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# Mechanisms of hemispheric lateralization: Asymmetric interhemispheric recruitment in the face perception network

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#### ABSTRACT

Perceiving human faces constitutes a fundamental ability of the human mind, integrating a wealth of information essential for social interactions in everyday life. Neuroimaging studies have unveiled a distributed neural network consisting of multiple brain regions in both hemispheres. Whereas the individual regions in the face perception network and the right-hemispheric dominance for face processing have been subject to intensive research, the functional integration among these regions and hemispheres has received considerably less attention. Using dynamic causal modeling (DCM) for fMRI, we analyzed the effective connectivity between the core regions in the face perception network of healthy humans to unveil the mechanisms underlying both intraand interhemispheric integration. Our results suggest that the right-hemispheric lateralization of the network is due to an asymmetric face-specific interhemispheric recruitment at an early processing stage - that is, at the level of the occipital face area (OFA) but not the fusiform face area (FFA). As a structural correlate, we found that OFA gray matter volume was correlated with this asymmetric interhemispheric recruitment. Furthermore, exploratory analyses revealed that interhemispheric connection asymmetries were correlated with the strength of pupil constriction in response to faces, a measure with potential sensitivity to holistic (as opposed to feature-based) processing of faces. Overall, our findings thus provide a mechanistic description for lateralized processes in the core face perception network, point to a decisive role of interhemispheric integration at an early stage of face processing among bilateral OFA, and tentatively indicate a relation to individual variability in processing strategies for faces. These findings provide a promising avenue for systematic investigations of the potential role of interhemispheric integration in future studies.

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#### Introduction

Perceiving human faces engages various brain regions, most prominently the occipital face area (OFA; Puce et al., 1996), the fusiform face area (FFA; Kanwisher et al., 1997) and the posterior superior temporal lobe (pSTS; Haxby et al., 1999). OFA, FFA and pSTS serve different functions (Hoffman and Haxby, 2000) and have jointly been referred to as the core of the face perception network (Haxby et al., 2000). Although these regions are typically activated in both hemispheres, the right lateralization of the face perception network is well established (De Renzi, 1986; Kanwisher et al., 1997; Puce et al., 1996; Wada and Yamamoto, 2001). Hence, the individual components of the network and their

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right-hemispheric dominance have been investigated thoroughly; however, the functional integration among these regions has received considerably less attention. We are currently lacking a deeper (mechanistic) understanding of the interplay between the face-sensitive regions and how hemispheric lateralization in the face perception network arises. Nevertheless, such a mechanistic understanding of the network dynamics is crucial for unraveling how the human brain processes faces, and might provide new insights into the pathophysiology of diseases where face perception is impaired (e.g., prosopagnosia, autism).

Only lately have pioneering studies begun to address the effective connectivity (i.e., directed interactions) among face-sensitive regions (Cohen Kadosh et al., 2011; Dima et al., 2011; Ewbank et al., 2013; Fairhall and Ishai, 2007; Ishai, 2008; Li et al., 2010). These studies, however, have only examined intrahemispheric connections, while neglecting the interhemispheric connections of the network. Critically, such an





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approach might be too restricted, as recent imaging studies have suggested a non-negligible role of face-sensitive regions in the left hemisphere during face perception (Bi et al., 2014; Meng et al., 2012). These studies speak to a fundamental functional dissociation between the homotopic regions which complement each other. Specifically, it has been suggested that right FFA is involved in face/non-face judgments whereas left FFA processes 'low-level' face resemblance (Meng et al., 2012). This is consistent with a more general dissociation between right and left hemispheres in terms of holistic and feature-based processing, respectively (Bradshaw and Nettleton, 1981), which might also play an important role for the hemispheric lateralization of the face perception network (Hillger and Koenig, 1991; Leehey et al., 1978; Rossion et al., 2000; Yin, 1970).

Here, we extend recent effective connectivity analyses and examine functional interactions in the bilateral core of the face perception network. We hypothesized that not only the intra- but also the interhemispheric integration of face-sensitive regions is crucial for face perception and for understanding its hemispheric lateralization. This follows from recent behavioral evidence using divided visual field stimulation (Compton, 2002; Mohr et al., 2002; Schweinberger et al., 2003). Specifically, in matching tasks that required observers to indicate whether a target face matched one of two probe faces, superior performance was generally obtained when matches involved acrosshemifield (as opposed to within-hemifield) presentation of faces, requiring interhemispheric interaction (Compton, 2002). Similarly, in other studies on face recognition, interhemispheric cooperation was indicated by enhanced performance when stimuli were simultaneously presented to both visual fields, compared to a single visual field. Importantly, this "bilateral gain" which had initially been demonstrated for words but not pseudowords in lexical decision tasks (Mohr et al., 1994) was most prominent for familiar faces compared to unfamiliar faces in face recognition tasks (Mohr et al., 2002; Schweinberger et al., 2003). Those findings were interpreted as face recognition accessing acquired memory representations, instantiated via cortical cell assemblies that are distributed across the two hemispheres. Finally, recent experiments which involved chimaeric presentation at the fovea of two hemifaces from either the same face (consistent) or from different faces (inconsistent) also showed behavioral evidence for crosshemispheric processing of facial information. Importantly, these effects were reduced or absent for inverted faces (Yovel et al., 2005). Because face inversion is generally thought to suppress holistic processing, the above effects suggest that interhemispheric integration takes place at a higher level of holistic representations of faces.

Hence, we here aimed at unraveling the potential role of the interhemispheric interactions in the face perception network. To this end, we adapted a recent paradigm (Stephan et al., 2007), presenting stimuli in one hemifield to restrict visual input to the contralateral hemisphere. Subjects fixated a central cross while covertly shifting attention to the stimuli in the periphery. Using dynamic causal modeling (DCM; Friston et al., 2003) for fMRI, we then tested whether interhemispheric integration played an important role for hemispheric lateralization of the face perception network. In this case, one might also expect correlations between functional measures of interhemispheric integration and hemispheric asymmetries in other modalities, particularly asymmetry of cerebral gray matter (Good et al., 2001). Notably, whereas we have concepts for understanding the function of the intrahemispheric connections (e.g., hierarchical forwarding of face-specific information from OFA to FFA; Haxby et al., 2000), the role of the interhemispheric connections for face perception is largely unknown. One possibility is that interhemispheric integration might play a role in the abovementioned dissociation between holistic and feature-based processing. Using measures of pupil size, which was recently suggested to be sensitive to holistic versus feature-based processing of visual stimuli (Conway et al., 2008; Naber and Nakayama, 2013), we performed an exploratory analysis to test this presently speculative link. In summary, using a multimodal approach which combines DCM with structural MRI and pupillometry, we aimed at developing a mechanistic model for the hemispheric lateralization of the core system for face perception and at shedding light on the potential role of interhemispheric connections in this system.

#### Materials and methods

#### Subjects

Twenty healthy subjects (8 male, age range: 21-30 years, mean age:  $24.2 \pm 2.6$  years) participated in the experiment. All were naïve to the purpose of the study, except for one (author SF). Subjects had normal or corrected-to-normal vision, were right-handed and gave written informed consent prior to the experiment. The study conformed to the Declaration of Helsinki and was approved by the local ethics committee of the Medical Faculty of the University of Marburg.

