Too Many Trees to See the Forest: Performance, Event-related Potential, and Functional Magnetic Resonance Imaging Manifestations of Integrative Congenital Prosopagnosia

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Abstract

■ Neuropsychological, event-related potential (ERP), and functional magnetic resonance imaging (fMRI) methods were combined to provide a comprehensive description of performance and neurobiological profiles for K.W., a case of congenital prosopagnosia. We demonstrate that K.W.'s visual perception is characterized by almost unprecedented inability to identify faces, a large bias toward local features, and an extreme deficit in global/configural processing that is not confined to faces. This pattern could be appropriately labeled *congenital integrative prosopagnosia*, and accounts for some, albeit not all, cases of face recognition impairments without identifiable brain lesions. Absence of face selectivity is evident in both biological markers of face processing, fMRI (the fusiform face area [FFA]), and ERPs (N170). Nevertheless, these two neural signatures probably manifest different perceptual mechanisms. Whereas the N170 is triggered by the occurrence of physiognomic stimuli in the visual field, the deficient face-selective fMRI activation in the caudal brain correlates with the severity of global processing deficits. This correlation suggests that the FFA might be associated with global/configural computation, a crucial part of face identification. ■

INTRODUCTION

Congenital prosopagnosia (CP) is a marked idiopathic impairment in identifying faces in the absence of other conspicuous sensory, cognitive, and neurological pathology. Individuals with CP usually report that these difficulties have been evident for as long as they can remember (presumably from birth) and some evidence suggests that it might run in families, hence labeled as "congenital" (Behrmann & Avidan, 2005; De Haan, 1999). Although it is a relatively rare condition, the number of reported cases is rapidly growing (Behrmann, Avidan, Marotta, & Kimchi, 2005; Duchaine & Nakayama, 2005; Kress & Daum, 2003a; de Gelder & Rouw, 2000; Bentin, Deouell, & Soroker, 1999; Ariel & Sadeh, 1996). Existent descriptions unveil a variable pattern of perceptual deficiencies associated specifically with face identification but very few, if any, deficits in neurological function. Most intriguing is that in the absolute majority of CP cases reported in the literature the ventrotemporal and occipitotemporal brain areas usually associated with face processing (including the fusiform face area [FFA])

are normally activated. In the present article, we report a comprehensive neuropsychological, electrophysiological, and neuroimaging investigation of an extremely severe case of CP without any increase in FFA activity to faces. Manifestations of perceptual characteristics within and outside the face processing domain are also presented. Given the severity of face identification in this case and the clear-cut results of the experiments, we believe that this investigation sheds light on the antecedents of CP and promotes the understanding of face processing characteristics, in general.

Intracranial electrophysiological recording (Allison, Puce, Spencer, & McCarthy, 1999) and numerous functional neuroimaging studies (e.g., Haxby, Hoffman, & Gobbini, 2000; McCarthy, 1999; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Gore, & McCarthy, 1995) have demonstrated face-selective activity in fairly well circumscribed regions of the human fusiform gyri, which have been jointly coined the fusiform face area (Kanwisher, McDermott, & Chun, 1997). In addition, face-sensitive areas were described in the occipitotemporal cortex (lateral occipital cortex [LO] and occipital face area [OFA]; Malach, Levy, & Hasson, 2002; Grill-Spector, Kourtzi, & Kanwisher, 2001). Over studies, face-selective activation has been more reliable in the right than in the left hemisphere, but in many individual subjects

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faces activate the fusiform gyri bilaterally. Exclusive left-hemisphere FFA is rarely observed and, to the best of our knowledge, there is no formal report of normal subjects in which no face sensitivity was found anywhere in the fusiform. Intriguingly, although studies of patients with prosopagnosia following brain damage strongly suggest that an intact (right) fusiform function might be necessary for successful accomplishment of face processing (e.g., Barton, Press, Keenan, & O'Connor, 2002; Wada, & Yamamoto, 2001), in all individuals with CP (except one) a face-specific activity was found in the fusiform (FFA) and was presumed normal (Avidan, Hasson, Malach, & Behrmann, 2005; Hasson, Avidan, Deouell, Bentin, & Malach, 2003). In the only reported case of CP with clearly abnormal FFA activity, this region responded more to houses than to faces, but the response to faces was greater than to objects, as found in normal observers (Hadjikhani & de Gelder, 2002). These findings indicate that a face-selective FFA does not ensure efficient face identification (see also Steeves et al., 2006). Although FFA sensitivity to faces is not in doubt, its specific role in face perception is not as clear as would be desired. Indeed, several studies suggest that selectivity in the FFA may be extended to objects such as cars or birds if the perceiver is an expert in identifying such objects (Tarr & Gauthier, 2000).

The use of event-related potentials (ERPs) in investigations of prosopagnosia is scarce. Most of these studies were aimed at exploring implicit evidence for covert face identification following brain damage (Bobes et al., 2003; Viggiano, 1996; Renault, Signoret, Debruille, Breton, & Bolgert, 1989). Furthermore, most of these studies focused on ERP components with relatively late onsets, associated with higher level processes and presumably reflecting face identification. However, the discovery of the N170 face-sensitive ERP component (Bentin, Allison, Puce, Perez, & McCarthy, 1996) provided an opportunity to investigate the integrity of early visual processes, theoretically associated with face detection and categorization. Nevertheless, only a handful of studies focused on the N170 in conjunction with impaired face processing, and their results are not as clear as one would hope. One study reported the absence of any face-elicited (or negative deflection in the N1 or N170 time range in a patient with prosopagnosia caused by brain damage in early infancy (Eimer & McCarthy, 1999). In contrast, robust N170 potentials were found in a prosopagnosic patient following substantial bilateral damage to the posterior ventral temporal cortex, including the FFA (Bobes et al., 2003). However, because the ERPs elicited by nonface objects were not reported in the latter study, we do not know whether this potential was, indeed, discriminative for faces.[1] This knowledge is relevant because (in contrast to functional magnetic resonance imaging [fMRI] results) two studies of N170 in prosopagnosic individuals reported conspicuous N170 responses to faces and

similarly conspicuous responses to nonface objects (Kress & Daum, 2003b; Bentin et al., 1999). In other words, the N170 component in these CP cases did not distinguish between faces and nonface objects. Finally, magnetic encephalographic studies reported a mixture of discriminative and nondiscriminative M170 (the putative magnetic analogue of the electrical N170) and N170 responses (Harris et al., 2005). Indifference of the N170 to faces in CP compared with the relatively normal fMRI activity in the FFA is intriguing and consistent with N170 probably being associated with a more upstream perceptual mechanism than the FFA (cf. Grill-Spector, Knouf, & Kanwisher, 2004).

Little is known about visual perceptual specificity in CP. The absence of basic-level visual perception deficits might indicate that CP is a manifestation of associative agnosia, reflecting either a disconnection between the perceptual and the semantic system or a problem at the semantic level affecting particularly the subordinate classification of faces. Characteristic to face identification is the necessity to select a unique exemplar from a large set of visually similar stimuli. However, despite the visual homogeneity among face exemplars, humans identify faces more accurately than they identify visually unique exemplars of other categories. Studies of normal face processing account for this outstanding perceptual efficiency by showing that, whereas unique exemplars of nonface categories are usually identified on the basis of distinctive features, face identification relies in addition, on deriving the spatial relations between face components (second-order configural processing, Maurer, Le Grand, & Mondloch, 2002; Farah, Wilson, Drain, & Tanaka, 1998; Tanaka & Sengco, 1997; Rhodes, 1988). Computation of a second-order configuration of the face elements is believed to be necessary because the first-order (global) configuration is identical across individuals. Indeed, deficient configural processing is assumed to be one of the major characteristics of ''acquired'' prosopagnosia (Barton, Zhao, & Keenan, 2003; Barton et al., 2002; Levine & Calvanio, 1989).

