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HEREDITARY PROSOPAGNOSIA: THE FIRST CASE SERIES

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Abstract

Prosopagnosia is defined as a specific type of visual agnosia characterised by a discernible impairment in the capacity to recognise familiar people by their faces. We present seven family pedigrees with 38 cases in two to four generations of suspected hereditary prosopagnosia, detected using a screening questionnaire. Men and women are impaired and the anomaly is regularly transmitted from generation to generation in all pedigrees studied. Segregation is best explained by a simple autosomal dominant mode of inheritance, suggesting that loss of human face recognition can occur by the mutation of a single gene. Eight of the 38 affected persons were tested on the Warrington Recognition Memory Test for Faces (RMF; Warrington, 1984), famous and family faces tests, learning tests for internal and external facial features and a measure of mental imagery for face and non-face images. As a group, the eight participants scored significantly below an age- and education-matched comparison group on the most relevant test of face recognition; and all were impaired on at least one of the tests. The results provide compelling evidence for significant genetic contribution to face recognition skills and contribute to the promise offered by the emerging field of cognitive neurogenetics.

Key words: prosopagnosia, face recognition, agnosia, congenital prosopagnosia, hereditary prosopagnosia

Introduction

First named by Bodamer (1947; see Ellis and Florence, 1990), prosopagnosia refers to a specific type of visual agnosia in which there is an impairment in recognising familiar people by their faces. Although traditionally associated with brain injury acquired in later life, a small number of reports of "developmental prosopagnosia" or "congenital prosopagnosia" have been published. These cases do not comprise a homogeneous group, however, and differ on a number of important variables, including aetiology, pathogenesis, the manner in which such cases came to clinical awareness and the type and extent of impairments.

Cases presented as "developmental prosopagnosia" can be classified into three main groups: (a) cases associated with early acquired brain injury (see Table I); (b) cases associated with concurrent neurodevelopmental disorders (e.g., Asperger syndrome; see Table II); and (c) cases not associated with early acquired brain defects or neurodevelopmental disorders (see Table III). This last group has also been described as congenital.

TABLE I

Cases of prosopagnosia associated with early acquired brain injury

Reference	Case	Age at testing	RMF	BFRT	FF% (controls)	Associated aetiology	Reported non-face impairments
Young and Ellis (1989)	K.D.	8-11	n/a	37/54	n/a	Meningococcal meningitis, hydrocephalus, and multiple operations (age 14 months to 4 years)	Spatial orientation and navigation, figure copying, object recognition, achromatopsia
de Gelder and Rouw (2000)	R.P.	49	32/50	31/54	"Severely impaired"	Closed head injury (age 6)	None reported
Barton et al. (2003)	G.A.	21	30/50	39/54	0 (n/a)	Cardiopulmonary arrest and coma (age 1)	Spatial orientation and navigation
	K.B.N.	31	23/50	39/54	n/a	Frequent seizures (since age 2)	Spatial orientation and navigation, reading difficulties
	K.T.	36	29/50	28/54	5.9 (n/a)	Respiratory arrest and vegetative state (age 6)	Spatial orientation and navigation, reading difficulties
Michelon and Biederman (2003)	M.J.H.	34	n/a	n/a	55 (97.5)	Traumatic brain injury leading to left visual cortex and right fusiform gyrus lesion (age 5)	Restricted visual field, comprehension of abstract drawings, mild learning disability, motor co-ordination, tics

Note. RMF = Warrington Recognition Memory Test for Faces, BFRT = Benton Facial Recognition Test, FF = famous faces test.

TABLE II
Cases of prosopagnosia associated with neurodevelopmental disorder

Reference	Case	Age at testing	RMF	BFRT	FF% (controls)	Associated aetiology	Reported non-face impairments
Kracke (1994)	H.D.	19	24/50	0/54	n/a	Asperger syndrome	Motor co-ordination
Ellis and Leafhead (1996)	Raymond	Late 30 sec	n/a	n/a	30 (91)	Asperger syndrome	Object recognition, visual memory, motor co-ordination
Cipolotti et al. (1999)	P.E.	29	23/50	40/54	n/a	Autism, Tourette syndrome, congenital deafness	Within-category discrimination (animals), tics
Njiokiktjien et al. (2001)	B	10	n/a	n/a	n/a	Asperger syndrome	Motor co-ordination, smell, gestalt perception, language (word finding, fluency, prosody), tactile perception on right
	C	6	n/a	n/a	n/a	Asperger syndrome	Motor co-ordination, tics
	D	8	n/a	n/a	n/a	Asperger syndrome	None reported
Duchaine et al. (2003a)	T.A.	42	n/a	n/a	12 (94)	Asperger syndrome	Object recognition
Pietz et al. (2003)	Unnamed	4	n/a	n/a	n/a	Asperger syndrome	Motor co-ordination

Note. RMF = Warrington Recognition Memory Test for Faces, BFRT = Benton Facial Recognition Test, FF = famous faces test.

Cases following childhood injury involve a diverse range of aetiologies, from complications of meningococcal meningitis, to seizure disorder and presumed anoxic injury (Table I). The majority of cases show other visuo-spatial impairments, particularly with spatial orientation and navigation. Cases with neurodevelopmental disorders (as outlined in Table II) all involve a diagnosis of Asperger syndrome, with the exception of case P.E. who had a diagnosis of concurrent autism, Gilles de la Tourette syndrome and congenital deafness. Many also had neuropsychological impairments typical of autism spectrum disorders (such as motor co-ordination difficulties); but four also report additional impairments in non-face visual perception.

Table III summarises cases of prosopagnosia not linked to acquired injury or other developmental disorders. Inclusion in this group was determined on the basis that subjects do not report any *other* developmental disorder. The majority of reports specifically exclude these factors, although in Kress and Daum's (2003a) study, patients S.O. and G.H. were described as "congenital prosopagnosics", despite there being no specific exclusion of other factors by the authors.

