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Spontaneous perceptual facial distortions correlate with ventral occipitotemporal activity

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ABSTRACT

Prosopometamorphopsia is a disorder of face perception in which faces appear distorted to the perceiver. The neural basis of prosopometamorphopsia is unclear, but may involve abnormal activity in face-selective areas in the ventral occipito-temporal pathway. Here we present the case of AS, a 44-year-old woman who reports persistent perceptual distortions of faces with no known cause. AS was presented with facial images and rated the magnitude of her distortions while activity in her core face areas and other areas in the ventral visual pathway was measured using functional magnetic resonance imaging. The magnitude of her distortions was positively correlated with signal changes in the right occipital face area (OFA) and right fusiform face area (FFA), as well as right V1–V3, and right lateral occipital cortex (LOC). There was also a trend for a significant correlation with signal in the left OFA and right inferior frontal gyrus (IFG), but not in the right or left superior temporal sulcus (STS). These results suggest that AS' prosopometamorphopsia reflects anomalous activity in face-processing network, particularly in the ventral occipitotemporal cortex.

1. Introduction

Prosopometamorphopsia is an unusual disorder of face perception in which faces appear distorted, with features drooping, floating, bulging, or shrinking, often to the distress of the perceiver (Hecaen & Angelergues, 1962). In Bodamer's (1947) seminal paper on prosopagnosia, he described a patient with prosopometamorphopsia who could recognize faces normally but perceived them as strangely disfigured. The patient reported that "a nurse's nose was turned sideways by several degrees, one eyebrow was higher than the other…". Distortions in prosopometamorphopsia are often restricted to faces and do not extend to non-face objects, and are sometimes limited to one side of the face or visual field (Brust & Behrens, 1977; Ebata, Ogawa, Tanaka, Mizuno, & Yoshida, 1991; Shiga, Makino, Ueda, & Nakajima, 1996; Miwa & Kondo, 2007; Nijboer, Ruis, van der Worp, & De Haan, 2008; Trojano, Conson, Salzano, Manzo, & Grossi, 2009). The wide variety of temporal, occipital, and parietal lesions seen in prosopometamorphopsic patients provides little information about where or how the perceptual distortions are generated.

Face processing involves a specialized and integrated network in human ventral occipitotemporal cortex (Haxby, Hoffman, & Gobbini, 2000). The posterior part of this system consists of three core areas: the occipital face area (OFA) in the inferior occipital gyrus, the fusiform face area (FFA) in the middle lateral fusiform gyrus, and face-selective regions in the posterior superior temporal sulcus (pSTS). Although the precise functions of these areas remain unclear, some have proposed that the OFA is involved in early processing of facial features (Gauthier et al., 2000; Haxby et al., 2000); the FFA in processing invariant aspects of faces such as facial identity (Grill-Spector, Knouf, & Kanwisher, 2004); and the pSTS in the processing of changeable aspects of faces, such as those involved in producing facial expression (Hasselmo, Rolls, & Baylis, 1989; Haxby et al., 2000), though more recent models suggest that there may be some overlap in function (Gobbini & Haxby, 2007; Haxby & Gobbini, 2011; Kanwisher & Barton, 2011). The proposed roles of these areas in face perception have been based primarily on evidence from neuropsychological (Bodamer, 1947; Benton, 1980; Damasio, Damasio, & Van Hoesen, 1982; Sergent & Signoret, 1992), neuroimaging (Kanwisher,

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McDermott, & Chun, 1997; McCarthy, Puce, & Gore, 1997), and transcranial magnetic stimulation (Pitcher, Charles, Devlin, Walsh, & Duchaine, 2009) studies, as well as single-cell recording in non-human primates (Tsao, Moeller, & Freiwald, 2008).

Recently intracranial brain stimulation in epilepsy patients has provided causal evidence for the involvement of core areas in face perception and suggested a possible neural basis of prosometamorphopsia. In one study, electrical brain stimulation to the right inferior occipital gyrus produced transient distortions in faces, such that the patient reported that facial elements appeared scrambled and the face was not perceived as a whole (Jonas et al., 2012). In another example, stimulation of face-selective cells in the FFA interfered with a patient's ability to classify visual stimuli as faces (versus scenes), and the amount of interference was correlated with the face selectivity of the cells (Chong et al., 2013). Finally, stimulation of posterior and mid-fusiform face-selective regions in a patient with medication-resistant epilepsy resulted in the perception of "facial metamorphoses" (Parvizi et al., 2012). When the stimulation was applied the patient reported that the experimenter's face began to distort: "It's almost like the shape of your face, your features drooped." (p. 14918). The effect was absent during sham stimulation, and, based on the patient's reports about objects in the room, was much less pronounced for object perception. These verbal reports are highly reminiscent of descriptions of prosopometamorphopsia, in which similar facial distortions occur spontaneously.

No studies have directly investigated the functional correlates of prosopometamorphopsia. While findings from stimulation studies of OFA (Jonas et al., 2012) and FFA (Parvizi et al., 2012) provide a possible link between these areas and the perception of facial distortions, measurement of neural activity during the spontaneous facial distortions in prosopometamorphopsia are needed to determine where and how these disturbing perceptions are being generated. Here we report the case of AS, a 44-year-old female with normal face recognition who contacted us because of disturbing perceptual distortions for faces that had begun spontaneously several months earlier. These distortions are dynamic and vary both qualitatively (appearance) and quantitatively (magnitude). Importantly, they are persistent and cause AS considerable distress. The variability of AS' distortions provides a unique opportunity to investigate the relationship between face perception and activity in core face areas and to determine whether the results from stimulation studies align with the neural basis of prosopometamorphopsia.

We used functional magnetic resonance imaging (fMRI) to measure activity in AS' core face areas while she viewed faces and rated the magnitude of her perceived distortions. Given that electrical stimulation of areas of the core face-processing network produced facial distortions (Jonas et al., 2012; Parvizi et al., 2012), we hypothesized that activity in one or more of AS' core face areas would be correlated with the magnitude of her distortions: that is, given that stimulation to OFA and FFA lead to perceptual experiences that are similar to those described in prosopometamorphopsia, we predicted greater activation in these areas when AS perceives more extreme facial distortions.