#### Experimental procedure

Subjects viewed either gray-scale neutral faces or scrambled images in the periphery while holding their gaze on a fixation cross in the center of the screen. Note that presenting the stimuli in the periphery is crucial here, as it allowed us to investigate more refined hypotheses on the interhemispheric integration in the face perception network (cf. Stephan et al., 2005, 2007). Faces were full-frontal photographs taken from the Center for Vital Longevity Face Database (Ebner, 2008). Scrambled images were the randomized Fourier transforms of the face stimuli (i.e., assigning random values to the phase component), thus discarding any shape information while leaving the amplitude spectrum (e.g., mean luminance) unaffected. Stimuli were presented as circular patches (radius: 2.17°) on a gray background (luminance equal to the average brightness of all stimuli) via an MRI-compatible LCD screen (LG SL9000, 60 Hz, 4:3,  $1024 \times 786$  pix) using the Presentation 11.0 software package (Neurobehavioral Systems, Albany, CA, USA, http://www. neurobs.com/). Subjects viewed the stimuli via a mirror mounted on the MR head coil. Faces and scrambled images appeared either in the right ("RVF") or left visual field ("LVF"), thus, the experimental design of the study was a 2-way repeated measures within-subject design (stimulus  $\times$  hemifield). The center of the circular patches was located 4.02° lateral to the fixation cross. Subjects were instructed to attend to and process the stimuli in the periphery while holding their gaze on the central fixation cross. Proper fixation was controlled for by recording the direction of eye gaze at a rate of 500 Hz using an MRIcompatible infrared-sensitive camera (EyeLink 1000, SR Research, Osgoode, ON, Canada). This ensured that subjects engaged in nonfoveal vision and that visual inputs therefore reached the primary visual area (V1) of the contralateral hemisphere only.

A number of control steps ensured the quality of subjects' fixation. First, adequate fixation was monitored on-line during the experiment by the experimenter. Second, post-hoc analyses tested for differences in eye gaze between the different experimental conditions. To this end, the mean gaze eccentricity was calculated for each subject and experimental condition, separately. Individual eccentricity values were then entered into a 2-way repeated measures ANOVA (within-subject factors: stimulus, hemifield) in IBM SPSS Statistics 20 (Armonk, NY: IBM Corp. Released 2011). The ANOVA revealed no significant main effect of stimulus ( $F_{(1,19)} = 2.99, p = 0.10$ ) or hemifield ( $F_{(1,19)} = 0.08$ , p= 0.78). Similarly, there was no significant effect for the stimulus imeshemifield interaction ( $F_{(1,19)} = 0.25$ , p = 0.62). This, however, does not rule out the occurrence of occasional shifts in gaze or some individuals not maintaining central fixation. Therefore, in a final step, the quality of subjects' fixation was investigated by estimating the percentage of time subjects properly fixated the cross in the center of the screen. In brief, a region centered on the fixation cross with a radius of 1° was defined. The radius was used to guarantee that for fixations within that region, subjects still perceived the stimuli in the periphery (the medial

edge of the stimulus patches was  $1.85^{\circ}$  lateral to the fixation cross). For each subject, the percentage of adequate fixation was then computed as the ratio between the gaze dwell time within the central region (i.e., the sum of the time for which the gaze was within that region) and the total duration of the stimulus trials. Similarly, the percentage of fixation on the stimulus was assessed. These analyses demonstrate that subjects fixated the central cross for the vast majority of the experiment (median = 98.6%; no subject less than 94.9%), with hardly any fixations on the stimulus ( $\leq 0.4\%$  for all subjects; median = 0.1\%; see Supplementary Table S1). In summary, the quality of subjects' fixation was high with little variability across subjects and no differences in fixation could be observed between the experimental conditions.

The experimental paradigm was a blocked design, that is, the four experimental conditions (i.e., "faces LVF", "faces RVF", "scrambled LVF" and "scrambled RVF") were presented in 20 successive blocks with a duration of 20.3 s each (corresponding to 14 functional whole brain scans) in a fixed pseudo-randomized order. Stimulus blocks were interleaved with blank periods of the same length where only the fixation cross was shown. Within each block, stimuli were shown for 150 ms interleaved with an ISI of 250 ms (i.e., 51 stimuli per block at a frequency of 2.5 Hz). To avoid fatigue, the experiment was divided into two parts, which were separated by approximately 60 s of rest. Subjects remained inside the scanner during this break and were not allowed to move (as the scanner continued to run).

#### Functional magnetic resonance imaging

#### Image acquisition

Subjects were scanned on a 3-Tesla MR scanner (Siemens TIM Trio, Erlangen, Germany) with a 12-channel head matrix receive coil at the Department of Psychiatry, University of Marburg. A  $T_2^*$ -weighted single-shot gradient-echo echo-planar imaging sequence (EPI) was used to provide 615 functional images sensitive to the Blood Oxygen Level Dependent (BOLD) contrast (30 slices, TR = 1450 ms, TE = 25 ms, matrix size 64 × 64 voxels, voxel size 3 × 3 × 4 mm<sup>3</sup>, FoV = 192 × 192 mm<sup>2</sup>, flip angle 90°). Slices of the functional scans covered the whole brain and were acquired parallel to the intercommissural (AC–PC) plane in descending order. Additionally, a high-resolution anatomical image was acquired using a T1-weighted magnetization-prepared rapid gradient-echo (3d MP-RAGE) sequence in sagittal plane (176 slices, TR = 1900 ms, TE = 2.26 ms, matrix size 256 × 256 voxels, voxel size 1 × 1 × 1 mm<sup>3</sup>, FoV = 256 × 256 mm<sup>2</sup>, flip angle 9°).

#### Image data processing

Functional images were analyzed using SPM8 (Statistical Parametric Mapping, version R4290, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk) and Matlab R2008b (Mathworks, Natick, MA, USA). The first four scans were discarded from the analysis. Individual images were realigned to the mean image, coregistered with the anatomical image, and normalized to the MNI standard space using the unified segmentation–normalization approach (Ashburner and Friston, 2005). During spatial normalization, functional images were reasampled to a voxel size of  $2 \times 2 \times 2$  mm<sup>3</sup>. The normalized functional images were then spatially smoothed with a 6 mm FWHM Gaussian kernel.

BOLD activity was identified in each voxel of every subject by means of a first-level General Linear Model (GLM; Friston et al., 1995; Worsley and Friston, 1995). Each condition (i.e., faces LVF, faces RVF, scrambled LVF and scrambled RVF) was modeled as a train of blocks which was then convolved with SPM's standard canonical hemodynamic response function. Realignment parameters were introduced as nuisance regressors to control for movement-related artifacts, and a high-pass filter was applied to remove low-frequency drifts in the data (cut-off frequency: 1/128 Hz). Face-sensitive activation was identified in each subject as the differential BOLD activity when contrasting faces against scrambled images, regardless of the visual field ("faces (LVF + RVF) > scrambled (LVF + RVF)"). The degree of lateralization of the face-sensitive activation was computed for each subject using the Bootstrap procedure implemented in the LI toolbox extension (Wilke and Lidzba, 2007). Additionally, activation to stimuli presented in the left hemifield and in the right hemifield was identified from the baseline contrasts "LVF (faces + scrambled)" and "RVF (faces + scrambled)", respectively. The individual contrast images were then entered into random effects group-level analyses (one-sample *t*-tests). Group-level BOLD activity was thresholded at p < 0.05, family-wise error (FWE)-corrected and anatomically localized using the Anatomy toolbox extension (Eickhoff et al., 2005).

