



Brain structural changes in blindness: a systematic review and an anatomical likelihood estimation (ALE) meta-analysis

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ABSTRACT

In recent decades, numerous structural brain imaging studies investigated purported morphometric changes in early (EB) and late onset blindness (LB). The results of these studies have not yielded very consistent results, neither with respect to the type, nor to the anatomical locations of the brain morphometric alterations. To better characterize the effects of blindness on brain morphometry, we performed a systematic review and an Anatomical-Likelihood-Estimation (ALE) coordinate-based-meta-analysis of 65 eligible studies on brain structural changes in EB and LB, including 890 EB, 466 LB and 1257 sighted controls. Results revealed atrophic changes throughout the whole extent of the retino-geniculo-striate system in both EB and LB, whereas changes in areas beyond the occipital lobe occurred in EB only. We discuss the nature of some of the contradictory findings with respect to the used brain imaging methodologies and characteristics of the blind populations such as the onset, duration and cause of blindness. Future studies should aim for much larger sample sizes, eventually by merging data from different brain imaging centers using the same imaging sequences, opt for multimodal structural brain imaging, and go beyond a purely structural approach by combining functional with structural connectivity network analyses.

1. Introduction

According to the World Health Organization, 2.2 billion people suffer from some degree of visual impairment (WHO, 2022). While the vast majority of these cases only show mild to moderate deficits that are treatable or correctable, over 43 million individuals are living with blindness. It is expected that in coming decades, this number will substantially rise due to increased longevity which leads to an augmentation in age-related diseases like macular degeneration, glaucoma and diabetes (WHO, 2022; Steinmetz et al., 2021). Hence blindness, particularly late-onset blindness, poses a serious health issue.

Losing sight is considered one of the most incapacitating events that can befall a person. A recent survey showed that blindness is considered as the worst disorder, surpassing even illnesses such as Alzheimer's disease, cancer, AIDS/HIV and heart diseases (Scott et al., 2016). These results are not surprising because vision plays a crucial role in sensorimotor and cognitive development. For infants, vision is the first incentive to explore the surrounding world, thereby sustaining the

development of gross and fine motor skills (i. e. crawling, standing, walking and reaching for objects). Vision also contributes to the development of cognitive processes such as the awareness of space and the appreciation of others' emotions and points of view (Piaget and Part, 2003; Lovell, 1959; Acredolo, 1990, 1978). Moreover, vision influences the development and calibration of other senses such as audition (Klatzky et al., 1987; Klatzky, 1998; Lederman and Klatzky, 1987; Bahrick and Lickliter, 2002; Ruff, 1984; Granier-Deferre et al., 2004; Lecanuet et al., 1995; Chan and Kane-Martinelli, 1997), reviewed in (Bremner et al., 2012), and contributes significantly to many different cognitive processes (Pylyshyn, 1999; Pomian, 2007). For instance, vision helps to navigate and orient easily by allowing to detect multiple landmarks simultaneously (Cattaneo and Vecchi, 2008) and to circumvent obstacles (Welsh, 1981), while at the same time offering crucial information to maintain balance (Maheu et al., 2017; Gandemer et al., 2017).

A blind person faces a multitude of challenges that make him or her more heavily dependent on the remaining sensory modalities such as

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touch and audition to accomplish vision-dependent tasks like spatial navigation and reading (Harrar et al., 2018). The increased usage and long-term training of a sense (e. g. tactile) to accomplish a task in another domain (e. g. reading, vision) often translates into superior abilities in the new modality (reviewed in Kupers and Ptito, 2014). It is now widely accepted that compared to normally sighted individuals, persons who were born blind or who have been blind from an early age (early blind, EB) have superior tactile acuity (Sterr et al., 1998; Van Boven et al., 2000; Alary et al., 2009), are better in pitch and auditory frequency discrimination (Gougoux et al., 2004; Voss and Zatorre, 2012) and at locating sound in the periphery of the horizontal axis (Paré et al., 2021; Lessard et al., 1998; Simon et al., 2002; Röder et al., 1999). Furthermore, EB individuals are better in certain olfactory tasks and have increased pain and thermal sensitivity (Murphy and Cain, 1986; Rombaux et al., 2010; Slimani et al., 2013, 2016, 2014). This supra-normal performance is less evident in people who have lost their sight later in life (late onset blindness, LB). Indeed, contradictory results have been reported for LB, some studies showing improved performance, others showing no difference with sighted controls. These discrepancies may relate to methodological factors such as the onset and duration of blindness, or the amount of training (reviewed in Ptito et al., 2021a). For instance, some studies demonstrated equal performance of EB and LB in binaural horizontal sound localization (Paré et al., 2021; Fieger et al., 2006) and pitch discrimination (Voss et al., 2004), poorer monaural sound localization in LB (Voss et al., 2004), but superior performance in auditory spatial bisection in LB (Amadeo et al., 2019). This additional training of the other senses to compensate for the loss of vision is associated with a reorganisation of the brain through cross-modal plasticity (reviewed in Pascual-Leone et al., 2005). Considering that the visual system occupies about one third of the surface of the cortical mantle, it is reasonable to assume that it will be recruited to accommodate other sensory modalities (Kupers and Ptito, 2014). Indeed, many studies showed that following visual loss, the visual cortex is cross-modally recruited by audition, touch and smell. This process allows the remaining senses to take over functions originally mediated by vision (reviewed in Harrar et al. (2018); Kupers and Ptito (2014); Ptito et al. (2021a); Pascual-Leone et al. (2005); Chebat et al. (2018)).

While the emphasis has been mostly on neuroplastic changes in occipital brain areas (Harrar et al., 2018; Kupers and Ptito, 2014; Ptito et al., 2021a; Pascual-Leone et al., 2005; Cecchetti et al., 2016a; Proulx et al., 2014), other reports have described anatomical changes in other parts of the blind brain, including cortical and subcortical structures such as the lateral geniculate nucleus of the thalamus (the primary visual relay), the hippocampus and corpus callosum (Cecchetti et al., 2016b; Ptito et al., 2021b, 2008a; Chebat et al., 2007). The precise mapping of these anatomical changes in early blindness is of utmost importance since they are associated with changes in behavioral performance (reviewed in Kupers and Ptito, 2014); Ptito et al., 2021a). Indeed, several studies have demonstrated a positive correlation between brain structures and various cognitive abilities. For example, studies have shown correlations between hippocampal volume and spatial learning, both in blind (Chebat et al., 2007; Fortin et al., 2008) and sighted subjects (Maguire et al., 2006, 2000). Other studies have shown that a thicker corpus callosum in early blind individuals is associated with improved interhemispheric communication and greater tactile sensitivity (Ptito et al., 2021a; Cecchetti et al., 2016b). In addition, increased volume of the olfactory bulb was associated with better odor discrimination and identification in early blind subjects (Rombaux et al., 2010).

A better understanding of the anatomical changes is also crucial for the development of vision-restoration neuro-prostheses (reviewed in Ptito et al., 2021a); Niketghad and Pouratian (2019); Fernandez (2018); Merabet et al. (2005)). As mentioned earlier, the visual system is capable of extensive reorganization following loss of vision, which means that its function can be altered. However, not all neuroplastic changes are beneficial and some can even be maladaptive, limiting the degree of adaptation. For instance, studies in prelingually deaf children

have shown that increased metabolism of the auditory cortex, as measured by PET-FDG, correlates negatively with success of cochlear implant therapy, suggesting that the auditory cortex has become permanently involved in the processing of other (non-auditory) sensory or cognitive functions (Lee et al., 2001, 2007). Therefore, a better understanding of these changes and the modulation of neuroplasticity is essential for the success of any visual neuroprosthesis (for a detailed discussion, see refs Ptito et al., 2021a); Niketghad and Pouratian (2019); Fernandez (2018); Merabet et al. (2005)).

For these reasons, we conducted a systematic meta-analysis of neuroimaging studies with a focus on neurostructural changes in humans with early and late onset blindness. We see this review as a tool for researchers and experts to easily find information on structural changes caused by blindness.

2. Methods

2.1. Research strategy

We performed a systematic search on brain structural changes following complete visual deprivation. The search focused on human individuals suffering from complete loss of visual input, or total blindness, resulting from peripheral (eye or optic nerve) pathologies or damages, but with an intact central nervous system. In the literature, there is no consensus on how to categorize blind individuals into congenitally blind (CB), early blind (EB) and late blind (LB); different age or other criteria have been used to separate between these categories. Due to the lack of a generally accepted criterium to separate CB from EB, we have merged these in the same category. We have used 7 years of age of onset of blindness to distinguish between EB and LB (Piaget and Part, 2003; Bremner et al., 2012). We defined 'structural brain changes' as any anatomical change in grey matter (GM) or white matter (WM) volumes, cortical thickness (CT), cortical curvature and diffusion imaging metrics: fractional anisotropy (FA), medial diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). Only statistically significant results were included in the analysis.

2.2. Identifying relevant studies

Our search strategy, as well as the screening and selection of studies included in the review and meta-analysis, was based on the PRISMA guidelines (Liberati et al., 2009). Thereon, a comprehensive literature search of seven databases (Pubmed, Embase, MEDLINE, Psychinfo, Global Health, ERIC, Web of Science) was performed in November 2021 (see Table 1). The search terms were based on key words commonly used in structural neuroimaging and in blindness studies. Finally, we selected the most relevant articles and reviewed their reference list with the goal to identify additional studies, a method called *snowballing* (Jalali and Wohlin, 2012).

Table 1 Sources and search terms

Search	Databases	Keywords
Search 1: Human Individuals with Total Blindness	Pubmed, Embase, MEDLINE, Psychinfo, Global Health, ERIC, Web of Science	("Magnetic Resonance Imaging" OR "MRI" OR "Morphometry" OR "Cortical Thickness" OR "Cortex Volume" OR "Diffusion Tensor Imaging" OR "DTI" OR "Diffusion Weighted Imaging" OR "DWI" OR "Tractography" OR "Fractional Anisotropy" OR "FA" OR "Voxel Based Morphometry" OR "VBM" OR "White Matter" OR "Grey Matter") AND ("Blind" OR "Blindness" OR "Visual Impairment" OR "Vision Loss")

2.3. Study selection

Relevant sources were imported into End-Note v.9.3.3 (Clarivate Analytics, PA, USA), after which they were exported into Covidence, a screening software for reviews (Veritas Health Innovation, Melbourne, Australia), where all duplicates were removed automatically. A two-stage screening process – first: title and abstract screening, second: full-text screening – was performed by two independent reviewers (SP, MB) to identify the most pertinent articles based on the inclusion criteria (see Table 2). Any conflicting decisions in the screening process were resolved by one of the senior authors (RK or MP).

Studies describing blind populations with additional disabilities (e. g. cognitive impairment, dementia, autism spectrum disorder, cerebral palsy, etc.) or cerebral lesions were excluded because these might influence or cause additional/confounding structural brain changes. Studies that involved individuals with cortical/cerebral or unilateral (monocular) visual impairments were also excluded. Studies that did not include sighted controls were also excluded.

2.4. Data extraction

Extracted data for every paper included details regarding author names, publication year, journal title, participant characteristics, methodology used, region(s) of interest analysed and significant results for measures of volume, CT, surface, FA, MD, RD and/or AD. Additionally, stereotactic coordinates of statistically significant foci were also extracted but only for the papers included in the ALE meta-analysis (see Section 2.5).

2.5. Anatomical likelihood estimation meta-analysis

In order to identify brain areas with consistent structural changes across studies, we carried out an Anatomical Likelihood Estimation (ALE) meta-analysis (Turkeltaub et al., 2002). We chose the ALE method for our meta-analysis because it is a powerful statistical tool that is well-validated and widely-used. The ALE method is also simple to use and does not require that users have expert knowledge of the region being studied and the tasks performed, as is often the case when using other methods (e.g. Functional Volumes Modeling techniques). ALE therefore significantly improves the reproducibility and objectivity of the analysis (Eickhoff et al., 2012, 2009). The ALE method uses the stereotactic coordinates of the reported statistically significant clusters to calculate the probability of these foci to converge (Eickhoff et al., 2012, 2009). Practically, the ALE method identifies brain regions for which results of multiple imaging studies converge more than expected by chance. The approach models reported statistically significant foci as Gaussian probability distributions that consider spatial uncertainty of neuroimaging data. This approach allows to summarize results from individual experiments while accounting for coordinate precision. ALE scores are then computed across voxels based on these maps and within-experiment effects are accounted for using proposed methods. Consequently, only studies that included the stereotactic coordinates of their significant foci are included in this type of analysis. In studies

where the authors reported results for groups other than completely blind or sighted individuals (i. e. low vision individuals), only significant foci for completely blind and sighted individuals were included. All coordinates of the reported foci are provided in MNI (Montreal Neurological Institute) space. Stereotactic coordinates originally reported in Talairach space were transformed in MNI space using the “icbm2tal” algorithm within SPM in GingerALE (Eickhoff et al., 2009; Lancaster et al., 2007). Measures of volume, CT and FA were analyzed separately; for each of these three measures, datasets for all possible contrasts were created: EB > SC; EB < SC; EB > LB; EB < LB; LB > SC; LB < SC. This resulted in 6 datasets per measure for a total of 18 datasets. As recommended (Lancaster et al., 2010), we applied to output images thresholds of $p < 0,01$ (cluster forming threshold) and 0,05 for cluster-level family-wise-error (FWE) with 1000 thresholding permutations. The ALE method created three NIfTI format images: an unthresholded ALE score, an unthresholded p value and a thresholded ALE score. The thresholded ALE score was used to display the results on the Colin27_T1_seg_MNI.nii anatomical template using Mango (Lancaster et al., 2010).

2.6. Organization of the results section

We structured the results from the literature analysis into eight sections: 1- Global measures; 2- Occipital lobe; 3- Temporal lobe; 4- Parietal lobe; 5- Frontal lobe; 6- Cingulate gyrus and mesial wall; 7- Subcortical areas, and 8- Long-range white matter pathways. In each of these sections, we first discuss the results for EB, then for LB and finally for the contrast between EB and LB. This was done so that the reader can easily find the information on specific brain areas for a specific population. Furthermore, results are reported using the same terminology as in the original study. Therefore, the results for the same brain region are sometimes reported using a different anatomical name (e. g. V1, calcarine, cuneus, etc.). The size of the structural alteration was reported (in percentage) if it was available in the original article. If not, we simply described the direction of the alteration (reduction or increase).

