

Impaired configurational processing in a case of progressive prosopagnosia associated with predominant right temporal lobe atrophy

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Summary

F.G., a 71-year-old right-handed man, presented with a slowly progressive deterioration in his ability to recognize faces of familiar and famous persons, contrasting with the relative preservation of other cognitive domains. His primary face perception skills were intact. Along with his face-recognition deficit, F.G. also exhibited a mild visual agnosia. A more detailed analysis of his performance on visuo-perceptual tests revealed a selective deficit in retrieving the configurational representation of complex visual entities and an over-reliance

on analysing individual features. Quantitative volumetric measurements of his temporal lobe structures showed a prevalent atrophy of the right fusiform gyrus and parahippocampal cortex. The results of the present study suggest that a right temporal variant of fronto-temporal lobar degeneration may be characterized over a period of several years by an impaired configurational processing of visually complex entities in the absence of any semantic deficit.

Keywords: progressive prosopagnosia; configurational face processing; fusiform gyrus; visual agnosia; right temporal lobe atrophy

Abbreviations: FRU = face recognition unit; IQ = intelligence quotient; MQ = memory quotient; MMSE = Mini-Mental State Examination; PPTT = Pyramids and Palm Trees Test; ROI = region of interest; WAIS-R = Wechsler Adult Intelligence Scale-R; WMS = Wechsler Memory Scale

Introduction

Progressive focal cortical atrophies, which selectively affect one sphere of mental functioning, represent a model of considerable value to the study of human brain functions and their neural substrates. They are degenerative processes that are characterized, in the early stages, by a rather selective impairment in one cognitive domain. These syndromes may affect language (primary progressive aphasia), speech (progressive dysarthria), semantic memory (semantic dementia), episodic memory (pure progressive amnesia), vision (posterior cortical atrophy) or gesture (progressive apraxia) (Mesulam, 1982; Benson *et al.*, 1988; Snowden *et al.*, 1989; Tyrrell *et al.*, 1991; Hodges *et al.*, 1992; Lucchelli *et al.*, 1994; Black, 1996; Miceli *et al.*, 1996; Didic *et al.*, 1998, 1999).

Prosopagnosia is a neurological deficit characterized by the inability to recognize faces of familiar individuals in the absence of severe intellectual and cognitive impairments (Sergent and Signoret, 1992). It usually results from bilateral occipitotemporal lesions, although several reports have described unilateral right-sided occipitotemporal lesions (Landis *et al.*, 1986). Much attention has focused in recent years on the nature of the processes that subserve face-recognition (Tanaka and Farah, 1993; Farah *et al.*, 1995; Barton *et al.*, 2001) and on their neural basis (Sergent *et al.*, 1992; Kanwisher *et al.*, 1997; Gauthier *et al.*, 1999; Haxby *et al.*, 2001).

Prosopagnosia as the manifestation of a neurodegenerative disorder remains very rare and has only been reported in a few

studies (De Renzi, 1986; Tyrrell *et al.*, 1990; Barbarotto *et al.*, 1995; Gentileschi *et al.*, 1999, 2001; Gainotti *et al.*, 2003). De Renzi (1986) was the first to describe two patients who presented with a progressive face recognition disturbance and visual agnosia. However, their dysfunction also involved more basic visuoperceptual deficits and extended to other domains of mental function. CT scans were reminiscent of a posterior atrophic process. Tyrrell *et al.* (1990) also reported a patient who suffered from progressive prosopagnosia along with visuoperceptual impairments, verbal and visual memory deficits, and naming difficulties. Structural brain imaging data were not available, but PET scanning showed hypometabolism in the superior temporal gyrus bilaterally with right hemisphere predominance. Evans *et al.* (1995) reported a patient, V.H., who was tested longitudinally over a 9-month period and presented with a slowly progressive face recognition deficit in the absence of other cognitive impairments. Patient V.H.'s face recognition deficit was initially interpreted as a visual, modality-selective, inability to access person-based semantic knowledge (her visuoperceptual, visuospatial and primary face perception skills were preserved), but her deficit eventually progressed 9 months later into a multi-modal loss of person-based semantic knowledge. MRI scans revealed predominant right hemisphere temporal lobe atrophy. The authors suggested that this highly atypical form of degenerative process may in fact reflect a right hemisphere form of semantic dementia. Semantic dementia, which affects characteristically the antero-temporal region involving predominantly the left hemisphere, is characterized by a progressive and insidious breakdown in semantic knowledge. Similar reports to V.H. of patients presenting with a cross-modal progressive defect in the recognition of familiar faces and/or persons have been described in recent years. For instance, patients M.F. (Barbarotto *et al.*, 1995), Maria (Gentileschi *et al.*, 1999) and Emma (Gentileschi *et al.*, 2001) also presented with a cross-modal person-recognition deficit. In all these patients, this cross-modal impairment was associated with a prevalent focal atrophy of the anterior parts of the right temporal lobe, thus suggesting a prominent role for this region in person-based semantic knowledge. More recently, Gainotti *et al.* (2003) reported the case of patient C.O., who showed a selective slowly progressive deficit in the recognition of familiar people. Although this patient performed well on perceptual tests, he was unable to access person-specific knowledge—not only through their face but also through their voice. In contrast, C.O. was able to access significantly more information through the name or through the verbal definition of a famous person. The locus of atrophy in C.O. also involved predominantly the right anterior temporal region. One of the hypotheses proposed by the authors was that this specific region might play a crucial role as a multimodal turntable in the integration of converging information from unimodal person-based recognition subsystems (i.e. face and voice recognition subsystems).

We report here the case study of a patient who presented with a progressive impairment in recognizing faces of

familiar persons, including family members and friends, in the absence of other language, visuoperceptual, visuospatial, praxic and executive functioning deficits. The patient underwent two detailed neuropsychological evaluations over a 1-year period in order to carry out an in-depth examination of the nature and evolution of his deficit. The purpose of this paper is: (i) to characterize the nature of his prosopagnosia (i.e. whether it resulted from a semantic breakdown or from a visuoperceptual impairment); (ii) to investigate the brain regions that were most affected by this degenerative condition using volumetric MRI; and (iii) to discuss the putative nature of the underlying pathological process.

