and *post hoc* one-way ANOVAs identified the *a priori* right FFA as having the most distinct correlation pattern, $F = 112.52$, $P = 5.22 \times 10^{-38}$ (Supplementary Fig. 5).

Lesion overlap with the identified network predicts subclinical facial agnosia in an independent dataset

By definition, positive functional connectivity with the identified right FFA and negative functional connectivity with our left frontal regions defines a brain network that encompasses our original 44 lesion locations causing prosopagnosia (Fig. 7A). We next generated a map of this network because it allows us to visualize locations in the brain that, when lesioned, would be expected to cause prosopagnosia, similar to prior studies on other syndromes (Laganiere *et al.*, 2016; Fasano *et al.*, 2017; Corp *et al.*, 2019; Padmanabhan *et al.*, 2019). Note that this prosopagnosia network extends beyond our original 44 lesion locations and could be used to predict whether new lesions in different locations are likely to impair facial recognition. To test this hypothesis, we examined an independent cohort of 31 posterior cerebral artery strokes (Martinaud *et al.*, 2012). Lesion locations associated with subclinical impairments in face recognition ($n = 11$) fell within our

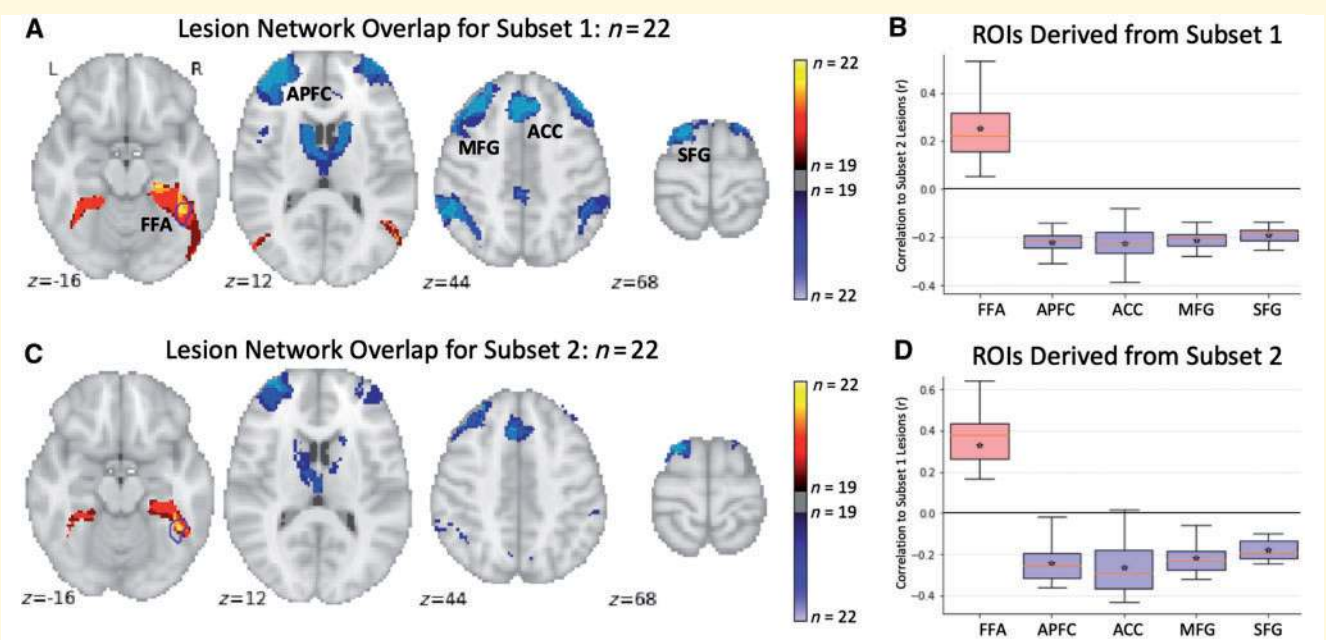

Figure 4 Split-half replication revealed a consistent pattern of lesion connectivity. A random division of our lesion sample into two independent subsets (**A** and **C**) demonstrated high reproducibility for lesion network overlap results. Consistent lesion network mapping regions identified from Subset 1, including the right FFA, the left anterior prefrontal cortex (APFC), the left middle frontal gyrus (MFG), the dorsal anterior cingulate cortex (ACC), and the left superior frontal gyrus (SFG), were also highly correlated with the lesions in Subset 2 (**B**), and vice versa for regions identified from Subset 2, with lesions from Subset 1 (**D**). Results are displayed at an overlap threshold of 75% to best illustrate the similarities across the two subsets. In all images, the *a priori* right FFA region is shown as a blue outline. All correlation distributions are significantly different from zero, $P < 0.001$. Red lines in box-plots indicate medians while stars indicate means. ROIs = regions of interest.