3. Results

3.1. Demographics and global overview

For this review, 5836 studies were imported of which 1696 studies were removed since they were duplicates. Out of the 4140 remaining studies screened, 3861 revealed to be irrelevant, leaving a total of 279 research articles. Of these, another 214 studies were excluded because they did not report structural results ($n = 131$), did not include completely blind subjects or lacked a sighted control group ($n = 81$), or were written in another language than English ($n = 1$). Therefore, 65 studies were included in this review (see PRISMA chart in Fig. 1A); of these, 37 included only EB participants, 6 included only LB participants and 22 included both groups. The average number of EB participants per study was 18 ± 11 , for LB 17 ± 12 and for SC 23 ± 15 (see Fig. 1B for a full distribution of the number of participants by study). Overall, there were 890 EB (325 women; age range: 6 months - 70 years; range of onset of blindness 0 – 6 years), 466 LB (186 women; age range: 6–78 years; age range of onset of blindness: 7–34 years) and 1257 SC (500 women; age range: 2–74 years). Four studies provided no information regarding the sex of the subjects (Rombaux et al., 2010; Noppeney et al., 2005; Lee et al., 2014a; Stevens, 2005), whereas two studies mentioned the sex only for their blind participants (Chebat et al., 2007; Andelin et al., 2019). It is worth noting that five studies had a mixed blind group of EB and LB (Lee et al., 2014a; Aguirre et al., 2016; Maller et al., 2016; Zhang et al., 2012; Wan et al., 2013). Therefore, their results were added to both the EB and LB sections. As for the brain imaging techniques applied, 18 used surface-based-morphometry (SBM), 12 Voxel-Based-Morphometry (VBM), and 22 Diffusion Tensor Imaging (DTI) or Diffusion Weighted Imaging (DWI). A manual segmentation (MS) approach was used in 14 studies and the 12 remaining studies used

Table 2
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion Criteria
• Must include participants with binocular blindness • Must include structural results (MRI, DTI, PET)	• Visual deprivation is unilateral or of cerebral origin (i. e. cerebral visual impairment, cortical blindness) • Participants are not totally blind (i. e. legal blindness or functional blindness) • Does not include a group of sighted controls • Presence of concomitant disabilities or conditions affecting the central nervous system functioning or anatomy

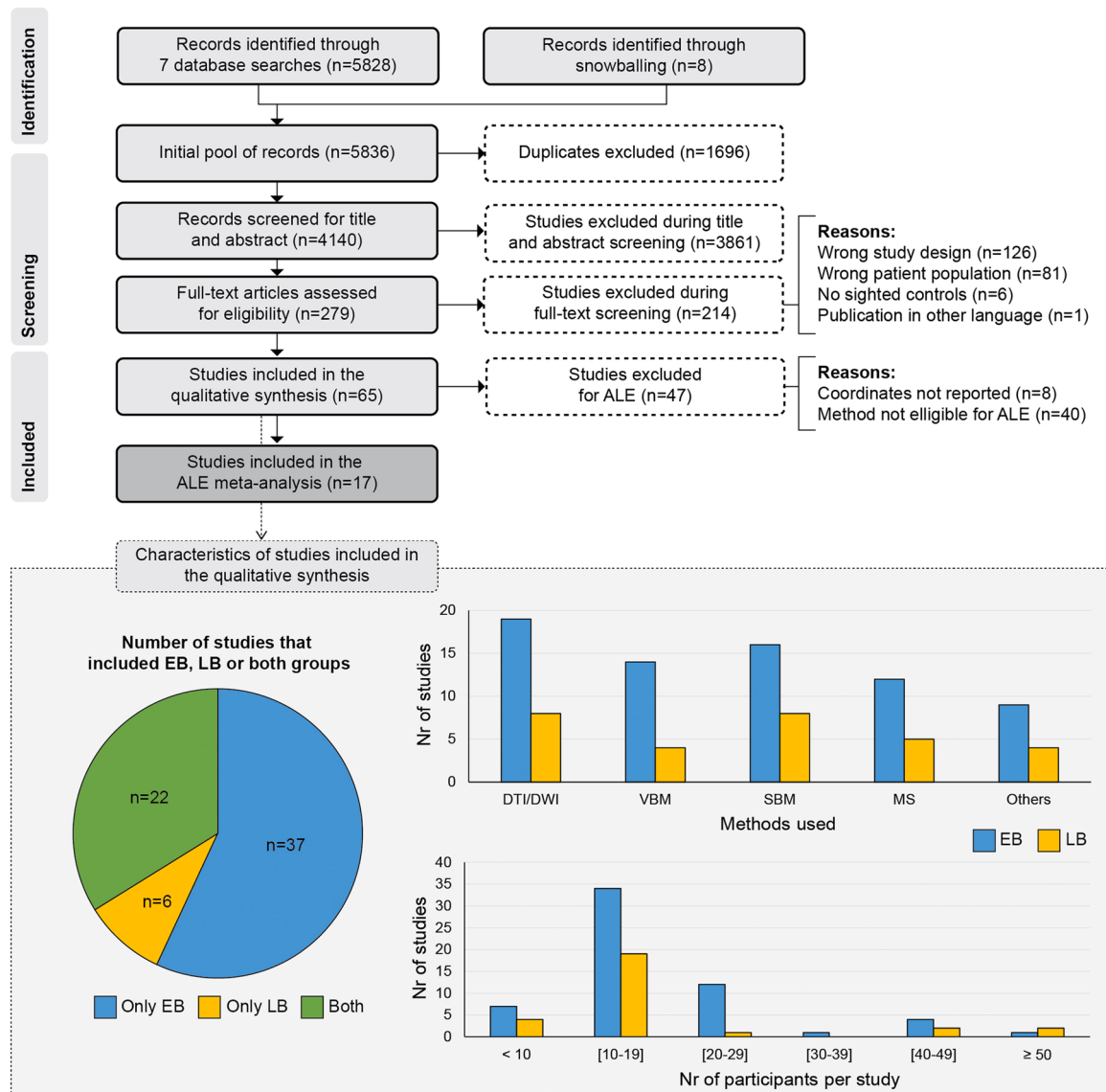


Fig. 1. Demographics and global overview of the systematic review. The top part of the figure displays the PRISMA chart of the literature review. Below, a pie chart of the number of articles that included EB, LB or both groups; a bar graph of the number of studies that used every neuroimaging technique and a second bar graph displaying the number of participants included per study. The category ‘Others’ in the technique bar graph includes in-house software, high angular resolution diffusion imaging (HARDI), proton magnetic resonance spectroscopy, tensor-based morphometry and positron emission tomography. Abbreviations: DTI: diffusion-tensor imaging; DWI: diffusion weighted imaging; MS: manual segmentation; SBM: surface-based morphometry, VBM: voxel-based morphometry.

various other methodologies (described in Fig. 1). In total, 33 studies used a whole brain voxel-by-voxel approach, 35 studies applied a region-of-interest (ROI) approach, and 10 studies combined a whole brain and ROI analysis (see Table 3).

The number of participants included per study varied from 4 to 52. After applying the criteria for inclusion in the ALE analysis, described in Section 2.5, 17 out of the 65 studies from our systematic review were judged eligible. The characteristics of the included studies are displayed in Fig. 1B and C.

3.2. Structural changes in human blindness

3.2.1. Global measures

Regarding global measures, significant volumetric and surface reductions were found for both EB and LB, whereas, reduced overall CT was reported only in LB. The detailed results of GM and WM global changes are described below and are summarized in Table 4.

EB. Five studies reported significant whole brain differences in early

blind individuals. These studies reported overall GM volume (Ptito et al., 2008a; Park et al., 2009), WM volume (Ptito et al., 2008a; Wan et al., 2013) and surface reduction (Park et al., 2009; Jiang et al., 2009; Atilgan et al., 2017). Wan et al. (2013) reported superior volume of the cerebellum (Wan et al., 2013), whereas Modi and colleagues (2012) reported reduced cerebellar volume (Modi et al., 2012). No significant overall change in cortical thickness was reported in any study.

LB. The alterations in LB are comparable to those in EB. Overall GM volume was reduced by about 7% (Park et al., 2009), WM volume was decreased (Wan et al., 2013), as well as surface area (Park et al., 2009; Jiang et al., 2009). In addition, one study reported an overall 4% reduction in CT (Atilgan et al., 2017). Leporé et al. (2010) reported a larger cerebellar volume in LB (Leporé et al., 2010), whereas Jonak and colleagues (2020) reported increases in the volume of the lateral (35%), third (19%) and fourth (32%) ventricles (Jonak et al., 2020).

EB vs LB. No differences in global measures between EB and LB were reported.

Table 3
Brain imaging techniques used in studies included in the systematic review.

	References		
	Whole brain approach	ROI approach	Both
VBM	(Bridge et al., 2009; Jiang et al., 2009; Leporé et al., 2010; Manara et al., 2015; Noppeney et al., 2005; Pan et al., 2007; Ptito et al., 2008a; Voss et al., 2014; Wan et al., 2013; Wang et al., 2013)	(Chebat et al., 2020b)	(Ankeeta et al., 2021)
SBM	(Bauer et al., 2017; Hasson et al., 2016; Inuggi et al., 2020; Jiang et al., 2009; Jonak et al., 2020; Leporé et al., 2010; Maller et al., 2016; Park et al., 2009)	(Bauer et al., 2018; Cecchetti et al., 2016b; Grochowski et al., 2021; Huttenlocher, 1984; Qin et al., 2013)	(Aguirre et al., 2016; Andelin et al., 2019; Anurova et al., 2015; Atilgan et al., 2017; Li et al., 2017)
DTI/ DWI	(Bridge et al., 2009; Dietrich et al., 2015; Lao et al., 2015; Lee et al., 2014b; Manara et al., 2015; Park et al., 2007; Reislev et al., 2016a; Shu et al., 2009b; Wang et al., 2013; Zhou et al., 2019)	(Bridge et al., 2009; Cavaliere et al., 2020; Hofstetter et al., 2019; Johnson and De Haan, 2015; Reislev et al., 2016b; Yu et al., 2007; Zhang et al., 2012)	(Aguirre et al., 2016; Anurova et al., 2019; Reislev et al., 2017; Shimony et al., 2006)
MS		(Cavaliere et al., 2020; Chebat et al., 2007; Fortin et al., 2008; Grochowski et al., 2021; Hofstetter et al., 2019; Johnson and De Haan, 2015; Leporé et al., 2010; Ptito et al., 2021b; Qin et al., 2013; Reislev et al., 2016a, 2017; Rombaux et al., 2010; Shimony et al., 2006; Voss et al., 2013)	
Others	(Lee et al., 2014a; Voss and Zatorre, 2012, 2015; Yang et al., 2014)	(Bauer et al., 2018; Huttenlocher, 1984; Inuggi et al., 2020; Leporé et al., 2010; Ptito et al., 2021b; Qin et al., 2013; Shu et al., 2009a; Voss and Zatorre, 2015)	

The category ‘Others’ includes in-house software, high angular resolution diffusion imaging (HARDI), proton magnetic resonance spectroscopy, tensor-based morphometry and positron emission tomography. Abbreviations: DTI: diffusion-tensor imaging; DWI: diffusion weighted imaging; MS: manual segmentation; SBM: surface-based morphometry, VBM: voxel-based morphometry.

3.2.2. Occipital lobe

A reduced volume in GM, WM and surface area within the occipital lobe was described in EB and LB. For cortical thickness, the results between EB and LB diverged with an increase in EB and a decrease in LB. The detailed results of GM and WM changes in the occipital lobe can be found below and are summarized in Table 5.

3.2.2.1. Changes in GM. EB. Reports of GM differences within the occipital lobe were amongst the most consistent. A total of 19 studies investigated GM volume changes of the occipital lobe in EB. These studies reported a bilateral volume reduction of the primary visual cortex (V1) (Aguirre et al., 2016: 70% reduction; Bauer et al., 2017; Bridge et al., 2009; Jiang et al., 2015; Leporé et al., 2010; Maller et al.,

Table 4
Alterations in global measures.

	Groups		
	EB	LB	EB vs LB
Total GM volume	(– Park et al., 2009; Ptito et al., 2008a)	(– Park et al., 2009)	
Total WM volume	(– Ptito et al., 2008a; Wan et al., 2013)	(– Wan et al., 2013)	
Overall cortical thickness		(– Atilgan et al., 2017)	
Total surface area	(– Atilgan et al., 2017; Jiang et al., 2009; Park et al., 2009)	(– Jiang et al., 2009; Park et al., 2009)	
Cerebellar volume	(+ Aguirre et al., 2016; – Modi et al., 2012)	(+ Leporé et al., 2010)	
Ventricles		(+ Jonak et al., 2020)	

Significant decreases are shown with a minus sign “–”, significant increases with a plus sign “+”.

2016; Noppeney et al., 2005; Ptito et al., 2008a), secondary visual cortex (V2) (Bridge et al., 2009), lingual gyrus (Jiang et al., 2015; Pan et al., 2007), superior occipital gyrus (Maller et al., 2016; Jiang et al., 2015), cuneus (Wan et al., 2013; Jiang et al., 2015; Pan et al., 2007) and visual association cortex (Ptito et al., 2008a; Leporé et al., 2010). However, five studies found a volume reduction only in the left hemisphere for V1 (Yang et al., 2014), the cuneus (Voss et al., 2014), the visual association cortex (Yang et al., 2014) and the middle occipital gyrus (Wan et al., 2013; Modi et al., 2012; Voss et al., 2014). In contrast, Voss et al. (2014) reported a GM volume increase in the right cuneus and lingual gyrus, but a diminution in the left cuneus (Voss et al., 2014). Concerning CT, 11 out of 14 studies reported an increase in at least one occipital lobe area. No study mentioned a reduction in CT. Occipital areas with increases in CT concern V1 (Aguirre et al., 2016; Jiang et al., 2009; Bridge et al., 2009; Anurova et al., 2015; Inuggi et al., 2020; Li et al., 2017; Qin et al., 2013), V2 (Jiang et al., 2009; Qin et al., 2013), lingual gyrus (Voss and Zatorre, 2012; Park et al., 2009; Anurova et al., 2015; Hasson et al., 2016), inferior occipital gyrus (Anurova et al., 2015; Voss and Zatorre, 2015), cuneus (Anurova et al., 2015), visual association cortex (Jiang et al., 2009; Qin et al., 2013) and lateral occipital cortex (Park et al., 2009; Voss and Zatorre, 2012: only in right hemisphere). Out of six studies examining cortical surface area, four reported significant reductions in V1 by about 16–21% (Andelin et al., 2019; Aguirre et al., 2016; Park et al., 2009). Cortical surface area reductions were also reported for the lingual gyrus (Maller et al., 2016; Park et al., 2009), inferior occipital gyrus and sulcus (Maller et al., 2016), superior occipital gyrus and sulcus (Maller et al., 2016), and lateral occipital cortex (Maller et al., 2016). At odds with these studies, Park et al. (2009) reported a larger surface area of the cuneus in EB (Park et al., 2009).

LB. Out of 13 studies investigating GM volume in the occipital lobe in LB, eight reported significant volume reductions, either in V1 (Aguirre et al., 2016: 16% reduction; Jiang et al., 2015; Leporé et al., 2010; Maller et al., 2016; Manara et al., 2015), cuneus (Wan et al., 2013; Jiang et al., 2015; Voss et al., 2014), lingual gyrus (Lee et al., 2014a; Jiang et al., 2015), superior occipital gyrus (Jiang et al., 2015), middle occipital gyrus (Jiang et al., 2015), left superior occipital and right inferior occipital gyri (Voss et al., 2014). Of the seven studies investigating CT modifications, only two found significant differences. Whereas Aguirre and colleagues (Aguirre et al., 2016) reported a 6% increase in CT in V1, Voss & Zatorre (Voss and Zatorre, 2012) found reduced CT in the cuneus, lingual gyrus, left inferior occipital gyrus and left middle occipital gyrus. Out of five studies examining cortical surface area, two mentioned surface reductions in V1 (Aguirre et al., 2016: 16% reduction; Park et al., 2009), mostly around the pericalcarine sulcus (Park et al., 2009), whereas one reported reduced cortical surface in the right lingual gyrus, superior occipital gyrus, lateral occipital gyrus, inferior

Table 5
Studies demonstrating alterations in cortical areas.