Case description

F.G. is a 71-year-old right-handed man and retired bank employee who presented at the Service de Neurologie et de Neuropsychologie at the Timone Hospital with complaints of increasing difficulty in recognizing familiar people, including friends and family members. He recalls that he was once approached in the street by a woman who began a conversation. At first, he was totally unable to recognize her and it was only after identifying her voice that he realized it was a woman with whom he had lived for several years and had had a child. This event went back 5 years and, since then, his problems have gradually increased. According to his family members, including his nephew who lives next door to him, his face recognition impairment had never been present before, and had been gradually and slowly worsening over the past 5 years. F.G. lives in a small town in Southern France and has an important number of acquaintances and friends there. He meets people he cannot recognize on a daily basis—a situation which he finds difficult. Even though he remembered very well the senior neurologist and the experimenter with whom he underwent neuropsychological testing over a period of several weeks (he could immediately recall their names), he was unable to recognize their faces each time he saw them. It was not until hearing their voices that he realized whom they were. He had no prior history of neurological insult. F.G. is completely independent in everyday life, lives alone, and has no problem finding his way in his environment. He is a well-spoken and cheerful man, is strongly aware of his deficit and is very insightful into developing strategies that can help him cope with his problems. F.G.'s ophthalmological assessment showed normal visual acuity and pupillary responses, and he performed normally on computer-based tests of motion and colour detection developed by the Service de Neurologie et de Neuropsychologie. F.G. gave informed consent before testing.

General neuropsychological assessment

F.G. underwent six neuropsychological evaluations over a 1-month period. F.G. was then tested again 1 year after his first evaluation in order to examine the evolution of his impairment. The results are summarized in Table 1. The results of

Table 1 Summary of F.G.'s neuropsychological profile

	First evaluation	Second evaluation (one year later)
General		
MMSE (30)	28	27
WAIS-R		
Verbal IQ	127 (96th percentile)	
Performance IQ	122 (93rd percentile)	
Full-scale IQ	128 (97th percentile)	
Visual perception		
Visual Object and Space Perception Battery		
Incomplete letters (20)	20	20
Silhouettes (30)	9*	8*
Object decision (20)	9*	9*
Progressive silhouettes (20)	15*	16*
Dot counting (10)	10	10
Position discrimination (20)	20	19
Number location (10)	10	10
Cube analysis (10)	9	10
Visual agnosia battery (PEGV)		
Entangled figures (12)	12	12
Figure decision (12)	12	12
Rey–Osterreich Figure (copy) (36)	24*	
Benton line orientation (30)	30	30
Executive functioning		
Wisconsin Card Sorting Test	6/6 categories	6/6 categories
Stroop Test	score = 32; impaired >37	
Trail Making Test		
Part A	48 s (mean 80 s)	50 s
Part B	108 s (mean 196 s)	82 s
Praxias		
Test of praxias (30)	30	30
Language		
Naming (DO80) (80)	73	66*
Oral comprehension (HDAE) (12)	12	12
Reading		
Regular and irregular words (121)	119	
Non-words (60)	60	
Written comprehension (121)	117	
Semantics (PPTT)		
Visual (52)	40*	37*
Verbal (52)	52	52
Memory		
WMS-R	MQ	
Verbal memory	92	
Visual memory	84	
Global memory	90	
Attention/concentration	123	
Delayed recall	75	
WMS-R subtest scores		
Logical memory I	7*	
Logical memory II	5*	
Forward span	7 numbers	
Backward span	5 numbers	
Kopelman Autobiographical Interview		
Childhood	Autobiographical memory	Personal semantics
Early adulthood	95.2	100
Recent life	88.1	100
	85.7*	100

*Indicates impaired scores. WMS-R = WMS-Revised. Numbers in brackets in the first column refer to maximum scores.

the standard neuropsychological evaluations indicate that F.G. has a full-scale IQ superior to average (global IQ = 128, 97th percentile) (Wechsler, 1989). He scored 28 in the Mini-Mental State Examination (MMSE) during the first evaluation (Folstein *et al.*, 1975). His language, praxic, executive functioning and visuoperceptual skills were all normal. In contrast to his IQ, however, his memory skills were mildly abnormal (verbal MQ = 92, visual MQ = 84) (WMS-R Wechsler, 1991). It appeared that his memory deficit resulted primarily from difficulties to retain newly acquired visual and verbal information. His memory impairment, however, was not apparent in a non-clinical setting. Although patient F.G.'s visuoperceptual skills were intact as a whole, he was impaired in three of the subtests of the Visual Object and Space Perception Battery (Warrington and James, 1985), i.e. the silhouettes, object decision and progressive silhouettes subtests. As well as undergoing a standard neuropsychological evaluation, F.G. also underwent detailed testing of various aspects of face processing.

Processing of familiar and unfamiliar faces

Unfamiliar face matching, perception and facial expression analysis

Face matching. We used the Facial Recognition Test developed by Benton *et al.* (1983) to measure F.G.'s ability to match unknown faces. In the first part of this test (part A), the subject is presented with a photograph of a face lit so as to reveal the central region of the face. The patient is required to match this face with an identical face among five other similar faces. In the second part of the test (part B), the patient is required to match the photograph of a face with three photographs of the same face viewed under different perspectives and lighting conditions, presented along with three other different faces.

Age and gender perception. The patient was presented with 40 pictures of full faces and was instructed to determine whether each face was 'old' (>50 years) or 'young' (<30 years). In the second task, the patient was presented with the same full face photographs and was asked to determine whether each face was male or female.

Facial expression analysis. In this task, F.G. was presented with a series of photographs taken from the Ekman and Friesen series (Ekman and Friesen, 1975). Each photograph displayed one of six possible emotional expressions (fear, anger, disgust, sadness, happiness and surprise). Some of the photographs—considered to be neutral—displayed no emotion at all. The names of the six emotions and the neutral condition were printed on separate pieces of paper, which were presented below the photograph. F.G. was instructed to match the printed emotion that best suited the facial emotion expressed on the photograph. F.G. successively viewed 110

photographs of faces that randomly depicted the seven emotions (including neutrality) described above.

Learning new faces. F.G.'s ability to recognize newly learned faces was measured using the Wechsler Memory Scale-III (WMS-III) facial recognition subtest (Wechsler, 2001). In the first part of this test, F.G. was asked to remember 24 new faces which were presented to him one by one. The patient then had to successively view 48 faces, of which 24 had been previously memorized and 24 were new. The 48 faces were presented in random order. For each face, F.G. had to determine if it was familiar or unfamiliar. This task was performed under both immediate and delayed recall conditions.

