Impairment of the face processing network in congenital prosopagnosia

Galia Avidan[1], Marlene Behrmann[2]

[1]Department of Psychology, Ben-Gurion University of the Negev, Israel, [2]Department of Psychology, Carnegie Mellon University, USA

TABLE OF CONTENTS

1. ABSTRACT

The goal of the current paper is to review recent findings concerning the neural basis of congenital prosopagnosia (CP), a lifelong impairment in face processing that occurs in the absence of explicit brain damage. As such, CP offers a unique model for exploring the psychological and neural bases of normal face processing. We start by providing background about face perception and representation, and then review behavioral evidence gleaned from individuals with CP. We then review recent functional and structural neural investigations which offer a comprehensive account of the mechanisms underlying CP and support a characterization of this impairment as a disconnection syndrome rather than as a syndrome related to focal brain malfunction. We end the paper by offering a general framework for CP which, we believe, best integrates the behavioral and neural findings, and offers a platform for generating hypotheses for future studies. There remain many open issues in our understanding of CP and, to address these unanswered questions, we lay out several future research directions and testable hypotheses for further investigation.

2. GENERAL BACKGROUND: FACE PERCEPTION AND REPRESENTATION

Face perception is probably the most developed visual perceptual skill in humans, most likely due to its unique evolutionary and social significance. In terms of image properties, faces are perceptually similar, homogeneous exemplars drawn from a single class and are all essentially composed of the same local elements (two eyes, a nose, cheeks and a mouth) in the same spatial layout (e.g., eyes above the nose). Despite this basic physical similarity, humans can identify individual faces accurately and rapidly even across radically different viewing conditions (e.g. lighting, vantage points) and structural changes of the face as the person ages or conveys different expressions. To add further complexity to the task of face perception, in addition to identity information, faces simultaneously carry a large amount of information (e.g. age, gender, emotional state, gaze direction), upon which human observers rely heavily for social interaction and communication. While there is some variability in face recognition abilities even within the normal population (e.g. (1-5)), most people, can represent the identity of an

almost unlimited number of faces and can easily come up with the relevant associated information such as the name and biographical knowledge pertaining to the presented face.

Given the particular image-based and task requirements for processing faces, it is perhaps unsurprising that there is a vast behavioral literature positing that, in healthy individuals, faces are processed and represented in a qualitatively different fashion compared to other object categories. Specifically, the claim is that deriving a rapid and accurate representation of the face requires disproportionate reliance on the configuration of the features relative to that required for non-face object recognition (see (6) for an in depth review of this topic). Any manipulation that disrupts the configuration of the face, then, would be predicted to affect face processing disproportionately compared with non-faces, and evidence to support this claim comes from a number of well-established behavioral experimental paradigms. For example, faces are more affected by inversion than is true for other visual objects (e.g. the face inversion effect (7)). Consistently, face processing benefits from the presence of the entire face, compared with the presence of just some components of the face, to a greater degree than is true for other objects (the whole versus part advantage (8)). Finally, the configuration of the face is apparently derived so automatically that even when instructed to attend selectively to only some parts of a face, normal observers cannot help but be sensitive to the entire face (e.g. the composite effect (9)). There is much ongoing research designed to further determine how these processing characteristics emerge over the course of development and experience and to flesh out further the nature of the representations that mediate these face-specific signatures and whether these effects (e.g. composite effect) might emerge for non-faces and under what particular conditions.

Because of the complexity of the process of face individuation and the observers' great facility in face perception, elucidating the neural underpinnings of successful face representation has been of much interest in visual neuroscience. Face selective cells have been identified in monkey inferior temporal cortex (see (10) and (11) for a recent review) and more recently, face-selectivity has been confirmed in the same regions in studies using functional magnetic resonance imaging (fMRI) (12, 13). Relatedly, in humans, a lesion to occipito-temporal cortex results in face recognition impairments, confirming the critical involvement of this area in face recognition. Our understanding of the neural substrate of face recognition, however, has received perhaps the greatest boost from the numerous functional magnetic resonance imaging (fMRI) studies investigating this issue. These studies, collectively, point to a number of regions that show a selective response to faces (compared to other stimuli) including the fusiform gyrus (also referred to as the fusiform face area, FFA), the posterior superior temporal sulcus (pSTS), and the inferior occipital gyrus (also referred to as occipital face area, OFA) (14-22) (and see (11, 23) for recent studies offering a more fine-grained parcellation of the core regions). In addition to these "core regions" of face processing (adopting the

terminology of Haxby and colleagues (20)), there are a number of other regions outside the occipito-temporal cortex that constitute an "extended" face recognition system and play a critical role in other aspects of face perception. These include for example, the anterior temporal lobe, which mediates aspects of identity, name and biographical information (24-26), and the amygdala, which subserves emotional aspects of face representations (19, 20, 27). Importantly, activation in homologous regions has also been documented in the monkey brain (28-31).

Largely as a result of the imaging studies, there is now a growing consensus that face perception is accomplished by the coordinated activity of a face processing network documented at both the functional (19, 32-35) and structural levels (36-38). Importantly, some nodes within this network, such as the FFA (39) and perhaps the OFA (22, 40), may be particularly critical for its intact function (and see (33, 34) for a computational approach for examining these issues). The goal of this review is to examine this network of brain regions using functional and structural imaging data in the context of CP in order to understand the neural underpinnings of this disorder and, by extension, to make inferences regarding the structure and function of the normal human face processing network.

3. PROSOPAGNOSIA

Prosopagnosia refers to an individual's inability to recognize faces despite normal sensory vision and normal intelligence. The term has been standardly applied to individuals who were pre-morbidly normal but who, following acquired brain damage, lost the ability to recognize faces. In such cases of acquired prosopagnosia (AP), the lesion is typically to the ventral visual cortex and is sustained during adulthood (for reviews, see (41, 42). Converging evidence implies that lesions to the right, but not left, occipito-temporal cortex are critical in eliciting the disorder in its "clean" form (i.e. a modality specific recognition disorder selectively affecting familiar faces as phrased recently in (43)). AP has provided a unique window into the psychological and neural substrate of face processing since its initial recognition (44). The disorder has often been differentiated into an apperceptive and an associative form: while the former is characterized by an inability to form an accurate perceptual representation of the face, in the latter case, perception is relatively intact but the association of the face to other related information is impaired (i.e. name, biographical knowledge etc; (45)). Anatomically, these forms of AP roughly coincide with posterior versus more anterior lesions along a rostral to caudal axis of ventral cortex but drawing clear boundaries between these subtypes has often been challenging (see (46) for a discussion of this issue in AP and (47) for an analogous discussion in CP).

3.1. Congenital prosopagnosia (CP)

Over the past several years, there has been recognition of an impairment in face processing analogous to AP but which occurs in the absence of brain damage. This disorder has been termed 'congenital prosopagnosia'

(CP) with the 'congenital' label adopted to reflect the fact that the disorder is apparently lifelong in duration, and occurs in individuals with normal intellectual function and who have had adequate opportunity to acquire normal face recognition skills (for recent review, see (48)).

CP can be differentiated from a developmental form of prosopagnosia (DP) which, although evident from early life too, is associated with acquired brain injury incurred as a result of, for example, respiratory arrest or a major fall early in the course of development (for example, see (49, 50)). It is important to note however, that some researchers use the term DP rather than CP, even in cases where no apparent brain injury has occurred to indicate that we cannot be certain when exactly face processing diverged from normal in these individuals (48, 51). Although we cannot definitively be sure in our own cases that the disorder was present from birth, these individuals have no medical history of any relevant neurological insult and no lesion apparent on conventional MRI, so we adopt the term CP to indicate this fact. For clarity, we use the term 'CP' in the present paper even when citing studies, which have used the term DP for cases which, according to our criteria, would fit the definition of CP. Again, the intent is not to confuse the cases with definitive brain damage with those in whom no damage is evident and so we use DP for the former and CP for the latter.

CP apparently has a familial basis (e.g. (51-53)) and, based on pedigree studies, some authors have suggested a heritable basis for this disorder and have proposed a simple autosomal dominant mode of inheritance (54). However, this account has been challenged by analyses of data collected from thousands of self-identified individuals with CP; such analyses reveal that the frequency of affected family members was smaller than that predicted by such a simple mode of inheritance. These latter analyses imply that CP may actually result from the cumulative effect of multiple genes rather than be single-gene based (48) (and see Section 5 for additional discussion of the genetic basis of neurodevelopmental disorders).

Although CP has attracted much scientific attention recently, even garnering the colloquial term 'face blindness' in the popular media, many aspects of its behavioral profile and underlying neural mechanism are still unclear. In the absence of a definitive neural or genetic marker characterizing CP, this disorder is currently diagnosed based on a number of behavioral characteristics and the common standard is to include only individuals who are impaired (>2SD from normal controls) on at least two diagnostic tests (but tests may vary across labs, see below for details). Additionally, participants are often also thoroughly interviewed to ensure lifelong experience of the disorder and to exclude possible other factors that may elicit face recognition deficits (e.g. Autism), and some labs even use interviews as their sole or main diagnostic measure (54). These different approaches and criteria for diagnosis are critical and might contribute to the heterogeneity in CPs' behavioral and

neural profile often found across studies (see more about this issue below).

Given these limited diagnostic procedures and no obvious genetic signature or biomarker, at present it is impossible to clearly determine whether CP represents a distinct pathological condition or whether these individuals represent the very low-end of the normal distribution of face processing abilities, which like any other human ability also have some variability. Indeed, some researchers have taken an individual differences approach for the disorder, and accordingly, have examined whether the behavioral (and concomitant neural) characteristics of CP fall under the umbrella of the general spectrum of face recognition and representation (1, 2). The absence of a standard diagnostic procedure and the fact that behavioral measures are currently the sole mechanism for diagnosing the disorder are clearly problematic and require further research and cooperation across labs. Particularly, this calls for larger scale studies in which such questions can be investigated. Additionally, considerations not just of quantitative deviation from the mean (i.e. how many SDs from control mean) but demonstrations of qualitatively different patterns of performance will also be useful in examining whether CP is a distinct entity (see for example (55, 56) for demonstrations of such qualitative differences).

3.2. Nature of face processing in CP

Most researchers would nevertheless agree that the hallmark of the disorder is the inability to recognize familiar faces, but many of these individuals also exhibit difficulties in the perception of unfamiliar faces (57) and in short term memory of newly learned faces (58). In fact, both recognition of famous faces and short term memory for unfamiliar faces have often been used in the literature as diagnostic tests (e.g. famous faces questionnaire devised in various labs (59), the Warrington Memory Test for Faces (RMF; (60)) and in recent years the popular Cambridge Face Memory Test, CFMT (58)).

A recent study also found face specific long-term memory impairments (over an interval of one year) in CP individuals (47) but these memory deficits are probably unsurprising if the original encoding of the face was not entirely normal. Interestingly, one study implies that CP individuals may show some improvement in identity recognition when aided by facial motion (61), a finding that may be consistent with their typical anecdotal self-reports regarding compensatory recognition strategies, which often include reliance on biological motion information. Note however, that this cue is obviously not sufficient in order to support normal face recognition.

Importantly, CP individuals show largely normal performance in tasks related to extracting non-identity aspects of the face, thereby delimiting the nature of the impairment. Thus, CP individuals show mostly normal recognition of facial expression (e.g. (2, 62-65), but see (66) for somewhat different results in a single participant) and of gender recognition (67, 68). They exhibit somewhat mixed results in attractiveness judgment but this ability has not been widely assessed (64, 67), and they exhibit mostly

normal performance in judgment of trustworthiness (69). The dissociations in the performance in identity versus non-identity face processing tasks are compatible with conceptual models of face perception implicating the existence of different routes for some of these processes (70) and also with neural data ascribing separate roles to different face-selective foci (20).

Taken together, these findings attest to an impairment in representing the geometry and identity of faces. The obvious next question is whether the deficit is definitively restricted to the perception of faces. Importantly, while clearly the most dramatic deficit exhibited by individuals with CP is with faces, when object perception is carefully examined and the non-face tests are equally challenging (i.e. they measure within category fine discrimination and are well matched with the face tasks), it becomes apparent that many (but not all) individuals with CP also exhibit difficulties in other non-face categories, albeit not as severely. (See, for example, the following studies in which, at least some CP exhibit object recognition abnormalities (47, 51, 57, 71, 72)).

3.3. Underlying psychological mechanisms

A final, related issue, which remains unresolved, is whether CP can be attributed to a more general visual perceptual impairment, and specifically to a deficit in holistic/configural processing known to be critical for intact face perception (8, 73). Moreover, if the key deficit is in holistic/configural processing, and much data indicates that this is so, the question still remains whether only face perception is affected or other non-face objects that require holistic perception are affected, as well. Adjudicating between these options would depend on an examination of a holistic impairment and its correlation with non-face object recognition difficulties. We are not aware of any studies examining this issue directly.