Previous classification of what was believed to be "early onset" prosopaganosia was confusing, given that some reviews used different criteria for inclusion in their studies. Barton et al. (2003) used a wide definition incorporating cases of early acquired injury, concurrent neurodevelopmental disorder and presumed hereditary cases without obvious brain pathology. Kress and Daum (2003b) specifically excluded any cases of brain damage during childhood, but still included the Kracke (1994) case with a diagnosis of Asperger syndrome. Different studies have also used

TABLE III
Assumed cases of hereditary prosopagnosia

Reference	Case	Age at testing	RMF	BFRT	FF% (controls)	Reported non-face impairments
McConachie (1976)	A.B.	12	n/a	n/a	n/a	Motor co-ordination, spatial orientation and navigation
de Haan and Campbell (1991)	A.B.	27	28/50	39/54	41 (96.9)	Object recognition, particularly within-category discrimination
Temple (1992)	Dr S	n/a	43/50	"Performed normally"	31 ('significantly poorer' than controls)	Spatial orientation and navigation, visual memory
Ariel and Sadeh (1996)	L.G.	8	n/a	4 (before test abandoned)	38 (n/a)*	Gestalt perception of letters, visual-motor integration, object recognition
Bentin et al. (1999)	Y.T.	36	32/50	41/54	3.6 (58)	None reported
Duchaine (2000)	B.C.	52	46/50	43/54	24 (94)	Central auditory processing, motor co-ordination
de Gelder and Rouw (2000)	A.V.	42	34/50	34/54	n/a	None reported
Jones and Tranel (2001)	T.A.	5	n/a	n/a	0 (96)*	Spatial orientation and navigation, visual perception and discrimination
Nunn et al. (2001)	E.P.	37	41/50	46/54	25 (90)	None reported
Kress and Daum (2003a)	S.O.	34	34/50	n/a	28 (93.5)	None reported
	G.H.	54	45/50	n/a	44 (93.5)	None reported
Duchaine et al. (2003b)	N.M.	40	26/50	n/a	60 (94)	Spatial orientation and navigation, within-category object recognition

Note. RMF = Warrington Recognition Memory Test for Faces, BFRT = Benton Facial Recognition Test, FF = famous faces test.
*Test was on pictures of familiar family members rather than famous people.

different labels for the conditions later considered under the label "developmental prosopagnosia", including "childhood prosopagnosia" (Young and Ellis, 1989) and "congenital prosopagnosia" (Ariel and Sadeh, 1996; Kress and Daum, 2003a).

As the term "developmental prosopagnosia" has been used as an umbrella term for all prosopagnosias that arise during childhood, it provides little substantive information about the aetiology of the case in question. In particular, it fails to distinguish between prosopagnosia acquired during birth (e.g., perinatal asphyxia) and hereditary types with very early onset. In the current study the term "hereditary prosopagnosia" is introduced to highlight the putative genetic contribution, and is used to describe a type of prosopagnosia which affects more than one family member in the absence of other potentially confounding factors (such as acquired brain damage or neurodevelopmental disorder).

A remarkable attribute of people with hereditary prosopagnosia is the significant variation in visual cognitive skills observed between individuals. Kress and Daum (2003b) reviewed performance on neuropsychological tests in cases of "congenital prosopagnosia" (including a case with a diagnosis of Asperger syndrome, but excluding acquired brain damage), and reported that 4 out of the 9 cases reviewed showed concurrent impairments in non-facial visual processing. These tended to be quite circumscribed, affecting only one other domain (such as object recognition or visual memory) rather than presenting as a general visual processing deficit. When reviewing performance on face specific tasks, they concluded that a severe impairment in recognising people on the basis of facial information is the core deficit in all cases, but that they differ substantially on other face processing functions. Face matching, in particular, was found to be deficient only in two patients (L.G. and V.A.), although when task difficulty was increased, two further patients were impaired. Furthermore, Kress and Daum (2003b) suggest that simple face matching tests will not necessarily detect impairments in face processing. The same applies to tests of face memory, e.g. the face subtest of the Warrington Recognition Memory Test for Faces (Warrington, 1984).

A possible reason why tests of face matching and face memory are not sensitive to the presence of congenital prosopagnosia has been suggested by Duchaine and Weidenfeld (2003). They assessed the use of non-face information in the completion of the Warrington Recognition Memory Test for Faces (RMF; Warrington, 1984) and the Benton Facial Recognition Test (BFRT; Benton et al., 1983). They showed that participants could easily score within the normal range on both tasks, despite all the face information having been blanked, due to the extra-face information such as clothing and hair.

Normal performance on these tests could reflect the weakness of such traditional tests for individuals who have not completely lost all face recognition capacity or who have been able to compensate given that they have not sustained an acquired brain injury. This is supported by Duchaine and Weidenfeld's (2003) findings, as well as from the day-to-day techniques that have been reported as being used by individuals with developmental prosopagnosia: B.C. reported using hairstyle, facial hair or clothing to recognise people (Duchaine, 2000); A.B. reported using clothing, voice or mannerisms as a form of identification (de Haan and Campbell, 1991), as did Y.T. (Bentin et al., 1999) and E.P. (Nunn et al., 2001).

However, one task on which subjects with hereditary prosopagnosia might be expected to perform poorly, given the lifetime of dysfunctional learning attached to faces, is that requiring the identification of "famous faces". In reports in which the RMF, BFRT and a famous faces test have been used, there is a tendency for relatively greater impairment in familiarity judgements for famous faces (see Table III). Unlike the RMF and BFRT, and in the absence of other diagnostic tests, the famous faces test has tended to be used as the main diagnostic indicator of hereditary prosopagnosia.

In previous research literature on developmental prosopagnosia, most cases, understandably perhaps, were discovered by chance. For example case Y.T. (Bentin et al., 1999) presented himself after a public lecture on face perception given by one of the researchers, whereas other cases have presented themselves serendipitously to clinicians (e.g., Ellis and Leafhead, 1996). As a result of the apparent rarity of such cases, no systematic attempt to date has been made to seek out relevant individuals in the wider population. This may have led to a sample bias, where individuals who do not find their face recognition difficulties grossly disabling in everyday life are not likely to be reported in the medical or neuropsychological literature. In a first survey performed by our workgroup among 689 randomly selected students in Münster we found 17 congenital prosopagnosics. Fourteen of them allowed us to interview their family member. In all 14 families we found at least one other family member with prosopagnosia (Kennerknecht et al., 2006). The affected persons lead normal lives and, for the most part, enjoy normal professional careers.

The first hint of possible familial transmission for face recognition deficits from mother to daughter was given by McConachie (1976). Only in 1999 (see Table III) was a familial history of congenital prosopagnosia in a father and two daughters and (probably) one son reported by de Haan (1999). The Online Mendelian Inheritance in Man (OMIM; http://www.ncbi.nlm.nih.gov/omim/) database contains a summary of the current state of knowledge about the heredity of prosopagnosia.

To demonstrate a selective impairment in face recognition in individuals who have no history of acquired brain injury or neurodevelopmental disorder, it is important to establish that they experienced functional impairments or significant biases away from using faces in day-to-day person-recognition tasks. One might also expect impairments in the recognition of famous faces, and impairments in face perception tasks that rely on internal facial features over and above age and sex matched controls.

In this study, we address some of these issues by describing an investigation into the functional or ecological disabilities in an adult sample, together with their neuropsychological test performance, in a series of previously unreported cases.