Results

The results of F.G.'s processing of unfamiliar and familiar faces are presented in Table 2. Overall, his ability to perceive age, sex and emotions was intact. His performance on the Benton Facial Recognition Test (Benton *et al.*, 1983) was in the low average range. Although his global performance was within the normal range (lower bound), it is interesting to note that he performed perfectly in part A (6/6) but not in part B (13/21): he was better at matching identical faces than at matching different perspectives of the same faces, and the second part of the test took him much longer to complete (reaction times were not measured). F.G. emphasized that he had to rely on the details of a face in order to succeed at this task.

F.G.'s performance on the Wechsler memory facial recognition subtest (Wechsler, 2001) also indicates that he was unable to recognize newly learned faces among a series of unknown faces. He scored 24/48 (chance level) for both immediate and delayed recall conditions (scaled score = 4, mean = 10, SD = 3).

Famous face recognition, naming and identification

Yes/no familiarity task. F.G. was shown 40 faces of famous personalities from the 1950s–1990s and 88 faces of persons he had never seen before. Photographs were randomly mixed and presented successively. F.G. was asked to determine whether each face was familiar or not.

Naming and identification of famous persons from photographs. F.G. was asked to name 40 faces of famous people including actors, singers and politicians from each of the decades 1950s–1990s. Relying upon these photographs, F.G. was then instructed to provide as much information as possible about each famous person. A famous person was considered to be identified correctly if at least two semantic attributes were accurately provided without any errors (e.g.

Table 2 F.G.'s processing of unfamiliar and familiar faces

	Evaluation 1	Evaluation 2	Controls
Unfamiliar faces			
Benton Facial Recognition Test	43	43	Normal range = 41–54
Part A	6/6	6/6	
Part B	13/21	13/21	
Age and gender perception	40/40	40/40	Mean score = 40/40
Facial Expression Analysis (Ekman and Friedman, 1975)	79%	NA	Mean score = 80%
WMS-III: facial recognition subtest (learning)			
Immediate recall	24/48*	26/48*	Mean score = 35/48
Delayed recall	24/48*	29/48	Mean score = 33/48
Famous faces			
Test of famous faces			
Familiar/unfamiliar	92/128*	NA	Mean score = 125/128
Naming	4/40*	3/40*	Mean score = 36/40
Identification	7/40*	3/40*	Mean score = 38/40
Identification from name	38/40	38/40	Mean score = 37.5/40

*Indicates impaired scores. NA = not available

John F. Kennedy was an American president who was assassinated).

Identification of famous persons from name. In order to determine whether F.G. had preserved semantic knowledge about the famous persons shown in the 40 photographs, we gave him the names of each celebrity during another evaluation and asked him to provide as much information as he could about them. Once again, a famous person was considered to be identified correctly if at least two semantic attributes were provided without any errors.

Results

F.G.'s ability to distinguish faces of celebrities from unknown faces was somewhat poor (he scored 92 correct responses; mean = 124.9; SD = 1.97; $P = 0.06$) (see Table 2). When compared with control subjects, F.G.'s ability to name famous persons from faces (4/40) was severely impaired (mean = 36/40; SD = 2.5; $P < 0.01$). F.G. was also significantly impaired at identifying these same celebrities from their face (6/40) when compared with control subjects (mean = 38/40; SD = 1.5; $P < 0.01$). He could only name and identify from their photographs the few celebrities who had very distinctive and unique facial features (e.g. Jacques Chirac). In stark contrast, when F.G. was asked to provide as much information as possible about the same celebrities during another evaluation upon verbal presentation of their names, he was able to provide precise information about 38 out of 40 of them (mean = 37.4/40; SD = 1.4; $P = 0.47$; mean age = 70.6 years), which implies that his semantic knowledge about these individuals is perfectly well preserved.

Facial configurational processing

The neuropsychological results indicate that F.G.'s primary visuo-perceptual and face processing skills are preserved. He

was normal at age, gender and facial expression analysis of unknown faces. He was also able to match identical faces on the Facial Recognition Test developed by Benton *et al.* (1983), although he performed worst when faces to be matched were presented under different perspectives. In contrast, he was unable to recognize faces of famous persons, although his knowledge about these same persons was intact when their names were spelled out. His person-based semantic knowledge of these persons was thus preserved. The present data lead us to suggest that F.G.'s severe impairment in identifying familiar faces may result from a selective inability to process the various details of a face into a global representation. In order to verify this hypothesis, we carried out a recent experiment devised by Barton *et al.* (2002), designed to test the holistic ability of prosopagnosic patients to discriminate faces in which the spatial configuration of features had been adjusted.

Apparatus and stimuli. The present test was devised to test holistic encoding of facial structures in prosopagnosic patients. In keeping with the study by Barton *et al.* (2002), face stimuli in the present experiment differed quantitatively along three possible dimensions: the vertical mouth position, interocular distance and eye colour. The first two involve second-order spatial relations, while the latter refers to a feature change that does not alter spatial relations. First-order relations refer to the categorical feature arrangement universal to all faces such as the eyes above the nose, nose above the mouth, etc., while second-order relations refer to the spatial arrangement of these features or the quantitative variations of feature position within these constraints, such as the distance between the mouth and the nose or between the eyes (Rhodes, 1988).

Our method and procedure was almost identical to that of Barton *et al.* (2002). We used full colour digitalized pictures (250 × 250 pixels) of one male and one female. For each

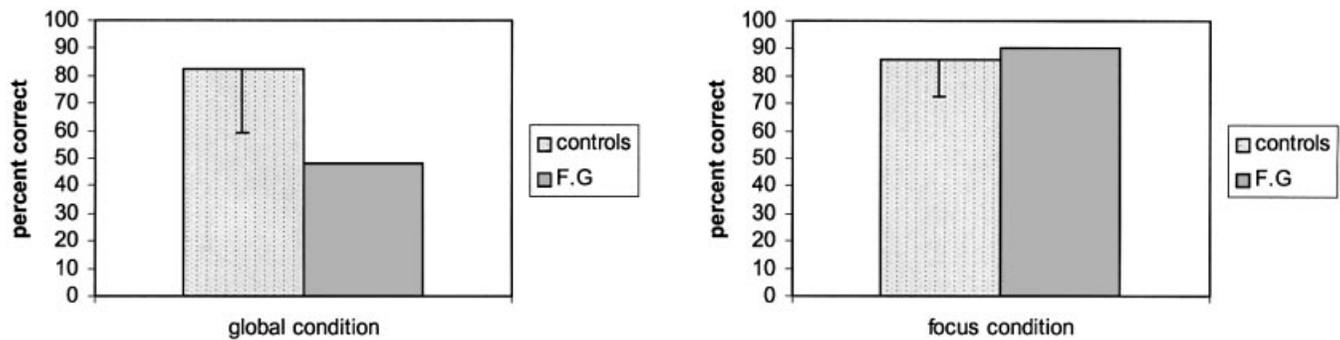


Fig. 1 Percentage of correct responses in the global processing and local processing conditions for discriminating second-order changes (changes in eyes and mouth position). The error bars represent mean SDs for controls.

