Behavioral/Cognitive

Effective Connectivity from Early Visual Cortex to Posterior Occipitotemporal Face Areas Supports Face Selectivity and Predicts Developmental Prosopagnosia

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Face processing is mediated by interactions between functional areas in the occipital and temporal lobe, and the fusiform face area (FFA) and anterior temporal lobe play key roles in the recognition of facial identity. Individuals with developmental prosopagnosia (DP), a lifelong face recognition impairment, have been shown to have structural and functional neuronal alterations in these areas. The present study investigated how face selectivity is generated in participants with normal face processing, and how functional abnormalities associated with DP, arise as a function of network connectivity. Using functional magnetic resonance imaging and dynamic causal modeling, we examined effective connectivity in normal participants by assessing network models that include early visual cortex (EVC) and face-selective areas and then investigated the integrity of this connectivity in participants with DP. Results showed that a feedforward architecture from EVC to the occipital face area, EVC to FFA, and EVC to posterior superior temporal sulcus (pSTS) best explained how face selectivity arises in both controls and participants with DP. In this architecture, the DP group showed reduced connection strengths on feedforward connections carrying face information from EVC to FFA and EVC to pSTS. These altered network dynamics in DP contribute to the diminished face selectivity in the posterior occipitotemporal areas affected in DP. These findings suggest a novel view on the relevance of feedforward projection from EVC to posterior occipitotemporal face areas in generating cortical face selectivity and differences in face recognition ability.

Key words: DCM; developmental prosopagnosia; effective connectivity; face perception; fMRI; network

Significance Statement

Areas of the human brain showing enhanced activation to faces compared to other objects or places have been extensively studied. However, the factors leading to this face selectively have remained mostly unknown. We show that effective connectivity from early visual cortex to posterior occipitotemporal face areas gives rise to face selectivity. Furthermore, people with developmental prosopagnosia, a lifelong face recognition impairment, have reduced face selectivity in the posterior occipitotemporal face areas and left anterior temporal lobe. We show that this reduced face selectivity can be predicted by effective connectivity from early visual cortex to posterior occipitotemporal face areas. This study presents the first network-based account of how face selectivity arises in the human brain.

Introduction

During the last two decades, functionally localized areas relevant for face processing in humans have been investigated. These face-selective areas show stronger blood oxygen level-dependent (BOLD) responses to faces compared to other objects (Kanwisher et al., 1997). However, these areas do not function in isolation, but rather as an integrated system (Moeller et al., 2008). A model

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of the functional integration of face-selective areas is required to understand the neural underpinnings of face processing. Most previous studies investigating connectivity in face-selective networks have focused on anatomical connections (Thomas et al., 2008; Gomez et al., 2015) or correlated BOLD responses between face-selective areas (functional connectivity) (George et al., 2001; Iidaka et al., 2001). A handful of studies have focused on the direction of information flow between face-selective areas (Fairhall and Ishai, 2007; Furl et al., 2013). A common limitation of these directional connectivity studies is that they do not isolate the flow of face-selective information from other information. Those few studies of the directional flow of face-selective information used network models limited to relatively few face-selective regions (Nagy et al., 2012; Furl et al., 2014). Here, we investigate the directional flow of face-selective information using the most comprehensive face processing network investigated to date. We further compare the flow of face-selective information between controls and people with developmental prosopagnosia (DP), a lifelong face recognition impairment.

Previous theory can guide hypotheses about the factors generating face selectivity. An influential proposal for the neural architecture for face processing separates face-selective areas into a core system that carries out visual analysis and consists of the occipital face area (OFA), fusiform face area (FFA), and posterior superior temporal sulcus (pSTS) and an extended system carrying out further, higher-level processing (Haxby et al., 2000). Extended areas process information such as knowledge about the owner of a face in the anterior temporal lobe (ATL) and emotional information in the amygdala. Formal models testing how interactions between these areas give rise to face selectivity have not been developed. Our first aim was to quantitatively compare plausible connectivity architectures using dynamic causal modeling (DCM; Friston et al., 2003).

Occipitotemporal contributions to face processing can be investigated by studying individuals with DP. People with DP have difficulty recognizing facial identity (Behrmann and Avidan, 2005; Duchaine and Nakayama, 2006) and sometimes have problems with other aspects of face processing as well (Nunn et al., 2001; Duchaine et al., 2006). Neural abnormalities in DPs have been reported. Behrmann et al. (2007) and Garrido et al. (2009) reported decreased gray matter in the fusiform gyrus, STS, and ATL of participants with DP. Gomez et al. (2015) and Song et al. (2015) found altered white matter around the FFA in DP. Furl et al. (2011) examined DP individuals and typical controls and showed that BOLD responses in bilateral FFA and ATL correlated with face recognition ability. Furthermore, Furl et al. (2011), Dinckelacker et al. (2011), and von Kriegstein et al. (2008) found participants with DP had reduced face selectivity in FFA. Avidan et al. (2014) found reduced activation in ATL and reduced functional connectivity between the core system and ATL in DP. To better understand decreased face selectivity associated with the DP population, our second aim was to contrast neural connectivity in participants with DP versus participants with normal face recognition.

To establish the network architecture of face processing, we estimated the directionality of informational flow, using DCM, when participants viewed faces. We further investigated the relevance of the state of this system for behavior by identifying how it is altered in DP. We found a network that best explains how face relevant information flows through a face-selective network where the presence or absence of faces modulates connectivity from early visual cortex (EVC) to posterior occipitotemporal areas (OFA, FFA, and pSTS). Also, We further show that the strength of face-specific modulation in connections from EVC to FFA and pSTS is diminished in DP.

Materials and Methods

Participants

We examined the same 15 DP and 15 control individuals from the study by Garrido et al. (2009), who returned for the fMRI experiment reported by Furl et al. (2011). The participants with DP reported great difficulties with face recognition in daily life and were diagnosed using the Cambridge Face Memory Test (in its original form; Duchaine and Nakayama, 2006) and the Famous Faces Test (Duchaine and Nakayama, 2005). Informed consent was obtained in accordance with procedures approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London.