Studies of configural processing ability in CP have provided mixed results. Deficient configural processing was suggested by the absence of the well-established face inversion effect in at least one prosopagnosic individual (De Gelder & Rouw, 2000). Face-matching performance in this person was not significantly reduced by face inversion as it is in normal observers. The typically impaired identification of inverted than of upright faces is usually explained as a disruption of second-order configural processing. However, the trend in this person's performance was normal. Moreover, using the same tests as those used by Levine and Calvanio (1998), neither Duchaine (2000) or Bentin et al. (1999) found signs of configural processing deficits in other CP cases. Furthermore, recent evidence casts some doubts on the assumption that inversion effects in general and the face inversion effect in particular exclusively reflect

the disruption of configural processes. For example, using a mixed rather than a block design, Riesenhuber, Jarudi, Gilad, and Sinha (2004) found similar effects of inversion on matching faces that differed on features or on configuration. Similar effects of inversion on detecting configural and featural changes were recently reported when testing people with CP[2] (Yovel & Duchaine, 2006).

Additional studies examine configural processing abilities in CP by using hierarchical patterns that differ in their global and local shapes (Navon, 1977). Slower responses to global than to local letters and reduced global-to-local interference in CP participants compared with non-CP participants were recently reported, suggesting that global perception might be associated with the face identification impairment in CP (Behrmann et al., 2005).

The above review indicates that current knowledge is insufficient to specify possible neural factors associated with CP or to characterize visual perception deficits that could account for deficient face identification in such cases. To begin to fill this gap, here we report the results of a comprehensive ERP, performance, and fMRI investigation of a case of severe CP (K.W.) with well-documented absence of any face-selective activity in either fusiform gyrus.

METHODS

Participants

In addition to K.W., 12 other undergraduates from the University of California, Berkeley, participated in the behavioral experiments. Another 12 undergraduates from the same pool were scanned in an fMRI session, and 24 undergraduates from the Hebrew University in Jerusalem formed the ERP control group. Men and women were represented in each group. All participants were free of any neurological symptoms, were not taking any prescribed medication, and had normal or corrected-to-normal vision. All participants were paid for participation and gave informed consent before starting the experiment.

Implicit Face Processing Tests

In the name classification test, participants were instructed to categorize a series of famous names of politicians or movie stars by pressing predesignated keys representing each type. On each of the 48 trials, a name was presented on the background of a stimulus that included a face (Figure 2A). In the congruent condition (12 politicians and 12 movie stars), the name and the face were of the same person. In the incongruent condition, the name of a politician was presented in the background of a movie star's face or vice versa. Each stimulus was presented until the response

was made, and 1500 msec separated the response from the next trial. The participants were instructed to ignore the face and respond as fast as possible to the name.

Both the identity matching and the expression matching tests were presented on a computer screen. In both tests, five colored faces were presented in each trial. One was the target and was placed above the four alternative test choices, which were placed at the four corners of a square (Figure 1). All were faces of young male and female students photographed specifically for constructing these tests. Each face was presented on a blue rectangle background, $3.95°$ wide and $4.83°$ tall, seen from a distance of 65 cm. In the *expression matching task*, the participants were instructed to select, among four alternatives, the face that expressed the same emotion (happiness, disgust, anger, or surprise) as the target face. All the photographs were frontal photographs. On half of the 40 trials, the four alternatives and the target were different photographs of the same face. On the other 20, the four alternatives were different photographs of one face, each expressing a different emotion, and the target was a different face. Matching was never between identical faces. Even in the same identity condition, the target and the correct alternative were two photographs of the same person, who mimicked the same expression each time in a slightly different way, to reduce pictorial similarity differences of the same face within and across expressions. These faces were selected in a pilot test so that there was no significant difference between the rated pictorial similarity of two pictures of the same person within and across conditions (Levy & Bentin, submitted). In the *identity matching task*, the participants were required to select the face among four test alternatives that represented the same person as the target. On half of the 72 trials, the target and the four alternatives expressed the same emotion (happiness or disgust), and on the other half, the four alternatives expressed the same emotion, which was different from the target. Whereas all targets were frontal photographs, within each expression condition the four alternatives were front faces in 12 trials, $45°$ rotated to the right in another 12 trials, and $45°$ rotated to the left in yet another 12 trials. As in the expression matching task, matching identity was never between identical pictures. In both tasks, the stimuli were presented without time constraints and offset after the response.

fMRI Recording

Functional images were acquired by using a gradient-echo-planar sequence (TR = 2000 msec, TE = 28 msec, matrix size = $63 × 64$, FOV = 22.4 cm) sensitive to blood oxygenation level dependent (BOLD) contrast. Each functional volume consisted of $18 × 5$-mm-thick axial slices for portions of the inferior cerebellum and

Figure 1. Examples of stimuli in the different conditions in the identity matching (top) and expression matching (bottom) tasks.

Identity Matching Task

Same expression   Different expression

Expression Matching Task

Same identity   Different identity
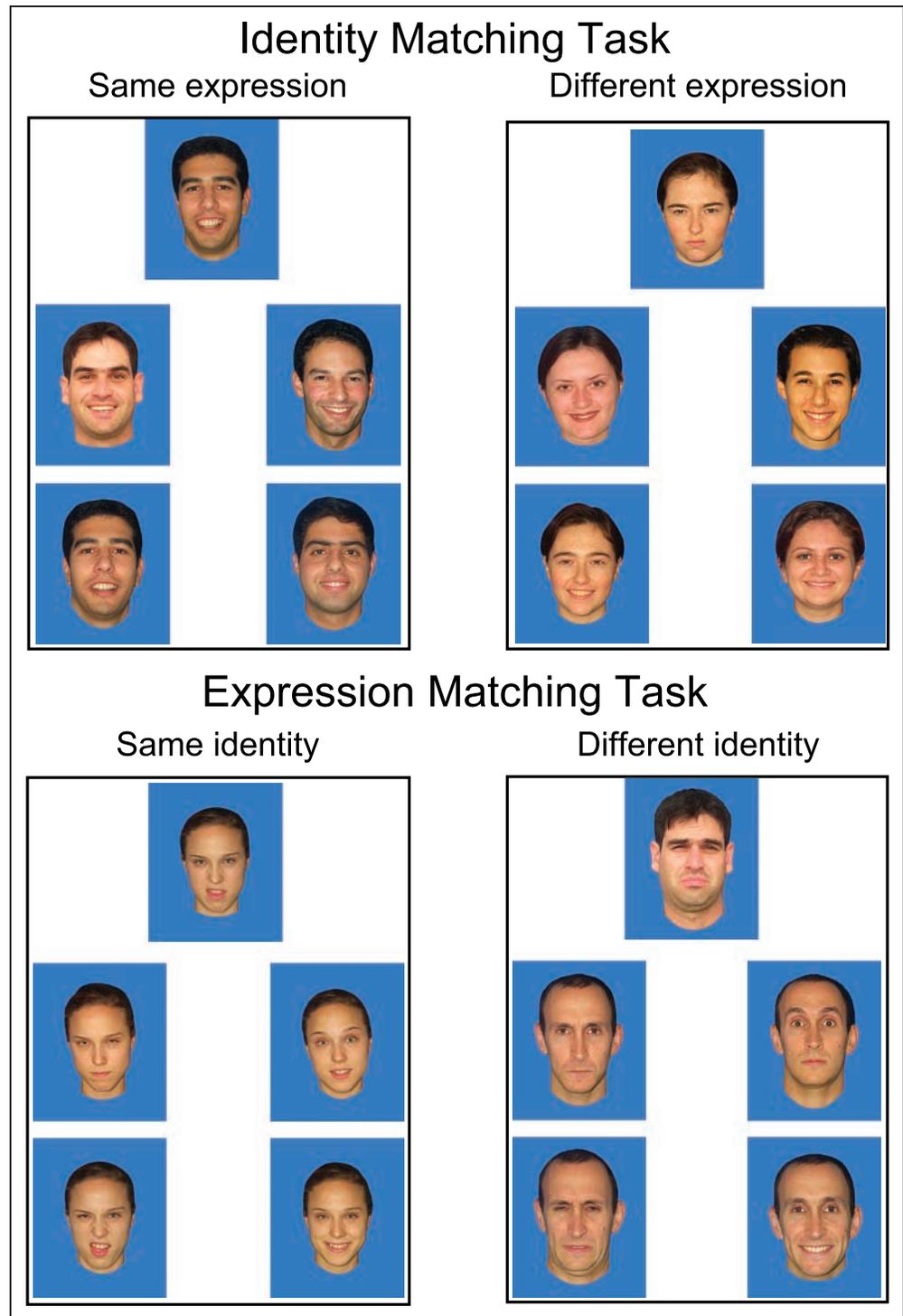
the most superior extent of the parietal lobe. For each scan, 30 sec of gradient and RF pulses preceded data acquisition. Participants viewed images in the scanner via back-projection onto a custom screen mounted at the participant's chest level and viewed via an angled mirror placed inside the head coil.

