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Spatial Integration in Normal Face Processing and Its Breakdown in Congenital Prosopagnosia

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Abstract

Congenital prosopagnosia (CP), a life-long impairment in face processing that occurs in the absence of any apparent brain damage, provides a unique model in which to explore the psychological and neural bases of normal face processing. The goal of this review is to offer a theoretical and conceptual framework that may account for the underlying cognitive and neural deficits in CP. This framework may also provide a novel perspective in which to reconcile some conflicting results that permits the expansion of the research in this field in new directions. The crux of this framework lies in linking the known behavioral and neural underpinnings of face processing and their impairments in CP to a model incorporating grid cell–like activity in the entorhinal cortex. Moreover, it stresses the involvement of active, spatial scanning of the environment with eye movements and implicates their critical role in face encoding and recognition. To begin with, we describe the main behavioral and neural characteristics of CP, and then lay down the building blocks of our proposed model, referring to the existing literature supporting this new framework. We then propose testable predictions and conclude with open questions for future research stemming from this model.

1. AN OVERVIEW OF THE BEHAVIORAL AND NEURAL CHARACTERISTICS OF CONGENITAL PROSOPAGNOSIA

1.1. Behavioral Findings

Individuals with congenital prosopagnosia (CP) [also referred to in some studies as developmental prosopagnosia (DP) (Duchaine & Nakayama 2006)] typically exhibit great difficulty in recognizing familiar faces, but also in perceiving unfamiliar faces and in short-term memory of newly learned faces (Dalrymple & Palermo 2016, Pertzov et al. 2020). Given the limited diagnostic procedures and lack of any obvious genetic signature or biomarker for this disorder, at present it is impossible to clearly determine whether CP represents a distinct pathological condition or whether individuals with CP represent the very low end of the normal distribution of face processing abilities (Avidan & Behrmann 2014, Barton & Corrow 2016, Bowles et al. 2009, Russell et al. 2012). When examined carefully, many individuals with CP also exhibit deficits in tasks requiring the fine discrimination of nonface stimuli, thus implying a potentially more general visual perceptual impairment (Behrmann et al. 2005, Gerlach et al. 2016, Geskin & Behrmann 2017). Such general deficits have often been ascribed to an impairment in holistic or configural processing, long considered a hallmark of face perception and a critical process subserving normal face processing (Gerlach et al. 2017). Of relevance to this discussion are studies revealing deficits in individuals with CP on tasks requiring the holistic integral perception of faces. As an example, **Figure 1** depicts results showing impaired holistic processing on the composite face effect, considered a gold standard for measuring holistic processing (Avidan et al. 2011, Richler & Gauthier 2014) (for related results, see also **Figure 4** below). However, importantly, individuals with CP also show deficits in holistic processing of nonfacial shapes (Avidan & Behrmann 2014; Avidan et al. 2011; Lange et al. 2009; Tanzer et al. 2013, 2016). Given the disproportionate reliance on holistic processing for faces compared to objects in daily life, such deficits would clearly be more accentuated for the former over the latter.

1.2. Neural Findings

Functional magnetic resonance imaging (fMRI) studies indicate that there are several core regions [the fusiform face area (FFA), occipital face area (OFA), and posterior superior temporal sulcus (pSTS)] (Haxby et al. 2000) that show selective responses associated with the visual properties of faces (compared to other stimuli). Additionally, there are regions outside the occipitotemporal cortex that constitute an extended face recognition system, including the anterior temporal cortex, inferior frontal gyrus, insula, orbitofrontal cortex, and amygdala; these regions mediate high-level attributes of faces such as memory (Kriegeskorte et al. 2007, Nestor et al. 2011, Simmons et al. 2009) and emotions (Fairhall & Ishai 2007, Gobbini & Haxby 2007, Haxby et al. 2000) (for findings relating to face patches in monkeys, see Furl et al. 2012; Hadj-Bouziane et al. 2012; Hesse & Tsao 2020; Tsao et al. 2008a,b). Beyond this localized description of the building blocks comprising the neural face system, there is a growing realization that face perception occurs via the coordinated activity of a face processing network that has been documented at both the functional (Cohen Kadosh et al. 2011, Davies-Thompson & Andrews 2012, Fairhall & Ishai 2007, Joseph et al. 2012, Zhen et al. 2013) and structural levels (Gschwind et al. 2012, Phillips et al. 2012, Pyles et al. 2013) (for evidence in support of this view in monkeys, see Moeller et al. 2008).