Data acquisition

T2*-weighted echoplanar functional brain volumes were acquired using the Siemens Trio 3T system. For each participant, three sessions were run with 430 volumes each for a total of 1290 volumes per participant. Images were acquired at a volume repetition time of 2176 milliseconds with an in-plane resolution of 3×3 mm, 2 mm slice thickness, a 1 mm slice gap, an echo time of 30 ms, and a flip angle of 90°. We discarded the two volumes commencing each session to avoid magnetic equilibrium contamination (Furl et al., 2011).

Experimental design

The experimental design included a repetition suppression paradigm. Stimuli comprised of images of emotional faces taken from the Karolinska Directed Emotional Faces database (Department of Clinical Neuroscience, Psychology Section, Karolinska Institute; Lundqvist and Litton, 1998) and photographs of cars.

Block designs have been shown to be statistically efficient for convolution models, such as DCM, and therefore practical for the present study (Mechelli et al., 2003a). There were two categories of blocks: faces and cars. Ninety-six blocks displayed faces, and 48 blocks displayed cars, distributed equally over three runs. Each block lasted 15.2 s with 4 s of fixation between blocks. Eight stimuli with alternating viewpoints (left and right three-quarters and frontal) were presented in each block for 1700 ms preceded by 200 ms fixation. Face blocks varied on whether facial expressions (happy, fearful, neutral, and angry) were different or the same within each block and whether identities (four male identities) were the same or different within each block. The car blocks varied on whether cars (four cars) were the same or different. All images were grayscaled, normalized to equal luminance mean and range, adjusted to similar size, and placed on a gray background. Faces were cropped to occlude hair and clothing (Furl et al., 2011).

Preprocessing and general linear model

Following Furl et al. (2011), data preprocessing was performed using SPM5 (Wellcome Trust Centre for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm/) with MATLAB (MathWorks). Preprocessing comprised realignment, normalization and 8 mm spatial smoothing. Slice timing was modeled in the DCM, where the precise acquisition time of each region of interest (ROI) was taken into account. This has been shown to be an effective solution to the slice time problem for DCM (Kiebel et al., 2007).

For ROI definition, we used general linear models (GLMs) from SPM8. First we analyzed the time series data at the individual participant level using a canonical hemodynamic response function, a low-pass filter of 1/256 Hz, AR(1) autocorrelation modeling, motion correction, and proportional scaling. Then, contrasts of interest (faces vs cars and all stimuli vs baseline; see below, ROI selection) were computed in each individual participant. The resulting contrast images were subjected, at a second level, to right-sided t tests treating participants as random effects. Results images from the second level were thresholded at $p < 0.005$ (uncorrected), and clusters were then identified that met familywise error correction at $p < 0.05$ across either the whole brain or a priori small volume correction using Gaussian random field theory.

To optimize the SPM for DCM, individual participant-level GLMs were recomputed in SPM12b using regressors for all visual inputs (faces and cars) and faces only (these regressors were collapsed over repetition condition and session), as well as covariates for each run and for head motion. This allowed us to assess the effective connectivity of face-selective information across all three runs.

ROI selection

We selected ROIs considered "core" face processing areas (i.e., OFA, FFA, and pSTS; Haxby et al., 2000). We also selected the ATL, because of its putative role in face recognition and coupling to areas in the core system (Haxby et al., 2000; Eifuku et al., 2004; Behrmann et al., 2007; Yang et al., 2014). Together, these areas were hypothesized to be the main occipitotemporal components in a circuit that processes faces. For inclusion in DCM, these areas had to show significant face selectivity at a second (group) level, right-sided *t* test of the "all faces > all cars" contrast using all participants (both controls and DP). From these criteria, we identified five face-selective ROIs: right OFA (rOFA), right FFA (rFFA), right posterior STS (rpSTS), left FFA (lFFA), and left ATL (lATL). The rOFA, lFFA, and lATL were small volume corrected using a 10 mm sphere around the functional peak coordinates of at least one previous study (Allison et al., 2000; Andrews and Ewbank, 2004; Winston et al., 2004; Rotshtein et al., 2005; Hein and Knight, 2008; Fox et al., 2009; Von Der Heide et al., 2013).

We also selected the early visual cortex as an ROI for DCM. The EVC is not face-selective, but is the first cortical area in the visual processing stream and, as expected, responded robustly to both faces and cars. Using models that assume that the information initially passes through EVC allowed us to estimate the signal sent into the face-selective system in a biologically plausible manner, instead of assuming that the signal remains unchanged until reaching a face-selective area. Such models also allowed us to explore pertinent theoretical explanations for face selectivity in which face-selective areas are receptive to low-level face-diagnostic information already present in early visual areas (see Discussion). We identified EVC using a second-level, one-sample, right-sided *t* test on an "(all faces + all cars) > rest" contrast and identified the peak activation around the posterior occipital lobes.

In accordance with conventional methods, we identified the locations of the ROIs in each individual participant (Mechelli et al., 2003b, 2004; Grefkes et al., 2008; den Ouden et al., 2012). Using the second-level (group) clusters to define a search space, we identified the individual participants' face-selective peak voxel within the second-level clusters (for EVC the visual versus baseline peak voxel was identified). Second-level (group) clusters used for search spaces consist of all voxels around the area of interest, which SPM recognized as a single cluster around the peak voxel. The clusters were identified with a significance level at an uncorrected threshold of $p < 0.005$ in a second-level SPM analysis. If a second-level (group) cluster was overlapping with another area, we limited the inclusion of $p < 0.005$ thresholded voxels within 10 mm of the peak voxel of the area. This was relevant for the EVC, rpSTS, and lATL. To ensure that the search spaces were not dominated by one of the groups, we also computed the clusters from each of the groups separately. We found that the peak of the control group and DP group clusters were located within the search spaces, which indicates that our search spaces were representative for each group. After identification of individual peak voxels for all selected ROIs, we created 6 mm spheres with no threshold around the peak voxels to create participant-specific ROIs. We extracted ROI mean percentage signal change across voxels (faces > cars contrast for face-selective areas and all visual > rest contrast for EVC) for ROI analysis using MarsBar 0.42 (Brett et al., 2002). This approach reduces the multiple comparison problem from a voxelwise issue to one involving only the number of ROIs investigated. This is done by focusing only on the activity within the ROI chosen (i.e., six ROIs) and removing the variability between voxel signals within the ROI by averaging the signal of the voxels, and therefore treating each ROI as a single signal measurement (Poldrack, 2007). We used two-sample, two-tailed *t* tests for testing group differences in ROI face selectivity. The analyses were multiple comparison corrected for the number ROIs tested (Poldrack, 2007). For DCM, the first eigenvariate time series of all participant-specific ROIs were extracted from the individual participant analyses.