Initial data preparation included image reconstruction, motion correction using a six-parameter, rigid-body, least squares alignment, and normalization of the time series of each voxel by its mean signal value to attenuate between-run scaling differences. Activation corresponding to each trial condition was assessed using multiple regression. In the model, additional nuisance covariates were included to model intercept and trial-specific baseline shifts. The convolution matrix included a time domain representation of the expected $1/f$ power structure and filters to remove frequencies at and above the Nyquist frequency (0.25 Hz) and below 0.02 Hz (the

portions of highest power in the noise spectrum). Covariates modeling BOLD responses for each subject during each trial were derived by convolving the vector of expected neural activity with the canonical hemodynamic response function. For each subject, parameter estimates yielded by the General Linear Model were contrasted and statistical significance was assessed using a liberal threshold of $t = 2.5$.

ERP Recording

The electroencephalogram (EEG) was recorded continuously by 64 Ag–AgCl Pin-type active electrodes mounted on an elastic cap (ECI; Eaton, OH) according to the extended 10-20 system (American EEG Society guidelines, 1994) and referenced to the tip of the nose. Eye movements as well as blinks were monitored by using bipolar horizontal and vertical electrooculogram derivations via two pairs of electrodes, one pair attached to the exterior canthi and the other to the infraorbital and supraorbital regions of the right eye. The analog signals were sampled at 250 Hz by using a Biosemi Active II (Amsterdam, The Netherlands) digital 24-bit amplification system with an active input range of -262 to $+262$ μV per bit without any filter at input. The digitized EEG was saved and processed off-line. A change in voltage of more than 75 μV during an epoch of 100 msec at any of the channels was considered an artifact, and the EEG recorded during 200 msec surrounding the artifact was eliminated from further analyses. After artifacts were removed, 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

Case History and Neuropsychological Findings

K.W. is a 26-year-old female undergraduate of good academic standing who has had severe difficulty in face identification for as long as she can remember. She has a myopic left eye and reduced contrast sensitivity in her right eye, but only for high spatial frequencies (6–16 cycles per degree; measured by Vision Contrast Test System, VCTS-6500, Vistech Consultants, Inc.; Dayton, OH). Her visual acuity as measured by Snellen chart at 35 cm (OD 20/20, OS 20/25) was normal as was her color vision as measured by Dvorine color plates (14/14). There was no evidence of diplopia or strabismus and no history of head trauma or cognitive deficits. Object recognition on the Boston Naming Test (BNT) was perfect (60/60), a score that is 1.1 SD above the normal mean. She had no problems merging object parts, as revealed by a score of 28/30 correct identifications of broken objects in the Hooper test (normal mean, 26.75; $SD = 1.97$). Unlike integrative agnosics, she was perfectly able to match the surfaces of different shapes (Efron

shape test; Efron, 1968). Finally, she had no impairment processing orientation as demonstrated by a perfect score on the Benton Line Orientation test.

Face Processing

K.W. identified only 10 of 60 faces of famous movie stars and politicians in a test adapted for college students (courtesy of Brad Duchaine). In comparison, a group of 12 undergraduates without face recognition problems identified an average of 38.75 faces out of the 60 with a lower 95% confidence limit of 32.02. However, K.W.'s face recognition impairments extended beyond semantic identification; K.W. could not form reliable representations of unfamiliar faces as well. She scored 39/75 on the Cambridge Face Memory Test (Duchaine & Nakayama, 2006), which is 1 point less than the average norm of individuals with CP and significantly below the normal mean performance of 58/75. In this test, participants are introduced to six target faces, and then they are tested with forced-choice items consisting of three faces, one of which is a target. For each target face, three test items contain views identical to those studied in the Introduction, five present novel views, and four present novel views with noise. Her performance on the Warrington Word Memory test verified that her impaired ability to learn new faces was not associated with a general visual learning disability. Although scoring below chance on the face subtest (23/50) she was 100% accurate (50/50) at memorizing the words. Such a discrepancy between word and face memory is larger than that observed in 95% of the normal population. Unlike other prosopagnosics reported in the literature who are within the normal range on matching faces for identity on the Benton Face Recognition Test (BFRT), K.W. scored 33/54, which placed her in the "severe impairment" category (cf. Duchaine & Nakayama, 2004). This low performance level in matching faces presented simultaneously for an unlimited time is consistent with a severe impairment in forming mental representations of faces.

Additional insights into the nature of K.W.'s impairment were gained by assessing her ability to process faces implicitly, that is, without awareness of the face identity. There is evidence that at least some, if not all, neurological patients who acquire prosopagnosia after brain injury covertly respond to the identity of faces they knew before injury (Barton, Cherkasova, & Hefter, 2004; De Haan, Bauer, & Greve, 1992; De Haan et al., 1987). In contrast, as reported with other prosopagnosics before her (Barton, Cherkasova, & O'Connor, 2001; Bentin et al., 1999; but see Jones & Tranel, 2001, for an exceptional case), we found no evidence for covert face identification in K.W. In one test of covert processing, the task was to classify each name as a politician or as a movie star, ignoring the faces. K.W. accomplished this task with little difficulty (95.8% correct), but her reaction times (RTs) showed no evidence of covert face

identification. She was just as fast to report the name when it was congruent with the face as when it was incongruent (Figure 2A). This pattern of performance is different from the normal pattern as well as from the performance of a group of 12 control participants who showed nearly a 200-msec congruency effect (970 and 1163 msec for congruent and incongruent conditions, respectively, albeit using a different set of stimuli; Bentin et al., 1999). It is consistent, however, with her never having recognized famous people by face alone.

