2005

Congenital Prosopagnosia: Face-Blind from Birth

Marlene Behrmann
Carnegie Mellon University

Galia Avidan
Carnegie Mellon University

Congenital prosopagnosia: face-blind from birth

Marlene Behrmann and Galia Avidan

Department of Psychology and Center for the Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh PA 15213-3890, USA

Corresponding author: Behrmann, Marlene (behrmann@cnbc.cmu.edu).

Congenital prosopagnosia refers to the deficit in face processing that is apparent from early childhood in the absence of any underlying neurological basis and in the presence of intact sensory and intellectual function. Several such cases have been described recently and elucidating the mechanisms giving rise to this impairment should aid our understanding of the psychological and neural mechanisms mediating face processing. Fundamental questions include: What is the nature and extent of the face-processing deficit in congenital prosopagnosia? Is the deficit related to a more general perceptual deficit such as the failure to process configural information? Are any neural alterations detectable using fMRI, ERP or structural analyses of the anatomy of the ventral visual cortex? We discuss these issues in relation to the existing literature and suggest directions for future research.

The failure to recognize faces can have devastating consequences for individuals suffering from this deficit. Prosopagnosia, as this disorder is termed, although rather rare has usually been documented in individuals who have sustained brain damage in adulthood. Acquired prosopagnosia (AP) has been recognized for a long time [1,2] and has provided a unique window into the psychological and neural substrate of face processing. In recent years, attention has been paid to an analogous impairment, congenital prosopagnosia (CP), which refers to the impairment in face processing that is apparent from birth in the absence of any brain damage, and occurs in the presence of intact sensory and intellectual functions. As is true in AP, CP individuals are typically able to acknowledge that a face is present but are unable to identify the face and, hence, rely on voice or other cues such as clothing, gait or accessories for person identification. CP can also be severely debilitating, affecting the recognition of even the most familiar individuals, such as family members or one's self [3]. But the deficit in CP may go beyond recognizing familiar faces – CP individuals also fail to discriminate between unknown faces, suggesting a perceptual, rather than memorial basis, for the deficit. Unlike AP, CP may go undetected as the individual has no means of comparison with normal face processing skills. Also, because CP individuals have had a lifetime to develop compensatory strategies, they are adept at using salient features such as hairline or eye brows for recognition and may even perform normally on standard face recognition tasks if speed is not measured [4,5].

Importantly, the term 'congenital' is used in CP specifically to denote the absence of an acquired lesion or any other neurological concomitant at any stage of development [6,7]. As such, this label excludes individuals with a face processing impairment resulting from visual deprivation, such as in cases of infantile cataracts (see Box 1), or from other developmental problems as in cases of Autism Spectrum Disorder [8]. CP also contrasts with the more general term 'developmental prosopagnosia', which includes individuals with CP but also individuals who have sustained brain damage either before birth or in early childhood [4,9–11]. An important diagnostic criterion for CP is that face perception was never normal in the lifetime of the individual; in most cases we can only rely on self testimony or parents' testimony, although in some cases there is supporting evidence from formal testing carried out during childhood (see [12,13] for a longitudinal case study and [6,14] for CP in children, although note that with the exception of [6], these cases have abnormal EEGs and so may not be pure CPs). A further crucial criterion is that no positive evidence for any neurological impairment should be present. Finally, there is accumulating evidence that there is a familial factor in many cases of CP (as detailed below) and thus, formal testing establishing face processing impairments in additional family members could further assist in the diagnosis of CP rather then AP.

In recent years, a growing number of CP cases have been reported [15], but whether this is because of increasing prevalence or increased recognition of the disorder is not known. In spite of this flurry of research activity, many questions remain unanswered. In additional, many inconsistencies are apparent, perhaps because of the heterogeneity of the disorder and the varying methods of assessment used. We begin by reviewing the existing behavioral studies. Among the issues addressed here are the nature and severity of the face-processing deficit in CP, the extent to which the disorder is selective for faces and the relationship between the deficit in face perception and other forms of perceptual impairments. There are also a few recent studies investigating a possible neural basis for CP and we review these next. We conclude by examining the potential contribution of studies of CP to understanding normal brain–behavior correspondences and by suggesting some directions for future research.

Nature and extent of deficit in CP

Although an impairment in face processing is de facto required for the diagnosis of CP, face processing is not monolithic and can involve, for example, detecting whether a face is present among non-face stimuli,

determining whether two faces are the same or different or recognizing the individual identity of a face [16,17]. Which of these processes is implicated in CP is unclear and this is explored in some recent papers [15]. Table 1 summarizes biographical and performance characteristics from five additional cases from a recent study [18]. Most cases of CP are able to detect faces from among other objects [11]. Also, some CP individuals succeed in relatively easy face matching tasks (perhaps because this can be achieved by matching individual features), but when reaction time or more detailed measures of discrimination such as A prime (A′) is measured and task demands are increased, the deficit is uncovered more clearly [15,18–20]. In these conditions, roughly half the CP cases can discern the gender and age of the face whereas the remaining half cannot [15], and the same holds true for comprehending emotional expressions [6,13,14]. The extent to which CP individuals can recognize famous faces has similarly yielded mixed results, with some apparent successes [21,22] but other clear failures [11,18,19]. One possible explanation concerns the images used in these tests: often these contain cues such as clothing (e.g. Reagan in a cowboy hat) or other salient facial cues (Stallone with a black eye) and reasonable performance may be supported by the presence of these cues. Whether CP individuals can show implicit or covert processing of faces in the absence of explicit knowledge also remains controversial. In one case [6], despite the CP individual's failure to explicitly identify familiar faces, larger amplitude skin conductance response s were measured for familiar compared with unfamiliar faces. This recognition without awareness is not obtained in all cases [13].