Dynamic causal modeling

DCM uses a generative Bayesian model of effective connectivity between hidden neuronal responses to predict fMRI BOLD responses in prespecified areas (Friston et al., 2003). DCM allows testing of specific hypotheses regarding effective connectivity. It uses Bayesian model selection (BMS) to determine which model of connectivity best explains the data. Furthermore, it allows for inference on individual connection parameters within a GLM framework (Penny et al., 2004; Stephan et al., 2010). It allows inference on three types of parameters. Endogenous connectivity (*A* parameters) is the estimated effective connectivity averaged over conditions. Modulatory connectivity (*B* parameters) models effects of a specific experimental factor on effective connectivity. Last, exogenous parameters (*C* parameters) model stimulus input effects on areas in the specified system. In the present paper, our primary interest was in measuring connections that are modulated by faces (*B* parameters). We used DCM12 to perform the DCM.

Model selection and parameter analysis. Our first goal was to ascertain a model architecture that demonstrates a likely mechanism for producing face selectivity in our face-selective ROIs. Once this model was established, we then could test whether this face selectivity generating mechanism differed in participants with DP and controls. Such differences would provide a potential account of the reductions in face selectivity in posterior areas that we observed in our sample of participants with DP (Furl et al., 2011).

We used BMS to infer which model best explained the data (Penny et al., 2004). This approach is based on the posterior probability associated with each model's evidence (free energy), summed across the participants. We performed BMS on the whole sample and separately for the control and DP groups to estimate the most likely model architecture for every group.

Using Bayesian model averaging, we estimated *A*, *B*, and *C* parameters, averaged over the model space and weighted by the exceedance probability of each model (the likelihood that one model is more likely than any other model, given all participant data). This approach to parameter estimation does not assume that participants all use the same model, but allows for different participants to have different model weighting (Penny et al., 2010; Stephan et al., 2010).

We compared the *B* parameters of controls versus DP participants. This analysis included face modulated connections present in the model architecture showing highest posterior probability in BMS (Fig. 1). This model architecture accounts for the flow of face information in the present data, and so differences in face-modulation strength in this model architecture may be relevant for the functional abnormalities in DP. We tested whether controls show greater face modulation than participants with DP by submitting *B* parameters (modulation by faces) to two-sample, right-sided *t* tests. The analyses were multiple comparison (Bonferroni) corrected for the number of connections tested.

Specification of model space. To identify which connections were most likely to create face selectivity in the face-selective ROIs, we tested modulation by faces on different configurations of connections. Given no a priori assumptions about how nonspecific visual information spreads through the system, we endogenously connected all areas reciprocally in all models. We assumed EVC to be the exogenous input area (where activity is driven by all visual experimental stimuli; see above, ROI selection).

This template was used to formulate the thirteen models that we tested (Fig. 1). The first six models were motivated by the Haxby et al. (2000) model of face processing and, specifically, the features of this model that refer to visual analysis of faces (i.e., a dedicated "core" system). In Models 1–3, face selectivity arises from face modulation between areas in the core system alone (i.e., between rOFA, FFA, and rpSTS), with feedforward (Model 1), backward (Model 2), or reciprocal (Model 3) face modulation. In Models 4–6, face selectivity arises from modulation by faces between the core system and lATL with either feedforward (Model 4), backward (Model 5), or reciprocal (Model 6) modulation. In Models 7–9, face selectivity arises from interactions between the EVC and down-

