

Functional Plasticity in Ventral Temporal Cortex following Cognitive Rehabilitation of a Congenital Prosopagnosic

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Abstract

■ We used functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to measure neural changes associated with training configural processing in congenital prosopagnosia, a condition in which face identification abilities are not properly developed in the absence of brain injury or visual problems. We designed a task that required discriminating faces by their spatial configuration and, after extensive training, prosopagnosic MZ significantly improved at face identification. Event-related potential results revealed that although the N170 was not selective for faces before training, its selectivity after training was

normal. fMRI demonstrated increased functional connectivity between ventral occipital temporal face-selective regions (right occipital face area and right fusiform face area) that accompanied improvement in face recognition. Several other regions showed fMRI activity changes with training; the majority of these regions increased connectivity with face-selective regions. Together, the neural mechanisms associated with face recognition improvements involved strengthening early face-selective mechanisms and increased coordination between face-selective and non-selective regions, particularly in the right hemisphere. ■

INTRODUCTION

Treating neurological deficits and characterizing the underlying neural changes can provide insights into the cognitive and neural nature of the dysfunction, can inform models of normal functioning, and can elucidate plastic changes involved in successful recovery. Functional magnetic resonance imaging (fMRI) and event-related potentials (ERPs) are particularly useful techniques for this approach because they allow the localization of training-related changes as well as their time course. Additionally, these techniques allow the assessment of training-induced neural connectivity changes, which can help elucidate whether remediation occurs by strengthening the “normal” network or by recruiting a compensatory network (Sun, Miller, & D'Esposito, 2004; Friston, 2002). In the present study, we measured fMRI and ERP while applying a training program for congenital prosopagnosia (CP), a disorder in which face recognition abilities are impaired. Face recognition is particularly amenable to the investigation of functional changes and neural plasticity resulting from training because this process has been amply investigated at the perceptual level and is sufficiently well-characterized at the neural level.

Congenital prosopagnosia is a marked impairment in identifying faces in the absence of other conspicuous sensory, cognitive, and neurological pathology. At the perceptual level, prosopagnosics are overwhelmed with visual details and have particular difficulties at visually integrating parts into a coherent whole (Bentin, DeGutis, D'Esposito, & Robertson, 2007; Behrmann & Avidan, 2005). Specifically, it has been shown that congenital prosopagnosics have deficits on tasks that require discrimination on the basis of subtle spacing differences between parts (Barton, Cherkasova, Press, Intriligator, & O'Connor, 2003, 2004; Joubert et al., 2003). This impairment particularly affects face identification, which involves computing spatial relations among inner face components and integrating this information into a holistic percept.

Neural mechanisms of face recognition involve face-selective networks in the ventral occipital temporal cortex. There are two well-studied markers of face processing: One is the selective activity elicited by faces in a ventral occipital temporal network, including the fusiform face area (FFA) and the occipital face area (OFA), and the other is the enhanced amplitude of the N170 ERP component in response to faces compared to objects. fMRI studies of prosopagnosics suggest that the FFA and the OFA and their functional connections are necessary for normal face recognition. In one severe case of CP, Bentin et al. (2007) showed a complete absence of face-selective activity anywhere in the ventral

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occipito-temporal cortex, suggesting that face-selective activity is a necessary condition for normal face recognition abilities. Other studies, however, showed that prosopagnosia can exist even if each of these regions is normally selective (Avidan, Hasson, Malach, & Behrmann, 2005; Hasson, Avidan, Deouell, Bentin, & Malach, 2003). Perhaps, as one report suggests, damage to the connections between the OFA and the FFA might be a critical factor accounting for prosopagnosia (Rossion et al., 2003). ERP studies consistently show that unlike normal controls, the N170 component in CPs is not selective to faces compared to objects. Although differences between fMRI and ERP measures indicate that they might tap different aspects of face processing, they both indicate that face selectivity is an important contributor to successful face identification.

Comparing face processing during EEG and fMRI before and after rehabilitation training could reveal whether face identification improvements are supported by neural mechanisms similar to normal subjects or by alternative compensatory mechanisms. The recruitment of normal versus compensatory mechanisms after training has been shown to vary by factors including the particular disorder, lesion extent, type of training, and duration of training (Temple et al., 2003; Wexler et al., 2000; for reviews, see Rijntjes & Weiller, 2002; Thirumala, Hier, & Patel, 2002). Studies suggest that generally improvements during initial rehabilitation training recruit compensatory mechanisms, whereas further improvements during prolonged training recruit a normalized pattern of brain activation. A recent attempt at prosopagnosia rehabilitation suggests that training-related improvements are accompanied by a normal pattern of brain activity in these patients. Behrmann and colleagues trained a prosopagnosic to improve at processing facelike objects (greebles) over several weeks (Behrmann, Marotta, et al., 2005). Training improved greeble identification (though unfortunately not face identification) and augmented processing of greebles in the right ventral occipital temporal cortex similar to normal controls trained with this stimuli. This demonstrates that in a prosopagnosic, improvements in object recognition recruit a normal pattern of activity for objects. If improvements in face recognition operate similarly in these patients, we would predict a normal pattern of face activity after successful face training. However, if training

face processing is qualitatively different from training object processing in prosopagnosics, face recognition improvements may be accomplished by alternative neural mechanisms than those used by normal controls.

In the current study, we developed a simple configural training task in which the perceiver learned to discriminate among faces on the basis of spacing among internal components. We found that training a congenital prosopagnosic (MZ) on this task improved face identification both on standard tests and in everyday life. Importantly, this improvement was accompanied by marked changes in activity and connectivity in the ventral occipital temporal cortex, as well as in the selectivity of the N170. The fMRI results demonstrate that improvements in face recognition correspond to changes in connectivity within regions in the face-selective network, particularly in the right hemisphere and between the face-selective network and several brain regions that are not face-selective. The N170 modulation demonstrated a substantial posttraining amplitude reduction for objects relative to faces, thus increasing face selectivity. This pattern suggests that face processing in CPs can be rehabilitated by training and that improvements are achieved by augmenting activity and connectivity of face processing systems rather than by recruiting compensatory mechanisms.

METHODS

Training Procedures

The training task was administered over a period of 14 months in two separate intervals (Figure 1). Training consisted of performing a face classification task in which MZ classified faces into two categories, which varied in the distance between the eyes and the eyebrows and in the distance between the mouth and the nose (see Figure 2A). Lifelike faces were created from the faces-composite-face-making software (Faces version 3.0, 1998). Using one face as a template, eyebrow height and mouth height were parametrically varied in 2-mm increments to make 10 faces (Figure 2A). At the beginning of training, MZ was shown the matrix of faces and told the categorization rule: “faces with higher eyebrows and lower mouths are generally in Category 1 and faces with lower

Figure 1. The timeline of face classification training, behavioral testing, fMRI scans, and EEG sessions.

