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Reorganization of thalamocortical connections in congenitally blind humans

Theo F. Marins[1,2] (iD) | Maite Russo[3] | Erika C. Rodrigues[1] | Marina Monteiro[1] | Jorge Moll[1] | Daniel Felix[1] | Julia Bouzas[1] | Helena Arcanjo[4] | Claudia D. Vargas[3] | Fernanda Tovar-Moll[1,2]

[1]D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil

[2]Post-Graduation Program in Morphological Sciences (PCM) of the Institute of Biomedical Sciences (ICB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

[3]Institute of Biophysics Carlos Chagas Filho (IBCCF), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

[4]Centro de Oftalmologia Especializada, Rio de Janeiro, Brazil

Correspondence
Fernanda Tovar-Moll, D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil.
Email: fernanda.tovarmoll@idor.org

Abstract

Cross-modal plasticity in blind individuals has been reported over the past decades showing that nonvisual information is carried and processed by "visual" brain structures. However, despite multiple efforts, the structural underpinnings of cross-modal plasticity in congenitally blind individuals remain unclear. We mapped thalamocortical connectivity and assessed the integrity of white matter of 10 congenitally blind individuals and 10 sighted controls. We hypothesized an aberrant thalamocortical pattern of connectivity taking place in the absence of visual stimuli from birth as a potential mechanism of cross-modal plasticity. In addition to the impaired microstructure of visual white matter bundles, we observed structural connectivity changes between the thalamus and occipital and temporal cortices. Specifically, the thalamic territory dedicated to connections with the occipital cortex was smaller and displayed weaker connectivity in congenitally blind individuals, whereas those connecting with the temporal cortex showed greater volume and increased connectivity. The abnormal pattern of thalamocortical connectivity included the lateral and medial geniculate nuclei and the pulvinar nucleus. For the first time in humans, a remapping of structural thalamocortical connections involving both unimodal and multimodal thalamic nuclei has been demonstrated, shedding light on the possible mechanisms of cross-modal plasticity in humans. The present findings may help understand the functional adaptations commonly observed in congenitally blind individuals.

KEYWORDS
congenital blindness, cross-modal plasticity, diffusion tensor imaging, thalamus

1 | INTRODUCTION

Blindness and vision impairment affects at least 2.2 billion people worldwide, and congenital conditions are one of its leading causes in children and young adults (WHO, 2019). Congenital blindness represents an intriguing model for understanding how the brain builds and maintains its fundamental principles of organization and hierarchy of processing without one of the major input sources. The impact of

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congenital blindness on spared sensory systems has also been a focus of study over the past years. A better characterization of the basis of blindness-related brain alterations, including the well-described phenomenon of cross-modal plasticity, can pave the way for developing and optimizing new inclusive devices and brain-machine interfaces.

Numerous brain alterations can occur in response to the lack of visual input, including in white matter (WM) and gray matter (GM) of both cortical and subcortical brain structures (Aguirre et al., 2016; Anurova et al., 2019; Lao et al., 2015). Congenitally/early blind individuals often exhibit atrophy of optic chiasm and reduced microstructural integrity of optic radiations and geniculocalcarine tract (Bridge et al., 2009; Noppeney et al., 2005; Park et al., 2007; Ptito et al., 2021; Reislev et al., 2016; Shu, Liu, et al., 2009), as investigated by Diffusion Tensor Imaging (DTI). Also, the splenium of the corpus callosum, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus, major WM bundles connecting different cortical areas involved in visual processing and perception, are impacted by the absence of visual input (Collignon et al., 2007; Dietrich et al., 2015; Leporé et al., 2010; Ptito et al., 2008; Reislev et al., 2016; Shu, Li, et al., 2009).