A classical distinction made between different forms of prosopagnosia is whether the deficit is 'apperceptive' or 'associative' in nature. The dichotomy, originally offered by Lissauer [23], attributes the former to a deficit in deriving a sufficiently intact percept whereas, in the latter type, the root of the impairment is at the level of recognition or assignment of meaning. Some CP individuals have been categorized as apperceptive [14] whereas others have been diagnosed as being associatively [6] prosopagnosic [24]. Most interesting perhaps is that the disorder may occur in the absence of any apparent deficits in low-level visual abilities [3,11,18,19]. But, as is probably evident, the clearest pattern that emerges from the literature is the heterogeneity of the disorder. Systematic investigations and perhaps standard methods of investigation are urgently needed especially with the recent influx of new cases (one paper reports that they have been contacted by over 150 individuals since they established a website for this purpose [4]) to be able to elucidate the range of behavioral impairments in CP.

Selectivity of the disorder

The extent to which CP (and AP) is specific to faces remains the subject of an ongoing controversy in the field of visual cognitive neuroscience. Neuropsychological case studies have demonstrated a double dissociation between the recognition of faces and objects, suggesting independence or segregation between these processes [25,26] and findings from functional imaging [27], ERP [28] and monkey physiology [29,30] studies indicate the existence of a neural system specialized, if not dedicated, to faces [31]. An alternative view, however, also supported by numerous neuropsychological and imaging investigations, is that there is a single, general-purpose visual process that subserves both objects and faces. The dissociations, then, arise because of the unusual demands placed on the system by faces, the only class of stimuli for which all humans have extraordinary expertise [32]. Because face processing typically involves individual identification (shown a face, one responds with the individual's identity) whereas other objects are usually recognized at a basic level (for example, as a chair or apple or house), faces entail fine-grained discrimination of perceptually similar exemplars within a category. Whether recognition of other visual non-face objects might also be impaired when homogeneous, complex stimuli are used, remains debatable. Several studies have shown that many AP patients have difficulties categorizing exemplars of within-class objects, which share the same complex configuration [13,33–35] although this does not seem to be true for all prosopagnosic subjects [24,36–38]. The controversy between a domain-specific organization of faces versus a more generic system has not been resolved (for further details, see [31,32,39–42]).

Of the nine cases of CP reviewed by Kress and Daum [15], two appear to be impaired in the recognition of non-face objects, one mildly (subject AB) and one severely (subject LG). We note, however, that the methods of assessment vary considerably and that reaction time is generally not used despite the possibility that the CP individuals might be inordinately slow or might even trade speed off against accuracy. Using an old vs. new recognition memory paradigm and measuring both A′ and reaction time, Duchaine and Nakayama [20] showed a clear dissociation between faces and other object categories (tools, cars, horses) in four out of their seven subjects. The five CP subjects studied by us [18] are all impaired at discriminating between common objects and between novel objects ('Greebles') especially when the discrimination is at the individual level (for example, two different chairs or two Greebles of the same family and gender) even when the pair to be discriminated is visible to the subject for an unlimited duration (see Table 1). Importantly, this deficit is less marked than that for faces and its severity varies considerably among the CP individuals [18]. Some CP subjects also read more slowly than their counterparts [14].

The relationship between configural and face processing in CP

The idea that configural processing is required for face processing is not new, and it has long been suggested that a loss of configural processing may underlie prosopagnosia. Recent support for this view comes from the finding that patients with acquired lesions of the fusiform face area are impaired at deriving the spatial relations between the components of the face [43]. The failure to take the spatial relations between elements into account (see Box 1) forces the individual to rely on a more

piece-meal or feature-based strategy in constructing face representations [44].

Evidence for the strong relationship between faces and configural processing also comes from studies comparing processing of upright versus inverted faces, relative to processing upright versus inverted objects. In normal individuals, recognition and discrimination of faces is notoriously better for upright than for inverted faces [45] and this holds to a lesser extent for objects. In general, this decrement under inversion or 'face inversion effect' is taken to be a hallmark indicator of the fact that faces in their upright configuration are processed as a whole; when they are inverted, the whole or configuration is no longer available and a more part-based system is utilized, leading to the cost in reaction time and accuracy for inverted compared with upright faces [46–48]. Individuals with AP often do not show the decrement under inversion and may even show better performance on inverted than upright faces (inversion superiority effect) presumably because their feature-based strategy can proceed unhampered by attempts at configural processing [49,50] (see Figure 1). Many CP individuals are also not adversely affected by inversion of faces [11,18] and can also show the inversion superiority effect (Figure 1).

The failure to derive configurations is thought to be particularly devastating for face processing relative to processing other objects, given the homogeneity between exemplars and the need to rely on the second-order rather than first-order statistics of the input [51]. A configural impairment may affect other visual stimuli too if, as is true for faces, the spatial relations between the components need to be represented to differentiate perceptually similar exemplars (see Figure 2). But what exactly constitutes configural processing is itself controversial [40] and the subject of an ongoing debate [52] (see Box 1).

Neural investigations of CP

Only a small number of studies have conducted neural investigations of CP. Two studies have used evoked response potentials (ERP) with specific exploration of the N170 potential, recorded from a relatively circumscribed region at the posterior-inferior aspect of the temporal lobe [28,53]. In one study, subject YT, monitored the frequency of occurrence of butterflies in a stream of pictures of faces, cars, furniture and nonsense stimuli (scrambled input). Although a conspicuous N170 was detected [54], it was elicited for objects as well as for faces, in contrast with the known face-selectivity in normal individuals, yielding a reduced amplitude difference between stimulus types. In a second study with two CP individuals [5], the finding was even more dramatic as neither individual showed any ERP difference between houses and faces. This lack of specificity in this early waveform suggests that the initial encoding of input may not be sufficiently precise to yield fine-grained discrimination.