Method

Participants

Face recognition impaired participants were initially identified among personal acquaintances of two of the authors (T.G. and M.G.). Further participants were recruited using the internet to invite members of a prosopagnosia mailing list to participate in the study. From all potential subjects initially identified, we drew family trees and interviewed all family members willing to volunteer.

Initial detection of face recognition difficulties was made using a semi-structured interview that took about 90 minutes. All participants were individually screened. Prior to accepting the likelihood of a face recognition deficit, all other causes of agnosias or visual impairments or, such as current or earlier visual defects and impairments of vision were excluded. We also excluded subjects with a history of neurological illness, trauma or acquired developmental or intrauterine infections or perinatal asphyxia. Finally, we asked for a history of psychiatric illness and any pervasive developmental disorders that could be accompanied by agnosias, e.g. Asperger syndrome (Ellis et al., 1994). Although we have confidently ruled out any significant neurological impairment or psychiatric illness, the participants were not brain-scanned to check for any potentially subtle or sub-clinical differences in neuroanatomical structure or function. Such investigations are intended as a future extension of the current study. From previous studies on people with congenital or hereditary prosopagnosia that have included neuroimaging investigations, it is unlikely that any significant differences in gross neuroanatomy will be apparent between members of the target group and matched controls (Kress and Daum, 2003a).

Hereditary prosopagnosia was only considered if at least one other first degree relative was affected. In all cases, we were able to identify one or more directly linked family members. Given the rarity of brain damage leading to an isolated prosopagnosia a coincidental occurrence of two or more cases of acquired prosopagnosia, although not impossible of course, is extremely unlikely. Therefore, the occurrence of two or more cases in directly linked family members may be considered as a strong indication of a hereditary origin of the disorder. In addition, we asked for third-person perspectives of the target group from a number of close family members. We were able to identify 38 affected persons in seven family trees (Figure 1). Eight persons from four pedigrees (marked with an asterisk in Figure 1) agreed to take part in further examinations and tests. Age, handedness and pedigree positions are listed in Table IV. These eight cases were compared with a comparison group consisting of 11 non-face-recognition impaired participants matched for age and education.

Self Report Questions on Face Perception in Everyday Life

Participants were initially asked to complete two detailed self-report questionnaires, the results of which are summarised in Table V (target group), Table VI (comparison group) and Table VII (both groups). The target group reported themselves as uniformly poorer on almost all aspects of face recognition, despite reporting good object discrimination. It is notable that they also report relatively poor discrimination on animals within species and orientation in an unknown city. This pattern is similar to cases reviewed in Table III and Kress and Daum's (2003b) review, where other aspects of non-facial visual processing and/or memory were impaired in people with what they called developmental prosopagnosia.

Tables V, VI and VII summarise the preferred strategies of person recognition reported by the target and comparison groups. It is clear from these data that the target group reported preference for recognition strategies that do not rely on face specific recognition.

The target group also reported experiences and behaviours in day-to-day life consistent with those that would be expected from subjects with prosopagnosia, supporting our claim that this group is face recognition impaired.

Family Pedigrees

Family pedigrees were plotted and shown in Figure 1, from which it can be seen that prosopagnosia is found in both men and women, and that all prosopagnosics have impaired sibs and/or parents or offspring. Thus, in all families the segregation of hereditary prosopagnosia through first degree relatives only is compatible with simple autosomal dominant inheritance. The

