Laboratories) both times. Patient 2 had two negative tests as well during the first week of hospital admission, first with cell-based assay with quantification by immunofluorescence (Associated Regional and University Pathologists) and second with cell-based assay with quantification by flow cytometry (Mayo Clinic Laboratories). Given test timing, use of cell-based assay, and multiple data points, we have no evidence that MOG antibody-associated disease was the etiology in these cases.

Potential Conflicts of Interest

Nothing to report.

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Is there an Association between Tuber Involvement of the Fusiform Face Area in Autism Diagnosis?

Kevin S. Weiner, PhD [1,2] and Ethan H. Willbrand, BA [1,2]

Cohen et al. report an association between tuber involvement of the right fusiform face area (FFA) and autism spectrum disorder (ASD) diagnosis.[1] We do not question that a focal neuroanatomical location of the right posterolateral temporal lobe is related to ASD diagnosis, as identified by voxelwise lesion symptom mapping (VLSM) analyses. Nevertheless, we question whether this cortical location aligns with the FFA for two main reasons.

First, despite meta-analyses across hundreds of studies that included thousands of participants, it is unclear if the location identified by the VLSM analyses is indeed face-selective. For example, the same cortical locus overlaps equally, and in some cases more so, with "reading," "letter," and "object" as search terms in Neurosynth (Fig 1B).[2] As such, the authors cannot be sure that the five voxels identified by the VLSM analyses are definitively face-selective. Furthermore, given probabilistic predictions of face-selective regions in >1,000 participants, the VLSM cluster is located in an anatomical location that is reflective of a face-selective region in only 18 out of 1,053 (1.7%) participants on average at the most liberal boundary (Fig 1C).[3]

Second, recent findings indicate a mismatch between neuroanatomical-functional mapping at the level of meta and group analyses relative to analyses conducted in individual participants. For example, Van Essen and Glasser[4] showed that a group "striplike" definition of the FFA does not align with the definition of face-selective regions on the FG in individual hemispheres – a mismatch reflective of a conversation in the broader human brain mapping field between a balance of large N studies and "precision imaging" studies in individual participants.[5,6]

As such, the present study by Cohen et al. motivates future research with (at least) two options: there is a relationship between tuber involvement of the FFA in ASD diagnosis in individual participants, or instead, there is a relationship between a focal neuroanatomical location of the posterolateral temporal lobe and ASD diagnosis outside of face-selective regions.[1]

In an ideal neurological world, the same neuroanatomical-functional correspondences would converge across approaches – and sometimes it does (Fig 1B, left; Fig 1C). However, this is not always the case, as identified here, which likely affects the interpretation of the present findings and future studies implementing a similar approach. As such, this neuroanatomical-functional mismatch across analysis approaches necessitates a conversation across fields (neurology, human brain mapping, cognitive neuroscience, and others) regarding how to accurately relate neuroanatomical-functional correspondences across analysis approaches in all areas of the cerebral cortex.