Brain structure	Grey Matter			White matter			
	CT	Surface	Volume	Volume	FA	MD	RD
<i>Occipital lobe</i>							
Cuneus	EB: (+ Anurova et al., 2015) LB: (– Voss and Zatorre, 2012) EB vs LB: (+ Park et al., 2009; Voss and Zatorre, 2012)	EB: (+ Park et al., 2009)	EB: (– Jiang et al., 2015; Pan et al., 2007; Voss et al., 2014; +/- Wan et al., 2013) LB: (– Atilgan et al., 2017; Li et al., 2017; Voss et al., 2014) EB vs LB: (+ Li et al., 2017)	EB: (– Voss et al., 2014; Wan et al., 2010) LB: (– Voss and Zatorre, 2012) EB vs LB: (– Shu et al., 2009a)	EB: (– Shu et al., 2009a)		
V1	EB: (+ Aguirre et al., 2016; Anurova et al., 2015; Bridge et al., 2009; Inuggi et al., 2020; Jiang et al., 2009; Li et al., 2017; Qin et al., 2013) LB: (+ Aguirre et al., 2016) EB vs LB: (+ Jiang et al., 2009; Li et al., 2017; Park et al., 2009)	EB: (– Andelin et al., 2019; Park et al., 2009) LB: (– Aguirre et al., 2016; Park et al., 2009)	EB: (– Aguirre et al., 2016; Bauer et al., 2017; Jiang et al., 2015; Leporé et al., 2010; Maller et al., 2016; Noppeney et al., 2005; Ptito et al., 2008a; Yang et al., 2014) LB: (– Aguirre et al., 2016; Jiang et al., 2015; Leporé et al., 2010; Maller et al., 2016; Manara et al., 2015) EB vs LB: (+ Shimony et al., 2006)	EB: (– Modi et al., 2012; Shimony et al., 2006)	EB: (– Park et al., 2007; Shimony et al., 2006)		
V2	EB: (+ Jiang et al., 2009; Qin et al., 2013)		EB: (– Bridge et al., 2009)	EB: (– Shimony et al., 2006)	EB: (– Shimony et al., 2006)		
Lingual gyrus	EB: (+ Anurova et al., 2015; Hasson et al., 2016; Park et al., 2009; Voss and Zatorre, 2012) LB: (– Voss and Zatorre, 2012) EB vs LB: (+ Park et al., 2009; Voss and Zatorre, 2012)	EB: (– Maller et al., 2016; Park et al., 2009) LB: (– Maller et al., 2016)	EB: (– Jiang et al., 2015; Pan et al., 2007; + Voss et al., 2014) LB: (– Jiang et al., 2015; Lee et al., 2014a)	EB: (– Maller et al., 2016; Voss et al., 2014; Wan et al., 2013) LB: (– Maller et al., 2016; Voss et al., 2014; Wan et al., 2013)	EB: (– Lee et al., 2014a; Shu et al., 2009a)	EB: (+ Zhou et al., 2019)	EB: (+ Zhou et al., 2019)
Visual association cortex	EB: (+ Jiang et al., 2009; Qin et al., 2013) EB vs LB: (+ Jiang et al., 2009)		EB: (– Leporé et al., 2010; Ptito et al., 2008a; Yang et al., 2014) EB vs LB: (+ Jiang et al., 2015)				
Lateral occipital cortex	EB: (+ Park et al., 2009; Voss and Zatorre, 2012) EB vs LB: (+ Park et al., 2009; Voss and Zatorre, 2012)	EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)		EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)			
Inferior occipital gyrus	EB: (+ Anurova et al., 2015; Voss and Zatorre, 2015) LB: (– Voss and Zatorre, 2012)	EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)	LB: (– Voss et al., 2014) EB vs LB: (+ Shimony et al., 2006; Voss et al., 2014)				
Inferior occipital sulcus		EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)					
Middle occipital gyrus	LB: (– Voss and Zatorre, 2012)		EB: (– Modi et al., 2012; Voss et al., 2014; Wan et al., 2013) LB: (– Jiang et al., 2015)		EB: (– Shu et al., 2009a)		
Superior occipital gyrus		EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)	EB: (– Jiang et al., 2015; Maller et al., 2016) LB: (– Jiang et al., 2015; Voss et al., 2014)	LB: (– Maller et al., 2016; Voss et al., 2014)	EB: (– Zhou et al., 2019)		
Superior occipital sulcus		EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)					
<i>Temporal lobe</i>							
Entire temporal lobe	EB: (– Jiang et al., 2009)						
Sub-gyral of temporal lobe					EB: (– Shu et al., 2009a)		
Inferior temporal cortex	EB: (+ Inuggi et al., 2020; – Park et al., 2009)		EB: (– Ptito et al., 2008a)		EB: (– Reisleve et al., 2016a)		

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Table 5 (continued)

Brain structure	Grey Matter			White matter			
	CT	Surface	Volume	Volume	FA	MD	RD
	LB: (– Voss and Zatorre, 2012) EB vs LB: (– Park et al., 2009)						
Middle temporal Gyrus			EB: (– Ankeeta et al., 2021; + Bridge et al., 2009; – Ptito et al., 2008a; Wan et al., 2013) LB: (– Ankeeta et al., 2021) EB vs LB: (+ Ankeeta et al., 2021)	EB: (+ Modi et al., 2012)			
Superior temporal gyrus	EB: (– Park et al., 2009)		EB: (– Ankeeta et al., 2021) LB: (– Ankeeta et al., 2021; Wan et al., 2013) EB vs LB: (+ Ankeeta et al., 2021)				
Superior temporal sulcus		EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)	EB: (– Maller et al., 2016)				
Lateral tansverse temporal gyrus		EB: (– Atilgan et al., 2017)		EB: (+ Modi et al., 2012)			
Fusiform gyrus	EB: (– Bauer et al., 2017; + Voss and Zatorre, 2015) LB: (– Jiang et al., 2009)		EB: (– Jiang et al., 2015; + Voss et al., 2014) LB: (– Jiang et al., 2015; Manara et al., 2015) EB vs LB: (+ Voss et al., 2014)	LB: (– Voss et al., 2014)			
Planum polare	EB vs LB: (– Jiang et al., 2009; + Voss and Zatorre, 2012) EB: (– Hasson et al., 2016)	EB: (– Atilgan et al., 2017)					
Entorhinal cortex	EB: (– Jiang et al., 2009; Voss and Zatorre, 2012) LB: (– Jiang et al., 2009)		EB: (– Chebat et al., 2007; Jiang et al., 2009)	EB: (– Voss et al., 2013)			
Parahippocampal gyrus			EB: (– Ankeeta et al., 2021; Wan et al., 2013) LB: (– Ankeeta et al., 2021; Wan et al., 2013)		EB: (– Zhou et al., 2019)		EB: (– Zhou et al., 2019)
Temporal pole	EB: (+ Inuggi et al., 2020; – Park et al., 2009)						
Anterior temporal lobe	EB: (– Li et al., 2017)			EB: (– Pan et al., 2007)			
<i>Parietal lobe</i>							
Primary sensory cortex			EB: (+ Chebat et al., 2020a)				
Central sulcus	EB: (– Voss and Zatorre, 2015)						
Postcentral gyrus	EB: (+ Anurova et al., 2015; – Hasson et al., 2016; + Inuggi et al., 2020; – Park et al., 2009; Voss and Zatorre, 2015) LB: (– Voss and Zatorre, 2012) EB vs LB: (– Park et al., 2009)	EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)	EB: (+ Jiang et al., 2015) EB vs LB: (+ Jiang et al., 2015)	EB: (– Maller et al., 2016)			
Postcentral sulcus	EB: (+ Anurova et al., 2015)			LB: (– Maller et al., 2016)			
Paracentral gyrus	EB: (+ Maller et al., 2016)	EB: (+ Maller et al., 2016)	EB: (+ Jiang et al., 2015; Maller et al., 2016)	LB: (+ Maller et al., 2016)			
Paracentral sulcus	LB: (+ Maller et al., 2016) LB: (+ Maller et al., 2016)	LB: (+ Maller et al., 2016)	LB: (– Jiang et al., 2015)	LB: (+ Maller et al., 2016)			
Anterior parietal cortex	EB: (– Li et al., 2017)						
Superior parietal cortex	EB: (+ Inuggi et al., 2020; – Voss and Zatorre, 2012) LB: (– Voss and Zatorre, 2012)	EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)	EB: (– Wan et al., 2013) LB: (– Wan et al., 2013)	EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)			
Intraparietal sulcus			EB: (+ Bridge et al., 2009; – Jiang et al., 2015) LB: (– Qin et al., 2013)				

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Table 5 (continued)

Brain structure	Grey Matter			White matter			
	CT	Surface	Volume	Volume	FA	MD	RD
Inferior parietal cortex	EB: (– Voss and Zatorre, 2015)		EB: (+ Bauer et al., 2017; – Modi et al., 2012)				
Subparietal sulcus	EB: (+ Hasson et al., 2016; – Wan et al., 2013)						
Brodmann area 7			EB: (– Leporé et al., 2010) LB: (– Leporé et al., 2010) LB: (– Leporé et al., 2010)				
Brodmann area 40							
Supramarginal cortex	EB: (– Park et al., 2009) LB: (– Voss and Zatorre, 2012)						
<i>Frontal lobe</i>							
Precentral sulcus			EB: (+ Bridge et al., 2009)				
Precentral gyrus	EB: (– Voss and Zatorre, 2015)		EB: (+ Jiang et al., 2015) LB: (– Jiang et al., 2015) EB: (– Leporé et al., 2010) EB: (+ Chebat et al., 2020a)				
Brodmann area 6							
Primary motor cortex							
Inferior frontal gyrus	LB: (– Voss and Zatorre, 2012)		EB: (– Ankeeta et al., 2021; + Bridge et al., 2009; – Wan et al., 2013) LB: (– Ankeeta et al., 2021; Wan et al., 2013) EB vs LB: (+ Ankeeta et al., 2021)				
Middle frontal gyrus	EB: (+ Anurova et al., 2015) LB: (– Voss and Zatorre, 2012)		EB: (+ Modi et al., 2012; – Wan et al., 2013) LB: (– Wan et al., 2013)				
Superior frontal sulcus	EB: (+ Anurova et al., 2015)		EB: (+ Bridge et al., 2009)				
Superior frontal gyrus	EB: (+ Anurova et al., 2015; – Voss and Zatorre, 2015) LB: (– Voss and Zatorre, 2012)		EB: (+ Jiang et al., 2015; – Ptito et al., 2008a) EB vs LB: (+ Jiang et al., 2015)	EB: (+ Modi et al., 2012)			
Orbital sulcus	EB: (+ Hasson et al., 2016)						
Orbitofrontal cortex	EB: (+ Inuggi et al., 2020; Park et al., 2009)						
Lateral orbital cortex			EB: (– Ptito et al., 2008a)				
Medial prefrontal cortex			EB: (+ Jiang et al., 2015) LB: (– Jiang et al., 2015)				
Insula	LB: (– Voss and Zatorre, 2012)		EB: (– Ankeeta et al., 2021) LB: (– Ankeeta et al., 2021; Ptito et al., 2008a)				
<i>Cingulate gyrus and mesial wall</i>							
Cingulate gyrus	EB: (+ Inuggi et al., 2020)					EB: (– Lee et al., 2014a) LB: (– Lee et al., 2014a)	
Subgenual area			EB: (– Leporé et al., 2010)				
Anterior cingulate cortex	EB: (+ Anurova et al., 2015)		EB: (– Ankeeta et al., 2021; Leporé et al., 2010; Maller et al., 2016) LB: (– Ankeeta et al., 2021)	LB: (– Maller et al., 2016)			
Posterior cingulate cortex			EB: (– Leporé et al., 2010; Yang et al., 2014)	EB: (– Wan et al., 2013) LB: (– Wan et al., 2013)			
Retrosplenial cortex						EB: (– Park et al., 2007)	
Precuneus			EB: (+ Jiang et al., 2015) LB: (– Wan et al., 2013)	EB: (– Maller et al., 2016; Wan et al., 2013) LB: (– Maller et al., 2016; Wan et al., 2013)		LB: (– Reislev et al., 2016a)	
Isthmus cingulate		EB: (– Park et al., 2009)					

Significant decreases are indicated with a minus sign “–”, significant increases with a plus sign “+”. For the EB vs LB contrast, numbers with a “+” indicate an increase in EB, numbers with a minus sign “–” indicate a decrease in EB.

occipital gyrus and sulcus, and left superior occipital sulcus (Maller et al., 2016).

EB vs LB. Four studies reported higher GM volumes in occipital lobe of EB compared to LB, more specifically in V1 (Ankeeta et al., 2021), inferior occipital gyrus (Ankeeta et al., 2021; Voss et al., 2014: only in right hemisphere), visual association cortex (Jiang et al., 2015) and cuneus (Voss et al., 2014). All five studies that investigated CT reported increased thickness in EB, either in V1 (Jiang et al., 2009; Li et al., 2017), around the pericalcarine sulcus (Park et al., 2009), left visual association cortex (Jiang et al., 2009), lingual gyrus (Voss and Zatorre, 2012; Park et al., 2009), cuneus (Park et al., 2009: right cuneus; Voss and Zatorre, 2012: left cuneus) or lateral occipital cortex (Park et al., 2009; Voss and Zatorre, 2012: left hemisphere). The only study that compared occipital lobe cortical surface area in EB and LB failed to find a significant difference (Jiang et al., 2009).

3.2.2.2. Changes in WM. **EB.** Whereas 19 studies investigated the effect of early blindness on occipital lobe GM volume, only ten tested for WM volume changes. Of these, two studies found a significant WM volume reduction in V1 (Modi et al., 2012; Shimony et al., 2006), one in V2 (Shimony et al., 2006), three in lingual gyrus (Maller et al., 2016; Wan et al., 2013; Voss et al., 2014), one in the cuneus (Wan et al., 2010), one in right cuneus only (Hasson et al., 2016), and one in lateral occipital cortex (Maller et al., 2016). Only five out of 14 diffusion imaging studies found significant alterations in occipital lobe WM. Areas with reduced FA were found in V1 (Shimony et al., 2006; Park et al., 2007), V2 (Shimony et al., 2006), lingual gyrus (Lee et al., 2014a; Shu et al., 2009a), cuneus (Shu et al., 2009a), right superior occipital gyrus (Zhou et al., 2019) and middle occipital gyrus (Shu et al., 2009a). Additionally, one paper found a significant increase in MD and RD in lingual gyrus (Zhou et al., 2019).

LB. Of the four studies examining occipital lobe WM volume, one described reductions in cuneus (Voss and Zatorre, 2012), one in lateral occipital and superior occipital gyri (Maller et al., 2016), and two in lingual gyrus (Maller et al., 2016; Wan et al., 2013). Out of eight diffusion imaging studies, only Voss et al., 2014 reported WM reductions in right lingual and right superior occipital gyri (Voss et al., 2014).

EB vs LB. The only study directly comparing the two blind groups reported lower WM volume in the cuneus for EB (Shu et al., 2009a).

3.2.3. Temporal lobe

The results for the temporal lobe also vary considerably. Several studies mentioned both decreases and increases in GM volume, CT and WM volume in EB, but at different anatomical locations. In LB, only reductions in GM and WM volume and in CT were reported. Detailed results of temporal lobe changes are described below and in Table 4.

3.2.3.1. Changes in GM. **EB.** Out of 19 studies, three reported a significant bilateral decrease in GM volume of the middle temporal gyrus (Ptito et al., 2008a; Wan et al., 2013; Ankeeta et al., 2021). For the fusiform gyrus, Voss et al., 2014 reported a larger GM volume in EB (Voss et al., 2014), whereas Ankeeta et al., 2021 reported a reduced volume in this area (Jiang et al., 2015). One study reported a GM reduction in superior temporal gyrus (Ankeeta et al., 2021) and sulcus (Maller et al., 2016), one in the right inferior temporal cortex (Ptito et al., 2008a). Two studies reported GM reductions in entorhinal cortex (Chebat et al., 2007; Jiang et al., 2009) and parahippocampal gyrus (Wan et al., 2013; Ankeeta et al., 2021). Concerning cortical thickness, eight out of 12 studies reported alterations, including reduced CT in right superior temporal gyrus (Park et al., 2009), right planum polare (Hasson et al., 2016), anterior temporal lobe (Li et al., 2017) and left entorhinal cortex (Voss and Zatorre, 2012; Jiang et al., 2009). Jiang et al., 2009 even reported reduced CT for the entire temporal lobe (Jiang et al., 2009). Mixed results were reported for other temporal lobe areas. For instance, for the fusiform gyrus, both increased (Voss and Zatorre,

2015) and decreased CT (Bauer et al., 2017) was reported. The same inconsistencies were found for the temporal pole and inferior temporal cortex. Inuggi and colleagues reported increased CT of the right temporal pole, (Inuggi et al., 2020) whereas Park et al., 2009 reported decreased CT of the left temporal pole (Park et al., 2009). For the right inferior temporal cortex, both reduced (Park et al., 2009) and increased (Inuggi et al., 2020) CT were reported. Of the seven studies that investigated cortical surface area, one found a significant reduction in the lateral transverse temporal gyrus and planum polare (Atilgan et al., 2017), and one in the left superior temporal sulcus (Maller et al., 2016).