Functional neuroimaging studies have shown that visual cortical structures in blindness often participate in the processing of non-visual information, which is called cross-modal plasticity. In blind individuals, this reorganization is commonly observed as a visual takeover by the auditory and tactile systems (Büchel et al., 1998; Burton et al., 2002; Röder et al., 1999; Sadato et al., 1996; Wan et al., 2010; Weeks et al., 2000). Still, it has also been reported involving language (Lane et al., 2015; Röder et al., 2002), olfaction, and gustation (Cuevas et al., 2009; Rosenbluth et al., 2000) very often leading to increased abilities and behavioral improvement in the remaining senses. In addition, recruitment of "visual" brain areas in blindness has been reported during auditory (Anurova et al., 2015; Collignon et al., 2011; de Volder et al., 1999; Gizewski et al., 2003; Hölig et al., 2014), tactile (Büchel et al., 1998), and linguistic (Lane et al., 2015) tasks, and the correlation with behavioral gains has also been shown (Gizewski et al., 2003; Gougoux et al., 2005; Stevens et al., 2007; Voss et al., 2008; Voss & Zatorre, 2012). Moreover, virtual lesions targeted to the "visual" cortex induced by transcranial magnetic stimulation (TMS) can temporarily impair performance on auditory (Collignon et al., 2007) and tactile (Cohen et al., 1997) tasks in blind individuals. Altogether, these findings suggest that the brain undergoes critical changes in the absence of visual input, which pave the way for cross-modal plasticity.

While evidence corroborates cross-modal plasticity in blindness, neuroanatomical correlates underlying this phenomenon are controversial and may involve a wide range of brain structural changes, including the development of new connections and unmasking/rewiring of the existing ones (Bavelier & Neville, 2002). Indeed, it is unclear how and which pathways convey non-visual information to the visual cortex in blind individuals. Most findings on the possible anatomical underpinnings of cross-modal plasticity and its mechanisms come from animal models of blindness studies. They point to the emergence of direct connections between deprived visual,

auditory, and somatosensory cortices, indicating that non-visual information would reach the visual cortex by direct corticocortical connectivity, a transient connection that becomes stabilized during development by the lack of appropriate visual stimuli (Charbonneau et al., 2012; Clavagnier et al., 2004; Falchier et al., 2002; Hall & Lomber, 2008; Karlen et al., 2006; Kingsbury et al., 2002; Rockland & Ojima, 2003). On the other hand, the preservation (Bridge et al., 2009; Pallas et al., 1999; Zhang et al., 2012), even though partially (Pan et al., 2007; Ptito et al., 2008; Reislev et al., 2016; Reislev et al., 2017), of geniculocalcarine pathways in blind individuals (Bridge et al., 2009; Pallas et al., 1999; Zhang et al., 2012) has been reported, which supports the idea that adaptive plasticity may rely upon the conservation of thalamocortical pathways. In the naturally blind mole rat, the remnant visual pathways carry auditory information to the visual cortex as their visual nuclei of the thalamus receive input from the inferior colliculus, an important auditory center (Bronchti et al., 1989; Doron & Wollberg, 1994). Moreover, in addition to the preserved thalamocortical connections, visual cortical areas receive information from auditory and somatosensory nuclei of the thalamus in blind mice and opossum (Karlen et al., 2006; Laemle et al., 2006). These findings suggest that robust changes in the thalamocortical connectivity may occur in response to the lack of visual input and could also explain the cross-modal plasticity observed in congenitally blind individuals.

Thus, despite remarkable changes that have been reported in the brain of congenitally blind individuals, the structural underpinnings of cross-modal plasticity are still uncertain in humans. In the present study, we used neuroimaging techniques based on diffusion-weighted imaging and probabilistic tractography to interrogate the thalamic (re) mapping of cortical connections of congenitally blind individuals. Specifically, we tested the hypothesis that structural changes of thalamo-cortical projections involved in visual and multimodal sensory processing would occur in response to the absence of appropriate visual input from birth. We also described the possible impacts of congenital blindness in the appropriate maturation of WM bundles and in the intrinsic organization of the thalamus. Our results point to a remapping of the thalamic connections with both temporal and occipital cortices in congenitally blind individuals compared to a matched sample of sighted controls and impaired microstructure of visual WM bundles.

2 | METHODS

2.1 | Subjects

This study was conducted in accordance with the ethical standards-compliant with the Declaration of Helsinki and has been approved by the IDOR/Copa D'Or Ethics and Scientific Committee. Ten congenitally blind (CB; mean age: 31.8, standard deviation: 8.7, 6 males) individuals and 10 sex- and age-matched sighted controls (SC; mean age: 32.2, standard deviation: 6.66, 6 males) were included in the study. All participants were right-handed, had no history of neurologic or

psychiatric diseases, and were not taking brain-active medication. For the inclusion of the CB individuals, their medical records and additional clinical exams (such as the visual evoked potentials) have been reviewed. Afterward, they were examined by an experienced ophthalmologist, confirming that they were totally blind or had only minimal residual light sensitivity. All blind participants were Braille readers. The cohort characteristics are summarized in Table 1.