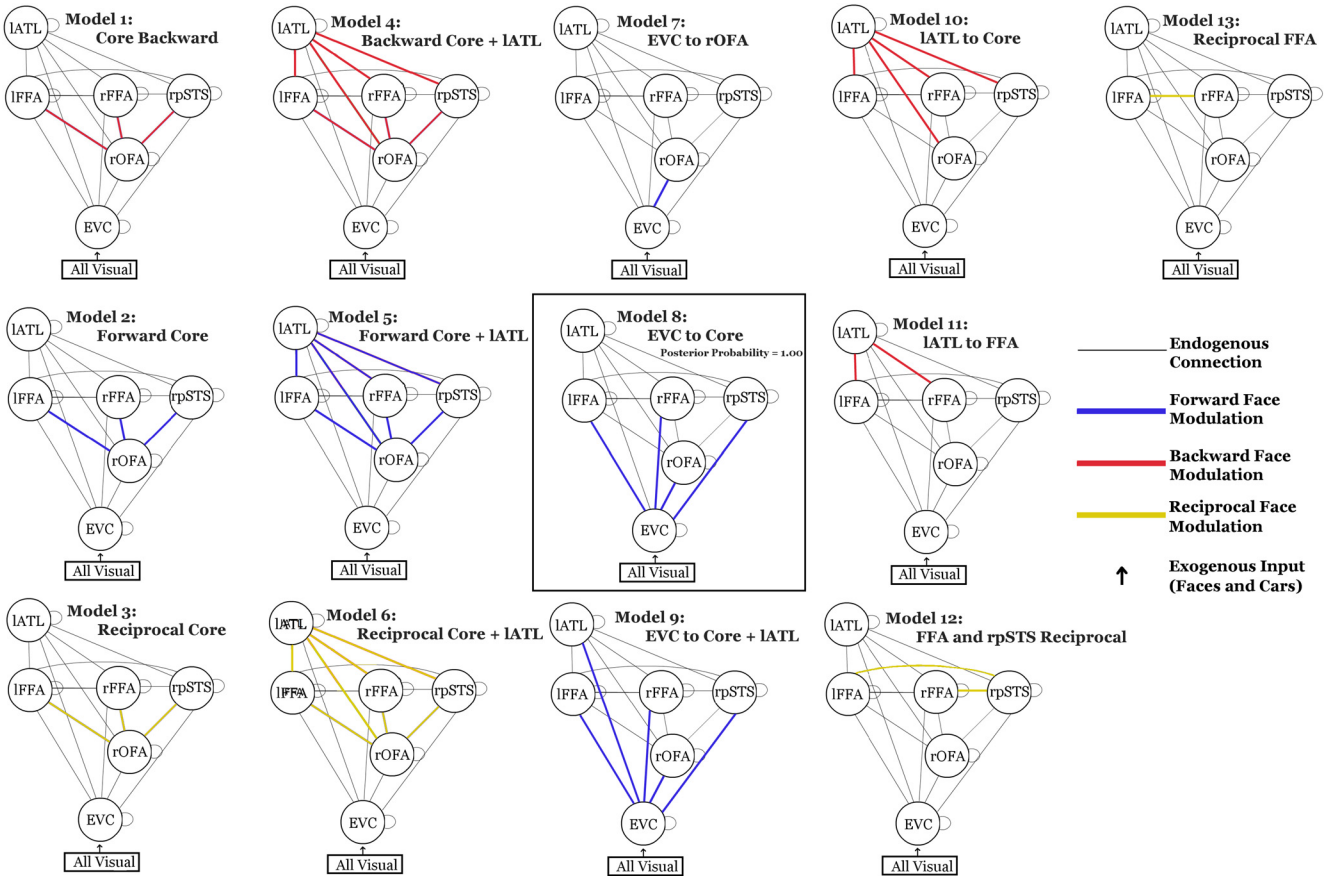

Figure 1. Model space. Thirteen models were chosen to test different hypotheses about the model architecture giving rise to face selectivity in a occipitotemporal network. The models vary only in which configuration of connections are modulated by faces. The titles above the models summarize which connections are modulated by faces. The colors of the bold lines between areas signify which direction are modulated by faces. All models are fully endogenously connected (including self connections) and have all visual stimuli (faces and cars) as driving input to EVC. Model 8 is highlighted because the BMS showed this model as the best explanation for the data in both groups.

stream face-selective areas. These three models instantiate networks where faces are discriminated from other objects through a feedforward mechanism from the EVC. Faces could modulate feedforward connections from the EVC to rOFA (Model 7), to the core system (Model 8), or to all face-selective areas (Model 9). In Models 10 and 11, face selectivity arises from backward/feedback modulation by faces from the ATL to FFA (Model 10) or to the core system (Model 11). Finally, in Models 12 and 13, face selectivity arises through horizontal modulation by faces between the left and right FFA (Model 12) or between the FFA and STS (Model 13). This model space explores the network mechanisms that are currently plausible for the selected areas, including possible feedforward, backward, and reciprocal interactions between the EVC, core system, and anterior temporal areas.

Results

SPM group analysis and ROI analysis

We performed an SPM group analysis of all the participants to test for face selectivity (i.e., faces > cars contrast) and to identify face-selective ROIs for DCM. Significant clusters and peaks at $p < 0.05$ (familywise error corrected) were identified. We observed significant face selectivity in rOFA, bilateral FFA, rpSTS, bilateral amygdala, precuneus, orbitofrontal cortex, and lATL. From these results and from our a priori assumption that occipitotemporal face-selective areas are associated with face recognition, we selected for DCM the face-selective areas rOFA, bilateral FFA, rpSTS, and lATL (Fig. 2). Furl et al. (2011) previously reported the face selectivity results separately for controls and DPs and found similar results. Here, the analysis combined all participants, as we intended to use the second-level (group) results to define a search space for ROI definition that could be applied to the whole sample.

We also report an ROI analysis using the participant-specific ROIs that we obtained from the whole sample search space and that we included in the DCM (Fig. 3). All p values for this ROI analysis are reported as uncorrected and are inferred to be significant according to a Bonferroni corrected α value: $\alpha = 0.0083$ ($\alpha = 0.05/6$). We observed significantly greater face selectivity in controls compared to the DP group in rFFA ($t_{(28)} = 3.304$, $p = 0.0026$), lFFA ($t_{(28)} = 3.172$, $p = 0.0037$), and rpSTS ($t_{(28)} = 2.970$, $p = 0.0061$). We found no significant group difference in face selectivity following Bonferroni correction in rOFA ($t_{(28)} = 0.379$, $p = 0.708$) and lATL ($t_{(28)} = 2.691$, $p = 0.012$), as well as no significant group difference in BOLD response (all visual > rest) in EVC ($t_{(28)} = 1{,}994$, $p = 0.055$). These results generally agree with the results found in Furl et al. (2011). However, we also identified an additional role for rpSTS in DP, and the comparison of lATL face selectivity in controls and DPs narrowly failed to reach significance after Bonferroni correction.