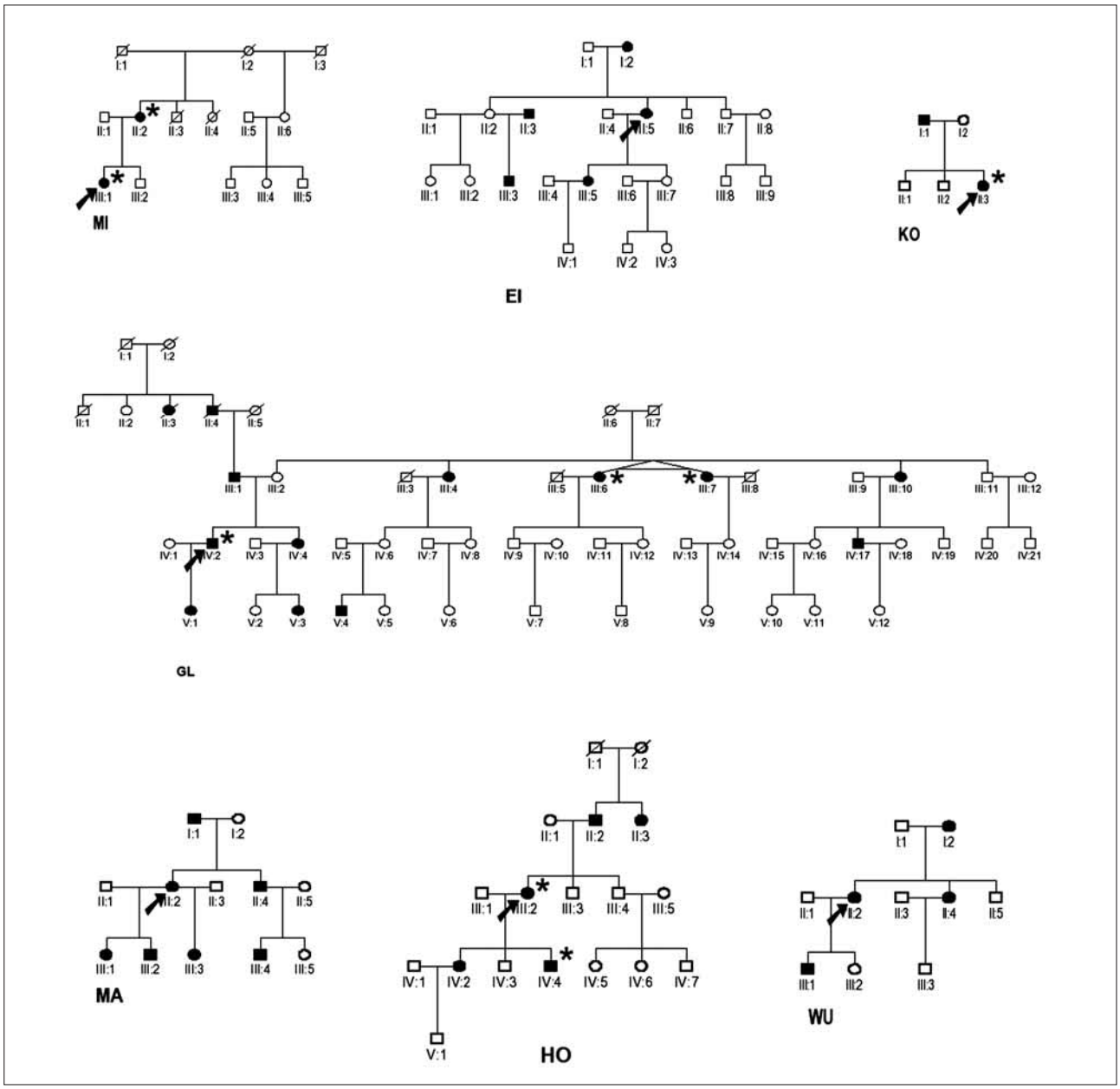

Fig. 1 – *Seven pedigrees. Black symbols denote affected persons, circles stand for female, squares for male. An arrow points to the index person and an asterisk to the probands tested in further detail in this study. There is a vertical transmission of prosopagnosia in men and women. The penetrance is (nearly) 100%. All pedigrees are compatible with an autosomal dominant mode of inheritance. In pedigree GL there are concordantly impaired monocygotic twins III:6 and III:7. The pedigrees G and L are linked by woman III:2. She is non consanguineous. A similar situation is in pedigree EI with woman II:2. Whether this woman might be a normal transmitter remains an open question. Her son III:22 most probably got the defect allele from his prosopagnosic father II:3 or even from both.*

pedigrees G and L are linked by a normal functioning woman III 2 and there is no hint for consanguinity. The same might be true in pedigree EI. Before we could test the father of IV 22, it was considered that his mother who was non-prosopagnosic would be a clinically normal transmitter for prosopaganosia. Most plausibly, male IV 22 appears to have derived the defect allele from his father II 15; but this does not exclude his mother as a carrier and that he also might be homozygous for the deficit alleles. Otherwise our pedigree data show a penetrance of 100%. This and the concordance in two monozygotic twins III 6 and III 7 further support that face recognition deficit is a monogenetic disorder.

Neuropsychological Tests of Face Perception

In order to establish more objectively the diagnosis of prosopagnosia both target group and controls were given a battery of face-processing tests designed to explore the specific nature of their deficits. The family faces test was only completed by the target group. Table IV provides details of the target group and controls, along with their scores on a computer-presented (although otherwise identical) version of the RMF and a modified

TABLE IV
Demographics and individual results of experimental measures for target and comparison groups

Participant	Pedigree position	Handedness	Age	RMF	Mean VVIQ*	Mean VVIQ* for face items	Mean VVIQ* for non-face items
G.I. (Female)	HO III:2	Right	56	38	4.16	4.75	3.56
M.A. (Male)	HO IV:4	Right	27	39	4.50	5	4
L.I. (Female)	GL III:6	Right	72	46	3.59	4.19	3
H.E. (Female)	GL III:7	Left	72	41	3.19	4.75	1.63
A.N. (Female)	KO II:3	Right	32	37	3.47	4.94	2
E.R. (Female)	MI II:2	Right	70	37	4.06	4.31	3.81
U.L. (Female)	MI III:1	Right	40	37	2.72	3.69	1.75
T.H. (Male)	GL IV:2	Right	46	41	4.00	4.13	3.88
Mean							
SD			51.86	39.5	3.71	4.47	2.95
			18.3	3.12	.58	.46	1.01
Comparison mean							
(N = 11)			53.09	41.64	1.86	2.0	1.7
SD			18.1	4.8	1.06	1.19	.93
Range			27-76	34-49	1-4.3	1-4.63	1-4

Note. VVIQ = Modified Marks Vividness of Visual Imagery Questionnaire, RMF = Warrington Recognition Memory Test for Faces. Lower scores indicate higher reported vividness on the VVIQ.
*One participant's data was excluded from the comparison group VVIQ scores due to incorrect completion of the scale.

version of the Marks' Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1973). Table VIII displays the results from the famous faces and family faces recognition test.

Experiment 1
Computerised Warrington Recognition Memory Test for Faces

Materials

The stimuli consisted of digitised versions of the stimuli from the Warrington RMF (Warrington, 1984) and were presented on a laptop computer. The images were scaled to have a height of 400 pixels with the original spacing and aspect ratio maintained, having an onscreen height of approximately 120 mm. Participant response was by a standard PC keyboard attached to the laptop.

Procedure

The procedure followed that of the original picture card version of the Warrington RMF (Warrington, 1984), except that the responses involved depressing one of two keys, rather than pointing. During the learning phase, 50 faces were sequentially presented on a white background at a rate of approximately one every three seconds, with the participant required to respond "yes" or "no" to each item according to whether he or she found it pleasant or unpleasant. During the test phase the participants were asked to place the index finger of each hand over response keys to the left and right hand sides of the keyboard.

The test phase consisted of 50 paired test images presented on a white background. Participants indicated which of the two faces had previously been seen by pressing the key corresponding to the side of the screen to which their selection appeared. After the participant had made a response, the pair of test pictures disappeared, leaving a blank screen for 250 msec before the next test pair appeared.

Results

The comparison group had a mean score of 41.64 (standard deviation of 4.8) compared with the target group mean of 39.5 (standard deviation of 3.12). The difference was not significant when compared with a two-tailed Mann-Whitney U test ($U = 32.0$, $z = -.998$, $p = .318$, $n = 19$). When individuals' scores were examined and compared with age adjusted norms (see Table IV), one member of the comparison group scored as impaired, compared with two members of the target group. The two target participants (A.N. and U.L.) who scored as impaired scored exactly on the cut-off, suggesting a borderline impairment only. As predicted from the work of Duchaine and Weidenfeld (2003), there was no significant difference between the target group and controls on this test. However, as discussed earlier, the Warrington RMF (Warrington, 1984) is not necessarily diagnostic for people with developmental prosopagnosia and the famous faces test provides a more appropriate test of face recognition deficits.

Experiment 2
Famous Faces Test

Materials

The stimuli were colour digital pictures of 20 famous and 20 non-famous people carefully matched for photographic quality and pose. All

TABLE V

Self report questions answered by target group

Reference	G.I.	M.A.	L.I.	H.E.	A.N.	E.R.	U.L.	T.H.
Pedigree	HO III:2	HO IV:4	GL III:6	GL III:7	KO II:3	MI II:2	MI III:1	GL IV:2
Sex	F	M	F	F	F	F	F	M
Age	56	27	72	72	32	70	40	46
Eyesight	Myopia	Normal	Presbyopia	Presbyopia	Myopia	Myopia	Myopia	Myopia
Discrimination of animals within species	P	P	P	P	P	P	G	F
Recognition of possessions among similar objects	Not answered	G	G	G	Yes	F	GG	
Orientation in unknown city	VP	P	F	F	P	P	G	P
Facial recognition of:								
Age	P	P	P	P	G	F	P	G
Gender	Yes	Rarely problems	F	F	No problem	F (use profile also)	Mostly OK	Yes
Attractiveness	Not interested	Yes	Yes	Yes	Yes	Don't know	Yes	Yes
Emotion	P	Excellently	Well	G	VG	G (use body also)	Well	Excellently
Recognition of well known actors/politicians in street	Maybe	No or perhaps	Depends on the person	Depends on the person	No	Yes perhaps	No	No
Do people often comment on failure to recognise them	Quite often	Quite often	Often	Often	Often	Often	Quite often	Quite often
Ability to decide immediately if a face is familiar	No	No	No	No	No	No	No	No
Known relatives with similar problems	Father, aunt daughter	Mother, maybe brother	Father	Father	Perhaps father	Daughter	Mother	Father, sister, aunts

Note. All non-normal eyesight was reported as corrected by appropriate visual aids. VP = Very poor, P = Poor, F = Fair, G = Good, VG = Very good.