#### Time series extraction

To investigate intra- and interhemispheric effective connectivity within the core face perception network, six regions of interest (ROI) were selected for DCM analyses, given the group-level SPM results. These six ROIs were located bilaterally in the primary visual area (V1), the occipital face area (OFA) and the fusiform face area (FFA). While bilateral OFA and FFA are key components of the core face perception network (Haxby et al., 2000), bilateral V1 served as the visual input regions in the DCMs. To account for inter-subject variability in the location of these regions, coordinates of the ROIs were determined for each subject individually as follows: First, the group-level peak activation coordinates of the face-sensitive contrast (faces > scrambled) served to identify bilateral OFA and FFA. Bilateral visual areas V1 were defined from the visual field baseline contrasts - that is, left and right V1 were determined from the RVF and LVF contrast, respectively. Second, individual ROI center coordinates were manually defined as the subject-specific maximum close to the respective group-level maximum under the following anatomical constraints: V1 had to be located in Brodmann area 17, OFA in the inferior occipital gyrus, and FFA in the fusiform gyrus (as determined by the Anatomy toolbox extension; Eickhoff et al., 2005). Third, BOLD signal time series were extracted from each subject-specific ROI as the first eigenvariate of all activated voxels within a 4 mm sphere centered on the individual coordinates (p < 0.001, uncorrected). Time series were mean-centered and movement-related variance was removed (by adjustment with regard to an effects-ofinterest F-contrast).

#### Dynamic causal modeling

Intra- and interhemispheric effective connectivity among the facesensitive brain regions was investigated by means of DCM (Friston et al., 2003). DCM represents a frequently used framework to analyze potential ways in which neural system dynamics and effective connectivity are perturbed by experimental manipulations. Mathematically, DCM describes the brain as a deterministic input–output system by means of a bilinear differential equation:

$$\frac{dz}{dt} = F(z, u, \theta) = \left(A + \sum_{j=1}^{m} u_j B^j\right) z + Cu$$

where z depicts the neuronal activities, A describes the endogenous (fixed or context-independent) connection strengths, B<sup>j</sup> defines how the experimental manipulation u<sub>j</sub> affects the connections among the network regions (modulatory connectivity), and C describes how the driving inputs directly influence the neuronal state of the network regions. Integrating the bilinear equation yields the dynamics of the neural state, which can then be transformed into a predicted BOLD signal time series using a hemodynamic forward model (Balloon–Windkessel model; Buxton et al., 1998; Mandeville et al., 1999). A Variational Bayes approach (Friston et al., 2007) under Gaussian assumptions on the prior and posterior distributions (Laplace approximation) is then used to compute the sufficient statistics of the posterior densities of the model parameters (i.e., conditional mean and covariance).

#### Definition of the model space

The model space was motivated by a recent effective connectivity approach for assessing the mechanisms underlying the interhemispheric integration in task-dependent lateralization (Stephan et al., 2007). A total of 16 models were constructed, representing distinct hypotheses on how the intra- and interhemispheric connections are modulated when perceiving faces and scrambled images. For all models, the endogenous connectivity and exogenous inputs (A- and C-matrix) were identical. Exogenous inputs were set to modulate neuronal activity within bilateral V1. Since visual stimuli were presented in the periphery, exogenous inputs were allowed to induce activity only in the contralateral V1 (e.g., LVF modulated right V1). Visual information then propagated through the network via intra- and interhemispheric connections. Forward and backward intrahemispheric connections were set between V1 and OFA, as well as between OFA and FFA (Haxby et al., 2000; Kotter and Stephan, 2003). Additionally, reciprocal endogenous connections were set between homotopic face-sensitive brain regions (Catani and Thiebaut de Schotten, 2008; Clarke and Miklossy, 1990; Park et al., 2008; Van Essen et al., 1982; Zeki, 1970). Notably, interhemispheric connections are less pronounced between heterotopic face-sensitive brain regions (Catani and Thiebaut de Schotten, 2008; Hofer and Frahm, 2006) and were thus not modeled in the present DCMs. Similarly, no interhemispheric connections were considered between bilateral V1. This is because postmortem data and diffusion weighted imaging studies suggested that in humans callosal projections are restricted to the V1/V2 border where the vertical meridian is represented (e.g., Dougherty et al., 2005), while the rest of V1 is considered to be acallosal (Catani and Thiebaut de Schotten, 2008; Clarke and Miklossy, 1990; Van Essen et al., 1982; Zilles and Clarke, 1997). At the same time, restricting interhemispheric connections to homotopic facesensitive regions prevented numerical problems by keeping model parameters at a reasonable number and reducing posterior covariance among the parameters. Various modulatory connectivity patterns were defined, representing distinct hypotheses on how experimental manipulations were allowed to perturb intra- and interhemispheric connections (Fig. 1). Connections could be modulated either by 1) the visual field of the stimulus presentation (VF), 2) the perception of faces (F), 3) both the visual field and the perception of faces (F + VF), or 4) the perception of faces, but only when the stimuli were presented in the respective visual field ( $F \times VF$ ). Implementing all possible combinations of modulatory inputs on the intra- and interhemispheric connections resulted in 16 different models. Notably, modulatory inputs on the intrahemispheric connections were restricted only to the forward connections. Whereas this assumption is reasonable for the coupling among OFA and V1, it might not hold for the connection from FFA to OFA. We therefore verified the above-mentioned approach for the present paradigm in an independent sample (Supplementary Data S1 and Supplementary Figure S1).

Experimental inputs were specified as block regressors, which were not mean-centered — that is, the endogenous parameter estimates represent the connection strengths in the absence of experimental manipulations. Model inversion was then performed using DCM10 as implemented in SPM8 (version R4290).

#### Bayesian model averaging

As the mechanisms of interhemispheric integration in the face perception network were of particular interest in the present study, the model space was divided into four different families, grouping models with identical modulatory inputs on the interhemispheric connections (rows in Fig. 1). Families were compared using random effects Bayesian model selection (BMS) at the family level (Penny et al., 2010; Stephan et al., 2009). Individual parameter estimates were then assessed by means of random effects Bayesian model averaging (BMA; Penny et al., 2010) across the models of the winning family within a pre-specified Occam's window (p < 0.05). The BMA parameter estimates were then entered into summary statistics at the group level. The significance of each parameter was assessed by a one-sample *t*-test at a statistical threshold of p < 0.05 (Bonferroni-corrected within each parameter class) to account for multiple comparisons.

#### Voxel-based morphometry

Individual gray matter (GM) volume maps were extracted from the high-resolution anatomical image using the standard DARTEL approach implemented in the VBM8 toolbox extension (http://dbm.neuro.unijena.de/vbm). This includes tissue segmentation, bias correction, normalization to the MNI standard space and spatial smoothing with a Gaussian kernel (8 mm FWHM). GM volume maps were corrected for non-linear warping only, in order to allow for inferences on the relative GM volume. Data quality was verified using the standard routines to identify (and exclude) outliers based on the covariance between GM volume maps. Individual GM volume maps were then subjected to a group-level linear regression analysis to unveil the anatomical correlates of the face-specific interhemispheric integration. To this end, the difference of the modulatory influences on the interhemispheric connections among bilateral OFA (i.e.,  $[OFA_L \rightarrow OFA_R] - [OFA_R \rightarrow OFA_L])$  served as the covariate in the regression analysis. To test for correlations explicitly within the OFA, a priori masks were defined as the group-level BOLD activations within the inferior occipital gyrus of each hemisphere. Within each mask, significance was then assessed using small volume correction at a statistical threshold of p < 0.05, FWE-corrected.