Reduction or elimination of face-selectivity was also reported in a functional magnetic resonance imaging study [55] in which similar activations for faces and houses were found in the fusiform face area (the pre-eminent area for face processing; FFA). In fact, there was no face-selective activation in any area along the ventral visual pathway even when a permissive threshold was used. However, it is important to note that two of the three subjects who participated in this study (GA and RP) and showed the most abnormal pattern of activation, sustained injuries during childhood (excluding them from the diagnosis of CP which we offer) and this might account for the lack of activation or face selectivity.

In contrast to these findings, subject YT, who showed reduced face selectivity in the ERP study reported above exhibited face-related activation in ventral visual cortex that mirrored that of normal individuals in terms of site of activation, activation profile and hemispheric laterality [56]. The only possible difference between YT and the controls was a slightly reduced degree of selectivity for faces over objects in the lateral occipital cortex. This finding has been replicated and extended in a group of four CP individuals [57] all of whom evinced a normal pattern of fMRI activation in the fusiform gyrus (FFA) and in other ventral occipito-temporal (VOT) areas, in response to faces, buildings and other objects, shown both as line drawings and as more natural images (see Figure 3). These CP individuals also showed normal adaptation levels and, like control subjects, exhibited evidence of global representation of faces in the FFA. The absence of a BOLD-behavioral correlation (impaired behavior, normal BOLD pattern) suggests that face-related activation in ventral cortical areas might be necessary but may not be sufficient for normal face identification. Interestingly, these CP subjects exhibited robust bilateral face-related activation in prefrontal regions (pre-central sulcus, inferior frontal sulcus, anterior lateral sulcus) in the context of a one-back, working memory task. This was in sharp contrast to their control group who only exhibited some right lateralized activation in the pre-central sulcus. The poor performance exhibited by CP subjects (Figure 3b) on the one-back task specifically for face stimuli suggests that this prefrontal activity is related to working memory [58–60]. Alternatively, this activity could reflect the recruitment of compensatory mechanisms under taxing perceptual conditions by the CP subjects. Further research is required to determine the exact role of this activation in face processing in CP individuals. As is apparent, the neural mechanism underlying CP remains unspecified and structural scanning typically reveals no observable impairment [6]. We should note that detailed structural MRI volumetric measurement of the ventral cortex suggests a smaller right temporal lobe. Relative to controls, YT had a smaller right temporal lobe [19]. We have now replicated this pattern in other CP individuals (Behrmann *et al.*, unpublished data); when the volumes are normalized for difference in head size by taking intracranial region into account, relative to matched controls, the CP subjects have a smaller right anterior fusiform region and a larger right mid/posterior-fusiform gyrus. No differences are observed in the hippocampus or parahippocampal region, suggesting that it is not the entire temporal cortex that is reduced but rather the fusiform gyrus, the pre-eminent structure for face

processing. Whether this structural difference is a result of CP, however, revealing atrophy from under-use or whether this is the underlying predisposition that triggers CP in the first place remains unknown and distinguishing between cause and effect will be crucial.

Conclusion

Aside from the intrinsic interest in the study of neurodevelopmental disorders, CP has the potential to inform our understanding of the psychological and neural mechanisms underlying face processing and their relationship to non-face processing. For example, the fact that CP exists at all and that, over the course of their lifetime the deficit is not resolved in these individuals, suggests that there is a limit on the plasticity of the human ventral visual system; this is in marked contrast with the rather widespread plasticity reported in other sensory domains as well as in higher-cognitive skills such as language [61,62]. Studying CP individuals also enables us to examine the neural mechanisms mediating face recognition using fMRI or other imaging techniques, unaffected by damage that might disrupt normal blood flow or neurovascularization in cases of AP [63]. Hence the fact that the CP individuals show normal BOLD activation of the fusiform face area and other ventral cortical structures is highly provocative and challenges us to generate a more refined and precise notion of the computational properties of these occipito-temporal areas. We should also note that CP might not be as rare as previously thought and, like other developmental disorders (see Box 2), questions about intervention and training will become more pressing.

Finally, many of the individuals with CP tested so far, both in our studies (see Table 1) and in the literature [20], have a family member who is also impaired at face processing. This familial component is of great interest and studies of the genetic predisposition and mechanism will allow us to start building bridges between behavior and cortical development. The only known genetic investigations of which we are aware to date (Grüter, M., MD thesis: Genetik der kongenitalen Prosopagnosie, University of Münster, Germany, 2004) reports that the cumulation segregation ratios are compatible with a simple autosomal dominant mode of inheritance but the molecular DNA and linkage studies have not been reported. Despite the recent progress in the characterization of CP, many outstanding questions exist (see Box 3) and a full explanation of the psychological and neural mechanisms giving rise to CP remains elusive.

Acknowledgements

The writing of this review was supported by a research award from the National Institutes of Mental Health (MH 54246).

References

1 Bodamer, J. (1947) Die Prosop-agnosie. *Archiv für Psychiatrie und Nervkrankheiten* 179, 6–53

2 Behrmann, M. and Moscovitch, M. (2001) Face recognition: evidence from intact and impaired performance. In *Handbook of Neuropsychology* (Vol. 4) (Boller, F. and Grafman, J., eds), pp. 181–206, Elsevier

3 Nunn, J.A. *et al.* (2001) Developmental prosopagnosia: should it be taken at face value? *Neurocase* 7, 15–27

4 Duchaine, B.C. and Nakayama, K. (2004) Developmental prosopagnosia and the Benton Facial Recognition test. *Neurology* 62, 1219–1220

5 Kress, T. and Daum, I. (2003) Event-related potentials reflect impaired face recognition in patients with congenital prosopagnosia. *Neurosci. Lett.* 352, 133–136