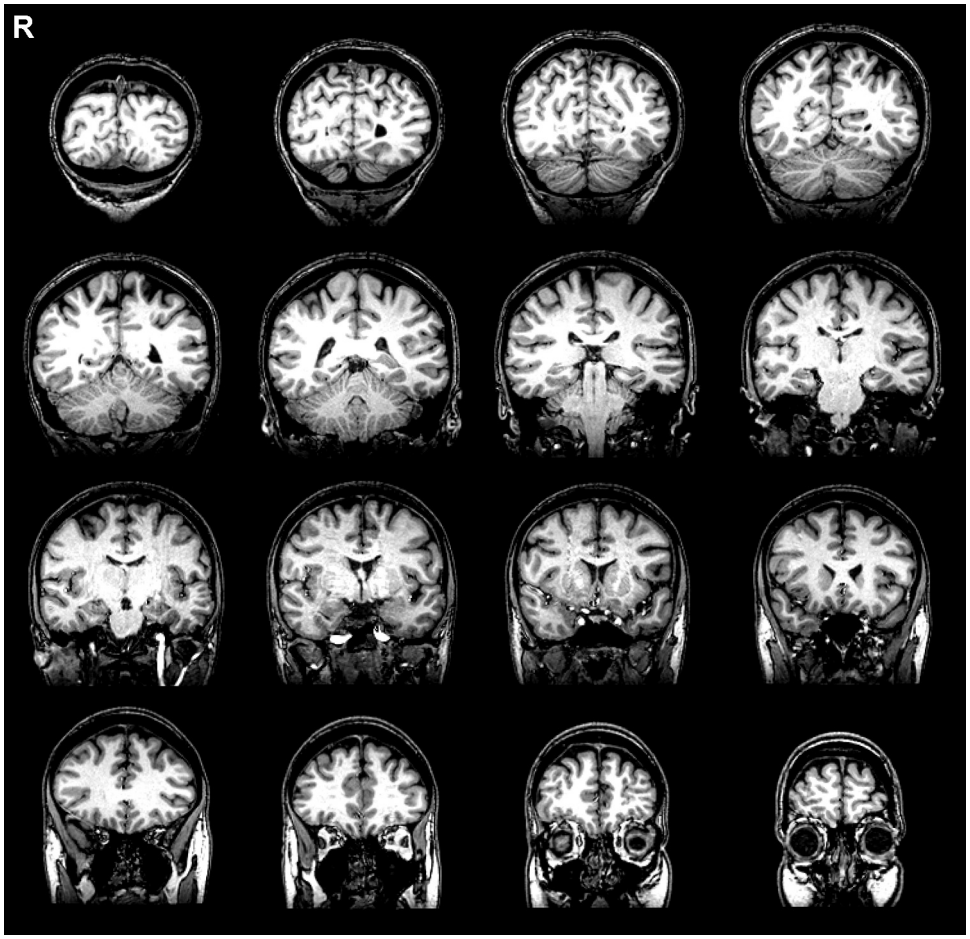


Fig. 1. Structural imaging of AS. Coronal T1-weighted magnetic resonance images from posterior (top left) to anterior (bottom right). No structural abnormalities are apparent.

2. Method

2.1. Participants

2.1.1. Case study: AS

AS is a 44-year-old right-handed woman who contacted us in November 2010 via our prosopagnosia research website, www.faceblind.org. She reported that she had begun to perceive facial distortions six to eight months earlier. AS wrote: "… when looking at faces, I see any minute asymmetry as grossly distorted. And over time (as in during a conversation) the other person's face begins to look almost like a caricature of them. With this perception of distortion comes a fight/flight response. This perception is worsening over time. Strangely this distortion is with people only- does not transfer to animals." These distortions began spontaneously in spring of 2010, though AS had suffered a concussion in late 2007. She also had a history of epilepsy in childhood, which was controlled with carbamazepine until it resolved by the age of 18. She reported occasional spontaneous perception of visual noise that had been diagnosed as migraine equivalent. This 'pixilation' of vision, much like television static, began in the past few years and appears mainly in her central vision. It occurs every few days to once a week, and each occurrence lasts anywhere from a few minutes to hours. She has no history of psychiatric illness, and reported only one experience with hallucinogenic drugs (lysergic acid diethylamide, LSD) in her youth.

AS participated in initial neuropsychological testing in the Social Perception Laboratory at Dartmouth College in November 2011. In March 2012 she visited the Human Vision and Eye Movement Laboratory at the Vancouver General Hospital for additional neuropsychological testing, as well as a structural and functional magnetic resonance imaging (MRI) session, and event-related potential recordings (ERP). Her structural MRI scans showed no evidence of brain damage (Fig. 1). ERP recordings analyzed with a previously described single-subject bootstrap technique (Dalrymple et al., 2011; Oruc et al., 2011) showed that AS has a normal N170 response to faces (Fig. 2), with larger amplitude to faces than to objects ($p=0.003$), (Jeffreys, 1989; Botzel, Schulze, & Stodieck, 1995; Bentin, Allison, Puce, Perez, & McCarthy, 1996), and larger amplitude ($p<0.001$) and greater latency to inverted compared to upright faces (Bentin et al., 1996; Eimer, 2000; Rossion et al., 2000). A 21-channel EEG performed during wakefulness, drowsiness and sleep, with photic stimulation and hyperventilation, showed no epileptiform discharges, focal cortical dysfunction, or diffuse encephalopathy. AS performed normally on most neuropsychological tests (Table 1). Her scores on the Wechsler Abbreviated Scale of Intelligence (WASI) indicated that she has above average intelligence. Her results on the National Adult Reading Test (NART, Nelson & Willison, 1991), Raven's Advanced Progressive Matrices (Raven, 1992), and forward and backward digit span tests from the Wechsler Adult Intelligence Scale (Wechsler, 1997) indicated normal cognitive functioning. AS scored normally on tests of face identity perception (Duchaine, Yovel, & Nakayama, 2007) and face memory (Duchaine & Nakayama, 2006). Her object recognition performance was also normal. In contrast, her performance on a test of facial expression recognition was impaired (Garrido et al., 2009).

It is difficult to measure perceptual distortions. Previous reports of prosopometamorphopsia have included patient drawings of faces that depict the distortions (Ebata et al., 1991; Shiga et al., 1996; Miwa & Kondo, 2007; Nijboer et al., 2008; Trojano et al., 2009). Instead of drawing her distortions, AS provided photos she found on the Internet that resemble her distortions (Fig. 3). AS explained that faces appear normal when she first sees them and then become progressively more distorted. We also asked AS to describe unfamiliar faces that were presented to her in the lab. Her verbal descriptions were transcribed (a subset of these images and her descriptions is shown in Table 2). There is a strong similarity between her descriptions and those of the patient experiencing electrical stimulation to the fusiform face area (Parvizi et al., 2012).

AS reported that familiar faces distort more than unfamiliar faces. Most faces distort to some degree, but some do not distort at all. Distortions generally occur for frontal views of the face, when both eyes and the majority of the face are visible. The most common feature to distort is the person's left eye (in AS' right visual field). Most faces appear normal at first, and distortions build over 5–10 s. For some faces, looking away for an equal period of time returns the facial percept to normal and the distortion builds again from this baseline. For more familiar faces, the distortions remain even after looking away. AS does not experience distortions for faces shown in profile (Table 2). She tries to control the distortions by consciously ignoring them or focusing on non-facial features (e.g. glasses) but these techniques are generally ineffective.

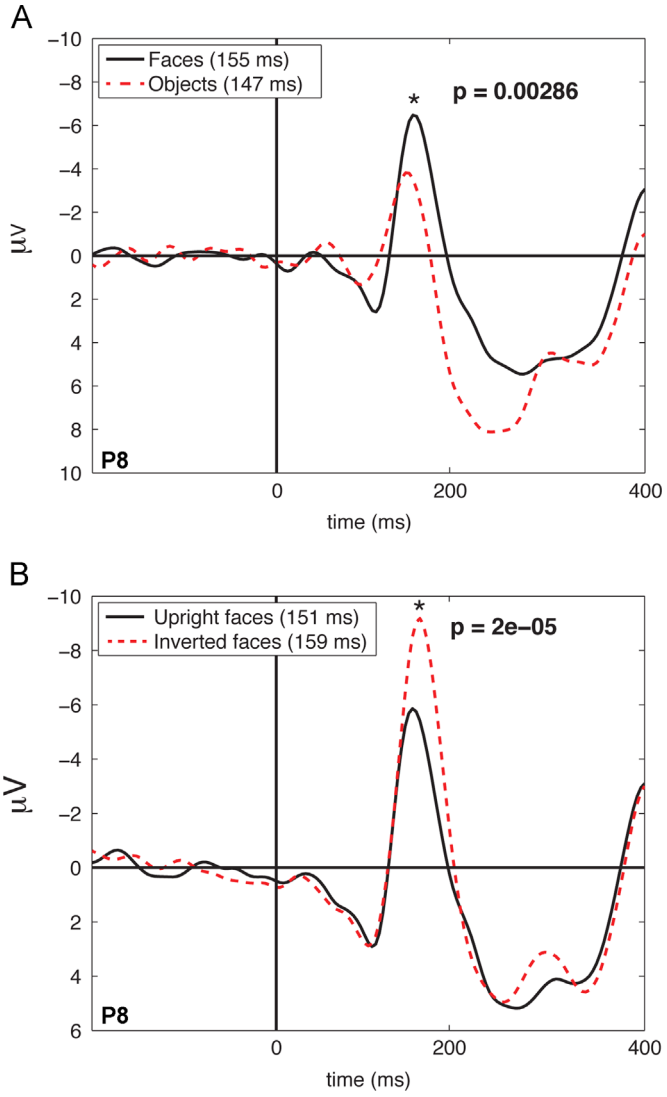


Fig. 2. ERP waveforms at P8 for (A) novel faces vs. objects, and (B) inverted vs. upright faces. The time of the peak amplitude of the N170 is indicated for each category (in ms). Significance is based on Bootstrap confidence intervals for average amplitude across a 40-ms window centered on the peak N170 value for each viewing condition. Asterisks show significant differences, with p values indicated. Plotting convention is for negative values upwards and positive values downwards.