Nevertheless, evidence for covert perception of faces was found by using two novel matching tasks. In both tasks, an unfamiliar target face and four unfamiliar test faces were presented on each trial. Targets and test faces varied along the dimension of identity as well as expression (Figure 1). In the expression matching task, participants selected the test face (ignoring identity) that matched the expression of the target, which was either the same as or different from the target. In the identity matching test, participants were instructed to select the face (ignoring expression) that matched the identity of the target, which was again either the same as or different from the target. Normal undergraduates matched expressions more accurately and faster when

Figure 2. Covert face processing in K.W. (A) Name classification speed in the congruent and incongruent conditions (example of stimuli shown on the right). The small trend of responding faster to names in the incongruent condition was not significant. (B) Response time and accuracy in the expression matching task. Although slightly slower than control participants, K.W. was more accurate and faster to match expressions when face identities were the same. (C) Response time and accuracy in the identity matching task. In agreement with her general impairment in face identification, K.W. was much slower and less accurate than control participants. Note, however, that her performance was better when the target and the alternatives had the same expression.
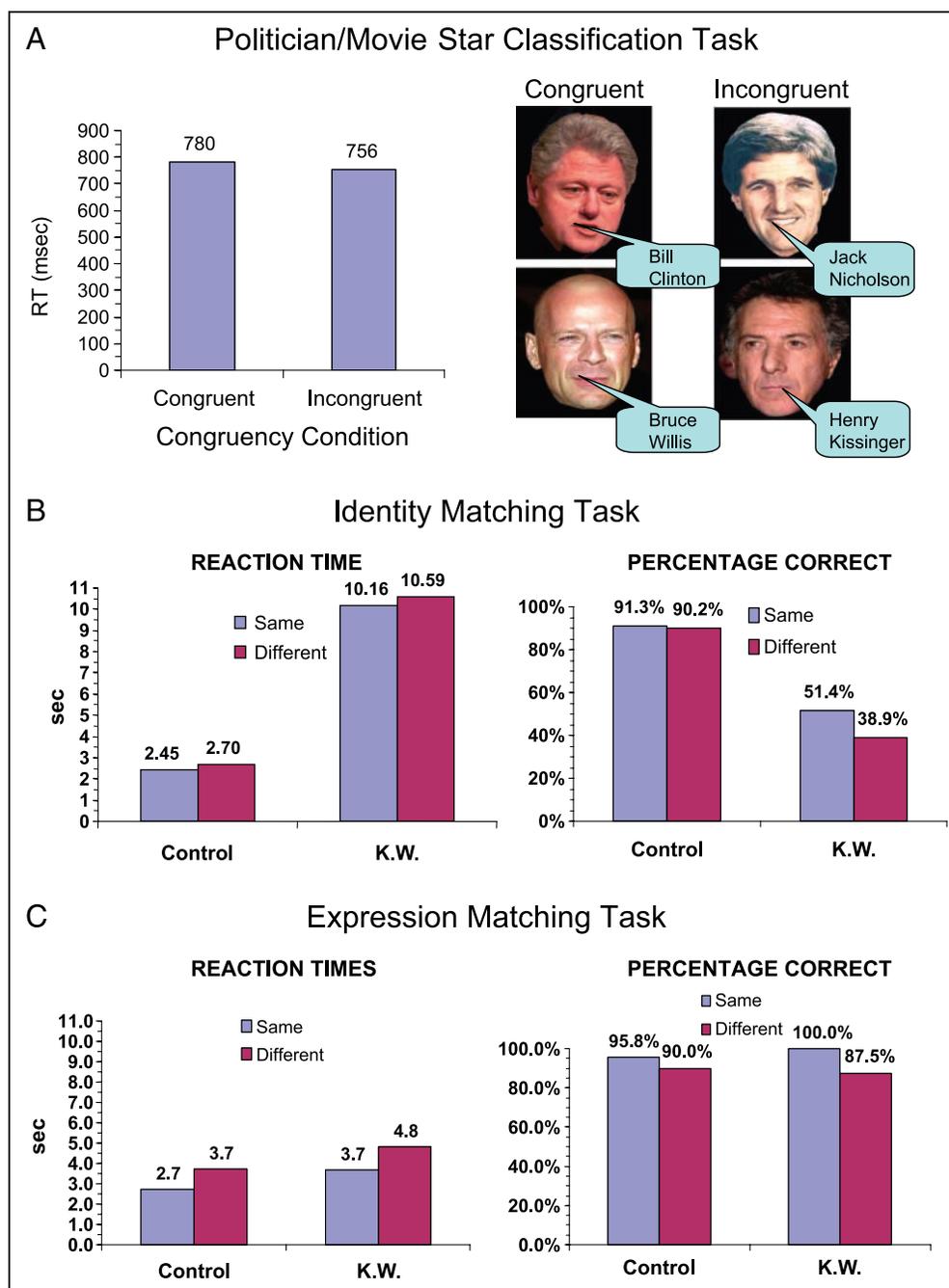
the test and target faces were of the same person. Although this pattern could involve a trivial factor of a person's idiosyncratic manner of expressing emotion within individuals, the impact of this factor on performance was reduced by asking the "actor" to mimic the same expression twice but in different ways (see Methods and Levy & Bentin, submitted, for details). Similarly, matching identity was faster and more accurate when the expressions on the target and test faces were the same.

In agreement with her poor performance in the BFRT, K.W. was extremely slow and inaccurate in matching identity, considerably slower and less accurate than the 95% confidence limits of the control group means (upper RT limits, 2.6 and 2.7 sec; lower accuracy limits, 89.3% and 88.4% for the "same" and "different" expression conditions, respectively). Indeed, based on the distribution of the control sample, K.W.'s z scores in the matching identity task were 29.6 and 14.9 for the RTs in the same and different conditions, respectively, and -12.5 and -18.3 for percentage correct in the same and different conditions, respectively. However, like control participants, her performance was considerably more accurate and faster when the correct alternative had the same expression as the target face than when the expressions differed (Figure 2B). In fact, it is interesting to note that K.W. was helped by identity of expression more than did the control participants in the RT (an effect of 0.43 sec for K.W. as opposed to 0.35 sec for controls; K.W., z score = 0.5) and particularly for accuracy (12.5% for K.W. compared with 1.2% for controls; K.W., z score = 3.43).

Also, like the control group, K.W. was faster and more accurate in matching expressions when the identity of the target and test faces was the same than when it differed (Figure 2C). Her RTs in the latter task (3.7 sec [z score = 2.5] and 4.8 sec [z score = 1.6] for the same and different identity conditions, respectively) were higher than the 95% upper confidence limit of the control group's mean (3.0 and 4.2 sec for the same and different conditions, respectively), but her accuracy did not differ from that of the control group (100% [z score = 1.13] and 87.55% [z score = -0.47] vs. the upper confidence limit of the control group's mean 93.5%, for the same and lower confidence limit of the control group's mean 86.6% for different identity condition). The higher accuracy of K.W. in matching expressions suggests that her relatively slow responses while matching expressions might reflect a speed/accuracy trade-off. More insightful, however, is that unlike the matching identity task, in the matching expressions task K.W. did not take advantage of face identity more than did the control group (an RT effect of 1.1 sec as opposed to 1.0 sec in the control group [K.W., z score = 0.18] and an accuracy effect percentage of 12.5% as opposed to 5.8% in the control group [K.W., z score = 1.26]). Again, the pattern of the results in these two

tests points to a severe impairment in explicitly extracting identity from faces. However, although weak, the evidence for covert processing of face identity in the expression matching task and processing of face expressions in the identity matching task suggests that K.W. is able to process some type of face-specific information even if she is not able to use this information for overt identification, or form face recognition nodes in long-term memory (as seen in the absence of inhibition when names and faces did not match in the De Haan et al. [1987] test).