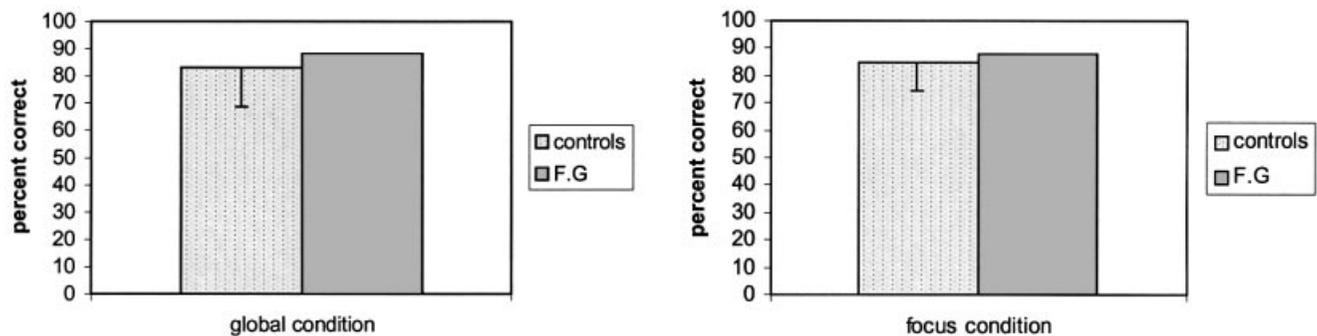


Fig. 2 Percentage of correct responses in the global processing and local processing conditions for discriminating first-order changes (changes in eye brightness). The error bars represent mean SDs for controls.

face, interocular distance was reduced by 2, 4, 6, 8, 10, 12, 14 or 16 pixels. To create faces with mouth displacement, distance between the mouth and the nose was reduced by 2, 4, 6, 8 or 10 pixels. For eye colour, brightness was increased by 40, 50, 60, 70 or 80%. For more details on the method, see the study by Barton *et al.* (2002).

During each trial, three faces were presented simultaneously in a triangular arrangement; two of the faces were the base face and one the target face. The target position was random throughout the experiment. F.G. had to indicate which face was different from the two others, with chance performance being 33% correct. Testing was performed using E-Prime 1.0 (Psychology Software Tools, 2001). One experimental block contained a total of 108 trials. Blocks of trials were presented with unlimited viewing duration and reaction times were collected. The order of blocks was randomized. In one additional block of unlimited viewing duration, the subject was told of the dimension that had been altered and could thus focus on variations in that specific feature rather than on the global configuration of target faces. Testing was also performed on a group of eight age-matched normal control subjects (mean age = 70 years, SD = 8.1), who had also given their consent to participate in the study.

Results

In the global face processing condition, patient F.G. was significantly impaired on discrimination of second-order

relations (eye and mouth position) compared with a group of age-matched control subjects ($P < 0.05$). In contrast, he was not significantly worse than the controls at discriminating feature changes in the same trials ($P = 0.21$). In the local face processing condition, F.G. did not score significantly differently from controls ($P = 0.22$ for second-order changes, and $P = 0.46$ for feature colour changes). Thus, his performance improved substantially when he was told to focus on a feature within the face that had been modified (e.g. distance between the mouth and the nose) rather than on the entire face. These results thus point out to a significant limit in F.G.'s capacity to process multiple aspects of facial geometry simultaneously—a finding similar to several patients reported by Barton *et al.* (2002). Figures 1 and 2 show more details.

The results of the reaction times also indicate that it took significantly longer for F.G. than for the controls to process faces in which second-order relations ($P < 0.01$) as well as feature colour changes ($P < 0.01$) had been altered in the global face processing experiment. As expressed in Fig. 3, F.G.'s reaction times for trials with global processing were considerably longer for discriminating second-order relations. In the local processing condition, F.G.'s performance was not significantly different from that of the controls for the condition in which second-order changes had been carried out ($P = 0.18$). However, his performance in the condition where feature colour changes had been carried out was significantly longer than that of the controls ($P < 0.01$).

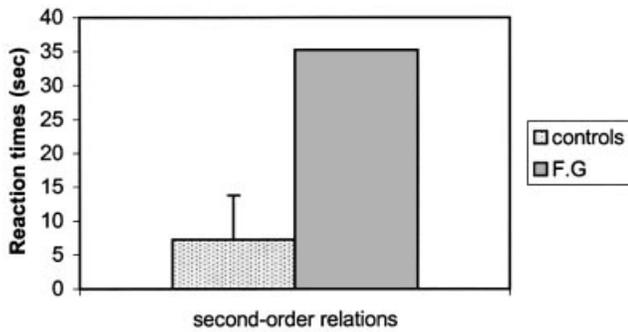


Fig. 3 Reaction times in the global processing condition for discriminating second-order changes (changes in eyes and mouth position). The error bar represents mean SD for controls.

Processing of other visually complex entities

Prosopagnosia often co-occurs with visual agnosia and is often more marked for the identification of natural kinds (e.g. animals and fruits) than that of man-made exemplars (Damasio *et al.*, 1989). This deficit appears to be ‘category-related’ rather than ‘category-specific’: in other words, subjects can fail to recognize some exemplars within certain categories, but can correctly identify other exemplars within the same categories (Damasio *et al.*, 1989). This may be related to the fact that certain visual entities bear a high degree of intra-categorical similarity (e.g. four-legged animals and rounded fruits) and are more likely to be mixed up than exemplars of other categories that are dissimilar (e.g. tools). In order to verify if F.G.’s face-recognition deficit extended to other categories of entities, he underwent a series of tests that aimed at evaluating his capacity to name and identify line drawings depicting different categories of natural and man-made entities (non-face non-unique exemplars), as well as photographs of famous monuments (non-face unique exemplars).