LB. Out of 14 studies, only four mentioned significant results, including GM volume reductions in the middle temporal and superior temporal gyri (Ankeeta et al., 2021), left superior temporal gyrus (Wan et al., 2013) and fusiform gyrus (Jiang et al., 2015; Manara et al., 2015). Two studies reported GM volume reductions in the parahippocampal gyrus, either bilaterally (Ankeeta et al., 2021) or in the right hemisphere only (Wan et al., 2013). Of the eight studies examining cortical thickness, one reported reduced CT in a large area covering the entire left temporal lobe, but most pronounced in the left fusiform gyrus and entorhinal cortex (Jiang et al., 2009) while another reported a reduction of CT in the right inferior temporal gyrus (Voss and Zatorre, 2012). Of the six studies investigating cortical surface, only one reported reduced cortical surface in left superior temporal sulcus (Maller et al., 2016).

EB vs LB. Six studies directly compared GM volume in EB and LB. Ankeeta et al., 2021 reported higher GM volume in the middle and superior temporal gyri in EB (Ankeeta et al., 2021), whereas Voss et al., 2014 reported higher GM volume in the right fusiform gyrus (Voss et al., 2014). Of the five studies comparing CT, one reported increased CT in left fusiform gyrus (Voss and Zatorre, 2012) whereas another reported a decreased (Jiang et al., 2009). One also showed decreased CT in right inferior temporal gyrus of EB (Park et al., 2009).

3.2.3.2. Changes in WM. **EB.** Of the eight studies, five reported WM volume modifications, including increased WM volume in the middle temporal and right lateral transverse temporal gyri (Modi et al., 2012), and WM volume reductions in the left entorhinal cortex (Voss et al., 2013) and in the anterior temporal lobe (Pan et al., 2007). Three out of ten diffusion imaging studies revealed reduced FA values, either in the inferior temporal cortex (Reislev et al., 2016a), right parahippocampal gyrus (Zhou et al., 2019), or sub-gyral (Shu et al., 2009a). Finally, one study reported higher RD values in the right parahippocampal gyrus (Zhou et al., 2019).

LB. Out of a total of 10 studies (four on WM volume and six on diffusion imaging), one reported WM volume reduction in the left fusiform gyrus (Voss et al., 2014), while another reported reduced FA in fusiform gyrus, bilaterally (Reislev et al., 2016a).

EB vs LB. No studies investigated WM differences between EB and LB in temporal lobe.

3.2.4. Parietal lobe

The results for GM and WM changes in the parietal lobe of EB are very disparate. For LB, however, GM and WM volumes were reduced, whereas CT and surface were increased. The detailed results of GM and WM changes in the parietal lobe are described below and in Table 4.

3.2.4.1. Changes in GM. **EB.** Out of 19 studies, one reported increased GM volumes in postcentral gyrus (Jiang et al., 2015), two in paracentral gyrus (Maller et al., 2016; Jiang et al., 2015) and one in primary sensory cortex (Chebat et al., 2020a). In contrast, one study mentioned reduced GM volumes in superior parietal cortex (Wan et al., 2013) and one in Brodmann area 7 (Lepore et al., 2010). Bauer et al., 2017 reported increased GM volume in right inferior parietal cortex (Bauer et al., 2017), whereas Modi et al., 2012 mentioned reduced GM volume in the left inferior parietal cortex (Modi et al., 2012). The results for the intraparietal sulcus are also inconsistent, with Bridge et al., 2015

reporting a bilaterally increased GM (Bridge et al., 2009), while Jiang et al. (2009) reported a GM decrease in the right hemisphere (Jiang et al., 2015). A total of 11 studies investigated CT, but also with inconsistent results. For instance, for the superior parietal cortex, Inuggi et al., 2020 reported a significant increase in CT (Inuggi et al., 2020), while Voss et al., 2012 reported reduced CT (Voss and Zatorre, 2012). The same inconsistency is found for the postcentral gyrus, with two studies reporting increased (Anurova et al., 2015; Inuggi et al., 2020) and one reduced CT (Hasson et al., 2016) in the right postcentral gyrus, one reporting reduced CT in the left postcentral gyrus (Park et al., 2009), and one a bilateral decrease in CT (Voss and Zatorre, 2015). Moreover, Hasson et al., 2016 reported increased CT in the right subparietal sulcus (Hasson et al., 2016), whereas Wan et al., 2013 reported reduced CT in this area, bilaterally (Wan et al., 2013). Changes in other areas were reported by only one study. For instance, one study reported reduced CT in the central sulcus (Hasson et al., 2016), one in the inferior parietal cortex (Voss and Zatorre, 2015), one in the anterior parietal cortex (Li et al., 2017) and one in the right supramarginal cortex (Park et al., 2009). One study reported increased CT in the right postcentral sulcus (Anurova et al., 2015) and another one in the right paracentral gyrus (Maller et al., 2016). Of the six studies that analysed changes in cortical surface, one study reported smaller surface area of the right superior parietal cortex and the left postcentral gyrus in EB, with increased surface area of the right paracentral gyrus (Maller et al., 2016).

LB. Five out of 12 studies reported significant GM volumetric changes, including GM volume reductions in the intraparietal area (Andelin et al., 2019), Brodmann areas 7 and 40 (Leporé et al., 2010), right superior parietal cortex (Wan et al., 2013) and paracentral gyrus (Jiang et al., 2015). Of the seven studies that analysed cortical thickness, one reported increased CT in the paracentral sulcus and right paracentral gyrus (Maller et al., 2016) whereas another reported a thinning of the supramarginal gyrus, the superior parietal gyrus and the postcentral gyrus (Voss and Zatorre, 2012). Out of six studies that explored surface of the parietal lobe in LB, only one found reduced cortical surface in superior parietal cortex and left postcentral gyrus, and increased surface area in right paracentral sulcus (Maller et al., 2016).

EB vs LB. Of the six studies comparing EB and LB, one reported larger GM volume in the postcentral gyrus of EB (Jiang et al., 2015), whereas another study reported reduced CT in the left postcentral gyrus of EB (Jiang et al., 2009).

3.2.4.2. Changes in WM. EB. Amidst 17 studies (nine for WM volume and eight for diffusion data), only one mentioned significant WM modifications, more specifically a reduced volume in the right superior parietal cortex and postcentral gyrus (Maller et al., 2016).

LB. Out of twelve studies, one study mentioned decreased WM volume in the postcentral gyrus and right superior parietal cortex, together with increased WM in paracentral gyrus and sulcus (Maller et al., 2016).

EB vs LB. No studies compared WM alterations between EB and LB in the parietal lobe.

3.2.5. Frontal lobe

Although close to half of the studies examining GM volume and CT in EB reported significant alterations, there was a large variability in the anatomical localizations of these changes. WM changes in frontal lobe in EB was reported in only one study. For LB, one third of the studies showed GM reductions but in widely varying locations. Only very few studies mentioned changes in CT, cortical surface, or WM volume in LB. The detailed results of GM and WM changes in the frontal lobe can be found below and in Table 4.

3.2.5.1. Changes in GM. EB. There is quite some heterogeneity regarding changes in GM in the frontal lobe. Among 18 studies, eight reported significant changes. Areas with reduced GM volume differed greatly across studies, and included the insula (Ankeeta et al., 2021),

Brodmann area 6 (Leporé et al., 2010), right lateral orbital cortex (Pitito et al., 2008a), right superior frontal sulcus (Anurova et al., 2015) and gyrus (51, (Wan et al., 2013), precentral sulcus (Bridge et al., 2009) and gyrus (Inuggi et al., 2020) medial prefrontal cortex (Jiang et al., 2015), and primary motor cortex (Chebat et al., 2020a). Two studies showed reduced volume of the inferior frontal gyrus (73: only in left hemisphere, 93), whereas another study mentioned increased volume of this area (Bridge et al., 2009). GM increases were also reported for the left middle frontal gyrus (Modi et al., 2012) and the left superior frontal gyrus (Jiang et al., 2015). Five out of eleven studies reported changes in cortical thickness. More specifically, increased CT was reported for the left middle frontal gyrus, right superior frontal sulcus (Anurova et al., 2015), the right orbital sulcus (Hasson et al., 2016) and orbito-frontal cortex (74: only in left hemisphere, 87). One study reported reduced CT in the precentral gyrus (Voss and Zatorre, 2015). Conflicting results were reported for the superior frontal gyrus (86: increased bilaterally, 91: decreased in left hemisphere). Six studies looked at the surface measures, but none reported significant alterations. Finally, one study demonstrated that the *Pli de Passage Fronto-Pariétal Moyen* of the central sulcus was less deep in EB (James et al., 2017).

LB. Five out of 14 studies reported GM volume reductions in various frontal areas, including the insula (Ankeeta et al., 2021), right posterior insula (Pitito et al., 2008a), precentral gyrus (Jiang et al., 2015), medial prefrontal cortex (Jiang et al., 2015), right middle frontal gyrus (Wan et al., 2013) and left (Wan et al., 2013) and bilateral inferior frontal gyrus (Ankeeta et al., 2021). Only one out of eight studies found reductions of CT in the inferior frontal gyrus, the left middle frontal gyrus, the right superior frontal gyrus and the insular gyrus (Voss and Zatorre, 2012). None of six studies of cortical surface found any significant alteration.

EB vs LB. Six studies compared GM volume, five CT and two cortical surface area in EB and LB. Results showed that EB had larger GM volume in inferior frontal (Ankeeta et al., 2021) and superior frontal (Jiang et al., 2015) gyri.

3.2.5.2. Changes in WM. EB. Out of a total of 18 studies investigated WM changes, only one study reported a significant increase in WM volume of the superior frontal gyrus (Modi et al., 2012).

LB. None of ten studies reported any significant WM alteration in the frontal lobe.

EB vs LB. No studies compared frontal lobe WM volumes between EB and LB.

3.2.6. Cingulate gyrus and mesial wall

In regions of the cingulate gyrus and mesial wall, volumetric reductions in both GM and WM and reduced CT was reported in EB, except for the precuneus. No surface results were reported. The detailed results of GM and WM changes in the cingulate gyrus and mesial wall can be found below and in Table 4.

3.2.6.1. Changes in GM. EB. Out of eighteen studies, two studies reported GM volumetric reductions in EB in posterior cingulate cortex (PCC) (Leporé et al., 2010; Yang et al., 2014), three in anterior cingulate cortex (ACC) (Maller et al., 2016; Leporé et al., 2010; Ankeeta et al., 2021) and one in subgenual cingulate (Leporé et al., 2010). One study reported a higher GM volume in the precuneus in EB (Jiang et al., 2015). Amidst eleven studies investigating cortical thickness, one reported increased CT bilaterally in ACC (Inuggi et al., 2020), and one in the right ACC only (Anurova et al., 2015). A total of six studies looked at cortical surface in these areas and one study reported an increase in the surface area of the right isthmus of the cingulate (Park et al., 2009).

LB. Out of twenty-eight papers (thirteen for GM volume, eight for CT and six for cortical surface), one study reported reduced GM volume in the ACC (Ankeeta et al., 2021) and another one in the precuneus (Wan et al., 2013).

EB vs LB. No significant group differences were reported out of thirteen studies.

3.2.6.2. Changes in WM. EB. Eight studies measured WM volume and ten used diffusion imaging. Two studies reported WM volume reductions in the precuneus (Maller et al., 2016; Wan et al., 2013) and one in the PCC (Wan et al., 2013). One study mentioned reduced FA in the cingulate gyrus (Lee et al., 2014a) and another one in the retrosplenial cortex (Park et al., 2007).

LB. Out of twelve studies, two reported WM reductions in precuneus (Maller et al., 2016; Wan et al., 2013), one in rostral ACC (Maller et al., 2016) and one in PCC (Wan et al., 2013). One study reported reduced FA in the cingulate gyrus (Lee et al., 2014a) in a mixed group of EB and LB individuals, and one in precuneus (Reislev et al., 2016a).

EB vs LB. No study compared differences in WM in the cingulate cortex or mesial wall area between EB and LB.

3.2.7. Subcortical structures

Subcortically, the results show volumetric reductions in the thalamus, predominantly in its visual nuclei (lateral geniculate and pulvinar). For other subcortical structures such as the hippocampus and the

basal ganglia, the reported alterations are more divergent. The detailed results of GM and WM changes in subcortical structures are described below and in Table 6.

3.2.7.1. Changes in GM. EB. Four out of 20 studies reported a volumetric reduction of the lateral geniculate nucleus (LGN) of the thalamus (Aguirre et al., 2016: 17% reduction; Cecchetti et al., 2016b; Ptito et al., 2021a,b: 50% reduction), and one of the pulvinar nucleus (Ptito et al., 2008a). In addition, two studies reported a bilateral volumetric reduction of 5–7% of the whole thalamus (Cecchetti et al., 2016b; Reislev et al., 2017). Five out of 21 papers investigating the hippocampus obtained significant structural modifications, mostly volumetric reductions. More specifically, volumetric reductions in the posterior hippocampus was reported in two studies (49, 50: only in right hippocampus), one study reported a reduction of the whole right hippocampus (Modi et al., 2012), and one of the cornu ammonis, subiculum and fascia dentata (Chebat et al., 2020a). In contrast, Fortin et al., 2008 reported a volume increase in the head of the hippocampus (Fortin et al., 2008). Disparate results were also described for the basal ganglia. Seven out of 17 studies reported significant changes within this structure, including both enlarged (Wan et al., 2013) and reduced GM volume of the

Table 6
Studies demonstrating alterations in subcortical areas.