Many studies reveal disrupted holistic processing of faces in CP using various paradigms such as upright/inverted faces, parts/wholes processing and the composite face effect (e.g. (55, 57, 74-76) but see (68) for somewhat different findings). The notion of disrupted holistic face perception in CP has also been supported by a recent computational model which showed that introducing weak connectivity to a network model representing faces, results in featural rather than holistic representation (77). Furthermore, the same computational model is cast within a conceptual account of CP which incorporates empirical evidence of a deficit in holistic face processing and the resultant serial, feature-by-feature face analysis (72).

Several studies have also examined holistic perception of non-face stimuli in CP individuals (e.g. (53, 57, 67, 74, 75, 78, 79) and the results are inconsistent. Thus, for example, Avidan et al., and Behrmann et al., (57, 74) found that individuals with CP exhibited a disruption in holistic processing for non-facial stimuli, using the Navon global/local compound letter identification task (80). Specifically, CP individuals, in contrast with a group of matched controls, showed a clear local bias as evident by faster local than global letter identification and greater local

to global interference. Notably, a similar local bias was also reported in a single case of CP (75).

A recent study used the Garner interference task to further examine the extent of the local bias for non-facial stimuli (56). This task is designed to assess the separability of perceptual dimensions, and avoids some of the known limitations of the Navon global-local task (81). Specifically, participants were asked to judge the width of rectangles regardless of irrelevant changes in their height. As expected, controls exhibited Garner interference (i.e. irrelevant changes in height influenced the participants' judgments of width) indicating that these two dimensions of the shape are integral. In contrast, CPs showed no such interference thereby providing further support for the local bias in processing even very simple shape dimensions. Importantly, CPs only exhibited difficulty in processing integral dimensions related to shape but not to other properties such as color. Finally, some CP individuals also show abnormal processing of biological motion, a process also thought to rely on configural processing (79). Together, these findings provide additional evidence for a holistic perception deficit in CP that is general and extends beyond just face perception.

However, not all studies support this conclusion. Specifically, in some studies, CP participants either exhibited the typical global superiority in the Navon task (78), or were impaired in configural processing of faces but not of houses (82), or had normal sensitivity to global form and motion (67) (similarly some cases of AP also show typical global superiority in the Navon global/local compound letter identification task (83, 84)). Unsurprisingly, then, there is still ongoing debate as to whether CP is a face-specific impairment, and, moreover, whether it has to do with holistic deficits that might adversely affect other stimuli too.

The discrepant findings from the different studies might also reflect the possibility that CP is a heterogeneous entity, potentially composed of several subtypes. Thus, small sample size, different tools used for diagnostic purposes (for example (1, 74, 85)) and the limited number of (different) tests used for the characterization of the disorder in different studies may easily give rise to divergent results. One recent study attempted to investigate this heterogeneity more systematically by acquiring data from a relatively large group of CPs on a range of face and object perception and short and long term memory tests (47). Based on the performance on these tests that span perceptual (encoding of face images), associative (associating encoded percepts with individual facial identities) and mnemonic (long-term association between a facial identity and a semantic identity) skills, CPs were clustered into four groups: The first group showed perceptual, associative, and mnestic difficulties that were restricted to faces. Clearly, their perceptual deficits could be the underlying cause for the additional associative and mnestic deficits. The second group exhibited long-term memory deficits which mostly affected face tasks, and did not show perceptual or associative deficits in either faces or objects. Performance in the third group was characterized

by deficits in face and object recognition that were more pronounced in tests of perceptual aspects but were also evident to some extent in the associative and/or amnestic type. The last group showed mild, and rather diffuse deficits, which, for the majority of the participants were restricted to faces. While this line of investigation is very important and provides some initial support for the existence of subtypes of CP, it is not yet sufficiently comprehensive, given the limited number of participants and the limited number of tests employed. Thus, for example, holistic perception of faces and other objects, which, as noted above, may have a critical role in this disorder was not evaluated and was not included in the clustering of the participants. Furthermore, another important characteristic that might be highly informative for CP subtype classification is the extent of implicit face processing and this was also not explored. Specifically, several studies have shown behavioral (59, 86, 87) and neural (88) evidence for implicit familiarity processing at least in a subgroup of CPs. This raises the possibility that, in these individuals, there is some rudimentary representation of the faces that is perhaps not coherent enough or not sufficiently well connected to semantic representations to support explicit overt recognition of the face. It remains to be seen whether the extent of implicit processing might enable the demarcation of subtypes of the disorder.

4. THE NEURAL BASIS OF CONGENITAL PROSOPAGNOSIA

As evident from the above review, CP is a complex disorder and there is much that remains unknown. While the behavioral characteristics are being unraveled, parallel efforts have been undertaken to understand the neural underpinnings of this disorder. This latter line of investigation encompasses studies using different methodologies including fMRI, which offers excellent spatial resolution and coverage, and event-related potentials (ERP) and magnetoencephalography (MEG), which provide fine temporal resolution. In addition, structural investigations have also been conducted using MRI, with a particular focus on volumetric cortical measures or on white matter properties.

As described above (Section 2), there has been a substantial shift in the understanding of the neural basis of face processing in the past few years. Specifically, while early studies focused mainly on face selective regions in occipito-temporal cortex, primarily on the FFA, and ascribed a modular nature to these regions (89, 90), more recently, there is growing consensus that face perception is supported by a distributed network of cortical and subcortical regions ((18, 27) and see also (91, 92) for an in-depth discussion of the distributed nature of visual representation). Further supporting evidence for this view also emerges from a number of imaging studies demonstrating multiple face-selective patches in the monkey brain. These patches, which share some homology with the human face network, are evident not only in occipito-temporal cortex but also in the anterior temporal cortex, prefrontal cortex and amygdala, and these regions

are anatomically and functionally connected (28-30, 93). Finally, advances in more sophisticated data analysis approaches, including tools from graph theory and complex network analyses also permit an examination of the properties of the face network as a whole (33). Other approaches such as multi voxel pattern analysis (MVPA) allow the specification of the computational contribution of the different face selective regions within the network at a much finer grain of resolution (e.g. (24, 25)).

4.1. Functional imaging investigations of CP
4.1.1. fMRI findings
4.1.1.1. Core face system

Several studies have examined the function of the core face network and particularly the FFA in CP. These studies have documented normal face-selective activation in the FFA as well as in other face-related foci in CP using a host of different paradigms (block design, event related, adaptation) and stimuli (line drawings, famous faces, emotional faces and even movies) (94-97). Consistently, across these different studies, the activation in each of the core regions (FFA, OFA, pSTS) appeared to be largely normal as determined by a host of various dependent measures such as the extent of face selectivity, the anatomical location (coordinates of peak activation), the number of activated voxels in each region, the adaptation profile (repetition suppression) and the extent of the right lateralization of the face activation.

Nevertheless, there are some reports of abnormal activation in the core regions in CP, and the source of the discrepancies across studies is not obvious (1, 75, 98, 99). Importantly, even among these studies, the results are somewhat mixed ranging from complete absence of face selectivity (e.g. (75, 98)) to more subtle and heterogeneous effects (1, 99). For example, in (99) face selective activation in the FFA or OFA was missing or reduced in some CP participants in some of the face conditions. Note, however, that, in the same study, some CPs actually showed enhanced responses compared to controls in FFA and OFA in some face conditions, and so the interpretation of these inconsistencies is not obvious. Dinkelacker et al., (64) also found reduced activation in a large group of CPs (n=24) compared to controls but this was specifically so in the left fusiform gyrus. Finally, Furl and colleagues (1) tested a relatively large group (n=15) of CPs who also completed many behavioral tests. This approach permitted the researchers to correlate the extent of face selectivity in various face-selective ROIs, as evident in the fMRI signal, and the magnitude and specificity of the behavioral impairment in the same participants. Importantly, while numerically CPs exhibited fewer activated face voxels, there were no significant differences between the two groups when directly contrasted. Moreover, when examined individually, most CP participants (12 out of 15) exhibited normally appearing activation in the right FFA and normal face adaptation effects, and this result is consistent with the studies discussed above showing normal activation and adaptation in this region (95, 96). Interestingly, differences between CPs and controls emerged when the aggregated performance on various face tasks was correlated with face selectivity with poorer

behavioral performance on face identify tasks associated with reduced face-selectivity in the fusiform gyrus. Notably, such brain-behavior correlations were not found in other studies (e.g. (97)), and, even in a training study of a single case of CP, improvement in recognition performance was not accompanied by a change in face selectivity in the core face regions (100). The correlation between face selectivity in the FFA and face processing abilities (1), and the approach of exploring individual differences in this context (2), raises the question of whether face recognition and their concomitant brain signals or underlying neural structures, actually form a continuum with many (or maybe even all) CPs lying along this spectrum, rather than composing a discrete group. This is an intriguing notion, which requires much research with large groups of participants and detailed behavioral and neural testing.

We note that, in some of the studies we have conducted, we observed a few minor group differences in core regions between CP and controls but these differences were inconsistent either across the different dependent measures used within a study (97) or were not replicable across studies (e.g. (94)). These subtle effects could either be spurious or might very well be related to the heterogeneity and extent of severity of the impairment among the CP individuals within our sample, but given the relatively small sample size, this is difficult to tell.

Thus, to a large extent, even if not entirely, activity in the core face network in CP appears comparable to that of the controls. The emergent view is that the differences between CPs and controls only become apparent when large samples are tested and that these neural differences are subtle and are most evident when correlation with behavior is taken into account. Of note is that such differences in core regions, may not necessarily represent inherent abnormality of these regions, but, rather, might result from abnormal feedback propagating back from the extended face system, a notion that will be discussed in more details in section 5.

We stress that these findings do not undermine the integral role of core regions such as the FFA and OFA in face processing. The contribution of these core regions is supported by numerous lesion studies (22, 42, 46) and corroborated by recent studies in which micro-stimulation is applied to these regions and face processing is subsequently altered (39, 40) . Rather, we postulate that these core regions, although necessary, may not be sufficient for successful recognition and that additional regions are necessarily involved. The findings from CP contrast with the classical neural profile attributed to AP, in which the lesion is typically more localized, affecting a particular node in the face network, usually (although not always) the FFA. Of course, damage to one such node can affect propagation of information through the face circuit. Hence, these findings have led to the hypothesis that the failure to recognize faces in CP (and perhaps in AP too, (46)) results from disruption of connectivity between the core and extended systems which would consequently be evident in abnormal activation of the extended regions related to face recognition. Below, we review studies that have examined the extended face network in CP and then discuss the network properties and connectivity in these individuals.

4.1.1.2. Extended face system

The extended face system includes many regions located outside occipito-temporal cortex and these regions may be grouped into two clusters, each focused on a particular functional aspect of face processing (20, 27). The first cluster is composed of regions thought to be involved in processing information related to person knowledge. These include the anterior paracingulate cortex representing personal traits, attitudes and mental states, the posterior STS/TPJ involved in understanding intentions and mental states (note that other functions of this region such as extracting dynamic, changeable aspects of the face such as expressions are attributed to the core network), the anterior temporal cortex mediating biographical and semantic knowledge and, finally, the precuneus/posterior cingulate involved in the representation of episodic memories. The second cluster is related to emotional processing and includes the amygdala, insula and striatum (20, 27).

As discussed earlier, the behavioral impairment in CP is mostly related to the perception and memory of faces (but clearly, memory deficits could stem from impaired encoding due to the perceptual difficulties) while emotional processing in these individuals is largely intact. This differential behavioral profile predicts a selective disruption in the activation of those parts of the extended network that mediate identity recognition and their related connectivity, while regions mediating emotional expression or other properties of faces should be intact.

To examine this prediction, we pay particular attention to two key regions: the anterior temporal cortex, related to identity representation and the amygdala, involved in emotion processing. In addition, we examine other regions belonging to the cluster of the extended system that is involved in person knowledge such as the precuneus/posterior cingulate and the anterior paracingulate cortex. So far only a few studies have systematically explored these regions whereas the majority of studies have characterized the core system in CP. One possible factor that may contribute to paucity of investigations into these extended regions is the inherent technical difficulty in imaging these more anterior and subcortical regions due to susceptibility artifacts and low signal-to-noise ratio.

