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MRI Evidence of Anterograde Trans-synaptic Degeneration After Eye Loss: Preserved Primary Visual Cortex Thickness Despite Lateral Geniculate Nucleus Atrophy

David Llanos

davllano@ucm.es

Hospital Clínico San Carlos https://orcid.org/0000-0001-7819-9839

Enrique Santos

Hospital Clínico San Carlos

Federico Saenz-Frances

Hospital Clinico San Carlos, Madrid

Íñigo de la Pedraja

Hospital Clínico San Carlos

Juan Arrazola

Hospital Clínico San Carlos

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Abstract

Background:
Anterograde trans-synaptic degeneration (ATD) of the visual pathway following eye loss is well recognized, but its in vivo characterization remains limited. We investigated structural changes in the lateral geniculate nucleus (LGN) and primary visual cortex (V1) using automated analysis of high-resolution 3-T magnetic resonance imaging (MRI).

Methods:
This cross-sectional study included 30 patients with unilateral or bilateral eye loss (≥6 months after enucleation or evisceration) and 75 healthy controls. All participants underwent standardized 3-T brain MRI. Automated LGN segmentation and cortical parcellation were performed using FreeSurfer version 7.2. Bilateral LGN volumes and mean V1 cortical thickness were compared between groups, and the relationship between LGN volume and time since eye loss was assessed.

Results:
Patients showed significantly smaller bilateral LGN volumes than controls (both $p < 0.001$). No significant association was found between LGN volume and time since eye loss, suggesting that most LGN atrophy develops early after visual deprivation. In contrast, mean V1 cortical thickness did not differ significantly between patients and controls (left hemisphere: $p = 0.704$; right hemisphere: $p = 0.106$).

Conclusions:
Eye loss is associated with marked bilateral LGN atrophy, but no significant reduction in V1 cortical thickness was detected with the methodology used, suggesting differential susceptibility of subcortical and cortical visual structures to ATD. Automated analysis of high-resolution 3-T MRI provides a practical, non-invasive method for investigating structural changes of the visual pathway in vivo.

Introduction

The eyes and the brain are both components of the central nervous system (CNS) and are therefore closely interconnected. Neurodegenerative changes can spread bidirectionally along the visual pathway[1]. For example, damage to retinal ganglion cells (RGCs) leads to degeneration of neurons in both lateral geniculate nuclei (LGN) and, ultimately, the visual cortex. Conversely, damage to the visual cortex results in degeneration of the ipsilateral LGN and of RGCs in both eyes. This phenomenon is known as trans-synaptic degeneration of the visual pathway and is termed anterograde when degeneration spreads from the retina to the brain and retrograde when it spreads from the brain toward the retina[2–4] (Figure 1).

Although the existence of anterograde trans-synaptic degeneration (ATD) of the visual pathway is well documented[2,5], postmortem studies are scarce and include only a limited number of specimens. Several in vivo MRI studies have been reported, but detailed characterization of trans-synaptic degeneration remains challenging. Accurate manual measurement of LGN volumes on MRI is difficult because of their

small size, irregular shape, and poor delineation, even on high-resolution images. Assessment of the primary visual cortex is also challenging, as V1 is among the thinnest regions of the cerebral cortex[6] and its boundaries are difficult to define manually. Another major limitation in the study of trans-synaptic degeneration is the heterogeneity of study populations, as previous studies have included patients with glaucoma or multiple sclerosis across a wide spectrum of disease severity.

Since the introduction and evolution of automated pipelines for the segmentation and parcellation of brain MRI studies, it is now possible to quantify with high precision the volume of deep grey matter nuclei, define the boundaries of different brain regions, and measure the thickness of the corresponding cortex while minimizing measurement errors and observer bias.

The aim of this study was to determine whether automated MRI segmentation and parcellation techniques can detect and quantify structural evidence of ATD following eye loss and whether degeneration extends beyond the LGN to involve the primary visual cortex.

METHODS

To characterize the long-term structural effects of ATD in the brain, we conducted a cross-sectional study of patients who had undergone unilateral or bilateral eye removal for a variety of conditions, thereby minimizing the confounding effects of heterogeneous degrees of visual loss. Thirty patients were recruited from the orbital pathology clinic. Patients with structural brain abnormalities on MRI unrelated to eye loss were excluded. Twenty-nine patients had undergone unilateral eye removal and one had undergone bilateral eye removal. The time elapsed since eye removal ranged from 6 months to 84 years. Some patients had impaired vision in the remaining eye; however, this was not an exclusion criterion.

