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Role of Population Receptive Field Size in Complex Visual Dysfunctions
A Posterior Cortical Atrophy Model

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➕ **Supplemental content**

IMPORTANCE The neuronal mechanism of visual agnosia and foveal crowding that underlies the behavioral symptoms of several classic neurodegenerative diseases, including impaired holistic perception, navigation, and reading, is still unclear. A better understanding of this mechanism is expected to lead to better treatment and rehabilitation.

OBJECTIVE To use state-of-the-art neuroimaging protocols to assess a hypothesis that abnormal population receptive fields (pRF) in the visual cortex underlie high-order visual impairments.

DESIGN, SETTING, AND PARTICIPANTS Between April 26 and November 21, 2016, patients and controls were recruited from the Hadassah-Hebrew University medical center in a cross-sectional manner. Six patients with posterior cortical atrophy (PCA) were approached and 1 was excluded because of an inability to perform the task. Participants underwent functional magnetic resonance imaging–based cortical visual field mapping and pRF evaluation and performed a masked repetition priming task to evaluate visuospatial perception along the eccentricity axis. The association between pRF sizes and behavioral impairments was assessed to evaluate the role of abnormal pRF sizes in impaired visual perception. Posterior cortical atrophy is a visual variant of Alzheimer disease that is characterized by progressive visual agnosia despite almost 20/20 visual acuity. Patients with PCA are rare but invaluable for studying visual processing abnormalities following neurodegeneration, as atrophy begins in visual cortices but initially spares other brain regions involved in memory and verbal communication.

EXPOSURES Participants underwent a magnetic resonance imaging scan.

MAIN OUTCOMES AND MEASURES Population receptive field sizes and their association with visual processing along the fovea-to-periphery gradient.

RESULTS Five patients with PCA (4 men [80%]; mean [SEM] age, 62.9 [3.5] years) were compared with 8 age-matched controls (1 man [25%]; mean [SEM] age, 63.7 [3.7] years) and demonstrated an atypical pRF mapping that varied along the eccentricity axis, which presented as abnormally small peripheral and large foveal pRFs sizes. Abnormality was seen in V1 (peripheral, 4.4° and 5.5°; foveal, 5.5° and 4.5° in patients and controls, respectively; $P < .05$) as well as in higher visual regions, but not in intermediate ones. Behaviorally, an atypical fovea-to-periphery gradient in visual processing was found that correlated with their pRF properties ($r = 0.8$; $P < .01$ for the correlation between pRF and behavioral fovea-to-periphery slopes).

CONCLUSIONS AND RELEVANCE High-order visuocognitive functions may depend on abnormalities in basic cortical characteristics. These results may fundamentally change approaches to rehabilitation in such conditions, emphasizing the potential of low-level visual interventions.

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Complex visual dysfunctions, such as agnosia, attracted scientists' attention because of the discrepancy between near-normal acuity and impaired visual processing. Posterior cortical atrophy (PCA), a rare visual variant of Alzheimer disease, is characterized by progressively disrupted visual abilities despite a patient having almost 20/20 visual acuity. Common visual symptoms of PCA are simultanagnosia, in which scenes and objects are perceived in a fragmentary manner, and foveal crowding, in which nearby stimuli disrupt image recognition. These symptoms present a paradox, because while simultanagnosia appears to result from restricted spatial integration, foveal crowding suggests the opposite.[1,2]

Cortical visual neurons typically respond exclusively to stimuli in their receptive fields (RFs).[3] These properties can be evaluated using a functional magnetic resonance imaging (fMRI)-based population RF (pRF) modeling technique that assesses RF characteristics of neural populations within each voxel. Receptive field size increases with eccentricity and along a visual hierarchy. Larger RFs in the periphery are associated with visual input integration, supporting gist processing. Small RFs in the fovea obtain high-resolution processing even in presence of clutter.[3,4]

We hypothesized that abnormal basic cortical characteristics (ie, RF size) explain PCA-associated deficits in high-order visuocognitive functions (ie, simultanagnosia and foveal crowding), thus laying the foundation for a new rehabilitation approach for these patients.