Of the different regions of the extended network, the anterior temporal cortex has triggered interest over the years and there is converging evidence implicating its critical role in semantic and identity representation of faces, which, in some cases, is also independent of modality (see (101, 102) for a detailed discussion of this issue)[1]. For example, in the visual domain, this region shows distinct patterns of EEG responses (103) and BOLD fMRI activation in response to individual faces (24-26, 104). Moreover, this region appears to play a critical role in normal configural face processing (105) and damage to this region can give rise to face processing deficits, as well (e.g. (43, 46, 106)).
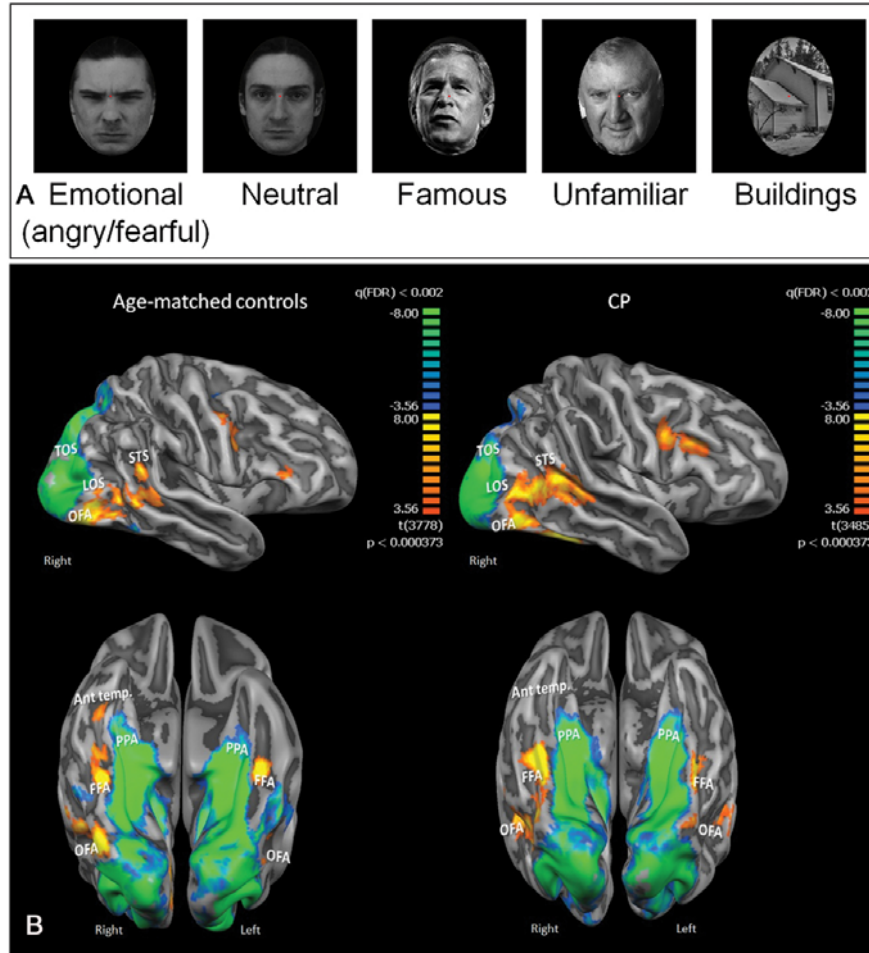
Figure 1. Visual stimulation experiment and activation maps in core face network and anterior temporal cortex. a. Examples of the stimuli used in the visual stimulation experiment conducted in (97). b. Averaged activation maps for controls (left panel) and CPs (right panel). The activation maps are overlaid on a group-averaged folded cortical mesh of each group and are presented in a lateral view (top row) and a ventral view (bottom row). The maps for the face activation were obtained by the contrast all faces>buildings (red to yellow colors). Note the similarity of the activation maps across groups in the core face network including bilateral OFA, LOS, FFA, and pSTS. This is in sharp contrast to the activation in anterior temporal cortex in the right hemisphere that is clearly evident in controls but is completely absent in the CP map. Also shown is the building selective activation obtained from the contrast buildings>all faces (blue to green colors) in the PPA and TOS which is also very similar across groups. The two group maps and both contrasts are presented in the same statistical threshold. Abbreviations: Ant. temp. – anterior temporal cortex. Adapted with permission from (97).

Using an intensive visual stimulation paradigm, which included blocks of famous, unfamiliar, emotional and neutral faces (see Figure 1a), we obtained sufficient signal in these extended regions and have uncovered, for the first time, the abnormal activation and connectivity pattern (discussed below) of the right anterior temporal cortex in CP. Not only was activation in this region absent in most CPs (see Figure 1b), in those few individuals who did have signal in this region, the profile was atypical and this was so even when we superimposed an externally-defined ROI and extracted the signal from this region (97). Importantly, this abnormal signal was obtained while, at the very same time within-individual, activity in the core system was largely or entirely intact. Finally, no brain-behavior correlation was evident in this study but this might be a function of the relatively small sample size. Consistently, Furl et al., (1) also report a lack of anterior temporal cortex activation in CP compared to controls when using a standard contrast (faces>cars) in a group analysis. Interestingly, when pooling together both CPs and controls, these authors did find a correlation between face selectivity in the vicinity of the left temporal pole and the aggregated score of a set of face identity tasks, thus indicating that the extent of face selectivity in this region could be used as a marker for the level of face identification. Note, however, that in Avidan et al., (97) the most consistent activation in control participants was found in the right and not the left temporal cortex, and was found more posteriorly compared to the region where the brain-behavior correlation was evident in Furl et al., (1).

Currently, the specific roles of the right vs. left anterior temporal cortex in face perception are not fully understood. Studies in acquired prosopagnosia patients imply that a lesion in right anterior temporal cortex leads to a loss of a feeling of familiarity and a difficulty in retrieval of person specific information whereas left anterior temporal lesions are more associated with a difficulty in naming famous people even from verbal descriptions (see (43, 107) for an in depth discussion in AP). Neuroimaging studies in healthy individuals have also documented differential roles for right vs. left anterior temporal cortex such that the right anterior temporal cortex has been implicated in linking the visual face information and person semantic information, while activity in the left region has been associated with mediating semantic person information and proper names (108). In a different study, however, when famous or familiar faces (i.e. faces with semantic association) were contrasted with unfamiliar faces, the right anterior temporal cortex was more activated by unfamiliar faces perhaps attesting to its role in extracting visual information while the left region was related to processing famous or familiar faces, indicating the greater sensitivity of this region to semantic information (101). Relatedly, in a study examining activation for familiar vs. unfamiliar voices in a single CP subject, activity in the left anterior temporal cortex was also reduced compared to controls, despite normal activation in the FFA; these results were accompanied by reduced functional connectivity between these two regions (109). The significance of the differences obtained across CP studies, in terms of the laterality of the observed activation (or hypoactivation) should be further investigated in future studies that directly manipulate face content. These initial findings regarding the role of anterior temporal cortex in CP are certainly intriguing and warrant further investigation using additional sophisticated and sensitive approaches. For example, MVPA would allow better understanding of the face representation in this region in CP (25).

Two other regions that are part of the extended system and are presumably involved in the representation of "person knowledge" are the precuneus/posterior cingulate and the anterior paracingulate cortex regions. These regions are often observed in studies in which activation for famous or personally familiar faces vs. unfamiliar faces is contrasted (27, 101, 110). Using a taxing, rapid-event related adaptation paradigm, we have shown that these two regions are not activated in CP individuals in response to famous compared to unfamiliar faces (96). Importantly, this result was obtained while during the same experiment, CP individuals exhibited activation as well as adaptation in the core face system that equaled that of the controls. Furthermore, in both groups, this activation was more pronounced for famous compared to unknown faces, thus indicating that the lack of activation in these extended regions is not due to the lack of statistical power. In contrast to these findings, Dinkelacker et al., (64) actually reported enhanced activation in the medial prefrontal cortex and anterior cingulate (Brodmann area 10) in a large group of CP individuals when contrasting faces bearing emotional expressions versus scrambled faces. This enhanced activation might be due to the compensatory recruitment of regions related to emotion processing rather than engaged in representing identity per se.

Indeed, in sharp contrast to the absence of activation in CP in regions of the extended network, which are involved in identity representation, during the very same study, the amygdala activation was equivalently robust in CP and controls (1, 64, 97). Moreover, the face selectivity in the right amygdala across both CP and controls was correlated with performance on a set of behavioral tasks tapping expression-related judgments but not with behavior on identity related tasks, thus further confirming the role of this region in emotional, rather than identity processing (1). The dissociation between abnormal activation in identity-related regions and the normally activated amygdala uncovers the specificity of the impairment in CP and provides a neural candidate for the observed behavioral dissociation between identity and emotion processing in individuals with this disorder.

A final area of interest that has been occasionally described in the CP literature is the prefrontal cortex. While this region was not explicitly defined as part of the extended face network by Haxby and colleagues (20, 27), face-selective activation has been found in prefrontal cortex in healthy individuals (e.g. (19, 111); note that the exact location varies across studies) and, interestingly, presumably homologous activation has also been reported in the monkey brain (28). Notably, in our studies, this prefrontal activation was located in the vicinity of the middle frontal gyrus and inferior frontal sulcus and gyrus and was stronger and more bilateral in CPs than in controls (95, 97) (but see (64) for evidence of reduced activation in dorsolateral prefrontal cortex (DLPFC) in CPs; note that this location is different from the location of the activation we report in terms of the exact coordinates). While these findings are intriguing and of potential interest, further research is required in order to understand the exact role and localization of this prefrontal activation in CP. One possible explanation for the enhanced activation found in our studies concerns the involvement of prefrontal regions (mostly DLPFC which has some overlap with the activation we report) in working memory (112, 113) as participants were performing a one-back task. Indeed, despite the relative ease of the task, CP participants exhibited impaired performance during the fMRI scans, that was evident only during the face conditions (95, 97). Interestingly, studies which specifically investigated working memory for faces showed modulation of the FFA according to the memory load (112) and also reported specific patterns of connectivity between FFA, prefrontal cortex and the hippocampus that were dependent on the memory load (113). Because, in our studies, we used a simple one-back task and did not manipulate the level of memory load, we were unable to explore such patterns directly but future studies should certainly clarify this possibility more directly.

Another potential role of the enhanced prefrontal activation, which is not mutually exclusive with that of working memory, might concern the impaired holistic/configural processing in CP (see Section 3) and the

potential role that DLPFC plays in this form of processing. Particularly, a recent TMS study demonstrated a double dissociation between right DLPFC, which was causally involved in configural face processing, and the left DLPFC that was involved in featural processing (114). These findings are also compatible with an fMRI study which showed selective responses in right and left DLPFC, respectively, for configural and holistic tasks in normal participants (115). Thus, a possible hypothesis is that prefrontal cortex and DLPFC more specifically, especially in the right hemisphere, may be inefficiently engaged in face processing tasks in CP, even if holistic processing is not explicitly required, thus leading to enhanced, compensatory activation in this region. Clearly, much research is required in order to determine the validity of this interpretation.

4.1.2. ERP and MEG findings

In contrast to the limited temporal resolution of the fMRI BOLD signal, ERP and MEG both offer superb millisecond resolution, which is advantageous for investigating the temporal dynamics of face processing. Specifically, these latter techniques may offer the means for differentiating between early perceptual vs. late associative deficits which are more related to post perceptual stages or to a disconnection between face perception and memory. This division of face perception may, in turn, facilitate the classification of individuals as exhibiting deficits analogous to apperceptive vs. associative prosopagnosia (see discussion of this classification in section 3).

4.1.2.1. Early face related potentials - N170/M170

In normal observers, there is a typical face-selective waveform peaking at about 130 to 200 msec after stimulus onset that can be detected in both ERP (N170) and MEG (M170) (116). Importantly, the N170 component is mostly associated with the perception and structural encoding of facial features and configuration (117) (its sensitivity to additional aspects such as face familiarity or facial expression is still debated (see (118, 119)). As such, in prosopagnosics, an abnormal N170 waveform would predict a rather early, perceptual deficit that is probably more in line with the definition of "apperceptive prosopagnosia", while, a normal N170 would be more consistent with a later, post-perceptual deficit which better fits the definition of "associative prosopagnosia". The MEG technique is not as widely used as ERP but the interpretation of the M170 waveform, in terms of its temporal dynamics is similar to that ascribed to the N170. Both methods have been used to examine the physiological patterns in CP but, as yet, the findings are equivocal.

On the one hand, several single case studies have shown that individuals with CP do exhibit the N170 component in response to faces, but that the face selectivity of the component was reduced compared to controls (75, 120, 121). This finding was interpreted as indicating an impairment in selecting and/or representing face-specific information in a way that is optimal for use by higher-level, dedicated face recognition units. In contrast, in another ERP study, 3 participants with CP exhibited a normal N170

response, while only one subject exhibited reduced face selectivity in the N170 response (122). Interestingly, following intensive training of a single CP individual on a face configuration task, the N170 selectivity for faces, which was abnormal prior to training, was significantly enhanced (100).

This heterogeneity across individuals was also apparent in a MEG study in which 2 out 5 CP individuals exhibited a normal M170 and normal N170 response but the remaining 3 did not exhibit a face selective response in their MEG profile (123). Another MEG study found overall reduced magnitude, particularly over left occipito-temporal areas of the M170 in a group of 7 CPs (124). This signal attenuation was not affected by face familiarity or orientation. Note that in this particular study, however, only faces were shown thus preventing direct comparison of the face selectivity of the M170 to other studies. Contrary to these abnormal findings, a recent MEG study reported normal M170 for all 6 CP participants (125).