6 Jones, R.D. and Tranel, D. (2001) Severe developmental prosopagnosia in a child with superior intellect. *J. Clin. Exp. Neuropsychol.* 23, 265–273

7 Galaburda, A.M. and Duchaine, B.C. (2003) Developmental disorders of vision. *Neurol. Clin.* 21, 1–16

8 Barton, J.J.S. *et al.* (2004) Are patients with social developmental disorders prosopagnosic? Perceptual heterogeneity in the Apserger and social-emotions processing disorders. *Brain* 127, 1706–1716

9 Barton, J.J.S. *et al.* (2003) Developmental prosopagnosia: a study of three patients. *Brain Cogn.* 51, 12–30

10 Farah, M.J. *et al.* (2000) Early commitment of neural substrates for face recognition. *Cogn. Neuropsychol.* 17, 117–123

11 de Gelder, B. and Rouw, R. (2000) Configural face processes in acquired and developmental prosopagnosia: evidence for two separate face systems? *Neuroreport* 11, 3145–3150

12 McConachie, H.R. (1976) Developmental prosopagnosia: a single case report. *Cortex* 12, 76–82

13 De Haan, E.H.F. and Campbell, R. (1991) A fifteen year follow-up of a case of developmental prosopagnosia. *Cortex* 27, 489–509

14 Ariel, R. and Sadeh, M. (1996) Congenital visual agnosia and prosopagnosia in a child. *Cortex* 32, 221–240

15 Kress, T. and Daum, I. (2003) Developmental prosopagnosia: a review. *Behav. Neurol.* 14, 109–121

16 Grill-Spector, K. *et al.* (2004) The fusiform face area subserves face perception, not generic within-category identification. *Nat. Neurosci.* 7, 555–562

17 Liu, J. *et al.* (2002) Stages of processing in face perception: a MEG study. *Nat. Neurosci.* 5, 910–916

18 Behrmann, M. *et al.* Detailed exploration of face-related processing in congenital prosopagnosia: 1. Behavioral findings. *J. Cogn. Neurosci.* (in press)

19 Bentin, S. *et al.* (1999) Selective visual streaming in face recognition: evidence from developmental prosopagnosia. *Neuroreport* 10, 823–827

20 Duchaine, B. and Nakayama, K. Dissociations in face and object recognition in developmental prosopagnosia. *J. Cogn. Neurosci.* (in press)

21 Duchaine, B.C. (2000) Developmental prosopagnosia with normal configural processing. *Neuroreport* 11, 79–83

22 Temple, C.M. (1992) Developmental memory impairment: faces and patterns. In *Mental Lives: Case Studies in Cognition* (Campbell, R. ed.), pp. 199–215, Blackwell

23 Lissauer, H. (1890) Ein fall von seelenblindheit nebst einem beitrage zur theorie derselben. *Arch. Psychiatr. Nervenkr.* 21, 222–270

24 De Renzi, E. *et al.* (1991) Apperceptive and associative forms of prosopagnosia. *Cortex* 27, 213–221

25 McNeil, M. and Warrington, E.K. (1993) Prosopagnosia: a face-specific disorder. *Q. J. Exp. Psychol.* 46, 1–10

26 Moscovitch, M. *et al.* (1997) What is special about face recognition? Nineteen experiments on a person with visual object agnosia and dyslexia but normal face recognition. *J. Cogn. Neurosci.* 9, 555–604

27 Kanwisher, N. *et al.* (1997) The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* 17, 4302–4311

28 Bentin, S. *et al.* (1996) Electrophysiological studies of face perception in humans. *J. Cogn. Neurosci.* 8, 551–565

29 Perrett, D.I. *et al.* (1979) Temporal lobe cells of the monkey with visual responses selective for faces. *Neurosci. Lett.* S3, S358

30 Rolls, E.T. (1984) Neurons in the cortex of the temporal lobe and in the amygdala of the monkey with responses selective for faces. *Hum. Neurobiol.* 3, 209–222

31 Kanwisher, N. (2000) Domain specificity in face perception. *Nat. Neurosci.* 3, 759–763

32 Tarr, M.J. and Cheng, Y.D. (2003) Learning to see faces and objects. *Trends Cogn. Sci.* 7, 23–30

33 Gauthier, I. *et al.* (1999) Can face recognition really be dissociated from object recognition? *J. Cogn. Neurosci.* 11, 349–370

34 Etcoff, N. *et al.* (1991) Can we lose memories of faces? Content specificity and awareness in a prosopagnosic. *J. Cogn. Neurosci.* 3, 25–41

35 Damasio, A.R. *et al.* (1982) Prosopagnosia: anatomic basis and behavioral mechanisms. *Neurology* 32, 331–341

36 Sergent, J. and Signoret, J-L. (1992) Functional and anatomical decomposition of face processing; Evidence from prosopagnosia and PET study of normal subjects. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 335, 55–62

37 Farah, M.J. *et al.* (1995) The inverted face inversion effect in prosopagnosia: evidence for mandatory, face-specific perceptual mechanisms. *Vision Res.* 35, 2089–2093

38 Duchaine, B.C. *et al.* (2004) Normal Greeble learning in a severe case of developmental prosopagnosia. *Neuron* 43, 469–473

39 Tarr, M.J. and Gauthier, I. (2000) FFA: a flexible fusiform area for subordinate-level visual processing automatized by expertise. *Nat. Neurosci.* 3, 764–769

40 Maurer, D. *et al.* (2002) The many faces of configural processing. *Trends Cogn. Sci.* 6, 255–260

41 Grill-Spector, K. (2003) The neural basis of object recognition. *Curr. Opin. Neurobiol.* 13, 159–166

42 Haxby, J.V. *et al.* (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293, 2425–2429

43 Barton, J.J.S. *et al.* (2002) Lesions of the fusiform face area impair perception of facial configuration in prosopagnosia. *Neurology* 58, 71–78