At the neural level, many studies demonstrate normal fMRI activation and adaptation in the core face-related posterior patches in individuals with CP (Avidan & Behrmann 2009, Avidan et al. 2005, Hasson et al. 2003; but see (Jiahui et al. 2018). This normal response may be related to intact processing of the face features (Henriksson et al. 2015), while the integration of these features may still be impaired, as we discuss in the following sections. Yet many studies have re-
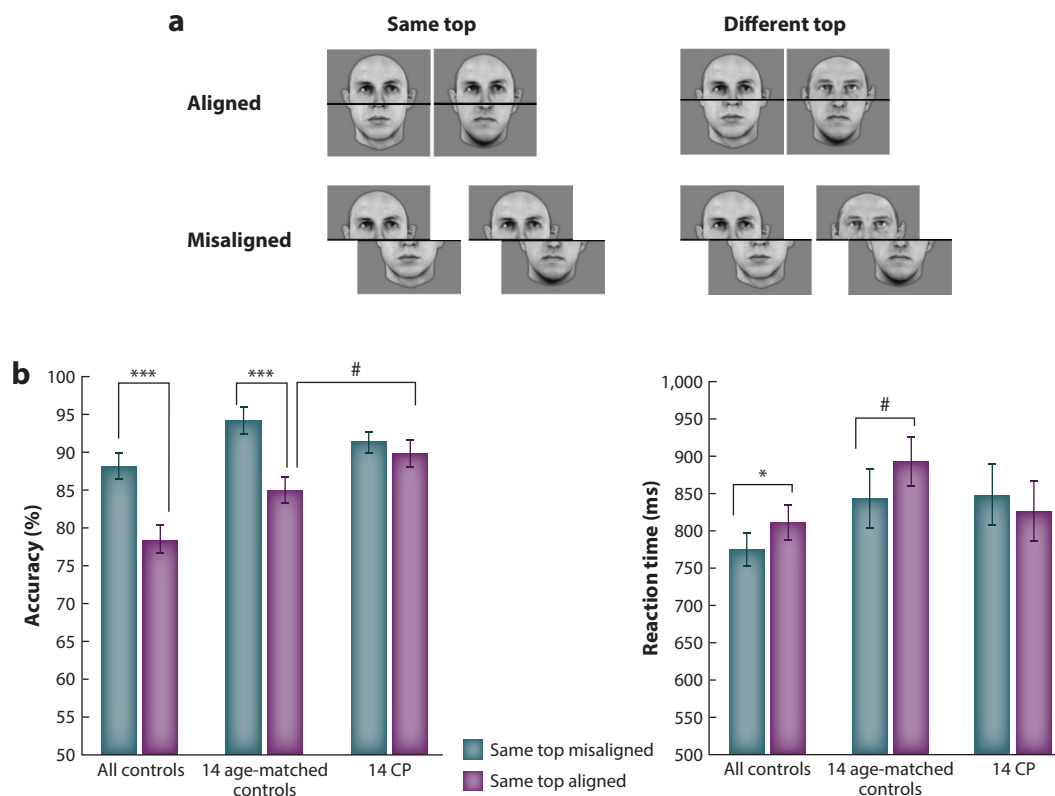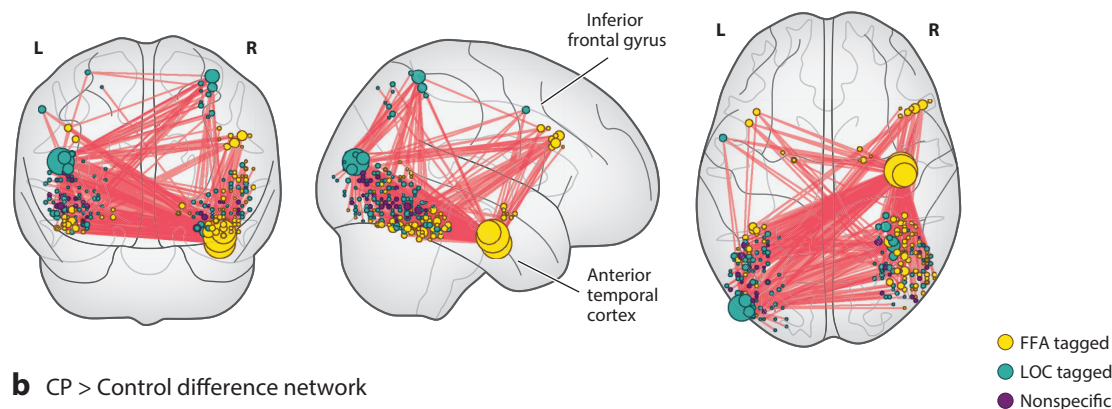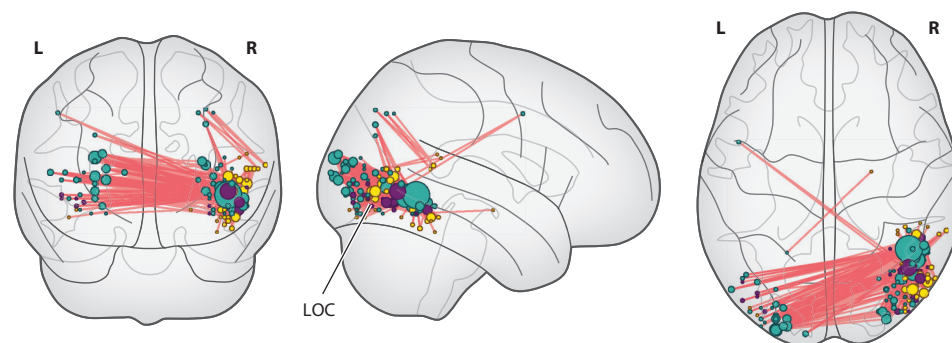
Figure 1

Behavioral findings of holistic impairment in congenital prosopagnosia (CP) on the composite task. (*a*) Examples of experimental stimuli showing the aligned (*top row*) and misaligned (*bottom row*) conditions used in the composite face experiment. (*b*) Mean accuracy (*left*) and reaction time (*right*) on the composite face task in a large and heterogeneous group of control participants in 14 age-matched controls for individuals with CP and in 14 CP participants on the same-top trials. Due to the holistic nature of face processing, even when instructed to judge only the top halves of aligned faces and to ignore the bottom parts, normal observers exhibit significant interference induced by the presence of the task-irrelevant bottom half of the composite face (which is always different in this version of the manipulation, referred to as the partial design). Thus, erroneously, they tend to judge two faces with identical tops as different rather than the same (i.e., make false alarms). This interference from the task-irrelevant bottom of the face is substantially reduced when configural information is disrupted, as in the misaligned condition. In contrast with controls, the CP group performed equivalently with aligned and misaligned faces and was impervious to (the normal) interference from the task-irrelevant bottom part of faces. This effect was evident in both accuracy and reaction time (RT). The difference between CP and controls is attributed to an impairment in holistic processing. Asterisks denote significance level: $* = p < 0.05$; $*** = p < 0.0005$. # indicates a p value that is marginally significant ($p = 0.06$ in the top graph and $p = 0.07$ in the lower graph). Error bars indicate $\pm$ standard error of the mean across participants. Figure adapted with permission from Avidan et al. (2011).

vealed patterns of abnormal structural and/or functional connectivity (FC) of the face network in CP (Avidan & Behrmann 2009, Avidan et al. 2014, Rosenthal et al. 2017, Zhao et al. 2018; but see (Furl et al. 2011, Jiahui et al. 2018). Specifically, studies using diffusion tensor imaging (DTI) have shown a reduction in long-range white matter tracts connecting the core face-related posterior patches and the anterior temporal lobe (ATL) face patch in CP (Odegard et al. 2009, Steinbrink et al. 2008, Thomas et al. 2009). Other studies have also reported local structural and functional atypicalities in the vicinity of face-selective regions (Gomez et al. 2015, Lohse et al. 2016, Song et al. 2015). FC studies have also documented abnormal deviations from the control profile in

a Control > CP difference network

b CP > Control difference network

Figure 2

Neural findings revealing impaired functional connectivity in CP. Functional connectivity networks are projected onto coronal, sagittal, and axial views of the brain. Functional connectivity in this study was assessed by the ISFC approach, which is designed to isolate stimulus-locked functional responses by correlating the response profile across the brains of multiple participants (Rosenthal et al. 2017). The colors of the nodes denote their a priori functional selectivity (face-selective, non-face-selective, and not exclusively selective for either of these stimuli). For visualization purposes, the size of the node is proportional to its degree (the larger is the node, the greater is its ISFC). To evaluate whether there were any statistical differences in the network structure across the two groups, the networks were directly compared using a permutation test. This resulted in a network analysis that captured the overall difference in the pattern of ISFC such that the edges indicate the significant difference between the two groups. The figure shows a descriptive, unthresholded statistical comparison for visualization purposes. (*a*) The control > CP difference network revealed that the ATL served as the main hub for controls but not for individuals with CP. (*b*) The CP > control difference network revealed that individuals with CP evince a significant difference in ISFC in posterior visual regions, which exhibited hyperconnectivity compared to controls. Figure adapted with permission from Rosenthal et al. (2017). Abbreviations: ATL, anterior temporal lobe; CP, congenital prosopagnosia; FFA, fusiform face area; ISFC, inter-subject functional connectivity; LOC, lateral occipital cortex.

the connectivity patterns between the core and extended nodes of the face system (Avidan et al. 2014, Rosenthal et al. 2017). These studies have also revealed that individuals with CP show an abnormal response in the right anterior temporal cortex. Whereas in controls this region, serving as a hub, is highly connected to many other face processing regions, this was not the case in individuals with CP. Instead, in this group, this hub-like connectivity was missing, and several core regions involved in processing the basic visual features of faces were more highly connected to one another (for FC maps, see **Figure 2**). Furthermore, the greater was this posterior hyperconnectivity, the better were the individual's face processing abilities, perhaps reflecting a compensatory, piecemeal-like encoding of faces. Interestingly, the extent of general hub-like cortical organization has been shown to generally predict the severity and extent of transdiagnostic cognitive symptoms

(i.e., symptoms that cut across existing categorical diagnoses) and learning difficulties common to different cognitive developmental impairments, implying that the hub-like pattern of connectivity may be more efficient or even provide some resilience against such impairments (Siugzdaite et al. 2020). Finally, individuals with CP also exhibit a reduction in the volume of the anterior fusiform gyrus compared to controls (Behrmann et al. 2007, Garrido et al. 2009). However, whether this reduction is a consequence of the alteration in white matter tracts in this area (perhaps due to reduced myelination) and/or of decreased gray matter volume is not yet clear. Moreover, the interplay between these findings and the alterations in FC remains to be definitively determined.