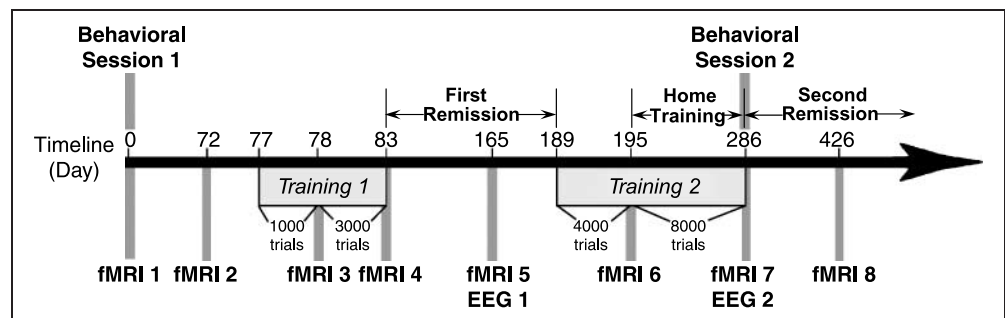
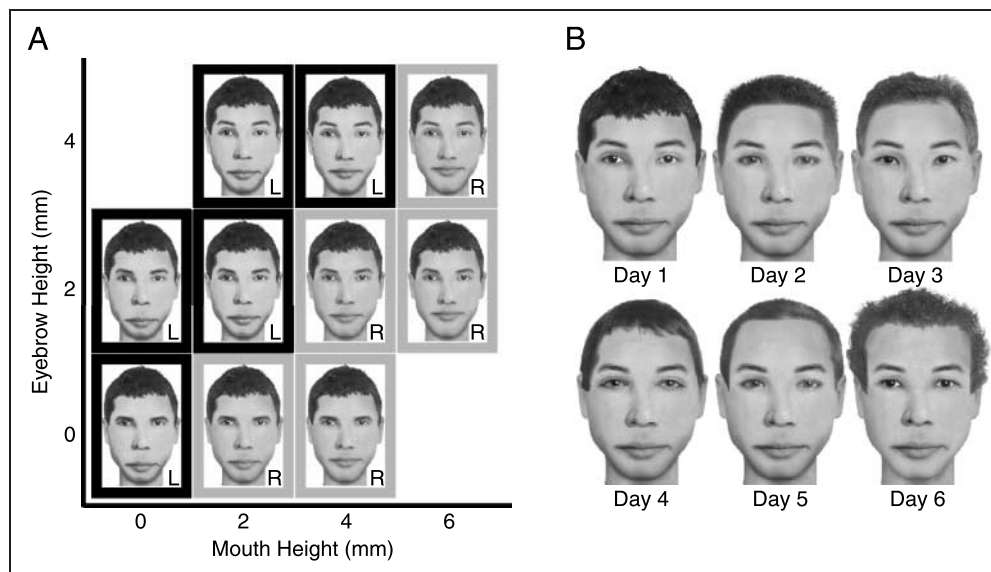


Figure 2. (A) Example of one of the faces used in classification training. Faces varied in their eyebrow height and mouth height to produce a matrix of 10 faces. Category L is marked in the figure by dark frames and category R by bright frames. The letter next to each face indicates the correct response: right (R) or left (L) button press with the right hand. (B) The different template faces used each day.



eyebrows and higher mouths are generally in Category 2.” Next, MZ received 250 trials of self-paced computer training where she saw a face and had to respond with a right-handed button press designating Category 1 or Category 2. Feedback (correct/incorrect) was provided immediately after each trial. After 250 trials, she took a break and received a feedback matrix that showed the accuracy and reaction time for each face. One 250-trial session was performed on the first training day and three were performed on each training day thereafter. To ensure that MZ actually computed the relational information rather than learning the individual 10 faces, new faces were used each day (see Figure 2B).

During the first training interval, MZ received 4000 trials of daily training over a 1-week period. After this interval, training was stopped for 105 days. During the second training period, MZ received another 4000 trials of the original face classification task daily for 1 week, using the same faces as in the previous training interval. At the end of this interval she was given a more difficult version of the task in which the relational changes were reduced in size (1-mm increments between feature values compared to 2-mm increments in the previous set), which she was given to use at home over a period of 3 months. Unsupervised training continued roughly on a daily basis for 140 more days, after which it was ceased.

Behavioral Training in Participants with Normal Face Recognition

Ten right-handed participants ranging in age from 22 to 29 years ($M = 25.4$ years) were recruited from the University of California at Berkeley. All participants were screened against medical, neurological, and psychiatric illnesses, and for use of prescription medications. All participants gave written informed consent prior to participation in the study according to the procedures

approved by the University of California at Berkeley Committee for Protection of Human Subjects. Participants performed the same training task as MZ for 6 days.

fMRI Image Acquisition

Functional images were acquired using a gradient echo-planar sequence ($TR = 2000$ msec, $TE = 28$ msec, matrix size = 64×64 , $FOV = 22.4$ cm) sensitive to blood oxygen level-dependent contrast. Each functional volume consisted of 18 5-mm-thick axial slices with 0.5 mm gap between each slice, providing whole-brain coverage except for portions of the inferior cerebellum and the most superior extent of the parietal lobe. For each scan, 30 sec of gradient and radio-frequency pulses preceded data acquisition to allow steady-state tissue magnetization and to allow the participant to habituate to the scanner noise before performing the task. Stimuli were presented using E-prime software and were viewed in the scanner via back-projection onto a custom screen mounted at the participant’s chest level and viewed via an angled mirror placed inside the head coil. Responses were made using a hand-held fiber-optic button box.

fMRI Data Analysis—Univariate

Functional images acquired from the scanner were reconstructed from k -space using a linear time-interpolation algorithm to double the effective sampling rate. Image volumes were corrected for slice-timing skew using temporal sinc-interpolation. Data were preprocessed with SPM2 (Wellcome Department of Cognitive Neurology, London). Images were realigned using a six-parameter, rigid-body, least-squares alignment and spatially smoothed with an 8-mm full-width, half-maximum Gaussian kernel. Images were spatially normalized to an EPI template on the basis

of the MNI305 stereotactic space, an approximation of Talairach space (Talairach & Tournoux, 1988). This was accomplished using a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions, and resampled the volumes to 2-mm cubic voxels. Univariate statistical analyses were performed with the general linear model (GLM) implemented in SPM2. The fMRI time-series data were modeled as a series of events convolved with a canonical hemodynamic response function (HRF). The resulting functions were used as covariates in a GLM. For the analysis of the face/scene one-back task, four covariates were used to model the fMRI data: faces during sessions without training, scenes during sessions without training, faces during sessions with training, and scenes during sessions with training. These covariates, along with a basis set of cosine functions that high-pass filtered the data, were included in a GLM. The least-squares parameter estimates of height and best fitting canonical HRF for each condition were used in pairwise contrasts. Significant regions of activation were identified using an uncorrected two-tailed threshold of $p < .001$ and a minimum cluster size of at least 5 contiguous voxels.