2.2 | Data acquisition

Brain imaging was performed at D'Or Institute for Research and Education (IDOR) in a 3 T Achieva scanner (Philips Medical Systems, the Netherlands) using an eight-channel SENSE head coil. Imaging consisted in a high-resolution 3D T1-weighted image (1 mm³ isotropic, TR/TE [ms] = 7.2/3.4, FOV = 240 × 240, matrix = 240, slice thickness = 1 mm) and diffusion-weighted (2 × 2 × 2 mm³ isotropic, no gap, TR/TE [ms] = 10,150/60, FOV = 224 × 224, matrix = 112 × 112) with diffusion sensitization gradients applied in 64 noncollinear directions, with a b factor of 1000 s/mm², one volume without diffusion weighting.

2.3 | Data analysis

Before data preprocessing, images were visually inspected for excessive movements or artifacts. Diffusion-weighted images were preprocessed and analyzed using FSL (Smith et al., 2004) toolboxes. In each subject, original data were corrected for the effects of head movement and eddy currents using eddy correct, and a brain mask was created by running BET (Smith, 2002) on the B = 0 (no diffusion weighting) image. We created FA images using FDT (with DTIFIT algorithm), part of FSL (Behrens et al., 2003). All subjects' data were aligned into standard space (Montreal Neurological Institute, MNI) using the nonlinear registration tool FNIRT, and the mean FA image was created and thinned to create a mean FA skeleton. The FA map of each subject was projected onto skeletonized FA, and the resulting data was fed into voxel-wise cross-subject statistics using TBSS (Smith et al., 2006). We tested for group differences with an unpaired

t-test using Randomise (Winkler et al., 2014) for permutation-based (5000 permutations) non-parametric testing of whole skeleton FA. Also, analysis restricted to the whole thalamus was separately conducted. WM structures that showed significant differences between groups were identified with the aid of a tract atlas (Warrington et al., 2020). Exploratory extraction of tract-based FA and mean diffusivity (MD) has been performed using the XTRACT toolbox (Warrington et al., 2020). Extreme outliers (values above Q3 + 3 × IQR or below Q1–3 × IQR) have been excluded. Group comparisons have been performed based on the previous findings (Reislev et al., 2016) in the optic radiation, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, forceps major, forceps minor, and the corticospinal tract.

Connectivity-based segmentation of the thalamus was also performed using FDT, as described previously (Behrens et al., 2003), in each hemisphere separately. Six cortical masks were predefined using the Harvard-Oxford atlas: Prefrontal, Precentral, Postcentral, Posterior Parietal (parietal cortex, except for the postcentral cortex), Occipital, and Temporal. Since the Oxford Thalamic Connectivity Probability Atlas does not include the lateral and medial geniculate nuclei (LGN and MGN, respectively), both right and left thalamic masks were obtained from an atlas on the Colin-27 Average Brain (Chakravarty et al., 2006). All masks were registered into the subjects' space using nonlinear registration. After BEDPOSTX (Behrens et al., 2003), probabilistic tracking was conducted with the PROBTRACKX (Behrens et al., 2003) tool, in which the unilateral thalamus was defined as the seed region and the six ipsilateral cortical masks as classification targets. Following, we calculated the number of samples reaching each target mask as a proportion of the total number of samples reaching any target mask. Then, the hard segmentation of each thalamus based on its connectivity to each of the six ipsilateral cortical areas was performed. The volume of each resultant segment of the thalamus was normalized by the volume of the ipsilateral thalamus at the subject level. Group analysis of the normalized volume was performed with SPSS 20.0 (IBM Corporation, New York) using a repeated-measures analysis of variance (ANOVA; within-subjects factors: "segment" and "side"; between-subjects factor: "group"). We used Bonferroni to adjust for multiple comparisons.