#### Pupillometry

Pupil diameter was recorded at a rate of 500 Hz using EyeLink. First, blinks were detected by the EyeLink software and then interpolated using cubic spline interpolation. The interpolated pupil size traces were then normalized to z-scores (i.e., zero mean and unit variance), and high-frequency noise was suppressed by averaging with a 50 ms wide sliding average. For each individual, the averaged pupil time courses after stimulus onset were computed separately for faces and scrambled images. The difference between maximum and minimum average pupil sizes within a 300 ms time period from stimulus onset yielded a measure of the individual's mean pupil constriction. Constrictions to either faces or scrambled images were correlated with the difference of the modulatory influences on the interhemispheric connections among bilateral OFA (i.e.,  $[OFA_L \rightarrow OFA_R]$ – $[OFA_R \rightarrow OFA_L]$ ). Face specificity of this correlation was tested by assessing whether pupil constrictions to face stimuli exhibited stronger correlations with the modulatory influences as compared to constrictions induced by scrambled images. Correlation coefficients were compared using Steiger's Z-test for bivariate correlations within a single population.

#### Results

Using a multimodal approach, we focused on a series of hierarchically structured questions. First, we located brain regions involved in passively viewing faces using fMRI, replicating earlier neuroimaging studies. Second, we aimed at unraveling the effective connectivity within this face perception network and at developing a mechanistic model for the hemispheric lateralization of the core system by taking into account both intra- and interhemispheric connections. Third, we searched for structural correlates of the interhemispheric integration using voxelbased morphometry (VBM) and examined whether modulation of the interhemispheric connectivity by face processing is linked to intersubject variability in brain anatomy. Fourth, we tested whether interhemispheric integration mediates the relation of holistic versus feature-based processing by correlating the asymmetry in the interhemispheric information transfer with the strength of pupil responses to the onsets of face stimuli.

### intrahemispheric



**Fig. 1.** Different plausible hypotheses of the effective connectivity in the face perception network. As the visual stimuli were presented in the periphery, RVF and LVF were the driving inputs to the contralateral V1 (not shown here). Forward and backward intrahemispheric endogenous connections were set between V1 and OFA, and between OFA and FFA. Additionally, reciprocal interhemispheric connections were set between bilateral OFA, and between bilateral FFA, but not between bilateral V1. Arrows indicate the presence and directionality of the endogenous connections. Whereas endogenous connectivity and driving inputs were the same for all models, modulatory influences differed. Connections were either modulated by 1) the visual field (VF), 2) face perception (F), 3) face perception and visual field (F + VF), or 4) face perception, but only when the stimuli were presented in the respective visual field (F × VF). All four possibilities exist for intra- and interhemispheric connections, hence, systematically varying all combinations resulted in 16 distinct models. Endogenous connections that were modulated are colored in blue. Models are named by first listing the type of interhemispheric modulation, followed by the type of intrahemispheric modulation. LVF = left visual field; RVF = right visual field; FP = face perception; L = left hemisphere; and R = right hemisphere.

#### Brain activity during face perception

Face-sensitive brain activity was assessed by means of a random effects group analysis (one-sample *t*-test) yielding brain regions that responded more strongly to faces than to scrambled images (p < 0.05, family-wise error (FWE)-corrected). We found a distributed network underlying the processing of faces. This face-sensitive network was lateralized to the right hemisphere (median laterality index: LI = -0.44) and was primarily located within the inferior occipital gyrus and the fusiform gyrus in both hemispheres, referring to OFA and FFA, respectively (Fig. 2A and Table 1). This replicates previous findings, as both regions have been assigned to the core network of face

perception (Haxby et al., 2000). Note that both OFA and FFA were activated in the left and right hemisphere regardless of whether the stimuli were presented in the RVF or the LVF (Supplementary Table S2). We found additional face-sensitive activations in the middle temporal and inferior frontal gyri, among others. However, since only bilateral OFA and FFA provided stable face-sensitive activations in each individual, and since we are focusing here on the effective connectivity within the core network, these were the only face-sensitive regions that were subjected to subsequent DCM analyses. Additionally, left and right V1 were consistently activated when stimuli were presented in the RVF (Fig. 2B, left) and LVF (Fig. 2B, right), respectively, and thus served as the visual input regions of the DCMs.



**Fig. 2.** BOLD activity during face perception in the group (N = 20). (A) Activation pattern shows brain regions that were more activated during the perception of faces as compared to scrambled images, assessed by the linear contrast: faces (LVF + RVF) > scrambled (LVF + RVF). (B) Activation patterns show brain regions that were more activated when stimuli (i.e., faces and scrambled images) were presented in the right or in the left visual field. Results are thresholded at a voxel-level threshold of p < 0.05 (FWE-corrected). Activation patterns were displayed on an anatomical template image (A) or rendered onto the surface of the anatomical template (B). L = left hemisphere; R = right hemisphere; A = anterior; P = posterior; LVF = left visual field; and RVF = right visual field.

#### Table 1

Coordinates, cluster sizes and Z scores for face-sensitive activations (faces > scrambled), as well as for the visual baseline contrasts (LVF/RVF). Shown are brain regions where activation was greater during the perception of faces as compared to the perception of scrambled images (faces > scrambled). Additionally, regions are shown that were significantly activated when stimuli were shown in the left visual field (LVF) or the right visual field (RVF). Analysis of the primary visual areas (V1) was restricted to Brodmann area 17 (dilated by a factor of 2). For all regions, MNI coordinates, cluster sizes (defined as the number of voxels in MNI space at a voxel size of  $2 \times 2 \times 2$  mm<sup>3</sup>) and Z-scores are reported. Results are thresholded at a voxel-level threshold of p < 0.05, FWE-corrected.

| Cortical region                    | Hemisphere | MNI coordinates |     |     | Cluster size | Z-score |
|------------------------------------|------------|-----------------|-----|-----|--------------|---------|
|                                    |            | x               | У   | Z   | (voxels)     |         |
| Faces > scrambled                  |            |                 |     |     |              |         |
| Inferior occipital (OFA)           | R          | 38              | -78 | -12 | 183          | 6.41    |
| Middle temporal                    | R          | 50              | -74 | 0   |              | 5.56    |
| Fusiform gyrus (FFA)               | L          | -36             | -64 | -14 | 198          | 6.11    |
| Inferior occipital                 | L          | -44             | -70 | -16 |              | 5.50    |
| Inferior occipital (OFA)           | L          | -36             | -88 | -10 | 65           | 5.82    |
| Middle occipital                   | L          | -42             | -80 | 4   |              | 5.04    |
| Inferior frontal gyrus             | R          | 44              | 14  | 24  | 52           | 5.49    |
| Fusiform gyrus (FFA)               | R          | 38              | -48 | -18 | 123          | 5.44    |
| Fusiform gyrus                     | R          | 40              | -60 | -18 |              | 5.36    |
| Fusiform gyrus                     | R          | 38              | -68 | -20 |              | 5.33    |
| Supramarginal gyrus                | R          | 56              | -42 | 26  | 6            | 5.40    |
| LVF (masked with Brodmann area 17) |            |                 |     |     |              |         |
| Right V1                           | R          | 10              | -88 | -4  | 115          | 7.16    |
| RVF (masked with Brodn             |            |                 |     |     |              |         |
| Left V1                            | Ĺ          | -6              | -90 | -6  | 216          | 6.64    |

Asymmetric interhemispheric recruitment underlies the lateralization of the face perception network

#### Bayesian model selection

For each subject, we analyzed the effective connectivity among the face-sensitive brain regions by means of DCM. One subject was excluded from subsequent DCM analyses due to signs of numerical instabilities in parameter estimation (positive values for self-connections). For the remaining sample, we used a random effects BMS procedure at the family level (Penny et al., 2010; Stephan et al., 2009) to compare a set of a priori models representing alternative mechanisms (Fig. 1). Here, model goodness is quantified by the negative free energy, an approximation to the log model evidence. To elucidate the mechanisms underlying interhemispheric integration in the face perception network, families were defined, grouping models with identical modulatory inputs on the interhemispheric connections. We found strong posterior evidence for the F + VF family (Table 2; exceedance probability: 0.951), which grouped models whose interhemispheric connections were modulated by both the visual field and the perception of faces (see Section 2 for detailed information).