Healthy controls were selected from a previously acquired dataset of subjects who had undergone brain MRI using the same scanner and imaging protocol as those used for the patient group (3-T Signa Architect scanner, GE Healthcare, Milwaukee, WI, USA). They had initially undergone MRI because of persistent memory complaints following COVID-19 infection, had fully recovered at the time of inclusion, showed no structural brain abnormalities on MRI, and had no clinical evidence of neurological disease. Seventy-five subjects were included, and their electronic medical records were reviewed to exclude any history of ocular disease; subjects with refractive errors of ≥5 dioptres were excluded.

The study was approved by the Ethics Committee of our institution, and all participants provided written informed consent for MRI acquisition and the use of their data for research purposes.

Three-dimensional T1-weighted MP-RAGE sequences with a 1-mm isotropic voxel size and axial T2-weighted FLAIR sequences were acquired, the latter to exclude incidental brain pathology.

LGN volumes and V1 cortical thickness were obtained using the FreeSurfer software package (version 7.2; https://surfer.nmr.mgh.harvard.edu)[7] and its standard recon-all pipeline.

Data obtained from the automated segmentation and parcellation of patients and controls were compiled into a database. The following variables were recorded: sex and age in both groups; laterality and time elapsed since eye loss in the patient group; and left and right LGN volumes and mean left and right V1 cortical thicknesses in all subjects.

For both patients and controls, each automated image analysis was individually reviewed to verify the correct identification and measurement of the structures of interest. No manual corrections were required in any subject.

Statistical analyses were performed using IBM SPSS Statistics software (version 19.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). The Shapiro–Wilk and Kolmogorov–Smirnov tests demonstrated that none of the recorded variables violated the assumption of normality. Levene's test confirmed the assumption of homogeneity of variances. Differences between groups were assessed using the independent-samples Student's t-test, and statistical significance was set at $p < 0.05$. To account for potential confounding by age and sex, additional multivariable linear regression analyses were performed with LGN volume as the dependent variable and group status, age, and sex as independent variables.

RESULTS

Descriptive statistics are summarized in Table 1 and Figure 2.

The mean age of the control group was 51.27 years (range, 23–77 years), whereas the mean age of the patient group was 61.53 years (range, 30–94 years). Patients were significantly older than controls ($p = 0.005$).

The mean left LGN volume was 191.13 ± 40.35 mm^3 in patients and 266.49 ± 33.27 mm^3 in controls, whereas the mean right LGN volume was 195.67 ± 38.16 mm^3 and 262.72 ± 37.39 mm^3, respectively. Both differences were highly significant (both $p < 0.001$).

Mean left V1 cortical thickness did not differ significantly between patients and controls (1.59 ± 0.14 vs. 1.58 ± 0.15 mm; $p = 0.704$). Mean right V1 cortical thickness was slightly greater in patients (1.59 ± 0.14 vs. 1.54 ± 0.15 mm), although this difference did not reach statistical significance ($p = 0.106$).

Linear regression analysis showed no significant association between the time elapsed since eye loss and LGN volume (all $p > 0.05$).

Because patients were significantly older than controls, additional multivariable linear regression analyses adjusted for age and sex were performed. After adjustment for age and sex, patient status remained independently associated with lower left and right LGN volumes (both $p < 0.001$).

DISCUSSION

In healthy controls, mean left LGN volume and mean left V1 cortical thickness were slightly greater than those of the right hemisphere, although these differences were not statistically significant. This subtle asymmetry may be related to the predominance of right-eye ocular dominance in the general population, together with the slightly greater proportion of retinal ganglion cell axons that decussate to the contralateral hemisphere.[8,9].

The absolute LGN volumes obtained in our control group were larger than those reported in previous histopathological and MRI studies[10,11]. However, direct comparisons are difficult because of the marked methodological heterogeneity among studies, including differences in specimen preparation, MRI acquisition protocols, magnetic field strengths, and segmentation software. The small size and complex anatomy of the LGN further contribute to measurement variability. Therefore, absolute volumetric values should be interpreted cautiously, and longitudinal or case-control studies should ideally use identical MRI protocols and segmentation pipelines.

