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Local but not long-range microstructural differences of the ventral temporal cortex in developmental prosopagnosia

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ABSTRACT

Individuals with developmental prosopagnosia (DP) experience face recognition impairments despite normal intellect and low-level vision and no history of brain damage. Prior studies using diffusion tensor imaging in small samples of subjects with DP ($n=6$ or $n=8$) offer conflicting views on the neurobiological bases for DP, with one suggesting white matter differences in two major long-range tracts running through the temporal cortex, and another suggesting white matter differences confined to fibers local to ventral temporal face-specific functional regions of interest (fROIs) in the fusiform gyrus. Here, we address these inconsistent findings using a comprehensive set of analyzes in a sample of DP subjects larger than both prior studies combined ($n=16$). While we found no microstructural differences in long-range tracts between DP and age-matched control participants, we found differences local to face-specific fROIs, and relationships between these microstructural measures with face recognition ability. We conclude that subtle differences in local rather than long-range tracts in the ventral temporal lobe are more likely associated with developmental prosopagnosia.

1. Introduction

People with prosopagnosia experience severe deficits with facial identity recognition despite normal low-level vision and normal intellect. Prosopagnosia can occur due to a failure to develop the mechanisms necessary for face recognition, and when it does so in the absence of more general neurodevelopmental disorders, it is referred to as developmental prosopagnosia (DP) or congenital prosopagnosia (Susilo and Duchaine, 2013; Behrmann and Avidan, 2005a, b). Rough estimates suggest that the prevalence of DP is about 2% (Kennerknecht et al., 2006, 2008). Not surprisingly, the social difficulties DP creates lead to elevated rates of psychosocial problems (Dalrymple et al., 2014a; Yardley et al., 2008).

Face recognition depends on a network of spatially distributed regions in the occipital and temporal cortices, and proper functioning of this network depends on the structural connections between these regions. A study by Thomas et al. (2009) implicated impaired microstructural integrity of the two major long-range tracts projecting from posterior occipito-temporal regions to anterior temporal and frontal lobe regions (the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) respectively) as a critical neural feature of DP. That study used diffusion tensor imaging (DTI) and deterministic tractography and found that, relative to a group of controls, six DP participants showed reductions in the integrity of the ILF and the IFOF bilaterally as assessed by mean fractional anisotropy (FA), numbers of fibers, and tract volume. In combination with functional MRI studies showing normal activity in posterior face-selective regions (Avidan et al., 2005, 2011; Hasson et al., 2003), these structural deficits were interpreted as evidence for DP as a disconnection syndrome: face processing deficits occur because intact posterior occipito-temporal regions that are responsible for visual analysis of faces are unable to communicate via the ILF and IFOF with more anterior temporal areas (Avidan and Behrmann, 2009; Avidan et al., 2014; Behrmann and Plaut, 2013).

However a more recent paper did not find any group

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differences between DP and control subjects in the ILF (they did not analyze the IFOF) (Gomez et al., 2015). This study compared eight subjects with DP to controls and instead found more localized differences within fibers defined by tractography from face-specific functional regions of interest located within a region in the fusiform gyrus (Gomez et al., 2015) known as the fusiform face area (FFA).

The study by Thomas et al. (2009), conducted during the early days of diffusion tensor imaging, employed limited scanning parameters for diffusion data (6 diffusion directions), that are now considered less than ideal for tractography (Berman et al., 2013, Thomas et al., 2014). Further, while both studies based much of their findings on tractography-based metrics, recent studies have demonstrated the substantial influence of different tracking algorithms on tracts identified, and called into question the ability of any tracking algorithm to be both sensitive and specific (Thomas et al., 2014), or able to differentiate superficial white matter fiber systems from long-range connections (Reveley et al., 2015). These studies point out the inherent limitations of tractography methods to distinguish between tracts.

For these reasons, we made the following substantial improvements in data collection and additions to data analyzes. We used scanning parameters for diffusion data (two datasets with 61 diffusion directions each) and corrections for susceptibility-induced image distortions (Andersson et al., 2003) that allows for more precise, reliable, and accurate tractography as well as better estimation of FA (Wang et al., 2012, Jones, 2011). We included a more thorough set of blinded analyzes that, defined tracts deterministically with varied curvature thresholds as well as probabilistically. Given the inherent limitations of tracting algorithms to differentiate between tracts, we also included voxel-wise comparisons within a mask that included all tracts and fibers of interest, given that voxel-wise comparisons do not rely on the accuracy of tractography. However, given the introduction of Type 1 errors with the problem of multiple voxel-wise comparisons, we used Monte-Carlo simulations to determine family-wise error to qualify findings. We additionally tested whole brain voxel-wise comparisons like those employed by Thomas et al. (2009) though that report did not highlight family-wise error as we do here. The problem of multiple comparisons increases dramatically with a whole brain search (Supplementary Section 1).