Methods

Participants and Data Acquisition and Analysis

From April 26 to November 21, 2016, we recruited 5 patients with PCA (4 men [80%]; mean [SEM] age, 62.9 [3.5] years) and 8 age-matched healthy volunteers (1 man; age, 63.7 [3.7] years; eTable 1 in the Supplement). Functional MRI data were acquired using a 3-T Siemens MAGNETOM Skyra scanner. A moving checkerboard bar stimulus was used, as detailed elsewhere[3,4] (eMethods in the Supplement). The Difference of gaussian pRF model was applied to capture pRF properties[3] (eMethods in the Supplement). Major outcomes included center and surround pRF size and surround suppression index (SI). These measures were assessed along the eccentricity axis in the primary visual cortex (V1) as well as in V2, V3, human V4 (hV4), and the object-associated (LO1&2) and motion-associated (TO1&2) visual field maps. Cortical atrophy in each region was also assessed.

Behavioral data were acquired using a masked repetition priming task (eMethods in the Supplement). The accuracy and reaction time (RT) of foveal (fixational) target identification were assessed as a function of the eccentricity of the primes. Statistical testing was performed using R, version 3.3.3 (R Foundation).

Results

Eccentricity and polar angle maps were sufficiently stable for delineating visual regions of interest. The variance explained did not differ between patients and control groups. Results

Key Points

Question What is the cortical basis of agnosia and abnormal foveal-crowding phenomena?

Findings In this case-control study, 5 patients with posterior cortical atrophy with simultanagnosia and foveal crowding underwent a behavioral assessment and population receptive field (pRF) size evaluation along the visual hierarchy via functional magnetic resonance imaging. Findings demonstrate a striking perceptual abnormal fovea-to-periphery gradient that is associated with an abnormal pRF size mapping along the eccentricity axis.

Meaning Smaller peripheral and larger foveal pRFs could explain simultanagnosia and foveal crowding, respectively; these findings explain high-order visuocognitive functions with basic cortical characteristics and may suggest new approaches to rehabilitation.

were not confounded by goodness-of-fit or gray matter volume differences (eResults, eFigure 1, and eTables 2 and 3 in the Supplement).

Abnormal pRF Size Mapping in PCA

Despite similar eccentricity mapping, pRF sizes differed between patients and controls. Interestingly, the pattern of change varied with eccentricity and along visual hierarchy (occurring in V1 and high-order visual processing areas but not in intermediate visual field maps; eFigure 2 in the Supplement). At low eccentricity, an increased pRF size was found in PCA. This was evident in V1 when modeling the center and in hV4 when modeling the surround pRFs (eTable 4 in the Supplement; **Figure 1**). At high eccentricity, reduced pRF size was evident in PCA. This was shown in V1 (center and surround) and in high-order visual processing areas (hV4: center and TO1/2: surround size). Similar findings were evident when assessing pRF size within predefined bins of eccentricity (eMethods in the Supplement). Average pRF sizes fit well to a regression line along the eccentricity axis, with a reduced, or even reversed, slope in patients' V1 and hV4 (eTable 5 in the Supplement; Figure 1C, E and F). Despite significant pRF size changes, the magnitude of surround suppression, as indicated by the SI, was similar in both groups in all tested visual areas.

Association of Atypical Fovea-to-Periphery Gradient of pRF Size With Atypical Gradient in Visual Processing

Visual processing was examined using a masked repetition-priming task that captured the RT benefit of a prime displayed in different eccentricities (**Figure 2**). Patients with PCA identified the foveal target as accurately as controls; however, their RTs were significantly prolonged (eTable 6 in the Supplement). To control for RT differences, RTs were transformed to z scores across all correct trials of a single participant. While an expected fovea-to-periphery gradient was found in controls, reflected as shorter RTs for target identification when primes appeared at a foveal location, similar RTs were found in patients with PCA irrespective of prime location (Figure 2B). Accordingly, the slope in RTs across prime positions was significantly smaller in PCA (Figure 2C). A shallower slope was strongly associated with larger pRFs in