TABLE 1 Cohort characteristics

Patient ID	Age	Gender	Cause of congenital blindness	Handedness	Braille
CB01	35	F	Anophthalmia	Right	Yes
CB02	36	M	Macular dystrophy	Right	Yes
CB03	32	F	Glaucoma	Right	Yes
CB04	18	M	Glaucoma	Right	Yes
CB05	40	M	Glaucoma	Right	Yes
CB06	27	M	Glaucoma	Right	Yes
CB07	22	M	Retinal detachment	Right	Yes
CB08	44	M	Unknown	Right	Yes
CB09	24	F	Retinopathy of prematurity	Right	Yes
CB10	40	F	Unknown	Right	Yes

Abbreviations: F, female; M, male.

To perform a voxel-wise analysis of the thalamocortical connectivity and compare them between groups, the resultant six segments at the subject level were transformed back to the MNI space. Each segment was overlapped to create a single mask, thus consisting of a sum of all individual segment masks from both groups. The voxel-wise analysis of the tractography-defined connectivity was conducted within this mask separately for each thalamic segment. These values are expressed as total connectivity and were used as dependent variables in the following analysis. Group differences were investigated with an unpaired t-test using Randomise (Winkler et al., 2014) for permutation-based (5000 permutations) non-parametric testing of the connectivity maps for each segment.

For simplicity, group differences are referred to as "increase" and "decrease" throughout the manuscript taking the SC group as a reference. The coordinates in the figures are given according to MNI space, and results are plotted on the MNI standard brain.

3 | RESULTS

3.1 | Reorganization of thalamocortical connections

The thalamus segmentation based on the structural connectivity patterns to six predefined cortical areas (Prefrontal, Precentral,

Postcentral, Posterior Parietal, Temporal, and Occipital) successfully resulted in six thalamic segments on each side (Figure 1) in all participants.

The analysis of thalamic volumes revealed an interaction effect between "segment × group" ($F[2.32, 41.80] = 4.76$, $p = .01$). Post-hoc analysis with Bonferroni correction for multiple comparisons on the interaction "segment × group" indicated that the SC and CB groups significantly differed in the volume of the Occipital segment ($p = .013$), being reduced in the CB group; and the Temporal segment ($p = .002$) being increased in the CB group (Figure 1; Table 2).

In addition, there was a main effect of "segment" ($F[2.32, 41.80] = 635,92$, $p < .005$) and an interaction between "segment × side" ($F[2.56\ 46.01] = 9.77$, $p < .005$). Pairwise comparisons were run to investigate the main effect of "segment" and interaction "segment × side" adjusting for Bonferroni (Table S1 and S2).