Dynamic causal modeling

Bayesian model selection

The model in which faces modulate the connections from EVC to the core system (EVC to core; Model 8) achieved a posterior probability of ~1.0 in both groups and in the whole sample

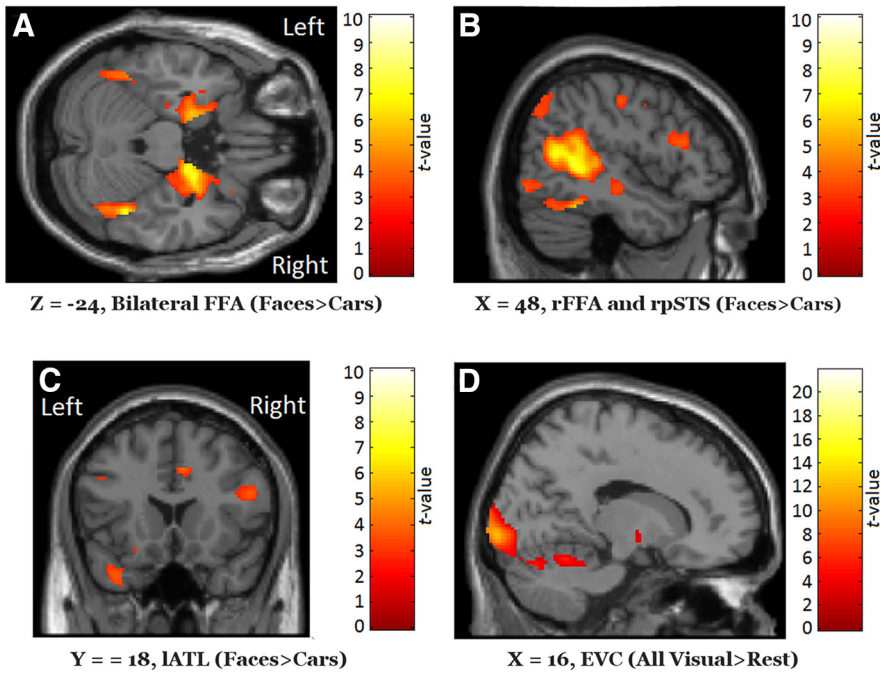

Figure 2. SPM group analysis. ***A–D***, SPM group analysis of the faces > cars contrast (***A–C***) and faces + cars > baseline (***D***). The threshold is $p < 0.005$ (uncorrected).

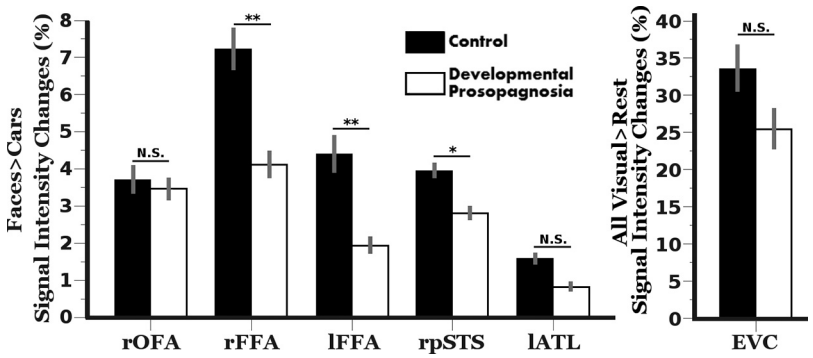

Figure 3. Group differences in ROI signal (faces > cars) intensities for face-selective areas. *$p < 0.05$; **$p < 0.01$. Error bars indicate 1 SEM.

(Table 1, Fig. 1). Model architecture in DP and control groups was therefore qualitatively similar.

Face processing is often regarded as primarily lateralized to the right hemisphere. To test whether some models were less likely due to interhemispheric connections (e.g., rOFA to lFFA), we also ran a *post hoc* model space containing only areas from the right hemisphere and the EVC (EVC, rOFA, rFFA, rpSTS). Again, these results showed that EVC to core areas was the most probable model in a BMS including all participants (posterior probability for EVC to core of ~1). This makes us confident that the original model space was not biased by interhemispheric connections in the model space, and all subsequent analyses are based on the original model space.

Face modulation parameters

We assessed the difference between controls and DPs in the magnitudes of their face-modulated B connections, which we considered relevant for face processing. We selected for comparison the four face-modulated connections present in the model architecture that had the highest posterior probability in both groups (i.e., Model 8). All p values are reported as uncorrected and are inferred to be significant according to a Bonferroni-corrected α value $\alpha = 0.0125$ ($\alpha = 0.05/4$).

Three out of the four effective connections that were modulated by faces in the most likely model architecture showed altered modulation strength between control and DP participants (Fig. 4). Face modulation on the connection from EVC to rOFA did not show a significantly greater face modulation for controls compared to the DP group ($t_{(28)} = -0.110$, $p = 0.5432$). In contrast, we found significantly greater face modulation for controls compared to the DP group on the connections from EVC to rFFA ($t_{(28)} = 2.536$, $p = 0.0085$), from EVC to lFFA ($t_{(28)} = 2.253$, $p = 0.0088$), and from EVC to rpSTS ($t_{(28)} = 2.912$, $p = 0.0035$).

Discussion

We aimed to understand network properties contributing to face processing and how these network properties support accurate face recognition. We assessed this latter question by investigating how the face processing network is altered in DP individuals, who cannot accurately recognize faces. We focused on effective connectivity using DCM and showed that the network model that best explains how face-relevant information flows through a face-selective network is one where the presence or absence of faces modulates feedforward effective connectivity from the EVC to occipitotemporal areas (OFA, FFA, and STS). This model was selected out of 13 different models in a BMS and best explained our data when analyzing DP and control groups separately or combined. We then related the properties of this network to facial recognition ability by testing for differences in modulation strength between DP and control groups on model-relevant parameters (i.e., modulation parameters present in the model that best explained our data). We found that modulation of connections from the EVC to rFFA, lFFA, and rpSTS was significantly diminished in DP relative to controls. Our results indicate that these connections may contribute to normal face-selective responses as well as accurate facial recognition.

Connections that give rise to face-selective responses

Most previous studies investigating directional flow of information between face-selective areas have not contrasted face information with other types of object stimuli when testing for modulations of effective connectivity (Fairhall and Ishai, 2007; Ewbank et al., 2013). The advantage of quantifying the relative contribution of face-specific modulation to connectivity strength is that it allows for an inference of how face selectivity arises as a function of connectivity. The few studies that modeled the effect of faces compared to other stimuli considered model spaces with relatively few regions (Nagy et al., 2012; Furl et al., 2014). Here, we

have performed the most comprehensive model space to date and found that the model that best explained our data contained face-modulated connections from EVC to occipitotemporal areas.