Famous monuments

Naming and identifying famous monuments from photographs. F.G. was asked to name and identify 20 famous monuments (e.g. the Eiffel tower, the Pyramids) upon presentation of their photographs. Photographs were presented one-by-one to F.G. until he provided a response. A famous monument was considered to be identified correctly if at least two correct semantic attributes were provided for each picture.

Identifying famous monuments from name. During another evaluation, F.G. was required to provide, upon verbal presentation, as much semantic information as possible about each of the same 20 famous monuments presented to him above. Again, a famous monument was considered to be identified correctly if at least two semantic attributes were provided for each photograph.

Table 3 F.G.’s picture naming performance (Snodgrass and Vanderwart, 1980)

	1st evaluation	2nd evaluation
Scores <50% correct answers		
Insects	1/8 (12.5%)	2/8 (25%)
Vegetables	1/13 (7.7%)	1/13 (7.7%)
Fruits	4/11 (36.4%)	1/11 (9.1%)
Animals	14/30 (46.7%)	1/30 (3.3%)
Birds	2/9 (22.2%)	2/9 (22.2%)
Musical instruments	3/9 (33.3%)	4/9 (44.4%)
Scores >50% correct answers		
Parts of the body	11/12 (91.7%)	11/12 (91.7%)
Articles of furniture	13/14 (92.9%)	13/14 (92.9%)
Weapons	6/7 (85.7%)	7/7 (100%)
Articles of clothing	17/19 (89.5%)	16/19 (84.2%)
Tools	9/12 (75%)	11/12 (91.7%)
Transportation	8/10 (80%)	8/10 (80%)
Toys	11/18 (61.1%)	15/18 (83.3%)

Results

F.G. was able to name only 4/20 famous monuments (mean = 16.7; SD = 1.1; $P < 0.01$) and identify 6/20 monuments correctly (mean = 17.1; SD = 1.1; $P < 0.01$) upon visual presentation of their photographs. Upon verbal presentation of their names, however, he could correctly identify 17/20 famous monuments (mean = 17.3; SD = 1.27; $P = 0.27$). This was not systematically tested, but F.G. was also impaired at naming and identifying other visually complex entities: he was unable to recognize specific car models as well as pictures of famous places he had visited and famous monuments in his hometown.

Picture naming of line drawings

In the standardized picture-naming test in French, the DO80 (Deloche and Hannequin, 1997), F.G. was only mildly impaired; he scored 73/80 during the first evaluation (lower bound for control subjects = 74/80). During testing, it was apparent that F.G.’s impairment did not reflect word-finding difficulties, but rather a problem in identifying the pictures and drawings of certain entities. F.G. always told the experimenter when he was unable to recognize the shape of a line drawing. In order to carry out a more extensive investigation of his picture identification impairment, we asked him to name and identify a series of 260 line drawings that represented different exemplars from natural and man-made categories (Snodgrass and Vanderwart, 1980).

Results

The results are summarized in Table 3. During the first evaluation, F.G. named 165/260 pictures correctly. When asked to describe the unidentified 95 line drawings upon verbal presentation of their names, he could provide precise structural and functional semantic information about each

single entity that he was unable to perceive in the visual modality. In our view, his verbal definitions were at least as precise as those that could have been produced by a normal person. Thus, his performance clearly indicates that his semantic knowledge concerning the exemplars he could not identify in the visual modality was preserved. F.G.'s impairment at identifying line drawings of natural and man-made objects was clearly category-related; it concerned mostly natural exemplars, with the notable exception of musical instruments. This pattern of co-occurring agnosia is likely to reflect the greater degree of visual resemblance within certain categories of exemplars than the disruption of certain 'modules' dedicated to the processing of specific categories. For instance, the patient showed a striking tendency to focus on salient details within an image rather than on the whole image during testing. The rabbit, squirrel, ostrich and penguin were all mistaken for a kangaroo because each exemplar 'sits on its back feet and jumps'. Interestingly, 1 year after the first evaluation, the patient's ability to identify line drawings of animals had worsened significantly (notably for animals, see Table 3), yet his recognition of man-made exemplars had remained stable.

Semantic memory

The results from the face-processing experiment and from the neuropsychological assessments indicate that F.G. is impaired at processing the geometry of faces. F.G. was also unable to recognize faces of famous persons upon presentation of their pictures even though he showed preserved person-based semantic knowledge upon verbal presentation of their names. The following tests were carried out to determine if F.G. was impaired in various domains of semantic memory.

Visual and verbal semantic matching

Pyramids and Palm Trees Test (PPTT) of semantic matching. (See Howard and Patterson, 1992). In the PPTT, the subject is instructed to match an image with a semantically related image beneath it that is presented along with another foil image. For example, when shown the drawing of a pyramid, the subject has to match it with either a palm tree or a pine tree. In the verbal part of the PPTT, the subject has to match two semantically related printed words among a set of three printed words.

Results

During the first evaluation, F.G. scored 40/52 on the visual part of the PPTT (mean = 98.5%, SD = 5.8% or three errors) and 52/52 on the verbal part of the test (mean = 98.5%, SD = 5.8% or three errors). During the second evaluation, he scored 37/52 in the visual modality and 52/52 in the verbal modality. Once again though, his inability to match

Table 4 F.G.'s score on the Test of famous public events (Thomas-Anterion et al., 1994)

	F.G. (% correct responses)	Controls (% correct responses)
Verbal memory		
Free recall	57.1	59
Multiple choice	88.6	77.1
Questions	34.3	49.7
Dates	63.3	59.7
Visual memory		
Free recall	7.4*	74.3
Multiple choice	59.3*	97.9
Questions	27.8*	74.7
Dates	51.9*	87.5

*Indicates significantly impaired scores.

semantically related pictures resulted from his underlying deficit in their perceptual identification.

Semantic memory of famous public events

Famous events battery. This is a standardized test of general knowledge of public events and figures throughout the decades 1920s–1990s (Thomas-Anterion et al., 1994). It has two parts. In the visual part of the test, the subject is shown a picture of a famous public event, such as the explosion of the atomic bomb, the destruction of the Berlin Wall, etc. First, in a recall condition, the subject is asked to provide as much information about the picture as possible. If the subject is wrong or provides insufficient information, a multiple choice of three possible answers is proposed. Then, the subject is asked two specific questions concerning the famous event. For example, concerning a picture of the first man on the moon, the subject is asked 'What is his name?' and 'What was the name of the space capsule?'. The subject is shown a total of 27 pictures. The verbal part of the test is identical in nature to the visual part, but instead of the subject seeing a picture, a question is asked aloud.