44 Levine, D.N. and Calvanio, R. (1989) Prosopagnosia: a defect in visual-configurational processing. *Brain Cogn.* 10, 149–170

45 Yin, R.K. (1969) Looking at upside-down faces. *J. Exp. Psychol.* 81, 141–145

46 Farah, M.J. (1996) Is face recognition 'special'? Evidence from neuropsychology. *Behav. Brain Res.* 76, 181–189

47 Donnelly, N. and Davidoff, J. (1999) The mental representation of faces and houses: issues concerning parts and wholes. *Vis. Cogn.* 6, 319–343

48 Leder, H. and Bruce, V. (2000) When inverted faces are recognized: the role of configural information in face recognition. *Q. J. Exp. Psychol. A* 53, 513–536

49 Farah, M.J. *et al.* (1996) What causes the face inversion effect? *J. Exp. Psychol. Hum. Percept. Perform.* 21, 1–7

50 Marotta, J.J. *et al.* (2002) The effects of inversion and rotation on face processing in prosopagnosia. *Cogn. Neuropsychol.* 19, 31–47

51 Rhodes, G. (1988) Looking at faces: first-order and second-order features as determinates of facial appearance. *Perception* 17, 43–63

52 Navon, D. (2003) What does a compound letter tell the psychologist's mind? *Acta Psychol. (Amst.)* 114, 273–309

53 Eimer, M. and McCarthy, R.A. (1999) Prosopagnosia and structural encoding of faces: evidence from event-related potentials. *Neuroreport* 10, 255–259

54 Bentin, S. and Deouell, L. (2000) Structural encoding and identification in face processing: ERP evidence for separate mechanisms. *Cogn. Neuropsychol.* 17, 35–54

55 Hadjikhani, N. and De Gelder, B. (2002) Neural basis of prosopagnosia. *Hum. Brain Mapp.* 16, 176–182

56 Hasson, U. *et al.* (2003) Face-selective activation in a congenital prosopagnosic subject. *J. Cogn. Neurosci.* 15, 419–431

57 Avidan, G. *et al.* Detailed exploration of face-related processing in congenital prosopagnosia: 2. Functional neuroimaging findings. *J. Cogn. Neurosci.* (in press)

58 Haxby, J.V. *et al.* (2000) Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage* 11, 380–391

59 Druzgal, T.J. and D'Esposito, M. (2003) Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *J. Cogn. Neurosci.* 15, 771–784

60 Sala, J.B. *et al.* (2003) Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. *Neuropsychologia* 41, 341–356

61 Elbert, T. and Rockstroh, B. (2004) Reorganization of human cerebral cortex: the range of changes following use and injury. *Neuroscientist* 10, 129–141

62 Neville, H. and Bavelier, D. (2002) Human brain plasticity: evidence from sensory deprivation and altered language experience. *Prog. Brain Res.* 138, 177–188

63 D'Esposito, M. *et al.* (2003) Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat. Rev. Neurosci.* 4, 863–872

64 Kimchi, R. (2003) Visual perceptual organization: a microgenetic analysis. In *Perceptual Organization in Vision: Behavioral and Neural Perspectives* (Kimchi, R. *et al.* eds), pp. 117–154, Erlbaum

65 Gauthier, I. and Tarr, M.J. (2002) Unraveling mechanisms for expert object recognition: bridging brain activity and behavior. *J. Exp. Psychol. Hum. Percept. Perform.* 28, 431–446

66 Le Grand, R. *et al.* (2001) Neuroperception. early visual experience and face processing. *Nature* 410, 890

67 Maurer, D. *et al.* (2005) Missing sights: consequences for visual cognitive development. *Trends Cogn. Sci.* DOI: 10.1016/j.tics.2005.01.006

68 Le Grand, R. *et al.* (2003) Expert face processing requires visual input to the right hemisphere during infancy. *Nat. Neurosci.* 6, 1108–1112

69 Behrmann, M. *et al.* Behavioral change and its neural correlates in prosopagnosia after expertise training (in press)

70 Demonet, J.F. *et al.* (2004) Developmental dyslexia. *Lancet* 363, 1451–1460

71 Peretz, I. and Hyde, K.L. (2003) What is specific to music processing? Insights from congenital amusia. *Trends Cogn. Sci.* 7, 362–367

72 Vargha-Khadem, F. *et al.* (1998) Neural basis of an inherited speech and language disorder. *Proc. Natl. Acad. Sci. U. S. A.* 95, 12695–12700

73 Lai, C.S. *et al.* (2001) A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 413, 519–523

74 Fisher, S.E. *et al.* (2003) Deciphering the genetic basis of speech and language disorders. *Annu. Rev. Neurosci.* 26, 57–80