Figure 1. Population Receptive Field (pRF) Sizes as a Function of Eccentricity in Patients With Posterior Cortical Atrophy (PCA) and Control Participants
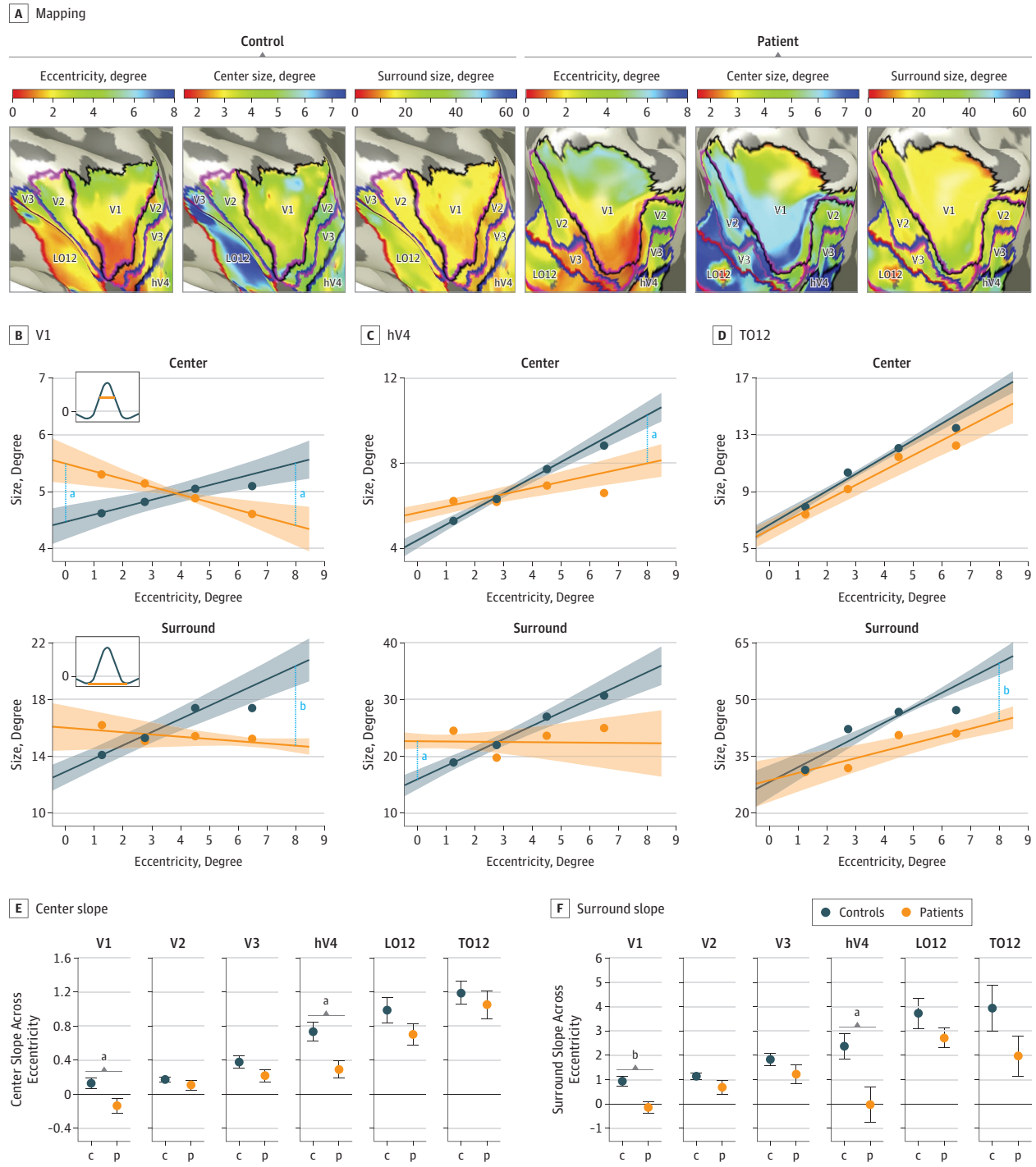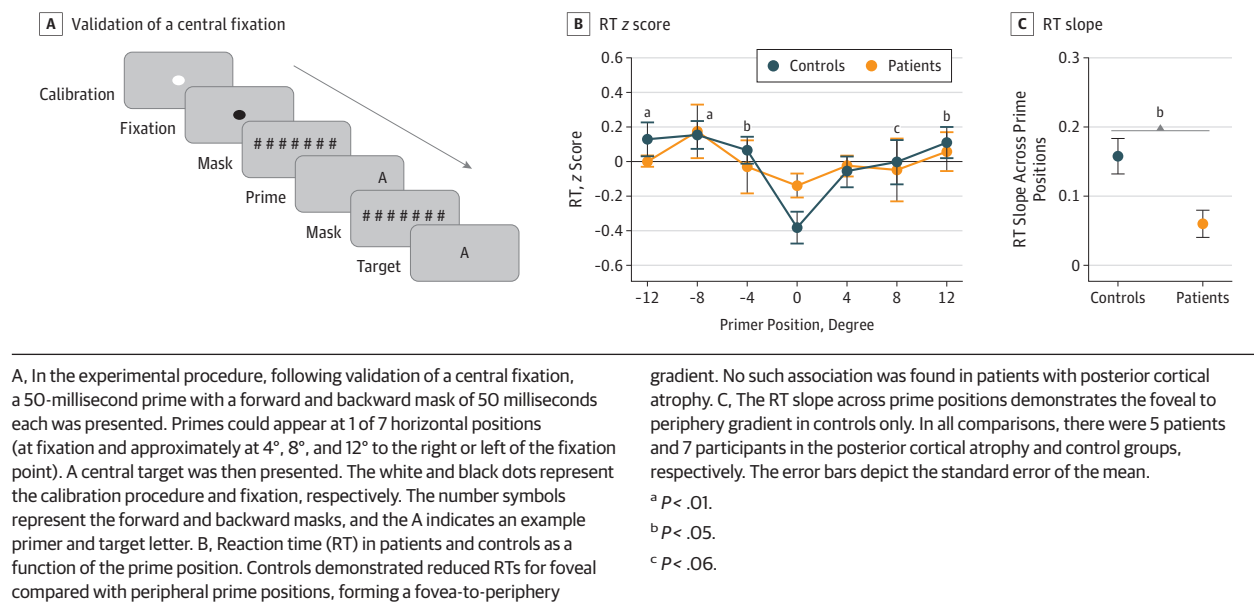