fMRI Assessment of Categorical Selectivity in Ventral Temporal Lobes

We explored K.W.'s categorical selectivity in the ventral temporal lobes with functional imaging using a localizer procedure. Sixteen-second blocks of faces, places (landscape scenes), or objects were shown (courtesy of Nancy Kanwisher, MIT). Each block presented 20 images for 300 msec each with a 500-msec fixation cross between each image. To keep K.W.'s attention equally focused on faces and places throughout the task, we used a "one-back" paradigm in which she was requested to press both thumbs on the response pad when the current image was the same as the image immediately preceding it (an average of one repetition occurred in each block). Overall, 14 blocks were presented, alternating between "face" and "place" blocks. In contrast to her poor performance in the BFRT and the identity matching test, K.W.'s performance in this task was almost perfect showing that when only one face was presented at a time she could match faces when exactly the same image was repeated. Her high-level performance in the one-back task demonstrated that her visual problems did not interfere with her seeing the stimuli sufficiently well to perform the task. However, subtracting the activity elicited during the place blocks from the activity elicited during the face blocks, we found no regions in either fusiform gyrus or other ventrotemporal areas that were activated by faces more than by places. In contrast, the parahippocampus place area (PPA; Epstein & Kanwisher, 1998) was normally selective to places. Using a similar procedure, we found that objects also elicited more activity than faces in the fusiform, opposite to that usually reported in normal perceivers (Figure 3). The latter result contrasts with the case described by Hadjikhani and de Gelder (2002), whose FFA was activated more by faces than by objects. Whereas these data are not evidence for the fact that the functional abnormality associated with K.W.'s fusiform gyri is restricted to faces, they clearly show that there is no region in her posterior ventral and lateral occipitotemporal areas that is selective for or sensitive to faces. The absence of face selective activation in the fusiform is particularly intriguing given the hints for implicit processing of faces reported above. A possible account for this paradox is
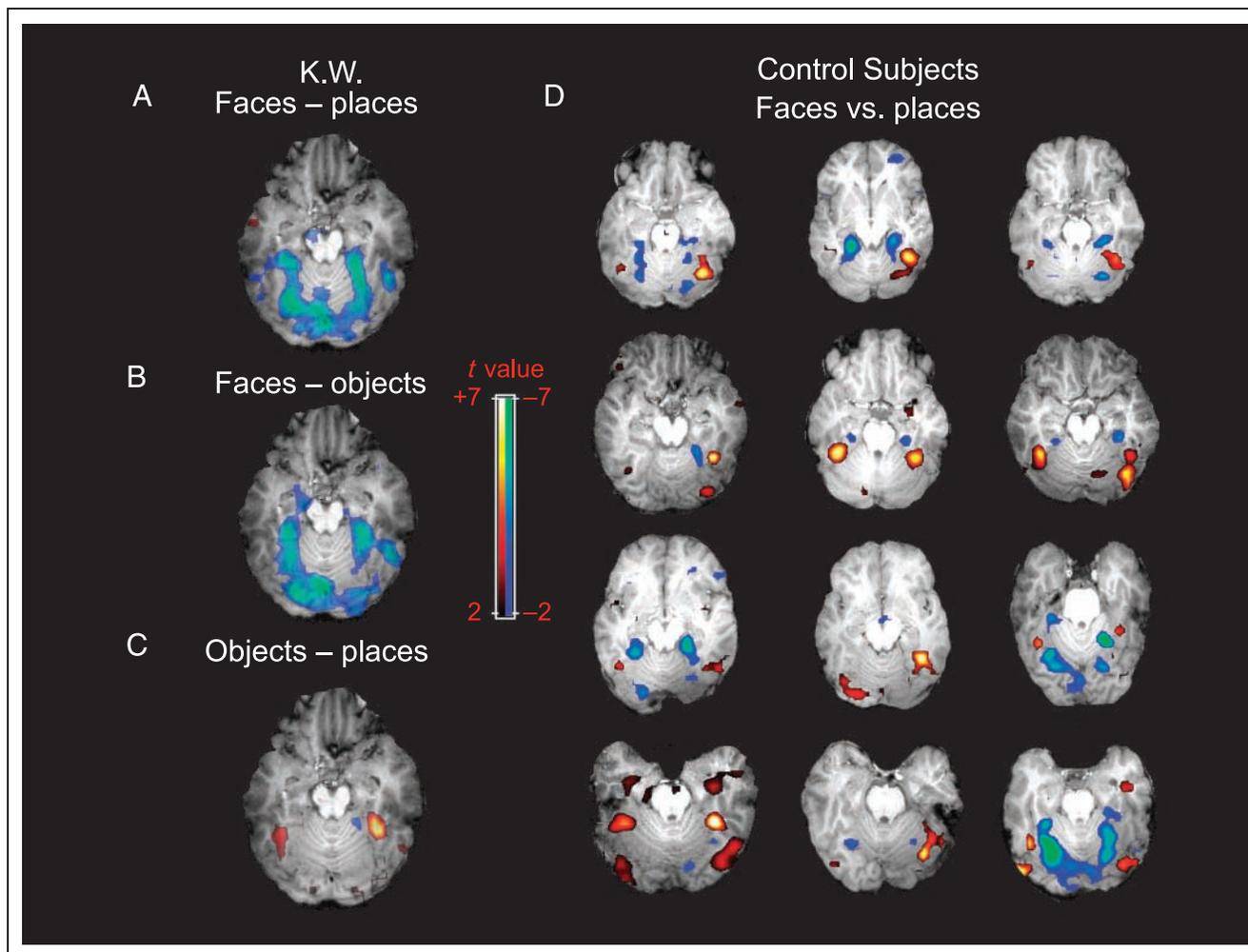
Figure 3. Distribution of face-selective voxels in the ventral temporal lobes of K.W. and 12 control subjects. Selectivity is displayed as *t*-test statistics with an equal threshold value of 2.5 across all images. The *t* value results from the comparison of face and places (A and D), face and objects (B), and objects and places (C). Notwithstanding the normal variability of exact location, all control subjects have well-circumscribed regions in the fusiform gyrus where the activity elicited by faces is significantly larger than that elicited by places (D). In contrast, no such regions appear for K.W., contrasted either with places (A) or with objects (B). Regions in her fusiform gyri, analogous in location to the FFA, respond more to objects than to faces (C), showing that the fusiform is active, but not selective for faces.

that the type of face-related information used by K.W. implicitly (e.g., identification of face features or first-order configuration) does not require (or does not trigger) the face process accomplished in the FFA. We will return to this issue in the Discussion.

Configural Processing

Led by the documented hypothesis that face identification is based primarily on the configuration of the inner components in the face space (for a review, see Farah et al., 1998) and by the evidence that K.W. can (at least implicitly) take advantage of local face features to improve her performance on a task involving faces, we explored K.W.'s ability to identify local and global aspects of other stimuli. Hierarchically constructed letters were presented where the perception of the large letter requires global processing and the perception of

its constituent (small) letters requires local processing (Navon, 1977). Ample evidence indicates that with this type of stimuli global processing typically preempts local processing (Navon, 2003).

In our version of the hierarchical letters task the "global" letters were 5.3° wide and 7.50° tall and the "local" letters were 1.15° tall and 1.35° wide. A global C was composed of 11 local letters and a global D of 14 local letters (Figure 4A). In the congruent conditions, the global and local letters were the same, and in the incongruent condition, the global C was composed of local Ds and the global D of local Cs. Following initial familiarization with the stimuli, K.W. was presented with two blocks of 128 trials each, equally divided between global Cs and global Ds and between congruent and incongruent conditions presented in random order. Each stimulus was presented for 100 msec. In the first block, K.W. was instructed to ignore the global letters
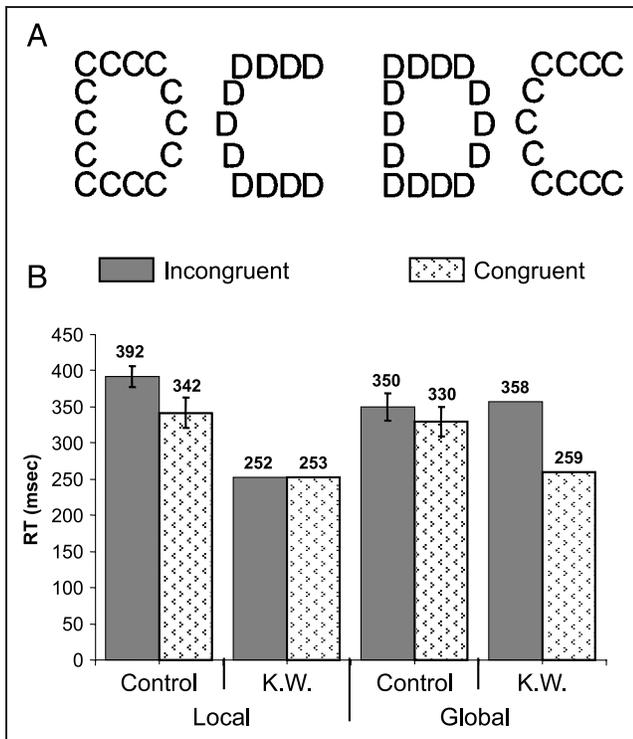
Figure 4. (A) The congruent and incongruent hierarchical letters used in the local/global letter identification task. (B) RTs of K.W. compared with the mean of the control group (*n* = 12) in the different congruency conditions when attending to local or global letters. Error bars denote 95% confidence limits. Note the absence of global interference on the identification of local letters by K.W. relative to controls, and the higher local interference on the identification of global letters.

and press a key if the local letters were Cs and another if they were Ds. In the second block, she was instructed to ignore the local letters and press the same keys for C and D, but now to report the global letter.