Brain structure	Grey Matter		White matter			
	Volume	Surface	Volume	FA	MD	RD
Thalamus	EB: (– Cecchetti et al., 2016b; Maller et al., 2016; Reislev et al., 2017) LB: (– Maller et al., 2016; Reislev et al., 2017)		EB: (– Park et al., 2007; Reislev et al., 2017) LB: (– Reislev et al., 2017) EB vs LB: (+ Wang et al., 2013)			
LGN	EB: (– Aguirre et al., 2016; Cecchetti et al., 2016b; Ptito et al., 2021a,b) LB: (– Aguirre et al., 2016; Ankeeta et al., 2021; Ptito et al., 2021b)					
Pulvinar	EB: (– Ptito et al., 2008a)		LB: (– Dietrich et al., 2015)			
Ventral thalamus			EB: (– Bridge et al., 2009)			
Posterior radiations			LB: (– Anurova et al., 2015)			
Basal Ganglia						
Lenticular nucleus	EB: (– Ptito et al., 2008a)					
Putamen	EB: (– Bridge et al., 2009; + Wan et al., 2013) LB: (– Wan et al., 2013)					
Globus pallidus	EB: (+ Wan et al., 2013) LB: (+ Wan et al., 2013)					
Pallidum	LB: (– Jonak et al., 2020)					
Caudate	EB: (– Ptito et al., 2008a)					
Fornix	EB: (+ Hasson et al., 2016; Park et al., 2009; – Ptito et al., 2008a; + Voss and Zatorre, 2015)					
Hippocampus	EB: (– Modi et al., 2012) LB: (+ Grochowski et al., 2021) EB vs LB: (+ Ankeeta et al., 2021)					
Head	EB: (+ Fortin et al., 2008) LB: (– Fortin et al., 2008)		LB: (+ Leporé et al., 2010)			
Posterior	EB: (– Chebat et al., 2007; Ptito et al., 2008a)		LB: (– Leporé et al., 2010)			
Cornu ammonis	EB: (– Chebat et al., 2020a)					
Subiculum	EB: (– Chebat et al., 2020a)					
Fimbria	LB: (– Grochowski et al., 2021)					
Fascia dentata	EB: (– Chebat et al., 2020a)					
Accumbens	LB: (– Jonak et al., 2020)					
Olfactory bulb	EB: (+ Rombaux et al., 2010)					
External capsule			EB: (– Park et al., 2007) EB: (+ Anurova et al., 2019) EB: (Anurova et al., 2019)			

Significant decreases are indicated with a minus sign “–”, significant increases with a plus sign “+”. For the EB vs LB contrast, numbers with a “+” indicate an increase in EB, numbers with a minus sign “–” indicate a decrease in EB.

putamen (Bridge et al., 2009), reduced GM volume of the caudate and lenticular nuclei (Ptito et al., 2008a), and enlarged GM volume of the globus pallidus (Wan et al., 2013). Three studies reported increased GM volume either in the right (Hasson et al., 2016), left (Park et al., 2009) or bilateral fornix (Voss and Zatorre, 2015), whereas a fourth study reported a bilateral decrease of this structure. Finally, Rombaux et al., 2010 reported a 32% volume enlargement of the olfactory bulb (Rombaux et al., 2010).

LB. A total of 12 studies looked at subcortical changes. Like for EB, there was a reduction in GM volume in bilateral LGN (Aguirre et al., 2016; Ptito et al., 2021b: 44% reduction), as well as of the whole thalamus bilaterally (Maller et al., 2016; Reislev et al., 2017), or left side only (Ankeeta et al., 2021). Only three out of thirteen articles that investigated structural changes in the hippocampus reported alterations. More specifically, one study reported GM volume reduction in the hippocampal head (Fortin et al., 2008), one an increased surface area of the right anterior part of the hippocampus combined with a decreased surface area in the posterior part (Leporé et al., 2010), and one an increased GM volume of the whole hippocampus (except for a 44% reduction of the right fimbria) in patients with Leber's hereditary optic neuropathy (Grochowski et al., 2021). Out of 11 studies related to the basal ganglia, one reported GM volume reduction in the pallidum (Jonak et al., 2020) and one in the right accumbens (Jonak et al., 2020), whereas two other studies reported a GM increase in the globus pallidus (Wan et al., 2013) or putamen (Wan et al., 2013).

EB vs LB. Out of three studies, one reported superior GM volume of the left hippocampus in EB (Ankeeta et al., 2021).

3.2.7.2. Changes in WM. **EB.** Five out of 22 studies found alterations in WM, mainly in the external capsule and the thalamus. One study reported increased MD in the left external capsule, increased RD in the anterior part of the external capsule (Anurova et al., 2019), together with decreased FA (Park et al., 2007). One study reported reduced WM volume (81: only in the ventral thalamus) and FA in the thalamus (Park et al., 2007; Reislev et al., 2017).

LB. Out of 22 studies, one reported reduced FA in the whole thalamus (Reislev et al., 2017) and one in the pulvinar (Dietrich et al., 2015). One other study reported WM reduction in the posterior radiations of the thalamus (Voss et al., 2014).

EB vs LB. Out of three studies, one reported higher FA in thalamus of EB (Wang et al., 2013).

3.2.8. White matter pathways

Several studies reported clear volumetric reductions throughout the retino-geniculo-striate pathway in both EB and LB. In the commissural tracts, the alterations seem predominant in the visual (splenium) part of the corpus callosum. Regarding long range white matter pathways, volumetric reduction of the inferior longitudinal fasciculi was a consistent finding; for the other pathways, results were heterogeneous. The detailed results of changes in white matter pathways can be found below and in Table 7.

3.2.8.1. Retino-geniculo-striate pathway. **EB.** All 14 studies of the retino-geniculo-striate pathway reported significant alterations in at least one area of this pathway. Volume reductions were found for the optic nerve (Aguirre et al., 2016; Ptito et al., 2021a,b: 52% reduction; Wan et al., 2010), optic chiasm (Noppeney et al., 2005; Ptito et al., 2021b: 53% reduction; Shimony et al., 2006), optic tracts (Bridge et al., 2009; Pan et al., 2007; Ptito et al., 2021a,b: 64% reduction; Shimony et al., 2006), and optic radiations (Ptito et al., 2008a; Noppeney et al., 2005; Pan et al., 2007). Diffusion imaging studies showed decreased FA and increased MD of the optic nerve (Zhang et al., 2012), and decreased FA of the optic tract (Park et al., 2007) and optic radiations (Lee et al., 2014a; Aguirre et al., 2016; Bridge et al., 2009; Shimony et al., 2006; Park et al., 2007; Shu et al., 2009a; Reislev et al., 2016a, 2017; Anurova

et al., 2019; Wang et al., 2013). Three studies reported increases in MD and RD in the optic radiations (Shu et al., 2009a; Reislev et al., 2016a; Anurova et al., 2019).

LB. The atrophy patterns reported in 9 studies were similar to those described in EB individuals. Volume reductions were observed in the optic nerve (Aguirre et al., 2016; Ptito et al., 2021b: 50% reduction), optic chiasm (Leporé et al., 2010; Ptito et al., 2021b: 47% reduction), optic tracts (Ptito et al., 2021b) and optic radiations (Manara et al., 2015). Diffusion imaging studies showed decreased FA of the optic tract (Manara et al., 2015) and optic radiations (Lee et al., 2014a; Aguirre et al., 2016; Manara et al., 2015; Reislev et al., 2016a, 2017; Wang et al., 2013; Hofstetter et al., 2019). One study reported decreased RD of the optic radiations (Manara et al., 2015), whereas one other study found increased RD and MD of the optic radiations (Reislev et al., 2016a).

EB vs LB. In five studies comparing both groups, no significant difference was reported for the retino-geniculo-striate pathway.

3.2.8.2. Commissural pathways. **EB.** Out of a total of 22 studies, 12 reported significant alterations. There is a relative consistency with respect to WM reductions in the splenium, the posterior part of the CC containing crossing fibers carrying visual information (Ptito et al., 2008a; Cavaliere et al., 2020). As for the other parts of the CC, the results are somewhat less consistent. For example, Tomaiuolo et al., 2014 reported a 20% increase in the isthmus and the posterior part of the body (Tomaiuolo et al., 2014), but this was not confirmed in another study (Cavaliere et al., 2020). Two studies reported increased thickness of the pericallosal sulcus (Maller et al., 2016; Hasson et al., 2016) while another study found it to be thinner in the right subcallosal area (Hasson et al., 2016). Tomaiuolo et al., 2014 reported decreased surface of the splenium, together with increased surface of the posterior mid-body and the isthmus (Tomaiuolo et al., 2014), whereas Maller et al., 2016 reported reduced surface of the right subcallosal area (Maller et al., 2016). One study described a more convex shape of the corpus callosum in EB (Tomaiuolo et al., 2014). Diffusion imaging studies revealed reduced FA of the splenium (Aguirre et al., 2016; Shimony et al., 2006; Park et al., 2007; Reislev et al., 2017; Anurova et al., 2019; Cavaliere et al., 2020), isthmus (Anurova et al., 2019), posterior (Lao et al., 2015) and rostral (Bridge et al., 2009) corpus callosum, and genu (Park et al., 2007). One study reported higher MD and RD in both the anterior and posterior corpus callosum (Anurova et al., 2019). Finally, Cavaliere et al., 2020 reported significantly reduced volume and FA in the posterior part of the anterior commissure (Cavaliere et al., 2020).

LB. The morphological changes of the corpus callosum of LB are very similar to those in EB, with volumetric reductions of the splenium (Cavaliere et al., 2020: 29% reduction; Voss et al., 2014: only in the left splenium) and reduced FA (Jiang et al., 2009). Other studies reported reduced surface area in the right subcallosal area (Maller et al., 2016) or in the entirety of the structure (Wang et al., 2013), and increased thickness in the pericallosal and subcallosal areas (Maller et al., 2016). Diffusion imaging studies further revealed reduced MD of the isthmus (Cavaliere et al., 2020). Finally, one study reported reduced FA in the posterior part of the anterior commissure, in line with findings in EB (Cavaliere et al., 2020).

EB vs LB. A direct comparison of the two blind groups revealed a superior volume of the splenium (48%) and midbody (32%) of EB (Reislev et al., 2016a), but a reduced volume of the isthmus (Cavaliere et al., 2020). One study reported reduced FA in the isthmus and the splenium (Cavaliere et al., 2020), whereas another study found higher FA values along the entire corpus callosum (Wang et al., 2013) in EB. Finally, MD was higher in EB compared in the anterior part of the corpus callosum, isthmus and splenium (Cavaliere et al., 2020).

3.2.8.3. Long-range white matter pathways. **EB.** Thirteen studies investigated long-range WM pathways in EB. Seven studies reported alterations of the inferior longitudinal fasciculi, including bilateral reduction

Table 7

Studies demonstrating alterations in white matter pathways.

Brain structure	Volume	Thickness	Surface	FA	MD	RD	AD	Shape
<i>Retinofugal pathway</i>								
Optic nerve	EB: (– Aguirre et al., 2016; Ptito et al., 2021a,b; Shimony et al., 2006) LB: (Aguirre et al., 2016; Ptito et al., 2021b)			EB: (– Zhang et al., 2012)	EB: (+ Zhang et al., 2012)			
Optic chiasm	EB: (– Noppeney et al., 2005; Ptito et al., 2021b; Shimony et al., 2006) LB: (– Jonak et al., 2020; Ptito et al., 2021b)							
Optic tract	EB: (– Bridge et al., 2009; Pan et al., 2007; Ptito et al., 2021a,b; Shimony et al., 2006) LB: (– Ptito et al., 2021b)			EB: (– Park et al., 2007)				
Optic radiations	EB: (– Noppeney et al., 2005; Pan et al., 2007; Ptito et al., 2008a) LB: (– Manara et al., 2015)			LB: (– Manara et al., 2015) EB: (– Aguirre et al., 2016; Hofstetter et al., 2019; Lee et al., 2014a; Manara et al., 2015; Reislev et al., 2016a, 2017; Wang et al., 2013) LB: (– Aguirre et al., 2016; Hofstetter et al., 2019; Lee et al., 2014a; Manara et al., 2015; Reislev et al., 2016a, 2017; Wang et al., 2013)	EB: (+ Anurova et al., 2019; Reislev et al., 2016a; Shu et al., 2009a) LB: (+ Reislev et al., 2016a)	EB: (+ Anurova et al., 2019; Reislev et al., 2016a; Shu et al., 2009a) LB: (– Manara et al., 2015; + Reislev et al., 2016a)		
<i>Commissural pathways</i>								
Corpus callosum				LB: (– Wang et al., 2013) EB vs LB: (+ Reislev et al., 2016a)				EB: (+ Tomaiuolo et al., 2014)
Genu	EB: (+ Ptito et al., 2008a)			EB: (– Park et al., 2007)				
Isthmus	EB: (– Cavaliere et al., 2020; + Tomaiuolo et al., 2014)		EB: (+ Tomaiuolo et al., 2014)	EB: (– Dietrich et al., 2015)	LB: (– Cavaliere et al., 2020)			
	EB vs LB: (– Cavaliere et al., 2020)			LB: (– Cavaliere et al., 2020) EB vs LB: (– Cavaliere et al., 2020)	EB vs LB: (+ Cavaliere et al., 2020)			
Splenium	EB: (– Cavaliere et al., 2020; Ptito et al., 2008a) LB: (– Cavaliere et al., 2020; Voss et al., 2014) EB vs LB: (+ Reislev et al., 2016a)		EB: (– Tomaiuolo et al., 2014)	EB: (– Aguirre et al., 2016; Anurova et al., 2019; Cavaliere et al., 2020; Park et al., 2007; Reislev et al., 2017; Shimony et al., 2006) LB: (– Aguirre et al., 2016) EB vs LB: (– Cavaliere et al., 2020)	EB vs LB: (+ Cavaliere et al., 2020)			
Anterior	EB: (– Cavaliere et al., 2020)			EB: (– Bridge et al., 2009)	EB: (+ Anurova et al., 2019) EB vs LB: (+ Cavaliere et al., 2020)	EB: (+ Anurova et al., 2019)		

(continued on next page)

Table 7 (continued)

Brain structure <i>Retinofugal pathway</i>	Volume	Thickness	Surface	FA	MD	RD	AD	Shape
Midbody	EB vs LB: (+ Reislev et al., 2016a)							
Posterior	EB: (– Tomaiuolo et al., 2014)		EB: (+ Tomaiuolo et al., 2014)	EB: (– Lao et al., 2015)	EB: (+ Anurova et al., 2019)	EB: (+ Anurova et al., 2019)		
Pericallosal		EB: (+ Hasson et al., 2016; Maller et al., 2016) LB: (+ Maller et al., 2016)						
Subcallosal		EB: (– Hasson et al., 2016) LB: (+ Maller et al., 2016)	EB: (– Maller et al., 2016) LB: (– Maller et al., 2016)					
Anterior commissure	EB: (– Cavaliere et al., 2020)			EB: (– Cavaliere et al., 2020) LB: (– Cavaliere et al., 2020)				
<i>Long range white matter pathways</i>								
Inferior longitudinal fasciculus	EB: (– Ptito et al., 2008a)			EB: (– Anurova et al., 2019; Bridge et al., 2009; Lao et al., 2015; Lee et al., 2014a; Qin et al., 2013; Reislev et al., 2016b) LB: (– Dietrich et al., 2015; Hofstetter et al., 2019; Lee et al., 2014a; Qin et al., 2013; Reislev et al., 2016b)	EB: (+ Anurova et al., 2019)	EB: (+ Anurova et al., 2019; Qin et al., 2013; Reislev et al., 2016a) LB: (+ Qin et al., 2013; Reislev et al., 2016b)		
Inferior fronto- occipital fasciculus	EB: (+ Ptito et al., 2008a)			EB: (– Anurova et al., 2019; Lao et al., 2015; Lee et al., 2014a; Qin et al., 2013; Reislev et al., 2016b; Shu et al., 2009b) LB: (– Dietrich et al., 2015; Hofstetter et al., 2019; Lee et al., 2014a; Qin et al., 2013)		EB: (+ Reislev et al., 2016b) LB: (+ Qin et al., 2013; Reislev et al., 2016b)	EB: (+ Anurova et al., 2019; Qin et al., 2013)	
Superior longitudinal fasciculus	EB: (+ Ptito et al., 2008a)							
Uncinate fasciculus	EB: (+ Bauer et al., 2018)			EB: (– Anurova et al., 2019; Lao et al., 2015)				
Arcuate fasciculus				EB: (+ Bauer et al., 2018)				
Frontopontine tract				EB: (– Anurova et al., 2019)				
Anterior thalamic radiations				EB: (+ Anurova et al., 2019; – Wang et al., 2013) LB: (– Wang et al., 2013)				
Internal capsule					EB: (+ Anurova et al., 2019)	EB: (+ Anurova et al., 2019)		
Sagittal stratum				LB: (– Dietrich et al., 2015)				
Medial lemniscus					EB: (+ Anurova et al., 2019)			
Lateral lemniscus					EB: (+ Anurova et al., 2019)			
Corticospinal tract				EB: (– Anurova et al., 2019; Lao et al., 2015; Reislev et al., 2016a; + Wang et al., 2013; Yu et al., 2007) LB: (– Dietrich et al., 2015; Hofstetter et al., 2019)	EB: (+ Anurova et al., 2019)	EB: (+ Anurova et al., 2019)	EB: (+ Anurova et al., 2019)	

Significant decreases are indicated with a minus sign “-”, significant increases with a plus sign “+”. For the EB vs LB contrast, numbers with a “+” indicate an increase in EB, numbers with a minus sign “-” indicate a decrease in EB.

in FA (Lee et al., 2014a; Bridge et al., 2009; Qin et al., 2013; Anurova et al., 2019; Lao et al., 2015; Reislev et al., 2016b), increased MD (Anurova et al., 2019), or increased RD (Qin et al., 2013; Anurova et al., 2019; Reislev et al., 2016b). Using VBM, Ptito et al., 2008 revealed a volumetric reduction of the left inferior longitudinal fasciculus, combined with an enlargement of the superior longitudinal fasciculi (Ptito et al., 2008a). A diffusion imaging study failed to find changes in FA, AD or MD in the superior longitudinal fasciculus (Kupers et al., 2022). Six studies reported reduced FA of the inferior fronto-occipital fasciculi (Lee et al., 2014a; Qin et al., 2013; Anurova et al., 2019; Lao et al., 2015; Reislev et al., 2016b; Shu et al., 2009b), one increased RD (Reislev et al., 2016b), two increased AD (Qin et al., 2013; Anurova et al., 2019) and one increased volume (Ptito et al., 2008a). For the uncinate fasciculi, lower FA bilaterally (Anurova et al., 2019; Lao et al., 2015) and superior volume in the left hemisphere (Bauer et al., 2018) were reported. One study reported reduced FA in the frontopontine tracts (Anurova et al., 2019), one increased FA in the left arcuate fasciculi (Bauer et al., 2018) and one increased MD and RD in the anterior limb of the internal capsule (Anurova et al., 2019). Contradictory results were reported for the corticospinal tract with three studies reporting increased FA (Wang et al., 2013; Yu et al., 2007), MD, RD and AD (Anurova et al., 2019) and three other studies reporting decreased FA (Reislev et al., 2016a; Anurova et al., 2019; Lao et al., 2015). For the right anterior thalamic radiations, both increased (Wang et al., 2013) and decreased FA (Anurova et al., 2019) were reported. Finally, one study mentioned increased MD in the ascending tracts of the medial and lateral lemnisci (Anurova et al., 2019).