A, Eccentricity, center size, and surround size mapping in 1 control participant and 1 patient with PCA. B-D, Average pRF sizes along the eccentricity axis in V1, human V4 (hV4), and TO12 for patients with PCA and control participants. The orange and black lines represent the averaged pRF size curve along the eccentricity axis in patients and controls, respectively. The light gray and orange shaded areas indicate the standard error of the mean along the curve. Orange and black dots depict weighted by variance–explained means in 4 bins along the eccentricity axis at 0.5° to 2°, 2° to 3.5°, 3.5° to 5.5°, and 5.5° to 7.5°. E (center)

and F (surround), Averaged slopes along the eccentricity axis in V1, V2, V3, hV4, LO1 and 2, and TO1 and 2 for patients with PCA (orange) and control participants (black). In all reported analyses, there were 5 patients and 8 participants in the PCA and control groups, respectively. Error bars indicate the standard error of the mean.

[a] $P < .05$.

[b] $P < .01$.

Figure 2. Spatial Perception as a Function of Eccentricity and Association With Population Receptive Field Size

A, In the experimental procedure, following validation of a central fixation, a 50-millisecond prime with a forward and backward mask of 50 milliseconds each was presented. Primes could appear at 1 of 7 horizontal positions (at fixation and approximately at 4°, 8°, and 12° to the right or left of the fixation point). A central target was then presented. The white and black dots represent the calibration procedure and fixation, respectively. The number symbols represent the forward and backward masks, and the A indicates an example primer and target letter. B, Reaction time (RT) in patients and controls as a function of the prime position. Controls demonstrated reduced RTs for foveal compared with peripheral prime positions, forming a fovea-to-periphery

gradient. No such association was found in patients with posterior cortical atrophy. C, The RT slope across prime positions demonstrates the foveal to periphery gradient in controls only. In all comparisons, there were 5 patients and 7 participants in the posterior cortical atrophy and control groups, respectively. The error bars depict the standard error of the mean.

[a] $P < .01$.

[b] $P < .05$.

[c] $P < .06$.

foveal V1 and a decreased slope of pRF size along the eccentricity axis in V1 (eTable 6 and eFigure 3 in the Supplement). Taken together, these results suggest that larger foveal pRFs in PCA are associated with a reduced fovea-to-periphery gradient in visual processing.

