NeuroImage 81 (2013) 222–230

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Long term cortical plasticity in visual retinotopic areas in humans with silent retinal ganglion cell loss

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ARTICLE INFO

Article history:
Accepted 5 May 2013
Available online 16 May 2013

Keywords:
Cortical plasticity
Visual loss
Retinotopic visual areas
Ganglion cells
Development
Mitochondrial gene mutations

ABSTRACT

Visual cortical plasticity induced by *overt* retinal lesions (scotomas) has remained a controversial phenomenon. Here we studied cortical plasticity in a *silent* model of retinal ganglion cell loss, documented by in vivo optical biopsy using coherence tomography. The cortical impact of non-scotomatous subtle retinal ganglion cell functional and structural loss was investigated in carriers of the mitochondrial DNA 11778G>A mutation causing Leber's hereditary optic neuropathy. We used magnetic resonance imaging (MRI) to measure cortical thickness and fMRI to define retinotopic cortical visual areas V1, V2 and V3 in silent carriers and matched control groups.
Repeated Measures analysis of variance revealed a surprising increase in cortical thickness in the younger carrier group (below 21 years of age). This effect dominated in extrastriate cortex, and notably V2. This form of structural plasticity suggests enhanced plastic developmental mechanisms in extrastriate retinotopic regions close to V1 and not receiving direct retinocortical input.

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Introduction

It is known that the brain is able to optimize neural connectivity, in particular during critical periods (Eysel, 2009). Cortical plasticity is characterized by the modification of wiring of neuronal cortical networks in response to changes in visual experience, leading to structural and functional reorganization. Even though developmental plasticity is a well-established phenomenon, adult plasticity still is a very controversial issue. The ability of the cerebral cortex to adapt to changes in visual experience and mechanisms underlying the compensation of loss of function is still highly debated (Wandell and Smirnakis, 2009). Nevertheless human studies have suggested that during the lifespan the cortex maintains the ability to structurally and functionally reorganize either to increased use or disuse due to lesions (Baseler et al., 2009; Bridge et al., 2008, 2010).

Animal model studies of artificially induced retinal lesions (for a review see Baseler et al. (2009)) suggest that the cortex preserves a certain degree of plasticity and is capable of rewiring in response to the loss of sensory inputs using the remaining intact portions of the retina. However, the mechanisms of visual plasticity induced by sustained silent loss of afferent retinal inputs in humans have hitherto not been studied.

We have addressed this issue by studying the silent stage of a human model of retinal ganglion cell (RGC) degeneration and death, Leber Hereditary Optic Neuropathy (LHON). LHON is an inherited genetic condition that may lead to the loss of vision that becomes suddenly apparent after years of subtle neural loss. It is one of the most common types of hereditary optic atrophies with an estimated prevalence rate of approximately 1 in 30,000 (Man et al., 2003; Newman and Biousse, 2004). This maternally inherited disorder caused by point mutations in the mitochondrial DNA (Kirkman et al., 2009b) is characterized by optic nerve atrophy and reduced retinocortical processing. After clinical onset it leads to bilateral visual impairment with dominant loss of central vision (Kirkman et al., 2009a).

Retinocortical information flow is routed from the optic nerve to the lateral geniculate nucleus (LGN) and then dominantly to the primary striate visual cortex (V1). Visual information is then redistributed to extrastriate V2, V3 and higher visual areas (Felleman and Van Essen, 1991). Retinal degeneration does therefore directly deprive V1 from receiving sensory information.

The main aim of this study was to elucidate the structural impact of silent early stage deprivation. An important question was whether indirectly deprived visual extrastriate regions would be affected, or instead reorganize.

It is worth emphasizing that we did not study here overt or late stage clinical cases, where the lack of direct input might lead to manifest cortical atrophy and gray matter thinning. Such overt loss might

Abbreviations: RGC, retinal ganglion cell; LHON, Leber Hereditary Optic Neuropathy; LGN, lateral geniculate nucleus; V1, primary visual cortex; LPZ, lesion projection zone; CT, cortical thickness.

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1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.05.032

explain putative cortical atrophy in lesion projection zones (LPZ) of clinically established retinal lesions. Accordingly, a study comparing gray matter density in visual cortex of foveal (age-related macular degeneration) and peripheral (open-angle glaucoma) retinal lesion models using Voxel Based Morphometry revealed reduction in gray matter density in the respective LPZs in the calcarine sulcus (Boucard et al., 2009). This shows that overt lesions as expressed by visual field scotomata may lead to retinotopic-specific structural loss in the visual cortex.

Our study focuses on the impact of widespread but clinically silent early afferent degeneration on primary striate and extrastriate cortex reorganization. We computed cortical thickness (CT) maps in a pedigree of LHON individuals carrying the 11778G>A mitochondrial DNA mutation in functionally defined early visual areas V1, V2 and V3 in comparison with age-matched controls. Importantly, we expected plasticity to occur mainly during cortical development and to be reduced in adulthood due to decreased plasticity and progression of silent neurodegeneration. It was therefore important to set late developmental cutoffs defined by the onset of early adulthood. We found evidence for differential reorganization in this age-dependent model of silently progressive loss.

Material and methods

Subjects

We have tested 15 asymptomatic LHON carriers (7 men, 8 women; mean age = 29.3 ± 13.50 [SD] years; age range, 8–47 years) (Table 1) that belong to a single homogeneous pedigree of confirmed presence of the mitochondrial DNA 11778G>A mutation (Grazina et al., 2007). Participants from the LHON group were submitted to MRI acquisition and data were compared to subjects from an age-matched control group (n = 15 participants; 11 men, 4 women; mean age = 26.2 ± 11.45 [SD] years; age range, 7–44 years).