prosopagnosia network (Fig. 7B versus Fig. 7C). Overlap with our network was significantly greater than for lesion locations associated with intact facial recognition (18.25 cm^3 versus 4.56 cm^3, P = 0.007) (Fig. 7D). Logistic regression also found that overlap with our prosopagnosia network was more informative than lesion size in predicting subclinical facial recognition deficits (Akaike information criterion, AIC 31.47, McFadden pseudo R^2 = 31.9% versus AIC 32.70, McFadden pseudo R^2 = 28.8%). Of note, while of less statistical power, lesion network mapping of subclinical facial agnosia was also consistent with the topology described above.

Discussion

We identified a network of brain regions that encompasses 44 lesion locations causing prosopagnosia. This network is defined by positive connectivity to right FFA, and negative connectivity to the left frontal cortex. Both connections are specific to lesions causing prosopagnosia and independent predictors of this deficit. Finally, we found that lesions partially intersecting this network are associated with subclinical facial impairments in an independent dataset.

The concept that specific stroke-related neuropsychological deficits map to specific brain networks is not new (Rorden and Karnath, 2004; Honey and Sporns, 2008; Carrera and Tononi, 2014; Fox, 2018; Karnath *et al.*, 2018), nor is the notion that face recognition requires a network of connected brain regions (Haxby *et al.*, 2000; Rossion *et al.*, 2012; Davies-Thompson *et al.*, 2014). Studies using functional and effective connectivity have also demonstrated strong connectivity between regions that demonstrate face-selective activity, finding strong connectivity between the FFA and OFA with regions in the intraparietal sulcus, precuneus, and superior colliculus, while the STS is more correlated with the amygdala and IFG, consistent with work suggesting the OFA and FFA play a larger role in face identification while the STS plays a larger role in social utilization of face information (Haxby *et al.*, 2000; Summerfield *et al.*, 2006; Fairhall and Ishai, 2007; Ishai, 2008; Li *et al.*, 2009; Suzanne *et al.*, 2010; Cohen Kadosh *et al.*, 2011; Davies-Thompson and Andrews, 2011, 2012; Dima *et al.*, 2011; Ethofer *et al.*, 2011; Herrington *et al.*, 2011; Goulden *et al.*, 2012; Joseph *et al.*, 2012; Nagy *et al.*, 2012; Rossion *et al.*, 2012; Ewbank *et al.*, 2013; Pyles *et al.*, 2013; Avidan *et al.*, 2014; Davies-Thompson *et al.*, 2014; O'Neil *et al.*, 2014; He *et al.*, 2015; Nomi and Uddin, 2015; Song *et al.*, 2015; Wang *et al.*, 2016; Isik *et al.*, 2017; Elbich *et al.*, 2019). Several papers have also demonstrated decreased connectivity among face-selective regions in individuals with developmental prosopagnosia (Avidan *et al.*, 2014; Song *et al.*, 2015). There have also been some