Discussion

Abnormal pRF properties in patients with PCA, even in early visual areas, may explain their high-order neurovisual pathologies. *Simultanagnosia*, defined as the inability to perceive more than 1 item at a time,[1] can be explained by abnormally small peripheral pRFs, restricting the size of input integration windows and causing impairment in parallel object processing. Foveal crowding, which was suggested to result from the pooling of target and distracting stimuli within the same RF,[1,2,5] may be explained by abnormally enlarged foveal pRFs.

An abnormal fovea-to-periphery spatial attention gradient was previously reported in simultanagnosia.[6] We suggest that abnormal pRF size is the neuronal substrate of this phenomenon. Changes in pRF size have been suggested as a neural mechanism that explains basic visual functional disabilities,[7] but this study demonstrates their association with high visual dysfunctions. Enlarged pRFs were evident already in V1, corresponding to previous indications on the role of V1 in mediating perceptual phenomena in PCA.[2,8,9]

Nevertheless, cortical atrophy and hypometabolism in PCA are generally characterized by changes in extrastriate visual areas, but to a lesser extent in V1.[2,10] Similarly, no evidence of V1 damage was found in this cohort. While RF properties may be modulated by feedback from high-order visual areas and intraregional lateral connections,[7,11,12] we suggest that it is feedback signals from high-level visual regions that lead to the abnormality in V1.
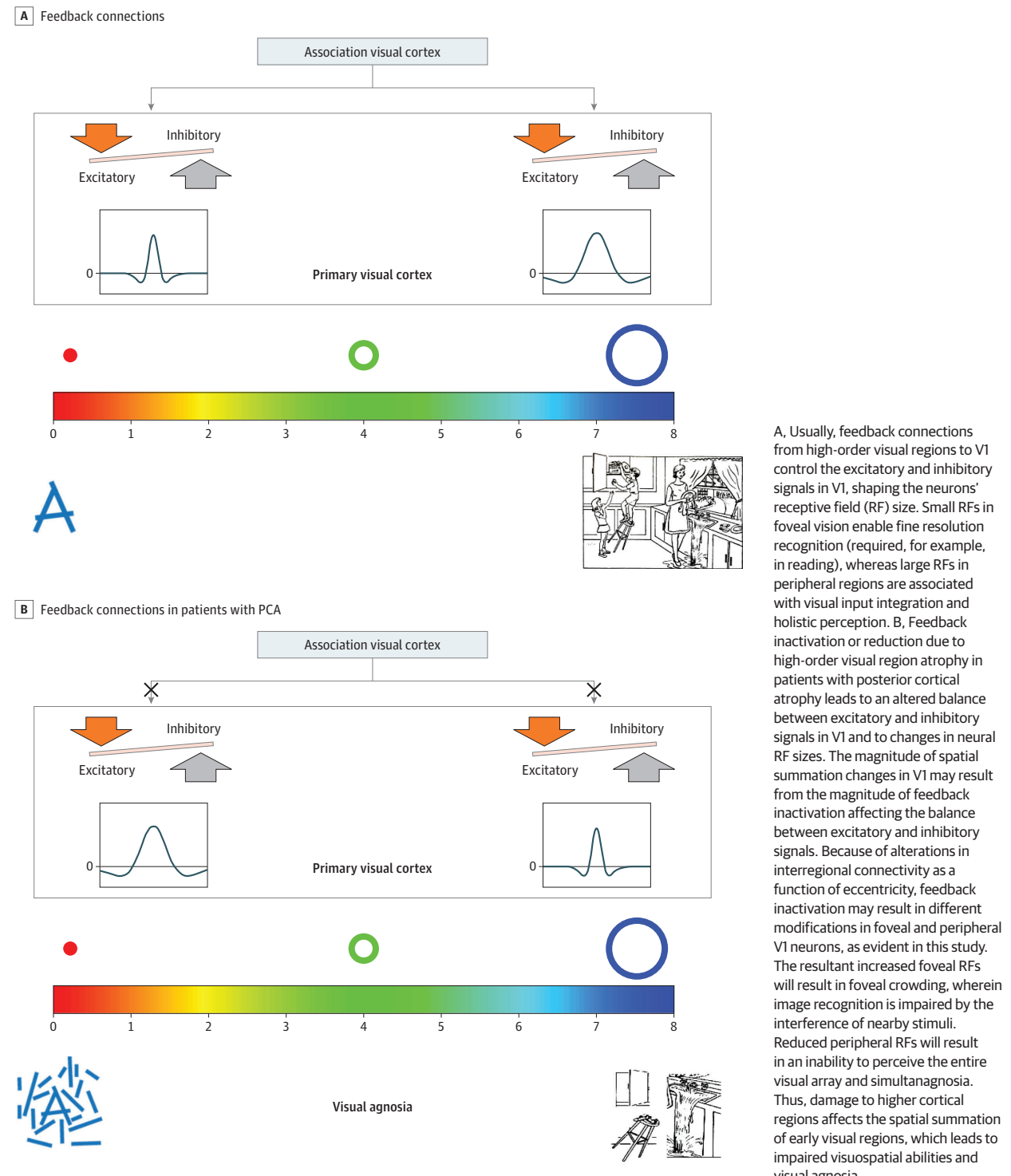
Unlike in V1, we suggest that pRF size changes in extrastriate areas of PCA (hV4 and middle temporal area) may originate from direct damage (atrophy), as well as from disrupted feedback connections. Patients with PCA were shown to have atrophy and atypical activations in MT as well as frontoparietal areas, which are connected to MT+ and hV4.[10,13]