2.1. Procedure

The protocol was approved by the Clinical Research Ethics Board at the University of British Columbia (UBC) and Vancouver General Hospital, and the Committee for the Protection of Human Subjects at Dartmouth College. Written informed consent was obtained in accordance with The Code of Ethics of the World Medical Association, Declaration of Helsinki (Rickhan, 1964).

2.1.1. Imaging parameters

Experiments were carried out using a Philips 3.0 T scanner at the UBC MRI Research Centre. T2*-weighted scans using echo planar imaging were used to collect data from 36 interleaved axial slices (TR 2 s, TE 30 ms, FOV = 240 × 216 mm, 3 mm thickness with 1 mm gap, voxel size 3 × 3 mm, 128 mm reconstruction matrix, reconstructed voxel size 1.88 × 1.6 mm). These were co-registered onto the subjects' T1-weighted anatomical image (EPI) sequence, 170 axial slices, FOV = 256 × 200 mm, voxel size = 1 × 1 mm, slice thickness 1 mm.

2.1.2. Localizer scan

The Human Vision and Eye Movement dynamic localizer scan (Fox, Iaria, & Barton, 2009, Fig. 4A) was run to identify face-selective regions of the visual cortex. The localizer consisted of grayscale video clips of faces and objects. Each stimulus block included six video clips lasting 1.5 s separated by a 500 ms blank screen. Stimulus blocks were separated by a 12 s fixation cross, with an initial 12 s fixation block preceding the first block. Each condition was repeated eight times per run, resulting in two runs that were 6 min, 36 s each (198 volumes). To increase SNR, the localiser was run twice, and the data averaged across the two scans. Attention was monitored by asking participants to press a button on an MRI-compatible button-box when the same video clip was presented twice in a row.

2.1.3. Correlation experiment

Sixteen famous faces were selected based on AS's report that distortion occurred for these faces. Each face was cropped tightly around the face and hair

Table 1
Neuropsychological assessment. The table reports AS' raw scores on each test.

Modality	Test	AS	Max
Basic cognitive			
Intelligence	**WASI verbal IQ**	119	–
	WASI performance IQ	125	–
Memory	**Digit span—forward**	13	**16**
	Digit span—backward	9	**14**
Vocabulary	**National Adult Reading Test—USA**	54	**61**
	Warrington recognition memory test—words	49	**50**
Objects	**Raven matrices**	12	**12**
High-level vision			
Faces—perception	**Cambridge Face Perception Test (CFPT)**	26 total 3.25 per trial	**Errors**
Faces—memory	**Cambridge Face Memory Test (CFMT)**	53	**72**
	Old-New Faces	46	**50**
Faces—expression	**Films**	39[a]	**58**
Objects—memory	**Cambridge Car Memory Test (CCMT)**	54	**72**
	Old-New horses	49	**50**
	Old-New cars	50	**50**
Other			
	Expression from voices	40	**50**

[a] Denotes impaired performance. (WASI=Wechsler Abbreviated Scale of Intelligence; CFMT=Cambridge Face Memory Test; CFPT=Cambridge Face Perception Test).

Fig. 3. Illustrations of distortions. AS provided these images after searching the Internet for images that accurately depict her experiences.

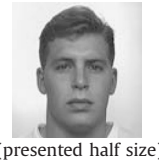
and presented twice in a pseudo-randomized order, resulting in a total of 32 trials. A trial consisted of a single face presented for 10 s, followed by a 10-s fixation cross (Fig. 4B): thus the experiment lasted 10 min, 40 s (320 volumes). Stimuli were back-projected onto a screen located inside the scanner bore, approximately 68 cm from subjects' eyes, using Presentation 14.0 (www.neurobs.com). The stimuli spanned approximately 11° of visual angle. The task was for AS to indicate, via button press, the degree to which the faces appeared distorted. Responses were collected via a 5-button response positioned in the right-hand, using a 5-point scale ranging from 1 'no distortion' (thumb) to 5 'extremely distorted' (little finger). AS could respond multiple times in a trial, as the level of distortion changed.

2.1.4. fMRI analysis

Statistical analysis of the fMRI data was carried out using FEAT (http://www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). The initial 8 s of data from each scan were removed to minimize the effects of magnetic saturation. Motion correction was followed by spatial smoothing (Gaussian, FWHM 6 mm) and temporal high-pass filtering (cut off, 0.01 Hz). After combining the two localizer runs, face-selective regions of interests (ROIs) were determined using the contrast "Faces > Objects", while object-selective regions of interest were identified using the inverse contrast "Objects > Faces" ($p < 0.001$ uncorrected). Visual cortex was identified as voxels responding to either faces or objects ($p < 0.001$, uncorrected) (V1–V3) that fell within the region of the calcarine cortex (intensity threshold: 20/100) probabilistic mask (Harvard-Oxford Cortical Structural Atlas; www.fmrib.ox.ac.uk/fsl). Finally, we identified all visually responsive regions outside the face- and object-selective regions (faces+objects > fixation) and all non-visually responsive regions (all regions not responding significantly to faces+objects > fixation), as well as the anatomically defined left and right amygdala (intensity threshold: 75/100) probabilistic mask (Harvard-Oxford Cortical Structural Atlas; www.fmrib.ox.ac.uk/fsl).

The time series of the BOLD response in all the voxels for a given ROI were averaged to produce a single time series in each ROI. For each ROI the time series of the BOLD response was then converted from image intensity units to percentage signal change by subtracting and then normalizing the mean response during the experiment scan $[(x-\text{mean})/\text{mean} \times 100]$ (Galvan et al., 2006; Davies-Thompson, Gouws, & Andrews, 2009; Andrews, Davies-Thompson, Kingstone, & Young, 2010).

Table 2
A subset of faces that AS viewed and her descriptions of those faces. Faces were taken from the Harvard Face Database. Prompts from the experimenter appear in italics.

	First off- the first thing I see is the moles on his face. And… the… Asian shape, so he's got no, there's no real indentation of the brow ridge, which makes his nose strangely stick out more and it makes his brow stick out more, which makes no sense because- yeah… and his- his eyes look crooked for some reason. And his eyes look really… askew, kind of like that parallelogram phenomenon that I was describing the other day. *Which one's higher?* His left. *Ok.* My right.
	Upside down! Uh … very… prominent large forehead, especially with the lighting hitting the widow's peak he's got in his hair… His nose is curving, the- the… the nostril end of his nose is slowly tipping over… to… my right, his left, it's like, deflating, almost, it looks like… Yeah, and also his mouth is tipping the other way so they're going opposite directions. *What about his eyes?* Other than the weird from being upside down they're not too bad. They're not really doing much.
	Wow—large nose, prominent eyebrows. The eyebrows are coming towards me. And… strangely, his right eye is getting larger. Like, opening more… yeah, both brows are coming towards me and his- his right eye is getting larger, it's the most prominent thing and the nose is just really prominent, it's almost three dimensionally coming off the screen.
 (presented half size)	It's whole lower face and chin are… almost ballooning. And his left eye is dropping down… still dropping down. It's really weird it's like I can tell it's not moving because I can look at it and see that but still it, it's moving down his face. It's just… hmmm… *Do you get anything with ears?* Ears don't really bother me. Ears aren't a thing. I guess, they're not part of a face.
	Is that the same guy I saw before, but turned to the side? Yeah, sideways doesn't really bother me. Doesn't… Dark haired guy, high cheekbones, mid-set ears. I just, you know, not doing anything. Again, racially flatter features… um….
	Yeah, his… his- his left eye is doing something weird. It's hard to- I - it's one of those I can't describe what it's doing… it's just… I mean his other eye is playing along so it's like one eye is going (descriptive sound). You know, it's defying physics. And his upper lip is doing something weird, too, it's like going out and down, kind of distending.