1.3. Working Hypothesis

As discussed in Section 1.2, given the current literature on CP, we cannot establish causality; however, the findings of abnormal connectivity between core and extended regions are related to, and might even underlie, abnormalities in other physiological, behavioral, and computational characteristics associated with the disorder. Thus, we consider the perturbed cortical topology and connectivity abnormalities in CP to make up the underlying deficit and assume that other behavioral and neural impairments characteristic of this disorder are a consequence of these abnormalities. Below, we discuss the potential outcomes of this disturbed connectivity in relation to other physiological properties and the demonstrated deficit in holistic processing in CP.

2. ACCOUNTING FOR THE BEHAVIORAL AND NEURAL IMPAIRMENTS IN CONGENITAL PROSOPAGNOSIA WITH GENERAL PHYSIOLOGICAL AND COMPUTATIONAL PRINCIPLES

2.1. A Deficit in Holistic Processing and Connectivity is Compatible with Individuals with Congenital Prosopagnosia Having Smaller Population Receptive Field Size in Face-Selective Regions

At the neural level, a general deficit in integral, holistic processing may be compatible with findings showing that, in individuals with CP, population receptive fields (pRFs), as measured with fMRI in face-selective regions and area hV4, are smaller and are mostly restricted to the contralateral visual field and concentrated around the fovea compared to controls (**Figure 3**). Furthermore, there is a reported correlation between performance and pRF size (only in these regions and not in early retinotopic regions) in both individuals with CP and controls, showing that those with larger pRFs perform better than those with smaller pRFs and suggesting that the pRF size and spatial integration play a role in normal face recognition (Grill-Spector et al. 2017, Witthoft et al. 2016). These results are further corroborated by findings in normal participants showing that pRF size and the resultant visual field coverage in face-selective regions (and not the primary visual cortex) are smaller and shifted downward for inverted compared to upright faces (Poltoratski et al. 2020). This result is reminiscent of findings showing gradual developmental changes in size and spatial coverage of pRFs in high-level visual areas selective for faces (Gomez et al. 2018). Moreover, eye tracking conducted in the same study revealed that the increase in pRF size in these high-level visual areas across development is related to changes in fixation patterns on faces (Gomez et al. 2018) (there are also analogous changes in word-selective areas).

Of relevance too are studies showing a linkage between the structural maturation of white matter fibers associated with face processing during development and changes in the functional profile of face-related regions (Scherf et al. 2014; for more evidence regarding the role of visual experience in the organization of the visual cortex, see also Gomez et al. 2019). While we cannot establish directionality, we hypothesize that structural connectivity changes and maturation may serve as the scaffolding for consequent changes in pRF size and in the development of normal
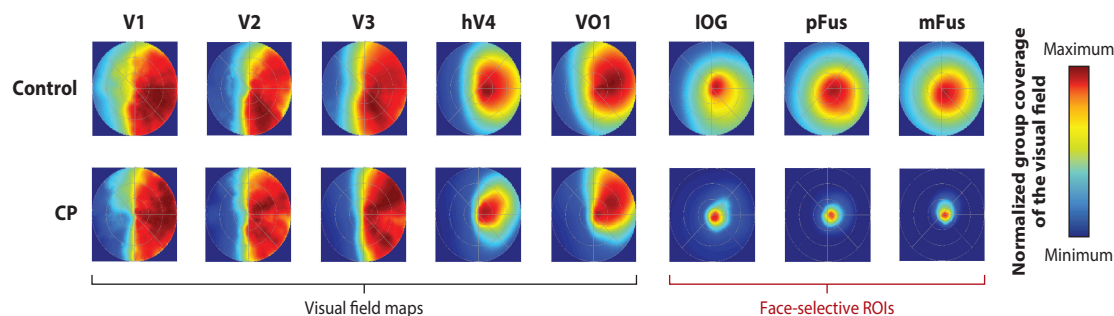
Figure 3

Visual field coverage along the ventral stream hierarchy in controls and in individuals with congenital prosopagnosia (CP). The panels show the average maximum profile of population receptive field (pRF) coverage of each retinotopic and face-selective region across subjects. Data from the right hemisphere are flipped across the vertical axis and combined with the left for each region of interest (ROI). In controls (*top row*), the V1–V3 display the expected coverage of the contralateral hemifield (in this case, the average contralateral field for the right and left hemisphere is shown), hV4 shows a bias toward the fovea, and VO1 shows a bias toward the upper visual field. In contrast, the face-selective ROIs show a strong bias toward the fovea with some ipsilateral coverage. In individuals with CP, V1–V3 coverage is similar to controls, while hV4 and VO1 show reduced coverage of the visual field. Note the substantially reduced coverage evident in individuals with CP in the face-selective ROIs, which does not extend to the ipsilateral visual field or the periphery and is largely confined to the central 3°. Figure adapted with permission from Witthoft et al. (2016).

looking behavior when shown a face (for related findings in nonhuman primates, see Arcaro et al. 2017). We return to discussing the relationship among pRF size, connectivity, and fixation patterns below. These findings imply that there is a fundamental difference between individuals with CP and controls in the spatial pooling of signals across the areas comprising the ventral stream hierarchy. To return to our working hypothesis, we suggest that this pattern of abnormal pooling and the resultant abnormal pRF size are the outcomes of abnormal connectivity between the lower- and higher-level areas of the ventral face hierarchy in this population.

Of relevance in this case are neurobiologically inspired computational models that simulate processing in the primate ventral visual cortex using deep convolutional neural networks (dCNNs) (Kar et al. 2019, Yamins & DiCarlo 2016). In such networks, neurons in higher levels, akin to cortical face-selective neurons, can effectively sample larger portions of the visual field, with some spatial overlap across neighboring neurons. That is, focusing on a certain location of the stimulus enables the processing of information at that location but also the generation of a prediction of the next location to be processed (Ji et al. 2013, LeCun et al. 2015) (for an illustration of a model dCNN as a coarse analogy to ventral pathway function, see **Figure 6a** below). Such sampling and predictions can be obtained, for example, by a sequence of eye movements required mostly for face learning. However, eye movements would inevitably be impaired when pRF size in face-selective regions is abnormal, despite normal-size pRFs in retinotopic regions, as detailed below. More generally, variations of these models, which achieve very high face recognition performance, are also important for shedding light on general biological principles of face representations and their potential disruption in CP. For example, one prominent model (FaceNet) learns the mapping from face images to a compact Euclidean space where distances directly correspond to a measure of face similarity. The resultant embeddings (or feature vectors) can then permit the efficient implementation of various face processing tasks (Schroff et al. 2015). Indeed, analogous principles of face embeddings were also found in nonhuman primates, where face-selective neurons were shown to distinguish facial features along specific axes in a multidimensional face space (Chang & Tsao 2017). Such a representation has been shown to be compatible with holistic processing and with the functions of the ventral stream visual pathway. Particularly, neurons in the more

anterior face patch exhibited a preference for face appearance (more akin to face identity), while more posterior face patches exhibited a preference for face shape (more akin to visual aspects of the face image) (for an illustration of a high-dimensional face embedding proposed to underlie face representation in the face-selective anterior temporal cortex, see **Figure 6a** below).