To investigate whether congenital blindness alters the anatomical connectivity pattern between the thalamus and the cortex, we conducted a group comparison using threshold-free cluster enhancement (TFCE, FWE-corrected, $p < .05$) of the probability maps of connectivity of each thalamic segment. This analysis revealed that the connectivity of the thalamic segment connecting with the Occipital and the Temporal targets significantly differed between groups, with the thalamo-temporal connectivity being increased and the thalamo-occipital connectivity being reduced in the CB group. Specific regions showing increased thalamo-temporal connectivity in the CB group
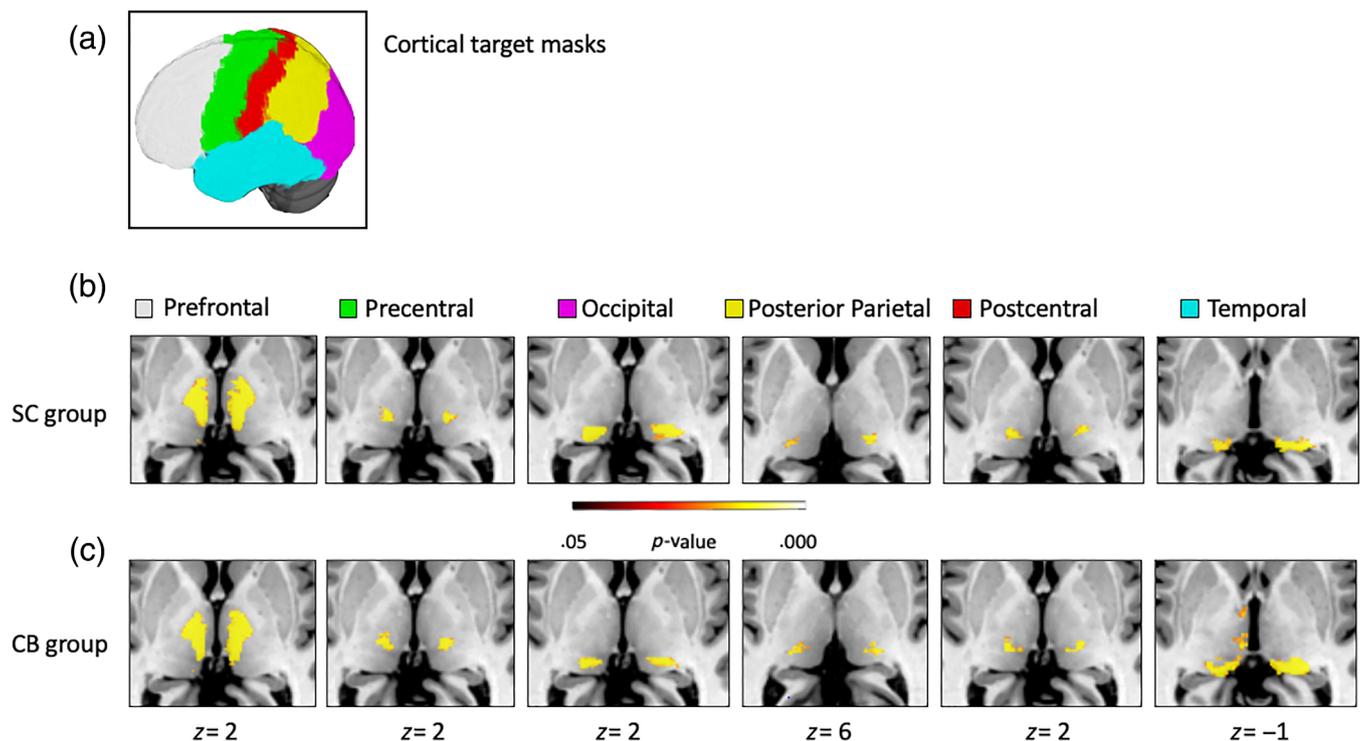

FIGURE 1 Thalamocortical connectivity in sighted controls and congenitally blind individuals. (a) Six cortical masks were predefined using the Harvard-Oxford atlas: Prefrontal, precentral, postcentral, posterior parietal (parietal cortex, except for the postcentral cortex), occipital, and temporal. Resultant thalamic segments showed statistically significant connectivity to each cortical area in the (b) SC (sighted controls) and (c) CB (congenitally blind) groups. The color bar represents the p-value after FWE correction. The normalized volume of the occipital and temporal segments showed group differences ($p < .001$, Bonferroni-corrected for multiple comparisons).

TABLE 2 Normalized volume comparisons of thalamic segments

Segment	Side	SC		CB	
		Mean volume	SD	Mean volume	SD
Prefrontal $p = .064$	R	0.561224	0.0372437	0.515953	0.0578148
	L	0.537903	0.0424005	0.505637	0.0457513
Precentral $p = .14$	R	0.055635	0.0125891	0.060761	0.0150288
	L	0.067851	0.0290276	0.078154	0.0259177
Occipital* $p = .013$	R	0.11052	0.0286398	0.071793	0.0451293
	L	0.138718	0.0443775	0.088397	0.0174996
Posterior parietal $p = .97$	R	0.065566	0.0267344	0.064867	0.0174419
	L	0.049694	0.026557	0.05505	0.0229696
Postcentral $p = .07$	R	0.044252	0.0156764	0.040539	0.0148974
	L	0.060081	0.0209732	0.071497	0.0407492
Temporal* $p = .002$	R	0.162803	0.0458977	0.246086	0.0842971
	L	0.145753	0.0363323	0.201264	0.0570562

Note: Mean volume refers to the normalized mean volume in arbitrary units.

Abbreviations: L, left thalamus; R, right thalamus.