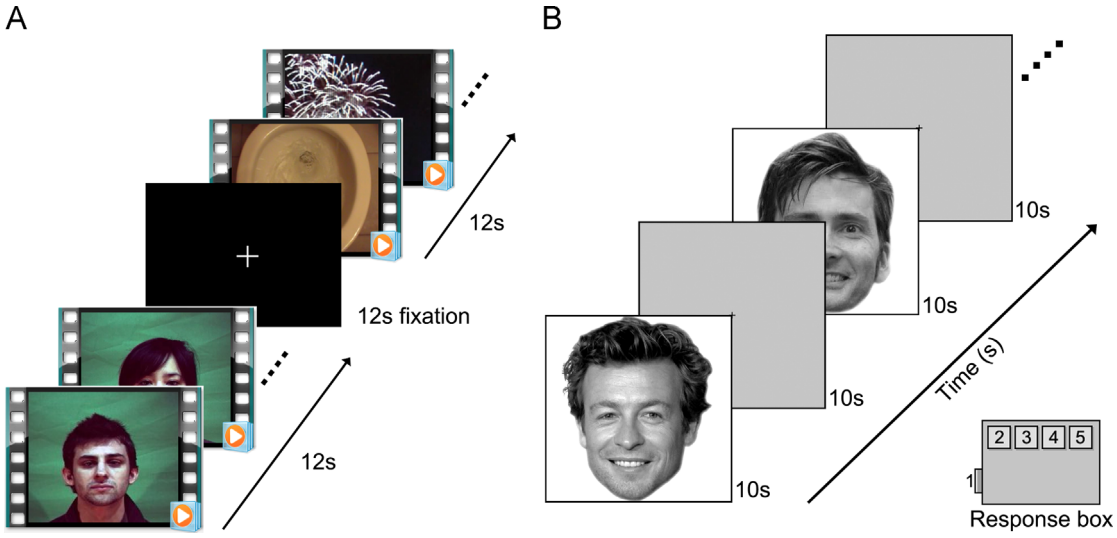


Fig. 4. Example stimuli used in the two functional MRI scans. (A) Localizer scan. Short videos of faces or objects were presented in a blocked design separated by a 12 s fixation cross. (B) Correlation experiment. Familiar faces were presented continuously for 10 s separated by a 10 s grey screen. A button response pad recorded AS' ratings on how distorted the face image appeared. Each face appeared twice, in pseudo-random order.

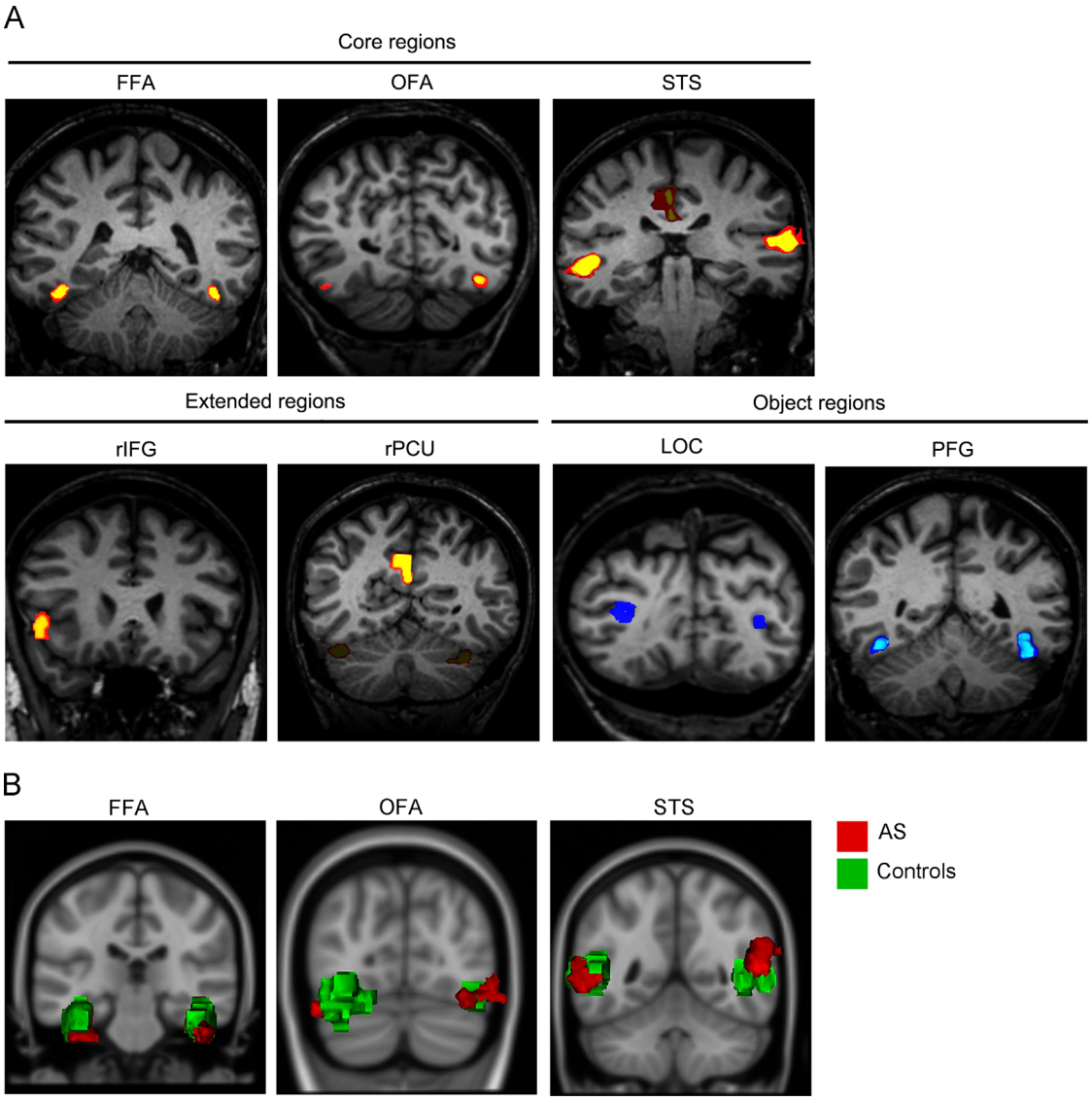


Fig. 5. (A) Regions responding to faces or objects in the localizer scan. Face-selective responses were found in all 'core" regions (r=right, l=left; FFA: fusiform face area; OFA: occipital face area; STS: superior temporal sulcus). The right inferior frontal gyrus (rIFG), and right precuneus (rPCU) also responded more to faces than to objects. Two bilateral regions responded more to objects than to faces—the lateral occipital cortex (LOC) and posterior fusiform gyrus (PFG). (B) Face responsive regions in AS and controls. Each control subjects' core face-responsive regions from the localizer scan (faces > objects). Regions above $p < 0.001$ (uncorrected) were transformed into standard MNI space and overlaid on top of one another (green). The same transformation was repeated for AS (red). This shows that the location of AS's core face regions are consistent with those identified in control subjects. Figure was created using 'DataViewer3D" (Gouws, Woods, Millman, & Green, 2009). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.1.5. Statistical analysis

To determine whether the neural responses in the face-selective ROIs were related to the perceptual experience of the subject, we extracted the time course data from the 3TRs (0, 2, 4 s) following any given button press. This approach has been used previously to show correlation between perception and neural activity (Andrews, Schluppeck, Homfray, Matthews, & Blakemore, 2002). Data from the 3TRs were then averaged to produce a single number, which was categorically assigned to the button response. This was done for each ROI individually, thereby allowing the relationship between the button responses and the BOLD response in each ROI to be examined. Finally, to determine the significance of this relationship, data from each region was entered into the non-parametric Kruskal–Wallis test to test for differences in the %MR signal as a function of distortion ratings (α=0.05 for planned comparisons). Any significant differences were then further examined using Mann–Whitney *U*.