#### DCM connectivity parameter estimates

Individual connectivity parameters were then estimated using Bayesian model averaging (BMA) across the four models of the winning F + VF family within a pre-specified Occam's window (p < 0.05). Individual parameter estimates were then entered into summary statistics at the group level (one-sample *t*-tests, Bonferroni-corrected for multiple comparisons). We found the endogenous intrahemispheric forward

#### Table 2

Random effects Bayesian model selection (BMS) results for the comparison of 16 alternative models, representing distinct hypotheses on the intra- and interhemispheric integration among the face-sensitive regions. Model comparison was based on the negative free energy, which serves as an approximation to the log model evidence. Expected and exceedance probabilities are shown for each model (model level), as well as for each family (family level), separately.

| Model                             | Expected probability |              | Exceedance probability |              |
|-----------------------------------|----------------------|--------------|------------------------|--------------|
|                                   | Model level          | Family level | Model level            | Family level |
| VF / VF                           | 0.028                | 0.102        | 0.002                  | 0.002        |
| VF / F                            | 0.042                |              | 0.008                  |              |
| VF/F + VF                         | 0.029                |              | 0.002                  |              |
| $VF / F \times VF$                | 0.060                |              | 0.020                  |              |
|                                   |                      |              |                        |              |
| F / VF                            | 0.029                | 0.089        | 0.001                  | 0.002        |
| F / F                             | 0.029                |              | 0.001                  |              |
| F/F + VF                          | 0.058                |              | 0.010                  |              |
| F / F 	imes VF                    | 0.028                |              | 0.002                  |              |
|                                   |                      |              |                        |              |
| F + VF / VF                       | 0.057                | 0.571        | 0.009                  | 0.951        |
| F + VF / F                        | 0.203                |              | 0.577                  |              |
| F + VF / F + VF                   | 0.144                |              | 0.224                  |              |
| $F + VF / F \times VF$            | 0.046                |              | 0.009                  |              |
|                                   |                      |              |                        |              |
| $F \times VF / VF$                | 0.029                | 0.238        | 0.002                  | 0.046        |
| $F \times VF / F$                 | 0.085                |              | 0.048                  |              |
| $F \times VF / F + VF$            | 0.105                |              | 0.082                  |              |
| $F \times VF \: / \: F \times VF$ | 0.030                |              | 0.002                  |              |

connections to be excitatory in both hemispheres (Fig. 3A and Table 3). Additionally, intrahemispheric feedback connections from FFA to OFA were inhibitory, whereas the feedback connections from OFA to V1 did not reach significance. Endogenous interhemispheric connections were excitatory among the bilateral OFA and inhibitory among the bilateral FFA (although this was not significant for the connection from left to right FFA).

We then tested whether hemispheric asymmetries in the endogenous connectivity per se could provide an explanation for the right lateralization of the face perception network (one-sided paired *t*-test). However, connection strengths within or towards the right hemisphere were not significantly larger than their counterparts within or towards the left hemisphere (all p > 0.05, uncorrected).

Beyond endogenous connectivity, within both hemispheres the forward connections from V1 to OFA and from OFA to FFA were positively modulated by the perception of faces (Fig. 3B and Table 3). This is in line with the common assumption of a hierarchical processing of face stimuli via OFA to FFA (but see Rossion, 2008; for evidence suggesting direct input to FFA, prior to OFA). Additionally, the interhemispheric connections among the bilateral OFA were strongly modulated by the presentation of faces, suggesting interhemispheric recruitment at the hierarchically early level of the OFA. We found such interhemispheric face-specific modulations for the connection from left OFA to dominant right OFA (1.074  $\pm$  0.537 Hz;  $t_{(18)} =$ 8.71, p < 0.001), but also for the connection from right to left OFA  $(0.599 \pm 0.504 \text{ Hz}; t_{(18)} = 5.18, p < 0.001)$ . This not only emphasizes the well-known significance of the right OFA, but also suggests a non-negligible role of the left OFA when passively viewing faces. No such face-induced interhemispheric recruitment was observed among left and right FFA. Nevertheless, these connections were positively modulated by all stimuli regardless of their category (faces and scrambled images) conditional on the visual field, i.e., the connection from left to right FFA was modulated by stimuli presented in the RVF (0.634  $\pm$  0.586 Hz;  $t_{(18)}$  = 4.71, p < 0.001), whereas the connection from right to left FFA was modulated by stimuli presented in the LVF (0.846  $\pm$  0.478 Hz;  $t_{(18)} =$  7.71, p < 0.001).

Again, we tested whether the right-hemispheric lateralization of the face perception network could be explained by hemispheric asymmetries in the modulatory influences on the intra- and interhemispheric connections. We found the face-specific modulatory influences to be significantly stronger (at a Bonferroni-corrected statistical threshold) for the connection from left to right OFA than for the connection from right to left OFA ( $t_{(18)} = 2.46$ , p = 0.01). No other differences between the hemispheres were observed: face-specific modulation did neither occur differentially for connections from V1 to OFA in left vs. right hemisphere, nor for the connections from OFA to FFA. Furthermore, the hemifield-dependent modulations among the bilateral FFA were not significantly different across hemispheres (all p > 0.05, uncorrected).

In summary, our model indicated that the most likely explanation for the right lateralization of the face perception network is an asymmetric face-specific interhemispheric information transfer among the bilateral OFA.



**Fig. 3.** Effective connectivity pattern of the bilateral face perception network. (A) Endogenous connectivity (A-matrix) among the visual input region (V1) and the core regions of the face perception network (OFA, FFA). Green arrows indicate positive (excitatory) connections, whereas red arrows represent negative (inhibitory) connections. (B) Modulatory influences (B-matrix) on the connectivity when perceiving faces regardless of the hemifield (green arrows) or when perceiving stimuli regardless of the stimulus type, but conditional on the hemifield (green-white arrows). Parameter estimates were computed using Bayesian model averaging (BMA) across the four models of the winning F + VF family (i.e., models whose interhemispheric connections were modulated by both the visual field and the presentation of faces; see Section 2 for detailed information). The strength of each connection is displayed in terms of the mean coupling parameter (in [Hz]). Only significant (p < 0.05, Bonferroni-corrected within each parameter class) connections are shown. For a complete description of the endogenous and modulatory parameter estimates, see Table 3.