Results

In the verbal identification part of the test (recall), F.G.'s general scores were within the normal range (score = 57.1%; mean = 59%; $n = 182$, age range = 65–75 years). In contrast, his scores were significantly impaired in the visual identification part of the semantic test (score = 7.4%; mean = 74.3%; $n = 182$, age range = 65–75 years). The results are presented in Table 4. The data indicate that F.G.'s semantic knowledge of famous public events and figures is preserved when the latter are presented aloud, but not when they are presented in the visual modality. F.G.'s performance during testing again suggests that he does not have a semantic impairment *per se*, but that his visuoperceptual impairment prevents him from accessing the meaning of visually complex scenes. For

Table 5 Volumes of the fusiform gyri, parahippocampal gyri, temporopolar cortices and hippocampi in F.G. and controls (in mm³)

	Controls			F.G.		
	Raw values	Normalized values	SD	Raw values	Normalized values	Percentage volume of controls
Temporopolar cortex						
Left	4232	4250	421	4037	3916	92
Right	3932	3962	459	2988	2898	73
Fusiform gyrus						
Left	4032	4074	530	2969	2880	71
Right	4059	4093	478	1359	1318	32
Parahippocampal gyrus						
Left	1196	1206	203	1010	980	81
Right	1180	1189	213	439	426	36
Hippocampus						
Left	2905	2925	375	2038	1977	68
Right	3113	3124	346	1490	1445	46

Results are presented as means and SDs. Volumes are normalized to the intracranial area at the level of the anterior commissure.

example, when shown a picture of the explosion of the atomic bomb and asked what it evoked to him, F.G. replied: 'it looks like a cloud, but with a very strange shape'.

Brain imaging

MRI acquisition

The patient's brain was imaged during the course of the second evaluation with a 1.5 T Magnetom (Siemens, Erlangen, Germany) using a standard head coil and tilted coronal gradient echo sequence [MP-RAGE (magnetization-prepared rapid gradient recalled echo): TR (repetition time) = 9.7 ms; TE (echo time) = 4 ms; TI (inversion time) = 250 ms; flip angle = 12°; FOV (field of view) = 256 × 260; matrix = 230 × 25; slice thickness = 1.1–1.5 mm]. Images were acquired in the axial plane and were later reconstructed in the sagittal and coronal planes using Brain voyager software (Brain Innovation B.V.). Regions of interest (ROIs) included the hippocampal, temporopolar, fusiform and parahippocampal regions. In order to delineate these regions, the following method was used: a midsagittal plane was drawn along the anterior and posterior portions of the hippocampi, and coronal images perpendicular to this plane were obtained and reconstructed into 1 mm thick contiguous slices. Coronal images covered the entire rostrocaudal length of the hippocampal, temporopolar, fusiform and parahippocampal regions.

Image analysis. After three-dimensional reconstruction had been performed, the images were reformatted to obtain 1 mm³ isotropic voxels and then magnified to allow a better view of the brain structures that had to be quantified. Segmentation of the grey matter was performed manually on coronal sections perpendicular to the grand axis of the hippocampus in an anterior-to-posterior fashion. ROIs were defined manually

section-by-section based on specific anatomical landmarks. The borders of the temporopolar cortices on MRIs in F.G. and control subjects ($n = 8$, mean age = 65 years, SD = 7.1) were defined using a protocol designed by Insausti *et al.* (1998). Borders of the fusiform gyrus were defined using a protocol designed by Pierce *et al.* (2001).

Volume measurements. Measurements of the ROIs were performed by a blind rater (A.S.), who was unaware of the clinical data of the patient and control subjects. The measured ROIs were outlined with a mouse cursor on each coronal section. Once the outlines of the regions had been defined, the number of voxels within each region were determined. In order to control the effect of inter-individual variability in the head size of subjects on the volumes of the studied structures, the volumes were normalized to intracranial area (Juottonen *et al.*, 1998; Eritaia *et al.*, 2000).

Results

The results are summarized in Table 5. Compared with the controls, F.G. showed a marked grey matter volume reduction of the fusiform gyrus, the parahippocampal gyrus in its posterior part and the hippocampus bilaterally, although the extent of the atrophy was far more extensive in the right hemisphere than in the left. The greatest extent of atrophy was found in the right fusiform gyrus compared with controls (see Fig. 4). Although there are no precise anatomical landmarks for defining the boundaries of the fusiform face area (FFA), the borders of the fusiform gyrus in this study corresponded grossly to the area encompassing the various voxels found to be activated by all subjects during face recognition in the study by Kanwisher *et al.* (1997). Finally, the temporopolar cortex was found to be far less affected than the other ROIs compared with the controls.

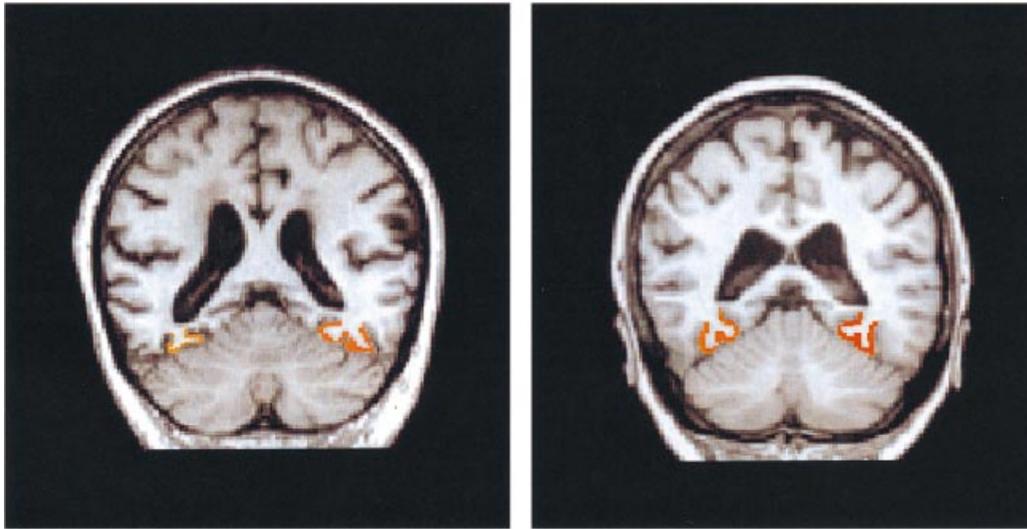


Fig. 4 Volume of grey matter of the fusiform gyrus in patient F.G. (left) and a control subject (right). Patient F.G. showed a 68% reduction of the fusiform gyrus in the right hemisphere and a 29% reduction in the left hemisphere compared with controls. (Radiographic conventions: left is right on the images.)