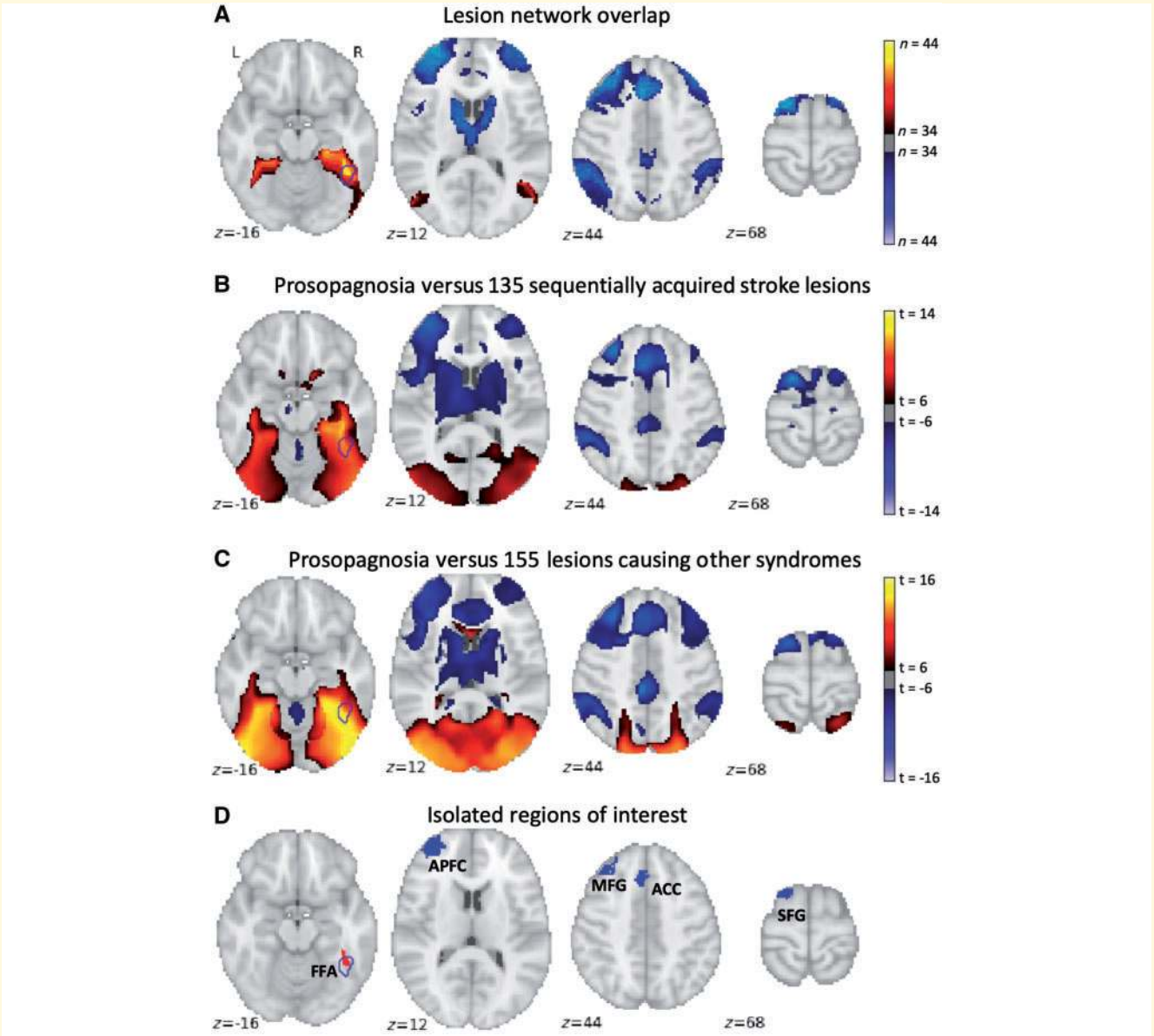

Figure 5 Connectivity to the right FFA and left frontal cortex is specific to lesions causing acquired prosopagnosia compared to control lesions and lesions causing other syndromes. Using our entire cohort of lesions causing prosopagnosia (n = 44), all lesion locations demonstrated positive and negative correlation to a specific set of locations (**A**). This pattern of connectivity was specific to lesions causing prosopagnosia compared to a large cohort of control lesions causing non-specific symptoms (**B**) or to lesions causing specific symptoms other than prosopagnosia (**C**). The conjunction of our sensitivity and specificity analyses (**D**) identified five locations including the right FFA, the left anterior prefrontal cortex (APFC), the left middle frontal gyrus (MFG), the dorsal anterior cingulate cortex (ACC), and the left superior frontal gyrus (SFG). In all images, the *a priori* right FFA region is shown as a blue outline.

