

The neural bases of prosopagnosia and pure alexia: recent insights from functional neuroimaging

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Purpose of review

To discuss whether recent functional neuroimaging results can account for clinical phenomenology in visual associative agnosias.

Recent findings

Functional neuroimaging studies in healthy human subjects have identified only two regions of ventral occipitotemporal cortex that invariantly respond to individual faces and visual words, respectively. The signature of face identity coding in the fusiform neural response was shown to be missing in a patient with prosopagnosia. Another case study established that a surgical lesion close to the region sensitive to visual words can result in pure alexia.

Summary

Evidence is increasing that functional specialization for processing face identity and visual word forms is restricted to two specialized sensory modules in the occipitotemporal cortex. A structural or functional lesion to face-sensitive and word-sensitive regions in the ventral occipitotemporal cortex can provide the most parsimonious account for the clinical syndromes of prosopagnosia and agnosic alexia. This review suggests that functional specialization should be considered in terms of whether exclusively one brain region (instead of many) underpins a defined function and not as whether this brain region underpins exclusively one cognitive function. Such functional specialization seems to exist for at least two higher-order visual perceptual functions, face and word identification.

Keywords

faces, functional magnetic resonance imaging, reading, visual agnosia, words

Abbreviations

FFA	fusiform face area
fMRI	functional magnetic resonance imaging
OFA	occipital face area
VWFA	visual word form area

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1350-7540

Introduction

The description of neuropsychological syndromes in the visual perceptual domain has been both striking and influential. Prosopagnosia, the inability to identify faces [1], and pure alexia [2], the inability to read, are strikingly selective visual associative agnosias that have been conceptually influential because they suggest that cortical regions or neural circuits may be specialized for processing selective category-related content [3,4]. Neurophysiological recording of brain activity during cognitive operations in the undamaged brain can test such concepts directly. Despite its undeniably poor temporospatial resolution, noninvasive functional neuroimaging of human brain activation has hence become important for understanding localized cognitive processes and their disturbance. Here, we review recent findings from functional magnetic resonance imaging (fMRI) studies in two domains of visual processing, faces and words. We analyze whether these findings provide an explanatory account of prosopagnosia and pure alexia. Finally, we discuss commonalities and differences between these two perceptual domains.

Functional neuroimaging studies of face identity processing

Faces convey a rich spectrum of sensory information including emotional expression, gaze direction, and facial movements such as speech and are hence especially important for social communication. Functional neuroimaging findings on these aspects are interesting in their own right but beyond the scope of this review. Instead, we focus on face identification because its failure is the constituent hallmark feature across subtle but meaningful variations of clinical phenomenology in patients with prosopagnosia [5]. Thus defined, our question appears less trivial. Early functional neuroimaging studies [6,7] delineated areas responding to faces more than to other visual stimuli (categorization) but did not establish which brain processes code face identity. In the hands of most investigators, categorical contrasts,

Curr Opin Neurol 19:386–391. © 2006 Lippincott Williams & Wilkins.

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AK receives financial support from the Volkswagen Foundation, Hannover, Germany, and Assistance Publique/Hôpitaux de Paris, France.

Current Opinion in Neurology 2006, 19:386–391

e.g. against objects, consistently yield two mostly bilateral but usually right dominant cortical activation foci in ventral temporooccipital cortex that respond preferentially to faces: a more posterior region that is contiguous or partly overlapping with the so-called lateral occipital complex, and a more anterior region in the fusiform gyrus. These two regions are often operationally labelled the occipital and fusiform face area (OFA and FFA), respectively.

What are these areas' functional response properties and do they involve face identity? At first glance, one might think that a critical test of the hypothesis of identity coding could be performed by mapping brain responses to faces in subjects with prosopagnosia who are deficient in this respect. Such studies [8[•],9,10,11[•],12[•]] have, for instance, been performed in patients with developmental or congenital prosopagnosia. This approach has several shortcomings, however. In part, these studies show FFA responses during face presentation but without testing whether actual face identity is coded in this persistent FFA signal. Fundamental limitations come from the fact that putative functional reorganization in congenital prosopagnosia does not permit extrapolation from neural response profiles in these subjects to those in unimpaired face perceivers.

Functional neuroimaging studies [13,14] in patients with postlesional prosopagnosia have also shown fusiform activation foci despite the perceptual impairment. These results have been taken as evidence that other areas and in particular the OFA are required to identify faces. This conclusion, however, ignores the fact that FFA activation in patients with prosopagnosia (as well as healthy subjects) may be accounted for by factors other than face identification. From a sensory perspective, stimulus-driven FFA activation can be obtained without presenting visual faces, e.g. by virtue of context of the visual scene [15], by haptic face processing [16], or by listening to voices [17[•]]. Interestingly, the latter effect depends on familiarity with the speaker and thus cross-modal association of individual faces and voices, which indirectly points at a role of the FFA in coding face identity. Over and above stimulus-driven effects, attention to and imagery of faces can also elicit FFA responses in healthy subjects [18,19]. As the aforementioned patient studies used blocked fMRI experiments, such 'top-down' mechanisms might account for FFA responses despite incontestable prosopagnosia from 'bottom-up' FFA deafferentation. Hence, it appears more informative that in a recent case study [20^{••}] of a patient with prosopagnosia, fMRI responses during face presentation persisted but no longer coded face identity.