*Segments that showed significant ($p < .05$) between-group differences after Bonferroni correction for multiple comparisons.
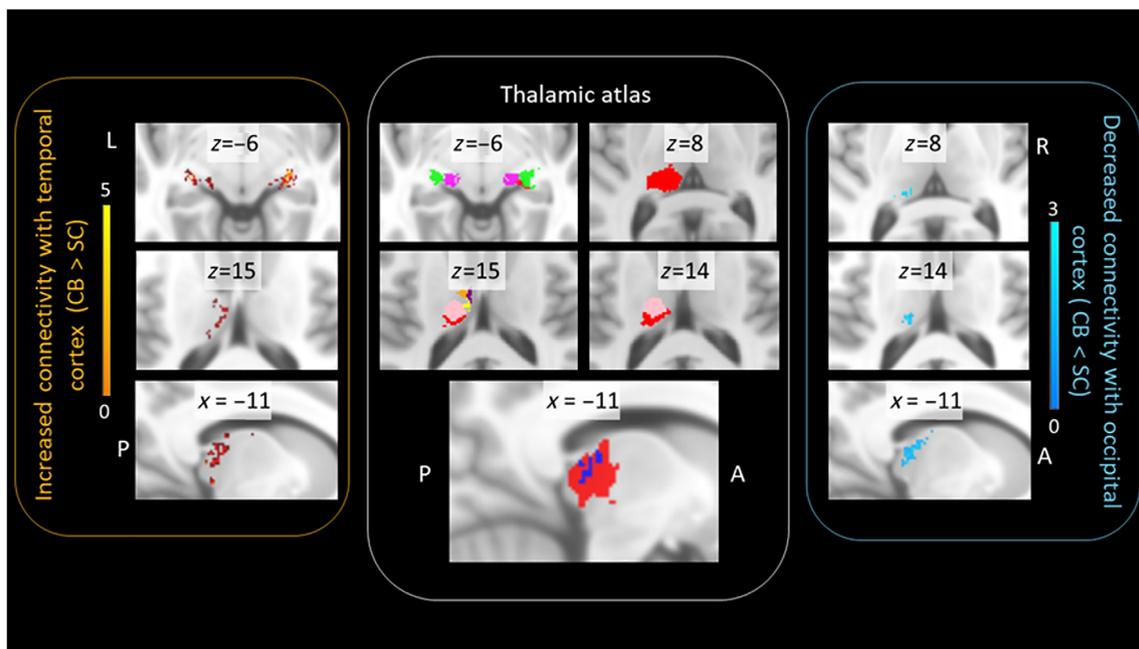

FIGURE 2 Thalamocortical connectivity changes in congenitally blind individuals. The yellow box (left) depicts thalamic areas that exhibited increased connectivity with the temporal cortex, including MGN, LGN, and pulvinar bilaterally. The blue box (right) depicts thalamic territory that exhibited decreased connectivity with the occipital cortex in congenitally blind individuals, namely the left pulvinar/lateral posterior nucleus. The white box (middle) shows thalamic territories obtained from an atlas based on the Colin-27 average brain (Chakravarty et al., 2006) and depicts the location of LGN (green), MGN (dark pink), pulvinar (red), medial dorsal (yellow), ventral anterior (orange), anterior (purple), and lateral posterior (light pink) nuclei. A graphical overlay (dark blue) of thalamic areas that exhibited both increased connectivity to the temporal cortex and decreased connectivity to the occipital cortex ($p < .05$, FWE-corrected) in CB individuals is shown (white box, bottom). a, anterior; L, left; P, posterior; R, right; . The coordinates are given according to the MNI space and plotted on the MNI standard brain. Color bars represent the t-value.

were observed in both thalami, specifically in the bilateral LGN, bilateral pulvinar, bilateral MGN, left medial dorsal nucleus, left anterior nucleus, left ventral anterior nucleus and left lateral posterior nucleus (Figures 2 and S1). On the other hand, reduced thalamo-occipital anatomical connectivity in the CB group was restricted to the territory of the pulvinar and lateral posterior nucleus on the left thalamus

(Figures 2 and S1). To determine what areas of the temporal and occipital cortices these resultant thalamic voxels are connected with, we performed separate probabilistic tractography analyses with these clusters localized inside LGN, MGN, and the pulvinar as seeds and their respective cortical area as targets. This analysis revealed that these clusters showed reliable connections with the Occipital and Temporal targets in both groups, with great overlap among individuals (Figures S2–S5).