#### Table 3

Group-level results for the endogenous (A-matrix) and modulatory (B-matrix) parameter estimates after Bayesian model averaging (BMA). Parameter estimates (i.e., endogenous and modulatory) for all connections across all subjects as revealed by BMA over the 4 models of the winning F + VF family (i.e., models whose interhemispheric connections were modulated by both the visual field and the presentation of faces; see Section 2 for detailed information) within a pre-specified Occam's window (p < 0.05). Significant group-level parameters (p < 0.05, Bonferroni-corrected within each parameter class) are printed bold.

| Connection                        | $\text{Mean}\pm\text{std}$           | Range            | р         |  |  |  |  |
|-----------------------------------|--------------------------------------|------------------|-----------|--|--|--|--|
| Endogenous parameters             |                                      |                  |           |  |  |  |  |
| $FFA_L \rightarrow FFA_R$         | $-0.358 \pm 0.669$                   | -1.334-1.681     | 3.14e-2   |  |  |  |  |
| $FFA\_L \rightarrow OFA\_L$       | $-\textbf{1.734} \pm \textbf{1.011}$ | -3.652 to -0.271 | 6.37e-7   |  |  |  |  |
| $FFA_R \rightarrow FFA_L$         | $\mathbf{-0.780} \pm 0.595$          | -2.567 - 0.172   | 2.04e-5   |  |  |  |  |
| $FFA_R \rightarrow OFA_R$         | $\mathbf{-2.027} \pm 1.182$          | -4.184-0.319     | 6.34e-7   |  |  |  |  |
| $OFA_L \rightarrow FFA_L$         | $\textbf{0.527} \pm \textbf{0.550}$  | -0.580-1.509     | 5.69e-4   |  |  |  |  |
| $OFA_L \rightarrow OFA_R$         | $\textbf{0.688} \pm \textbf{0.625}$  | -0.386-1.962     | 1.45e-4   |  |  |  |  |
| $OFA_L \rightarrow V1_L$          | $-0.182 \pm 0.769$                   | -2.080 - 0.976   | 3.17e – 1 |  |  |  |  |
| $OFA_R \rightarrow FFA_R$         | $\textbf{0.359} \pm \textbf{0.316}$  | -0.122-0.897     | 1.02e-4   |  |  |  |  |
| $OFA_R \rightarrow OFA_L$         | $\textbf{0.504} \pm \textbf{0.538}$  | -0.403-1.549     | 6.99e-4   |  |  |  |  |
| $OFA_R \rightarrow V1_R$          | $0.000\pm0.348$                      | -0.647 - 0.530   | 9.98e - 1 |  |  |  |  |
| $V1_L \rightarrow OFA_L$          | $\textbf{0.535} \pm \textbf{0.143}$  | 0.288-0.811      | 3.00e-12  |  |  |  |  |
| $V1\_R \to OFA\_R$                | $\textbf{0.431} \pm \textbf{0.124}$  | 0.149-0.711      | 1.13e-11  |  |  |  |  |
| Modulatory parameter              | rs (RVF)                             |                  |           |  |  |  |  |
| $FFA_L \rightarrow FFA_R$         | $\textbf{0.634} \pm \textbf{0.586}$  | -0.442-1.731     | 1.73e-4   |  |  |  |  |
| $OFA_L \rightarrow FFA_L$         | $0.119 \pm 0.296$                    | -0.315 - 0.799   | 9.59e – 2 |  |  |  |  |
| $OFA_L \rightarrow OFA_R$         | $-0.226 \pm 0.758$                   | -1.776-0.767     | 2.11e-1   |  |  |  |  |
| $V1\_L \to OFA\_L$                | $0.128\pm0.422$                      | -0.265 - 1.693   | 2.04e - 1 |  |  |  |  |
| Modulatory parameter              | rs (LVF)                             |                  |           |  |  |  |  |
| $FFA_R \rightarrow FFA_L$         | $\textbf{0.846} \pm \textbf{0.478}$  | -0.122 - 1.774   | 4.12e-7   |  |  |  |  |
| $OFA_R \rightarrow FFA_R$         | $0.106 \pm 0.245$                    | -0.349 - 0.860   | 7.59e – 2 |  |  |  |  |
| $OFA_R \rightarrow OFA_L$         | $-0.036 \pm 0.668$                   | -1.734 - 1.056   | 8.18e – 1 |  |  |  |  |
| $V1\_R \to OFA\_R$                | $0.091\pm0.360$                      | -0.277 - 1.188   | 2.87e – 1 |  |  |  |  |
| Modulatory parameters (faces)     |                                      |                  |           |  |  |  |  |
| $FFA\_L \rightarrow FFA\_R$       | $-0.343 \pm 0.614$                   | -1.853 - 0.224   | 2.55e - 2 |  |  |  |  |
| $FFA_R \rightarrow FFA_L$         | $-0.170 \pm 0.435$                   | -1.027 - 0.917   | 1.06e - 1 |  |  |  |  |
| $OFA_L \rightarrow FFA_L$         | $\textbf{0.491} \pm \textbf{0.519}$  | -0.209 - 1.589   | 6.33e-4   |  |  |  |  |
| $OFA\_L \rightarrow OFA\_R$       | $\textbf{1.074} \pm \textbf{0.537}$  | 0.146-2.050      | 7.15e-8   |  |  |  |  |
| $OFA\_R \to FFA\_R$               | $\textbf{0.276} \pm \textbf{0.322}$  | -0.108 - 0.891   | 1.50e-3   |  |  |  |  |
| $OFA_R \rightarrow OFA_L$         | $\textbf{0.599} \pm \textbf{0.504}$  | -0.584-1.913     | 6.35e-5   |  |  |  |  |
| $V1_L \rightarrow OFA_L$          | $\textbf{0.651} \pm \textbf{0.481}$  | -0.013-1.479     | 1.37e-5   |  |  |  |  |
| $V1\_R \to OFA\_R$                | $\textbf{0.758} \pm \textbf{0.451}$  | 0.000-1.677      | 8.24e-7   |  |  |  |  |
| Modulatory parameters (faces RVF) |                                      |                  |           |  |  |  |  |
| $OFA\_L \rightarrow FFA\_L$       | $0.019\pm0.039$                      | 0.000-0.141      | 4.78e - 2 |  |  |  |  |
| $V1\_L \to OFA\_L$                | $0.030\pm0.078$                      | 0.000-0.333      | 1.15e – 1 |  |  |  |  |
| Modulatory parameters (faces LVF) |                                      |                  |           |  |  |  |  |
| $OFA\_R \to FFA\_R$               | $0.006\pm0.016$                      | -0.022 - 0.051   | 1.33e – 1 |  |  |  |  |
| $V1\_R \to OFA\_R$                | $0.035\pm0.083$                      | 0.000-0.339      | 8.04e - 2 |  |  |  |  |

Asymmetry in the face-specific interhemispheric recruitment is linked to differences in the OFA's gray matter volume

Since the effective connectivity analyses emphasized the importance of asymmetric face-specific interhemispheric recruitment among the OFAs, we asked whether this functional characteristic was grounded in structural properties of the face perception network and therefore examined differences in the brain anatomy of the two hemispheres. To this end, we tested whether gray matter volume, revealed by VBM, related to asymmetries in the modulatory influences on the interhemispheric connections among bilateral OFA (i.e.,  $[OFA_L \rightarrow OFA_R]$ - $[OFA_R \rightarrow OFA_L]$ ). Using a functionally defined a priori mask of the left and right OFA (see Section 2 for detailed information), we found a significant correlation between local gray matter volumes and asymmetries in modulation of interhemispheric connections between the OFAs at a statistical threshold of p < 0.05, FWE-corrected (small-volume correction, Fig. 4A). The correlation was positive for the right OFA, whereas a negative correlation was observed for the left OFA (Fig. 4B). That is, the more right-lateralized the functional interhemispheric recruitment, the larger the gray matter volume of the right OFA and the smaller the gray matter volume of the left OFA. Notably, subjects who did not show any asymmetries in their face-specific modulatory influences on the interhemispheric connections among bilateral OFA did not show any asymmetries in the gray matter volume of the OFA either (as is evidenced by the intersection of the regression lines close to x = 0, Fig. 4B).