As shown in Figure 4B, K.W.'s responses to local letters was faster than to global letters, and they were not influenced by global incongruence. By contrast, responses to global letters were considerably slowed when the local letters were incongruent with the correct global response. For the control group of undergraduate students, the normal pattern was opposite and consistent with the literature: Responses to local letters were slower than to global letters and slowed even more by global incongruence. Compared with this group, K.W. was faster then controls in the local task (*z* scores = −1.89 and −1.69 for the incongruent and congruent conditions, respectively) and similar to the control group in the globally directed condition; indeed, she tended to be faster in the congruent condition (*z* score = 0.12 and −1.06 for the incongruent and the congruent conditions, respectively). Her accuracy for congruent stimuli was very high, 96.8% in the globally directed task and 93.7% in the locally directed task. More importantly, as shown in Table 1, whereas global information had no effect on

her identification of local letters, the local-to-global interference was considerably larger in K.W. (98 msec) than the upper 95% confidence limit in the normal population's mean (32.5 msec). Using the control sample distribution, the *z* score of the global-to-local interference for K.W. was −1.8 and the *z* score for the local-to-global interference was 4.2. Similarly, whereas in the control group identification accuracy in the incongruent conditions was better for global (93.9%) than for local letters (85.3%), K.W. identified local letters more accurately (90.6%) than global (81.25%). This pattern suggests that local processing for K.W. is compulsory perceptual strategy and opposite that of normal priorities in perceptual processing that actually interferes with her ability to process global information.

ERP Evidence for Sensitivity to Face Details

Support for K.W.'s particular sensitivity to face details (as opposed to second-order configuration) was provided by electrophysiological recording focused on a negative face-sensitive ERP component (N170). There is ample evidence that the N170 recorded over the posterior temporal scalp is not modulated by face familiarity (Bentin & Deouell, 2000) and is significantly larger and delayed in response to face components when the face contour is absent or if the face is inverted (Itier & Taylor,

Table 1. Distribution of Global-to-local and Local-to-global Interference (in Milliseconds) and Percentage of Correct Classification of Incongruent Stimuli in the Local and the Global Task for the Control Group and K.W.

Case No.	Local Task		Global Task	
	Global Effect	*% Correct*	*Local Effect*	*% Correct*
SS 1	124.5	43.8	11.8	95.3
SS 2	46.4	90.6	8.8	84.4
SS 3	23.3	98.4	40.2	96.9
SS 4	39.7	93.8	63.6	96.9
SS 5	65.7	93.8	11.7	98.4
SS 6	60	95.3	32.1	89.1
SS 7	28	70.3	−10.1	85.9
SS 8	21	84.4	22.2	90.6
SS 9	24.2	96.9	22.5	98.4
SS 10	53.6	65.6	11.8	92.2
SS 11	66.5	96.9	9	100.0
SS 12	54.2	93.8	24	98.4
Mean	50.59	85.29	20.63	93.88
SD	28.63	16.8	18.67	5.3
K.W.	−1	90.6	99	81.2

2004; Rossion et al., 2000; Bentin et al., 1996). Based on these results Bentin and his associates suggested that the N170 is associated with a perceptual mechanism activated by the detection of physiognomic features, global or local, alike (Sagiv & Bentin, 2001). More importantly, for the present purposes, a recent study in our laboratory demonstrated that the N170 is particularly sensitive to local processing in the eyes region (Bentin, Golland, Flaveris, Robertson, & Moscovitch, 2006). Consequently, we expected the N170 in K.W. to show normal sensitivity to face components (local processing) but not necessarily to full faces (global processing).

During EEG recording, different types of stimuli with and without physiognomic value were presented one at a time at the center of a CRT computer screen. K.W. was requested to monitor the screen and press a button each time the presented stimulus was a flower. The physiognomic stimuli were regularly configured faces, faces with a random configuration of inner components (scrambled faces), regularly configured inner components without the face contour, and random configuration of inner components without the face contour (scrambled inner components); the nonphysiognomic stimuli were watches and watches with scrambled interiors. Seventy-five different stimuli were included in each category. Examples of these stimuli are presented in Figure 5A. Each stimulus was presented for 350 msec with an interstimulus interval that ranged between 850
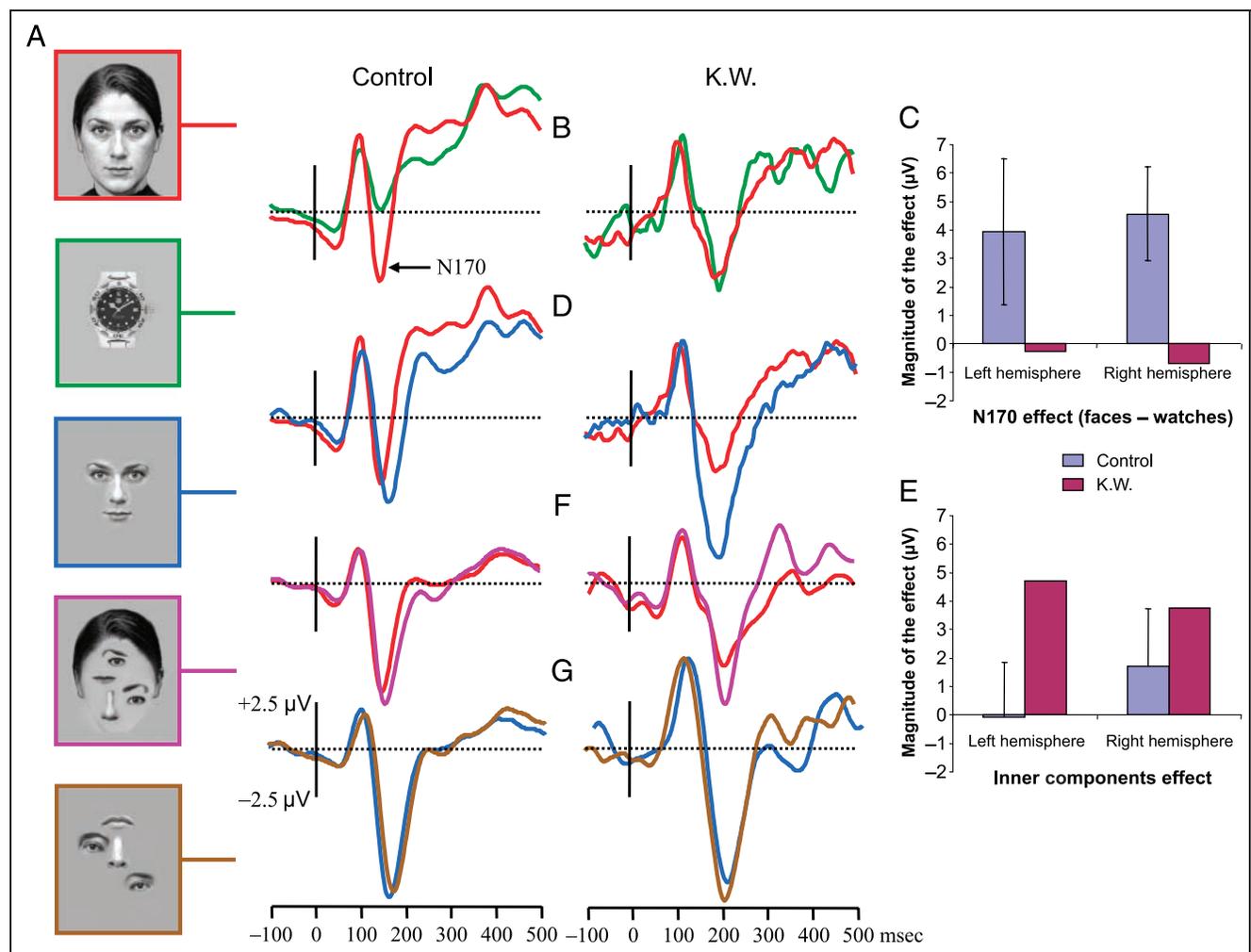
Figure 5. (A) Example of the stimuli used in the ERP experiment. (B) ERPs elicited by faces (red line) and watches (green line) in the control group (*n* = 24) and in K.W. The significant difference between the N170 elicited by faces and watches in the control group is totally absent in K.W. (C) The difference between faces and watches in K.W. is below the lower 95% confidence limit of the control group's mean. (D) N170 elicited by regularly configured faces (red line) and faces with scrambled inner components. Note that the absence of normal configuration has very little influence in the control group, whereas eliciting a more robust N170 in K.W. (E) N170 elicited by faces (red line) and isolated face components (blue line). The normally larger N170 in response to face components than to faces is considerably enhanced in K.W. (F) The difference between inner components and faces in K.W. is above the upper 95% confidence limit of the control group's mean. (G) The configuration of inner components has no influence on the N170 either in control participants or in K.W. The presented ERPs were recorded at posterior right temporal sites. (Data concerning scrambled faces and scrambled inner components was collected in a different group of 16 participants and a different recording session with K.W.)