We found that models [inspired by the work of Haxby et al. (2000)] where connections from OFA to FFA and STS created face selectivity in occipitotemporal areas were suboptimal. This result is consistent with findings in patients with lesions covering face-selective areas. Steeves et al. (2006) presented a patient (DF) who had bilateral lesion of OFA but continued to show face selectivity in FFA and STS. Similarly, patient PS, who had lesioned rOFA and lFFA, showed preserved face-selective responses in rFFA (Rossion et al., 2003). In addition, two patients with lesioned rOFA and rFFA still had face-selective responses in rpSTS (Dalrymple et al., 2011). These neuropsychological studies are in accordance with a model where face selectivity is created through effective connectivity from EVC to all core face processing areas (OFA, FFA, and STS).

Several of the models that we tested were theoretically motivated, but were nevertheless found to be suboptimal. For example, our results offer support for some features of the model proposed by Haxby et al. (2000). Our results agree on "core" areas responsible for visual analysis (OFA, FFA, pSTS). We found that face selectivity in the core areas was driven by visual cortex. Nevertheless, Haxby et al. (2000) further predicts that FFA and STS receive facial feature information from OFA. We did not find a special role for OFA in driving face selectivity in FFA and STS. Our results instead partly accord with a previous study showing face-relevant effective connectivity from Brodmann area 18 (BA18; partly equivalent to EVC here). Furl et al. (2014) showed that face modulation on the connection from BA18 to OFA (but not FFA) partly creates face selectivity in posterior occipitotemporal areas.

Table 1. Bayesian model selection

	Posterior probability		
Model architecture	Controls	DP	All
Backward core (Model 1)	0	0	0
Forward core (Model 2)	0	0	0
Reciprocal core (Model 3)	0	0	0
Backward core + lATL (Model 4)	0	0	0
Forward core + lATL (Model 5)	0	0	0
Reciprocal core + lATL (Model 6)	0	0	0
EVC to rOFA (Model 7)	0	0	0
EVC to core (Model 8)	1	1	1
EVC to core + lATL (Model 9)	0	0	0
lATL to core (Model 10)	0	0	0
lATL to FFA (Model 11)	0	0	0
Reciprocal FFA and rpSTS (Model 12)	0	0	0
Reciprocal FFA (Model 13)	0	0	0

Posterior probabilities for specified model architectures are shown. Posterior probabilities were estimated for control participants and DP participants separately as well as all participants combined. Model architectures are illustrated in Figure 1.

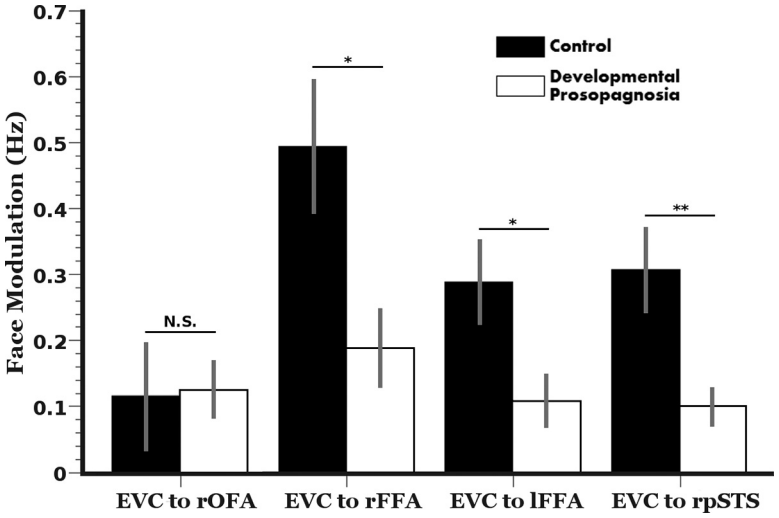

Figure 4. Group differences in modulation of connectivity by faces. *$p < 0.05$; **$p < 0.01$. Error bars indicate 1 SEM.

Our model space also tested the possibility that backward influences, including those from ATL, contributed to face selectivity. The present results suggest no role for ATL in creating face-selective responses in posterior areas. Instead, the face-selective responses observed in ATL appear to be either a function of the dynamics created in the interaction between EVC and occipitotemporal areas or a result of a mechanism that was not captured in the present model space. For example, face selectivity generated in core areas (resulting from their coupling with EVC) could be propagated forward to ATL via endogenous (unmodulated) connections. It should be noted that these results do not imply that interactions between other areas do not occur or are not involved in generating other functional responses that are relevant to face processing. We show that face-selective occipitotemporal responses are supported by effective connectivity from EVC to occipitotemporal core areas, rather than by interactions between different core areas or ATL.

A network-based account of diminished face recognition ability in DP

DP has been proposed to result from a disconnection between posterior and anterior face-selective areas (Behrmann and Plaut, 2013), in part, on the basis of diffusion tensor imaging (DTI) results. Thomas et al. (2008) found evidence for diminished axonal integrity in major pathways projecting between posterior occipitotemporal areas and anterior areas in ATL and frontal cortex. Because Avidan et al. (2005) found evidence that functional BOLD signal is not altered in DP within occipitotemporal areas, Thomas et al. (2008) proposed that DP is related to disconnection with ATL, rather than dysfunctional processing in posterior occipitotemporal areas. However, more recently, two studies reported that white matter deficits were not present in major pathways in DP; instead, DP was associated with atypical white matter structure around the FFA (Gomez et al., 2015; Song et al., 2015). These findings are in accordance with our findings implicating the connectivity of FFA in face processing. A limitation of previous studies investigating DP is the small sample sizes such as four (Avidan et al., 2005) or six (Thomas et al., 2008) participants with DP and the lack of appropriately powered group statistics. In contrast, our data (15 DP and 15 control participants) showed that DP had diminished BOLD response in posterior occipitotemporal areas [originally reported by Furl et al. (2011); Dinckelacker et al. 2011; von Kriegstein et al. 2008]. We here expand on the results by Furl et al. (2011) by identifying potential network explanations for the differences between DP and the normal population. In this study we find evidence for diminished effective

connectivity from EVC to FFA and EVC to pSTS that results in reduced activation in occipitotemporal areas to faces, compared to other objects, as well as reduced face recognition performance (Furl et al., 2011).