LB. Six out of ten studies that investigated long-range WM pathways reported significant modifications. Four studies reported decreased FA in the inferior longitudinal fasciculi, bilaterally (Lee et al., 2014a; Qin et al., 2013; Dietrich et al., 2015; Reislev et al., 2016b). However, one study found changes only in its posterior part (Hofstetter et al., 2019). The same studies reported reduced FA in the fronto-occipital fasciculi (Lee et al., 2014a; Qin et al., 2013; Dietrich et al., 2015), or in its posterior inferior part (Hofstetter et al., 2019). Two studies reported bilateral increased RD for the inferior longitudinal and the fronto-occipital fasciculi (Qin et al., 2013; Reislev et al., 2016b). Finally, reduced FA of the corticospinal tract (Dietrich et al., 2015; Hofstetter

et al., 2019), the anterior thalamic radiations (Wang et al., 2013) and the sagittal stratum (Dietrich et al., 2015) were reported.

EB vs LB. None of the four studies that compared EB and LB found any significant group differences.

3.2.9. Anatomical Likelihood Estimation meta-analysis

EB. A total of 17 articles met the inclusion criteria for ALE, including a total of 241 EB and 295 SC. The analysis revealed seven consistent clusters across studies (see Table 8 and Fig. 2A), three indicating volumetric reductions in GM and/or WM, two indicating areas of changes in cortical thickness, and two indicating brain areas with alterations in FA.

The largest cluster shows reduced volume mainly in the occipital lobe (Ptito et al., 2008a; Noppeney et al., 2005; Wan et al., 2013; Modi et al., 2012; Bauer et al., 2017; Bridge et al., 2009; Pan et al., 2007; Voss et al., 2014), covering the lingual gyrus, cuneus and extending dorsally in the precuneus. A second cluster shows reduced volume of an area which includes the left lentiform nucleus, extending into the parahippocampus and thalamus, in a region overlapping with the location of the LGN (Ptito et al., 2008a; Wan et al., 2013; Pan et al., 2007). The third cluster shows a volumetric reduction of the left posterior cingulate cortex, extending ventrally in occipital areas (Ptito et al., 2008a; Wan et al., 2013; Pan et al., 2007). Two clusters showed changes in cortical thickness, one indicating a reduction in CT in the right postcentral gyrus, extending into the precentral gyrus (Voss and Zatorre, 2012, 2015). The other cluster is indicative of increased CT in the left lingual gyrus (Voss and Zatorre, 2012; Anurova et al., 2015). Finally, two clusters indicated reduced FA of the left (Shu et al., 2009a; Zhou et al., 2019; Reislev et al., 2016a) and right (Reislev et al., 2016a, 2017) optic radiations (see Fig. 2).

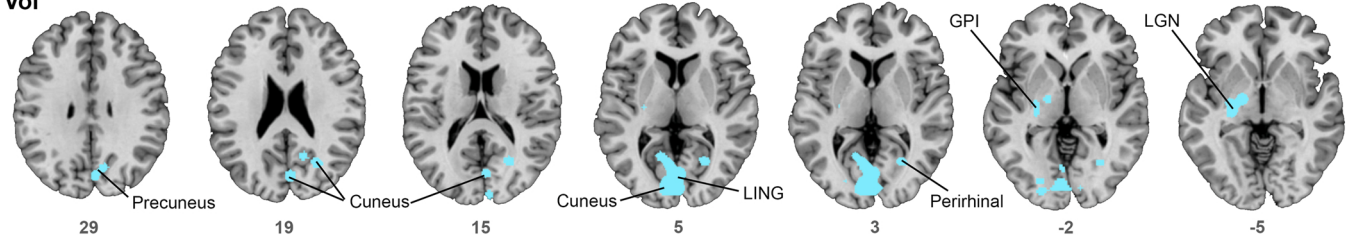
LB. A total of seven studies, covering 136 LB and 132 SC, were included in the ALE. The meta-analysis revealed five convergent clusters across studies (see Table 9 and Fig. 2B), 2 of which showed reductions in GM and/or WM, and two with alterations in FA. The first two clusters showed areas of reduced GM/WM in the right (Wan et al., 2013; Voss et al., 2014) and left occipital lobe (Atilgan et al., 2017; Li et al., 2017), extending into the vermis of the cerebellum. Clusters 3 and 5 showed reductions in FA in left and right optic radiations, extending into lingual and middle temporal gyri, and posterior cingulate gyrus (Reislev et al.,

Table 8
Characteristics of the clusters from the ALE meta-analysis in EB.

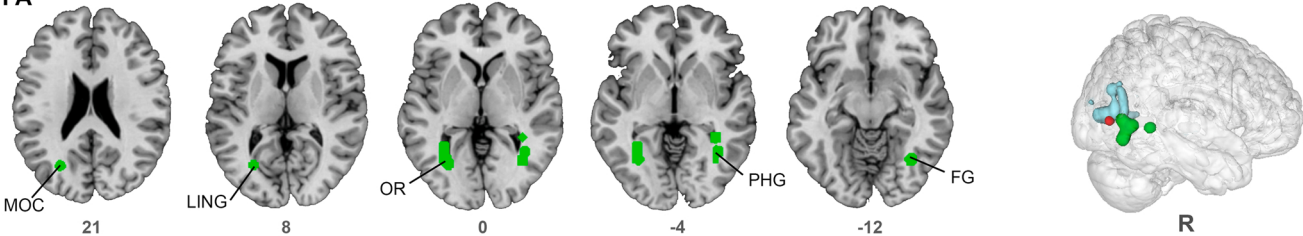
Cluster	Location	Tissue type	Measure	Center coordinates (MNI space)			Size (mm ³)	Contributing studies
				x	y	z		
1	Lingual Gyrus (59.8%), Cuneus (29.8%), Precuneus (5.7%), Culmen (3.4%)	37.2% WM	Reduced volume	4.4	-75.6	11.5	16088	(Ptito et al., 2008a; Noppeney et al., 2005; Wan et al., 2013; Modi et al., 2012; Bauer et al., 2017; Bridge et al., 2009; Pan et al., 2007; Voss et al., 2014)
2	Lentiform nucleus (91.8%), Parahippocampal gyrus (1.9%), Thalamus (1.9%)	58.2% WM	Reduced volume	-20.7	-14.1	-7.6	2600	(Ptito et al., 2008a; Wan et al., 2013; Pan et al., 2007)
3	Posterior cingulate (57.7%), Lingual gyrus (33.3%), Cuneus (8.1%)	61.7% WM	Reduced volume	-19.8	-69.8	20.3	2152	(Ptito et al., 2008a; Wan et al., 2013; Pan et al., 2007)
4	Postcentral gyrus (40.8%), Sub-gyral (5.5%), Precentral gyrus (4.7%)	30.0% WM	Reduced thickness	16.4	-36.6	74.5	2094	(Voss and Zatorre, 2012, 2015)
5	Lingual gyrus (84.4%)	34.9% WM	Increased thickness	-3.6	-78.9	-0.4	2456	(Voss and Zatorre, 2012; Anurova et al., 2015)
6	Optic Radiations (53.4%), Lingual gyrus (12.2%), Parahippocampal gyrus (9.2%), Middle occipital gyrus (7.6%), Posterior cingulate (7.6%), Cuneus (4.8%), Lateral ventricle (2.2%), Extra-nuclear (1.7%), Fusiform gyrus (1.3%)	82.3% WM	Reduced FA	-29.8	-62.7	4.1	4328	(Shu et al., 2009a; Zhou et al., 2019; Reislev et al., 2016a)
7	Optic Radiations (50.8%), Declive (15%), Parahippocampal gyrus (13.1%), Fusiform gyrus (10.5%), Lateral ventricle (2.8%), Middle occipital gyrus (2.8%), Lingual gyrus (2.6%)	72.3% WM	Reduced FA	36.4	-57.6	-4.7	3672	(Shu et al., 2009a; Reislev et al., 2016a)

EB vs SC

Vol



FA



CT



Reduced volume
Reduced FA
Increased thickness

Fig. 2. ALE analysis of structural changes in EB. *Top:* clusters of significant volumetric differences between EB and SC. *Middle:* clusters of significant differences in fractional anisotropy between EB and SC. *Bottom:* clusters of significant differences of cortical thickness between EB and SC. A 3D rendering of the significant clusters is shown to the right (references in Table 7). Brain slices are shown in axial view and the z-coordinates in MNI space are displayed under each slice. FG, fusiform gyrus; GPI, globus pallidus internus; LGN, lateral geniculate nucleus; LING, lingual gyrus; MOC, middle occipital cortex; OR, optic radiations; PHG, parahippocampal gyrus.

Table 9
Characteristics of the clusters from the ALE meta-analysis in LB.

Clusters	Location	Tissue type	Measure	Center coordinates (MNI space)			Size (mm ³)	Contributing studies
				x	y	z		
1	Cuneus (89.7%), Precuneus (10.3)	33.8% WM	Reduced volume	3	-70.9	19.7	8928	(Wan et al., 2013; Voss et al., 2014)
2	Cuneus (47.9%), Lingual gyrus (28.6%), Culmen of Vermis (14.3%), Posterior cingulate (4.3%), Culmen (2.9%)	60.6% WM	Reduced volume	17.6	-86	26.1	2072	(Wan et al., 2013; Voss et al., 2014)
3	Optic radiations (52.4%), Parahippocampal gyrus (16.4%), Superior temporal gyrus (15.1%), Lateral ventricle (5.9%), Fusiform gyrus (4.6%), Transverse temporal gyrus (3.1%), Middle temporal gyrus (2.5%)	79.0% WM	Reduced FA	-37.1	-43.5	1.3	3816	(Reislev et al., 2016a; Dietrich et al., 2015)
4	Extra-nuclear (24.5%), Thalamus (23.1%), Lentiform nucleus (3.4%)	24.8% WM	Reduced FA	17	-15.5	-6	2808	(Reislev et al., 2016a; Dietrich et al., 2015)
5	Optic radiations (58.5%), Lingual gyrus (29.9%), Middle occipital gyrus (9.4%), Posterior cingulate (1.6%)	76.4% WM	Reduced FA	29	-71.5	5.2	2544	(Reislev et al., 2016a; Dietrich et al., 2015)

2016a; Dietrich et al., 2015). Finally, cluster 4 showed an area of reduced GM around the thalamus (LGN) and the lentiform nucleus (Reislev et al., 2017; Cavaliere et al., 2020) (see Fig. 3).

3.3. Conjunction analysis

Finally, a conjunction analysis of the EB and LB ALE analyses revealed one cluster of reduced GM/WM volume and two of reduced FA (Table 10 and Fig. 3). The cluster of reduced GM/WM volume was within the right cuneus, slightly extending into the left cuneus (Ptito et al., 2008a; Modi et al., 2012; Voss et al., 2014). Two clusters of reduced FA were found in the left parahippocampal gyrus (Reislev et al.,

2016a, 2016b) and the right lingual gyrus (Zhou et al., 2019; Dietrich et al., 2015; Shu et al., 2009b).

4. Discussion

In this study, we performed both a qualitative synthesis and an ALE meta-analysis of the literature on brain morphometric changes in humans following the loss of vision, early or later in life. The qualitative analysis comprised 65 studies, covering 890 EB, 466 LB and 1257 sighted controls. More than 85% of the studies in EB that examined changes in GM/WM or CT reported significant alterations. For LB subjects, the numbers were between 55% and 75%. Diffusion imaging

LB vs SC

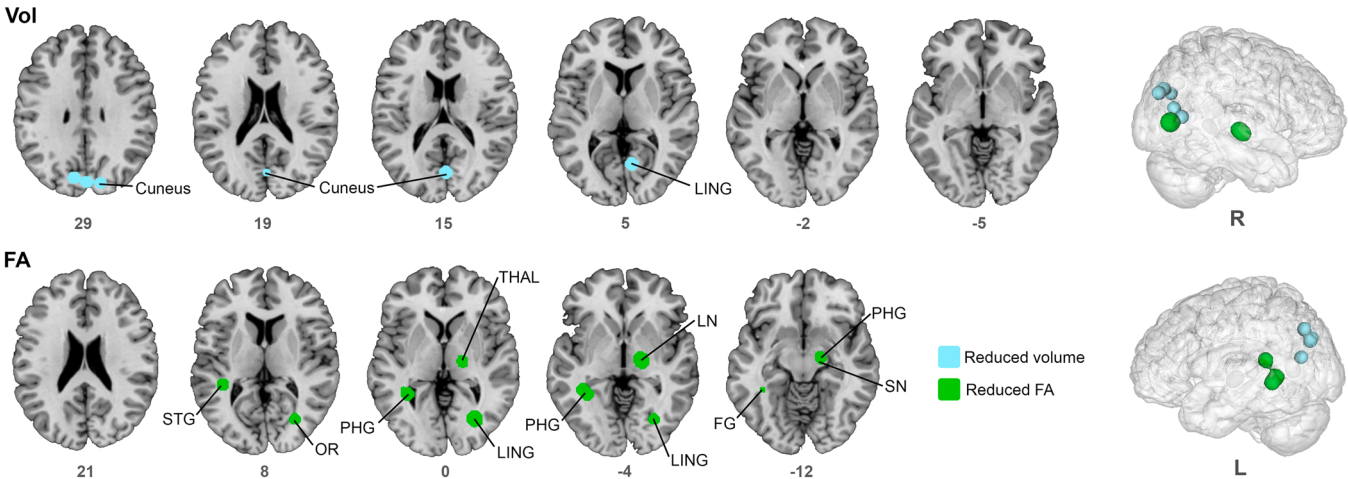


Fig. 3. ALE analysis of structural changes in LB. *Top*: clusters of significant volumetric differences between LB and SC. *Middle*: clusters of significant differences in fractional anisotropy between LB and SC. A 3D rendering of the brain showing the significant clusters is shown to the right (references in Table 8). Brain slices are shown in axial view and the z-coordinates in MNI space are displayed under each slice. FG, fusiform gyrus; LGN, lateral geniculate nucleus; LING, lingual gyrus; LN, lentiform nucleus; OR, optic radiations; PHG, parahippocampal gyrus; STG, superior temporal gyrus; THAL, thalamus.