and 1250 msec. ERPs were measured averaging stimulus onset-time-locked epochs of EEG after removing trials with eye movements, blinks, and amplifier-blocking artifacts (less than 5%).

As revealed in Figure 5B, in contrast to the normal pattern, K.W.'s N170 did not distinguish between faces and objects and was slightly delayed relative to control participants. It is intriguing that the absence of face object discrimination reflects an enlargement (relative to controls) of the N170 elicited by watches, which suggests that K.W. processes watches like faces (rather than the other way around). This result is consistent with previous findings in ERP studies of people suffering from CP (Kress & Daum, 2003b; Bentin et al., 1999). As shown in Figure 5C, the difference in the amplitudes of the N170 elicited by faces and watches (the "N170 effect") in K.W. was smaller then the lower 99% confidence limits of a control group's mean, based on 24 participants (relative to the sample distribution, K.W.'s N170 effect z score was -1.1 for the left hemisphere and -1.98 for the right hemisphere). Most interestingly, the N170 elicited by face components was much larger than that elicited by faces and was not delayed (Figure 5D). Compared with control participants, the difference between the amplitude of the N170 elicited by face components and that elicited by full faces in K.W. exceeded the upper 95% confidence limit of the control group's mean (Figure 5E). (Relative to the control sample's distributions the z scores for K.W.'s difference between inner components and regular faces were 2.1 for the left hemisphere and 1.46 for the right hemisphere.) Moreover, similar to control participants, scrambling the spatial configuration of the inner components either within a face contour or without the face contour had very little effect on the N170 elicited by faces (Figure 5F) and inner components (Figure 5G), respectively. This pattern supports the hypothesis that the perceptual mechanism manifested by the N170, although sensitive to face components, is not affected by face configurations. Hence, the finding that the N170 was considerably larger for K.W. when the face configuration was absent suggests that configural aspects of the face might, indeed, have interfered with her processing the face details. This pattern is consistent with the enhanced perceptual sensitivity of K.W. to local elements in general (which might have enhanced the N170 to watches) and local face components in particular.

DISCUSSION

The present study presents a rare combination of fMRI, ERP, and behavioral performance studies of an intriguing neuropsychological disorder—congenital prosopagnosia. Unlike many other cases of CP published in the literature, K.W. presented with a nearly complete inability to identify faces, but she was also apperceptive for faces as demonstrated by her severe impairment in matching unfamiliar faces. In addition, she was overwhelmed by details and insensitive to global aspects of the stimulus. Attempts to localize face-induced activation in the fusiform gyri failed. Indeed, to our knowledge, K.W. is one of the very few cases in which faces did not elicit preferential activity in any occipitotemporal region compared with any other stimulus types.[3] Moreover, ERP studies demonstrated severe impairments in early visual processing. It is important to note that faces elicited an N170 component that was as robust as in control participants, but it was delayed and, most importantly, not selective for faces; objects elicited a negative component as large as faces and with a similar scalp distribution. Because the N170 is among the earliest face-sensitive neural responses in the ERP, absence of selectivity at this perceptual level suggests that for K.W. physiognomic information is not distinctively categorized or the configuration of the face is deficiently encoded.

Configural Deficits

Absence of early selectivity for faces cannot be attributed to an early-vision impairment that obstructs registration of physiognomic features. As reflected in her covert ability to use face identity in matching expressions as well as the conspicuous difference between the N170 elicited by face parts (regardless of their configuration) and full face gestalts, K.W. was sensitive to face features. Evidence for implicit processing of face identity on performance might suggest that like patients with acquired prosopagnosia, K.W. was able to configure the face identity, but not to bring this configuration into her awareness (Barton, Cherkasovam, et al., 2004; Bobes et al., 2003; Viggiano, 1996; Renault et al., 1989; De Haan et al., 1987; see also Van Honk & De Haan, 2001).[4] Indeed, implicit global processing ability has also been found in patients with Balint's syndrome and patients with dorsal simultagnosia (Jackson, Swainson, Mort, Masud, & Jackson, 2004; Karnath, Ferber, Rorden, & Driver, 2000). However, it is also possible that K.W.'s ability to integrate the features and adequately build a face configuration might be impaired. Although in normal perception face identity as well as face expressions involve integration of features, both face expression and identity matching could also be achieved by relying on feature matching strategies, for example, using the hairline and eyebrows (Duchaine & Weidenfeld, 2003). This hypothesis echoes a similar claim made by de Gelder and Rouw (2000) after finding no face inversion effect in a CP case. It is conceivable that K.W.'s disability to compute second-order face configurations is associated with a more general impairment in global processing induced by an inability to shift processing resources from the local level to the global level as demonstrated

by her abnormal performance with hierarchical letters. Normally, global letters interfere with processing local letters when the global and local letters are incongruent but not vice versa (i.e., there is global precedence; Navon, 1977). More importantly, K.W. showed the opposite pattern. The identification of local letters was not affected by incongruent global letters, whereas incongruent local letters significantly delayed the identification of global letters. In addition, unlike controls, K.W. was faster to respond to local than global letters. Difficulties with processing global information using hierarchical letters as stimuli were also reported in a group of five patients with CP (Behrmann et al., 2005) as well as in another patient studied in our laboratory (DeGutis, Bentin, D'Esposito, & Robertson, 2004). Although K.W.'s abnormal preference for local information was considerably more conspicuous than in all other CP cases reported to date, the similar performance patterns suggest that a general global processing deficit may well be part of the syndrome. As stated above, this deficit could reflect difficulty in switching processing resources from local to global levels. In fact, this difficulty was expressed explicitly by K.W., who claims that she is "bothered by too many details," as well as by her normal performance in the Hooper test (in which she was able to identity broken objects). Note that a major difference between the demand characteristics of the Hooper test and the Navon hierarchical letter classification is that in the former there are only up to three details and that these details are meaningless parts of the object. In other words, there was no reason for K.W. to be "hooked" on processing the parts (cf. Bentin et al., 2006). This processing deficit appears to be primarily expressed (but perhaps not exclusively) in a failure to identify faces. It is possible that the imposing role of face components during visual processing impedes K.W.'s ability to compute the spatial relations between the components to create an adequate spatial representation that would be necessary for explicit identification. This problem is not particularly surprising because, except for special cases of visual expertise (cf. Tarr & Gauthier, 2000), only the processing of faces (identification at the single exemplar level) is based on second-order configural computations.