Discussion

F.G. was first seen in the context of difficulties recognizing familiar faces, including those of family members, friends and famous individuals on television or in magazines. During the first neuropsychological examination, F.G. scored in the very high range on the Weschler Adult Intelligence Scale-Revised (WAIS-R) test. All of his mental functions were preserved, apart from a relatively circumscribed anterograde memory deficit. A more in-depth examination of F.G.'s primary face processing skills indicated that at least some perceptual functions used in viewing faces were intact since he could identify correctly the gender, age, and emotions of unknown persons in full face photographs. On the other hand, F.G. was unable to name or identify faces of famous persons upon seeing their photographs. When the names of these famous persons were spoken aloud, however, he could provide precise semantic information about these individuals. Our patient was thus unable to access person-based semantic knowledge via the visual modality, while retrieving this same knowledge in the verbal modality remained intact. In a subsequent experiment devised at discriminating global versus analytic processing of faces, it was shown that F.G. was significantly impaired in tasks requiring configurational processing of faces. Although F.G.'s performance was poorer than that of controls, the results indicate that he registered some familiarity with famous persons upon seeing their faces, although he could not access semantic information from these faces. This may be due to the fact that an over-reliance on certain details of faces may, under certain circumstances, be sufficient to trigger some familiarity.

F.G. also presented with a mild form of visual agnosia for pictures of certain types of exemplars. He was particularly impaired at naming line drawings of insects, vegetables,

fruits, birds and animals, while his performance at naming different categories of man-made objects was considerably better. In contrast, the patient showed preserved semantic knowledge about the objects he could not recognize. F.G.'s visual modality impairment also extended to the domain of famous buildings and famous public events. Overall, our patient presents with a severe prosopagnosia that undermines him in daily life, along with a mild agnosia for visually complex exemplars that becomes apparent in a clinical setting. In our view, this co-occurring agnosia, which affects primarily certain categories of exemplars bearing a degree of visual resemblance (e.g. hopping animals), is likely to result from the same perceptual dysfunction in fine geometric assessments.

F.G.'s face recognition impairment interpreted in light of face processing models

Current models of face recognition assume that access to person-based semantic knowledge is achieved by a number of distinct cognitive processes (Bruce and Young, 1986; Valentine *et al.*, 1991; Burton and Bruce, 1992, 1993). For instance, recognizing a person from his face requires structural encoding of its perceptual elements, which leads to a global and abstract three-dimensional representation of the face. Once built, this representation is compared with a store of known faces, which contains face-recognition units (FRUs). The next step will consist in activating the person-identity node (PIN), which allows access to biographical knowledge about the person. According to recent versions of these models (Burton *et al.*, 1990, 1991), familiarity occurs at the PIN level, rather than at the FRU level as was initially proposed. In addition, access to person-based knowledge may

also be achieved via the name, by the activation of the corresponding name recognition unit (Valentine *et al.*, 1991; Burton and Bruce, 1992, 1993). Both face and name recognition units are thought to be potentially functionally and anatomically independent, although they share a common semantic system. In the case of F.G., he is unable to retrieve semantic information about famous persons from their faces although he is perfectly able to do so from their names. If according to these face-processing models there is a common semantic store to both face recognition and name recognition units, his impairment does not reflect degraded person-based semantic knowledge but rather a selective deficit in accessing that information via the visual modality. F.G. shows a striking dissociation between his preserved ability to access verbal semantics and his inability to access visual semantics.

Does F.G.'s prosopagnosia reflect a semantic or a perceptual impairment?

A distinction has been made between apperceptive prosopagnosia and associative (or amnesic) prosopagnosia (De Renzi *et al.*, 1991). In apperceptive prosopagnosia, functional damage may occur at various processing levels of visual perception from elementary visuoperceptual processes to a more elaborate structural encoding stage 'which represents the final product of perceptual analysis and yields a three-dimensional, abstract representation of the stimulus, which is independent of the context and the viewpoint from which it is observed' (De Renzi, 1997). Associative prosopagnosia, in turn, reflects an inability to access or to retrieve the stored semantic representations of persons (person-specific knowledge) or the memories that pertain to familiar persons. In this case, the deficit is mainly amnesic and may also extend to other semantic categories.

Results from the experiment and the neuropsychological assessments indicate that F.G.'s visual modality-specific impairment results from an underlying inability to build a global representation of facial geometry. At first, it appeared that F.G. did not reveal any consistent pattern of impairment at the perceptual level. His performance proved that his basic visuoperceptual and visuospatial processes were intact (see Table 1). Nonetheless, he was significantly impaired at three of the eight subtests of the Visual Object and Space Perception (VOSP) Test (Warrington and James, 1985)—namely the silhouettes, object decision and progressive silhouettes subtests. All three subtests have a basic common feature: they require the patient to identify and build a mental representation of various objects based on unconventional perspectives and contours. Their shapes are often distorted and presented in non-canonical views, and they do not contain any internal details. F.G. was considerably impaired in this type of task. Further evidence came from F.G.'s poorer performance on the second part of the Facial Recognition Test developed by Benton *et al.* (1983), in which one has to match different perspectives of an unfamiliar face. In this

task, we assume that F.G. was unable to extract the physiognomic invariants that allow building an abstract configurational representation of an unfamiliar face. Thus, his performance during testing highlights his deficit in accessing a global representation.

This point was confirmed in the configurational face processing experiment. The test, which was devised to test processing of the geometry of facial structures in prosopagnosic patients (Barton *et al.*, 2002), required that F.G. discriminate faces in which the spatial configuration of certain features had been modified. The patient had to discriminate which one of three faces presented simultaneously was different from the two others. Results show that patient F.G. was significantly impaired at discriminating changes in the global spatial configuration of a face, but not in feature colour, compared with a group of control subjects.