Table 10
Characteristics of the clusters from the ALE conjunction meta-analysis for similarities between EB and LB.

Cluster	Location	Tissue type	Measure	Center coordinates (MNI space)			Size (mm ³)	Contributing studies
				x	y	z		
1	Cuneus (88.2%), Lingual gyrus (11.8%)	100% GM	Reduced volume	3.1	-74.4	12.6	944	(Pitito et al., 2008a; Modi et al., 2012; Voss et al., 2014)
2	Parahippocampal gyrus (100%)	100% GM	Reduced FA	-32.8	-50.3	-2	600	(Reislev et al., 2016a, 2016b)
3	Lingual gyrus (100%),	100% GM	Reduced FA	33.2	-66.8	1.8	184	(Zhou et al., 2019; Dietrich et al., 2015; Shu et al., 2009b)

studies reported the highest percentage of changes in both EB and LB, with all studies reporting changes in at least one diffusion parameter, in most cases FA. Fig. 4.

Despite a relatively important variability with respect to the brain

areas affected, a general consistent finding is that early and late blindness are characterized by important volumetric reductions along the whole extent of the retino-geniculo-striate pathway. Not surprisingly, at the cortical level, the most conspicuous alterations were observed in

EB ∩ LB

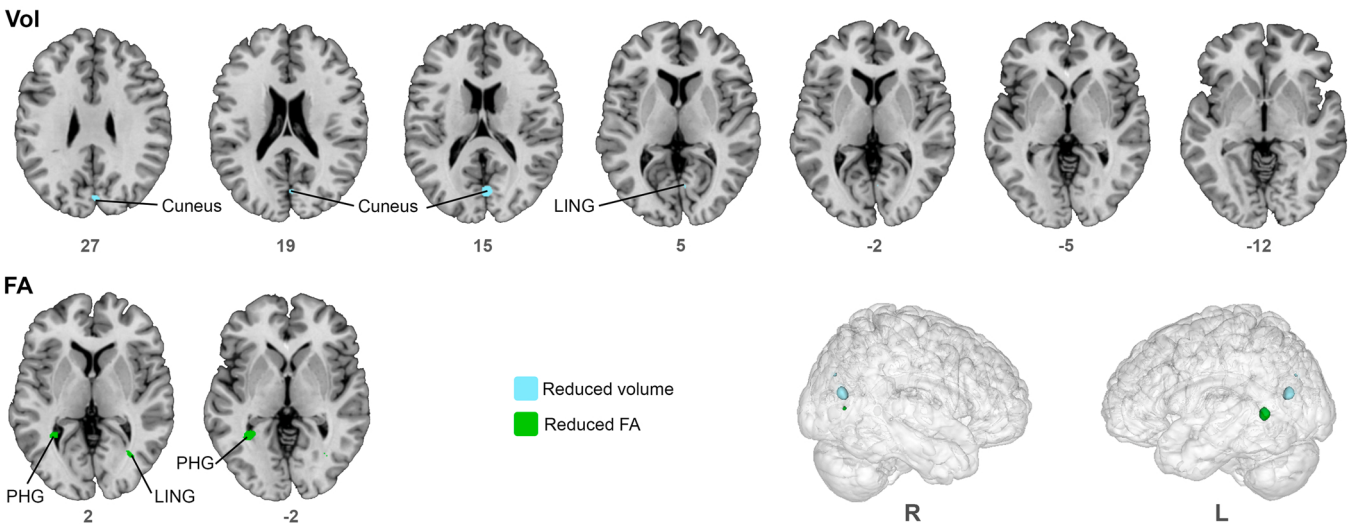


Fig. 4. ALE conjunction analysis of structural changes in EB and LB. *Top*: clusters of significant common volumetric reductions in EB and LB in occipital cortex. *Bottom*: common clusters of significantly reduced fractional anisotropy in EB and LB. A 3D rendering of the brain showing the significant clusters is shown to the right (references in Table 9). Brain slices are shown in axial view and the z-coordinates in MNI space are displayed under each slice. LING, lingual gyrus; PHG, parahippocampal gyrus.

striate and extra-striate visual cortical areas. Although morphometric changes were also measured outside the visual cortex, such as in temporal, parietal and prefrontal cortices, only in few cases were these changes reproducible across multiple studies. This observation was confirmed in the ALE analysis which predominantly showed changes in visual cortex. A second overall trend was that nearly all changes go in the direction of losses of GW/WM volume, decreases in cortical thickness (except in early visual cortical areas), and reductions in integrity of WM microstructure. With the exception of a few isolated reports, there was no evidence in support of “adaptive” neuroplastic changes as expressed by for instance, an enlargement of the cortical territory of auditory, somatosensory, prefrontal or olfactory areas. This is at odds with some reports from the animal literature which have shown such changes. For instance, using the blind opossum as a model, [Karlen and Krubitzer \(2009\)](#) showed that prenatal enucleation is associated with a significant increase in the size of the somatosensory cortex ([Karlen and Krubitzer, 2009](#)). In congenitally anophthalmic mice, significant volumetric increases were observed within olfactory areas, piriform cortex, orbital areas and amygdala ([Touj et al., 2021](#)).

4.1. Global modifications in the blind brain

Our meta-analysis did not confirm important and consistent alterations in global measures. Only two studies reported an overall reduction in total GM, two in total WM and three in total surface area in EB subjects. For LB individuals, the numbers were even lower. This suggests that the brain is relatively spared structurally by the absence of visual input in terms of global measures. Caution is needed when interpreting these numbers since it is unclear whether they are due to the fact that only few authors investigated or mentioned global numbers. In a recent study from our group, we performed a morphometric analysis of changes in EB, using 7 T MRI imaging. The results showed that EB subjects had lower overall cortical volume, total subcortical GM, and cerebellar cortex and WM ([Kupers et al., 2022](#)). These changes were substantial, with reductions of around 10% in volume compared to normal sighted controls. In accordance with this finding, studies in the congenitally blind opossum also revealed an overall decline in total brain volume of the same magnitude ([Karlen and Krubitzer, 2009](#)).

4.2. Modifications within the retino-geniculo-striate system

One of the most consistent findings of both the systematic review and the ALE analysis is the strong effect of early and late-onset blindness on the retino-geniculo-striate system. Indeed, all components of this pathway, including the optic nerves, optic chiasm, LGN, optic radiations, and primary visual cortex were affected in both EB and LB subjects. The fact that the optic nerves and the optic chiasm did not show up in the ALE analysis is due to the fact that most studies of the optic nerve and chiasm were done in native space and did not provide stereotaxic coordinates, which excludes them from an ALE analysis. The LGN was reduced in four studies only. This is probably due to the fact that in most studies the thalamus was segmented in a classical way, taking all thalamic subnuclei together. This procedure dilutes the volumetric change of the LGN which is relatively small compared to some other thalamic subnuclei. Studies that segmented the thalamus in its constituent nuclei, using either in-house developed tools or advanced plug-ins for software packages like Freesurfer, consistently reported LGN volumetric reductions between 30% and 50% in both EB and LB ([Cecchetti et al., 2016b](#); [Ptito et al., 2021b, 2008a](#); [Aguirre et al., 2016](#)). Cortico-thalamic feedback projections from V1 and local plastic changes may explain why the LGN remains partly spared and metabolically active in the complete absence of afferent visual input from the retina ([Kupers et al., 2011](#)). Feedback projections from the cortex to the thalamus largely outnumber the feed-forward projections from the thalamus to the cortex ([Herrero et al., 2002](#); [Jones, 2012](#)). Since the primary visual cortex responds to various forms of non-visual sensory input in

blind subjects ([Kupers et al., 2011](#)), feed-back projections may explain why the LGN is partly spared. A second possible mechanism is intra-thalamic rewiring. Studies from our laboratory have shown that tactile information is funneled to the visual cortex via the thalamus. In congenitally blind subjects, tactile input first reaches the VPL from which it is further relayed to the LGN, and then to V1 ([Müller et al., 2019](#)). Both the descriptive and the ALE meta-analysis showed that the optic radiations were altered in volume and in WM microstructural properties in EB and LB participants. The diffusion imaging data revealed a decrease in FA in EB and LB, indicating reductions in fiber density, axonal diameter, and/or myelination. Finally, both EB and LB showed alterations within the cuneus, although the nature of the alterations depended on the group. The ALE analysis revealed both a volumetric reduction and an increase in CT in EB, whereas LB only showed a reduction in cortical volume. Some of the studies that quantified GM loss in the cuneus reported reductions between 30% and 40% ([Ptito et al., 2008a](#); [Kupers et al., 2022](#)), which is at par with the reduction observed in the LGN. The increase in CT of the cuneus in EB has been interpreted as an indication of a reduction in cortical pruning due to the lack of visual experience in early life, leaving normally aberrant connections in place ([Kupers and Ptito, 2014](#); [Park et al., 2009](#); [Jiang et al., 2009](#); [Anurova et al., 2015](#); [Hardan et al., 2006](#); [Huttenlocher, 1984](#); [Johnson and De Haan, 2015](#); [Johnson and Gilmore, 1996](#); [Bourgeois et al., 1989](#); [Stryker and Harris, 1986](#); [Waites et al., 2005](#)). This may also explain why higher metabolism has been found in visual cortex of EB ([Veraart et al., 1990](#); [Wanet-Defalque et al., 1988](#)). Others have explained this abnormal metabolic activity by reinforced corticocortical connections responsible for cross-modal plasticity in the visually deprived brain early in life ([Kupers and Ptito, 2014](#); [Müller et al., 2019](#); [Karlen et al., 2006](#); [Berman, 1991](#); [Kingsbury et al., 2002](#); [Ioannides et al., 2013](#); [Kupers et al., 2009a](#); [Ptito et al., 2008b](#); [Kupers et al., 2006](#)). The fact that no CT changes were found in LB individuals is compatible with the cortical pruning hypothesis, as this takes normally place in this group ([Huttenlocher, 1984](#); [Huttenlocher et al., 1987, 1982](#)). Of note, a recent study investigated CT in blind children, aged between two and 12 years ([Hasson et al., 2016](#)). In line with earlier results, the authors confirmed increased CT in primary visual cortex in CB children. However, increases in CT were also observed in areas outside the visual cortex, including superior parietal, anterior-cingular, orbito-frontal and mesial precentral regions. Whereas with ageing, CT remained increased in primary visual cortex, it normalized in the non-visual areas, resembling CT in normal sighted subjects ([Inuggi et al., 2020](#)). Together, this suggests that the effect of visual impairment on CT is an early phenomenon that cannot merely be explained by a reduction in cortical pruning due to lack of visual input. Finally, it is interesting to compare the CT data in EB and LB with those reported in patients with partial vision loss such as in macular degeneration. These patients have significantly smaller CT in the region of the visual cortex that normally receives visual input from the damaged area of the retina. Conversely, peripherally responsive primary visual cortex demonstrated significantly increased CT relative to controls ([Burge et al., 2016](#)).

4.2.1. Ventral and dorsal visual stream

Our review highlights significant volumetric reductions within the ventral visual stream, including the lingual gyrus and the ILF and IFOF, two of its major white matter tracts. The lingual gyrus is the sole cortical structure within the two visual streams that had structural modifications in both the systematic review and the ALE analysis. The lingual gyrus is a heavily interconnected structure that is mostly known for its involvement in fundamental visual processes such as eye movements ([Zhou and Shu, 2017](#)), visual sensation ([Zhang et al., 2016](#)) and visual cognition: visual memory ([Zhang et al., 2016](#)) and visual imagery ([Zhang et al., 2016](#); [Belardinelli et al., 2009](#)). The lingual gyrus is also involved in the early stages of face processing ([Nomi et al., 2008](#); [Palejwala et al., 2021](#)). It is therefore not surprising that blindness affects the anatomical integrity of this structure. What is interesting, however, is that we did

not find any consensual morphological alterations in more anterior cortical regions of the visual ventral pathway like the fusiform face area (FFA), a crucial structure for face recognition (Kanwisher and Yovel, 2006), or the visual word form area (VWFA), a structure that is critical for reading (McCandliss et al., 2003). Similar results were found for the ILF and IFOF, with two studies reporting that the microstructural alterations were more pronounced in their posterior section, closer to the lingual gyrus, than in anterior regions, proximal to the FFA and VWFA (Lao et al., 2015; Reisle et al., 2016b). Together, these results suggest that early loss of vision less affects the ventral visual pathway outside early visual areas and support the hypothesis of reinforced cortico-cortical connections in blindness (Kupers and Ptito, 2014; Müller et al., 2019). This hypothesis further suggests that the extra-striate cortices rely on tactile or auditory input to perform their normal role (e. g. reading, object and face recognition), just as they do in sighted individuals (Sadato et al., 1996; Striem-Amit and Amedi, 2014; Plaza et al., 2015; Dai et al., 2022).

The ALE analysis did not reveal any significant GM changes in the dorsal stream. The systematic review showed that out of nineteen studies that investigated structural changes in area hMT+, only three reported a significant volume reduction (Ptito et al., 2008a; Wan et al., 2013; Ankeeta et al., 2021). Several studies have shown that area hMT+ can develop its functional specialization as motion-sensitive structure independently of vision (Huber et al., 2019; Amemiya et al., 2017; Van Kemenade et al., 2014; Matteau et al., 2010; Ricciardi et al., 2007). Indeed, area hMT+ processes motion-related information derived from auditory and tactile inputs. However, the functional organization of area hMT+ in EB differs from that in sighted subjects; whereas tactile motion stimuli activate both the anterior and posterior part of hMT+ in EB, in sighted individuals only the anterior portion is activated while the posterior part is deactivated (Matteau et al., 2010; Ricciardi et al., 2007).

A possible explanation for the differential effects of blindness on the dorsal and ventral visual streams might be their different temporal profile of structural maturation (Reisle et al., 2016b). Whereas the structural maturation of the ventral stream fibers reaches a plateau as early as of 7 years, dorsal stream fibers mature until early adulthood (reviewed in Klaver et al., 2011). Therefore, cross-modal plasticity processes have a much longer time-period by which they can influence maturation and development for the dorsal stream than for the ventral stream. These results are also in line with data from a paper showing a greater diminution of resting-state functional connectivity for the ventral as compared to the dorsal stream in EB (Qin et al., 2013).

4.2.2. Somatosensory and motor cortex

Results for the somatosensory and motor cortices showed a large variability, especially for the postcentral area. Consequently, the ALE analysis did not reveal any global change in cortical volume measures for either somatosensory or motor cortex. Considering the strong reliance on tactile input by blind subjects, this absence of a volumetric change is rather surprising. In the congenitally blind opossum, the primary somatosensory cortex is significantly larger than in normal sighted controls (Karlen and Krubitzer, 2009). A possible explanation for this negative finding in humans could be the variability in sensory substitution approaches to cope for the loss of vision, going from Braille reading to the usage of tools like vocal synthesizer and guide dogs.