2.2. The Neural Tuning Size or Face Size Is a Key Parameter Accounting for Holistic Face Processing (Akin to Receptive Field Size and Spatial Sampling)

RF size and spatial integration are also highly relevant for behaviors linking face size, or its equivalent, the optimal distance of presentation, to holistic processing. Generally, these studies reveal that holistic processing follows an inverted U–shaped function with an optimal range at presentation distances of 2–10 m, a sharp drop at distances shorter than 2 m, and a more gradual drop at distances greater than 10 m (Loftus & Harley 2005, McKone 2009, Ross & Gauthier 2015). Relatedly, the viewing of videos of approaching walkers elicited optimal face decoding in the face network during an fMRI scan but only when the faces of walkers were viewed from a relatively close distance (Hahn & O'Toole 2017). These findings imply that optimal face processing, which presumably results from holistic processing, operates in tandem with spatial integration across the face image, which is a direct outcome of the properties of the RF size of neurons in the relevant face-related regions and their spatial coverage. As noted above, RF size and spatial coverage, in turn, are related to specific patterns of connectivity. Thus, in individuals with CP, the impaired connectivity is also consistent with the deficit in pRF size and the abnormal spatial integration. Overall, the resultant pattern of these related deficits (i.e., abnormal pRF size and abnormal spatial integration) would be a general deficit in holistic perception that has a disproportionately detrimental effect on face processing as compared to the processing of other objects.

One pertinent computational model of the ventral visual pathway argues that a key parameter accounting for performance in gold-standard tasks measuring holistic face processing is the neural tuning size (Tan & Poggio 2016). This parameter essentially controls the extent of the spatial convergence from neurons in an intermediate layer to neurons in the higher level of the model, akin to face-selective neurons that are somewhat tolerant to changes in location and scale (Zoccolan et al. 2007). That is, this parameter determines the extent of the connectivity and ultimately the RF size of neurons in the highest level of the neural face network (usually considered to be the ATL). Also related are computational models that have examined the relation between perturbed connectivity in the face network and its implications for impaired holistic processing. For example, in one such model, a predisposition to weak connectivity in the network resulted in a featural, rather than holistic, representation of faces (Stollhoff et al. 2011).

2.3. Eye Movement in Congenital Prosopagnosia

As outlined above, spatial integration is a critical component of normal face perception. However, in lab settings, experiments are usually conducted with face stimuli briefly presented and subjects fixating, whereas, in real life, spatial integration occurs naturally through eye movements (Hessels 2020). This involvement of eye movements reflects an active, sequential motor component even in face processing, which is considered a paradigmatic example of a process associated primarily with the function of the ventral processing pathway. Consistent with this perspective, face- and house-associated gaze profiles could be discriminated by fMRI multivariate pattern analysis in the FFA and parahippocampal place areas (PPA), respectively, and this was true even when participants executed face- or house-related eye movements in the absence of stimuli (Wang et al. 2019). Thus, eye movements clearly play an important role in face processing and, as we discuss below, are atypical in CP.

Before describing abnormalities of spatial integration across eye movements in CP, we first need to understand the role of eye movements in normal face processing. It has long been argued that, during free viewing of faces, normal scanning patterns generally involve a T-shaped distribution with more fixations to the central regions of the face, including the eye region (with higher density to the left), the nose, and to a lesser extent the mouth, thus enabling the perception and integration of the separate features of a face as a whole. Such a pattern is considered faster and more effective than feature-based scanning (Schwarzer et al. 2005, Weiss et al. 2016). Over the past several years, this canonical scheme has been challenged by studies showing that this sequencing template reflects the average scan pattern across subjects, while individual scanning patterns are more idiosyncratic yet consistent within subjects across time (Arizpe et al. 2017).

What is the role of eye movements in face processing, and how do their spatiotemporal dynamics relate to different aspects of face processing? That is, what particular spatial locations of the face are scanned, in what order, and for how long? Of most relevance to this discussion are eye movements related to face identity processing. However, it is important to differentiate between eye movements executed during face learning or encoding (when we encounter a new face) and those executed during face recognition or identification (when we look at a face with which we are already familiar). Consistent with the notion of holistic processing, it has been argued that two fixations are sufficient to identify a known face successfully, and that these fixations occur at optimal landing positions within the face (Hsiao & Cottrell 2008). However, it has been shown that optimal face encoding and learning require many fixations and involve the gradual integration of feature information over time. This learning process would, in turn, lead to the formation of a holistic representation that can be rapidly activated during recognition and would then only require very few fixations (Arizpe et al. 2019).

Notably, individuals with CP exhibit abnormal eye movement scanning patterns of faces (Malaspina et al. 2017). The exact deviation from the normal pattern described in this population somewhat varies across studies and tasks, and not all studies address both the temporal and spatial dynamics (Bobak et al. 2017, Malaspina et al. 2017, Schmalzl et al. 2008, Schwarzer et al. 2007). However, a common theme that emerges is that those with CP exhibit a more dispersed gaze profile that often includes fixations toward external facial features (for example, hairline) or toward internal features such as the mouth that are less explored by controls. That is, individuals with CP show a clear deviation in the spatial distribution of their eye movements compared to controls, and these deviations are evident during the perception of both familiar and unfamiliar faces and during conditions of both encoding and recognition (Avidan et al. 2011, Bobak et al. 2017, Schmalzl et al. 2008, Schwarzer et al. 2007, Wilcockson et al. 2020).

The relation between such deviations and the extent of the deficit or success or failure in face recognition is not straightforward and varies across studies. Indeed, the relation between viewing strategies and face recognition abilities is not obvious even within the normal population. For example, Arizpe and colleagues (2019) did not observe any obvious relationship between the idiosyncratic gaze behavior preferences of participants and face recognition abilities. In contrast, other studies imply that greater reliance on the eye regions, particularly the left eye, is correlated with better face recognition abilities (Royer et al. 2018). Extending these findings to super-recognizers [whose performance is significantly better than ordinary face recognition ability (Russell et al. 2009)], as well as to individuals with CP, revealed a positive correlation between the use of the eyes or eyebrows, as well as of the mouth, with face recognition ability (Tardif et al. 2019). Along similar lines, a group study that examined face recognition abilities in both individuals with CP and super-recognizers revealed that participants with more severe prosopagnosia also tended to focus less on the inner facial features (Bobak et al. 2017). Relatedly, in a case study of a child with

CP, recognition performance improved and even generalized to new faces following a training program that entailed focusing on internal face features (Schmalzl et al. 2008; for successful training of an individual with CP instructed to focus on the relation between internal facial features, see also DeGutis et al. 2014). These studies also imply a casual relation between a normal scanning pattern and face processing abilities. Detailing the eye movement patterns in CP also appears to shed light on the heterogeneity of the disorder and potentially the different phenotypes of CP. Indeed, Peterson and colleagues (2019) showed that participants with CP who tended to fixate more on the lower part of the face (lower lookers) exhibited deficits in both face perception and face memory. Other individuals with CP tended to fixate more toward the upper part of the face (upper lookers), and these individuals only exhibited deficits in face memory (but not face perception) (Peterson et al. 2019).