Definition of Face-selective Regions

For each fMRI session, the right and left FFA, the right OFA, and the parahippocampal place area (PPA) were functionally defined in MZ's native anatomical space using the contrast of faces minus scenes in the face/scene one-back task. The FFA was defined using the peak voxel in the fusiform gyrus that responded more to the faces minus scenes contrast and selecting the nine most significant contiguous voxels to the peak voxel. If the threshold had to be dropped below a t value of 1.5 to find the peak voxel, then this region was excluded. Activity within this region of interest (ROI) was averaged across all voxels.

fMRI Data Analysis—Coherence

To identify networks of functional connectivity for the left FFA, the right FFA, and the right OFA, we generated coherence maps using the coherence between these regions and all other regions in the brain. To identify network changes in the functional connectivity of the left FFA, the right FFA, and the right OFA, we contrasted the coherence maps for face viewing before and after training. This method is discussed in detail by Sun et al. (2004), and is outlined in five steps below:

- (1) Selection of reference voxels. We used the average of the voxels within the right FFA, the right OFA, and the left FFA as seeds for the coherence analyses.
- (2) Generation of condition-specific time series. Time series were separated into face and scene blocks for each session. Each time series had a total of 112 data points.
- (3) Estimation of coherence maps. Coherence estimates were computed using a fast Fourier transform algorithm implemented in Matlab 6.5 (www.mathworks.com). We used Welch's periodogram-averaging method to estimate the condition-specific coherence of each seed ROI with all other voxels in the brain (using a 64-point discrete Fourier transform, Hanning window, and overlap of 32 points). We then generated coherence maps for each seed ROI for each condition using the estimate of the band-averaged coherence within the bandwidth of the HRF (0–0.15 Hz) (Sun et al., 2004).
- (4) We applied an arc-hyperbolic tangent transform to the coherency, as described in Rosenberg, Amjad, Breeze, Brillinger, and Halliday (1989) so that the coherency magnitudes approaches a zero-centered normal distribution.
- (5) Next, we extracted mean coherence values from each ROI for each session. Because the face-selective ROIs were derived in native space, we extracted mean coherence values between these regions in native space. For the ROIs derived from the whole-brain mapwise comparison, we normalized the coherence maps from each session and extracted the mean coherence values between each region and the right FFA, right OFA, and left FFA.

fMRI Results in Participants with Normal Face Recognition

A group of 13 right-handed participants ranging in age from 19 to 31 years ($M = 22.9$ years) were recruited from the University of California at Berkeley. All participants were screened against medical, neurological, and psychiatric illnesses, and for use of prescription medications. All participants gave written informed consent prior to participation in the study according to the procedures approved by the University of California at Berkeley Committee for Protection of Human Subjects. Participants received no face classification training and performed one session of the face/scene one-back task. Face-selective ROIs were derived in native space using the same protocol as with MZ (see above). All participants had a left FFA, right FFA, and right OFA.

ERP Recording

The EEG was recorded continuously by 64 Ag–AgCl Pin-type active electrodes mounted on an elastic cap (ECI) according to the extended 10–20 system (American EEG Society Guidelines, 1994), and referenced to the tip of the nose. Eye movements and blinks were monitored using bipolar horizontal and vertical EOG derivations via two pairs of electrodes—one pair attached to the exterior canthi, and the other to the infraorbital and supra-orbital regions of the right eye. The analog signals were sampled at 250 Hz using a Biosemi Active II digital 24 bits

amplification system with an active input range of -262 mV to $+262$ mV per bit without any filter at input. The digitized EEG was saved and processed off-line. A change in voltage of more than 75 μ V during an epoch of 100 msec at any of the channels was considered artifact and the EEG recorded during 200 msec surrounding the artifact was eliminated from further analyses. After removing artifacts, the ERPs were extracted by segmenting and averaging stimulus-onset-locked epochs of EEG. No ERP was based on less than 50 single trials.

RESULTS

Pretraining Neuropsychological and Neuroimaging Profile¹

MZ, a 48-year-old right-handed woman, presented with severe difficulty in face identification abilities. In contrast, she did not complain about problems in identifying animals or nonliving objects. She has normal visual acuity as measured by Snellen chart, normal contrast sensitivity as measured by the Vis Tech chart, and normal color vision as measured by Ishihara plates. There was no evidence of diplopia or strabismus and no history of head trauma or cognitive deficits. Performance on these tests demonstrated that her face recognition impairments were not a consequence of low-level visual dysfunction.

In an informal test, MZ identified 5 out of 20 famous faces compared with an average identification of 16/20 in a normative group. Formal tests prior to training revealed that she was severely impaired in tests of visual memory for faces but not for words (Warrington Recognition Memory Test [WRMT]: 37/50 and 49/75 for faces and words, respectively). In addition, she was severely impaired at unfamiliar face matching (Benton Facial Recognition Test [BFRT]: 34/54). Because CPs frequently perform within the normal range on the Benton and Warrington tests (Duchaine & Nakayama, 2006), this pattern suggests that MZ is a particularly severe example of prosopagnosia, with an aperceptive factor (Figure 3A).

Like other CPs reported in the literature, MZ's anatomical MRI revealed a structurally normal brain (Avidan et al., 2005; Behrmann & Avidan, 2005; Hasson et al., 2003). To assess functional brain activity and selectivity for faces and scenes, we acquired fMRI scans while MZ viewed briefly presented faces and scenes in a standard blocked one-back task (Figure 4A). We chose this task because it is simple, it can be performed on the basis of superficial features, and previous studies indicated that it can be successfully accomplished by prosopagnosics (Avidan et al., 2005; Behrmann & Avidan, 2005; Hasson et al., 2003). Like normal observers as well as other CPs (Avidan et al., 2005; Behrmann & Avidan, 2005; Hasson et al., 2003), before training, MZ showed evidence of areas within the ventral occipito-temporal cortex that were selective for faces and scenes. The face-selective regions were bilateral in the right and left middle fusiform gyri (right and left FFA (Kanwisher, McDermott, & Chun, 1997)) as well as in the right posterior fusiform/inferior occipital gyri (right OFA (Gauthier et al., 2000)). The scene-selective regions were bilateral in the parahippocampal/lingual gyri (see Figure 4B). Selective activity in these regions provided the baseline to assess changes during and after training for MZ.