3. Results

3.1. Localizer scan

Fig. 5 and Table 3 show the regions of interest in AS, including regions responding more to faces than to objects, regions responding more to objects than to faces, and the visual cortex. Bilateral regions on the lateral surface of the inferior occipital gyrus (occipital face area; OFA) responded more to faces than to objects, along with bilateral regions on the lateral temporal portion of the fusiform gyrus (fusiform face area; FFA), and bilateral posterior segment of the superior temporal sulcus (pSTS). Fig. 5B shows that the locations of AS' core face-selective regions are consistent with those identified in control subjects. In addition to these 'core' face-selective regions, face-selective responses were also observed in the inferior frontal gyrus (IFG) and the precuneus (PCU). Bilateral object-responsive regions were observed in the lateral occipital cortex (LOC) and posterior fusiform gyrus (PFG). The coordinates and size of these regions (Table 3) are consistent with those described in previous studies of face and object-selectivity (Malach et al., 1995; Grill-Spector, Kourtzi, & Kanwisher, 2001; Fox et al., 2009; Chan & Downing, 2011; Davies-Thompson & Andrews, 2012; Rossion, Hanseeuw, & Dricot, 2012).

Table 3
Peak MNI coordinates of the regions of interest for AS. *Z*-scores signify the degree of face-selectivity (as compared to objects), within the peak voxel.

Region		Coordinates			*Z*-score	Size (cm³)
		X	*Y*	*Z*		
Face-selective regions						
OFA	**L**	−46	−78	−22	5.2	0.9
	R	36	−82	−16	7.5	2.8
FFA	**L**	−38	−60	−25	7.8	2.1
	R	42	−60	−25	7.2	3.5
STS	**L**	−60	−66	0	9.9	3.1
	R	54	−58	22	5.5	4.1
IFG	**R**	48	20	−6	6.2	4.3
PCU	**R**	4	−58	32	6.8	6.2
Object-selective regions						
LOC	**L**	−30	−86	10	6.0	2.6
	R	32	−86	6	5.5	0.9
PFG	**L**	−42	−52	−14	8.5	10.3
	R	44	−50	−18	8.0	4.7
Other						
V1–V3	**L**	−10	−96	−4	19.1	11.0
	R	14	−90	−4	18.3	6.3

3.2. Correlation experiment

AS made a total of 41 distortion ratings across the 32 trials (she provided two ratings on 9 trials). These ratings ranged from 2 to 4 (no ratings of 1 or 5 were made), with a mean rating of 2.61 out of 5 (minimum distortion=1; maximum distortion=5). There was a significant correlation between AS' ratings for the first and second presentation of the images $r=0.74$, $p=0.004$. Supplementary Fig. 1 shows the distribution of these ratings per time point during the correlation scan. Due to the low number of '4' responses (and no '1' or '5' responses), a whole-brain analysis comparing low versus high distortions ratings was not conducted, and analysis was restricted to regions of interest only.

Fig. 6 shows the response time courses from the core face-selective regions (bilateral OFA, FFA, and STS), with the distortion ratings overlaid. As we were interested in how the %MR signal may change as a function of subjective distortion rather than the images *per se*, trials in which more than one rating was made were treated independently (the %MR signal was extracted for each response, regardless of whether they occurred within the same trial). Average %MR signal across the distortion ratings (bar graphs) showed an increase in the neural response of some but not all components of the core face network as the ratings increased. The Kruskal–Wallis test showed that this increase was significant in the right OFA ($\chi^2=8.7$, $p=0.01$), but not the left OFA ($\chi^2=5.5$, $p=0.06$). Mann–Whitney *U* test revealed that the significant effect in the right OFA was driven by a larger response during 3 ratings as compared to 2 ratings ($2<3$; $U=72$, $p=0.01$, $r=0.46$), but no difference between $3<4$ ($U=30$, $p=0.51$, $r=0.15$). The same pattern was observed in the FFA, with a significant effect in the right ($\chi^2=6.2$, $p=0.04$), but not the left ($\chi^2=4.7$, $p=0.10$) hemisphere. The significant effect in the right FFA was driven by a significant difference between the neural response during ratings for $2<4$ ($U=23$, $p=0.04$, $r=0.38$), but no difference between $2<3$ ($U=109$, $p=0.12$, $r=0.32$) or $3<4$ ($U=24$, $p=0.24$, $r=0.26$). There was no obvious pattern in the neural responses across distortion ratings for either the left STS ($\chi^2=0.3$, $p=0.86$) or right STS ($\chi^2=0.8$, $p=0.66$). Table 4 shows a summary of these results.

For regions of the extended face network (Supplementary Fig. 2), although there was a positive trend between the neural response in the right IFG and perceptual ratings, it was not significant ($\chi^2=5.9$, $p=0.051$). There was no obvious pattern in the right PCU as a function of distortion rating ($\chi^2=0.0$, $p=0.99$).

To determine whether the perceptual experience of the distortions was correlated with the neural response of other visually responsive regions, we examined the difference in the neural response in object-selective regions (Supplementary Fig. 3) and early visual cortex (Supplementary Fig. 4). Although there was a significant difference in the neural response in the right LOC as a function of distortion ratings ($\chi^2=6.0$, $p=0.050$), this was not found in the left LOC ($\chi^2=3.8$, $p=0.15$). For the right LOC, this was driven by a difference between $2<3$ ($U=81$, $p=0.01$, $r=0.41$), but not between $3<4$ ($U=34$, $p=0.76$, $r=0.07$). There was also no obvious pattern in the neural responses across distortion ratings for either the left PFG ($\chi^2=3.7$, $p=0.16$) or right PFG ($\chi^2=3.8$, $p=0.15$). Finally, early visual regions of occipital cortex (V1–V3) showed a significant increase in the neural response as a function of distortion ratings in the right hemisphere ($\chi^2=6.8$, $p=0.03$), but not in the left hemisphere ($\chi^2=4.3$, $p=0.12$). The significant effect in the right hemisphere was caused by a greater neural response during 3 ratings as compared to 2 ratings ($2<3$; $U=76$, $p=0.01$, $r=0.44$), but no difference between $3<4$ ($U=29$, $p=0.46$, $r=0.17$).

One possible explanation of these results is that they are being driven by general arousal. To address this, we examined the response in all visually responsive regions outside face- and object-selective regions, all non-visually responsive regions, and the anatomically-defined amygdala. Fig. 7 shows the response in all visually and non-visually responsive regions as a function of AS' distortion ratings. Although visually responsive regions outside the face- and object-selective regions showed a pattern of increased MR signal as a function of ratings, this was not significant ($\chi^2=5.1$, $p=0.08$). This mask included voxels within the visual cortex, which could account for this pattern. No significant correlations were observed in non-visually responsive regions ($\chi^2=2.0$, $p=0.38$), nor the amygdala (left: $\chi^2=4.9$, $p=0.09$; right: $\chi^2=4.8$, $p=0.09$) (Supplementary Fig. 5).

4. Control

Our analysis of AS compares the signal when she is viewing different faces that produce different degrees of distortion. One possible confound is that the variation in signal is related to stimulus differences between these faces, and not actually related to the experience of distortion. Therefore, to determine whether the findings observed in AS were a function of the stimuli or task, rather than her distortions, we performed the same procedure with age-matched controls ($n=3$ females, mean age 44.7 years). The response in the core face areas (FFA, OFA, STS), extended face areas (rIFG, rPCu), object areas (pFG, LOC), primary visual cortex (V1–V3), amygdala, and visually responsive and non-visually responsive regions, for each subject were correlated with the button presses made by AS. Unlike the significant differences between the %MR signal and the button responses made by AS, the %MR response for the control subjects did not significantly differ as a function of AS' distortion ratings (Table 4), suggesting that the findings observed in AS were not a function of the stimuli or task.