reports of connectivity differences between the FFA and frontal cortex, often the right IFG, related to diagnosis or behaviour variables (Rissman *et al.*, 2008; Kleinhans *et al.*, 2008; Li *et al.*, 2009; Bollinger *et al.*, 2010; Frühholz *et al.*, 2011; Davies-Thompson and Andrews, 2012; Miller and D'Esposito, 2012; Liu *et al.*, 2014, 2018; Steinhauser *et al.*, 2016; Lynn *et al.*, 2018; Lin *et al.*, 2019). However, we are not aware of any studies that reported negative correlations between FFA and left frontal regions. Note that prior studies often focused on connectivity between FFA and other specific brain regions or used methods that would not have detected negative connectivity.

It should be noted that the lesion network mapping approach differs from traditional functional connectivity studies in two important ways: (i) instead of using face-selective regions, such as the FFA, as *a priori* seeds, lesion locations causing prosopagnosia, regardless of location, are used to derive a network necessary for facial recognition; and (ii) large-scale normative functional connectivity data (1000 participants) are used to construct

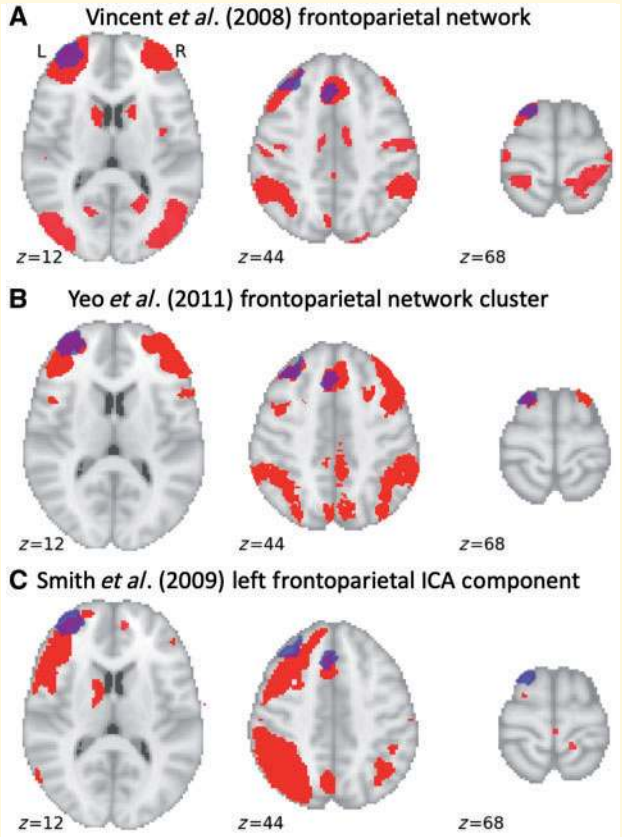

Figure 6 Identified left frontal regions overlapped with previously identified frontoparietal control networks. Left frontal regions from the lesion network mapping of acquired prosopagnosia overlap with (**A**) the frontoparietal control network described in Vincent *et al.* (2008), (**B**) functional connectivity based parcellation of the brain into major components (Yeo *et al.*, 2011), and (**C**) independent component analysis of resting state data (Smith *et al.*, 2009).

the connectivity pattern of each lesion location, greatly increasing the power to detect consistent patterns beyond the typical clinical study. Here, we show that lesions causing prosopagnosia all localize to a single functionally connected brain network defined in part by connectivity to the right FFA. This result was not driven by anatomical intersection with the right FFA, as lesions sparing an *a priori* right FFA generate this same result. Connectivity to the right FFA was also the most sensitive and specific predictor for prosopagnosia compared to connectivity to other previously reported face-selective regions. One interpretation of this finding is that the network of brain regions connected to the right FFA are all important for facial recognition, with each region performing a distinct function necessary for facial recognition (Mattson *et al.*, 2000; Barton, 2008). For example, prior work has suggested the anterior temporal cortex may play a specific role in face identification (Kriegeskorte *et al.*, 2007; Simmons *et al.*, 2010; Nestor *et al.*, 2011; Pancaroglu *et al.*, 2011; Avidan *et al.*, 2014, Barton and Corrow, 2016*b*; Yang *et al.*, 2016). Another possibility, based on the concept of diaschisis (Carrera and Tononi, 2014), is that lesions in different locations disrupt facial recognition through remote functional effects on the right FFA itself (Bruce and Young, 1986; Haxby *et al.*, 2000). These interpretations are not mutually exclusive, and both highlight the importance of network connectivity in facial recognition.