TABLE VI

Self report questions answered by comparison participants

	K.A.	K.O.	M.A.	U.A.	C.H.	G.E.	G.U.	F.O.	H.I.	L.A.	E.L.
Sex	F	M	F	F	F	F	M	F	F	F	F
Age	56	27	72	40	36	75	45	62	68	31	73
Eyesight	Myopia	Myopia	Myopia	Myopia	Normal	Myopia	Normal	Myopia	Myopia	Normal	Myopia
Discrimination of animals within species	VG	VG	G	F	G	VG	G	G	VG	G	VG
Recognition of possessions among similar objects	VG	VG	G	G	G	VG	G	G	G	G	G
Orientation in unknown city	G	G	G	F	G	F	G	F	VP	G	P
Facial recognition of:											
Age	G	G	G	G	P	G	F	P	G	G	G
Gender	VG	VG	G	VG	G	G	G	G	G	VG	G
Attractiveness	G	VG	G	G	G	G	VG	G	G	VG	VG
Emotion	G	G	G	VG	VG	VG	G	G	G	VG	VG
Recognition of well known actors/politicians in street	No	Yes	Yes	Probably	Probably	Probably	Probably	Yes	Yes	Yes	Yes
Ability to decide immediately if a face is familiar	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do people often comment on failure to recognise them	Some-times	No	No	Rarely	Can happen	No	No	No	No	No	No

Note. All non-normal eyesight was reported as corrected by appropriate visual aids. VP = Very poor, P = Poor, F = Fair, G = Good, VG = Very good.

TABLE VII
Person recognition strategies reported as percentages of target group and controls

	Target group			Comparison group		
	Most	Less	None	Most	Less	None
Whole person	50	37.5	12.5	100	0	0
Face	12.5	50	37.5	81.8	0	0
Spontaneous recognition	12.5	50	37.5	90.9	0	0
Voice	75	25	0	54.6	27.3	0
Gait	100	0	0	9.1	72.7	0
Distinctive bodily features	75	25	0	0	72.7	9.1
Distinctive clothing or hair	37.5	37.5	25	18.2	45.4	18.2

images were cropped to a height and width of 300 × 300 pixels and had an approximate onscreen height of 90 mm. Pictures were chosen so that the face was centred, occupied the majority of the frame, included no additional identifying objects (such as distinctive hats, jewellery or clothing) and involved the pictured person facing or mostly facing the camera so a front view of the face was plainly visible. The faces of famous people used were celebrity images taken from the internet and popular magazines. The non-famous faces were selected from portfolios of small commercial modelling agencies to match for attractiveness and image quality, and were matched for gender and approximate age. Participant response involved using a standard PC keyboard attached to the laptop and by oral report.

Procedure

The faces were presented in a pseudo-random order, centred on the screen with a white background. Participants were asked to respond with the keyboard using the keys "v" for *vertraut* (familiar) or "n" for *nicht vertraut* (not familiar). "Vertraut" and "nicht vertraut" prompts were positioned below the images and remained on-screen for the duration of the experiment. If the participant responded with "n" (not familiar) the current picture disappeared and the next was displayed after 150 msec delay. If the participant responded with "v" (familiar) an on-screen prompt appeared asking the participant to give identifying details of the person he or she had indicated was familiar. The experimenter then prompted the software to present the next stimulus once the participant was ready.

Results

Hits were scored as "vertraut" (familiar) responses to a famous face, correct rejections as "nicht vertraut" (unfamiliar) responses to a nonfamous face. The comparison group had a mean hit rate of 14.27 (standard deviation of 3.86) compared with a target group mean correct score of 9.38 (standard deviation of 4.53); this was significantly fewer than the comparison group mean when compared using a one-tailed Mann-Whitney U test ($U = 16.0$, $z = -2.32$, $p < .01$, $n = 19$). There was no significant difference between groups in the number of correct rejections (one-tailed comparison, Mann Whitney $U = 30$, $z = -1.180$, $p = .127$, $n = 19$). An informal analysis of the oral report data suggested that the target group provided more general identifying information (e.g., 'film star', 'not sure, maybe a politician') than the comparison group after a "vertraut" (familiar) response. These results suggest a relative impairment in the target group for recognising familiar faces and provide evidence for the presence of a prosopagnosia-like face recognition impairment. When individual hit rates were examined (see Table VIII) and compared with the comparison group performance, six members of the target group (G.I., L.I., H.E., A.N., E.R., T.H.) scored below 10.4 (one standard deviation below the comparison group score) and two (G.I., A.N.) scored below 6.6 (two standard deviations below the comparison group score). Although only two members of the target group scored below two standard deviations of the comparison group mean (the traditional cut-off for neuropsychological impairment) it is unlikely that a developmental disorder would consistently result in the severity of prosopagnosia that might be seen after acquired brain damage. From these results, hereditary prosopagnosia would seem to be a relative, rather than absolute, deficit in face recognition.

Experiment 3
Family Faces Test

Materials

The stimuli were 40 face pictures, including a mixture of family faces and novel, unfamiliar face pictures. The families of the target group members were asked to provide recent photographs of immediate family members. These were used to create a unique family faces set for each target group participant. As a small number of photographs provided were black and white, all pictures in this test were presented as monochrome images to prevent any confounds from colour

TABLE VIII

Results for famous faces test and family faces test

Participant	Famous Faces Test					Family Faces Test				
	Total familiar	Hits	% hits	Correct rejections	% correct rejections	Total familiar	Hits	% hits	Correct rejections	% correct rejections
Sex										
G.I.	20	5	25	19	95	2	1	50	0	100
M.A.*	20	16	80	19	95	–	–	–	–	–
L.I.	20	10	50	16	80	17	14	82	23	100
H.E.	20	9	45	17	85	17	11	65	23	100
A.N.	20	4	20	19	95	2	1	50	38	100
E.R.	20	8	40	18	90	12	11	92	28	100
U.L.	20	16	80	18	90	20	17	85	20	100
T.H.	20	7	35	16	80	13	11	85	27	100
Mean	20	9.38	46.88	17.75	88.75	11.86	9.43	72.71	22.71	100
SD	0	4.53	22.67	1.28	6.41	7.24	6.16	17.57	11.57	0
Comparison mean (N = 11)	20	14.27	71	18.27	91	–	–	–	–	–
SD	0	3.88	19	2.24	11	–	–	–	–	–
Range	20-20	8-19	40-95	13-20	65-100	–	–	–	–	–

Note. The family faces test was not used with the comparison group.
*Participant M.A. did not complete the family faces test.