Integrative Congenital Prosopagnosia

K.W.'s impediment to efficiently integrate face features is reminiscent of cases of integrative visual agnosia following brain lesions (e.g., Humphreys, 1999). Indeed, one of the most salient deficiencies demonstrated by the well-known case, H.J.A., is processing the spatial relations between the local parts of objects (Riddoch, Humphreys, Blott, Hardy, & Smith, 2003). Although in the absolute majority of published cases, integrative visual agnosia was acquired following brain damage, there is one conspicuous case (L.G.) in which this detriment appears to be congenital (Ariel & Sadeh, 1996). Not surprisingly, one of the most common symptoms in all patients with integrative visual agnosia, including L.G., is dense prosopagnosia. However, all of these patients had severe problems identifying objects as well as faces. In contrast, object recognition was not obviously impaired in K.W., either at the basic or at the subordinate[5] level (cf. Behrmann et al., 2005). Furthermore, it is possible that the characteristic problems in patients with integrative associative agnosia are different from those with integrative prosopagnosia. Whereas integrative visual agnosics are able to perceive wholes and parts but unable to integrate the parts into wholes, at least in K.W. the absence of integration seems to be based on an inability to switch from local to global information. She is overwhelmed by parts. We suggest that K.W.'s face identification deficits could be safely labeled as *integrative congenital prosopagnosia* and mirror a previously described case with "configural apperceptive prosopagnosia" following right-hemisphere occipitotemporal lesions (Bliem & Danek, 1999).

Associative and Apperceptive Prosopagnosia

Configural processing deficits are not the only impediments that might obstruct normal face identification in otherwise normal individuals. In fact, it is not even a necessary condition for CP to occur. Although in the absence of standard testing procedures, comparing global/configural processing of CP cases across studies requires caution, it is notable that none of eight recently tested cases of CP had global perception problems as measured by global motion (Le Grand et al., 2003). Another individual with CP (B.C.) performed normally in tasks requiring the reconstruction of visual configurations (Duchaine, 2000). Also Y.T., the first published congenital prosopagnosic with a nondiscriminative N170 (Bentin et al., 1999), had no difficulty processing global information (as tested both by performance with hierarchical stimuli and with brain imaging (Hasson et al., 2003). These data indicate that normal configural processing, although necessary, is not sufficient for face identification. Indeed, prosopagnosia can have sources at different levels of processing and, like general visual agnosia, could either manifest as an apperception for faces with a special deficit in integrative aspects or as associative problems reflecting a disconnection between a configured face and its identity.

N170 and FFA as Markers of Face Processing

Like all other congenital prosopagnosics in which ERPs were reported (Sagiv, Barnes, & Robertson, 2000; Bentin, at al., 1999), K.W. showed no N170 difference between face and nonface stimuli. In addition, she showed no

fMRI evidence of any activity specialized for faces. In contrast, in a previous CP in which both fMRI and N170 data were reported, normal FFA activation was found despite the absence of the N170 effect (Hasson et al., 2003; Bentin et al., 1999). Together, these findings suggest that the perceptual mechanisms manifested by the N170 and those manifested by the FFA are dissociated. They also support the view that the N170 is not directly associated with second-order configural computations needed for face identification, but rather triggered by the categorization of a stimulus as a face and probably reflecting the additional processing of the face features as part of the identification process. In terms of the FFA, the correlation between the ability to compute the spatial organization of face inner components and face selectivity of the FFA might suggest that this area is a crucial node in the neural network performing configural computations during structural encoding of faces (cf. Rossion & Gauthier, 2002). This hypothesis is supported by a double dissociation between consistent deficits in perception of spatial relations by patients with lesions involving the FFA (Barton, Cherkasovam, et al., 2004) and a recent report of an acquired visual agnosic and prosopagnosic person (D.F.), who demonstrates face selectivity in the FFA and can use configural information for categorizing faces (Steeves et al., 2006).

The hypothesized association between the FFA and configural processing is, however, challenged by two lines of evidence. The strongest argument against it comes from a recent report by Avidan et al. (2005) showing FFA activation within the normal range in the same five CP cases with global perception deficits reported by Behrmann et al. (2005). These data show that congenital prosopagnosics may exhibit impairments in deriving global configurations from the visual input even with a normally face selective FFA. However, neither that study nor any other study that we know found normal configural processing with fusiform gyri lesions or in the absence of face selectivity in the fusiform (FFA). Furthermore, close inspection of the data of Avidan et al. reveals that normal face selectivity was limited in prosopagnosic individuals to the right FFA. Left FFA selectivity was not present in the CP group, whereas both right and left FFA activity was robust in the control group. Although unilateral (usually right hemisphere) face-selective activation is seen occasionally in people without prosopagnosia, bilateral FFA is a more frequent finding. Hence, although the Avidan et al. study casts doubt on complete dependence of configural processing of faces and the FFA, the currently available data are insufficient to exclude the possibility that face-specific activation in the fusiform gyri is associated with the computation of configural aspects of faces during structural encoding.

The second line of evidence against attributing configural processing to the FFA comes from studies exploring the modulation of face-specific activity in the fusiform gyri during face matching. A recent study showed similar FFA activity comparing conditions in which the difference among matched faces was based on configural compared to local cues (Yovel & Kanwisher, 2004). However, the target stimulus in this study was always the same face (repeated in different conditions). It is likely that after a few repetitions the participants established reliable (perceptual) representations of the different forms in which this face appeared that reduced the need to identify the face for the task. Considering on the one hand the clinical correlations between dysfunctional FFA and deficits in configural processing and, on the other hand, arguments against such correlations emerging from the two lines of counterevidence cited above, FFA functionality seems to affect configural processing of faces, but its necessity and sufficiency are still debatable.

Conclusion

In the present report of a severe case of CP, neuropsychological findings showed excessive perceptual reliance on features, ERP results suggested abnormal sensitivity to physiognomic parts, configural processing was abnormal in behavioral performance, and selectivity for faces in fMRI maps was absent in both hemispheres. Although the present data demonstrate that deficient global processing is not limited to face perception, it manifests in K.W.'s difficulty to identify faces but not other objects. Under normal circumstances, only the former process is heavily based on the spatial relations between the inner components. K.W. seems to represent a class of CP with apperceptive problems, which could be safely labeled congenital integrative prosopagnosia.

Notes

1. It should also be mentioned that, at least as reflected in the computed tomographic scan of this patient, although covering the middle fusiform, the lesion was anterior to the posterior occipital–temporal sulcus, where the N170 is presumably generated.
2. This condition was labeled by these authors as *developmental prosopagnosia*.
3. Indeed, she is the first case in our laboratory to show absolutely no face preference anywhere in the fusiform gyrus or posterior temporal lobes.
4. According to this interpretation the absence of a congruency effect in the name categorization task would be explained

only by the fact that K.W. has never learned the faces of the famous people, the names of whom she new.

5.   K.W. was able to pick up her own bag among others or her own pen among several mixed on the table. However, subordinate object identification was not formally tested.

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