Training Effects on Performance

During the initial 250 training trials, MZ was severely deficient at the face classification task, taking nearly 13 sec to make each judgment (see Figure 5A). During the second training day, she made significant improvement in the response speed (from 13 sec to approximately 3 sec per judgment) without a reduction in accuracy. At the end of the week (4000 trials) she attained similar accuracy as 10 control participants with normal face recognition abilities. Although her reaction times were still significantly slower than the control group (MZ RT mean = 1350 msec, control group RT mean = 980 msec, $SD = 43$ msec, z -score = 8.6), they were 10 times faster than when she started. After a period without training, the second interval of training demonstrated savings in relearning (see

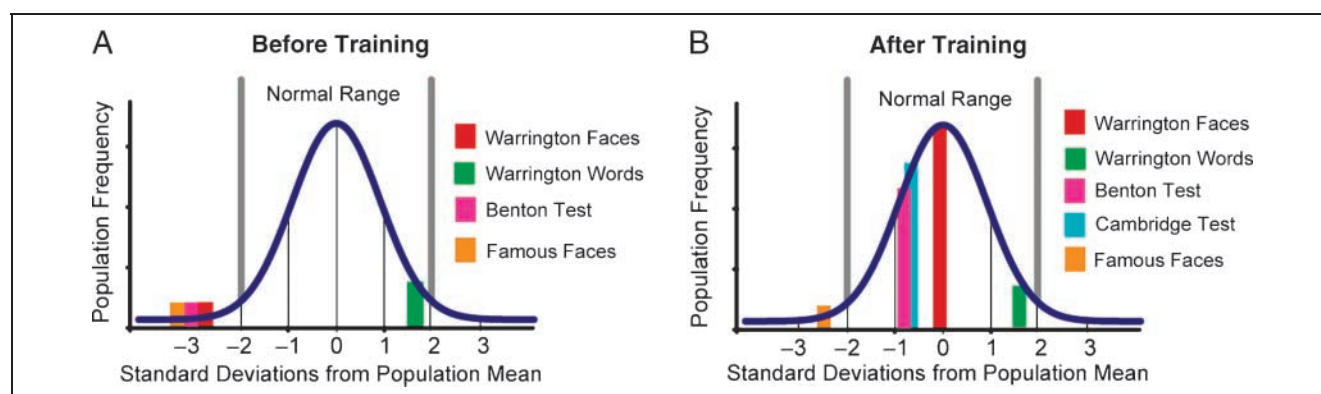


Figure 3. MZ's performance on neuropsychological tests relative to the normal range before (A) and after training (B).

Figure 4. (A) The face/scene one-back task. In the one-back task, participants were shown 16-sec blocks of either faces, scenes, or fixation. To keep the participant's attention focused on the images throughout the task, they were instructed to press both thumbs on the response pad when the current image was the same as the image immediately preceding it (on average, one response was required for each block of images). (B) Face- and scene-selective regions in MZ before training derived from contrasting face and scene blocks in the face/scene one-back task, threshold at $p < .001$, uncorrected.

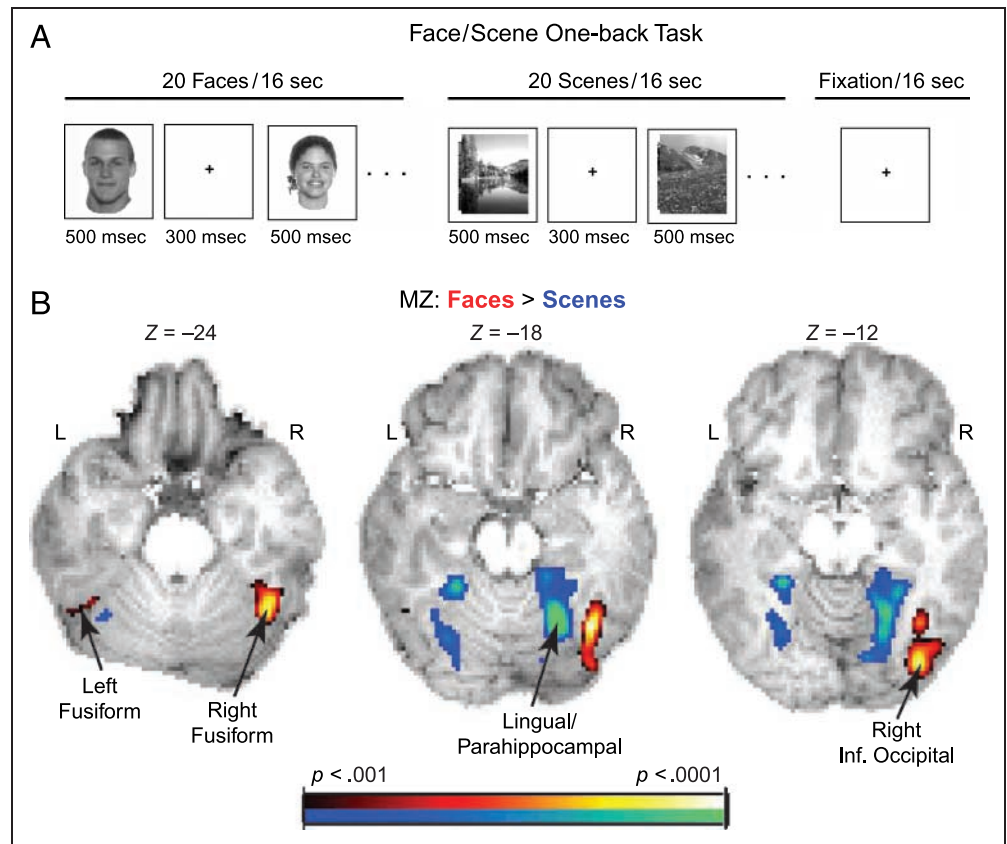
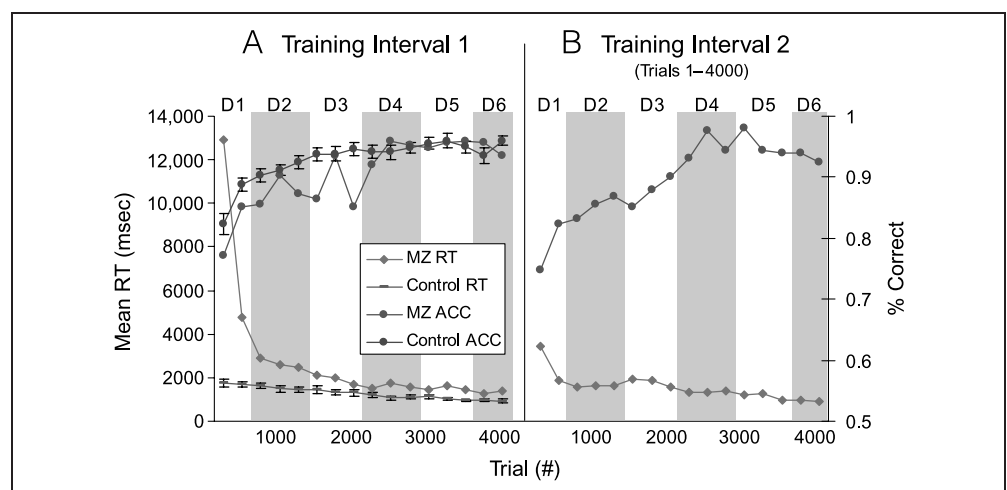


Figure 5B). Already on Day 1 she was considerably faster than when she started the first training interval and, on Day 2, MZ's mean RTs were under 2 sec, a level that was not reached until Day 4 in the initial training session. Furthermore, on Day 6 of the second training interval, MZ's mean RT reached 893 msec, similar to participants with normal face recognition abilities. Although there were no visible savings on accuracy (as she had previously reached normal accuracy after 4 days), she was no less accurate than in the first training interval, suggesting that there was no speed-accuracy tradeoff. Importantly, following

training, MZ reported dramatic improvements in face recognition in her daily life. Unfortunately, this subjective feeling disappeared after approximately a month without training. These periods without training when MZ's face recognition abilities deteriorated will henceforth be referred to as periods of "remission" (Figure 1). Fortunately, during the second training interval, according to her report, her everyday face recognition abilities reemerged.