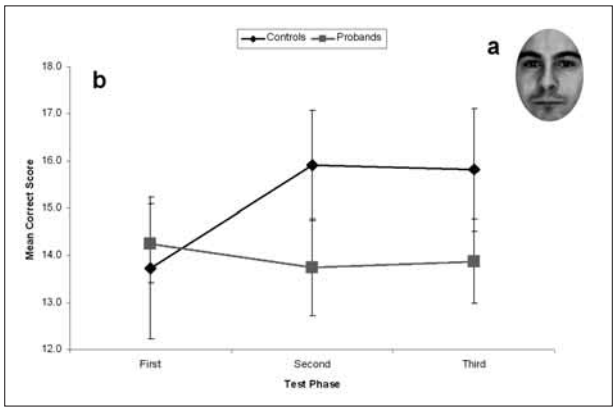

Fig. 2 – *Mean correct identifications on Cardiff central facial features learning task by target and comparison groups. Example of stimuli used for (a) central features learning task. Learning effect during representation of central facial features task shown by comparison group but not by target group (significant interaction at p < .05) shown in (b), demonstrating no significant learning of facial features by target group.*

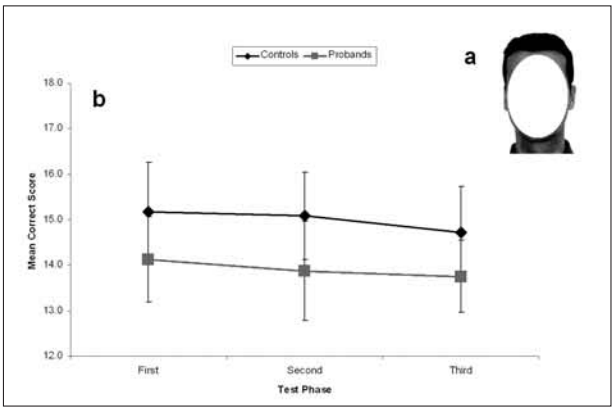

Fig. 3 – *Mean correct identifications on external facial features learning task by target and comparison groups. Example of stimuli used for (a) external features learning task. No learning effect during representation of external facial features task shown by either group.*

picture recognition advantages. Owing to differences in the number of supplied photographs, and constraints on picture suitability (as with the famous faces test, only clear, largely front facing face pictures, without distinctive objects or clothing were used) the number of usable family face pictures varied for each individual (see Table IV). Unfamiliar face pictures consisted of pictures taken by the researchers of friends and colleagues, unknown to the target group participants. Each familiar family face was matched with an unfamiliar face of the same gender and approximate age. To ensure that each participant saw 40 pictures in total, the remaining unmatched trails were filled with randomly selected unfamiliar pictures, drawn from the same pool of face pictures taken by the researchers. All photographs were otherwise prepared in a similar way to the famous faces pictures, but additionally had the background blanked out to remove any potentially confounding non-face objects that members of the target groups might be familiar with in the family pictures.

Procedure

The experiment was conducted using the same procedure as the famous faces test.

Results

No comparison group data were collected for this test, and target group participant M.A. was not tested as family photographs could not be obtained from the immediate relatives. As can be seen in Table VIII, the number of family faces correctly identified as familiar varied from 50% to 92%. Although no comparison group data exist for this test, informal questioning of non-affected family members of the target group suggests that identification rate from the family photographs would typically reach 100%. Crucially however, when the relationship between target group hit rates for family faces and hit rates on the famous faces test was tested using a Spearman's rho test, the results were significant and highly correlated ($r = .95$, $p < .005$), suggesting each is tapping similar facial recognition abilities. This provides some evidence for the validity of both the famous and family faces test, and suggests that the levels of performance on these tests by the target group reflect genuine impairments in face recognition.

Experiment 4
Cardiff Repeated Recognition Test for Faces

Internal facial features have shown to be used preferentially by adults (Ellis et al., 1979) and children (Bonner and Burton, 2004) to recognise faces as they become more familiar, and are therefore important in demonstrating a face-specific recognition deficit.

Materials

This task had two conditions: (A) stimuli consisting of photographs showing central facial features only (Figure 2a), while a second, otherwise identical task (B) used stimuli showing extra-face features only (such as hair, clothing and jewellery; see Figure 3a). The tasks involved a stimulus set consisting of 10 target faces and 3 series of 10 distractor faces taken from the AR face database (Martinez and Benavente, 1998). Equal numbers of male of female pictures were chosen both for the target and distractor sets. Pictures of individuals with glasses or visible jewellery were excluded from the internal facial features condition.

Procedure

In the test phase participants were asked to watch and remember the 10 target images as they

TABLE IX
Correct responses on the Cardiff repeated recognition test for faces (Experiment 4)

	Target group			Comparison group		
Participant	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3
G.I.	15	10	11	11	11	14
M.A.	14	15	14	17	15	16
L.I.	15	14	16	15	15	14
H.E.	13	16	14	13	14	12
A.N.	16	14	15	14	13	13
E.R.	11	12	13	13	12	12
U.L.	16	16	16	14	13	13
T.H.	14	13	12	16	18	16
Mean	14.25	13.75	13.88	14.125	13.875	13.75
SD	1.67	2.05	1.81	1.89	2.17	1.58
Comparison mean (N = 11)	13.73	15.91	15.82	15.18	15.09	14.73
SD	3.00	2.34	2.60	2.14	1.92	2.00
Range	9-17	10-18	10-19	12-19	12-18	12-19

were presented on-screen for 2 seconds each. The three test phases involved the same 10 target images being presented with 10 novel distractor images in a pseudo-random order (different distractor images were used for each test phase) as a single probe recognition test with participants responding by keypress to indicate whether the displayed face was familiar or not. There was no delay between test blocks and the participants experienced the test phases as one unified testing stage. The next stimulus was presented 250 msec after participant response.