In an attempt to resolve the mixed findings regarding the nature of the N170 in CP, recently, Towler et al., (126) tested a large group of 16 CPs and their matched controls. Importantly, in this group, which is the largest tested so far with ERP in a single study, N170 responses for upright faces were normal in selectivity and magnitude compared to the control group. Moreover, of these 16 CPs, 12 participants exhibited a normal N170 also at the individual subject level, 2 exhibited a N170 that was face selective although the selectivity did not reach statistical significance, and only 2 CPs showed a N170, which was not face selective and was even stronger for houses (note that a similar breakdown of the profiles of control participants is not provided). Thus, these results provide strong support for the claim that CPs do exhibit largely normal N170 response. Interestingly, in this study, the differences between CPs and controls emerged for inverted faces. Specifically, controls exhibited the typical effects of face inversion on the N170 such that, relative to upright faces, inverted faces elicited enhanced and delayed N170 components. In sharp contrast, no such effects were observed in the CP group for either young or old participants, and the N170 even tended to be stronger for upright faces. Clearly, this finding is consistent with the behavioral impairment in holistic processing typically observed in CP. When examined individually, only 3 CPs exhibited the typical inversion effect while the remaining 13 did not. Most critically, there were no obvious correlations between the N170 inversion effect and the different behavioral diagnostic face processing tasks. This result is somewhat surprising given the relatively large group tested here and also findings showing correlations between the behavioral findings and the ERP inversion effect in normal participants (127, 128). Moreover, recent findings also exhibited a correlation between the fMRI face selectivity and face processing diagnostic tests across both CPs and controls (1). However, such a correlation was found in the present study only for the CP group (but not for controls) when correlating their N170 inversion effect and their behavioral inversion effect measured concomitantly.

Overall, the emergent view from this recent, large study is that the N170 component for upright faces is similar in CP and controls and that the divergence arises in the response for inverted faces in which CPs do not show the typical N170 inversion effect. This latter finding may be related to the disrupted holistic/configural processing in CP which is often exhibited by a reduced behavioral face inversion effect with some individuals even showing an inversion superiority (e.g. (57, 74) and see (128) for a discussion on the delayed N170 for inverted faces). In fact, even in the study by Towler et al., (126), reduced sensitivity for face inversion was reported in the Cambridge Face Recognition Test (CFPT) (although this was not correlated with the N170 response).

Finally, there are no obvious correspondences between the N170 selectivity and face selective activations, as revealed with fMRI, in those few cases that have been tested in both methods. For example, subject YT, who showed reduced N170 selectivity for faces (120), exhibited a normal response for faces in the occipito-temporal cortex across a range of different experimental tasks. The CP participants whose ERP N170 response is reported in (122) also participated in a later fMRI study (99) and here too, there is no direct correspondence between findings obtained in the two methods. For example, the one CP participant who had abnormal N170 selectivity actually showed a rather normal response pattern for faces in fMRI. Along similar lines, the CP participant who went through intensive behavioral training (100) exhibited an abnormal N170 response prior to training but, at the same time her face activation, as measured with fMRI, appeared normal. Moreover, her behavioral training enhanced the face selectivity of the N170 response but not the fMRI response for faces (there was an increase in the functional connectivity across regions, and this will be discussed in Section 5). While the source of the BOLD fMRI signal and the ERP responses are physiologically very different and so are their respective temporal resolutions, there is evidence for a correlation between the N170 face selective component and face selective response as measured with fMRI in regions such as the FFA and pSTS (but not OFA) (129, 130) (and see also (131) for a correlation between fMRI and behavioral face inversion effect). So far, only a handful of cases with CP have been tested using both methods, but this was done under different experimental paradigms and so it is hard to draw any obvious conclusions from such comparisons. Nevertheless, given the complementary nature of these two approaches in the spatial and temporal domains, and the promising findings obtained in normal subjects (130), the hope is that as more individuals are tested using both ERP and fMRI and as the behavioral and neural procedures become increasingly standardized across experiments and labs, the emerging pattern of the underlying neural response for faces in this disorder will become clearer (and see (132) for a recent review of this literature).

4.1.2.2. Late ERP components – N250; P600f; induced Gamma-Band Responses (iGBRs)

The N170 component, associated with perceptual aspects of face processing, is the component described predominantly in ERP studies of CP, although later components, which have a more general response, have also been examined to study additional aspects of face processing such as sensitivity to familiarity. For example, one recent study examined the N250 component in a group of 12 CP individuals as a means of uncovering physiological evidence indicating implicit face processing (88); this component is linked to visual face memory and face recognition and is observed over occipito-temporal regions when famous faces are explicitly recognized but not when faces just look familiar (133). Specifically, in this study, participants judged the familiarity of famous and unfamiliar faces, and trials were then sorted into those in which famous faces were recognized, or those in which the famous faces were not explicitly recognized, or those in which unknown faces were presented (see (59) for a similar analysis of behavioral data indicating behavioral implicit processing). Interestingly, in 6 of the 12 CP tested, trials that included famous faces, which were not explicitly recognized, elicited an occipito-temporal N250 component that is related to the stored visual memory of known faces. These findings provide physiological evidence for implicit identity processing, at least in a subgroup of the CPs. The other 6 participants did not show such effects despite similar recognition rates of the famous faces, perhaps again attesting to the heterogeneity of the group. Of note is that in those individuals who did evince the N250, the few trials in which famous faces were explicitly recognized elicited a normal signal. Moreover, there was a positive correlation between the appearance of the N250 and face recognition task in that those CP participants who showed a reliable N250 to non-recognized famous faces performed significantly better on the CFMT than participants with CP who did not show an N250. This result is consistent with the research in AP indicating that the extent of implicit face recognition is related to the quality of the face representation in visual memory (134).

Finally, a later, more general component, the P600f, which is thought to be indicative of semantic processing related to face identity, was not triggered by the non-recognized famous faces in any of the CPs. The evidence of implicit processing (88) and the absence of a semantic response is consistent with the notion of a disconnection between the visual, stored representation and semantic face-related information and this issue will be discussed in detail below in Section 5 (and see (59, 87, 125) for evidence for behavioral implicit processing).

While all the ERP and MEG studies described above examined the stimulus-locked, evoked response to faces, there is one MEG study that has investigated induced Gamma-Band Responses (iGBRs) - oscillatory bursts of brain activity (25–100 Hz) which occur mostly around 150–400 ms after stimulus onset during face processing (135). These responses, which are assumed to reflect higher-level perceptual representations of a face including familiarity information, were reduced in CP compared to controls, mostly in the left fusiform area. We note however, that this approach is somewhat controversial and, hence, requires further validation in future studies.

Thus, consistent with the disconnection account, with the fMRI studies showing intact visual activation in core face regions (94-97), and with the intact N170 (126), these findings further imply that the activation of stored visual representations in occipito-temporal cortex, may be necessary but, in and of itself, are not sufficient to ensure intact face recognition.

4.2. Structural alteration in the CP brain

Thus far, the emphasis has been primarily on functional aspects of brain responses in CP. We now examine the evidence in favor of alterations of brain structure. Firstly, it is important to note that standard structural MRI scans do not reveal any abnormality in the brains of CP individuals, as indicated in many studies (1, 95-97, 99, 100). Thus, any abnormalities at the structural level are not obviously apparent to the naked eye. There have, however, been some findings, using more sophisticated analyses, which do suggest possible structural perturbations. Whether the structural changes give rise to the functional results or vice versa is unknown and determining causality is not easily achieved.

4.2.1. Volumetric alterations

Using systematic statistical analysis to compare the volumes of all sub-regions that were anatomically defined in occipito-temporal cortex across CPs and controls we observed that, overall, the CP group had a larger volume than the controls in the anterior and the posterior portion of the middle temporal gyrus (averaged across both hemispheres) (136). Of greater interest is that the CP individuals had reduced volume (albeit in a slightly larger temporal lobe) of the anterior fusiform gyrus compared with controls (see (120) for a similar finding in a single case of CP). Importantly, this region in the anterior fusiform gyrus was located anteriorly to the functionally defined FFA as delineated in the fMRI studies and did not overlap it. Furthermore, the FFA region overlapped with the anatomically defined posterior fusiform and critically, in this region, no structural alterations were observed. Of much importance, we found that these volumetric alterations in the anterior fusiform gyrus were correlated with the behavioral profile of face processing in CP, suggesting that these changes have functional significance. Specifically, we found a correlation between the volume of the anterior fusiform and the level of performance on the famous face recognition questionnaire such that reduced performance was accompanied by a smaller volume. Finally, the observed enlarged volume in both the anterior and posterior portions of the middle temporal gyrus in CP were not significantly related to any behavioral measure. One possible explanation for this latter finding might be that that this enlarged volume is a result of a compensatory response for the reduced volume in the anterior fusiform and, therefore, is not directly related to the behavioral profile in CP (136). Whether the reduction in volume observed in CP is one of gray matter, or white matter, or both was not possible to discern in this anatomical investigation.

Using voxel-based morphometry (VBM) in a relatively large group of CP individuals and matched controls (n=17, 18 respectively), Garrido et al., (2) found that CP individuals exhibited reduced gray matter volume in the right middle fusiform and inferior temporal gyrus, mid-superior temporal sulcus, middle temporal gyrus bilaterally and right anterior inferior temporal lobe. Of these regions, gray matter volume in the left superior temporal sulcus/middle temporal gyrus and the right middle fusiform gyrus/inferior temporal gyrus was correlated with an aggregated score on a set of face identity tasks. As is evident, similar to Behrmann et al., (136), the present study also found reduced volume in the anterior temporal lobe, but, in addition, observed reduced gray matter volume in other face-related regions in CP. The brain-behavior correlations were also not completely consistent across the two studies but these discrepancies might be related to differences in the method of analysis as (136) measured whole brain volume where (2) measured only gray matter volume, and different behavioral measures were also used in the two studies.

Another recent study (64) which used the VBM approach and also tested a large group of CPs, reported reduced gray matter density in a number of brain regions including the bilateral lingual gyrus, right middle temporal gyrus and left prefrontal cortex (among others). Of these regions, the volume reduction in the left lingual gyrus and left prefrontal cortex (DLPFC) was correlated with long-term memory for faces. Somewhat surprisingly, the reduced volume in the right middle temporal gyrus (also reported in (2)) was correlated with performance on a building-memory task, and so it is not entirely clear how the volume changes relate to face processing in this study. Of note is that, in this study, there was no obvious correspondence between the functional profile (as measured using fMRI; see section 4.1.1) and anatomical alterations in the tested CPs.

As is evident, the volumetric data collected are inconsistent across studies and so, further research is clearly warranted. However, the tentative conclusion is that, just like in the functional studies, there are no obvious volumetric alterations in key regions of the core face-processing network and thus, an explanation for CP must be sought beyond occipito-temporal cortex. In the following section, we examine whether the reported volumetric alterations might be accounted for by alteration of the white matter fibers that connect the different functional nodes that participate in face recognition.

4.2.2. White matter alterations

So far, only a single study has assessed the white matter integrity in CP. In this study (137), we adopted a conservative approach and focused our analysis on the two main fiber tracts connecting the OFA and FFA with the anterior portion of the temporal lobe and with the frontal lobe: i. the inferior longitudinal fasciculus (ILF), which passes through the fusiform and lingual gyri and the cuneus and traverses the superior, inferior and middle temporal gyri as well as the hippocampus and parahippocampus and ii. the inferior fronto-occipital fasciculus (IFOF), which projects between the lingual, fusiform and inferior temporal gyri and the infero-lateral and dorso-lateral prefrontal
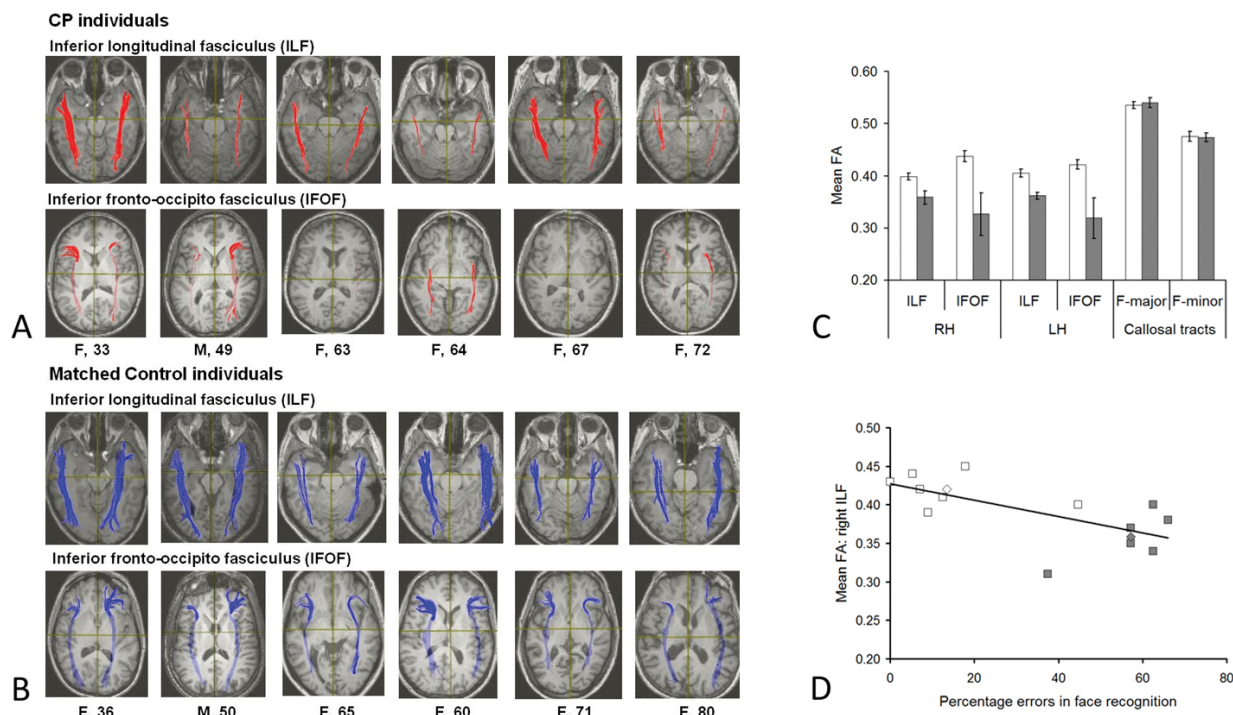
Figure 2. DTI analyses of the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) in CP. a. Axial slices showing the bilateral ILF and the IFOF in individuals with CP b. and their matched controls. The gender and age of each individual with CP and their matched control is indicated below each slice. The images qualitatively depict the reduction in both ILF and IFOF in CP compared to controls. c. The graph summarizes the quantitative analysis of the DTI data showing a reduction in the microstructural integrity, as measured by fractional anisotropy (FA), of the bilateral ILF and IFOF but not in the two callosal tracts in CP compared with the controls. LH, left hemisphere; RH, right hemisphere. d. A reduction in the mean fractional anisotropy in the right ILF was associated with an increase in errors in face recognition across the CP and control groups. Error bars indicate s.e.m. Modified with permission from (137).