The first finding of this study was the marked reduction in bilateral LGN volumes in patients with eye loss (Figure 3). This observation is consistent with previous experimental and clinical evidence demonstrating anterograde trans-synaptic degeneration following retinal deafferentation. Moreover, the absence of a significant association between time since eye loss and LGN volume suggests that most of the atrophic process occurs relatively early after visual deprivation and subsequently reaches a stable plateau.

In contrast, no significant differences in mean V1 cortical thickness were observed between patients and controls. Although this finding was initially unexpected, accumulating evidence suggests that the structural response of the primary visual cortex to visual deprivation is complex. Previous studies have reported that some regions of V1 may become thinner, whereas others may become thicker, possibly because of altered synaptic pruning[12,13], resulting in little overall change in mean cortical thickness. In addition, cross-modal plasticity and the preservation of inputs from other brain regions[14,15] may contribute to maintaining the structural integrity of V1 despite severe retinal deafferentation (Figure 4).

Notably, the only patient with bilateral eye loss, who had undergone eye removal 47 years before MRI, exhibited left and right LGN volumes below the corresponding control group means (184.7 and 190.5 mm^3, respectively), whereas left and right V1 cortical thicknesses remained above the corresponding control means (1.60 and 1.68 mm, respectively). Although no conclusions can be drawn from a single case, this observation is consistent with the overall preservation of V1 cortical thickness observed in the present study, even after prolonged visual deprivation.

The main strengths of this study are the relatively large number of patients with eye loss, the use of a homogeneous imaging protocol on a single 3-T scanner, and the application of a fully automated segmentation pipeline. Several limitations should also be acknowledged. First, patients were significantly older than controls, although the association between eye loss and reduced LGN volume remained significant after adjustment for age and sex. Second, some patients had impaired vision in the

remaining eye, which may have increased the degree of visual deprivation. Third, the cross-sectional design precluded direct assessment of the temporal evolution of LGN atrophy and cortical remodelling after eye loss.

Finally, the preservation of V1 cortical thickness despite profound LGN atrophy may have implications for future visual restoration strategies. While these interpretations should be approached with caution, our findings suggest a preserved structural integrity that warrants further investigation. The observation that the primary visual cortex remains structurally intact even decades after eye loss supports the theoretical rationale for approaches aimed at delivering visual information directly to the cortex, bypassing the severely degenerated LGN.

CONCLUSIONS

Automated segmentation of high-resolution 3-T MRI data enables *in vivo* quantification of ATD of the visual pathway.

Eye loss is associated with marked bilateral LGN atrophy, supporting the concept that retinal deafferentation leads to substantial degeneration of subcortical visual relay nuclei. The absence of an association between time since eye loss and LGN volume suggests that this atrophic process occurs early and subsequently stabilizes.

In contrast, no significant reduction in primary visual cortex thickness was detected with the methodology used. This observation suggests that long-term visual deprivation may not necessarily result in measurable cortical thinning of V1, although more subtle structural or functional changes cannot be excluded.

Overall, these findings improve our understanding of the structural consequences of visual deafferentation and may have implications for future strategies aimed at restoring vision by directly interfacing with the visual cortex.

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Table

Table 1. Demographic characteristics and MRI measurements in controls and patients with eye loss.

Variable	Controls (n = 75)	Eye loss (n = 30)	p value
Age, years	51.27 ± 12.06	61.53 ± 17.23	0.005
Female sex, n (%)	54 (72.0)	17 (56.7)	0.198
Left LGN volume, mm^3	266.49 ± 33.27	191.13 ± 40.35	<0.001
Right LGN volume, mm^3	262.72 ± 37.39	195.67 ± 38.16	<0.001
Left V1 cortical thickness, mm	1.58± 0.15	1.59 ± 0.14	0.704
Right V1 cortical thickness, mm	1.54 ± 0.15	1.59 ± 0.14	0.106

Data are presented as mean ± standard deviation (SD) unless otherwise indicated. LGN = lateral geniculate nucleus; V1 = primary visual cortex.

P values were obtained using the independent-samples Student's t-test for continuous variables and the χ^2 test for categorical variables.