Neuropsychological tests administered at the end of the second training interval showed marked improvements as well: in both the BFRT (43/54) and the Warrington

Figure 5. (A) MZ's face classification performance during the first training interval compared to 10 control participants. The dark and light columns demarcate the separate training days. (B) MZ's face classification performance during the initial 4000 trials of the second training interval.



tests (49/50 and 44/50, for the Words and Faces subtests, respectively), MZ achieved face recognition performance at normal levels (see Figure 3B). To rule out test repetition effects, we also administered the Cambridge Face Memory Test, which was a novel test (for MZ) of unfamiliar face learning, and presented a new test of famous face recognition (courtesy of Brad Duchaine). MZ performed in the normal range on the Cambridge test (52/72; normal mean performance of 58/72). She was still impaired in recognizing famous faces, which is not surprising because she had never learned to recognize these faces before.

After the second training interval, training effects were allowed to fade for 140 days. To determine whether MZ's face recognition improvements were specific to training with upright faces, she was trained daily for 2 weeks (8000 trials) using the same procedures as during initial training, except that the faces were now inverted. The effects of this training were tested using an upright and inverted face matching task that was administered before and after training. On each trial, a target face presented in front view was matched with one of four test faces presented in 3/4 view. A total of 60 trials were presented with each face orientation. Over the 2 weeks of training on the inverted face classification task, MZ showed strong improvements in the training task itself (Day 1: ACC = 0.68, RT mean = 1490 msec; Day 14: ACC = 0.91, RT mean = 774 msec). The results of the face matching test showed that these improvements corresponded to improvements in inverted face recognition with new faces: before training her accuracy with inverted faces was 53%, after training her accuracy with inverted faces was 78%. In contrast, inverted face training did not generalize to upright faces: before training her accuracy with upright faces was 81%, after training her upright face accuracy slightly decreased to 72%.

Neural Mechanisms Underlying Functional Changes

Electrophysiological Evidence

ERPs were first recorded during the first remission period, prior to the second training interval, and again while she was actively training at home (Figure 1). As reported with other CPs (Kress & Daum, 2003; Bentin, Deouell, & Soroker, 1999), in the first EEG session, MZ's N170 component (that is sensitive to faces in normal perceivers) was not selective. Faces and watches both produced robust N170 components, but there were no amplitude or latency differences (i.e., no N170 face-selective effect) (Figure 6A). In contrast, during active training, a conspicuous selectivity emerged (Figure 6B), which was the same magnitude as observed in a group of 24 normal controls (Figure 6C).

Functional MRI evidence

MZ's brain activity was assessed during several training and no-training periods using fMRI. Specifically, MZ performed the face/scene one-back task during eight different scanning sessions over 14 months: Two scans were acquired before training, four were acquired at different times during active training, and two were acquired during remission (82 days and 140 days post-training; see Figure 1). As expected, her performance in the one-back task was perfect during all test sessions. In each of these sessions, face-selective regions were evident bilaterally in the middle fusiform gyri (left FFA/right FFA) and in the inferior occipital gyrus (right OFA) (see Figures 3 and 7). The location of these regions and their level of face selectivity were similar to those found in normal controls and did not significantly change with training (Figure 8). Furthermore, except for a relatively lower

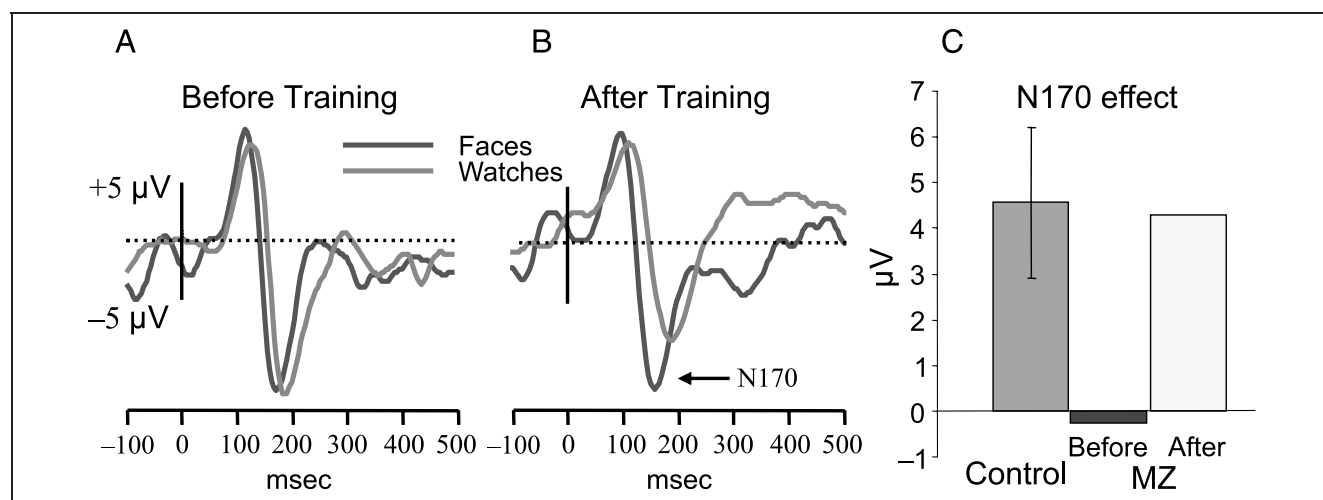


Figure 6. N170 component elicited by faces and watches in MZ before (A) and after (B) training. (C) The difference between faces and watches (the N170 effect) in MZ relative to a control group of 24 participants. The error bars for the control group represent the 95% confidence limits of the mean.