Further analysis revealed that both group-differences in thalamo-cortical connectivity (increased thalamo-temporal connectivity and decreased thalamo-occipital connectivity) partially shared a common neural territory on the left pulvinar (Figure 2). Thalamic projections to the Prefrontal, Precentral, Postcentral, and Posterior Parietal targets did not show statistically significant differences between groups.

3.2 | Microstructural changes in blind subjects

We investigated differences in WM microstructure using TBSS for fractional anisotropy (FA). Whole-brain (threshold-free cluster enhancement [TFCE], corrected $p < .05$) analysis showed decreased FA in the major WM structures connecting the occipital cortex in the CB group, such as in parts of the forceps major, bilateral inferior fronto-occipital fasciculi, bilateral middle longitudinal fasciculi and bilateral optic radiations (Figure 3). Additional analysis restricted to the whole thalamus revealed a diffuse decrease in FA in the CB group, including left and right pulvinar, medial dorsal nucleus, right LGN, right ventral lateral nucleus, right lateral posterior, and left lateral nucleus

(Figure 3). Group comparisons for the MD maps did not show significant results.

Group comparison of mean FA in a priori WM tracts showed an interaction effect between "tract × group" (ANOVA, $F[41, 451] = 1.52$, $p = .023$). Post-hoc analysis with Bonferroni correction for multiple comparisons indicated that CB showed reduced FA in the bilateral optical radiation, left arcuate fasciculus, and part of the right superior longitudinal fasciculus (Figure 4). MD analysis did not lead to statistically significant results. Mean FA and MD have been extracted from 42 WM bundles for descriptive purposes (Table S3).

4 | DISCUSSION

The present findings indicate that the absence of appropriate visual input from birth in humans leads to robust WM changes. For the first time, we described a structural remapping of thalamocortical connectivity, which may help understand the functional adaptations commonly observed in congenitally blind individuals.

The analysis of a sample of right-handed CB individuals, Braille readers, brought new evidence of reduced thalamic areas projecting to/from the occipital cortex compared to SC. On the other hand, a greater volume of the thalamic territory dedicated to connections with the temporal cortex was observed in CB compared to SC. Additionally, the voxel-wise analysis revealed that thalamic nuclei, such as bilateral LGN, MGN, and pulvinar, were more connected to the temporal cortex in CB. In contrast, the left pulvinar and lateral posterior nuclei displayed weaker projections to the left occipital
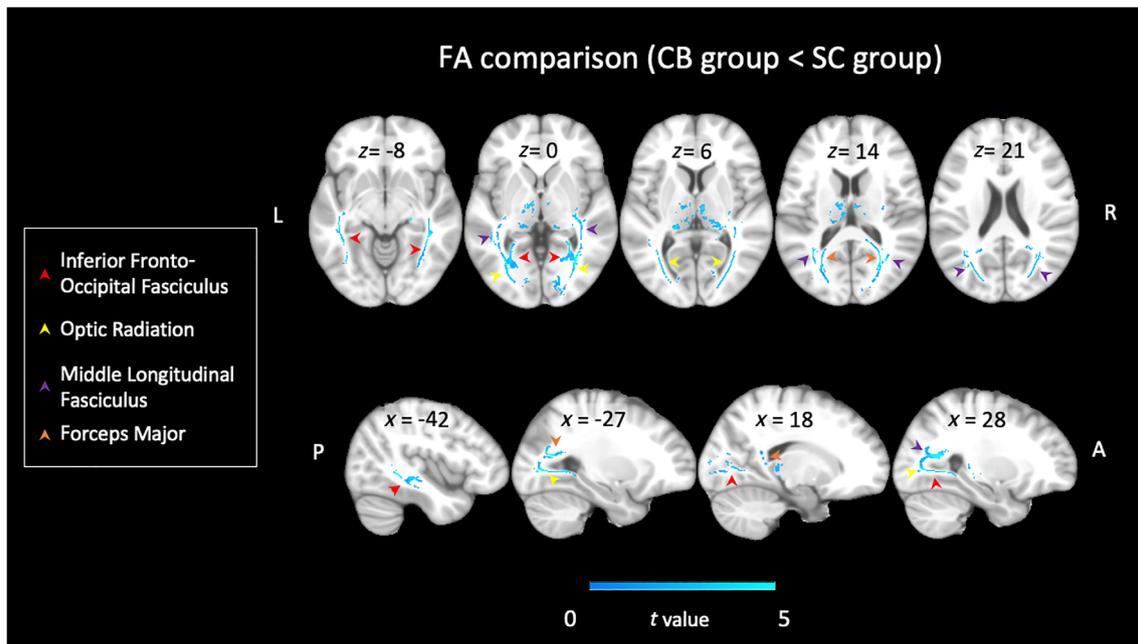