In contrast, the ALE analysis revealed a thinning of the postcentral gyrus in EB. However, care should be taken when interpreting this finding which was driven by only two studies from the same research group, using the same participants (Voss and Zatorre, 2012, 2015). The finding of a cortical thinning of SI can be reconciled by MEG, functional MRI and functional connectivity studies (Müller et al., 2019; Bola et al., 2015, 2014; Xu et al., 2022; Wu et al., 2022; Wu and Sabel, 2021). For instance, a recent MEG study from our group showed reduced directed functional connectivity from SI to thalamus in the beta frequency range in EB (Müller et al., 2019).

4.2.3. Subcortical structures and commissural fibers

Our ALE analysis revealed a large cluster of reduced GM volume in EB in an area including the thalamus, the lentiform nucleus and the posterior part of the parahippocampus. This cluster was not observed in the LB group. The lentiform nucleus comprises the putamen and the globus pallidus, and forms together with the caudate nucleus the dorsal striatum. The striatum is connected to the cortex via several recurrent loops. One of these loops is visual in nature, and connects the extrastriate and inferior temporal visual cortices to the tail of the caudate (Saint-Cyr et al., 1990; Seger, 2008). The globus pallidus receives major input from the striatum, the subthalamic nucleus, and several cerebral cortical regions, and projects to the thalamus, which relays further to prefrontal and other cortical regions (Saga et al., 2017). The principal role of the striatum is to control conscious and proprioceptive movements. Considering the role of vision in motor planning, the volumetric reduction of the lenticular nucleus may be related to the difficulties for the blind in fine motor, balance and trunk control (Bouchard and Tetreault, 2000). However, the striatum is also involved in decision making, reward and motivation, which all require integration of sensory information. A recent study showed that lesions of the posterior putamen impair the integration of olfactory and visual input in normal sighted subjects (Honma et al., 2018).

The large ALE cluster also included the posterior parahippocampus. Together with the hippocampus, the parahippocampus plays a critical role in memory and navigation (Douglas, 1967; Olton et al., 1979; Fyhn et al., 2007; Eichenbaum et al., 2007). Despite the GM reduction in the parahippocampus, EB subjects are not impaired in spatial cognition. When provided with the same amount of information than sighted individuals (e.g. via sensory substitution), EB can navigate and learn new maps as efficiently as their sighted counterparts (reviewed in Chebat et al., 2020b). In addition, in order to detect obstacles and landmarks, EB individuals rely more on sensory-motor areas such as the supramarginal gyrus, Brodmann area 3a (central sulcus) and 4p (primary motor cortex), instead of solely the classic network of hippocampus, entorhinal cortex and dorsal stream (Chebat et al., 2020a).

The ALE analysis did not reveal GM changes in the hippocampus proper. Results on morphometric changes of the hippocampus in EB vary substantially, with some studies showing a volumetric reduction of its posterior part (Ptito et al., 2008a; Chebat et al., 2007), one study reporting a volume increase of the hippocampal head (Fortin et al., 2008) and one study reporting a volume increase of the whole hippocampus (Modi et al., 2012). These studies used a rather crude segmentation which divided the hippocampus in three segments, head, body and tail, and were conducted using a low field (1.5 T) MRI scanner. A recent 7 T MRI study using a more fine-grained hippocampal segmentation procedure reported increases in right subiculum, right CA1 and right whole hippocampal body in LB with Leber's hereditary optic neuropathy (Grochowski et al., 2021).

Finally, the ALE cluster also included the thalamus. The systematic analysis revealed that only three studies have reported changes in thalamic volume in EB, and two in LB. Nevertheless, the reduction in thalamic GM volume was confirmed in the ALE analysis for EB but not for LB. A reduction in thalamic volume was also reported in the congenitally blind opossum (Karlen and Krubitzer, 2009). Studies that have segmented the thalamus in its constituent nuclei have shown that although the largest volumetric reductions are found in the LGN, other thalamic subnuclei are also affected (Cecchetti et al., 2016b; Kupers et al., 2022). It has been hypothesized that in EB, the thalamus forms new synapses between its visual and non-visual nuclei, thus, allowing non-visual inputs to reach the visual system via the LGN (also reviewed in 24) or the pulvinar (Bridge and Watkins, 2019). Indeed, a recent study from our group demonstrated a new fast rerouting of tactile information to V1 directly from the visual nucleus LGN in EB (Müller et al., 2019). Surprisingly, only one study has reported a GM reduction of the pulvinar nucleus (Ptito et al., 2008a), which suggests that this nucleus is relatively insensitive to the effect of visual deprivation, despite its known

role in visual processing (Grieve et al., 2000; Baldwin et al., 2017).

4.3. Structural modifications in the early versus late blind brain

Although our analysis revealed that there are many overlaps in the brain areas that are affected by early and late onset blindness, there are a number of differences as well. Overall, more changes were detected in EB than LB. The ALE analysis showed that the only consistent alterations in LB are a reduction in volume or fractional anisotropy in the retinogeniculo-striate visual system (retinofugal projections, LGN, and V1) (Ptito et al., 2008a; Noppeney et al., 2005; Lee et al., 2014a; Aguirre et al., 2016; Maller et al., 2016; Wan et al., 2013; Leporé et al., 2010; Bauer et al., 2017; Bridge et al., 2009; Jiang et al., 2015; Voss et al., 2014; Manara et al., 2015; Reislev et al., 2016a, 2017; Wang et al., 2013; Hofstetter et al., 2019) and in the ILF and IFOF (Lee et al., 2014a; Qin et al., 2013; Dietrich et al., 2015; Reislev et al., 2016b). There were no systematic alterations in cortical thickness in the LB group, and areas outside the visual system seem spared. A direct comparison of EB and LB revealed that EB have stronger GM reductions in the posterior cingulate cortex and in the cerebellum, and a thicker cortex.

There may be different explanations for this larger effect in EB. First, there are nearly more than double the amount of EB compared to LB in the studies reviewed, giving stronger statistical power for the EB group. Next, whereas the EB groups are quite homogeneous, this is not the case for the LB groups which may contain individuals which vary greatly both in age of onset of blindness and number of years of blindness. These factors are discussed in more details in the following section 22 (Section 4.3).

4.4. Methodological issues and future directions

There are a number of important methodological and conceptual challenges when reviewing the effects of blindness on brain morphometry. First, there is no objective physiological or neuro-developmental criterion to distinguish between EB and LB. Neither is there a consensus with respect to which age to use to separate EB from LB. This has resulted in divergent definitions of late onset blindness. For instance, some researchers have chosen their “cut-off” age for LB based on a vaguely defined critical period of the development of the visual system (beyond 14 and 16 years) (Cohen et al., 1999; Sadato et al., 2002). Others have used a much earlier cut-off of nine years (Fieger et al., 2006), 8 years (Cappagli et al., 2017; Burr and Gori, 2012), or four years (Ankeeta et al., 2021), without justifying their choice. This inconsistency in the definition of LB strongly increases statistical variability, affecting conclusions about morphometric changes for both EB and LB.

A related problem is that our group of EB comprises both individuals who are born blind or became blind early post-natally, as is the case in retinopathy of prematurity, and those who lost their vision before the age of seven. Whereas the former have a very limited or no visual repertoire, the latter have had a normal (or reduced) visual input in their early years. Lumping these two categories together can be strongly challenged from a neuro-developmental perspective. Ideally, one should distinguish between CB, EB and LB. A task force should be created to propose scientifically-based criteria, based on age or behavior, for distinguishing between these three categories. In studies of deafness, it is common to use the age of acquisition of language to separate prelingually from post-lingually deaf individuals (Grégoire et al., 2022). Maybe a similar criterion could be found to distinguish between EB and LB. Since most studies did not distinguish between CB and EB, it was not possible to conduct a separate analysis for these groups. A practical problem is that the age of onset of blindness is often not mentioned in medical records, or this information cannot be retrieved because it is not available in a digitized form. This is particularly problematic for individuals who lost sight before medical records became digitized. In many cases, information on blindness onset is therefore based on patient's verbal report, without the possibility to check the veracity of this

information. A similar problem is encountered for residual light perception. This information is usually also taken at face validity without any behavioural or electrophysiological verification. Future studies should hence perform more appropriate assessment of residual visual perception (e. g. light, shades, forms, etc.). Again, an international task force could define standard protocols for such testing.

Another challenge is the large heterogeneity in the etiology of blindness. Blindness can be caused by various mechanisms (genetic, medical diseases such as anophthalmia, diabetes or glaucoma, ageing, physical injury, etc...); moreover, the disease onset can be immediate (e. g. accidents), rapid or slow, sometimes taking years. Different causes of blindness may affect the brain differently. For instance, the LGN is reduced by about 25–30% in cases of open-angle glaucoma or albinism (Schmidt et al., 2018; Schmitz et al., 2003; Lee et al., 2014b; Kosior-Jarecka et al., 2020; Gupta et al., 2009), whereas in retinopathy of prematurity, the volumetric reductions is by about 50% (Ptito et al., 2021b, 2008a). It is therefore important to take into account the etiology of blindness. Unfortunately, most studies group together all different aetiologies which increases intersubject variance, and negatively affects statistical power. One possibility to circumvent this problem is to perform multicenter studies. When blindness is associated with other medical conditions, great care should be taken to dissociate the effects of loss of vision from more general effects on brain morphometry related to the medical condition. For instance, retinopathy of prematurity is a common cause of congenital blindness. Since pre-term birth can have important effects on brain morphometry in normal sighted individuals (Nosarti et al., 2014; Shang et al., 2019), an additional control group of sighted pre-terms should be added to control for the effect of pre-term birth per se (Reislev et al., 2016a).

Other features that may have an effect on brain plastic changes are compensatory behavioral adaptations such as Braille reading (Siuda-Krzywicka et al., 2016; Matuszewski et al., 2021; Molendowska et al., 2021) or the use of echolocation (Thaler and Goodale, 2016). Although some papers mention whether blind participants practice Braille reading or not, only rarely do they provide quantitative data on reading speed, number of hours of daily practice etc. Likewise, differences in musical pitch and melody discrimination across EB subjects may relate to differences in thickness of the occipital cortex (Voss and Zatorre, 2012). A similar problem is encountered in the study of congenital deafness whereby most early deaf individuals acquire sign language which by itself has a strong impact on brain morphometry (Grégoire et al., 2022). This problem is often resolved by including a second control group consisting of hearing controls who have also acquired the capacity of sign language (Grégoire et al., 2022).

For late onset blindness, things are even more complicated since both age at onset of blindness and number of years of blindness are factors that need to be taken into account. Losing vision during early childhood when the visual system and the brain in general are still under continuous development is different from losing vision in adulthood when cortical pruning is finished and the brain white matter connectivity is fully established. Next, blindness duration also has an important effect on brain morphometry (Grochowski et al., 2021; Reislev et al., 2016b). Moreover, the interaction between blindness onset and blindness duration is not necessarily the same in childhood and adulthood. All this makes the study of late onset blindness complex. To cope to some extent with the effects of blindness onset and blindness duration in LB, we proposed the blindness duration index (Meaidi et al., 2014). The blindness duration index provides a score that takes into account both the age of onset of blindness and the age of the participant at the time of data collection. It is calculated by according to the formula “(age–age onset blindness)/age”. The score varies from 0 to 1, expressing the relative amount of time an individual has been blind, with low scores indicating recent onset of blindness and high scores long duration of blindness. All studies on late onset blindness should take into account the blindness duration index of their LB participants. For instance, we showed before that there is a positive correlation between this index and

FA in ventral stream white matter tracts (IFL and IFOF) (Reislev et al., 2016b).

A wide range of MRI techniques for data acquisition and data analysis is available, that can all influence the results in various manners. For instance, different segmentation approaches (manual vs semi-automatic or fully automatic), different statistical packages (e. g. Freesurfer vs. VBM or in-house written software) may lead to different results. To illustrate, only one study reported an overall change in hippocampal volume. However, the studies that have segmented the hippocampus in its substructures have found evidence for regional changes within the hippocampus (Chebat et al., 2007; Grochowski et al., 2021). The same holds true for the corpus callosum whose overall volume was not found to be affected, whereas a regional volumetric decrease of its posterior part has been consistently reported (Tomaiuolo et al., 2014; Shi et al., 2015). The vast majority of the brain morphometry studies have used 1.5 or 3 Tesla MRI. Future studies should consider using higher magnetic field strengths (e. g. 7 T) which allow for a more precise estimation of cortical thickness. Besides a classical 3D T1-weighted image, additional MRI sequences should be acquired, e. g. a proton-density scan, that allow better segmentation of subcortical nuclei. Future studies should also consider looking at alterations in cortical folding or gyrification in EB and LB (Kupers et al., 2022) that can provide additional information on brain structural (Richman et al., 1975; Kroenke and Bayly, 2018) and functional connectivity (Müller et al., 2019; Bola et al., 2015, 2014; Xu et al., 2022; Wu et al., 2022; Wu and Sabel, 2021).

A final issue to take into account is that brain structural changes should always be seen in combination with brain functional and behavioral changes. Important discrepancies can exist between these different metrics. For instance, whereas several behavioral studies have reported improved tactile sensitivity of the fingertips, this has not been associated with reports of volumetric changes within the somatosensory cortex in blind individuals. Another example is provided by the volumetric reductions in primary visual cortex. Despite the important volumetric reduction of area V1 in early blind subjects, there is a large body of evidence from functional neuroimaging studies that this area not only remains active in early blind subjects (De Volder et al., 1997), but that it also becomes a cross-modal space, responding to various types of non-visual input (reviewed in Harrar et al., 2018); Kupers and Ptito (2014); Ptito et al. (2021a); Pascual-Leone et al. (2005)). Relying solely on morphology may therefore lead to an incomplete understanding of the full scope of the neuroplastic changes in the blind brain. Electrophysiological measures such as EEG or MEG should also be added to study alterations in functional connectivity that cannot be captured by MRI-based methods (Müller et al., 2019; Wu and Sabel, 2021). Finally, there is also a need for getting a better insight in the underlying metabolic changes that take place in the visually-deprived brain. For instance, cross-modal responses could be driven by changes in inhibitory or excitatory neurotransmission in the occipital cortex (Weaver et al., 2013). There is ample evidence that the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) plays an important role in neuroplasticity (reviewed in Desgent and Ptito, 2012). GABA-ergic concentrations can be measured in-vivo in the human brain using magnetic resonance spectroscopy (H-MRS) at high magnetic field strengths (Kupers et al., 2009b; Near et al., 2013). Combined H-MRS and fMRI studies in sighted individuals have shown an inverse relationship between GABA levels in the occipital cortex and the magnitude of the BOLD response to visual stimulation in the occipital cortex (Muthukumaraswamy et al., 2009). Similar combined H-MRS and fMRI studies in the blind brain could further shed some light on the role of GABA-ergic transmission in the cross-modal response to non-visual stimuli in the occipital cortex in the blind brain.

5. Conclusion

We presented a systematic review and ALE coordinate-based meta-analysis on structural modifications in EB and LB. The main structural

modifications induced by early blindness are volumetric reductions in GM and WM within the retino-geniculo-striate system, combined with a thickening of the striate cortex, suggesting that the loss of vision early in life causes neuronal loss and a reduction in synaptic pruning. Other significant morphological alterations were also closely linked to vision-related structures such as the lingual gyrus, splenium of the corpus callosum, parahippocampus, lentiform nucleus, and ventral stream tracts ILF and IFOF. In late onset blindness, only the retino-geniculo-striate system and the lingual gyrus showed a consistent volumetric reduction; contradictory results were obtained for other brain areas. The less consistent findings in LB subjects may at least be partly explained by the absence of a clear-cut criterion of late onset blindness. We discussed a number of particular challenges related to the study of brain morphometric changes in blindness. We provided suggestions of how by combining structural and neurophysiological techniques, future studies could ultimately lead to a better understanding of blindness induced plasticity. This could lead to improved strategies for helping visually-impaired individuals to overcome some of the challenges they face in their daily lives.

Data availability

Data will be made available on request.

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