Acknowledgments

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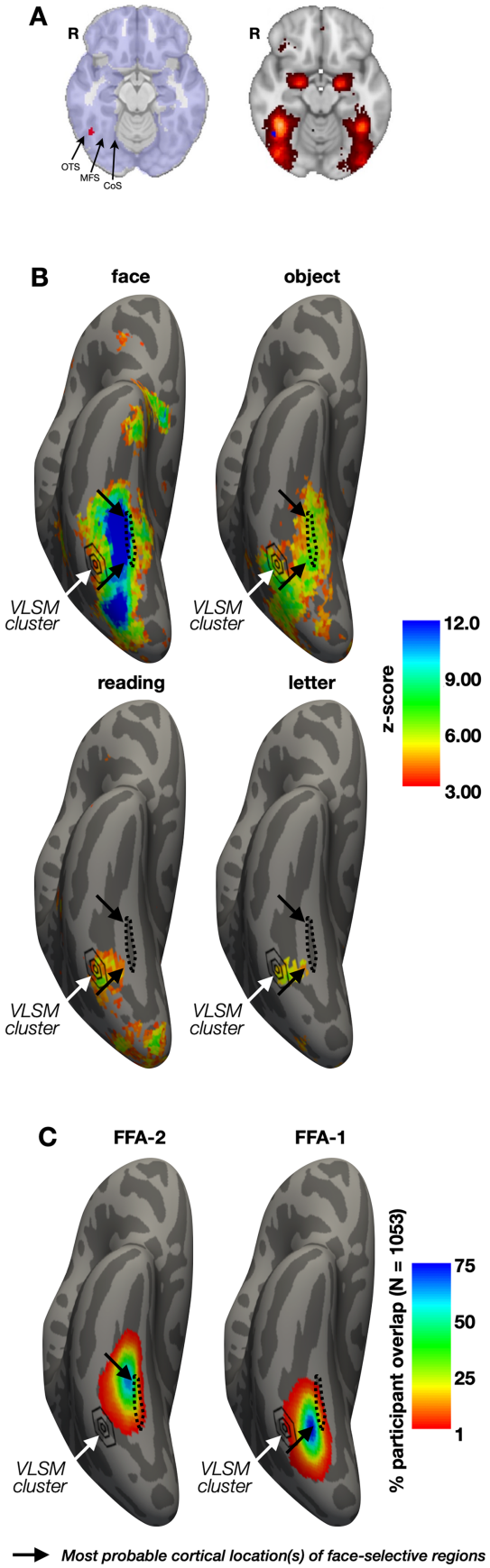

(Figure legend continues on next column.)

FIGURE 1: Is there an association between tuber involvement of the fusiform face area (FFA) in autism diagnosis? (A) Axial images from Figures 4 (left) and 5 (right) from Cohen et al. with three sulci in the ventral temporal cortex identified: occipito-temporal sulcus (OTS), mid-fusiform sulcus (MFS), and collateral sulcus (CoS). For visualization purposes, the images are flipped from the original versions to mirror (B) and (C), such that the right hemisphere (R) is on the left. The voxelwise lesion symptom mapping (VLSM) cluster is situated in the posterior extent of the OTS, whereas the most predictive location of face-selective regions in individual participants,[7] meta-analyses, and group analyses is the anterior and posterior extents of the MFS (dotted black outline in B and C). (B) Inflated cortical surface reconstruction of a right hemisphere from FreeSurfer ("fsaverage," which is a cortical surface produced from an average of 39 individuals) with different Neurosynth[2] meta-analysis association maps projected onto the surface. The search terms reflected in the map are included at the top of each image. Top row: "face" (studies = 896, # activations = 31,842), "object" (studies = 851, # activations = 29,742); lower row: "reading" (studies = 521, # activations = 21,842), "letter" (studies = 173, # activations = 6,818). For visual consistency, all maps are thresholded between z-scores of 3–12 (the minima accounts for the minimum scores across all maps, and the maxima is the average maxima across all maps). The black penumbras on each cortical surface coincide with the location of the significant VLSM tuber cluster (identified based on the Montreal Neurological Institute coordinates in reference 1, the white arrow). The vertex coinciding with the Montreal Neurological Institute coordinate is dilated three different times (three concentric circles) to provide surface estimates of the tuber location from liberal to more conservative locations (smallest to largest: 2×, 5×, 10×). The average z-score within each dilated level of the VLSM estimate was similar for "face" (2× = 3.17, 5× = 3.40, 10× = 3.80), "reading" (2× = 4.66, 5× = 4.30, 10× = 3.38), "letter" (2× = 3.64, 5× = 2.68, 10× = 1.78), and "object" (2× = 4.90, 5× = 5.16, 10× = 4.74) search terms. Thus, using a meta-analytic approach, it is unclear that this VLSM cluster is located within the face-selective cortex, as opposed to regions that are selective for objects, words, or letters. (C) Same as (B), except with maximum probabilistic predictions of face-selective regions from manually identified regions of interest in >1,000 individual participants.[3] Left surface: mFus-faces/FFA-2; right surface: pFus-faces/FFA-1. Note that these maps are thresholded between 1% and 75% of overlap between participants—which generally corresponds from a relevant minimum (1% = ~11 participants) to the maximum percentage overlap for each region of interest (75% = ~790 participants). The average percentage within each dilated level of the VLSM estimate was low for both mFus-faces/FFA-2 (2× = 0%, 5× = 0%, 10× = 0.1%) and pFus-faces/FFA-1 (2× = 0.5%, 5× = 0.8%, 10× = 1.7%). Note that across approaches (meta-analytic [B] or maximum probabilistic [C]]), the most probable location of face-selectivity (blue in B [top left] and C [both images]) is adjacent to the MFS (dotted black line) with high overlap across approaches (Dice coefficient = 0.89). However, the VLSM cluster is centimeters away. Altogether, there is a focal neuroanatomical location of the posterolateral temporal lobe that is related to autism spectrum disorder diagnosis, as identified by VLSM analyses by Cohen et al.[1] From our quantifications, there is a low probability that this locus overlaps with face-selective regions. [Color figure can be viewed at www.annalsofneurology.org]