Figures

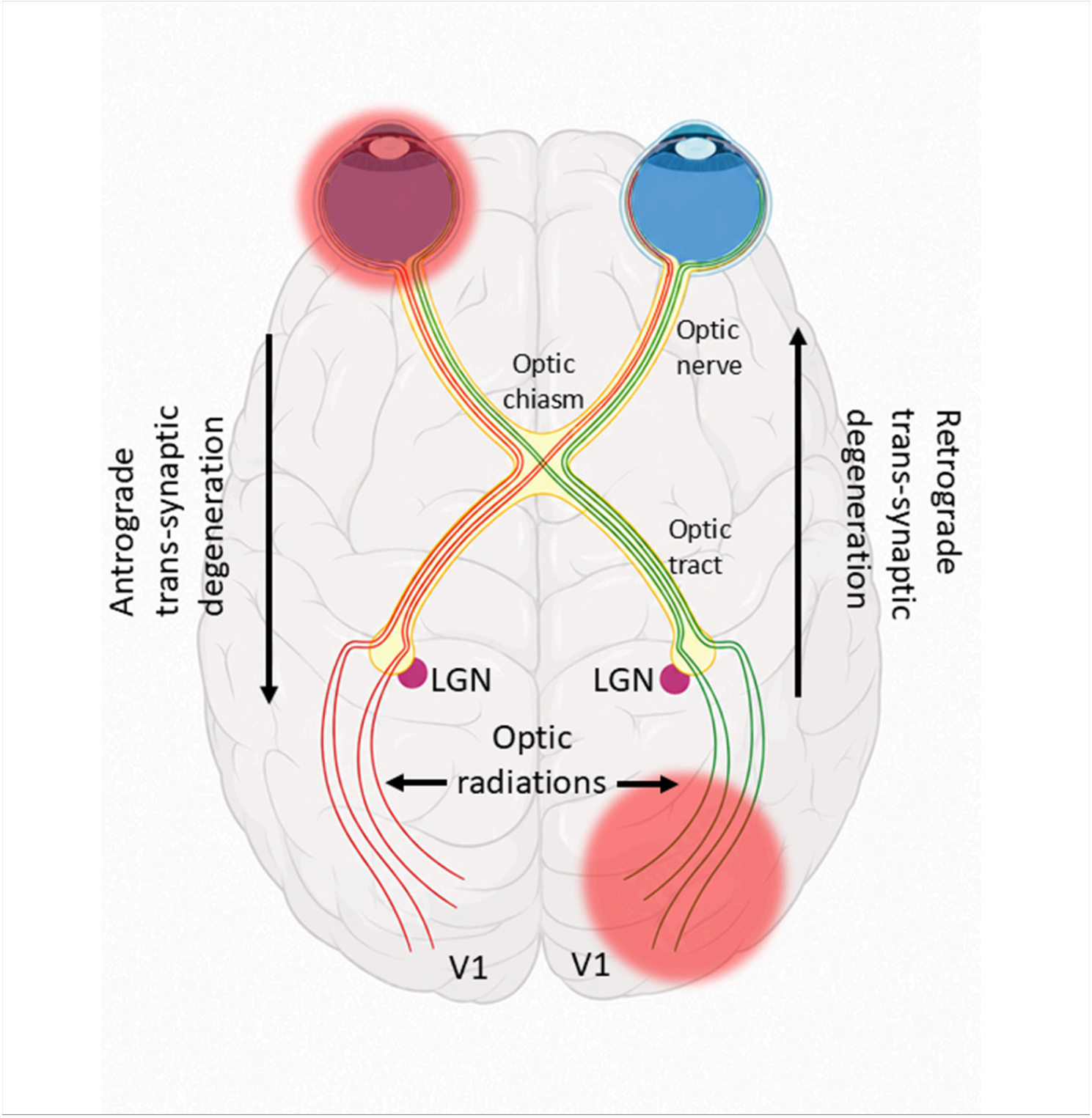


Figure 1

Schematic representation of the human visual pathway and the direction of trans-synaptic degeneration. Injury to the retina or optic nerve leads to anterograde trans-synaptic degeneration, which propagates from retinal ganglion cells to the lateral geniculate nucleus (LGN) and subsequently to the primary visual cortex (V1). Conversely, lesions affecting the visual cortex produce retrograde trans-synaptic

degeneration, with neuronal loss extending from V1 to the LGN and ultimately to retinal ganglion cells. Red shading indicates the site of injury. Modified from Sharma et al[1].