This latter approach of tracing identity coding in the FFA response to faces builds on previous findings in healthy

subjects. It makes use of fMRI response adaptation when identical as opposed to different faces are presented in succession. Several studies [21–24,25[•],26^{••}] have now established that FFA response adaptation to face identity remains invariant over different pictures of the same face. Moreover, studies [27^{••}] have suggested possible coding schemes that might be implemented neurally and that extend to identity representation. Together, these results go beyond previous approaches (e.g. Hoffman and Haxby [28]) to identity processing that studied attentional modulation or used view repetition where identity processing can rely on portraits, i.e. largely stable sensory stimuli, and thus affect low-level visual processing. Conversely, invariant sensitivity to face identity in areas beyond the FFA has so far been reported only when face identity was confounded with face familiarity or recognition, a point we reconsider below [26^{••},29–32].

Functional neuroimaging studies of visual word processing

Similar to face processing, early functional neuroimaging studies provided reproducible evidence for domain-selective neural responses in the midportion of the left fusiform gyrus by contrasting visual words or letter strings with objects such as faces or houses [6,33] or low-level visual stimuli [34,35]. The precise relevance of these neural sites for visual word form analysis was at first speculative, however.

From a visual perceptual perspective, reading involves fast computation of an ordered representation of abstract letter identities that is invariant over position and size but also over category-specific parameters such as font or case. Accordingly, the core deficit in pure alexia, even in moderate cases, is the loss of parallel letter recognition, with the ensuing emergence of letter-by-letter reading strategies [3,4]. Recent evidence has accrued that the functional demands in visual word form analysis that become deficient in pure alexia are underpinned by a localized and specialized neural circuitry in the left midfusiform gyrus that shows invariance to case changes [36], preference for familiar letters over matched pseudo-letters [37], and sensitivity to orthographic regularity [35]. Furthermore, there are indications that within this greater visual word form area (VWFA) successive peaks can be distinguished that display a gradual increase in invariance for location and in dependence on letter order, from letter detectors to bigram and possibly morpheme detectors [38,39]; see also Flowers *et al.* [40] and Pernet *et al.* [41] for responses to single letters. Moreover, the VWFA has recently been more clearly functionally distinguished from response properties in neighboring cortex. Lateral to the VWFA, inferior temporal cortex responds to both visual and auditory words and is subject to influences from task structure, and it activates particularly during explicit access to sublexical

information [42–44]. Temporal regions anterior to the VWFA are involved in supramodal semantic processing (reviewed by Jobard *et al.* [45]). In itself, VWFA activity is also modulated by nonvisual word features, e.g. during cross-modal auditory-visual priming [42] or semantic priming [46•]. Such effects, however, which are not observed with subliminal primes [47], do not disqualify the VWFA as a prelexical visual region [48,49] as they can be accounted for by top-down influences similar to those that voice or person familiarity seem to exert on the FFA.

Together, reading-specific functional properties of the VWFA are in good agreement with the clinical features of pure alexia. Accordingly, reduced or absent VWFA responses have been observed in patients with pure alexia both from remote lesions with subsequent VWFA deafferentation [34,50–52] as well as recently for a restricted surgical lesion closely colocalized with the presurgically mapped VWFA [53••]. As we stated for FFA activity in patients with prosopagnosia, persistent VWFA activations in patients with pure alexia do not rule out a critical role of this region for reading. For instance, patients with a structurally intact but deafferented VWFA may show residual activation during effortful letter-by-letter reading but not during passive word perception [52,53••].

Functional parallels between neural face and visual word processing

The recent functional neuroimaging evidence for two specialized processing modules in advanced stages of the visual processing chain and for their critical role in face and word identification is complemented by corresponding electrophysiological signatures and congruent results from analyses of lesion topography, which we do not have the space to discuss here [51,54]. Nonetheless, the neuropsychological and neurophysiological literature continues to debate whether neural responses to faces and visual words are just special cases of those active in object perception. Some computational approaches to object recognition build on generic frameworks that can also handle faces and words as visual inputs [39,55•]. Current computational general purpose models, however, cannot predict whether neural processing of faces and words relies entirely on a circuitry embedded into that for objects or whether specific functional aspects such as identification are supported by a segregated neural machinery. From a neurobiologic perspective, it is clear that low-level processing must be shared across different categories of visual input, and accordingly, functional neuroimaging studies [56] show distributed and overlapping responses across categories. Moreover, these distributed patterns appear to be as informative for categorization of visual input as localized responses, but these analyses do not address identification [57,58•].