cortex (138). Both the temporal and frontal lobes have been shown to be important for completion of face identification and for fine detailed discrimination (103, 139, 140) and so the rationale was that an alteration in these tracts might account for the behavioral profile in CP.

Briefly, we adopted both macrostructural and microstructural measures and characterized the number of fibers, number of voxels through which the fibers pass (index of volume) and the average fractional anisotropy (FA) of the fibers in the tracts of interest (normalized by the entire brain volume and, hence, expressed as percentages). Six individuals with CP and 17 age and gender matched controls participated in this study. Interestingly, we found that CP individuals exhibited reduced structural integrity in all dependent measures (%voxels, %fibers, mean FA) in both left and right ILF and IFOF compared to controls (see Figure 2a,b).

A similar analysis was conducted on the forceps major and the forceps minor. The forceps major is of particular importance as this fiber system projects to the lateral and inferior occipital regions that are part of the core regions involved in face processing (141). The forceps minor is a u-shaped fiber system, which is thought to be restricted to the frontal cortex. Therefore, while the forceps

major was examined in order to test whether reduced connectivity would also be observed in other tracts that are presumably involved in face processing, the forceps minor serves as a control system that would allow us to determine whether the alterations observed in CP are restricted and limited to the ventral-occipital temporal cortex and face processing or whether the alterations are more general, affecting multiple cortical tracts. Interestingly, in the forceps major, we found some evidence for reduced structural integrity but this was only evident in terms of the % voxels and not in any of the other measures. This provides some evidence that the disruption in structural connectivity in CP may not be isolated only to the ILF and IFOF but might also be observed, although not to the same extent, in tracts connecting more posterior face related regions located in bilateral inferior and lateral occipital cortex. In contrast, in the forceps minor, no differences whatsoever were obtained between CP and controls, suggesting that the reduction in structural integrity in CP is restricted to the ventral occipito-temporal cortex.

Importantly, when both CP and controls were pooled together (unfortunately, there were too few CPs to assess as group in isolation), there was a correlation between the reduction in the right ILF (and to some extent with the right IFOF) and the competence in face

recognition, revealing a functional role for the white matter fiber tracts. Finally, CP individuals did not suffer from a compromise of white matter integrity in the whole brain, thus further highlighting the specificity of the findings (see Figure 2c,d for a graphic depiction summarizing these findings).

These diffusion tensor imaging (DTI) findings are compatible with the previous results, too. Of note is that the ILF and IFOF both pass through some of the foci which exhibited reduced volume in CP compared to controls in the volumetric studies described above. For example, the ILF passes through the fusiform and lingual gyrus and the middle temporal gyri, which were all found to show reduced volume (2, 64), and so a perturbation of these fibers could account, at least partially, for the disparate volumetric changes described in these regions, or even for some of the observed functional deficits associated with these regions (see section 4.1). Along similar lines, the forceps major projects to the lateral and inferior occipital regions which are involved in face processing and perhaps subtle abnormalities to this tract might be associated with functional alterations in related regions such as the OFA (Section 4.1.1.1). As noted above, causality is difficult to determine, too --- whether the volumetric reduction is a result of reduced activation, which, in turn, might be a result of reduced connectivity is unknown. Other causal relations are possible, too.

It is important to indicate that DTI can only inform us of a reduction in structural connectivity but cannot provide any information regarding the directionality of the information flow. It is well known that information flows in a bidirectional fashion such that regions like the FFA propagate information to more anterior temporal and frontal cortex, and that they also receive reciprocal connections from the very same regions. The exact role of this top down information is not fully determined but several hypotheses have been raised (139, 142). In any event, it is possible that the observed disconnection affects both feedforward and feedback in the face processing network in CP.

More advanced, mathematically sophisticated approaches for analyzing DTI data, such as those using graph theory in order to characterize the structure of brain networks may be required to reveal more complicated aspects of the architecture of the white matter connectivity of the face processing network and its disruption in CP (143, 144).

5. THE DISCONNECTION HYPOTHESIS

The studies described thus far have demonstrated that individuals with CP have a largely normal fMRI response pattern in regions belonging to the core face network in occipito-temporal cortex. They do, however, exhibit impaired activation in regions of the extended network that are involved in identity representation such as the posterior/anterior cingulate and the anterior temporal cortex. Furthermore, they show a dissociation as regions involved in emotional processing, such as the amygdala,

and those involved in processing dynamic aspects of faces, such as the STS, are normally activated (64, 97).

The above patterns of functional activation observed in CP both during visual stimulation and at rest (in the absence of any cognitive task) were also reflected in the connectivity patterns in the core and extended network (Figure 3). In particular, there was a largely normal pattern of functional connectivity within the core face network but connectivity between the core system and regions of the extended system was dissociated; connectivity to the anterior temporal cortex was impaired in CP compared to controls, while connectivity to the amygdala was normal or even enhanced. The enhanced connectivity to the amygdala could perhaps represent compensatory mechanisms that are mediated by the normal emotion recognition typical to CP. These findings strongly support the structural perturbations described above and uncover circuits in ventral cortex (36, 145) whose disruption can give rise to very particular behavioral profiles.

The converging results, stemming from functional and structural neural investigations have led to the hypothesis that CP does not result from a specific lesion or an alteration in the core face system (although both these options have not been fully excluded), but rather is more likely the result of an abnormal propagation of information between the core and extended regions (and perhaps vice versa). This notion is also consistent with the large body of evidence showing that face processing, even in the normal brain, relies on the activity of a face network rather than of single regions (18). Furthermore, normal development is apparently accompanied by changes in the connectivity pattern in this network (34, 146).

Pertinent to this framework, are studies on acquired prosopagnosia, and particularly associative prosopagnosia, which has also been implicated as a disconnection syndrome between face recognition units, where the encoded percept or facial memory is stored, and personal identity nodes (46, 147). Specifically, on this account, if early perceptual encoding is performed in inferior occipital regions (e.g. OFA and FFA), and more conceptual knowledge related to faces is represented in anterior temporal regions, associative prosopagnosia might result from a disconnection of the tracts connecting the posterior occipito-temporal regions with more anterior temporal regions, e.g. the inferior longitudinal fasciculus (ILF). The ILF, as noted above, is the very same tract that showed structural alterations in CP and moreover its integrity was correlated with the face recognition skills across CPs and controls. Similarly, structural integrity of white matter fibers and specifically the inferior longitudinal fasciculus (ILF) was also shown to be critical in a case of progressive prosopagnosia (148).

Further support for this view comes from behavioral and neural evidence showing implicit face processing in CP (59, 87, 88). Such partial or fragmented face knowledge, where a face elicits some visual representation that is sufficient only for implicit, but not explicit recognition could very well be the outcome of a
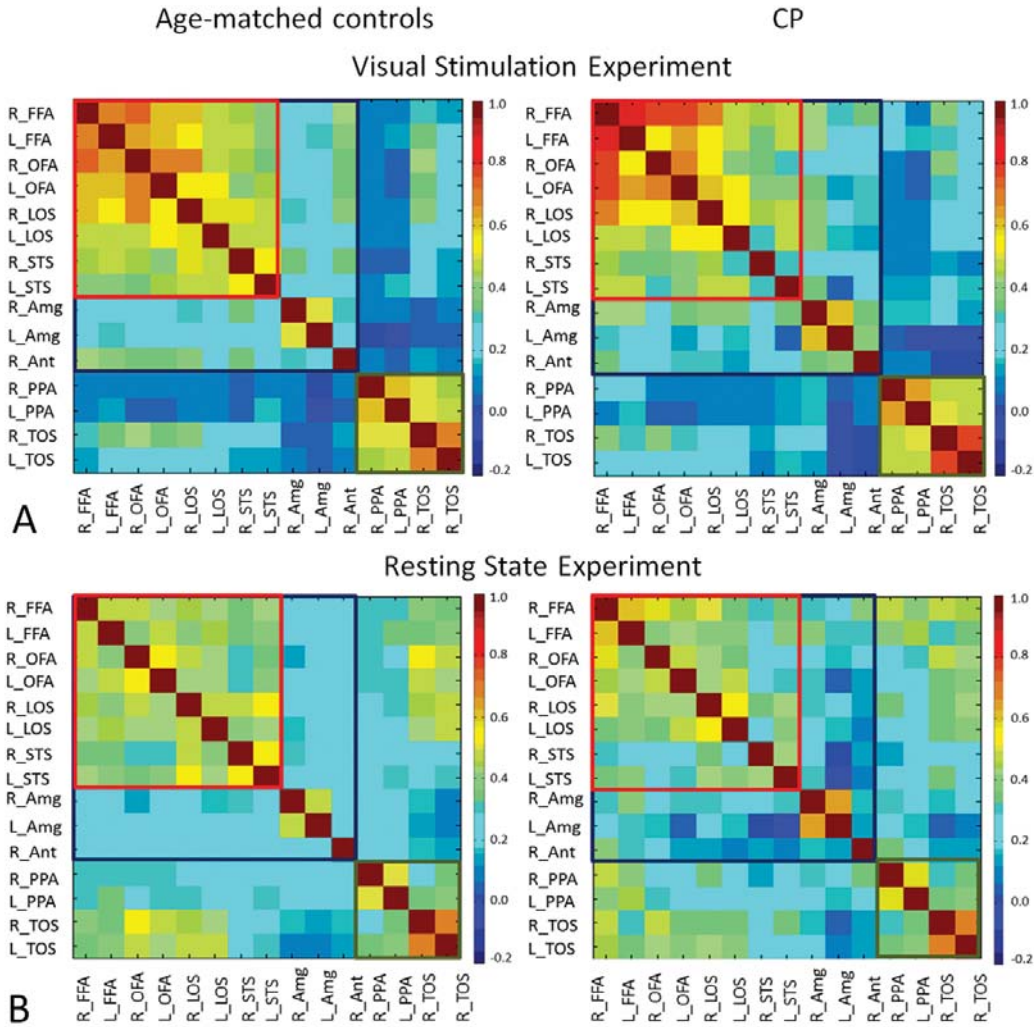
Figure 3. Functional connectivity maps obtained from localizer (a) and resting state scan (b). Matrices show all pairwise correlations between regions within the core face network (outlined by red rectangle), regions in the extended face network (outlined by blue rectangle) and regions that are building selective (outlined by green rectangle). All ROIs were sampled from the visual stimulation experiment and activation profiles were extracted from this experiment (a) and from the resting state scans (b). The color code indicates the level of correlation calculated between each pair of regions in each subject and then averaged across groups. Adapted with permission from (97).

disconnected or disrupted system (and see for example (149, 150) for similar accounts for implicit face processing in AP although we note that implicit processing could also be potentially associated with a more localized lesion either in AP or CP). It could also be the case, that the atypical holistic face processing in CP (and perhaps also in the processing of other stimuli requiring holistic perception) is the outcome of an impaired network rather than being related to an alteration at a particular region, or a deficit in the core network and this notion is now supported by a number of studies. For example, intensive training on a configural face task in a single case of CP, did not alter the fMRI activity within core face regions in this individual but rather, elicited greater coherence among face selective nodes (100). An additional study by Stollhoff and colleagues (77), combining both theoretical modeling and empirical data provides further support. Specifically, these authors trained a neural network model to represent face images with two different algorithms: When a predisposition towards decreased network connectivity was implemented in the model, it resulted in a featural representation of faces. In contrast, when the network was trained for optimal information encoding, it led to holistic representation of faces. In a follow-up experiment, ten prosopagnosic and twenty age-matched controls were asked to discriminate between faces that were manipulated according to the featural representation or to the holistic representation implemented by the network model. Compared to controls, prosopagnosic participants were impaired only in discriminating holistic changes of faces but showed no impairment in detecting featural changes (but see for example (55) for a different notion on what constitutes a holistic deficit in CP). These results provide empirical validation to the network model and imply that

structural differences in the network connectivity may lead to impaired holistic face processing and may underlie CP.