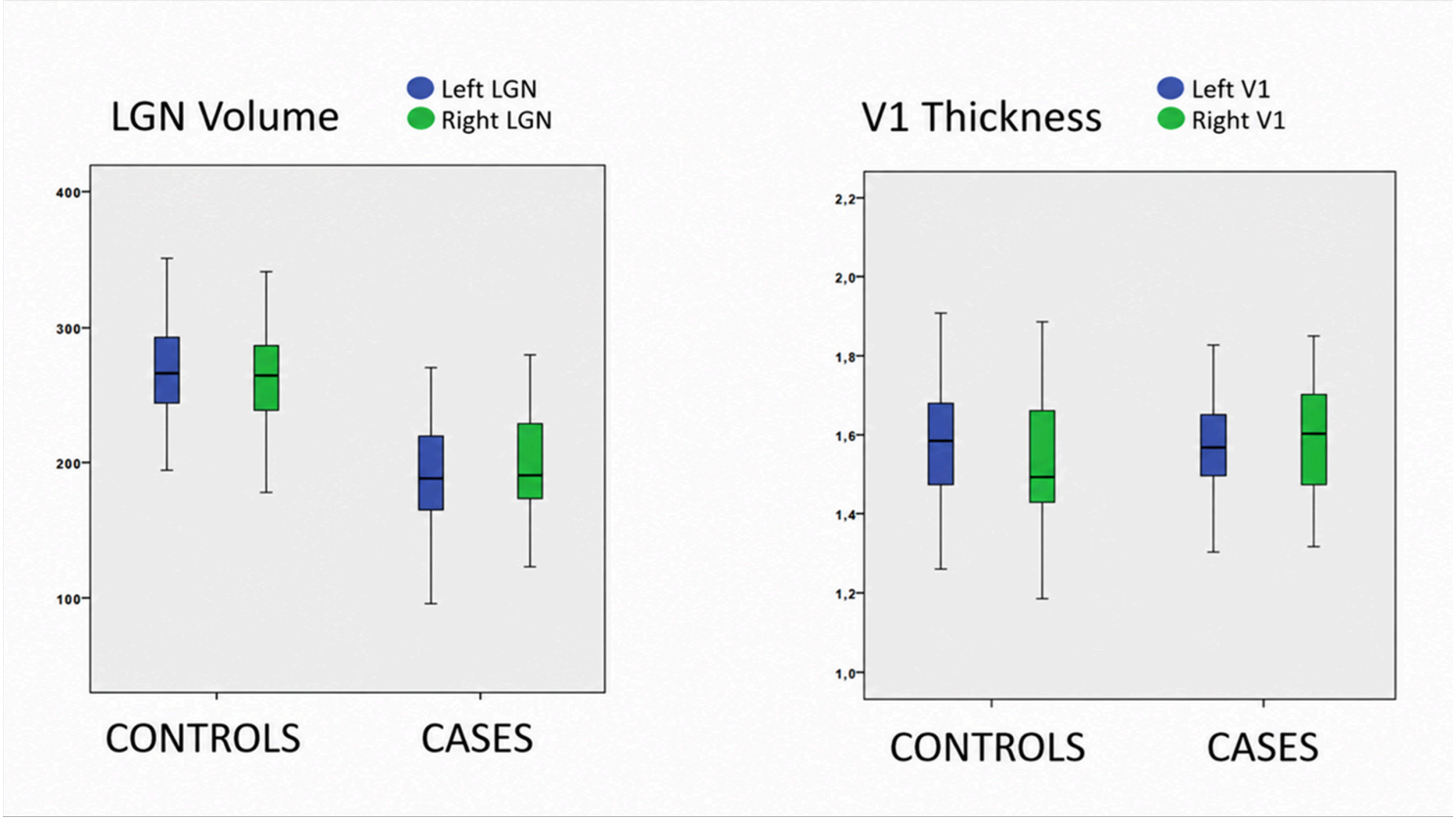


Figure 2

Boxplots showing LGN volumes (mm^3) and mean V1 cortical thickness (mm) in controls and in patients with eye loss. Boxes represent interquartile ranges (IQR), horizontal lines indicate medians, and whiskers indicate 1.5 x IQR