Conversely, neuropsychological studies contribute two important observations: that functional segregation must exist and that within a particular domain a specific functional process can be selectively affected rather than all functions pertaining to that domain. Thus, perception is not a single-purpose process but covers a hierarchical family of diverse operations that can be differentially probed by tests of detection, discrimination, recognition, and so forth. When attempting to account for selective agnosias by neurophysiological data, the crucial question is hence whether functional specialization can be shown for exactly those specific operations within a domain that are deficient in selective agnosias. Recent neurophysiological evidence shows that FFA and VWFA are invariantly sensitive to individual faces and visual words, respectively, and to the best of our knowledge there has been no such unconfounded evidence for any other brain regions.

Invariant representation of faces and visual words is not sufficient for face recognition and reading but is required for these processes. Face recognition and reading evoke larger contexts, e.g. person knowledge for faces or semantic associations for words, and are related to a distributed cortical circuitry [59–63,64•]. The study of such large-scale cognitive processes is therefore probably not helpful in defining the neural substrates of selective agnosias. Conversely, the recent findings on FFA and VWFA suggest that structural or functional lesions to these modules can provide a parsimonious and exhaustive account of prosopagnosia and pure alexia because these lesions hit bottlenecks and thus deprive face recognition and reading networks of a critical perceptual input.

Functional differences in neural specialization for faces and visual words

How does this conclusion relate to the ongoing debate whether areas such as FFA and VWFA are functionally specialized for one type of stimulus category? Neurophysiological evidence for domain-specific segregation, i.e. localized category-selective response preferences, is more firmly established for faces than for visual words [65•,66•,67••]. Yet whether an area is critical for a perceptual function does not depend on its domain specificity but on whether this is the only function of this area that cannot be sufficiently well upheld by other brain areas. In other words, FFA and VWFA lesions could yield prosopagnosia or alexia, respectively, even if these areas were less selective to faces and visual words than they appear to be. The clinical selectivity would then result from more distributed processing for object categories other than faces and visual words. How reasonable is this latter assumption?

A commonality between faces and visual words is that as categories of visual stimuli they are in a predictable way

quite distinct from other objects. Faces show regularities of configuration and words are composed of a restricted set of line-drawn elements. Both perceptual domains hence require discriminating subtle differences between items that are similar overall, a demand that might benefit from a localized cortical circuitry. Accordingly, FFA specialization has been related to expertise in discriminating exemplars across various categories [68]. Currently available data [30,69–71] suggest, however, that if there is a generic expertise effect on FFA activity, it is constrained by the degree of face-like sensory stimulus properties and does not extend to exemplar identification across categories nor to proficiency in this process.

This suggestion leads to the idea that categorical selectivity of perceptual brain mechanisms reflects the non-continuous sensory structure of natural visual stimuli we receive. Hence, the distinctiveness (and importance) of faces in the real world could phylogenetically or ontogenetically drive and tune dedicated brain mechanisms. Artificial stimuli could also be processed by such dedicated circuits as a function of their similarity with faces. Indeed, several studies [72,73*] have elicited relatively strong FFA responses without using face stimuli. One potential explanation is that the more face-like a stimulus is or the more the task requires those visual faculties that are most challenged in face perception, the greater activation can be obtained in this area. It is not FFA activity that would determine the collateral damage to perceiving these objects in prosopagnosia, however, but the degree to which other neural circuits are helpful in recognizing them [74,75].

Do these considerations apply to visual words and alexia as well? Visual words are a cultural artefact and we acquire reading expertise through learning. Surprisingly, developmental neural changes in face processing extend well into the age range where we learn to read [76,77], but still we become acquainted with faces much earlier in life. At first glance, written language might appear to constitute a very special class of visual stimuli but script symbols reflect features that are prominent in natural visual scenes [78**]. Perceiving written language could hence benefit from evolutionary or experience-dependent tuning of visual response properties to natural visual scenes, and perceptual expertise may thus complement motor constraints in making letters look the way they look [79*]. As a consequence, it would therefore appear possible if not likely that a VWFA should also respond to other visual input types and maybe even to a similar extent. Functional specialization in the sense of a critical role, i.e. loss of a function in case of damage, reflects whether a given region is the exclusive cortical locus for that particular function, however, and not whether it is exclusively engaged by that function [80]. In other words,

nondegenerate functions can be implemented in multipotent structures [81].

Within the face domain, similar considerations apply to the FFA. This region responds not only to face identity but also to several other face-based features, such as, for instance, the mere presence of a face or its emotional expression [82–84]. Yet the FFA is not the exclusive site to represent these other features. The clinical phenomenology of prosopagnosia is in accord with the ensuing neurophysiological prediction that FFA function should not be as critical for face-related perceptual processes other than identification [85]. Generally, it therefore appears wise to address functional specialization not only by studying localized response preferences but also in terms of the distribution of neural response properties across the entire brain.

Conclusion

Recent functional neuroimaging studies in healthy human subjects have provided evidence that neural responses in face-sensitive fusiform cortex invariantly code face identity and those in visual word-sensitive cortex invariantly code visual word form. The most parsimonious tenable hypothesis for the neural bases of selective agnosias as prosopagnosia and pure alexia is hence a structural or functional lesion to such specialized regions, and two recent case studies with fMRI have provided support for this account. More complex scenarios cannot be ruled out but require less intuitive assumptions [86].

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 428–430).

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