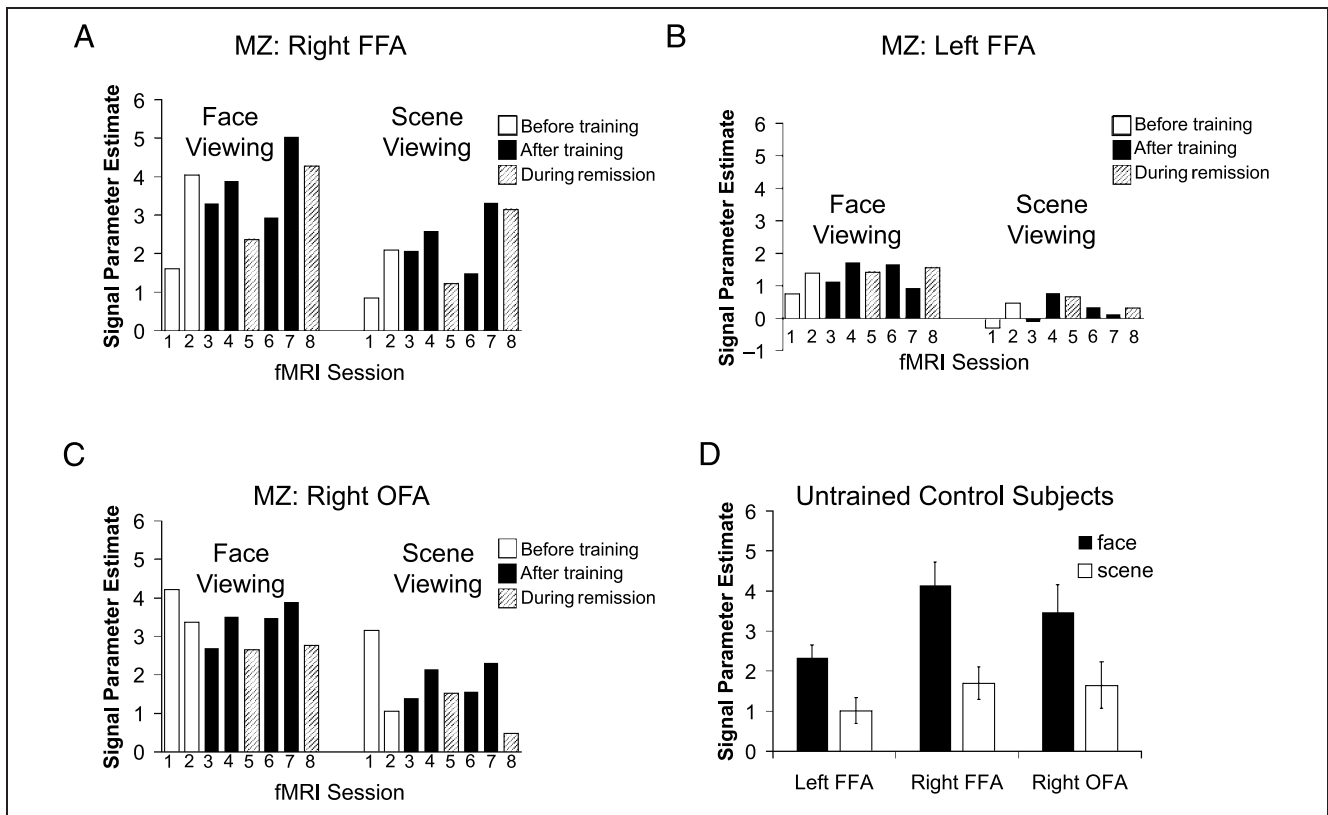


Figure 7. (A, B, C) Activity in MZ's face-selective regions during the face/scene one-back task before training, after training, and when training effects faded, respectively. (D) Activity in face-selective regions during the face/scene one-back task in 13 untrained control participants.

absolute signal in the FFA during the very first scanning session, none of these face-selective regions showed significant differences in absolute activity between trained and untrained states. These findings indicate that activity in face-selective regions did not significantly change with training or with MZ's face recognition improvements. However, we did find significant changes in coherence within the face-selective network. This latter analysis showed that only the coherence between the right OFA and the right FFA was different after training relative to before (Figure 9).

To explore training-related changes in brain activity, we first used a whole-brain mapwise analysis. This analysis unveiled a number of regions that showed significant training-related changes (Table 1). To further explore the relevance of these changes to face processing, we computed the coherence between each of these regions and the face-selective areas before and after training. This analysis revealed that training increased coherence with face-selective regions by and large: 17/22 regions showing greater posttraining coherence with the left FFA, 19/22 showed greater posttraining coherence with the right FFA, and 19/22 showed greater posttraining coherence with the right OFA. Interestingly, the most conspicuous change in coherence was between the posterior fusiform (particularly the right pFus) and the OFA. Further, there was a tendency for both lingual gyri to increase coherence posttraining more than other regions with the left

FFA. Thus, the major changes in coherence between face-selective regions and other areas of the cortex were observed primarily in the right hemisphere.

DISCUSSION

This study is the first to show that an adult with prosopagnosia who never developed the skill to identify faces could attain normal levels of face identification through perceptual training. The face processing improvement reported here was accompanied by changes in brain activity and connectivity within face-selective regions and between these regions and nonselective visual cortical areas. ERPs showed that the nonselective N170 prior to training became normally selective after training. fMRI showed that the level of activity in face-selective regions did not change with training, but the coherence between the OFA and the FFA in the right hemisphere increased with training. In addition to face-selective regions, a whole-brain mapwise analysis unveiled 22 regions that showed significant differences when comparing activity before and after training. Whereas, the relevance of these widespread changes in activity during face processing is not yet fully understood, it is interesting to note that the majority of these regions increased coherence with face-selective regions after training. Within this network, the most conspicuous posttraining increase in coherence was between the posterior fusiform (particularly