However, other studies have not shown a clear relationship between eye movement patterns and behavior. For example, in a group of individuals with CP, deviations from the normal pattern of face scanning resulted in both successful and unsuccessful face recognition. Likewise, in the same study, normal scanning patterns of internal features in controls were not related to recognition success (Schwarzer et al. 2007). Additionally, individuals with CP exhibited similar patterns of scanning behavior for both upright and inverted faces despite showing overall lower recognition performance for inverted faces, thus implying no obvious relation between recognition performance and scanning behavior in these individuals (Malaspina et al. 2017) (see **Figure 4**).

As for the temporal dynamics of eye movements, during face encoding, participants with CP exhibited a differential eye movement pattern that involved more frequent, shorter, and more distant fixations compared to controls (Malaspina et al. 2017). This scanning pattern presumably reflects the failure to represent information from the previous fixations and thus the need to acquire more information from the face to properly encode it. However, as is evident in the overall poorer performance of individuals with CP compared to controls, such scanning is still not sufficient for adequate coding of the face. Of relevance also are the differences between individuals with CP and controls when encoding inverted faces, as described above, which further support the notion that individuals with CP have reduced holistic processing of upright faces (for related findings, see Verfaillie et al. 2014).

Finally, of interest are findings showing abnormalities in scanning patterns not only for faces but also for within-class object processing. More specifically, individuals with CP exhibited more frequent, shorter, and more dispersed fixations compared to controls during a hard flower discrimination task (Malaspina et al. 2017). Importantly, these measures were highly correlated across the face and flower tasks. Moreover, performance was normal on an easy object processing task, and eye movement measures between this task and the face task or the flower task were not correlated. These results imply that the deficit in spatial integration in CP is evident not only for faces but also for within-class object individuation, although presumably the deficit in spatial integration and its relation to holistic processing would have a more detrimental effect for face processing (Malaspina et al. 2017). Because individuals with CP performed normally on the easy object task, and they did so in a way that was similar to controls and entailed a part-based strategy, it is conceivable that they were able to utilize the information that was extracted from each single fixation to correctly recognize the object. Along similar lines, individuals with CP exhibited normal performance and normal eye movement patterns in a car processing task, and their eye movements during this task were not correlated with those during face processing tasks involving either identity or expression (Peterson et al. 2019).

Such abnormalities in scanning faces (and within-class objects) are generally consistent with the notion that spatial integration is reduced in CP and manifests more profoundly in tasks that
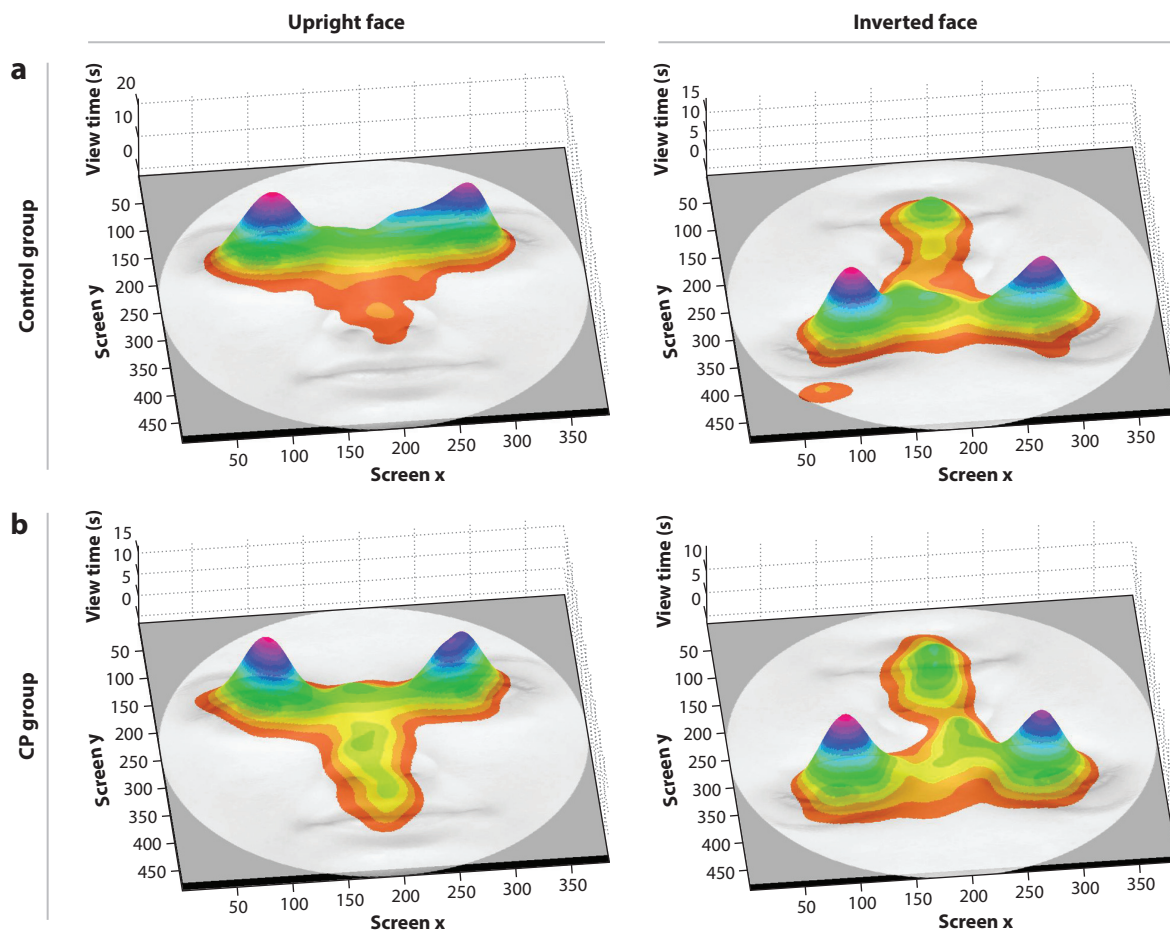
Figure 4

Abnormal eye movements during face scanning in congenital prosopagnosia (CP). Three-dimensional representation of eye scanning patterns during encoding of upright (*left column*) and inverted (*right column*) faces for (*a*) controls and (*b*) participants with CP are shown. Inversion disproportionately disrupts face processing compared to its effect on processing of other objects, and this effect is often considered to reflect holistic processing. In line with previous research, controls exhibited differential scanning patterns for upright and inverted faces (i.e., an increase in the number of fixations and their duration during the presentation of inverted, compared to upright, faces). In contrast, individuals with CP demonstrated the same pattern of scanning irrespective of face orientation (i.e., similar number of fixations of the same duration and similarly distributed), thus implying impaired holistic processing. Areas of progressively colder colors indicate the areas that were fixated the most, and vice versa for warmer colors. Areas with a uniform background color indicate regions that were fixated for a period of time less than or equal to the threshold value. Figure adapted with permission from Malaspina et al. (2017).

depend on spatial integration across fixations. Specifically, each fixation provides only relatively local information, which is presumably correctly extracted; however, additional fixations over the face and their integration are generally required. Moreover, in accordance with the results described above (Grill-Spector et al. 2017, Witthoft et al. 2016), as pRFs are small and are more restricted to the fovea, even though more fixations are executed, their overall integration does not suffice to elicit a normal percept of the face. This finding is also consistent with the computational model of the neural tuning size described above (Tan & Poggio 2016).