#### Does the interhemispheric integration mediate holistic versus featurebased processing?

The functional meaning of the face-specific interhemispheric recruitment among the bilateral OFA is still unknown. Following the notion that the right hemisphere processes faces holistically, whereas the left hemisphere engages in a more feature-based processing (Hillger and Koenig, 1991; Leehey et al., 1978; Rossion et al., 2000), one potential explanation relates inter-subject variability in interhemispheric integration to different hemispheric strategies for holistic and feature-based processing of face stimuli. Here, we addressed this question in an exploratory manner using pupil size measures. This rests on recent psychophysical studies which have demonstrated that pupil size might be sensitive to (among many other influences) holistic as opposed to feature-based processing of visual stimuli, such as faces (Conway et al., 2008) and scenes (Naber and Nakayama, 2013). Compatible with these suggestions, we found transient pupil constrictions to the onsets of faces to be stronger than those to the onsets of scrambled images (Fig. 5A; faces:  $0.026 \pm 0.014$ ; scrambled:  $0.013 \pm 0.008$ ;  $t_{(18)} = 4.66, p = 1.93e - 4$ ).

In a next step, to address the idea that the individual degree of asymmetry in interhemispheric interactions among the OFA during face processing is related to individual tendencies towards holistic vs. feature-based processing strategies in face perception, we examined the correlation between asymmetries in modulatory influences on interhemispheric connections among the OFAs and the average strength of pupil constrictions to the onsets of faces. We found the two variables to be positively correlated (r = 0.50, p = 0.03; Fig. 5B). Notably, this correlation was specific for face stimuli: it was significantly higher for pupil constrictions to faces compared to scrambled images ( $Z_{(16)} =$ 1.94, p = 0.03); in fact, the correlation was absent for pupil constrictions to scrambled images (r = 0.05, p = 0.83). Similarly, this correlation between OFA asymmetries in interhemispheric connectivity and pupil constriction to faces was significantly higher than the one between the asymmetry of stimulus-specific modulation of interhemispheric connections among bilateral FFA and the strength of pupil constrictions either to faces (r = -0.05;  $Z_{(16)} = 1.95$ , p = 0.03) or to scrambled images (r = -0.04;  $Z_{(16)} = 1.81$ , p = 0.04). This suggests that the correlation between the asymmetry in the interhemispheric recruitment and the strength of transient pupil constrictions was specific in two ways: to the hierarchical level of the OFA and to the perception of faces.

#### Discussion

Our results provide a mechanistic account of both the intra- and interhemispheric functional integration among the core regions of the face perception network, suggesting that the typical right lateralization is explained by an asymmetric face-specific interhemispheric recruitment at the hierarchical level of the OFA. As a structural correlate of the functional integration, we found the anatomical variations in OFA's gray matter volume to be correlated with the asymmetry of the functional recruitment. This suggests that interhemispheric information transfer is a stable property of the face perception network. Moreover, we found preliminary evidence for a relation between the individual degree of interhemispheric integration asymmetries between left and right OFA and the individual's tendency towards holistic vs. featurebased processing styles when passively viewing faces.

In line with previous studies (Kanwisher et al., 1997; Puce et al., 1996), we found bilateral face-sensitive activation in the OFA and FFA,



**Fig. 4.** Correlation of OFA gray matter volume with the asymmetry of the interhemispheric recruitment. (A) Brain regions that showed significant (p < 0.05, FWE-corrected, small-volume correction within an a priori mask built from the group-level BOLD activation in the inferior occipital gyrus) correlations of the gray matter volume with the difference in the modulatory influences on the interhemispheric connections among bilateral OFA (i.e.,  $|OFA_L \rightarrow OFA_R|$ – $|OFA_R \rightarrow OFA_L|$ ). L = left hemisphere; R = right hemisphere. (B) The sign of the correlation was positive for the peak voxel within the right OFA (red) and negative for the peak voxel within the left OFA (gray). This suggests that subjects with a strong rightward asymmetry in the interhemispheric recruitment also displayed a larger gray matter volume in the right OFA and a smaller gray matter volume in the left OFA; and vice versa for subjects with a strong leftward asymmetry.

lateralized to the right hemisphere. We then investigated the functional integration among these regions of both hemispheres, taking into account intra- and interhemispheric connections. Specifically, presenting the stimuli in the periphery allowed us to test different hypotheses on the interhemispheric integration in the face perception network (cf. Stephan et al., 2005, 2007). This extends the purely intrahemispheric approach from previous effective connectivity studies on the face perception network, which either limited their analyses to the (dominant) right hemisphere or investigated the two hemispheres independently (Cohen Kadosh et al., 2011; Dima et al., 2011; Ewbank et al., 2013; Fairhall and Ishai, 2007; Ishai, 2008; Li et al., 2010). Only recently have functional connectivity studies begun to emphasize the relevance of interhemispheric couplings among the face-sensitive regions of the core system (Davies-Thompson and Andrews, 2012). Critically, functional connectivity merely provides correlative measures and is thus limited (Stephan, 2004), whereas effective connectivity offers mechanistic models of the directed interactions underlying network dynamics.

In the present DCM framework, we found faces to be processed in a forward manner within each hemisphere, reproducing findings from previous effective connectivity studies (Cohen Kadosh et al., 2011; Fairhall and Ishai, 2007). Beyond this confirmation, the present framework provides a mechanistic model for the typical right lateralization of the face perception network, pointing to an asymmetric facespecific interhemispheric recruitment at the hierarchically early level of the OFA. This recruitment was mediated by excitatory modulations of the interhemispheric connections among left and right OFA. The modulation of the connection from left to right OFA was significantly stronger than that from right to left OFA, thus giving rise to the right lateralization of the activation pattern. This observation fits with the general notion of asymmetries in the exchange of information between hemispheres (Hoptman and Davidson, 1994; Marzi et al., 1991). Notably, the present modulations were independent of the hemifield in which the faces were presented. Hence, the right OFA was recruited not only when the face stimuli entered the visual system in the left



**Fig. 5.** Correlation of the strength of pupil constrictions with the asymmetry in the interhemispheric recruitment. (A) Transient pupil constrictions to the onsets of faces are larger than those to the onsets of scrambled images. (B) The strength of pupil constrictions to the onsets of faces (black circles) is correlated with the difference in the modulatory influences on the interhemispheric connections among bilateral OFA (i.e., [OFA\_L  $\rightarrow$  OFA\_R]–[OFA\_R  $\rightarrow$  OFA\_L]). No correlation was observed between pupil constrictions to scrambled images (gray circles) and the difference in the modulatory influences.

hemisphere, but also when the stimuli entered the right hemisphere. Critically, the same applies for the left OFA. This speaks to a nonnegligible role of the left OFA in the face perception network, in contradiction to previous findings (Pitcher et al., 2007). The present results are more compatible with recent studies, which suggested an important role of the left-hemispheric regions in face perception — although solely in the context of the FFA (Bi et al., 2014; Meng et al., 2012). Whereas the functional relevance of the left FFA has thus been investigated at least to some degree, the role of the left OFA remains uncharted territory so far. Our results, however, claim a decisive role of bilateral OFA and suggest that face-specific information is primarily exchanged across hemispheres at the early stage of the OFA, and then forwarded to the FFA, where higher analyses (e.g., identification) might take place. A more thorough investigation of both OFAs and their functional integration is thus essential for a deeper understanding of the face perception network.