Unexpectedly, all 44 lesion locations were also connected to regions in left frontal cortex, part of a previously described left frontoparietal control network (Dosenbach *et al.*, 2007; Vincent *et al.*, 2008; Smith *et al.*, 2009; Yeo *et al.*, 2011). This network is activated by a diverse array of stimuli and tasks (Dosenbach *et al.*, 2007; Fedorenko *et al.*, 2013) compared to the domain-specificity of the right FFA (Downing *et al.*, 2006), and in particular by tasks requiring increased attention to specific features of a visual stimuli (Ranganath *et al.*, 2000; Pollmann *et al.*, 2007; Beck and Kastner, 2009; Miller *et al.*, 2011; Farooqui *et al.*, 2012). The anterior prefrontal cortex has been implicated in attention shifts towards 'exploratory'/novel stimuli (Daw *et al.*, 2006; Pollmann *et al.*, 2007; Mansouri *et al.*, 2015; Raja Beharelle *et al.*, 2015) and in variable aspects of face processing, e.g. perception of fearful faces (Kiss and Eimer, 2008) and the detection and evaluation of social gaze cueing (Schilbach *et al.*, 2006; Kuzmanovic *et al.*, 2009). Frontopolar cortex demonstrates differential responses during gaze curing experiments (Pelphrey *et al.*, 2004; Grossmann *et al.*, 2008) and during 'face-to-face' conversation (Suda *et al.*, 2010).

Finally, these left frontal regions are negatively correlated with lesion locations causing prosopagnosia, in contrast to the positive correlations seen with the right FFA. This negative correlation is not an artefact of processing methodology, as it is present independent of global signal regression (Murphy and Fox, 2017). When spontaneous brain activity at the lesion location decreases, spontaneous activity in the right FFA also decreases but spontaneous activity in left frontal cortex increases. While further work is needed to understand how brain activity changes in functionally connected regions following a brain lesion, both positive and negative correlations appear to be important for linking lesion locations to a common brain network (Boes *et al.*, 2015; Darby *et al.*, 2017*b*; Corp *et al.*, 2019). For example, subcortical lesions associated with new-onset visual hallucinations are positively correlated with the thalamus and negatively correlated with extrastriate visual cortex (Boes *et al.*, 2015; Darby *et al.*, 2017*b*).

The finding that lesion locations causing prosopagnosia are all connected to two distinct brain areas, and are therefore part of two distinct brain networks, has been seen in other lesion-induced disorders that we have studied (Boes *et al.*, 2015; Darby *et al.*, 2017*a, b*; Corp *et al.*, 2019). Although speculative, this finding may have implications for understanding facial recognition. One possibility, based on similar findings in lesion-induced delusions (Darby *et al.*, 2017*b*), is that prosopagnosia is a 'two-hit' disorder that requires disruption of two distinct functions,