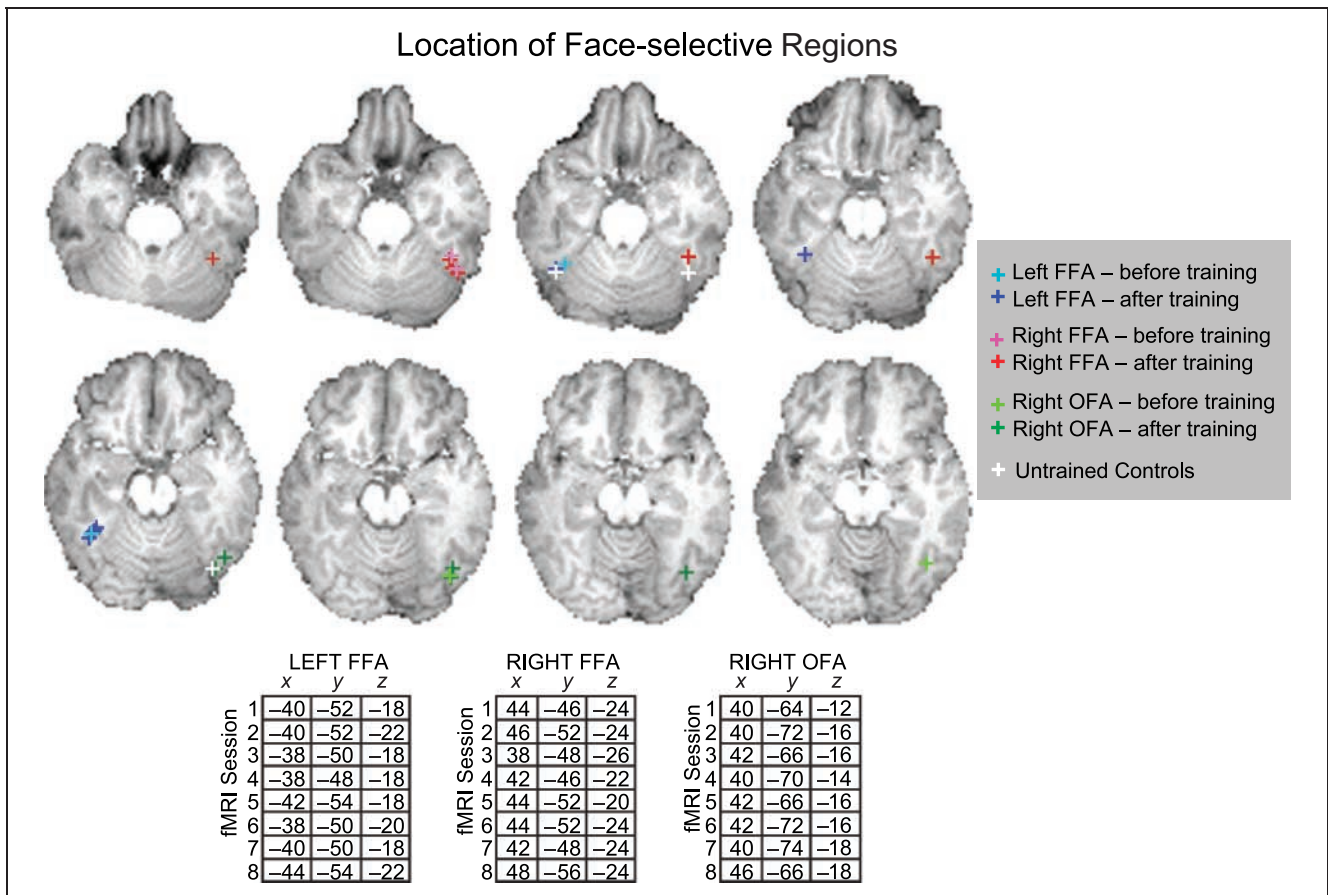


Figure 8. Location of the peaks of MZ's face-selective regions before and after training compared to the average of 13 untrained control participants.

in the right hemisphere) and the OFA. These results might suggest that the improvements in face identification following configural training involved strengthening connectivity between face-selective regions in the right hemisphere and in the right posterior fusiform gyrus (pFus).

Processing spatial relations among features is important for face identification, and many prosopagnosics are

impaired on tasks that require this type of processing (Behrmann, Avidan, et al., 2005; Barton et al., 2004). Therefore, the training task we developed was designed to improve MZ's ability to focus on, and compute the spatial relations between inner face components. Not surprisingly, with training MZ got better on this task. Whereas at the beginning of training, she needed six times more time than a typical control group to reach a similar level of accuracy, after training, MZ was as fast and as accurate as the controls. More importantly, this training generalized to other formal tests of face processing as well as to her subjective feeling about her face identification ability.

Formal tests of face processing showed significantly better performance after training than before, indeed, her performance after training was within normal range. This pertains not only to repeated tests in which improvement could result from repetition per se (such as the WMRT) but also on tests in which MZ received no feedback during the pretraining testing session (like the BFRT) and, more importantly, also generalized to another test that taps similar face memory abilities as the WRMT (Cambridge Face Memory Test). We therefore argue that strengthening the configural processing abilities in MZ enhanced her ability to efficiently process faces.

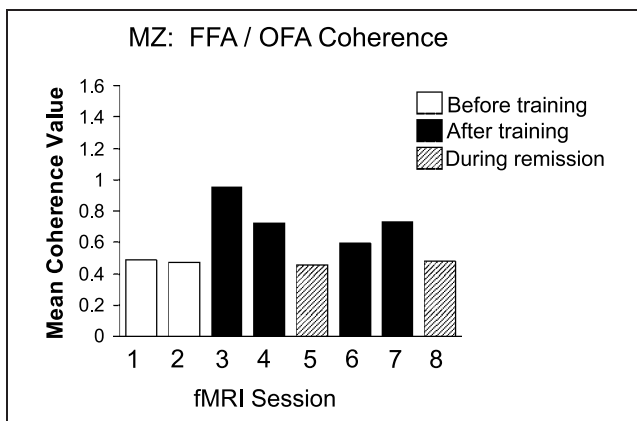


Figure 9. MZ's training-related coherence results between the right OFA and the right FFA during face viewing in the face/scene one-back task.

Table 1. Results of Univariate Mapwise Contrast between Viewing Faces before and after Training

Region	Univariate Results			Coherence Changes		
	MNI Coordinates (x, y, z)	Hemisphere	t Value	Right OFA	Right FFA	Left FFA
<i>Trained > Untrained</i>						
Posterior fusiform gyrus	38, -76, -20	Right	11.79	0.44	0.19	-0.03
Middle fusiform gyrus	20, -56, -16	Right	8.86	0.05	0.02	-0.06
Cuneus	16, -83, 44	Right	8.85	-0.04	-0.05	0.04
Posterior fusiform gyrus	-38, -72, -20	Left	7.95	0.29	0.21	0.12
Superior occipital gyrus	-18, -80, 46	Left	7.30	0.06	0.16	0.06
Superior parietal lobule	46, -50, 60	Right	5.87	0.17	0.16	0.09
Middle fusiform gyrus	-28, -50, -18	Left	5.57	-0.02	0.11	0.25
Precentral gyrus	58, 2, 40	Right	5.39	-0.01	0.03	0.06
Middle frontal gyrus	32, 50, 28	Right	5.39	0.20	0.15	0.24
Precentral gyrus	-40, 0, 42	Left	5.24	0.15	0.11	0.07
Lingual gyrus	-10, -58, -4	Left	5.09	0.17	0.23	0.34
<i>Untrained > Trained</i>						
Putamen	-26, 2, -4	Left	7.73	0.16	0.06	0.20
Medial superior frontal gyrus	-2, 50, 38	Left	6.36	0.14	-0.07	-0.09
Inferior temporal gyrus	56, -50, -20	Right	6.01	0.14	0.18	0.13
Inferior occipital gyrus	40, -80, -10	Right	5.96	0.06	0.26	-0.08
Middle frontal gyrus	-42, 24, 34	Left	5.94	0.19	0.20	0.24
Lingual gyrus	18, -56, 2	Right	5.87	0.11	-0.01	0.07
Superior parietal lobule	28, -60, 52	Right	5.57	0.22	0.06	-0.05
Superior temporal gyrus	60, -40, 14	Right	5.30	0.15	0.23	0.08
Medial superior frontal gyrus	-6, 62, 12	Left	5.26	0.14	0.08	0.07
Middle frontal gyrus	44, 24, 38	Right	5.12	0.19	0.08	0.01
Inferior frontal gyrus	-36, 46, 4	Left	5.00	0.21	0.21	0.06

The columns on the right are the coherence difference (after training minus before) between each region and the right OFA, right FFA, and left FFA.

The improvement in face processing could reflect a general improvement in the ability to compute the configuration of visual features, improvement of face-specific mechanisms, or some combination of the two. The current training task emphasized the integration of subtle spacing differences between facial features. The current training task was likely successful because it allowed MZ to become sensitive to spacing differences around the eye region and nose/mouth region and encouraged her to integrate the spacing of these features into a coherent representation of a face.