5. Discussion

This study is the first to demonstrate a relationship between the bizarre and often disturbing facial distortions perceived in prosopometamorphopsia and neural activity in face-selective areas in the core and distributed face-processing network. We measured neural activity in an individual with prosopometamorphopsia while she

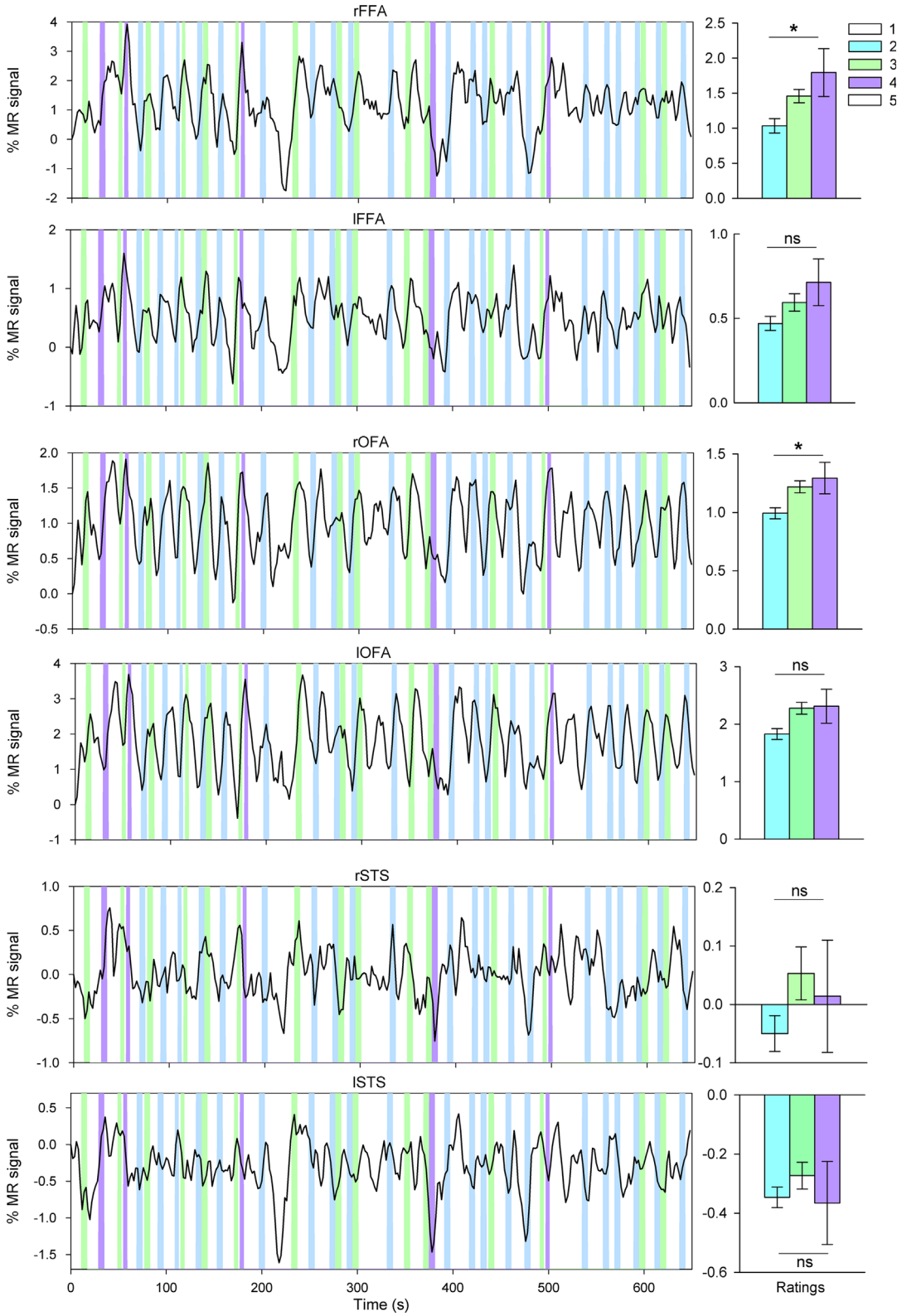


Fig. 6. Response time courses from the core face-selective regions with the distortion ratings overlaid (1 = minimal distortion, 5 = major distortion). Bar graphs show the average %MR signal for each distortion rating. No '1' or '5' ratings were made. Kruskal–Wallis tests for rank order effects show significant differences in the neural responses as a function of distortion ratings in the right OFA and right FFA. (FFA: fusiform face area; OFA: occipital face area; STS: superior temporal sulcus; ns: not significant; $^{*}p < 0.05$).

looked at faces and rated the magnitude of her perceived distortions. All visually responsive regions in inferior occipito-temporal cortex showed a pattern of increased %MR response as a function of AS' perceived distortion, but this was only significant in right OFA, right FFA, right V1–V3, and right LOC. There was a trend for a significant correlation in left OFA and right IFG, but not in the right or left STS. The correlations were also non-significant for other control regions of the extended face-processing network (i.e. right PCU),

and the left and right amygdala. Finally, an analysis on all visually responsive regions outside face- and object-selective regions, and on all non-visually responsive regions, showed no significant correlations with AS' distortions suggesting that, consistent with the findings from the amygdala, the significant effects observed elsewhere are not due to a general increase in arousal.

The results from the core face-processing regions are consistent with recent reports of intracranial electrical stimulation in patients with medication-resistant epilepsy. Stimulation of the posterior and mid-fusiform gyrus of one epilepsy patient caused perception of facial distortions (Parvizi et al., 2012). The patient's descriptions of his distortions are similar to those of AS. For example, when looking at the experimenter, he reported, "…It's almost like the shape of your face, your features drooped…" (p.14918). When looking at a picture of a male face, AS reported, "… his left eye is dropping down…" In another study, stimulation of the right inferior occipital gyrus produced transient distortions, such that the patient reported not seeing the face as a whole and that facial elements appeared mixed up or in disarray (Jonas et al., 2012).

These results suggest that abnormal activity in OFA and FFA, but not STS, may be related to the facial distortions AS experiences. How do these results fit with previous findings about the involvement of the core face areas in face processing? Significant correlations between the magnitude of AS' perceived facial distortions and right (but not left) OFA, FFA, and early visual cortex, and the trend in right IFG, are consistent with findings that face processing is a predominantly right hemisphere function (Sergent, Ohta, & MacDonald, 1992; Kanwisher et al., 1997; Fox et al., 2009). Others have speculated that prosopometamorphopsia results from increased activity in a subset of face-responsive neurons, which may lead to certain features being affected more than others (e.g. the eyes) and insensitivity to spatial relations between facial features (ffytche & Howard, 1999). The idea that some features may be affected more than others is consistent with the reports of abnormal facial features by many patients. For example, AS said of one face, "her right eye is bigger than her left, so it's… coming kind of up and towards me. Like, it almost seems like it's pushing her nose over to her left…" Given the putative role of the OFA and the FFA in facial feature processing (Haxby et al., 2000; Gobbini & Haxby, 2007), such distortions may be specifically related to anomalous activity in these areas.

Both the OFA and the FFA have been implicated in the processing of invariant aspects of faces for identity perception (Haxby et al., 2000; Gobbini & Haxby, 2007). Identity recognition is normal in some cases of prosopometamorphopsia (Bodamer, 1947; Nijboer et al., 2008), but impaired in others (Whiteley & Warrington, 1977; Heutink, Brouwer, Kums, Young, & Bouma, 2012). Interestingly, although her face recognition is normal, AS reports that her distortions are more severe for familiar than for unfamiliar faces. Other reports have discussed the role of familiarity in prosopometamorphopsia, for example, the case of a

Table 4
Correlations between AS' distortion ratings and the neural responses in each ROI, as determined by the Kruskal–Wallis test.