As a structural correlate of interhemispheric integration, we found the gray matter volume of the OFA to be correlated with the asymmetry in interhemispheric recruitment. Subjects with a strong rightward asymmetry in the information transfer among the OFAs displayed larger gray matter volume in the right OFA and smaller gray matter volume in the left OFA; vice versa for subjects with a leftward asymmetry. A potential hypothesis interprets this finding in line with local plasticity changes in bilateral OFA, occurring as a consequence of the extensive experience of humans in face perception. Such local plasticity of the human brain has been frequently described using VBM, probably most well-known from the pioneering study (Maguire et al., 2000) which found differences in the hippocampal volume between London taxi drivers and control subjects. The alternative hypothesis suggests that the observed asymmetry in the OFA's gray matter volume may be attributable to innate predisposition, and thus differences in brain anatomy determine the asymmetry in the interhemispheric recruitment. Such innate cerebral asymmetry has, for instance, been suggested to underlie hemispheric differences of the planum temporale (Chi et al., 1977; Preis et al., 1999). Obviously, from the merely correlative measures obtained by the present study, none of the two alternatives can be excluded. Nevertheless, the observed link between effective connectivity and brain anatomy suggests that the asymmetric interhemispheric recruitment at the hierarchical level of the OFA is a stable and decisive property of the face perception network. Future studies will need to corroborate this finding and delineate its directionality.

Critically, these analyses do not reveal the exact cognitive process mediated by face-induced coupling across the hemispheres. To shed light on this question, we performed an exploratory analysis, testing whether individual differences in the asymmetry of interhemispheric recruitment might reflect individual differences in hemispheric processing strategies, with respect to how strongly face perception relies on holistic vs. feature-based processing. This follows the longstanding notion that the right hemisphere employs a holistic (synthetic) strategy, whereas the left hemisphere may engage in a feature-based (analytic) strategy (Bradshaw and Nettleton, 1981). This has also been observed for face perception in behavioral (Hillger and Koenig, 1991; Leehey et al., 1978), clinical (Yin, 1970) and neuroimaging studies (Rossion et al., 2000). Additionally, recent behavioral studies have pointed towards a link between interhemispheric integration and holistic representations of faces (Yovel et al., 2005).

Providing preliminary evidence for a link between interhemispheric recruitment among the OFA and holistic/feature-based processing strategies, we found the asymmetry of the recruitment to be positively correlated with the strength of pupil constrictions to the onsets of face stimuli. This initial analysis was inspired by recent findings that transient pupil constrictions to upright human faces are greater than those to scrambled versions, inverted versions, or macaque monkey faces (Conway et al., 2008). Similarly, Naber and Nakayama (2013) showed that pupil constrictions are larger to upright as compared to inverted images of scenes. Collectively, these findings suggest that pupil size could serve as a physiological marker of individual differences in

processing strategies (holistic vs. feature-based processing of visual stimuli) during face perception. We would like to emphasize, however, that this account presently remains speculative, since several competing explanations exist. For example, larger transient pupil constrictions might also be related to the familiarity or relevance of face stimuli (Mondloch et al., 2006). Future studies will thus need to corroborate the observations made in the present study by using more sophisticated experimental paradigms. For example, holistic versus feature-based processing of faces has commonly been investigated using the face inversion effect (Yin, 1969) and the composite effect (Young et al., 1987). Hence, combing behavioral experiments probing these effects in individual subjects with the multimodal approach of this paper using effective connectivity, structural and physiological measures, may offer a promising avenue for future studies on the role of interhemispheric integration during face processing.

Notably, despite extending previous approaches investigating the effective connectivity of the face perception network, the present approach is also subject to limitations. First, we only investigated the functional integration among the core regions (OFA, FFA) involved in processing faces. However, faces are multidimensional stimuli, conveying information not only about a person's identity or gender, but also about emotions, intentions, fame or trustworthiness. Integrating all of this information requires a more distributed network, encompassing additional regions such as the pSTS and regions of the extended system such as the amygdala, insula or the orbitofrontal cortex (Ishai, 2008). Notably, in the present study (which used faces of individuals unknown to the participants, conveying no emotional expressions), no significant group-level activation was found in these regions. This is consistent with recent work claiming that activation of these regions is not necessary for pure (passive) face detection or identification (Grill-Spector et al., 2004), but serves additional face-related functions. For instance, the processing of changeable facial features (e.g., gaze direction, lip movements) has been associated with the pSTS (Haxby et al., 2000; Hoffman and Haxby, 2000; Puce et al., 1998) acting in concert with a distributed cortical network (Nummenmaa et al., 2010). With respect to facial identity, it may also become important for future work to consider differences in the neuronal representation related to the familiarity of faces (Eger et al., 2005), and to address whether interhemispheric integration plays an even greater role in the case of familiar vs. unfamiliar faces (Mohr et al., 2002; Schweinberger et al., 2003). Second, we only defined one FFA per hemisphere. However, it has recently been suggested that there are multiple face-sensitive regions in the fusiform gyrus (Weiner and Grill-Spector, 2012). Critically, the exact role of these regions is still largely unknown and thus well-founded hypotheses on their interplay rarely exist. Third, recent studies have emphasized the possibility of a direct route from early visual areas to FFA, bypassing OFA (Atkinson and Adolphs, 2011; Rossion, 2008). This route has been proposed to mediate low-level categorization abilities such as discriminating faces from objects, raising the question whether input from early visual areas enters OFA or FFA first. In this work, we have restricted our DCM analyses to the more classical view of a hierarchical relation between OFA and FFA. This was for two reasons: to keep the set of hypotheses as focused as possible (altering the V1-OFA/FFA connections would have added another factor to the factorial structure of our model space), and to avoid numerical instabilities during inversion of models with V1 connections to both OFA and FFA. The latter was suggested by exploratory analyses indicating that, for the present setting, models no longer converged under the default upper bound on iterations (i.e., 128 iterations). This is probably because the additional parameters introduce non-negligible parameter interdependencies in the likelihood function. High parameter interdependencies reflect badly behaved regimes of the objective function (e.g., ridges or ravines), which, in turn, can undermine the convergence of the variational Bayesian optimization scheme (Daunizeau et al., 2011). While global optimization schemes, such as Markov Chain Monte Carlo or Gaussian process optimization (Lomakina et al., 2015), are currently under development and promise great potential for enabling more complex network models, their utility for overcoming the problem mentioned above remains to be tested. In future studies, we therefore aim at developing more sophisticated experimental paradigms and at exploiting methodological advances to current DCM implementations, which will jointly allow us to build bilateral models covering a more extended network. Despite these limitations, the results presented here provide novel insights into functional interactions among the two face-sensitive regions essential for face detection and identification: OFA and FFA (Grill-Spector et al., 2004; Kanwisher, 2000; Rossion et al., 2003). Extending this approach will lead to a richer understanding of how the human brain processes faces and their inherent social cues.

In conclusion, perceiving faces activates a distributed cortical network in the human brain, with its components strongly interacting with each other, instead of forming isolated functional entities. Our results indicate that the interhemispheric integration among bilateral OFA is a crucial property of the face perception network with structural correlates in brain anatomy and potentially mediating individual strategies for holistic vs. feature-based processing during face perception.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.neuroimage.2015.09.055.

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