Finally, as pointed out by both Thomas et al. (2009) and Gomez et al. (2015), the small numbers of subjects included in those studies ($n=6$ and $n=8$) required validation in larger numbers of subjects. Here, we address past inconsistent findings in a cohort of subjects with DP that is larger than both prior DTI studies combined ($n=16$), with the added benefit that these subjects have been well characterized behaviorally (Dalrymple et al., 2014b; Garrido et al., 2009), using task-related functional MRI (Furl et al., 2011), and with voxel based morphometry to look at gray matter abnormalities (Garrido et al., 2009). Our aim was to conduct analyzes of white-matter integrity in these subjects to offer a comprehensive description of a large cohort of subjects with DP, and to investigate whether a deficit in local rather than long-range connections in the ventral temporal lobe was associated with developmental prosopagnosia.

2. Materials and methods

2.1. Participants

Sixteen individuals with DP and 16 age-matched controls volunteered for this study. We have previously reported analyzes of their behavioral data (Dalrymple et al., 2014b; Garrido et al., 2009), gray matter volume (Garrido et al., 2009), and functional responses (Furl et al., 2011). The current study includes the same participants listed in Garrido et al. (2009) except for one DP (DP14) and two controls (C4 and C6) whose DWI scans were suboptimal due to technical problems. For FFA fibers, we used for the tracking the face-specific functional regions of interest for these participants, which are reported in Furl et al. (2011). In particular, the right and left FFA were definable in 13 of the 16 DP participants and 15 of the 16 control participants.

The 16 DP participants (10 females) were between 20 and 46-years-old and had a mean age of 31 years (SD=8) while the 16 controls (10 females) had a mean age of 30 (SD=6). All participants were right-handed. All DP participants reported significant problems in recognizing faces in their daily lives, and each performed significantly below normal on two tests of face recognition: the Cambridge Face Memory Test (Duchaine and Nakayama, 2006) and a Famous Faces Test. Individual results on these tests and complete behavioral profiles are reported in Garrido et al. (2009).

Dimensionality reduction on behavioral performance measures was carried out using principal component analysis using Statistical Package for the Social Sciences 11.0 (SPSS Inc, Chicago, IL, USA) as described in Garrido et al. (2009). The four face identity recognition measures were the only measures to load highly on the first principle component, and therefore the participant loadings (factor scores) on this first component appear to provide a composite measure of facial recognition ability. Factor scores on the first component were found to be associated with gray matter density and face selectivity in the posterior fusiform gyrus and anterior temporal cortex (Garrido et al., 2009; Furl et al., 2011). Further, our factor scores capture variability in common with five facial identity recognition tasks while covarying out orthogonal sources of variability in three object recognition and three emotion recognition tasks. For these reasons, this first component was used as a measure of facial recognition ability in the current report. We have included a table in the supplementary section that lists individual scores on individual tests along with scores for this first component (Supplementary Table S1).

2.2. Scanning parameters

Scanning was conducted at the Wellcome Trust Center for Neuroimaging in London, UK. All MRI data were collected on a 3T Tim Trio scanner (Siemens Healthcare, Erlangen, Germany) using single-channel body coil excitation and a 12–channel receive-only head coil for acquisition. For diffusion data, a locally-implemented version (Nagy et al. 2007) of the twice-refocused spin echo diffusion sequence (Feinberg and Jakab, 1990; Reese et al., 2003) was collected twice. The two diffusion data sets were identical except the phase encoding blip direction was reversed to allow for adequate combination to correct susceptibility induced distortions (Andersson et al., 2003; Ruthotto et al., 2012) and vibration artifacts that were induced by fast switching of the large diffusion-encoding gradients (Gallichan et al., 2010; Mohammadi et al. 2012). Each diffusion data set contained images acquired using the following parameters: TE/TR=90/150 ms, FOV=220 × 220 mm^2, 96 × 96 acquisition matrix, resolution=2.3 × 2.3 × 2.3 mm^3, first 7 volumes at a b-value of 100 s/mm^2 that were averaged to generate a low b-value volume followed by 61 brain volumes at a b-value of 1000 s/mm^2 in 61 evenly-distributed directions. The protocol also included a 3D T1–weighted MDEFT image (Diechmann et al., 2004) (TE/TR=2.48/7.92 ms, FOV=256 × 240 mm^2, 256 × 240 acquisition matrix, resolution=1x1 × 1 mm^3).

2.3. Diffusion data analyzes

Prior to data analyzes, diffusion data were subject to state-of-