Region		AS		Control 1		Control 2		Control 3	
		X^2	p	X^2	p	X^2	p	X^2	p
Face-selective regions									
OFA	**L**	5.5	0.06	1.8	0.40	1.6	0.45	1.0	0.62
	R	**8.7**	**0.01***	3.2	0.20	–	–	0.3	0.88
FFA	**L**	4.7	0.10	2.8	0.25	–	–	1.2	0.54
	R	**6.2**	**0.04***	4.9	0.09	4.9	0.09	2.7	0.26
STS	**L**	0.3	0.86	0.7	0.72	0.1	0.93	1.1	0.57
	R	0.8	0.66	0.7	0.70	4.2	0.12	0.3	0.88
IFG	**R**	5.9	0.05	1.3	0.52	1.5	0.47	1.6	0.45
PCU	**R**	0.0	0.99	–	–	4.2	0.13	0.2	0.90
Object-selective regions									
LOC	**L**	3.8	0.15	0.1	0.94	0.1	0.94	0.1	0.94
	R	**6.0**	**0.05***	0.7	0.71	1.2	0.56	0.5	0.80
PFG	**L**	3.7	0.16	0.7	0.72	0.6	0.73	0.1	0.95
	R	3.8	0.15	1.2	0.55	0.8	0.66	0.1	0.96
Other									
V1–V3	**L**	4.3	0.12	0.5	0.80	0.5	0.79	0.5	0.77
	R	**6.8**	**0.03***	0.7	0.70	1.0	0.61	0.6	0.73
Amygdala	**L**	4.9	0.09	0.5	0.79	0.3	0.86	1.0	0.61
	R	4.8	0.09	1.8	0.41	1.7	0.42	0.1	0.95
Visual responsive regions		5.1	0.08	2.7	0.26	2.7	0.26	1.0	0.61
Non-visual responsive regions		2.0	0.38	1.3	0.52	0.7	0.70	0.0	0.98

* $p < 0.05$.

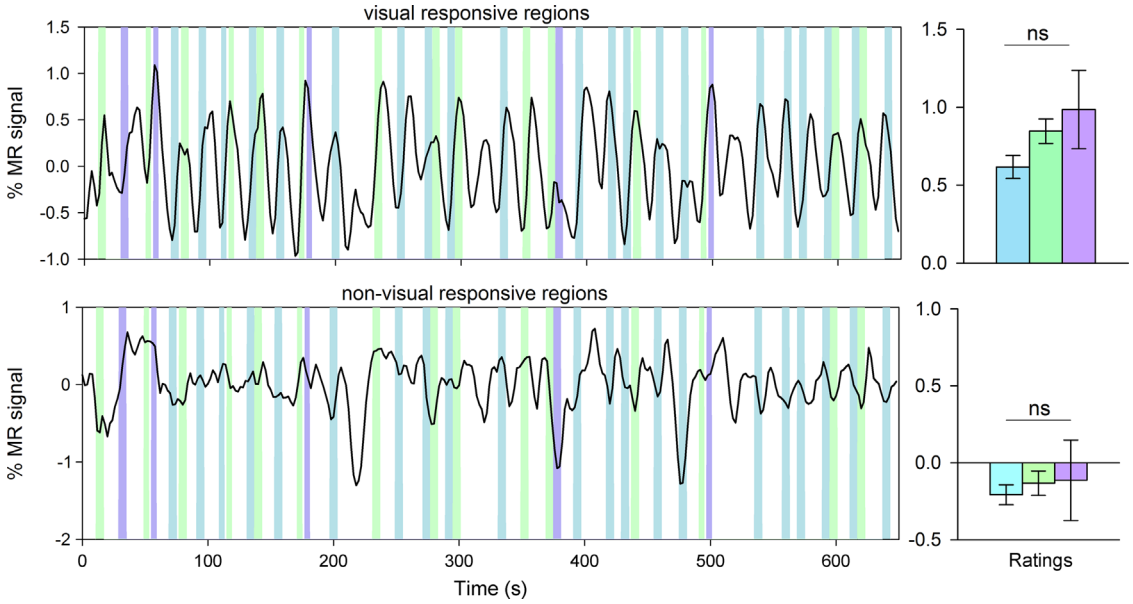


Fig. 7. Response timecourses from visuallyresponsive and non-visually responsive regions with the distortion ratings overlaid. Bar graphs show the average %MR signal for each distortion rating. Kruskal–Wallis tests for rank order effects show no significant differences between the neural responses as a function of distortion ratings in these regions (ns: not significant).

woman whose distortions were restricted to familiar faces (Heutink et al., 2012). For this woman, close family members looked bizarre and sometimes grotesque, yet strangers appeared normal. Although AS experiences distortions for most faces, it is possible that for her, the relationship between the magnitude of her distortions and the identity of the face is related to the increased activity in her OFA and FFA. However, the precise relationship between these areas and facial familiarity *per se* is unclear.

The STS is the only core face selective region that did not show a relationship between its activity and the magnitude of AS' perceived distortions.[2] On the one hand, this may seem surprising given the dynamic nature of AS' perceptual experience and the proposed role of the STS in the processing of changeable aspects of faces (e.g. for facial expression recognition, Haxby et al., 2000). Indeed, Santhouse, Howard, and ffytche (2000), proposed that spontaneous visual hallucinations of grotesque faces with exaggerated eyes and teeth in the context of Charles Bonnet Syndrome was related to pathological increases of activity in the STS, and less likely the FFA. This was based on the prominence of the eyes in the hallucinations, and the proposed relationship between the STS and the perception of eye movements and gaze (Bentin et al., 1996; Wicker, Michel, Henaff, & Decety, 1998). They also suggested that these hallucinations are unlikely to be related to increased activation in the FFA. On the other hand, ffytche, Howard, Brammer, Woodruff, and Williams (1998) reported a relationship between activity in the middle fusiform gyrus and facial hallucinations in Charles Bonnet syndrome. Our results are consistent with this latter finding, with AS' perceived distortions correlating with MR signal changes her FFA, but not STS. Recent findings that support the importance of the FFA in the processing of eye information: (1) prosopagnosic patients with lesions of the fusiform gyrus often show greater impairment for processing the eye region (Barton, 2008), and, (2) there is more adaptation in the OFA and FFA to the eyes than other facial regions (Lai, Pancaroglu, Oruc, Barton, & Davies-Thompson, 2012).

Consideration of results about the tuning of neurons in macaque face patches may also shed light on our findings. Most face-sensitive neurons in the macaque middle face patch show monotonic tuning curves such that cells produce maximal responses to extreme, rather than intermediate, features values (Freiwald, Tsao, & Livingstone, 2009). Applied to prosopometamorphopsia, perceived facial distortions (e.g. enlarged or exaggerated features) may be related to abnormal or spontaneous enhancement of firing of face-sensitive neurons. Other findings from single-cell recording studies may help explain certain commonalities in patient reports. For example, Freiwald et al. (2009) detected a particularly high incidence of tuning to eyes and facial layout (face aspect ratio, face direction, and height of features within the facial contour) compared to other features such as the mouth and nose, which may explain the common discussion of changes to eyes in prosopometamorphopsia (e.g. AS, see Table 2; ffytche & Howard, 1999; Santhouse et al., 2000) and the report of changes in feature location in general (e.g. eyes, mouth, drooping). Additionally, Freiwald et al. (2009) reported greater firing for features that were presented in the context of a whole face than in isolation. This is consistent with AS reporting that most of the face needs to be visible for her distortions to be triggered.

In the extended face network, we found a trend for a correlation between AS' distortions and the neural response in the right IFG. Though the involvement of prefrontal regions in face processing is less established than the involvement of the core face areas, prefrontal regions have been implicated in categorization of famous faces by profession (Sergent et al., 1992), face matching (Haxby et al., 1994), working memory for facial identity (Courtney, Ungerleider, Keil, & Haxby, 1996), encoding of unfamiliar faces (Kelley et al., 1998), and expression categorization (Marinkovic, Trebon, Chauvel, & Halgren, 2000; Nakamura et al., 1999). Interestingly, as with direct electrical stimulation of the OFA (Jonas et al., 2012) and FFA (Parvizi et al., 2012), stimulation to the right anterior inferior frontal gyrus led to distorted perception of faces in a patient with intractable frontal lobe epilepsy (Vignal, Chauvel, & Halgren, 2000). Specifically, the patient reported, "…it was as if you changed your face, that it was remodeled and that it became another face…" (p.287). This patient's report is similar to descriptions provided by AS (Table 2). This relationship between face distortions and stimulation to IFG could explain the trending correlation between AS' distortions and the neural response in her right IFG.