Further support for this view, relating holistic processing to a network property comes from a TMS study which implicated the right, but not left dorsolateral prefrontal cortex in holistic face processing ((114) and see also (115)). Thus, it could be that in CP, connectivity of this region to occipito-temporal cortex, most probably via the IFOF, is compromised thus contributing to their impaired holistic processing. Importantly, as noted above, in CP, prefrontal activation, mostly in the right hemisphere was shown to be enhanced relative to controls perhaps indicating an inefficient or compensatory recruitment of the neural circuits involved in holistic processing presumably located in this region (95, 97).

In our concluding remarks, we consider the neurodevelopmental perspective of CP which is relevant for its framing as a disconnection syndrome. This approach may also provide insights into the understanding of how these impaired connectivity patterns come about. Specifically, it is important to evaluate the behavioral, functional and structural abnormalities described in CP in light of the progress that has been made in other neurodevelopmental disorders, and particularly, developmental dyslexia, and to consider the possibility that CP may be rooted in similar neurobiological mechanisms. There is now germane evidence indicating that developmental dyslexia may be primarily caused by genetically driven focal cortical abnormalities related to neuronal migration (e.g. ectopias and microgyri) that occur in particular areas of the left perisylvian cortex known to be involved in phonological representations (151-153). Specifically, early postmortem studies in humans have laid the basis for an understanding of these underlying microstructural neural abnormalities. Analogous abnormalities are currently being examined in an animal model of the disorder, which also enables the mapping of susceptibility genes that have been associated with particular aspects of the cognitive and neural characteristics of the disorder (153). Importantly, at the macroscopic level, specific cortical alterations resulting from the microstructural abnormalities, affect the white and gray matter along the fronto-temporo-parietal network that is involved in reading, and are associated with dyslexia. This macroscopic pattern is compatible with the notion that developmental dyslexia is a disconnection syndrome (e.g. see (154)), analogous to the model we propose for CP.

As suggested by Ramus, 2004 (152) and as discussed in a recent review on developmental prosopagnosia by Susilo and Duchaine (48), it is possible that a similar model might pertain to other neurodevelopmental disorders aside from CP. In this case, abnormal neural migration is expected to occur in regions of the face processing network along the occipito-temporal cortex and even in more extended regions of this network. The exact locus and extent of the abnormal neural migration would obviously lead to variations in the characteristics of the disorder among different individuals, and perhaps could account for the heterogeneity of the behavioral and neural findings described in the CP literature and reviewed in the present paper. Importantly, a basic assumption in this model is that neurodevelopmental disorders are multi-genetic in origin, and so this approach challenges an existing account which suggested a simple autosomal dominance mode of inheritance for CP (54). Clearly, CP research is far behind the current understanding of the neurobiological basis of developmental dyslexia. Progress in CP research, however, may develop along similar lines in the future, especially if a large-scale collaborative effort were to emerge in which different labs combined to yield large enough groups of participants. Importantly, research along these lines, which will enable the establishment of clear biomarkers, will also be pivotal in determining whether CP is indeed a pathological, distinct condition rather than being related to the very low-end of the normal distribution of face perception.

6. OUTSTANDING ISSUES

Despite the growing number of studies on CP, there are still many critical outstanding issues and controversies, some of which have been raised throughout the paper and some of which we outline here (and clearly this is not an exhaustive list). We hope these questions will be addressed and perhaps even resolved in future studies.

1. What is the genetic basis of CP and how does it determine the neural and behavioral characteristics of the disorder.

2. Is CP a definitively distinct entity or do these individuals simply fall at the tail end of the normal distribution? Determining qualitative as well as quantitative means of answering this question remains a challenge.

3. How would the genetic and behavioral profiles of CP be reflected at the neural network level? Will these measures allow constructing a genetic finger print or a biomarker? Will it be possible to reveal several different subtypes of the disorder based on these measures that will have different patterns of functional/anatomical (dis)connectivity? Alternatively, using such multimodal approach it may be possible to reveal a continuum of symptoms severity in relation to the extent of the functional and/or structural disconnection.

4. What is the correspondence between findings indicating abnormal face processing in CP, obtained using different imaging methods such as fMRI and ERP?

5. Is there potential for rehabilitation of this disorder? So far only a few attempts have been reported using behavioral training manipulations, each with only a single CP and there is no reported long-term follow up in these cases (100, 155). A recent interesting attempt to temporarily alleviate face processing in CP has been conducted using intranasal inhalation of the hormone oxytocin, previously suggested to improve face processing in healthy individuals (156). This study provides the first evidence that oxytocin may potentially improve face processing in CP and paves

the way to future investigations of the behavioral and neural underpinnings of this effect.

6. What is the developmental trajectory of the disorder? How early can we detect CP in children? How would the behavioral and neural markers change with development? Some initial studies have examined this issue from a behavioral perspective (53, 157) and so neural investigations along similar lines are sorely needed.

We have argued that CP represents a disconnection syndrome and have rallied some evidence in favor of this claim based on alterations in volume, in white matter and in functional activation profile and connectivity. The nature of causality between these different aspects is not fully explicated and we recognize that further research is required to definitively rule in the disconnection account we have offered.

7. ACKNOWLEDGEMENTS

8. REFERENCES

1. Furl, N., L. Garrido, R. J. Dolan, J. Driver & B. Duchaine: Fusiform gyrus face selectivity relates to individual differences in facial recognition ability. *J Cogn Neurosci*, 23, 1723-40 (2011)

2. Garrido, L., N. Furl, B. Draganski, N. Weiskopf, J. Stevens, G. C. Tan, J. Driver, R. J. Dolan & B. Duchaine: Voxel-based morphometry reveals reduced grey matter volume in the temporal cortex of developmental prosopagnosics. *Brain*, 132, 3443-55 (2009)

3. Rotshtein, P., J. J. Geng, J. Driver & R. J. Dolan: Role of features and second-order spatial relations in face discrimination, face recognition, and individual face skills: behavioral and functional magnetic resonance imaging data. *J Cogn Neurosci*, 19, 1435-52 (2007)

4. Zhu, Q., Y. Song, S. Hu, X. Li, M. Tian, Z. Zhen, Q. Dong, N. Kanwisher & J. Liu: Heritability of the specific cognitive ability of face perception. *Curr Biol*, 20, 137-42 (2010)

5. Wilmer, J. B., L. Germine, C. F. Chabris, G. Chatterjee, M. Williams, E. Loken, K. Nakayama & B. Duchaine: Human face recognition ability is specific and highly heritable. *Proc Natl Acad Sci U S A*, 107, 5238-41 (2010)

6. Behrmann, M., J. J. Richler, G. Avidan & R. Kimchi: Holistic face perception. In: Oxford Handbook of Perceptual Organization. Ed: J. Wagemans. Oxford University Press, New York (2013)

7. Farah, M. J., J. W. Tanaka & H. M. Drain: What causes the face inversion effect? *J Exp Psychol Hum Percept Perform*, 21, 628-34 (1995)

8. Tanaka, J. W. & M. J. Farah: Parts and wholes in face recognition. *Q J Exp Psychol (A)*, 46, 225-45 (1993)

9. Young, A. W., D. Hellawell & D. C. Hay: Configurational information in face perception. *Perception*, 16, 747-59 (1987)

10. Gross, C. G.: Visual functions of inferotemporal cortex. In: Handbook of Sensory Physiology. Ed: R. Jung. Springer-Verlag, Berlin (1972)

11. Weiner, K. S. & K. Grill-Spector: Neural representations of faces and limbs neighbor in human high-level visual cortex: evidence for a new organization principle. Psychol Res, 77, 74-97 (2013)

12. Tsao, D. Y., W. A. Freiwald, T. A. Knutsen, J. B. Mandeville & R. B. Tootell: Faces and objects in macaque cerebral cortex. Nat Neurosci, 6, 989-95 (2003)

13. Tsao, D. Y., W. A. Freiwald, R. B. Tootell & M. S. Livingstone: A cortical region consisting entirely of face-selective cells. *Science*, 311, 670-4 (2006)

14. Sergent, J., S. Ohta & B. Macdonald: Functional neuroanatomy of face and object processing. A positron emission tomography study. *Brain*, 115, 15-36 (1992)

15. Puce, A., T. Allison, J. C. Gore & G. McCarthy: Face-sensitive regions in human extrastriate cortex studied by functional MRI. *J Neurophysiol*, 74, 1192-9. (1995)

16. Kanwisher, N., J. McDermott & M. M. Chun: The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.*, 17, 4302-4311 (1997)

17. McCarthy, G., A. Puce, J. C. Gore & T. Allison: Face specific processing in the human fusiform gyrus. *J Cogn Neurosci.*, 9, 605-610 (1997)

18. Ishai, A.: Let's face it: it's a cortical network. *Neuroimage*, 40, 415-9 (2008)

19. Fairhall, S. L. & A. Ishai: Effective connectivity within the distributed cortical network for face perception. *Cereb Cortex*, 17, 2400-6 (2007)

20. Haxby, J. V., E. A. Hoffman & M. I. Gobbini: The distributed human neural system for face perception. *Trends in Cognitive Sciences*, 4, 223-233 (2000)

21. Gauthier, I., M. J. Tarr, J. Moylan, P. Skudlarski, J. C. Gore & A. W. Anderson: The fusiform "face area" is part

of a network that processes faces at the individual level. *J Cogn Neurosci*, 12, 495-504. (2000)

22. Rossion, B., R. Caldara, M. Seghier, A. M. Schuller, F. Lazeyras & E. Mayer: A network of occipito-temporal face-sensitive areas besides the right middle fusiform gyrus is necessary for normal face processing. *Brain*, 126, 2381-95 (2003)

23. Pinsk, M. A., M. Arcaro, K. S. Weiner, J. F. Kalkus, S. J. Inati, C. G. Gross & S. Kastner: Neural representations of faces and body parts in macaque and human cortex: a comparative FMRI study. *J Neurophysiol*, 101, 2581-600 (2009)

24. Kriegeskorte, N., E. Formisano, B. Sorger & R. Goebel: Individual faces elicit distinct response patterns in human anterior temporal cortex. *Proc Natl Acad Sci U S A*, 104, 20600-5 (2007)

25. Nestor, A., D. C. Plaut & M. Behrmann: Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proc Natl Acad Sci U S A*, 108, 9998-10003 (2011)

26. Simmons, W. K., M. Reddish, P. S. Bellgowan & A. Martin: The selectivity and functional connectivity of the anterior temporal lobes. *Cereb Cortex*, 20, 813-25 (2009)

27. Gobbini, M. I. & J. V. Haxby: Neural systems for recognition of familiar faces. *Neuropsychologia*, 45, 32-41 (2007)

28. Tsao, D. Y., N. Schweers, S. Moeller & W. A. Freiwald: Patches of face-selective cortex in the macaque frontal lobe. *Nat Neurosci*, 11, 877-9 (2008)

29. Tsao, D. Y., S. Moeller & W. A. Freiwald: Comparing face patch systems in macaques and humans. *Proc Natl Acad Sci U S A*, 105, 19514-9 (2008)

30. Hadj-Bouziane, F., N. Liu, A. H. Bell, K. M. Gothard, W. M. Luh, R. B. Tootell, E. A. Murray & L. G. Ungerleider: Amygdala lesions disrupt modulation of functional MRI activity evoked by facial expression in the monkey inferior temporal cortex. *Proc Natl Acad Sci U S A*, 109, E3640-8 (2012)

31. Furl, N., F. Hadj-Bouziane, N. Liu, B. B. Averbeck & L. G. Ungerleider: Dynamic and static facial expressions decoded from motion-sensitive areas in the macaque monkey. *J Neurosci*, 32, 15952-62 (2012)

32. Davies-Thompson, J. & T. J. Andrews: Intra- and interhemispheric connectivity between face-selective regions in the human brain. *J Neurophysiol*, 108, 3087-95 (2012)

33. Zhen, Z., H. Fang & J. Liu: The hierarchical brain network for face recognition. *PLoS One*, 8, e59886 (2013)

34. Joseph, J. E., J. E. Swearingen, J. D. Clark, C. E. Benca, H. R. Collins, C. R. Corbly, A. D. Gathers & R. S. Bhatt: The changing landscape of functional brain networks for face processing in typical development. *Neuroimage*, 63, 1223-36 (2012)