Results

As Figure 2b indicates, the target group and controls performed at an equivalent level after the initial presentation of images in the internal features condition. Thereafter, the performance of the two groups differed markedly: the target group's scores did not improve with repeated presentations. For the controls, however, there was a significant improvement in scores between phase one and two, and the maintenance of the high level of recognition at phase three (we speculate that this plateau in recognition performance may be due to retroactive interference from the presence of additional distractors). This interaction was significant when compared using a two way group × test phase ANOVA [$F(2, 34) = 5.037$, $p < .05$]. The results for individual target group members, displayed in Table IX, shows that only one participant from the target group (E.R.) made a sustained improvement in recognition across all three test phases.

These results suggest that the members of the target group can acquire information from unfamiliar faces but, unlike controls, cannot easily build upon that when given an opportunity to learn the faces over repeated presentations. This again indicates a characteristic selective deficit for face recognition in the target group. In contrast, although the mean recognition performance was generally better for the comparison group on the external features condition (see Figure 3b), the difference was not statistically significant. This suggests that the target group performed in a largely similar manner to the comparison group when relying on non-facial recognition cues and that their deficit seems to be face specific. Previous reports on congenital prosopagnosia cases have suggested that other visuo-perceptual deficits may also be present. The poorer performance of the target group on the external facial features test, although not significantly different from the comparison group, may indeed reflect additional (albeit relatively less severe) impairments in general visuo-perceptual performance.

Imagery Assessment

Participants were also asked to complete a modified version of the Marks Vividness of Visual Imagery Questionnaire (MVIQ; Marks, 1973). In the original version, the questionnaire requires aspects of four imagined scenes (a relative or friend, a rising sun, a familiar shop and a country scene) to be rated for the vividness of imagery on a scale of 1 to 5, with 1 being the most vivid. In our version, the "familiar shop" and "relative or friend" items were replaced by items asking about the vividness of imagery for a relative or friend, but focusing on local facial features (shape of face and hairline, colour and shape of eyes, nose, mouth and lips) and emotional facial expressions (happiness, worry, surprise, anger). One of the comparison participants completed the scale incorrectly and so was not included in this analysis.

As can be seen from Table IV, the target group has a higher mean MVIQ score across all items, indicating less vivid mental images. This difference proved significant when tested with a one-tailed Mann-Whitney U test ($U = 8$, $z = -2.845$, $p < .005$, $n = 18$). A further analysis using a 2 × 2 mixed

ANOVA was carried out to assess the relationship between group effects and mean MVIQ score for face and non-face items. There was a significant main effect for group [$F(1, 16) = 19.745$, $p < .0005$] in that the comparison group reported significantly lower MVIQ scores (and hence more vivid imagery) than the target group. There was also a significant main effect for item type [$F(1, 16) = 26.39$, $p < .005$] in that non-face items were reported as more vivid than face items. The interaction (group × item type) was also significant [$F(1, 16) = 11.802$, $p < .005$], in that the target group reported face items as significantly less vivid than non-face items when compared with the comparison group. This suggests that the target group may be impaired in mental imagery *per se*, but particularly when applied to face-related images.

Discussion

Thus far, the report by de Haan (1999) is the only paper to describe three cases of prosopagnosia in one family. In de Haan's (1999) study, the famous faces test was the only test administered, because the family was unwilling to cooperate further. A recent review listed nine single cases of developmental prosopagnosia, five of which mention at least one relative with face recognition problems (Kress and Daum, 2003b). Quite recently, some researchers have examined larger groups of congenital prosopagnosics. Duchaine and Nakayama (2006) have introduced a face memory test taylored to the assessment of congenital prosopagnosia and tested it on eight prosopagnosics. Behrmann, Avidan and their co-workers published a behavioural study on five prosopagnosics and a fMRI study on four of them (Behrmann et al., 2005; Avidan et al., 2005). Though the behavioural data confirmed the face recognition deficit, the fMRI study failed to show any conclusive face processing peculiarities in the prosopagnosic participants. The starting-point for this study was different and required us to develop a standardised questionnaire and a semi-structured interview (Kennerknecht et al., 2002; Grueter, 2004). Some of the interviews proved difficult, partly because those participants with prosopagnosia are often aware of what they consider to be an embarrassing condition, and do not always find it easy to talk to others about it, as has been previously noted in the literature (Damasio et al., 1990). Several participants who indicated face recognition deficits on initial testing did not permit further testing. However, eight affected participants helped us to test the validity of the functional interview by allowing us to test them on a battery of face recognition tests. All members of the target group showed a deficit in at least one test of face recognition when compared with age matched controls. Nevertheless, with a sample of just eight of the initially identified 38 cases, appropriate caution needs to be exercised in assuming that this sample is representative of the wider population of potentially face-recognition impaired individuals until further studies are conducted.

One of the most striking aspects of hereditary prosopagnosia is that, despite poor face recognition abilities, most affected people are able to navigate daily life with relatively little impairment, and may even be unaware of any impairment until quite late in life. In fact, salient facial attributes such as gender and attractiveness are reported as being relatively well perceived by our target group. There is little doubt that hereditary prosopagnosia is a condition, which would normally not cause people to see a doctor or a psychologist. The few we interviewed who saw a doctor about it were often turned away without further diagnostic procedures. Owing to the use of a range of compensatory strategies, however, it is likely that recognising people in everyday life would not be particularly compromised in hereditary prosopagnosia. For example, case B.C. (Duchaine, 2000) relied on various non-face coping strategies for recognising people in everyday life but found his situation unmanageable when he joined the Navy, where the appearance of his colleagues in uniform made adequate recognition all but impossible (an almost identical experience is reported by case T.A. after he joined the army; Duchaine et al., 2003a).

As with colour-blindness, prosopagnosics may be quite unaware that they have a specific deficit until they find themselves in situations where it becomes obvious. They tend to avoid such situations and attribute their difficulties to more general explanations such as having a "bad memory" or "poor eyesight". Indeed, case L.G. (Ariel and Sadeh, 1996) described his problems to the researchers as having "some problems with my eyes". An inherited disadvantage for face recognition could be significantly modulated both on the behavioural and neurodevelopmental levels by, for example, the action of carers in promoting social interaction, and therefore, interest and experience with faces. This sort of effect, as well as any number of possible interactions with other cognitive skills, genetic traits and learned compensatory strategies could lead to a highly-variable functional outcome.