Outside of the core and extended face areas, we found a significant correlation between the magnitude of AS' perception of facial distortions and activity in right LOC and right V1–V3. Although AS' primary complaint is of metamorphopsia for faces, when probed, she reports that some patterns (i.e. complex ones) can appear mildly distorted. Like AS, the epilepsy patient who reported facial distortions in response to electrical stimulation of FFA also reported subtle effects with objects (e.g. the TV, a balloon, Parvizi et al., 2012). Likewise, two patients with primary complaint of unilateral prosopometamorphopsia were found to experience subtle perceptual distortions when viewing objects that the authors explained by general low-level perceptual distortions that are more noticeable for faces than objects (Nijboer et al., 2008). Thus, although facial distortions dominate AS' visual complaints, her report of mild distortions of non-face objects is not surprising, and is consistent with our neural findings from right LOC and right V1–V3.

It is worth noting that similar patterns of activity (i.e. increased signal with increased perception of distortion) were observed in left OFA, left FFA, and left V1–V3, suggesting the relationship between MR signal change and AS' distortions may be more widespread. However, these effects were not significant (all $ps > 0.05$) and the consistency of the correlations between the right hemisphere regions and AS's distortions suggest a definite right hemisphere bias. This bias is consistent with the well-established finding that face processing tends to be right hemisphere dominant (De Renzi, 1986; Landis, Cummings, Christen, & Bogen, 1986; Sergent et al., 1992; Kanwisher et al., 1997; Fox et al., 2009). Further, if the correlations were due to a general increase in arousal, we would expect to find correlations between AS' perceptual distortions and many other regions of cortex. However, we found no correlations between AS' perceived distortions and the activity in the amygdala, visually responsive regions outside the face- and object-selective regions, nor non-visually responsive regions.

Finally, it is important to consider the direct or indirect involvement of visual attention on the present findings. As mentioned above, the right predominance of correlations between the MR signal and AS' distortions could reflect the involvement of face-selective regions. However, visual spatial attention is also primarily right hemisphere dominant (Bogen & Gazzaniga, 1965; Corballis, Funnel, & Gazzaniga, 2002; Heilman & Van den Abell, 1979), providing an alternate explanation for the present results. Alternatively, visual attention may have played a modulatory role on face-selective regions (Engell & McCarthy, 2010; Furey et al.,

[2] Deactivation in this area may be explained by the contrast between the dynamic localizer and the use of static images during the experiment, or due to zero-correction of the time series. However, the key finding is not the exact value of the %MR signal in the STS, but rather the lack of relationship between the activity in this region and the distortion ratings, which are independent of constant values used for zero-correction.

2006; Haxby et al., 1994; Vuilleumier, Armony, Driver, & Dolan, 2001; Wojciulik, Kanwisher, & Driver, 1998). The precise contribution of visual attention to the present results is difficult to determine. However, given that AS' distortions are face-specific, one plausible explanation is that face-selective areas such as right OFA and right FFA generated the effects and that the activity in other areas was subsequently affected by attention to the morphing faces. Further investigation is needed to test this possibility.

What are the potential causes of prosopometamorphopsia? Other prosopometamorphopsic cases have been associated with damage or abnormalities in various brain areas spanning the temporal (Nass, Sinha, & Solomon, 1985; Sun & Lin, 2004; Miwa & Kondo, 2007; Nijboer et al., 2008; Heutink et al., 2012), occipital (Hecaen & Angelergues, 1962; Mooney, Carey, Ryan, & Bofin, 1965; Satoh, Suzuki, Miyamura, Katoh, & Kuzuhara, 1997; Sun & Lin, 2004; Nijboer et al., 2008; Trojano et al., 2009), parietal (Hecaen & Angelergues, 1962; Mooney et al., 1965; Nijboer et al., 2008) and frontal lobes (Critchley, 1951). Many of these studies also reported abnormal EEG findings in these patients. For example, one early report described a patient who had normal anatomic scans, but frequent spikes in the EEG from the right posterior temporal–occipital area (Brust & Behrens, 1977). Sun and Lin (2004) reported right occipital infarct, but sharp EEG waves over bilateral temporal areas. Another patient was reported to have delta wave activities in the right temporal region (Miwa & Kondo, 2007). In this latter case, the authors speculated that the patient's prosopometamorphopsia may have been a manifestation of epilepsy, although anti-epileptic medication did not reduce the patient's perception of facial distortions. However, the administration of the anti-epileptic medication carbamazepine did resolve prosopometamorphopsia in a 14-year-old epileptic patient who had posterior temporal slow and sharp wave activity (Nass et al., 1985) and in another epileptic patient who experienced the perception of unilateral facial distortions (Mendez, 1992). Combined with results from the present study, these findings suggest that possibility that at least in some cases of prosopometamorphopsia, hyperactivity in core or distributed face areas, without the presence of lesions, may be a causal factor. In the case of AS, there is no evidence of brain damage on her anatomic scans, her ERP shows normal face-selectivity of the N170 potential, and her EEG was normal. However, she did have epilepsy and currently complains of recurring episodes of 'visual noise', possibly a migraine equivalent or focal optical seizures. Both seizures and migraine equivalents can be indices of abnormal cortical excitability, particularly in occipital cortex in the case of visual migraine equivalents (Chronicle, & Mulleners, 1996; Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998; Brighina, Piazza, Daniele, & Fierro, 2002; Pietrobon, 2005; Aurora & Wilkinson, 2007). Although there is no proof that her prosopometamorphopsia is actually due to seizure activity, one might speculate that a sub-clinical degree of hyperexcitability in a specific part of occipital and temporal cortex is responsible for the fact that faces can induce these distortions.

It is worth considering whether AS' distortions could be the result of drug use. AS reported one experience with lysergic acid diethylamide (LSD), a hallucinogenic drug that can cause a variety of symptoms including visual hallucinations. Though the effects are often acute, there have been reports of users experiencing prolonged or recurrent perceptual distortions up to one year after use (e.g. Robbins, Frosch, & Stern, 1967; Asher, 1971). Perceptual distortions related to LSD use typically consist of coloured patterns, geometric imagery, halos, afterimages, and can progress to include animate figures (Baggott, Coyle, Erowid, Erowid, & Robertson, 2011; Manford & Andermann, 1998). The DSM-IV-TR refers to prolonged or recurrent perceptual effects as Hallucinogen Persisting Perception Disorder (HPPD). In a study of HPPD, Baggott et al. (2011) found that the visual experiences associated with LSD were more likely with increased drug exposure. Thus while it is possible that AS' single experience with LSD many years ago contributed to the sudden onset of facial distortions in her forties, the time since use and the fact that it was a single use, makes this unlikely. Interestingly, based their review of the literature of long-term effects of hallucinogenics, Baggott et al. suggested that some cases of HPPD may have been more appropriately diagnosed as seizure disorders or migraine aura without headache. In the case of AS, we believe that these latter diagnoses are more likely to account for her distortions.

In summary, the current study investigated the relationship between perceived facial distortions in prosopometamorphopsia and activity in the core and extended face processing areas. The magnitude of the facial distortions perceived by AS was related to the level of activity of regions within the core face processing network, particularly the right OFA and right FFA, but not in the STS. There was a trend for a correlation between her distortions and activity in the right IFG, a region of the extended face-processing network. AS' minor complaints of distortions for objects may be accounted for by activity in right LOC and right V1–V3, which was also correlated with the magnitude of her distortions. The quality of AS' facial distortions, which are feature-centered and more pronounced for familiar compared to unfamiliar faces, is consistent with the proposed role of the core face areas in face perception. Although the exact mechanisms underlying prosopometamorphopsia remain unclear (and there are likely to be multiple), for AS, disturbing perceptions of facial distortions appear to result from increased neural firing or general hyperactivity in temporal, occipital, and even frontal areas.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2014.05.005.

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