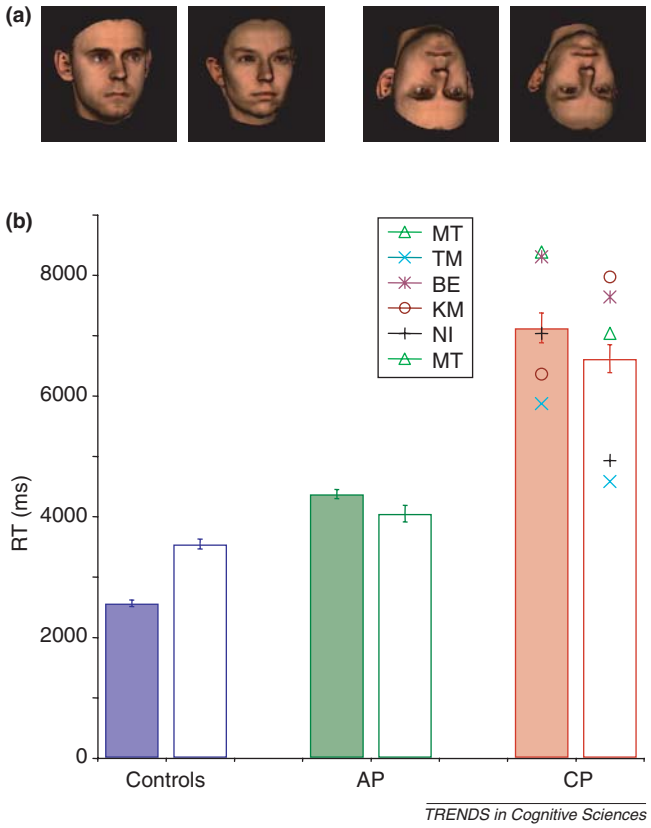

Figure 1. Face processing in congenital and acquired prosopagnosia. CP, AP and control subjects participated in a two-alternative forced choice task that included discrimination of upright and inverted faces [18]. The faces used in this task were unfamiliar to the participants, hence the task was largely perceptual and did not require the use of previous knowledge or memory about the faces. The inclusion of inverted faces enables the evaluation of configural processing in the prosopagnosic subjects (both acquired and congenital). **(a)** Examples of the stimuli used in the experiment. **(b)** Mean reaction time (RT) (±1 SE) for controls, AP and CP individuals (with individual symbols to denote each CP subject separately) for upright (filled bars) and inverted (open bars) faces. Note that despite the fact that this was a perceptual discrimination task that did not require face recognition, both patient groups were dramatically impaired compared with the control group. Interestingly, CP subjects were even slower than the AP subjects. Both AP and CP groups exhibited the inversion-superiority effect (although not all individual subjects exhibited this effect), which supports the notion that their configural face processing is impaired.

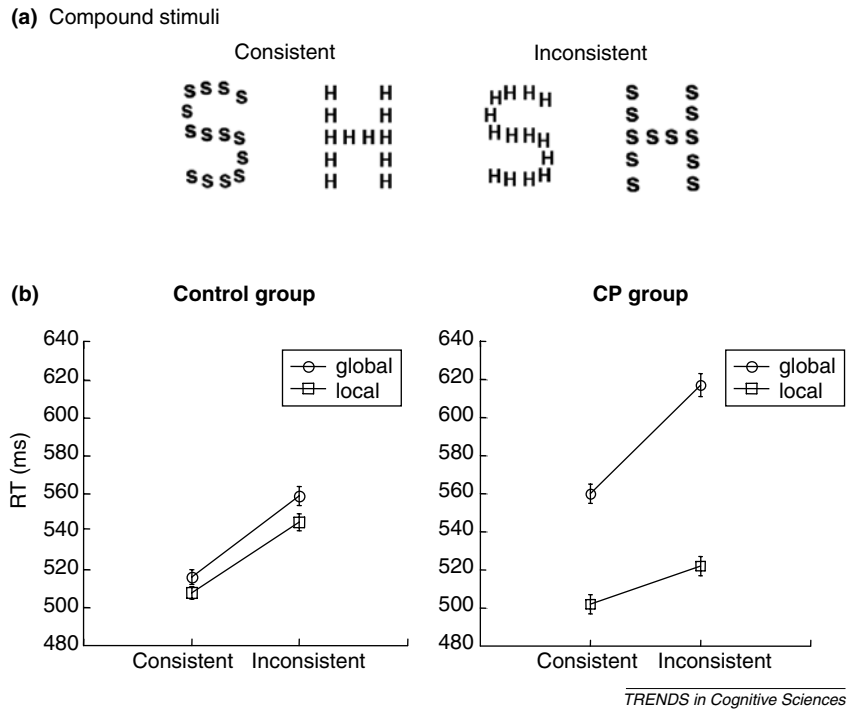

Figure 2. Deriving global from local elements in CP. Five CP individuals and controls identified compound letters at a global or local level in separate blocks of trials. Each stimulus remained on the screen until response (key press: H or S). **(a)** Examples of four stimuli, two of which have identities that are consistent at the local and global level and two of which have identities that are inconsistent. **(b)** Mean RT (±1SE) for controls and CP individuals [18]. As is evident, CP individuals show normal

speed in identifying local letters but are slow at deriving the global whole from the local elements, suggestive of a failure in representing the spatial relations between components of a display and this form of configural processing may have direct impact on face processing. Note that when the global letter is inconsistent with the local identity but must be identified, interference from the local onto the global (additional RT cost) is observed in CP. In a second, related experiment (see [18]), CP individuals, in contrast with normal controls, are primed by the elements in a display rather than by the overall shape. Thus, when shown an ambiguous display such as a square made of small circles, performance was enhanced for a subsequent display containing circles rather than for a display containing a square. Controls were primed for the square and showed a bias for global shape perception [64].