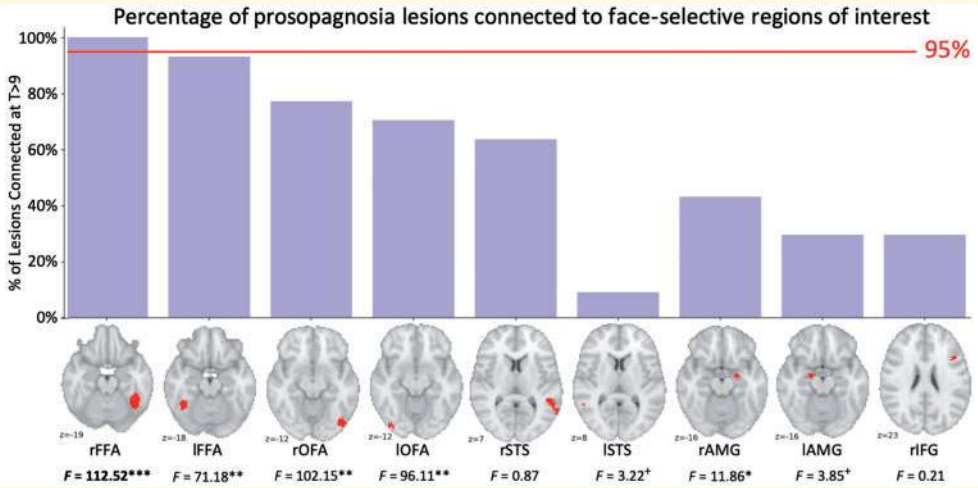

Figure 7 Different *a priori* face-selective regions of interest show different connectivity to lesion locations causing prosopagnosia. Nine regions of interest previously associated with face-selective activity are displayed on transverse brain slices (red regions). The bar height above each region shows the percentage of prosopagnosia lesion locations functionally connected to that region. The right fusiform face area (rFFA) is the only region connected to >95% of acquired prosopagnosia lesions (red line). *F*-values below each region label reflect the specificity of this connectivity compared to control lesions (*post hoc* one-way ANOVAs) (Supplementary Fig. 5). Asterisks denote statistical significance of these *F*-values: $^{+}P < 0.05$, $^{*}P < 0.0001$, $^{**}P < 1 \times 10^{-25}$, $^{***}P < 1 \times 10^{-35}$. The right FFA is the most sensitive and the most specific connection for prosopagnosia lesions. AMG = amygdala; IFG = inferior frontal gyrus; l = left; OFA = occipital face area; r = right; STS = superior temporal sulcus.