3. A FRAMEWORK FOR UNDERSTANDING CONGENITAL PROSOPAGNOSIA

While face perception is primarily linked to the ventral visual cortex and is known to be somewhat tolerant to stimulus-specific information such as scale or position (e.g., DiCarlo & Cox 2007), eye movements are generally associated with the active, motor aspects of the dorsal pathway and involve more precise stimulus sampling. How are the mechanisms associated with face processing and representation, and their impairment in CP, anatomically and computationally linked to eye movements? Surprisingly, this question has largely been overlooked.

Our proposed framework addresses this issue by incorporating recent findings revealing grid-like cells in the entorhinal cortex of nonhuman primates (Killian et al. 2012). While the responses of these cells are generally similar to those found in rodents, these responses were obtained during visual exploration of the environment that did not involve locomotion but, rather, involved eye movements (**Figure 5a,b**). These results imply that, in nonhuman primates, and potentially in humans too (Bellmund et al. 2016, Jacobs & Lee 2016, Julian et al. 2018, Nau et al. 2018), spatial representation of visual stimuli can be encoded while visual exploration is done at a distance from
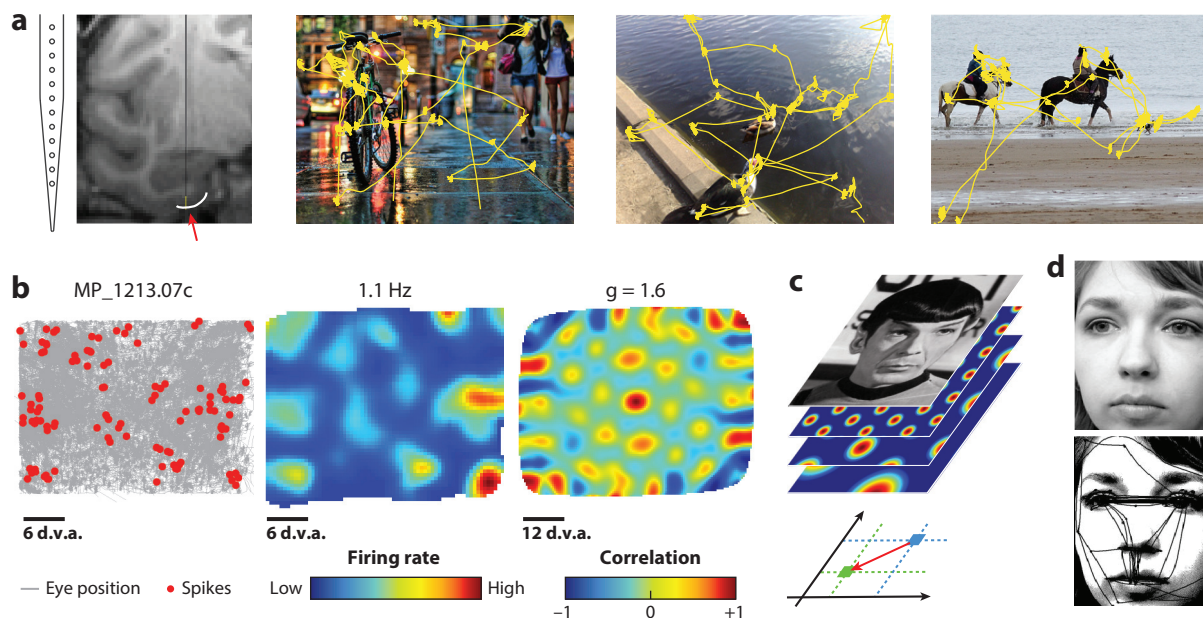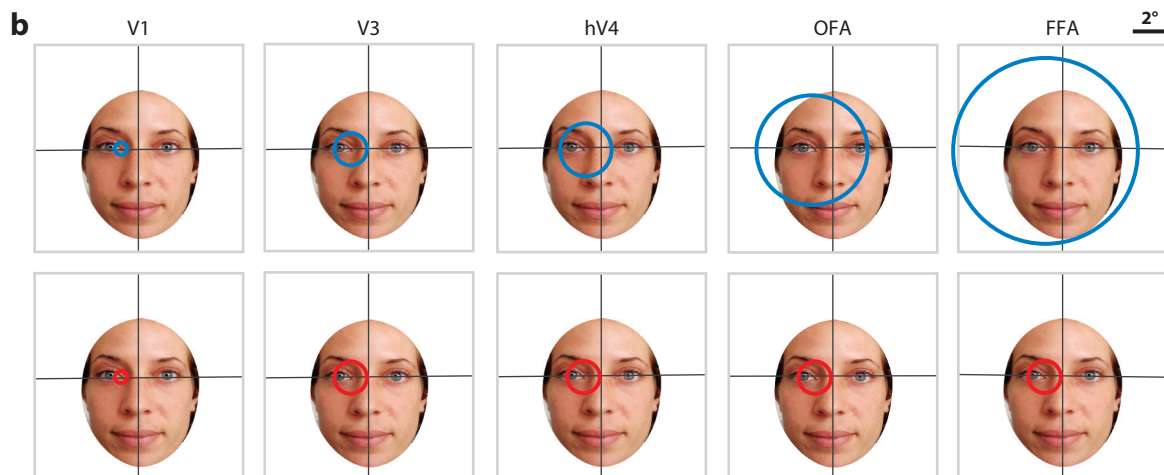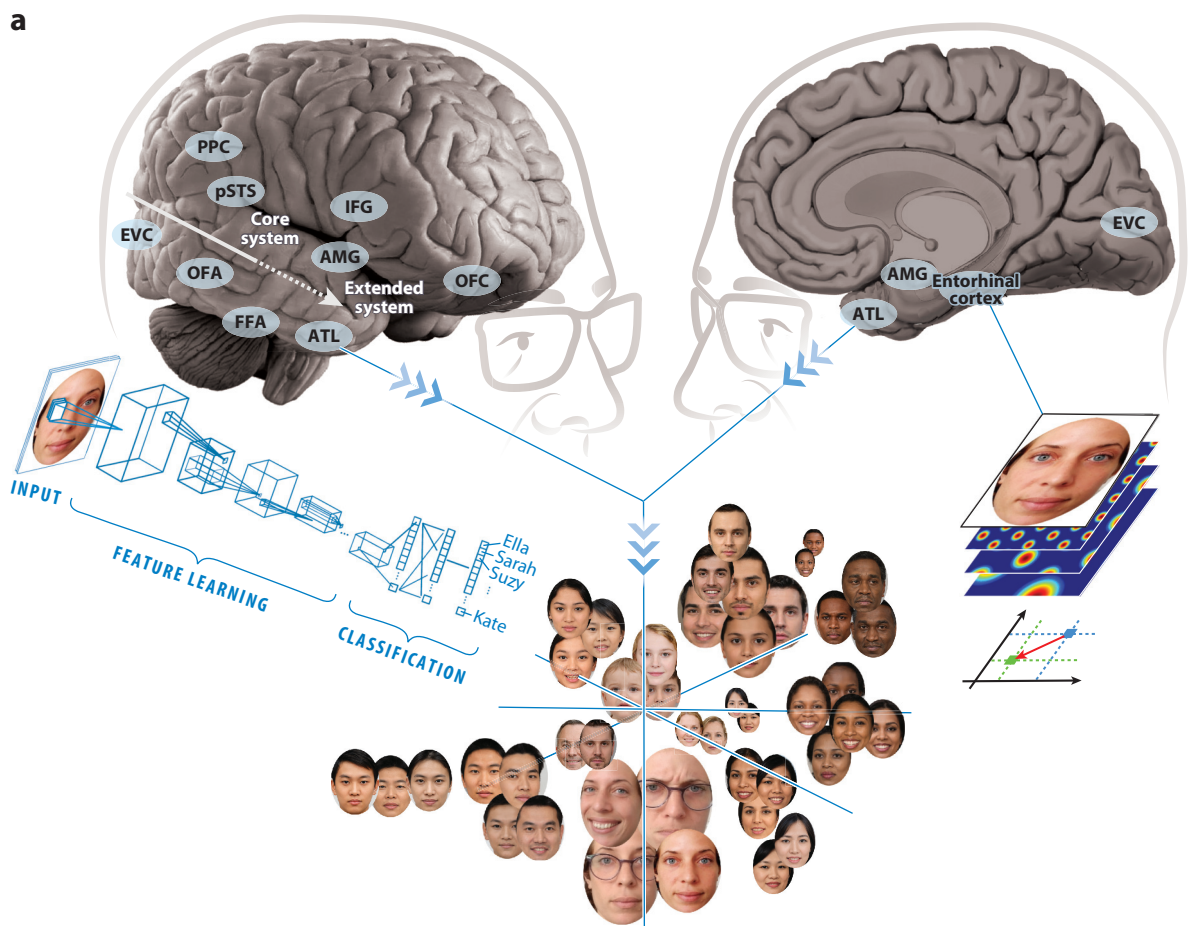