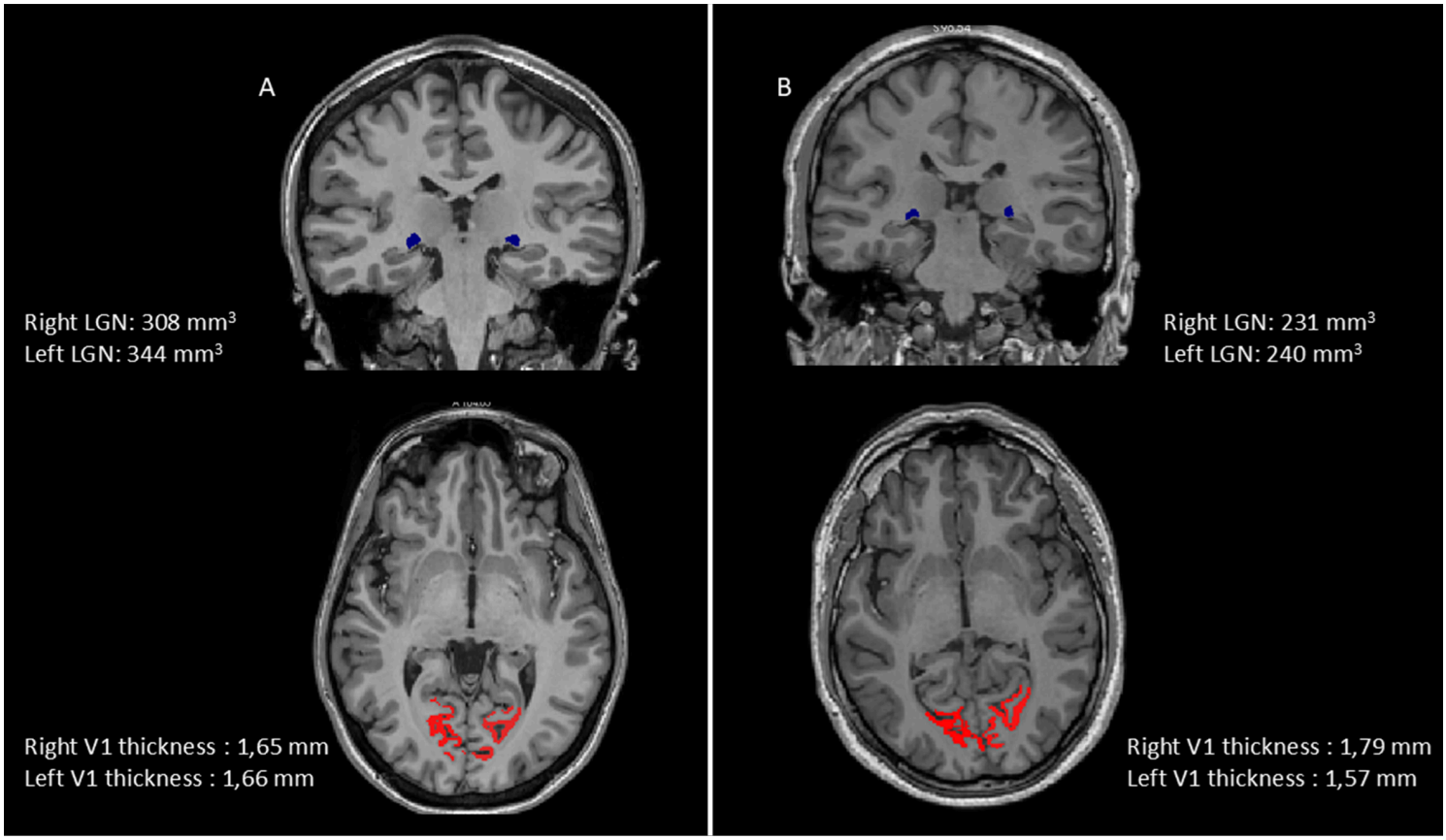


Figure 3

Representative examples of automated segmentation of the lateral geniculate nuclei (LGN) and cortical parcellation of the primary visual cortex (V1). (A) Healthy 27-year-old female control with normal bilateral LGN volumes and V1 cortical thickness. (B) 30-year-old man examined 6 months after left eye enucleation, showing marked bilateral LGN atrophy despite preserved V1 cortical thickness within the range observed in healthy controls. Automatically segmented LGNs are shown in blue, and the cortical parcellation of V1 is shown in red.