Avidan et al. (2014) found reduced functional connectivity between core areas and ATL. However, in the present study, the model identified to be most likely to give rise to face selectivity (model 8) did not contain face-modulated effective connectivity to or from lATL. lATL connections, therefore, are not a good candidate for explaining the reduced face selectivity observed in posterior areas in our sample of DP participants. Nevertheless, there is reduced gray matter and functional responses in ATL associated with DP (Behrmann et al., 2007; Garrido et al., 2009; Furl et al., 2011). It is possible that these abnormalities in the ATL of people with DP may instead be caused by chronically diminished propagation of face-specific activity from more posterior areas, or they may be a separate manifestation of the dysfunctions associated with DP.

Conclusions

We have presented evidence for a model of how face selectivity arises in the human brain and how this model is compromised in DP. We have shown that a model in which face selectivity arises from effective connectivity from EVC to posterior occipitotemporal areas is more likely than other plausible models tested. Furthermore, we suggest that the functional BOLD response in FFA and rpSTS and behavioral deficits in DP can partly be accounted for by diminished effective connectivity from EVC to posterior occipitotemporal areas.

References

Allison T, Puce A, McCarthy G (2000) Social perception from visual cues: Role of the STS region. Trends Cogn Sci 4:267–278. CrossRef Medline

Andrews TJ, Ewbank MP (2004) Distinct representations for facial identity and changeable aspects of faces in the human temporal lobe. Neuroimage 23:905–913. CrossRef Medline

Avidan G, Hasson U, Malach R, Behrmann M (2005) Detailed exploration of face-related processing in congenital prosopagnosia: 2. Functional neuroimaging findings. J Cogn Neurosci 17:1150–1167. CrossRef Medline

Avidan G, Tanzer M, Hadj-Bouziane F, Liu N, Ungerleider LG, Behrmann M (2014) Selective dissociation between core and extended regions of the face processing network in congenital prosopagnosia. Cereb Cortex 24: 1565–1578. CrossRef Medline

Behrmann M, Avidan G (2005) Congenital prosopagnosia: face-blind from birth. Trends Cogn Neurosci 9:180–187. CrossRef

Behrmann M, Avidan G, Gao F, Black S (2007) Structural imaging reveals anatomical alterations in inferotemporal cortex in congenital prosopagnosia. Cereb Cortex 17:2354–2363. CrossRef Medline

Behrmann M, Plaut DC (2013) Distributed circuits, not circumscribed centers, mediate visual recognition. Trends Cogn Sci 17:210–219. CrossRef Medline

Brett M, Anton J, Valabregue R, Poline J (2002) Region of interest analysis using an SPM toolbox. Paper presented at Eighth International Conference on Functional Mapping of the Human Brain, Sendai, Japan, June.

Dalrymple KA, Oruç I, Duchaine B, Pancaroglu R, Fox CJ, Iaria G, Handy TC, Barton JJ (2011) The anatomic basis of the right face-selective N170 IN acquired prosopagnosia: a combined ERP/fMRI study. Neuropsychologia 49:2553–2563. CrossRef Medline

den Ouden DB, Saur D, Mader W, Schelter B, Lukic S, Wali E, Timmer J, Thompson CK (2012) Network modulation during complex syntactic processing. Neuroimage 59:815–823. CrossRef Medline

Dinckelacker V, Gruter M, Klaver P, Gruter T, Specht K, Weis S, Kennerknecht I, Elger CE, Fernandez G (2011) Congenital prosopagnosia: multistage anatomical and functional deficits in face processing circuitry. J Neurology 258:770–782. CrossRef

Duchaine B, Nakayama K (2005) Dissociations of face and object recognition in developmental prosopagnosia. J Cogn Neurosci 17:249–261. CrossRef Medline

Duchaine B, Nakayama K (2006) The Cambridge Face Memory Test: Results for neurologically intact individuals and an investigation of its validity using inverted face stimuli and prosopagnosic participants. Neuropsychologia 44:576–585. CrossRef Medline

Eifuku S, De Souza WC, Tamura R, Nishijo H, Ono T (2004) Neuronal correlates of face identification in the monkey anterior temporal cortical areas. J Neurophysiol 91:358–371. Medline

Ewbank MP, Henson RN, Rowe JB, Stoyanova RS, Calder AJ (2013) Different neural mechanisms within occipitotemporal cortex underlie repetition suppression across same and different-size faces. Cereb Cortex 23: 1073–1084. CrossRef Medline

Fairhall SL, Ishai A (2007) Effective connectivity within the distributed cortical network for face perception. Cereb Cortex 17:2400–2406. CrossRef Medline

Fox CJ, Moon SY, Iaria G, Barton JJ (2009) The correlates of subjective perception of identity and expression in the face network: an fMRI adaptation study. Neuroimage 44:569–580. CrossRef Medline

Friston KJ, Harrison L, Penny W (2003) Dynamic causal modeling. Neuroimage 19:1273–1302. CrossRef Medline

Furl N, Garrido L, Dolan RJ, Driver J, Duchaine B (2011) Fusiform gyrus face selectivity relates to individual differences in facial recognition ability. J Cogn Neurosci 23:1723–1740. CrossRef Medline

Furl N, Coppola R, Averbeck BB, Weinberger DR (2013) Cross-frequency power coupling between hierarchically organized face-selective areas. Cereb Cortex 2409–2420.