In a previous attempt to remediate prosopagnosia, Behrmann, Marotta, Gauthier, Tarr, and McKeeff (2005) taught a patient to discriminate novel objects that required integrating parts of complex shapes (“gree-

bles”; Gauthier & Tarr, 1997). Replicating previous reports (Duchaine, Dingle, Butterworth, & Nakayama, 2004; Gauthier & Tarr, 1997), their patient became highly proficient at this task, but extensive training actually worsened his face recognition (Behrmann, Marotta, et al., 2005). This outcome suggests that training configural skills to remediate prosopagnosia must involve regular faces in order to be effective. Supporting this view, 8000 training trials with inverted faces improved MZ’s ability to classify inverted faces but did not improve her performance with upright faces. A previous study reported a similar failure to train configural processing using inverted faces in subjects with normal face processing abilities (Robbins & McKone, 2003). The specificity of configural training effects with upright faces could be because there is a limit

to the amount of transfer in perceptual learning (Fahle, 2005) or because training with inverted faces does not improve configural processing per se, but rather improves perceptual strategies that could help processing inverted faces but be irrelevant for facial recognition in upright faces (Kanwisher, 2000; Farah, 1996).

Thus, the current results suggest that MZ learned (implicitly or explicitly) to focus attention on the configural aspects that vary most among faces and, consequently, are used for face identification. However, the ERP results suggest that ineffective configural processing before training might have also been associated with an earlier and more general dysfunction. When tested in a period of remission from the initial training effects, MZ's N170 components did not demonstrate the typical distinction between faces and objects. Interestingly, as for all other CPs reported in the literature (Kress & Daum, 2003; Bentin et al., 1999), this absence of selectivity did not manifest a smaller-than-normal N170 for faces but rather a higher-than-normal N170 for objects. After an additional period of training, the selectivity of the N170 became evident. Perhaps not surprising, the increased selectivity of the N170 was not due to enhancement in amplitude in response to faces but due to a decrease in the amplitude of the N170 elicited by watches. It appears that, before training, MZ used the same type of perceptual strategies for both faces and objects. Applying configural processing nonselectively reduces the signal-to-noise ratio between the two categories and disrupts face recognition abilities. As a result of training, MZ's configural processing became focused to faces. It is possible that augmenting the domain specificity of configural encoding back-propagated to more upstream mechanisms, improving the posttraining selectivity of the N170. This interpretation is in line with the view promoted by Bentin and his associates that the N170 manifests a face detection mechanism rather than the structural encoding of faces (Bentin et al., 2007; Zion-Golumbic & Bentin, 2002; Sagiv & Bentin, 2001). In sum, the idea is that early selection of faces is important for downstreaming faces and objects via a face-specific configural encoding system on the one hand and a general encoding system on the other. In the absence of such early selection, face-structural encoding mechanisms become overloaded. This increases the noise in the configural encoding system and reduces the benefit that faces gain from being processed by a system that, by default, extracts the configural information on which efficient within-category face identification relies.

The above interpretation also accommodates the training-induced changes in neural activity as reflected by the fMRI experiments. Previous studies have indicated that the right FFA and the right OFA are integral to face identification. Activity in the right FFA correlates with face detection and identification on a trial-by-trial basis (Grill-Spector, Knouf, & Kanwisher, 2004), and the presence of right FFA activity is likely necessary for

normal face identification (Bentin et al., 2007). Moreover, Rossion et al. (2000) demonstrated that the right FFA was more responsive when attending to face configurations, which are more important for face recognition, compared to when analyzing face parts. Although a more recent study did not find evidence for direct involvement of the FFA in configural processing (Yovel & Kanwisher, 2004), it seems that although not sufficient, the FFA is an essential part of a face identification network. On the other hand, the importance of the right OFA for face processing is demonstrated by the fact that the most common lesion site in acquired prosopagnosia approximates the OFA (Steeves et al., 2006). Moreover, two recent studies of prosopagnosic patients with lesions in the right OFA found that, despite these lesions and the prosopagnosia, these patients had a normally functioning FFA (Steeves et al., 2006; Rossion et al., 2003). This result demonstrates that although the input to the FFA is partly independent of the OFA, the interaction between these two structures is essential for normal face identification. Consistent with these findings, our present results demonstrate that behavioral manipulations that improved face identification also enhanced the connectivity between the FFA and the OFA in the right hemisphere.

What could be the role of the OFA in face processing and how does it interact with the FFA? The right OFA is part of the larger lateral occipital complex system, which is involved in the detection of object's form (Grill-Spector, Kourtzi, & Kanwisher, 2001; Malach et al., 1995). Arguably, the right OFA responds earlier in the visual processing than the right FFA and, indeed, one model of face recognition suggests that the right OFA processes specific facial feature information which is then fed into the right FFA (Haxby, Hoffman, & Gobbini, 2000). Thus, increased functional connectivity between the right OFA and the right FFA with training may be due to an increased coordination between specific facial feature analysis of the right OFA and configural processing of the right FFA. The presence of a right FFA without a right OFA may allow face detection (Steeves et al., 2006; Rossion et al., 2003), but the interaction between the right FFA and the right OFA is probably crucial for applying second-order configural computations. Without the right OFA and its connections, the right FFA might still be able to process the global structure that allows face detection, but more detailed face identification is severely impaired.

In addition to connectivity increases between the right OFA and the right FFA, the mapwise whole-brain analysis revealed several regions of activity that significantly changed with training. Interestingly, the majority of these regions (83%) showed increased functional connectivity with face-specific regions after training. This result supports the idea that improvements in performance can be accomplished by strengthening connections between task-related brain regions (Buchel, Coull, & Friston, 1999). Activity in the right pFus was particularly related to MZ's improvement. This region became

significantly more active during successful face recognition intervals and was less active during prosopagnosic intervals. Additionally, the right pFus region demonstrated increased functional connectivity with the right OFA after training. These effects are consistent with EEG and MEG dipole source localization studies that found a major source of the N170 and M120, respectively, in the posterior fusiform and inferior occipital cortex, in the vicinity of the OFA and the pFus, rather than in the FFA (Shibata et al., 2002; Linkenkaer-Hansen et al., 1998).

Although not central to the goals of this report, it is interesting to note that MZ reported that her face recognition improvements induced by training faded after several weeks without training. The ERP results support her report, showing that after 90 days without training, MZ's N170 lacked face selectivity. However, retraining MZ required fewer trials than initial training, showing some savings in relearning. At present, we do not know what accounts for these fluctuations. The mechanism could fade because she regresses to her default mode of perceiving faces or because the nature of the current task and training parameters are not optimal for enduring improvements. Nevertheless, the training parameters do appear sufficient to sustain improvement. MZ continued to train every day in order to enhance her ability to recognize faces in everyday life.

In sum, in the current study, we have shown that training a prosopagnosic patient to selectively associate configural processes with faces improved her overall ability to process and classify individual faces. fMRI results showed that training increased the connectivity between face-selective occipito-temporal regions in the right hemisphere and possibly incorporated additional regions that are not face-selective into a face processing network. ERP results suggest that behaviorally associating configural processing selectively with faces can help early categorization and, consequently, reduce the overload on configural encoding mechanisms. This pattern and the fluctuation of these effects between periods of training and remission unveils a highly plastic face processing system in the brain, and might set the way for the development of new and more effective rehabilitation programs.

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Note

1. ERPs were initially tested prior to the second training period (Figure 1).

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