Figure 5

Representation of spatial visual information and hypothesized computational properties of the entorhinal cortex. (*a,b*) Representation of spatial visual information in the nonhuman primate entorhinal cortex. (*a*) Location of the electrode placement used for recordings (*red arrow*) and three examples of 10-s eye movement scan paths (*yellow*). (*b*) An example of an entorhinal grid cell; the label indicates the monkey's name and unit number. (*Left*) Plots of eye position and spikes reveal nonuniform spatial density of spiking obtained from a single unit in one monkey. (*Middle*) Spatial firing rate maps show multiple distinct firing fields. The maximum firing rate of the map is indicated at the top. (*Right*) The spatial periodicity of the firing fields is shown against spatial autocorrelations. (*c, d*) A model of grid cell–based vector computations and visual recognition memory in the entorhinal sulcus. The model implies that visually driven grid cells encode vectors between salient stimulus features in visual space to drive saccades for the purpose of visual recognition. (*c*) A noncolinear axis, based on coding of grid cells in different spatial scales, allows computation of two-dimensional vectors in the stimulus (e.g., vectors between facial features that guide eye movements, as shown in panel *d*). (*d*) A face presented with superimposed saccadic eye movement trajectories. Panels *a* and *b* adapted with permission from Killian et al. (2012). Panels *c* and *d* adapted with permission from Bicanski & Burgess (2019). Abbreviations: d.v.a., degrees of visual angle; g, gridness score.

the stimulus, akin to the way that humans explore faces (as well as other visual input) (for a relevant perspective on a potential linkage between spatial navigation or scene perception and face identification and memory, see Woolnough et al. 2020; for a relevant case study in CP, see Bate et al. 2019).

To further establish this framework, we also rely on a computational model inspired by physiological findings, which tracks a sequence of saccades as a trajectory on a two-dimensional plane, rather than on the free movements of rodents in a two-dimensional space (Bicanski & Burgess 2019; for a related computational model, see also Lewis et al. 2019). Accordingly, visually driven grid-like neurons encode inter-feature movement vectors (e.g., saccades among the nose, eye, and mouth), generating the spatial layout of stimuli such as faces in a stimulus-specific coordinate system. These saccadic eye movement vectors move from one salient feature to the expected location of the next feature and in that way generate accumulating evidence confirming an initial hypothesis regarding stimulus identity in relation to the obtained feature spatial layout (**Figure 5c,d**). Thus, this model goes beyond the recognition of individual features and is therefore consistent with holistic face processing, which, as discussed above, is critical for intact face perception and is known to be impaired in individuals with CP. In line with the studies described above regarding the differences in eye movements during face learning and recognition (Arizpe et al. 2019), it is conceivable that the predictive saccades presumably generated by grid-like cells in the entorhinal cortex would be even more relevant to face encoding and learning, which rely more strongly on eye movements, than to face recognition, for which two saccades are apparently sufficient (Hsiao & Cottrell 2008).

We suggest that this model (**Figure 5**) may be useful for understanding the neural and behavioral underpinnings of CP (**Figure 6**). The impaired patterns of connectivity observed in CP between posterior and anterior face-related regions (**Figure 2**), in tandem with the abnormally small RF (**Figure 3**), impaired eye movements for faces (**Figure 4**), and impaired holistic perception and spatial integration (**Figures 1, 3**, and **4**), fit well within this suggested framework. Anatomical connectivity between the entorhinal cortex and face-selective regions were documented in both the macaque and human brains (Collins & Olson 2014, Grimaldi et al. 2016, Murray et al. 2007), further supporting the potential role of this region in face processing. These findings are also supported by computational simulations implying that disconnecting the grid cells from occipitotemporal inputs may result in prosopagnosia-like symptoms (Bicanski & Burgess 2019). The results are also compatible with findings in the macaque brain showing that personally familiar faces elicit selective activation in additional regions beyond those involved in general face processing. These regions are located in the temporal pole and the perirhinal cortex, further stressing the involvement of these structures in face recognition (Landi & Freiwald 2017).