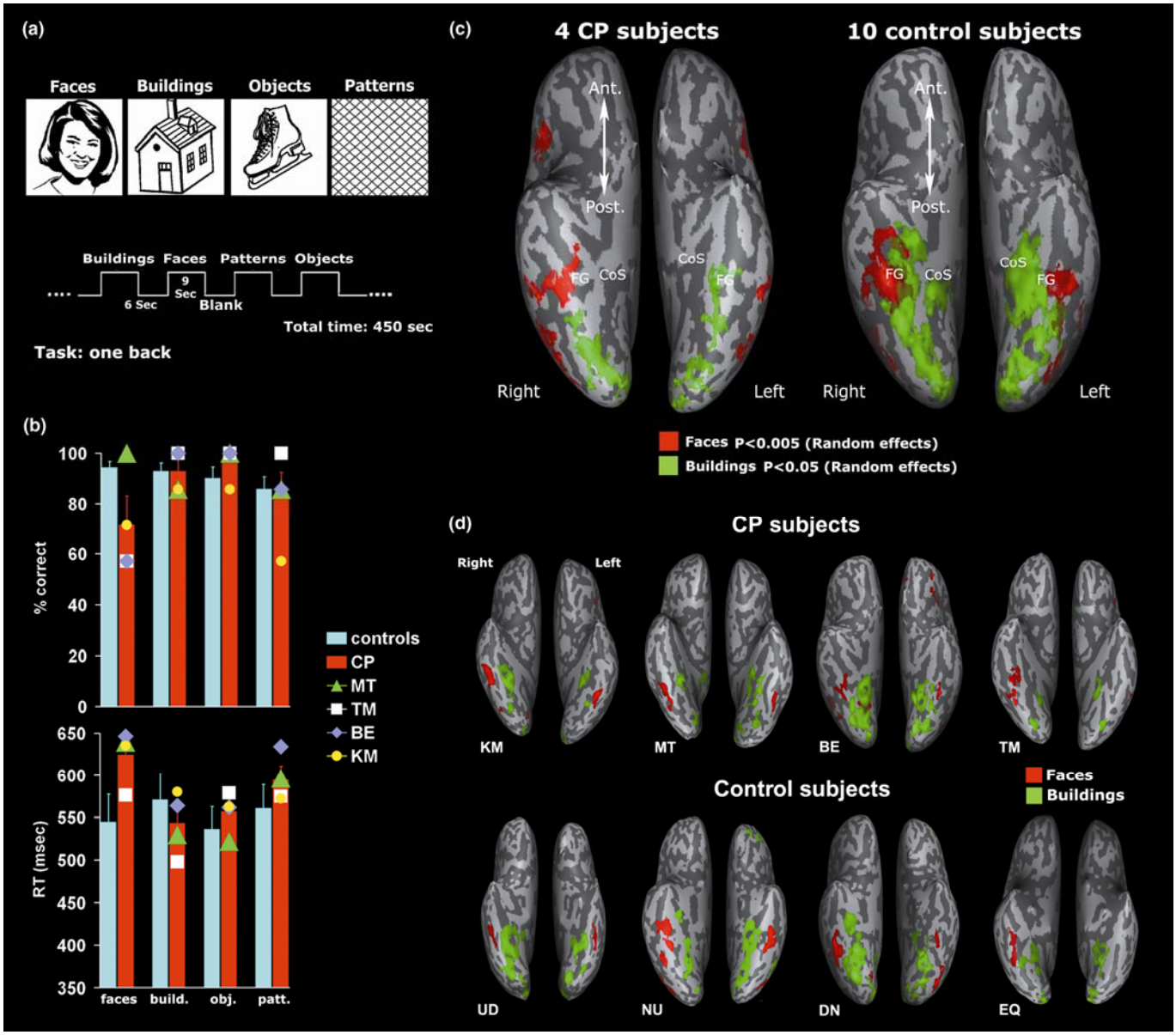

Figure 3. fMRI face-related activation in congenital prosopagnosia. Four congenital prosopagnosia (CP) subjects were tested on a conventional object mapping experiment [57]. **(a)** Subjects viewed short epochs containing line drawings of faces, buildings, common objects or geometrical patterns, while maintaining fixation and performing a one-back memory task. **(b)** Percent correct and reaction time on the one-back memory task performed in the scanner for the CP (red) and control subjects (light blue); error bars indicate standard error of the mean (SEM) across subjects in each group, and colored symbols the data for individual CP subjects. Note that the CP group was both less accurate and slower than the control group on performance of this task. However, there was some variability within the group with some subjects trading off speed for accuracy or vice versa (compare subjects TM and MT). **(c)** Averaged face (red) and building (green) activation maps of the CP subjects and control subjects projected on an inflated brain representation shown from a ventral view. The activation is projected on the same brain and is shown in the same statistical threshold (multi-subject GLM statistics, faces: p<0.005 buildings: p<0.05 random effects) to enable direct comparison between the two groups. Note that both controls and CP subjects exhibited bilateral face-related activation in the fusiform gyrus and lateral occipital region and building-related activation in the collateral sulcus. Abbreviations: FG, fusiform gyrus; CoS, collateral sulcus; Ant., anterior; Post., posterior. **(d)** Face and building activation maps are shown for each of the CP subjects and for four representative control subjects. Note the substantial similarity in the activation pattern exhibited by all CP subjects and controls.

Box 1. The contribution of early visual experience to the development of intact configural face processing.

Faces are complex visual stimuli and their processing therefore involves several different psychological processes [40,48,65]. Le Grand *et al.* [66] recently used a sensitive behavioral task to study some of these processes in a group of individuals born with congenital bilateral cataracts. Crucially, the cataracts precluded retinal stimulation until surgical removal (62–187 days following birth in these individuals) and so studying this patient group allows the assessment of early visual deprivation on the development of normal face processing (see also [67]. In the task

they used, faces could be differentiated from each other in two ways (see Figure I): either the face features were changed (featural set) or the features remained constant but the spacing between them varied (configural set). Interestingly, bilateral cataract patients were substantially impaired compared with control subjects on the configural but not on the featural task, suggesting that very early visual experience (first few months of life) is necessary for the normal development of expert face processing which largely relies on second-order, configural processing. That these individuals do not acquire these abilities even after many years of exposure to faces (like case with CP) implies that plasticity is limited and that the normal development of face processing is to a large extent experience-dependent.