All participants were submitted to a complete ophthalmological examination, including best-corrected visual acuity obtained with Snellen chart, ocular tension (Goldmann applanation tonometer, slit lamp biomicroscopy and fundus examination (Goldmann lens)). Control subjects were required to have good visual acuity and not to have any visual field defect (as defined by normative data). Our participants from the LHON carrier group had normal ocular examination, with normal visual acuity and no fundus changes. Visual functional evaluation (see Table 1) showed subclinical impairment in chromatic contrast sensitivity for all color axes (Cambridge Colour Test — Cambridge Research Systems, Rochester, UK: Protan: $p = 0.002$; Deutan: $p = 0.006$; Tritan: $p = 0.007$). Subtle changes in the visual field sensitivity, in spite of the absence of scotomas (Octopus — Haag-Streit AG, Germany), with impact in the global threshold parameters (mean ± SD), mean defect (MD): 3.76 ± 2.10 dB; and loss of variance (LV): 8.36 ± 7.31 dB^2, could also be found (Table 1). The normal range considered for MD and LV is ±2 dB and <6 dB^2, respectively. Structural evaluation of the neural retina was performed using optical coherence tomography, a form of optical biopsy (Stratus OCT3 — Humphrey, Carl Zeiss Meditec, Dublin, CA, USA, axial resolution ~10 μm, for details see below). Exclusion criteria were established pseudophakic and aphakic eyes, significant media opacities, other retinal diseases, high ammetropy (sphere > +4D; cylinder > +2D) and other neuro-ophthalmologic pathology, besides LHON. The study followed the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board. Informed consent was obtained from each participant, after research procedures had been fully explained.

Table 1
Demographics and measures of visual acuity and visual field (MD, mean defect; LV, loss of variance) of both left (LE) and right (RE) eyes of LHON carriers. Normal range: MD ±2 dB and a LV <6 dB^2. Visual dysfunction consistent with subclinical loss is evident.

Patient	Gender	Age (y)	Visual acuity		Visual field			
					MD (dB)		LV (dB^2)	
			LE	RE	LE	RE	LE	RE
1	M	47	20/16	20/16	0.7	−0.7	3.3	3.8
2	F	47	20/20	20/20	1.7	1.8	4.4	5.2
3	F	43	20/20	20/20	3.8	2.8	10.3	4.9
4	M	41	20/16	20/16	4.0	4.2	8.3	4.0
5	F	40	20/20	20/20	4.4	4.0	6.6	3.1
6	F	39	20/20	20/20	3.8	5.0	7.9	2.1
7	F	37	20/16	20/16	0.9	1.8	5.1	5.2
8	F	30	20/16	20/16	7.8	7.0	9.1	10.8
9	M	21	20/16	20/16	7.8	5.5	20.4	32.3
10	F	22	20/16	20/16	6.6	3.9	26.7	9.2
11	M	17	20/16	20/16	5.0	3.3	24.1	10.9
12	M	19	20/16	20/20	5.2	2.8	15.2	10.5
13	M	10	20/20	20/20	6.9	4.1	15.7	4.3
14	F	18	20/16	20/16	7.6	7.8	6.7	9.2
15	M	8	20/16	20/20	3.1	3.1	7.9	9.9

Retinal imaging

Optical coherence tomography (Stratus OCT3, Humphrey, Carl Zeiss Inst., CA, USA) provides a cross-sectional tomography of retinal tissue in real time, based on optical interferometry, using infra-red (843 nm), low coherence light. Cross-sectional images of retinal anatomy were thus obtained, with an axial resolution of ≤10 μm. Retinal thickness was computed as a 9 region bidimensional interpolated thickness map, with a central circle of 1 mm diameter and 2 outer circles with diameter of 3 and 6 mm (Fig. 1).

Stimuli and task design

Retinotopic mapping

Early visual areas are retinotopically arranged in the human visual cortex and mirror/nonmirror representations of adjacent areas of the visual field correspond to the turning points in horizontal and vertical meridians. Visual field mapping fMRI data were acquired using visual stimuli encoding polar coordinates. We used the standard traveling-wave method (phase-encoded retinotopy) (Engel et al., 1994; Sereno et al., 1995). Presented stimuli were: (i) polar angle encoding stimuli (Fig. 2B) comprising a rotating (anticlockwise) black and white checkered wedge flickering at 8 Hz (48 s full cycle, 4 cycles/scan, three scans per subject) and (ii) an eccentricity mapping paradigm (Fig. 2C), using an expanding black and white checkered annulus flickering at 8 Hz (48 s each full expansion, 4 expansions/scan, one scan per subject), while the subject was instructed to fix an orange-colored central point. The stimuli spanned 23° * 23° of visual angle (diameter). This method allowed the mapping of the visual field angular position and eccentricity in relation to the center of the gaze (see below details of fMRI analysis).

Data acquisition

High resolution MRI data was acquired in a 3T scanner (Siemens Magnetom TrioTim 3T Erlangen, Germany) at the Portuguese Brain Imaging Network, with a 12 channel head coil. The MRI acquisition protocol for each participant was: (i) two 9-minute long T1-weighted (T1w) three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequences, repetition time (TR) 2.3 s, echo time (TE) 2.98 ms, flip angle (FA) 9°, field of view (FoV) 256 × 256 mm^2, yielding 160 slices with 1 × 1 × 1 mm^3 voxel size; (ii) four functional runs (three polar angle and one eccentricity stimuli) using single shot echo planar imaging (EPI) acquired in the axial plane orthogonal to the anterior commissure covering the occipital, temporal and frontal cortices, TR 2 s, TE 39 ms with a 128 × 128 imaging matrix, interslice time 76 ms, FA 90°, FOV 256 × 256 mm^2, yielding 26 slices with 2 × 2 × 2 mm^3 voxel size.

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