Furl N, Henson RN, Friston KJ, Calder AJ (2014) Network interactions explain sensitivity to dynamic faces in the superior temporal sulcus. Cereb Cortex 25:2876–2882. Medline

Garrido L, Furl N, Draganski B, Weiskopf N, Stevens J, Tan GC, Driver J, Dolan RJ, Duchaine B (2009) Voxel-based morphometry reveals reduced grey matter volume in the temporal cortex of developmental prosopagnosics. Brain 132:3443–3455. CrossRef Medline

George N, Driver J, Dolan RJ (2001) Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing. Neuroimage 13:1102–1112. Medline

Gomez J, Pestilli F, Witthoft N, Golarai G, Liberman A, Poltoratski S, Yoon J, Grill-Spector K (2015) Functionally defined white matter reveals segregated pathways in human ventral temporal cortex associated with category-specific processing. Neuron 85:216–227. CrossRef Medline

Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR (2008) Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. Neuroimage 41: 1382–1394. CrossRef Medline

Haxby JV, Hoffman EA, Gobbini MI (2000) The distributed human neural system for face perception. Trends Cogn Sci 4:223–233. CrossRef Medline

Hein G, Knight RT (2008) Superior temporal sulcus–It's my area: or is it? J Cogn Neurosci 20:2125–2136. CrossRef Medline

Iidaka T, Omori M, Murata T, Kosaka H, Yonekura Y, Okada T, Sadato N (2001) Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. J Cogn Neurosci 13:1035–1047. CrossRef Medline

Kanwisher N, McDermott J, Chun MM (1997) The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 17:4302–4311. Medline

Kiebel SJ, Klöppel S, Weiskopf N, Friston KJ (2007) Dynamic causal modeling: a generative model of slice timing in fMRI. Neuroimage 34: 1487–1496. CrossRef Medline

Lundqvist D, Litton JE (1998) The Karolinska Directed Emotional Faces (KDEF). CD ROM. Stockholm, Sweden: Karolinska Institutet.

Mechelli A, Price CJ, Henson RN, Friston KJ (2003a) Estimating efficiency a priori: a comparison of blocked and randomized designs. Neuroimage 18:798–805. CrossRef Medline

Mechelli A, Price CJ, Noppeney U, Friston KJ (2003b) A dynamic causal modeling study on category effects: bottom-up or top-down mediation? J Cogn Neurosci 15:925–934. CrossRef Medline

Mechelli A, Price CJ, Friston KJ, Ishai A (2004) Where bottom-up meets top-down: neuronal interactions during perception and imagery. Cereb Cortex 14:1256–1265. CrossRef Medline

Moeller S, Freiwald WA, Tsao DY (2008) Patches with links: a unified system for processing faces in the macaque temporal lobe. Science 320: 1355–1359. CrossRef Medline

Nagy K, Greenlee MW, Kovács G (2012) The lateral occipital cortex in the

face perception network: an effective connectivity study. Front Psychol 3:141. CrossRef Medline

Nunn JA, Postma P, Pearson R (2001) Developmental prosopagnosia: should it be taken at face value? Neurocase 7:15–27. CrossRef Medline

Penny WD, Stephan KE, Mechelli A, Friston KJ (2004) Comparing dynamic causal models. Neuroimage 22:1157–1172. CrossRef Medline

Penny WD, Stephan KE, Daunizeau J, Rosa MJ, Friston KJ, Schofield TM, Leff AP (2010) Comparing families of dynamic causal models. PLoS Comput Biol 6:e1000709. CrossRef Medline

Poldrack RA (2007) Region of interest analysis for fMRI. Soc Cogn Affect Neurosci 2:67–70. Medline

Rossion B, Caldara R, Seghier M, Schuller AM, Lazeyras F, Mayer E (2003) A network of occipito-temporal face-sensitive areas besides the right middle fusiform gyrus is necessary for normal face processing. Brain 126: 2381–2395. CrossRef Medline

Rotshtein P, Henson RN, Treves A, Driver J, Dolan RJ (2005) Morphing Marilyn into Maggie dissociates physical and identity face representations in the brain. Nat Neurosci 8:107–113. CrossRef Medline

Song S, Garrido L, Nagy Z, Mohammadi S, Steel A, Driver J, Dolan RJ, Duchaine B, Furl N (2015) Local but not long-range microstructural differences of the ventral temporal cortex in developmental prosopagnosia. Neuropsychologia 78:195–206. CrossRef Medline

Steeves JK, Culham JC, Duchaine BC, Pratesi CC, Valyear KF, Schindler I, Humphrey GK, Milner AD, Goodale MA (2006) The fusiform face area is not sufficient for face recognition: evidence from a patient with dense prosopagnosia and no occipital face area. Neuropsychologia 44:594–609. CrossRef Medline

Stephan KE, Penny WD, Moran RJ, den Ouden HE, Daunizeau J, Friston KJ (2010) Ten simple rules for dynamic causal modeling. Neuroimage 49: 3099–3109. CrossRef Medline

Thomas C, Avidan G, Humphreys K, Jung KJ, Gao F, Behrmann M (2008) Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. Nat Neurosci 12:29–31. CrossRef Medline

Von Der Heide RJ, Skipper LM, Olson IR (2013) Anterior temporal face patches: a meta-analysis and empirical study. Front Hum Neurosci 7:17. Medline

von Kriegstein K, Dogan O, Grüter M, Giraud AL, Kell CA, Grüter T, Kleinschmidt A, Kiebel SJ (2008) Simulation of talking faces in the human brain improves auditory speech recognition. Proc Natl Acad Sci U S A 105:6747–6752. CrossRef Medline

Winston JS, Henson RN, Fine-Goulden MR, Dolan RJ (2004) fMRI-adaptation reveals dissociable neural representations of identity and expression in face perception. J Neurophysiol 92:1830–1839. CrossRef Medline

Yang H, Susilo T, Duchaine B (2014) The anterior temporal face area contains invariant representations of identity that can persist despite the loss of right FFA and OFA. Cereb Cortex 26:1096–1107. Medline