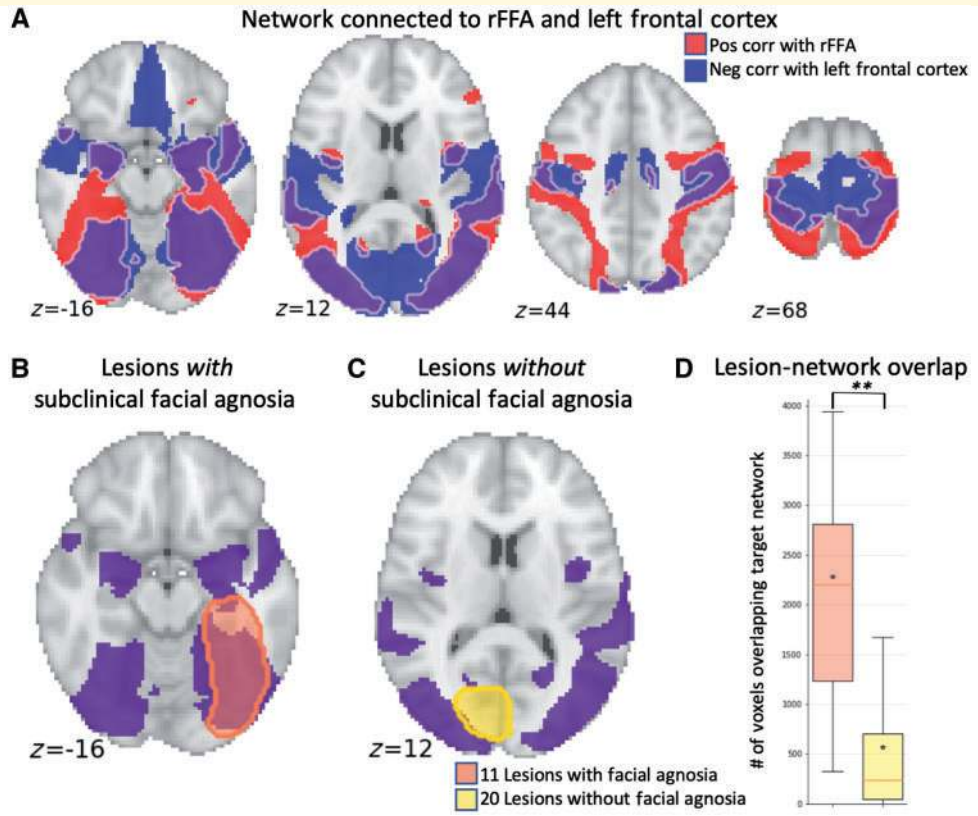

Figure 8 Lesion connectivity with the right FFA and left frontal cortex predicted subclinical facial agnosia. The intersection of positive connectivity with our identified right FFA (red shading) and negative connectivity with our left frontal regions (blue shading) defined a specific network of areas (purple shading) (**A**) highly likely to cause prosopagnosia if lesioned. Posterior cerebral artery strokes from an independent dataset that were associated with subclinical facial agnosia (**B**), versus lesions associated with intact facial perception (**C**), were significantly more likely to intersect this network (**D**). ($^{**}P < 0.01$). Red lines in box-plots indicate medians while stars indicate means.

one mediated by the right FFA network and another mediated by the left frontal network. Note that this 'two-hit' model does not require two separate lesions, as a single lesion that intersects two separate networks could potentially disrupt two distinct functions. Consistent with this hypothesis, prosopagnosic patients have impaired facial perception, presumably mediated by the FFA network, but also fail to attend to features useful for recognition such as the eye region, which may be mediated by the left frontal network (Caldara *et al.*, 2005; Pancaroglu *et al.*, 2016).

A second possibility, based on similar findings in lesions associated with criminality (Darby *et al.*, 2017*a*), is that the right FFA and left frontal cortex are engaged in a competitive 'push-pull' relationship, and lesions connected to both regions disrupt a balance away from gestalt or holistic face processing and towards detail-oriented face processing. As noted above, there seems to be a 'push-pull' relationship between these two networks along a number of similar dimensions, including detail processing versus gestalt recognition (Gauthier *et al.*, 1999; Pollmann *et al.*, 2007; Beck and Kastner, 2009; Miller *et al.*, 2011; Farooqui *et al.*, 2012), exploratory versus exploitative behaviour (Daw *et al.*, 2006; Pollmann *et al.*, 2007; Mansouri *et al.*, 2015; Raja Beharelle *et al.*, 2015), and invariant versus configurable face processing (Pelphrey *et al.*, 2004; Schilbach *et al.*, 2006; Grossmann *et al.*, 2008; Kiss and Eimer, 2008; Kuzmanovic *et al.*, 2009). Evidence supporting this 'push-pull' hypothesis include bias towards feature-based processing in patients with acquired prosopagnosia (Caldara *et al.*, 2005). In this framework, prosopagnosia lesions would shift the balance between the FFA and left frontal cortex in favour of the latter, resulting in a shift from rapid domain-specific gestalt processing supporting facial recognition to an over-reliance on domain-general feature-based processing.

Future work can potentially discriminate between these two speculative hypotheses. First, one could study patients with left frontal lesions that intersect the currently described left frontal network, i.e. locations anticorrelated with lesion locations causing prosopagnosia. Our two-hit model predicts that these patients would have impaired facial recognition, while our push-pull model predicts that these patients might have enhanced facial recognition. To our knowledge, detailed testing of facial recognition in patients with left frontal lesions has yet to be conducted. A second possibility would be to study individuals with superior objective face recognition skills, so-called 'Super-recognizers' (Ramon *et al.*, 2019); however, there has yet to be a systematic neuroimaging study of this population identifying the relevant brain regions. Finally, transcranial magnetic stimulation (TMS) has been used to transiently disrupt face processing, typically focusing on occipital cortex (Pitcher *et al.*, 2012; Solomon-Harris *et al.*, 2013). The effect of TMS to the left frontal regions described here on facial recognition has received limited investigation and remains unclear (Renzi *et al.*, 2013; Maurer *et al.*, 2017). A particularly interesting hypothesis is whether inhibitory TMS to left frontal regions could improve facial recognition.