In a second study, Le Grand and colleagues [68] explored hemispheric differences in face processing by testing congenital left eye deprivation (right hemisphere) or right eye deprivation (left hemisphere) cataract patients. Crucially, left but not right eye cataract patients exhibited a specific right hemisphere dependence on second-order configural but not featural processing. This suggests that the right hemisphere is more crucial for the development of intact configural processing. Whether the impairment in configural processing exhibited by these patients is unique to the domain of faces or whether it will also be evident for other stimulus categories when configural processing is required remains to be explored. These findings, however, advance our understanding of the development of different components of normal face processing [40] and raise several interesting questions in relation to CP. First, if and to what extent might CP evolve from lack of exposure or 'training' of the visual system and, if so, what underlying neuronal impairment induces such 'deprivation'. Furthermore, why does face processing and its neural substrate lack plasticity to a large extent [10], and given this, what training regimes might ameliorate these processes in different patient populations (cataract, CP, AP). Future studies combining behavioral and imaging techniques will be required to address these fascinating issues [69].

Figure I. Face stimuli used in the study by Le Grand *et al.* [66]. **(a)** Faces that differ in the spacing among features. **(b)** Faces that differ in the shape of individual features (eyes and mouth). Reproduced with permission from [66].

Box 2. Relationship to other neurodevelopmental disorders

Interestingly, just as a deficit in visual perception may arise congenitally and without an obvious neural basis (i.e. CP), parallel disorders exist in other visual and non-visual domains. The most obvious parallel is with developmental dyslexia (DD), also known as specific reading disability. DD is also characterized as a disorder in which sensory and intellectual functions are intact and in which motivation and opportunities for acquiring reading are normal [70]. As with CP, understanding the biological origin of DD is of major importance and detailed analysis of the phonological disorder, its specificity, sensitivity to remediation and neural correlate is the topic of many recent investigations. The increased prevalence of DD (roughly 5–17% of the population) relative to CP may be partially attributed to the enormous obstacle faced by an individual in a society that demands literacy whereas the consequences of CP are not as pressing. Many functional imaging studies have been conducted in individuals with developmental dyslexia but much controversy exists concerning the cortical structures that are implicated in this disorder [70].

A further disorder, which seems remarkably similar to CP but which occurs in the auditory domain is congenital amusia. This disorder manifests in dramatic difficulties in appreciating, perceiving and memorizing music, but no difficulties recognizing and processing non-music material such as voices, spoken lyrics or environmental sounds. Like CP, congenital amusia cannot be explained by sensory or brain anomalies, low intelligence or music deprivation. Similar questions to those raised in relation to CP, concerning the specificity of the disorder to music and the possibility of a more fundamental perceptual impairment, giving rise to the amusia have been studied [71]. It has been suggested, for example, that a more fundamental deficit in pitch discrimination may underlie congenital amusia but as in the case of CP the disorder may not be homogeneous, as a problem in the temporal domain of music perception has also been reported in some individuals. An anatomical MRI scan of one such individual's brain failed to reveal any macrostructural abnormalities [71]. Finally, congenital amusia also seems to run in families, suggesting the possibility that again, similar to CP, this defect may be genetically determined.

There is one final congenital disorder that is relevant and it affects language and speech production as well as oromotor control and articulation [72]. Of particular interest for the case of CP is that genetic testing in the KE family, half of whom suffer from this disorder, has identified a mutation in the FOXP2 gene [73,74]. Functional MRI studies have shown differences between affected and unaffected family members in Broca's area with the affected members revealing a more posterior and more extensively bilateral pattern of activation in all speech tasks. Detailed volumetric analysis has shown that the volume of the caudate nucleus, especially in the superior portion, was reduced bilaterally in the affected family members compared with both the unaffected members and the group of age-matched controls. These findings suggest that the FOXP2 gene is involved in the development of the neural systems that mediate speech and language. Whether similar mutations (and accompanying cortical volumetric changes) will be found in CP remains to be determined but the possibility of doing so lies tantalizingly before us.

Box 3. Questions for future research

- Whereas normal individuals are capable of recognizing almost an unlimited number of different faces, CP individuals are markedly impaired and typically recognize only a limited subset of faces. How is the neuronal representation of familiar faces different from those of unfamiliar ones, in both normal and CP individuals?
- To what extent do CP individuals exhibit evidence for covert recognition of faces? Can we find behavioral (such as increased priming) and neuronal correlates of covert recognition in these individuals?
- Given that CP individuals never develop normal face recognition despite seemingly normal exposure to faces throughout their life, it is important to understand whether and to what extent face processing in such individuals can be improved following specifically designed training regimes. Related questions are what regimes will be maximally effective to achieve this goal and what underlying neuronal changes will accompany such behavioral improvement.
- There is growing evidence suggesting that there is a familial factor in CP. It will be crucial to determine whether there is an underlying genetic basis for CP. Establishing a link between a specific genetic makeup and high-level cognitive functions such as face processing will be a dramatic breakthrough in the way we understand human cognition.
- In addition to the visual cortex, face processing involves other brain regions such as prefrontal cortex. It will be important to understand the role of these regions in face processing and representation in both normal and CP individuals. This issue is of great interest as there is now evidence suggesting that prefrontal cortex might be engaged differently in face processing in CP individuals compared with normal individuals.

Table 1. Behavioral and fMRI data for individuals with CP

Initials	Gender	Age	[a]Intelligence	Basic visual processes	Affected relatives	[b]Recognition (famous faces)	Face discrim.	Non-face discrim.	Configural processing	fMRI face and object activation
TM	M	27	N	N	Mother (KM)	N–	N–	N–	N–	N
KM	F	60	N	N	Son(TM)	N–	N–	N–	N–	N
NI	M	40	N	N	Unknown	N–	N–	N–	N–	Unknown
MT	M	41	N	N	Father?	N–	N–	N–	N–	N
BE	F	29	N	N	Mother mildly affected	N–	N–	N–	N–	N

[a]N, normal, [b]N–, abnormal. The five CP subjects listed here participated in a detailed behavioral study testing their low-level visual processing as well as their face and object processing [18]. Four of these subjects also participated in a functional imaging experiment [57] (see Figure 3).