Potential Conflicts of Interest

Nothing to report.

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Reply to "Is There an Association between Tuber Involvement of the Fusiform Face Area in Autism Diagnosis?"

Alexander L. Cohen, MD, PhD [1,2,3]
Mallory R. Kroeck, MA,[1,3] and
Michael D. Fox, MD, PhD, [3,4,5] on behalf of
the TACERN Study Group

We thank Weiner and Willbrand for their interest in our recent work.[1] We commend their focused analysis relating the location of tubers associated with diagnosis of autism spectrum disorder (ASD) in our paper[2] to visually selective regions in the right temporal lobe, including the right fusiform face area (FFA). They note a spatial offset between the voxel-wise lesion symptom mapping (VLSM) peak derived from tuber locations and the FFA as defined by functional neuroimaging. We agree with their observation, and note a few potential reasons for this offset.

First, due to differential rates of development, there are likely slight differences in the location of visually selective regions in children and adults.[3] The average age of the patients in our study was 3 years old, whereas the FFA and other visually selective regions derived here from functional neuroimaging were based on adults. The location of the FFA may be different in children, with one study reporting a face-related peak that was posterior and lateral to the adult FFA, similar to our VLSM peak.[4] It is worth noting that these studies are in children as young as ages 5 to 8 years, and to our knowledge the location of FFA in 3-year-olds (as defined by functional neuroimaging) remains unknown.

Second, there may be a difference in localization of function based on brain lesions versus functional neuroimaging. For example, cortical tubers could affect the rFFA, due to irritation of surrounding tissue or impairment of surrounding connectivity. Thus, the localization we identified may represent the location "closest" to the rFFA where tubers naturally occur – it may be possible that tuber involvement of the tracks *leading to* the FFA may be equivalently damaging to face processing compared to damage to the FFA itself. This would be consistent with our prior analysis of lesions resulting in prosopagnosia where we also found a slight offset between lesion and functional magnetic resonance imaging (fMRI) localization of the FFA (Figure).[5]

Third, there may be technical reasons for the spatial offset. Registering data from 3-year-old children to an adult atlas space may result in a less-than-ideal registration. There is significant gyrification that happens after 3 years of age[6] and it is possible that this results in a minor shift in registration. Similarly, moving a coordinate or localization from a volumetric group average to surface space is not straightforward,[7] and may also induce an offset. Future work can consider how to best localize tubers in the surface space.

Finally, it is possible that there is indeed a true difference in localization, and the VLSM peak associated with autism diagnosis might be different from a VLSM peak associated with impaired facial recognition. Impaired facial recognition is just one of many early deficits in ASD, and the location in the inferior temporal that confers risk for ASD may have a different functional specialization than selective activation to faces. Although facial recognition was not tested in the current tuberous sclerosis complex (TSC) cohort, we are in the process of collecting these data to test for convergence across lesion-related deficits in the same patients.

In summary, we appreciate the results demonstrated by Weiner and Willbrand and encourage efforts to complement lesion symptom mapping with results from other techniques. Here, we expect that the question raised by Weiner and Willbrand will need to be empirically answered by future analysis of fMRI localization of these regions in children with TSC, combined with the lesion symptom mapping of facial recognition deficits in these patients.

Acknowledgments

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