These results confirm the view that F.G.'s impairment relies upon an inability to grasp the various features of a face and their spatial relations into a global geometric arrangement. We assume that this stage of processing is specific to faces, but that it can also be required in the identification of visually complex objects (e.g. buildings, places, famous events), objects presented in non-conventional views (e.g. non-canonical views, silhouettes) and objects lacking inherent details with a high degree of intra-categorical similarity (e.g. line-drawings of living exemplars). Impairment at this functional level is relatively difficult to assess clinically because perceptual processes may appear normal at first using conventional visuoperceptual and visuospatial neuropsychological tests, and the configurational deficit may go unnoticed (or wrongly interpreted as a semantic or an associative disorder). Therefore, we assume that the apperceptive prosopagnosia presented by F.G. stands at an elaborate visuoperceptual level. This patient contrasts clearly with previous reports of progressive prosopagnosia, all of whom demonstrated a cross-modal loss of person-knowledge in the absence of any perceptual deficits (Barbarotto *et al.*, 1995; Evans *et al.*, 1995; Gentileschi *et al.*, 1999, 2001; Gainotti *et al.*, 2003). Patient Maria (Gentileschi *et al.*, 1999), however, did show some basic visuoperceptual deficits, although they remained secondary to her cross-modal person-recognition impairment.

Neural correlates of F.G.'s impairment

The present study provides interesting neuroanatomical data concerning the role of the fusiform gyrus in face processing. These data show that the greatest extent of atrophy in patient F.G. was found in the right fusiform gyrus. These results support the view that the right hemisphere plays a critical role in face configurational mechanisms (Rhodes, 1993). More specifically, the holistic coding mechanism involved in the rapid binding of the global aspects of features is most likely subserved by the right hemisphere occipitotemporal region, while the left operates in a slow analytical, feature-by-feature approach (Damasio *et al.*, 1989). This view is also supported

by recent neuroimaging data which have shown that the right fusiform face area responds more strongly during processing of whole faces whereas the left fusiform face area responds more strongly during the imposed processing of parts presented in complete faces (Rossion *et al.*, 2000). Patient F.G. also showed a marked atrophy of adjacent right parahippocampal cortex. This region has been demonstrated to respond more strongly in functional MRI to scenes depicting places than other types of visual stimuli (parahippocampal place area) (Epstein *et al.*, 1999). Interestingly, patient F.G. appears to present a topographical agnosia (an inability to recognize famous and familiar places, including buildings), despite normal orientation in familiar space. For instance, he is unable to recognize famous monuments he sees in his hometown on a daily basis (e.g. the opera house), although he can find his way around the city without getting lost.

Does F.G.'s condition reflect a right hemisphere variant of frontotemporal degeneration?

Patient V.H. (Evans *et al.*, 1995) showed initially a strikingly similar clinical profile to that of F.G.. V.H first presented with a deficit in accessing person-specific semantic information through the visual modality and 9 months later developed a cross-modality semantic impairment (associative prosopagnosia). The underlying focal lobar atrophy involved predominantly right anterior temporal structures, mirroring those left hemisphere structures ordinarily affected in semantic dementia (Hodges *et al.*, 1992). Based on the aggravation of the semantic impairment and on the locus of the atrophy of patient V.H., Evans *et al.* (1995) suggested that this rare form of progressive prosopagnosia represented a right hemisphere variant of semantic dementia. A similar interpretation was formulated concerning patients Maria, Emma and C.O. (Gentileschi *et al.*, 1999, 2001; Gainotti *et al.*, 2003).

Semantic dementia is known to affect primarily the temporal poles, although the distribution of atrophy is always more important on the left side (Hodges *et al.*, 1992; Snowden *et al.*, 1996). Recent neuroimaging studies relying on modern volumetric techniques have found a rather consistent pattern of atrophy with an anteroposterior gradient that includes left inferior and middle temporal gyri, the fusiform gyrus and the amygdala (Mummery *et al.*, 2000; Chan *et al.*, 2001; Galton *et al.*, 2001). The superior temporal gyrus is usually preserved, while divergent findings have been observed concerning the hippocampus and the entorhinal cortex (the latter regions were found to be preserved in the study by Mummery *et al.*, 2000). F.G.'s temporopolar cortices were relatively spared (as evidenced by MRI volumetry) and the regions found to be most affected were located in the posterior temporal regions. These findings are consistent with the fact that F.G.'s semantic memory was untouched and that his inability to access semantic knowledge via the visual modality resulted from an inability to process visually

complex entities into configurational representations. Thus, in our view, F.G. clearly does not show a right hemisphere counterpart of semantic dementia. The locus of atrophy in patient F.G. also differs from previous case reports of progressive prosopagnosia, where the anterior portions of the right temporal lobe were always found to be the most affected (Barbarotto *et al.*, 1995; Evans *et al.*, 1995; Gentileschi *et al.*, 1999, 2001; Gainotti *et al.*, 2003). The different neuroanatomical locus of atrophy may thus account for the differences in the nature of the person recognition impairment observed between our patient and previous case-reports of progressive prosopagnosia.

Taken as a whole, both neuropsychological and neuroanatomical data tend to suggest that F.G.'s neuropsychological pattern of impairment and locus of atrophy does not reflect, at this stage of the disease, a right hemisphere variant of semantic dementia. However, longitudinal data obtained with patient V.H., for instance, showed that this pattern of clinical deficit may progress to semantic memory disturbances. Therefore, although the neuropathological process responsible for F.G.'s condition remains unknown, the results of the present study suggest that right temporal variant of frontotemporal lobar degeneration (FTLD) may be characterized during several years, in some patients, by an impaired configurational processing of visually complex entities in the absence of any semantic deficit.

General conclusions

Patient F.G. presented with a conspicuous impairment at recognizing faces of famous persons, family members and friends. A more detailed neuropsychological investigation showed that F.G. was unable to access person-based semantic knowledge as well as more general semantic knowledge via the visual modality. Preserved semantic knowledge of the same famous persons from their name highlights the functional dissociation between the visual and verbal modalities. In an experiment devised at discriminating global versus analytic processing of faces, it was found that F.G. was significantly impaired in tasks requiring configurational processing of faces. These results as a whole show that: (i) the patient's progressive prosopagnosia results from a deficit in processing faces to build a global configurational representation; (ii) this progressive condition was associated with a predominantly right hemisphere focal cortical atrophy affecting primarily the right fusiform and parahippocampal areas; and (iii) this pattern of impairment may reflect a right temporal variant of frontotemporal lobar degeneration.

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