We suggest that individuals with CP are impaired in generating the normal predictive learning of faces that is obtained by eye movement scanning of the face, particularly during encoding, and that this learning is likely supported by the grid-like neurons in the entorhinal cortex. Such deficits may also elicit more widespread impairments in processing other types of visual information. Indeed, a recent review has argued that roughly two-thirds of individuals with CP also exhibit some deficit in highly demanding object tasks (Geskin & Behrmann 2017) (for related eye movement data that are described above, see Fisher et al. 2020, Malaspina et al. 2017). Further supporting evidence for this notion comes from findings implicating the potential role of medial temporal lobe (MTL) structures in nonmnemonic functions such as perception (Murray et al. 2007). Of great relevance are findings gleaned from lesion studies showing that patients with explicit MTL lesions evince a general visual discrimination deficit for faces, scenes, and high-ambiguity objects (Freud et al. 2016). Importantly, evidence for the involvement of the MTL in demanding visual discrimination tasks and particularly in face-related tasks was also documented in fMRI (O'Neil et al. 2009, 2013) and FC studies in normal participants (O'Neil et al. 2014).

a

b

(Caption appears on following page)

Figure 6 (*Figure appears on preceding page*)

The proposed framework for understanding CP. (*a, left*) A lateral view of the human brain and graphic depiction of the core and extended face system in the human brain. Regions along the ventral visual pathway are assumed to process visual information using principles akin to those captured in deep convolutional neural networks, as depicted in the illustration. (*Right*) A medial view of the brain showing the location of the ATL, AMG, entorhinal cortex, and EVC. Face identity representation in the ATL is hypothesized to be based on a high-dimensional face embedding model. Representation of spatial visual information in the entorhinal cortex is hypothesized to be based on grid-cell coding across several different spatial scales, which enables computation of two-dimensional vectors in the stimulus that consequently drive eye movements. (*b*) An illustration depicting the facial features processed by pRF size across the ventral visual cortex. (*Top*) Normal increase in pRF size along the ventral visual hierarchy in controls. As is evident, spatial information along the hierarchy of ventral visual areas is integrated across increasingly larger regions of the face. At the higher stages of the hierarchy, an entire face can be processed by the neural population within a voxel. (*Bottom*) Abnormally small pRFs in these areas, as documented in individuals with CP, imply impaired spatial integration. Note that the pRF remains unchanged from V3 through the OFA and FFA (Witthoft et al. 2016). Circles represent pRFs at 1° eccentricity. Each circle is drawn at ±2 pRF sizes. The depicted face is sized to simulate a face seen from a conversational distance of 1 m, approximately 6.5°. Panel adapted with permission from Grill-Spector et al. (2017). Abbreviations: AMG, amygdala; ATL, anterior temporal lobe; CP, congenital prosopagnosia; EVC, early visual cortex; FFA, fusiform face area; IFG, inferior frontal gyrus; OFA, occipital face area; OFC, orbitofrontal cortex; PPC, posterior parietal cortex; pRF, population receptive field; pSTS, posterior superior temporal sulcus.

4. PREDICTIONS STEMMING FROM THE NEW FRAMEWORK FOR CONGENITAL PROSOPAGNOSIA

Our proposed framework is consistent with and related to mounting evidence showing that hippocampal–entorhinal circuits are involved in organizing spatial but also nonspatial information into relational and metric configurations (Bussey & Saksida 2002, Bussey et al. 2003). Such configurations capture low-dimensional geometry and have been shown to extend to several cognitive domains such as statistical regularities of events, semantic relationships, and even the relationship between characters in social interactions (Bottini & Doeller 2020). The extension of such maps to face representations has already been suggested, as in the computational model described above (Bicanski & Burgess 2019). As summarized in **Figure 6**, this framework also implies that holistic perception is embedded in neurobiologically and computationally tangible underpinnings. Further studies should provide empirical evidence to support this kind of computation in normal observers and to document the consequences of impaired spatial and metric mapping in CP. Several predictions stemming from this framework are outlined below.

SUMMARY POINTS

1. Individuals with CP exhibit deficits in various aspects of face processing; these deficits are often attributed to impaired holistic processing, which is known to be critical for face recognition.

2. Individuals with CP show a generally normal pattern of BOLD response in core face-related regions. However, they exhibit impaired functional and structural connectivity between these core areas and more anterior parts of the face system. Moreover, the entire face network in these individuals exhibits substantial topological differences compared to controls.

3. The deficit in integral, holistic processing typical to CP may be compatible with findings showing that, compared to controls, pRFs in face-selective regions and area hV4 in these individuals are smaller and are concentrated around the fovea. Such deficits inevitably result in limited spatial coverage of the input.

4. Consistent with having limited spatial coverage, compared to controls, individuals with CP exhibit a more dispersed gaze profile accompanied by more fixations that are typically shorter in duration. In contrast to controls, these individuals' fixations are also often directed toward external facial features (for example, hairline) or toward internal features such as the mouth.

5. We propose a theoretical and conceptual framework that may account for the underlying cognitive and neural deficits in CP. We suggest that individuals with this disorder are impaired at generating the normal predictive learning that is obtained by eye movement scanning of the face, particularly during encoding. Furthermore, we propose that this information is likely supported by the grid-like neurons in the entorhinal cortex, which encode spatial matrices between face parts and, thus, support the planning of eye movement.

6. The overall pattern of cognitive and neural deficits typical to CP may also elicit more widespread impairments in processing other types of visual information, as is often found in individuals with this disorder.

FUTURE ISSUES

1. Future studies may reveal whether the connectivity and topological impairments are indeed the cause, as we suggest in this review, rather than the outcome of the alterations in RF size.

2. The proposed framework predicts the existence of potential abnormalities of the volume, functional activation patterns, and/or connectivity of the entorhinal cortex and implies that such patterns would be correlated with the extent of the face processing deficits and the abnormalities in eye movements. Behrmann et al.'s (2007) research has already alluded to volumetric differences in the vicinity of the anterior temporal cortex between individuals with CP and controls. However, in this study, the anterior temporal cortex was not further dissected into finer subdivisions. Thus, a more fine-grained analysis of this area at both the anatomical and functional levels is clearly warranted.

3. The computational account that we propose also implies that idiosyncratic differences between subjects could transfer between different tasks as long as these tasks employ the grid-cell mechanism. This notion should be explored within the normal population and in relation to individual differences in face or object processing. This conjecture is also consistent with abnormal eye movement patterns in CP during within-class object discrimination. Future studies should further examine the relationships between face and object abnormalities and particularly their manifestations in abnormal eye movements. Such a potential general mechanism, which may account for deficits in object processing, might additionally account for reports in the literature suggesting that at least some individuals with prosopagnosia also suffer from topographical agnosia (Bate et al. 2019, Corrow et al. 2016, Klargaard et al. 2016, Piccardi et al. 2019; for a linkage between spatial navigation and face identification, see Woolnough et al. 2020).

4. The relation and correspondence between face embedding in a multidimensional space implied by both empirical (Chang & Tsao 2017) and computational studies (Schroff et al. 2015) and the current proposed model are of much interest. Specifically, it will be important to examine the relation between face space mapping and dimensions, as represented in higher-order face areas (Chang & Tsao 2017), and the suggested low-dimensional geometrical representation in the entorhinal cortex; this examination can be accomplished in both humans and nonhuman primates.

5. There is evidence indicating a modest improvement in face processing abilities in individuals with CP who were trained on paradigms involving mandatory modifications in scanning paths of faces (Pizzamiglio et al. 2017, Schmalzl et al. 2008). In light of these findings and the important role of eye movements in normal face recognition, as outlined in this review, further research should examine the benefits of such training regimes. It will also be important to examine the accompanying neural changes related to such behavioral changes and, particularly, potential changes to the entorhinal cortex at both the structural and functional levels.

6. Finally, another important question, which is beyond the scope of this review, is how gaze toward faces supports face-to-face interaction. In this context, it will be particularly important to compare gaze behavior of both individuals with CP and controls under constrained laboratory conditions versus real-life interactions. We refer the readers to a recent comprehensive review on these topics (Hessels 2020).

DISCLOSURE STATEMENT

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