Our results may also shed light on impaired or altered face processing ability in individuals without overt brain lesions, such as patients with developmental prosopagnosia (Duchaine and Nakayama, 2006) or autism spectrum disorder (Wolf *et al.*, 2008; Harms *et al.*, 2010; Weigelt *et al.*, 2013). In addition to face recognition deficits, these patient populations show functional imaging abnormalities in both occipitotemporal cortex and prefrontal areas (Bookheimer *et al.*, 2008; Herrington *et al.*, 2015; Towler *et al.*, 2017), potentially consistent with the above two-hit model. Furthermore, individuals with developmental prosopagnosia have difficulty extracting global interpretations from local features (Behrmann *et al.*, 2006; Gerlach *et al.*, 2017), potentially consistent with our push-pull model. In fact, improvement in face recognition has been demonstrated when holistic (versus feature-based) face training is explicitly targeted (DeGutis *et al.*, 2014).

One important aspect of the current study is the ability to use lesion network mapping to predict subclinical deficits in an independent lesion cohort (Ferguson *et al.*, 2019). While clinically evident prosopagnosia post-stroke is quite rare (Barton and Corrow, 2016*a*), subclinical deficits detectable on formal testing may be quite common (Martinaud *et al.*, 2012). Our results suggest that connectivity profiles of specific symptoms based on rare but severe cases may be useful to screen for subtle but more common deficits in other patients. The ability to predict subclinical deficits based on lesion connectivity alone, prior to reaching the threshold of clinical significance, could be useful for patient screening, preventative therapies, and rehabilitation programmes.

Limitations

Several limitations of lesion network mapping have been previously addressed, but bear mentioning here. First, our primary cohort (n = 44) was identified based on a systematic literature search, prone to publication bias, and limited by the clinical information reported in these papers. For example, investigators may be more likely to report cases of acquired prosopagnosia that conform to expectations regarding intersection with the right FFA and known face-selective regions. Reproducibility of our results with split-half replication and with the 15 lesions that did not intersect the right FFA help mitigate this concern. Similarly, due to limited clinical information, we were unable to look for network differences based on subtypes of prosopagnosia, i.e. purely apperceptive (face perception deficits) versus purely associative (intact face perception but deficit in face recognition) prosopagnosias (De Renzi *et al.*, 1991; Corrow *et al.*, 2016), or test for associations between lesion connectivity and the severity of facial recognition deficits.

Second, 2D representations of lesion locations shown in published images do not capture the full 3D geometry of the actual lesion. However, prior work has shown that

lesion networks generated using 2D lesion sections are nearly identical to lesion networks generated from the full 3D lesion (Boes *et al.*, 2015; Darby *et al.*, 2017*b*), a result which we replicated here using prosopagnosia lesions (Supplementary Fig. 2). Further, any inaccuracy in lesion tracing or in using a 2D representation of a 3D lesion should bias us against the current results, namely a common network for all lesions causing prosopagnosia.

Third, we used a normative group connectome (n = 1000) to approximate the connectivity pattern of each individual patient at the time of their lesion. While this provides signal-to-noise advantages and allows for technique standardization, it ignores individual differences in connectivity that may be important. It is possible that results could be improved by using a connectome better matched to the disease, gender, or average age of the lesion patients. That said, prior work from our group suggests that using age-matched or disease-matched connectomes makes little difference with respect to network mapping (Fox *et al.*, 2014; Boes *et al.*, 2015; Darby *et al.*, 2017*a*). Similarly, lesion network mapping results are robust to methodological differences in how one processes connectome data, e.g. global signal regression versus other artefact removal strategies (Boes *et al.*, 2015), a result we replicate for prosopagnosia lesions (Supplementary Fig. 4).

Finally, the goal of the present study was to test whether lesion locations causing prosopagnosia map to a common brain network, to define this network, and to validate this network using an independent dataset of lesion patients with subclinical deficits. The goal of this study was not to predict the location or direction of functional imaging abnormalities seen in patients with acquired prosopagnosia (Davies-Thompson *et al.*, 2014; Corrow *et al.*, 2016). These approaches are complimentary, and future work testing whether the regions and networks identified here are abnormal in patients with facial recognition deficits is an important topic for future work.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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