Top-down feedback and atrophy are not the only mechanisms that can affect pRF size. Cognitive processes, including attention, were shown to modulate RF size as a function of eccentricity. The association of attention with foveal vision may lead to a reduced spatial summation window, resulting in the ability to exclude contextual nonattended information. In terms of peripheral vision, as a detailed analysis of visual scenes is not possible due to reduced visual resolution, enhancing facilitative interactions by attention could promote an increased summation window, leading to a more integrative scene analysis, and highlight attended peripheral objects as targets for impending eye movements (bringing it into foveal vision for detailed analysis).[14] Thus, RF changes in PCA, demonstrating the opposite pattern, contradict functionality. Increased RF size in PCA foveal cells hampers the exclusion of irrelevant contextual information, leading to central crowding; furthermore, a reduction of pRF size in peripheral locations impairs integrative scene analysis, leading to simultanagnosia.

Conclusions

Abnormal pRF properties mapping in patients with PCA is associated with their atypical visuospatial processing. We suggest that altered pRF sizes are attributed to a combined mechanism by which atrophy of high-order association cortices simultaneously causes attention processes impairment and a disruption of basic visual processes via

Figure 3. Simplified Model to Explain Feedback Connection Associations With V1 Spatial Summation Properties and Resulting Perception

A, Usually, feedback connections from high-order visual regions to V1 control the excitatory and inhibitory signals in V1, shaping the neurons' receptive field (RF) size. Small RFs in foveal vision enable fine resolution recognition (required, for example, in reading), whereas large RFs in peripheral regions are associated with visual input integration and holistic perception. B, Feedback inactivation or reduction due to high-order visual region atrophy in patients with posterior cortical atrophy leads to an altered balance between excitatory and inhibitory signals in V1 and to changes in neural RF sizes. The magnitude of spatial summation changes in V1 may result from the magnitude of feedback inactivation affecting the balance between excitatory and inhibitory signals. Because of alterations in interregional connectivity as a function of eccentricity, feedback inactivation may result in different modifications in foveal and peripheral V1 neurons, as evident in this study. The resultant increased foveal RFs will result in foveal crowding, wherein image recognition is impaired by the interference of nearby stimuli. Reduced peripheral RFs will result in an inability to perceive the entire visual array and simultanagnosia. Thus, damage to higher cortical regions affects the spatial summation of early visual regions, which leads to impaired visuospatial abilities and visual agnosia.

altered feedback. Hence, PCA provides a human model of feedback connection interference due to atrophy of higher visual regions, resulting in a modulation of pRF properties in V1. Nevertheless, these changes in basic cortical characteristics are clinically manifested as a grouping of high-order visuocognitive functions (**Figure 3**). Future studies should assess the rehabilitation powers of altering visual input and saliency (which can be driven from abnormal pRF[15]) to enable the tailoring of new rehabilitation approaches for these patients.

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