35. Cohen Kadosh, K., R. N. Henson, R. Cohen Kadosh, M. H. Johnson & F. Dick: Task-dependent activation of face-sensitive cortex: an fMRI adaptation study. *J Cogn Neurosci*, 22, 903-17 (2011)

36. Gschwind, M., G. Pourtois, S. Schwartz, D. Van De Ville & P. Vuilleumier: White-matter connectivity between face-responsive regions in the human brain. *Cereb Cortex*, 22, 1564-76 (2012)

37. Pyles, J. A., T. D. Verstynen, W. Schneider & M. J. Tarr: Explicating the face perception network with white matter connectivity. *PLoS One*, 8, e61611 (2013)

38. Phillips, J. S., A. S. Greenberg, J. A. Pyles, S. K. Pathak, M. Behrmann, W. Schneider & M. J. Tarr: Co-analysis of brain structure and function using fMRI and diffusion-weighted imaging. *J Vis Exp* (2012)

39. Parvizi, J., C. Jacques, B. L. Foster, N. Witthoft, V. Rangarajan, K. S. Weiner & K. Grill-Spector: Electrical stimulation of human fusiform face-selective regions distorts face perception. *J Neurosci*, 32, 14915-20 (2012)

40. Jonas, J., M. Descoins, L. Koessler, S. Colnat-Coulbois, M. Sauvee, M. Guye, J. P. Vignal, H. Vespignani, B. Rossion & L. Maillard: Focal electrical intracerebral stimulation of a face-sensitive area causes transient prosopagnosia. *Neuroscience*, 222, 281-8 (2012)

41. Bouvier, S. E. & S. A. Engel: Behavioral deficits and cortical damage loci in cerebral achromatopsia. *Cereb Cortex*, 16, 183-91 (2006)

42. Barton, J. J.: Disorders of face perception and recognition. *Neurol Clin*, 21, 521-48 (2003)

43. Gainotti, G. & C. Marra: Differential contribution of right and left temporo-occipital and anterior temporal lesions to face recognition disorders. *Front Hum Neurosci*, 5, 55 (2011)

44. Bodamer, J.: Die prosop-Agnosie. *Archiv für Psychiatrie und Nervenkrankheiten*, 179, 6-53. (1947)

45. De Renzi, E., P. Faglioni, D. Grossi & P. Nichelli: Apperceptive and associative forms of prosopagnosia. *Cortex*, 27, 213-221 (1991)

46. Fox, C. J., G. Iaria & J. J. Barton: Disconnection in prosopagnosia and face processing. *Cortex*, 44, 996-1009 (2008)

47. Stollhoff, R., J. Jost, T. Elze & I. Kennerknecht: Deficits in long-term recognition memory reveal

dissociated subtypes in congenital prosopagnosia. *PLoS One*, 6, e15702 (2011)

48. Susilo, T. & B. Duchaine: Advances in developmental prosopagnosia research. *Curr Opin Neurobiol*, 23, 423-9 (2013)

49. Barton, J. J., M. V. Cherkasova, D. Z. Press, J. M. Intriligator & M. O'Connor: Developmental prosopagnosia: a study of three patients. *Brain Cogn*, 51, 12-30 (2003)

50. Farah, M. J., C. Rabinowitz, G. E. Quinn & G. T. Liu: Early commitment of neural substrates for face recognition. *Cogn Neuropsychol*, 17, 117-23 (2000)

51. Duchaine, B. C., L. Germine & K. Nakayama: Family resemblance: Ten family members with prosopagnosia and within-class object agnosia. *Cognitive Neuropsychology*, 24, 419-430 (2007)

52. De Haan, E. H.: A familial factor in the development of face recognition deficits. *Journal of Clinical and Experimental Neuropsychology*, 21, 312-315 (1999)

53. Schmalzl, L., R. Palermo & M. Coltheart: Cognitive heterogeneity in genetically based prosopagnosia: a family study. *J Neuropsychol*, 2, 99-117 (2008)

54. Grueter, M., T. Grueter, V. Bell, J. Horst, W. Laskowski, K. Sperling, P. W. Halligan, H. D. Ellis & I. Kennerknecht: Hereditary prosopagnosia: the first case series. *Cortex*, 43, 734-49 (2007)

55. Kimchi, R., M. Behrmann, G. Avidan & R. Amishav: Perceptual separability of featural and configural information in congenital prosopagnosia. *Cogn Neuropsychol*, 29, 447-63 (2012)

56. Tanzer, M., E. Freud, T. Ganel & G. Avidan: General-holistic impairment in congenital prosopagnosia: Evidence from Garner's speeded-classification task. *Cogn Neuropsychol*, In press

57. Behrmann, M., G. Avidan, J. J. Marotta & R. Kimchi: Detailed exploration of face-related processing in congenital prosopagnosia: 1. Behavioral findings. *J Cogn Neurosci*, 17, 1130-49 (2005)

58. Duchaine, B. & K. Nakayama: The Cambridge Face Memory Test: results for neurologically intact individuals and an investigation of its validity using inverted face stimuli and prosopagnosic participants. *Neuropsychologia*, 44, 576-85 (2006)

59. Avidan, G. & M. Behrmann: Implicit familiarity processing in congenital prosopagnosia. *Journal of Neuropsychology*, 2, 141-164 (2008)

60. Warrington, E. K.: Recognition Memory Test. NFER-Nelson. (1984)

61. Longmore, C. A. & J. J. Tree: Motion as a cue to face recognition: evidence from congenital prosopagnosia. *Neuropsychologia*, 51, 864-75 (2013)

62. Humphreys, K., G. Avidan & M. Behrmann: A detailed investigation of facial expression processing in congenital prosopagnosia as compared to acquired prosopagnosia. *Exp Brain Res*, 176, 356-373 (2007)

63. Duchaine, B. C., H. Parker & K. Nakayama: Normal recognition of emotion in a prosopagnosic. *Perception*, 32, 827-38 (2003)

64. Dinkelacker, V., M. Gruter, P. Klaver, T. Gruter, K. Specht, S. Weis, I. Kennerknecht, C. E. Elger & G. Fernandez: Congenital prosopagnosia: multistage anatomical and functional deficits in face processing circuitry. *J Neurol*, 258, 770-82 (2011)

65. Nunn, J. A., P. Postma & R. Pearson: Developmental prosopagnosia: should it be taken at face value? *Neurocase*, 7, 15-27 (2001)

66. Duchaine, B. C. & K. Nakayama: Developmental prosopagnosia: a window to content-specific face processing. *Curr Opin Neurobiol*, 16, 166-73 (2006)

67. Le Grand, R., P. A. Cooper, C. J. Mondloch, T. L. Lewis, N. Sagiv, B. de Gelder & D. Maurer: What aspects of face processing are impaired in developmental prosopagnosia? *Brain Cogn*, 61, 139-58 (2006)

68. DeGutis, J., G. Chatterjee, R. J. Mercado & K. Nakayama: Face gender recognition in developmental prosopagnosia: Evidence for holistic processing and use of configural information. *Visual Cognition*, 20, 1242-1253 (2012)

69. Todorov, A. & B. Duchaine: Reading trustworthiness in faces without recognizing faces. *Cogn Neuropsychol*, 25, 395-410 (2008)

70. Young, A. W. & V. Bruce: Understanding person perception. *Br J Psychol*, 102, 959-74 (2011)

71. Righart, R. & B. de Gelder: Impaired face and body perception in developmental prosopagnosia. *Proc Natl Acad Sci U S A*, 104, 17234-8 (2007)

72. Stollhoff, R., J. Jost, T. Elze & I. Kennerknecht: The early time course of compensatory face processing in congenital prosopagnosia. *PLoS One*, 5, e11482 (2010)

73. Maurer, D., R. L. Le Grand & C. J. Mondloch: The many faces of configural processing. *Trends Cogn Sci*, 6, 255-260 (2002)

74. Avidan, G., M. Tanzer & M. Behrmann: Impaired holistic processing in congenital prosopagnosia. *Neuropsychologia*, 49, 2541-52 (2011)

75. Bentin, S., J. M. Degutis, M. D'Esposito & L. C. Robertson: Too many trees to see the forest: performance, event-related potential, and functional magnetic resonance imaging manifestations of integrative congenital prosopagnosia. *J Cogn Neurosci*, 19, 132-46 (2007)

76. Palermo, R., D. Rivolta, C. E. Wilson & L. Jeffery: Adaptive face space coding in congenital prosopagnosia: typical figural aftereffects but abnormal identity aftereffects. *Neuropsychologia*, 49, 3801-12 (2011)

77. Stollhoff, R., I. Kennerknecht, T. Elze & J. Jost: A computational model of dysfunctional facial encoding in congenital prosopagnosia. *Neural Netw*, 24, 652-64 (2011)

78. Duchaine, B. C., G. Yovel & K. Nakayama: No global processing deficit in the Navon task in 14 developmental prosopagnosics. *Soc Cogn Affect Neurosci*, 2, 104-113 (2007)

79. Lange, J., M. de Lussanet, S. Kuhlmann, A. Zimmermann, M. Lappe, P. Zwitserlood & C. Dobel: Impairments of biological motion perception in congenital prosopagnosia. *PLoS One*, 4, e7414 (2009)

80. Navon, D.: Forest before trees: The precedence of global features in visual perception. *Cognitive psychology*, 9, 353-383 (1977)

81. Dakin, S. & U. Frith: Vagaries of visual perception in autism. *Neuron*, 48, 497-507 (2005)

82. Yovel, G. & B. Duchaine: Specialized face perception mechanisms extract both part and spacing information: evidence from developmental prosopagnosia. *J Cogn Neurosci*, 18, 580-93 (2006)

83. Busigny, T. & B. Rossion: Holistic processing impairment can be restricted to faces in acquired prosopagnosia: Evidence from the global/local Navon effect. *J Neuropsychol* (2010)

84. Barton, J. J.: What is meant by impaired configural processing in acquired prosopagnosia? *Perception*, 38, 242-60 (2009)

85. Kennerknecht, I., T. Grueter, B. Welling, S. Wentzek, J. Horst, S. Edwards & M. Grueter: First report of prevalence of non-syndromic hereditary prosopagnosia (HPA) *Am J Med Genet A*, 140, 1617-22 (2006)

86. Rivolta, D., R. Palermo, L. Schmalzl & M. Coltheart: Covert face recognition in congenital prosopagnosia: A group study. *Cortex* (2012)

87. Rivolta, D., R. Palermo & L. Schmalzl: What is overt and what is covert in congenital prosopagnosia? *Neuropsychol Rev*, 23, 111-6 (2012)

88. Eimer, M., A. Gosling & B. Duchaine: Electrophysiological markers of covert face recognition in developmental prosopagnosia. *Brain*, 135, 542-54 (2012)

89. Kanwisher, N. & G. Yovel: The fusiform face area: a cortical region specialized for the perception of faces. *Philos Trans R Soc Lond B Biol Sci*, 361, 2109-28 (2006)

90. Kanwisher, N.: Functional specificity in the human brain: a window into the functional architecture of the mind. *Proc Natl Acad Sci U S A*, 107, 11163-70 (2010)

91. Behrmann, M. & D. C. Plaut: Bilateral hemispheric processing of words and faces: evidence from word impairments in prosopagnosia and face impairments in pure alexia. *Cereb Cortex*, In press

92. Behrmann, M. & D. C. Plaut: Distributed circuits, not circumscribed centers, mediate visual recognition. *Trends Cogn Sci*, 17, 210-9 (2013)

93. Moeller, S., W. A. Freiwald & D. Y. Tsao: Patches with links: a unified system for processing faces in the macaque temporal lobe. *Science*, 320, 1355-9 (2008)

94. Hasson, U., G. Avidan, L. Y. Deouell, S. Bentin & R. Malach: Face-selective activation in a congenital prosopagnosic subject. J Cogn Neurosci, 15, 419-31 (2003)

95. Avidan, G., U. Hasson, R. Malach & M. Behrmann: Detailed exploration of face-related processing in congenital prosopagnosia: 2. Functional neuroimaging findings. J Cogn Neurosci, 17, 1150-67 (2005)

96. Avidan, G. & M. Behrmann: Functional MRI reveals compromised neural integrity of the face processing network in congenital prosopagnosia. Curr Biol, 19, 1146-1150 (2009)

97. Avidan, G., M. Tanzer, F. Hadj-Bouziane, N. Liu, L. G. Ungerleider & M. Behrmann: Selective dissociation between core and extended regions of the face processing network in congenital prosopagnosia. Cereb Cortex (2013)

98. Hadjikhani, N. & B. De Gelder: Neural basis of prosopagnosia: An fMRI study. *Hum Brain Mapp*, 16, 176-182 (2002)

99. Minnebusch, D. A., B. Suchan, O. Koster & I. Daum: A bilateral occipitotemporal network mediates face perception. *Behav Brain Res*, 198, 179-85 (2009)

100. DeGutis, J. M., S. Bentin, L. C. Robertson & M. D'Esposito: Functional plasticity in ventral temporal cortex following cognitive rehabilitation of a congenital prosopagnosic. *J Cogn Neurosci*, 19, 1790-802 (2007)