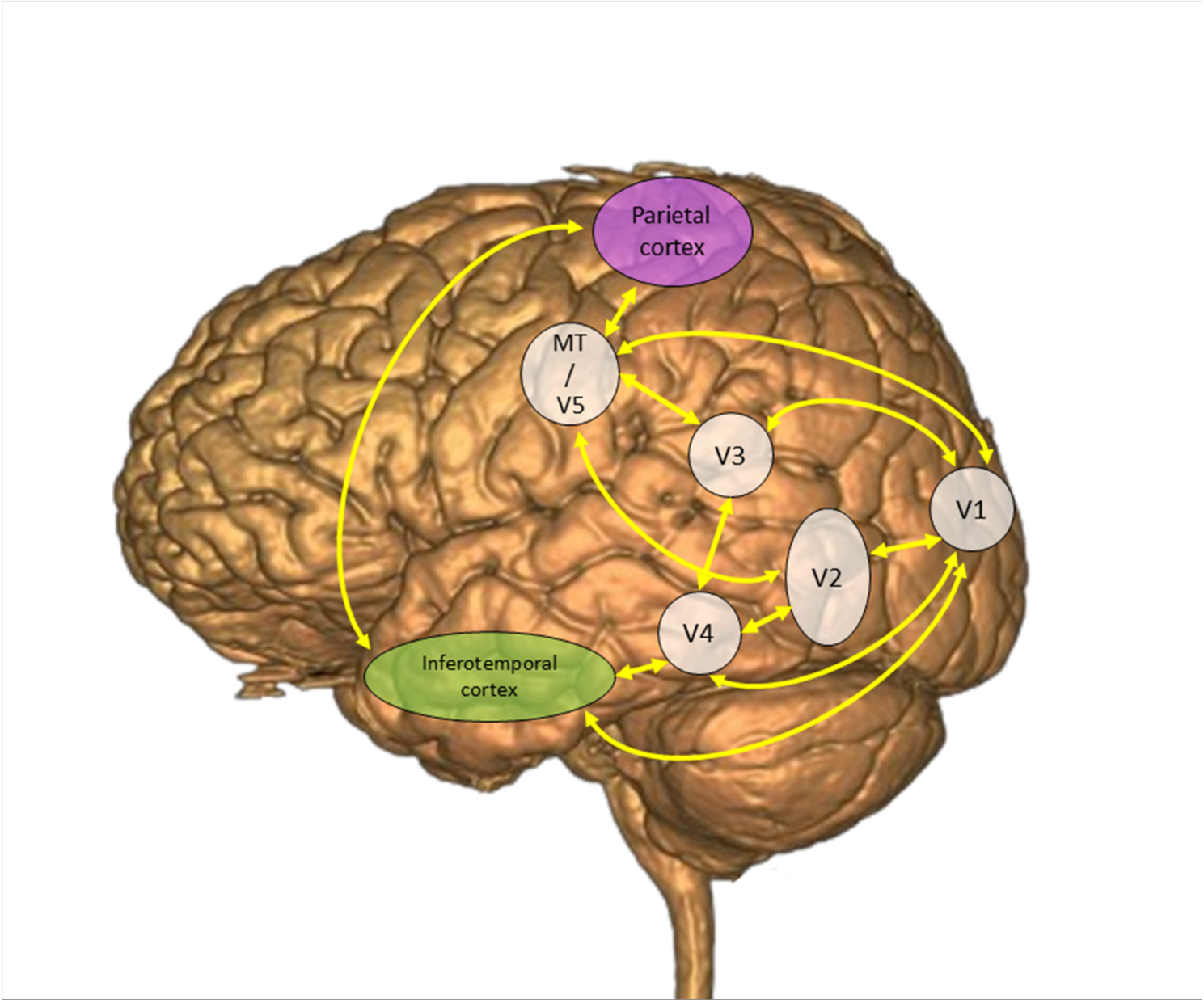


Figure 4

Simplified schematic representation of the main connections between the primary visual cortex (V1) and extrastriate visual areas. Bidirectional corticocortical connections link V1 with V2, V3, V4, and the middle temporal area (MT/V5).