In terms of the traditional distinction between apperceptive and associative prosopagnosia made in the literature on adult-acquired injury, the face recognition impairments of the target group in this study more closely resemble the latter. All affected persons reported a normal perception of attractiveness and an easy identification of gender. This suggests that the perception of facial structures was not grossly distorted. The data collected so far suggest that people with hereditary prosopagnosia

are unable to adequately distinguish between faces and represent them as "distinctive" in some way. However, in spite of this apparent similiarity between hereditary prosopagnosia and associative prosopagnosia resulting from adult acquired injury cases, caution must be exercised in over-extrapolating models from the adult literature to congenital impairments. Both Karmiloff-Smith (1992) and Bishop (1997) have strongly argued that dissociations in task performance and the fractionation of cognitive processes observed after lesions to the adult brain are not a good basis from which to infer the cognitive effects of developmental disorders. Because modularisation occurs as a dynamic process during development, any congenital or early-acquired cognitive impairments may result in a cognitive structure that, while being able to tackle similar tasks, may do so idiosyncratically, or in ways that have resulted as a compensatory response to the impairment. Because of this, the apperceptive-associative distinction could be misleading when applied to hereditary prosopagnosia and is probably best avoided.

Currently, there is no generally accepted sub-classification of prosopagnosia based on when or how the deficit was acquired. Barton et al. (2001) use "developmental" to denote prosopagnosia acquired in childhood and "acquired" for a prosopagnosia occurring later in life. Kress and Daum (2003b) use the term "developmental" for prosopagnosia without overt cause. Ariel and Sadeh (1996) use the term "congenital" for their case of prosopagnosia in a five-year-old child. Only in cases of early-onset prosopagnosias without noticeable exogenic cause and when at least one or more first degree family members are affected, is it really possible to assume a hereditary aetiology. In five of nine single case reports reviewed by Kress and Daum (2003b), the authors mentioned an affected relative, though this was not specially followed up. Therefore, it seems reasonable to classify prosopagnosias according to either a hereditary or an acquired form. Regarding the time of onset, the acquired form may be further subdivided into a childhood and an adult type to better differentiate between aetiologies that may have distinct cognitive implications.

The finding that mental imagery also seems to be particularly impaired in hereditary prosopagnosia adds to what seems to be a complex relationship between imagery and face perception. Mental imagery assessment may help to establish the diagnosis of hereditary prosopagnosia on an individual basis. However, as these results are based on a self-report measure of mental imagery, they need to be extended and supported by further experimental studies, and should be treated as preliminary, albeit interesting, findings. Nevertheless, previous studies have found similar results. Nunn et al. (2001) reported that case E.P. had normal visual imagery for objects but not for faces, suggesting that face perception and imagery may be linked in some way. However, an extensive investigation of imagery for faces with case M.J.H. (who had acquired prosopagnosia after injury at 5 years of age) showed that, although he performed in the lower range on tests designed to tap mental imagery for faces, he did not fulfil the criteria for impairment.

In contrast, M.J.H. was clearly impaired on tasks involving face perception. Curiously, this pattern held true for faces he had learned since becoming prosopagnosic, suggesting imagery was compensating in some way for a piecemeal perception of novel faces. Work with adults has shown that face imagery and face perception may doubly dissociate (Bartolomeo et al., 1998; De Renzi and di Pellegrino, 1998) and that the extent of impairment in imagery may be dependent on lesion location (Barton and Cherkasova, 2003), with imagery only being abolished with anterior temporal lesions. There are perhaps two pertinent questions here: how does imagery relate to the stages of normal face recognition? And: is imagery essential for the development of face recognition? The exact relationship between imagery and the stages of face recognition has yet to be teased out, although Young et al. (1994) have argued that deficits in face imagery may relate directly to the stage at which face processing is impaired. Furthermore, the direction of causality in this relationship is still not known as it remains to be clarified whether imagery necessarily relies on perception for all stages of face processing. It should also be noted that no one of the target group performed at floor level in our tests. In hereditary prosopagnosia, the affected persons' face recognition abilities are measurably weaker than average, but not completely absent.

There are two possible explanations: hereditary prosopagnosia might not be a discrete entity but reflect the lower end of the normal continuum of face recognition skills. Indeed, results from previous literature and from the cases reported here, suggest that hereditary prosopagnosia is not and should not be conceived as behaviourally equivalent to acquired prosopagnosia. Moreover there seems to be a significant individual variation between cases, both quantitatively and qualitatively, despite the fact that all seem to show a selective deficit in face recognition abilities of some type. However, the uniform mode of inheritance across all pedigrees and the marked lack of mental imagery in all members of the target group, suggest that the hereditary prosopagnosia is based on, at least in part, a common neural dysfunction. However, with the proposed mode of autosomal dominant inheritance for face recognition deficits presented in this study the recurrence risk is 50% and it should be possible therefore, to identify children affected by hereditary prosopagnosia at an early age, which may allow for a careful

observation of how these particular skills develop in parallel.

It has also been suggested by Kress and Daum (2003b) that developmental prosopagnosia may be associated with autistic traits. Grelotti et al. (2002) has argued that the well-attested differences in face processing of people diagnosed with an autistic spectrum disorder (ASD) might be due to their lack of social interest, and, therefore, relative inexperience with viewing faces in critical development periods. In all families, we examined this assertion, but could not confirm it. If hereditary prosopagnosia would cosegregate with autistic traits, we would expect to see at least a few cases of ASD in these families.

Though the familial clustering of cognitive deficits has been described, there are no previous reports about the heredity transference of a visual cognitive deficit. Of the recognised cognitive functions, only a few have been shown to be under genetic influence. This includes abilities such as absolute pitch (Baharloo et al., 2000) and some skills involved in language comprehension that have been identified as impaired in developmental dyslexia (Taipale et al., 2003). So far, only one disorder has been subject to successful gene mapping. A single but large family in which half of the members displayed orofacial dyspraxia and a severe speech and language impairment was studied and a point mutation was found in the FOXP2 (forkhead box P2) gene cosegregating with the disorder (Lai et al., 2001).

The pedigree segregation pattern of hereditary prosopagnosia reported in this study can be best explained by simple autosomal dominant inheritance. A coincidental occurrence or environmental influences common to subjects within a family could mimic a hereditary disorder, but then one should expect in such a large collection a certain number of normal transmitters as well as sporadic or isolated familial cases. None of these phenomena was found in the pedigrees presented here. This is also true when considering the concept of polygenic inheritance with major gene(s) or quantitative trait loci in which a threshold effect plays a role.

A selection bias towards familial cases can be excluded as all families were recruited by a single person, most of which were not aware of other affected family members. Whether prosopagnosia is a single trait or a cluster of related subtypes with distinct aetiologies remains an open question. In this paper we have focused on what might be referred to as a global deficit using general diagnoses (for example to recognise a familiar face or not), but we are aware of intra- and interfamilial variability. Genetic dissection will show whether the phenotypic variability is due to pleiotropic (i.e., one mutation causing different phenotypes) and/or heterogenic gene effects (i.e., distinct genes can cause the same phenotype respectively).

In conclusion, there is strong evidence that inheritance plays a role in face recognition deficits. Establishing the potential candidate genes and their role in the development of neuropsychological mechanisms involved in face perception remains as the next step.

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