101. Von Der Heide, R. J., L. M. Skipper & I. R. Olson: Anterior temporal face patches: a meta-analysis and empirical study. *Front Hum Neurosci*, 7, 17 (2013)

102. Gainotti, G.: Is the right anterior temporal variant of prosopagnosia a form of 'associative prosopagnosia' or a form of 'multimodal person recognition disorder'? *Neuropsychol Rev*, 23, 99-110 (2013)

103. Puce, A., T. Allison & G. McCarthy: Electrophysiological studies of human face perception. III: Effects of top-down processing on face-specific potentials. *Cereb Cortex*, 9, 445-58. (1999)

104. Rajimehr, R., J. C. Young & R. B. Tootell: An anterior temporal face patch in human cortex, predicted by macaque maps. *Proc Natl Acad Sci U S A*, 106, 1995-2000 (2009)

105. Williams, M. A., G. Savage & M. Halmagyi: Abnormal configural perception in a patient with right anterior temporal lobe atrophy. *Neurocase*, 12, 286-91 (2006)

106. Damasio, A. R., D. Tranel & H. Damasio: Face agnosia and the neural substrates of memory. *Annu.Rev.Neurosci.*, 13, 89-109 (1990)

107. Gainotti, G.: Different patterns of famous people recognition disorders in patients with right and left anterior temporal lesions: a systematic review. *Neuropsychologia*, 45, 1591-607 (2007)

108. Tsukiura, T., H. Mochizuki-Kawai & T. Fujii: Dissociable roles of the bilateral anterior temporal lobe in face-name associations: an event-related fMRI study. *Neuroimage*, 30, 617-26 (2006)

109. von Kriegstein, K., A. Kleinschmidt & A. L. Giraud: Voice recognition and cross-modal responses to familiar speakers' voices in prosopagnosia. *Cereb Cortex*, 16, 1314-22 (2006)

110. Bobes, M. A., A. Lage Castellanos, I. Quinones, L. Garcia & M. Valdes-Sosa: Timing and tuning for familiarity of cortical responses to faces. *PLoS One*, 8, e76100 (2013)

111. Chan, A. W. & P. E. Downing: Faces and eyes in human lateral prefrontal cortex. *Front Hum Neurosci*, 5, 51 (2011)

112. Ranganath, C., J. DeGutis & M. D'Esposito: Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Brain Res Cogn Brain Res*, 20, 37-45 (2004)

113. Rissman, J., A. Gazzaley & M. D'Esposito: Dynamic adjustments in prefrontal, hippocampal, and inferior temporal interactions with increasing visual working memory load. *Cereb Cortex*, 18, 1618-29 (2008)

114. Renzi, C., S. Schiavi, C. C. Carbon, T. Vecchi, J. Silvanto & Z. Cattaneo: Processing of featural and configural aspects of faces is lateralized in dorsolateral prefrontal cortex: a TMS study. *Neuroimage*, 74, 45-51 (2013)

115. Maurer, D., K. M. O'Craven, R. Le Grand, C. J. Mondloch, M. V. Springer, T. L. Lewis & C. L. Grady: Neural correlates of processing facial identity based on features versus their spacing. *Neuropsychologia*, 45, 1438-51 (2007)

116. Rossion, B. & C. Jacques: The N170: Understanding the time course of face perception in the human brain. In: The Oxford Handbook of Event-Related Potential Components. Ed: E. S. K. Steven J. Luck. Oxford University Press, New York (2011)

117. Bentin, S., T. Allison, A. Puce, E. Perez & G. McCarthy: Electrophysiological studies of face perception in humans. *J Cogn Neurosci*, 8, 551-565 (1996)

118. Caharel, S., M. Ramon & B. Rossion: Face familiarity decisions take 200 msec in the human brain: Electrophysiological evidence from a Go/No-go speeded task. *J Cogn Neurosci.*, 26, 81-95 (2014)

119. Rellecke, J., W. Sommer & A. Schacht: Emotion effects on the N170: a question of reference? *Brain Topogr*, 26, 62-71 (2013)

120. Bentin, S., L. Y. Deouell & N. Soroker: Selective visual streaming in face recognition: evidence from developmental prosopagnosia. *Neuroreport*, 10, 823-7. (1999)

121. Kress, T. & I. Daum: Event-related potentials reflect impaired face recognition in patients with congenital prosopagnosia. *Neurosci Lett*, 352, 133-6 (2003)

122. Minnebusch, D. A., B. Suchan, M. Ramon & I. Daum: Event-related potentials reflect heterogeneity of developmental prosopagnosia. *Eur J Neurosci*, 25, 2234-47 (2007)

123. Harris, A. M., B. C. Duchaine & K. Nakayama: Normal and abnormal face selectivity of the M170 response in developmental prosopagnosics. *Neuropsychologia*, 43, 2125-36 (2005)

124. Dobel, C., C. Putsche, P. Zwitserlood & M. Junghofer: Early left-hemispheric dysfunction of face processing in congenital prosopagnosia: an MEG study. *PLoS One*, 3, e2326 (2008)

125. Rivolta, D., R. Palermo, L. Schmalzl & M. A. Williams: Investigating the features of the M170 in congenital prosopagnosia. *Front Hum Neurosci*, 6, 45 (2012)

126. Towler, J., A. Gosling, B. Duchaine & M. Eimer: The face-sensitive N170 component in developmental prosopagnosia. *Neuropsychologia*, 50, 3588-99 (2012)

127. Jacques, C. & B. Rossion: Early electrophysiological responses to multiple face orientations correlate with individual discrimination performance in humans. *Neuroimage*, 36, 863-76 (2007)

128. Jacques, C., O. d'Arripe & B. Rossion: The time course of the inversion effect during individual face discrimination. *J Vis*, 7, 3 (2007)

129. Horovitz, S. G., B. Rossion, P. Skudlarski & J. C. Gore: Parametric design and correlational analyses help integrating fMRI and electrophysiological data during face processing. *Neuroimage*, 22, 1587-95 (2004)

130. Sadeh, B., I. Podlipsky, A. Zhdanov & G. Yovel: Event-related potential and functional MRI measures of face-selectivity are highly correlated: a simultaneous ERP-fMRI investigation. *Hum Brain Mapp*, 31, 1490-501 (2010)

131. Yovel, G. & N. Kanwisher: The neural basis of the behavioral face-inversion effect. *Curr Biol*, 15, 2256-62 (2005)

132. Towler, J. & M. Eimer: Electrophysiological studies of face processing in developmental prosopagnosia: neuropsychological and neurodevelopmental perspectives. *Cogn Neuropsychol*, 29, 503-29 (2012)

133. Gosling, A. & M. Eimer: An event-related brain potential study of explicit face recognition. *Neuropsychologia*, 49, 2736-45 (2011)

134. Schweinberger, S. R. & A. M. Burton: Covert recognition and the neural system for face processing. *Cortex*, 39, 9-30 (2003)

135. Dobel, C., M. Junghofer & T. Gruber: The role of gamma-band activity in the representation of faces: reduced activity in the fusiform face area in congenital prosopagnosia. *PLoS One*, 6, e19550 (2011)

136. Behrmann, M., G. Avidan, F. Gao & S. Black: Structural imaging reveals anatomical alterations in inferotemporal cortex in congenital prosopagnosia. *Cereb Cortex*, 17, 2354-2363 (2007)

137. Thomas, C., G. Avidan, K. Humphreys, K. Jung, F. Gao & M. Behrmann: Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nat Neurosci,* 12, 29-31 (2009)

138. Catani, M., D. K. Jones, R. Donato & D. H. Ffytche: Occipito-temporal connections in the human brain. *Brain*, 126, 2093-107 (2003)

139. Bar, M., K. S. Kassam, A. S. Ghuman, J. Boshyan, A. M. Schmid, A. M. Dale, M. S. Hamalainen, K. Marinkovic, D. L. Schacter, B. R. Rosen & E. Halgren: Top-down facilitation of visual recognition. *Proc Natl Acad Sci U S A*, 103, 449-54 (2006)

140. Summerfield, C., T. Egner, M. Greene, E. Koechlin, J. Mangels & J. Hirsch: Predictive codes for forthcoming perception in the frontal cortex. *Science*, 314, 1311-4 (2006)

141. Dougherty, R. F., M. Ben-Shachar, R. Bammer, A. A. Brewer & B. A. Wandell: Functional organization of human occipital-callosal fiber tracts. *Proc Natl Acad Sci U S A*, 102, 7350-5 (2005)

142. Hochstein, S. & M. Ahissar: View from the top: hierarchies and reverse hierarchies in the visual system. *Neuron*, 36, 791-804 (2002)

143. van den Heuvel, M. P., R. S. Kahn, J. Goni & O. Sporns: High-cost, high-capacity backbone for global brain communication. *Proc Natl Acad Sci U S A*, 109, 11372-7 (2012)

144. van den Heuvel, M. P. & O. Sporns: Rich-club organization of the human connectome. *J Neurosci*, 31, 15775-86 (2011)

145. Turk-Browne, N. B., S. V. Norman-Haignere & G. McCarthy: Face-Specific Resting Functional Connectivity between the Fusiform Gyrus and Posterior Superior Temporal Sulcus. *Front Hum Neurosci*, 4, 176 (2010)

146. Cohen Kadosh, K., R. Cohen Kadosh, F. Dick & M. H. Johnson: Developmental changes in effective connectivity in the emerging core face network. *Cereb Cortex*, 21, 1389-94 (2011)

147. Young, A. W.: Simulating face recognition: Implications for modelling cognition. *Cognitive Neuropsychology*, 16, 1-48 (1999)

148. Grossi, D., A. Soricelli, M. Ponari, E. Salvatore, M. Quarantelli, A. Prinster & L. Trojano: Structural connectivity in a single case of progressive prosopagnosia: The role of the right inferior longitudinal fasciculus. *Cortex* (2012)

149. Burton, A. M., A. W. Young, V. Bruce, R. A. Johnston & A. W. Ellis: Understanding covert recognition. *Cognition*, 39, 129-66 (1991)

150. Farah, M. J., R. C. O'Reilly & S. P. Vecera: Dissociated overt and covert recognition as an emergent property of a lesioned neural network. *Psychol Rev*, 100, 571-88 (1993)

151. Galaburda, A. M., J. LoTurco, F. Ramus, R. H. Fitch & G. D. Rosen: From genes to behavior in developmental dyslexia. *Nat Neurosci*, 9, 1213-7 (2006)

152. Ramus, F.: Neurobiology of dyslexia: a reinterpretation of the data. *Trends Neurosci*, 27, 720-6 (2004)

153. Giraud, A. L. & F. Ramus: Neurogenetics and auditory processing in developmental dyslexia. *Curr Opin Neurobiol*, 23, 37-42 (2013)

154. Steinbrink, C., K. Vogt, A. Kastrup, H. P. Muller, F. D. Juengling, J. Kassubek & A. Riecker: The contribution of white and gray matter differences to developmental dyslexia: insights from DTI and VBM at 3.0 T. *Neuropsychologia*, 46, 3170-8 (2008)

155. Schmalzl, L., R. Palermo, M. Green, R. Brunsdon &
M. Coltheart: Training of familiar face recognition and
visual scan paths for faces in a child with congenital
prosopagnosia. *Cogn Neuropsychol*, 25, 704-29 (2008)

156. Bate, S., S. J. Cook, B. Duchaine, J. J. Tree, E. J.
Burns & T. L. Hodgson: Intranasal inhalation of oxytocin
improves face processing in developmental prosopagnosia.
Cortex (2013)

157. Wilson, C. E., R. Palermo, L. Schmalzl & J. Brock:
Specificity of impaired facial identity recognition in
children with suspected developmental prosopagnosia.
Cogn Neuropsychol, 27, 30-45 (2010)

Footnotes: [1]Note that the face recognition deficit in CP
seems to be restricted to the visual domain, rather than
being multimodal. For example, performance of a group of
8 CPs was significantly better in recognizing the names of
famous individuals rather than their pictures (score for
names=96.1%±1.6; pictures=58.0%±7.2; (average ± SEM);
p<0.0005). In contrast, in a group of 25 controls there was
no difference in performance of the two tasks (score for
names=92.4%±4.1;   pictures=91.3%±1.7;   p=0.82).
Moreover, while we did not assess voice recognition skills
directly, anecdotal reports of CP participants often indicate
reliance on voice as part of their compensatory recognition
strategy. These self-reports should be further corroborated
in an experimental setting but nevertheless they provide
some support to the notion that congenital prosopagnosia is
related to a visual impairment in face recognition rather
than being a more multimodal disorder.

Key Words: Face Processing, Functional Connectivity,
Neurodevelopmental Disorders, Prosopagnosia, Ventral
Visual Cortex, Review

Send correspondence to: Galia Avidan, Department of
Psychology, Ben Gurion University of the Negev, POB
653, Beer Sheva 84105, Israel, Tel: 972-8-6428518, Fax:
972-8-6428348, E-mail: galiaa@bgu.ac.il