FIGURE 3 FA comparison (CB group < SC group). White matter tracts (whole brain) showed reduced FA (fractional anisotropy) in the CB (congenitally blind) group, as compared to SC (sighted controls) group. FA difference in the thalamus, resulting from a separate analysis, is also displayed. The color bar represents the t value corrected for multiple comparisons (FWE-corrected, $p < .05$). CC, corpus callosum; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus.

FIGURE 4 Mean FA has shown group × tract interaction in an ANOVA. Post-hoc analysis (Bonferroni-corrected, $p < .05$) pointed to differences in the left arcuate fasciculus, bilateral optic radiation, and part of the right superior longitudinal fasciculus. The same analysis performed with extracted MD did not show significant "group × tract" interaction. CB, congenitally blind group; SC, sighted control group
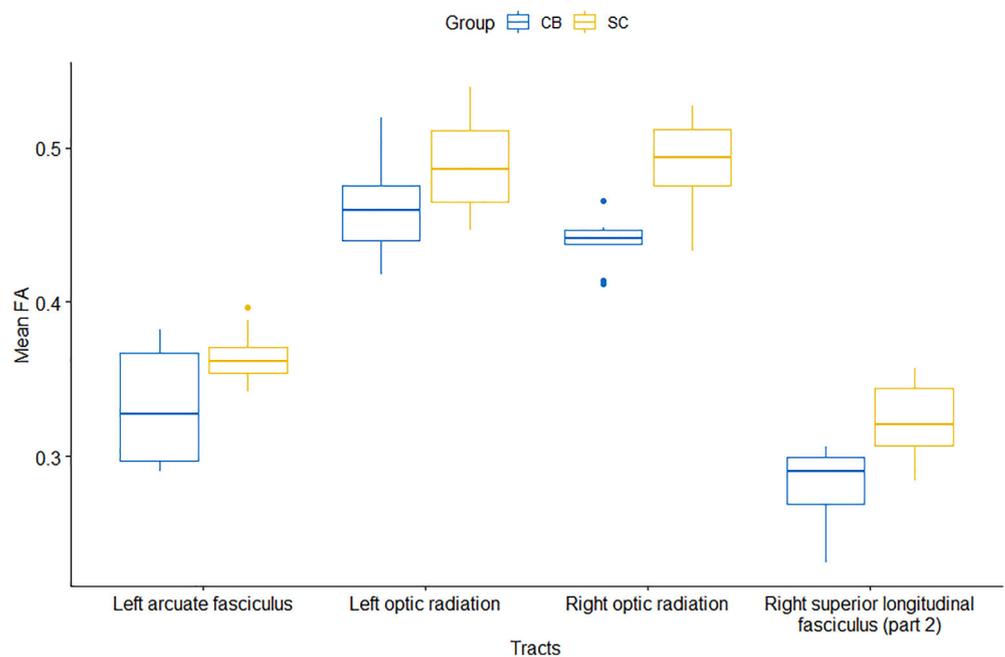
cortex in this group. Interestingly, we found strengthened connectivity of the left pulvinar to the temporal cortex over the occipital cortex, suggesting a possible rerouting of the pulvinar connections in CB. Moreover, we confirmed previous findings by showing a diffuse impairment in the microstructure of major visual WM bundles.

Our findings bring new evidence in line with previous studies showing impairment of thalamic nuclei involved in visual and multimodal processing, such as LGN and pulvinar. Using voxel-based morphometry (VBM), previous studies have shown volume reductions in thalamic visual centers in CB individuals, including dorsal LGN and pulvinar (Cecchetti et al., 2016; Ptito et al., 2008), identified with the aid of brain atlases. A similar approach has been used to describe volume reduction in WM close to the LGN in six bilaterally anophthalmic subjects compared with sighted subjects (Bridge et al., 2009). However, it is worth noting that the present study was not limited to comparing the volume of thalamic structures between groups. Instead, we went beyond by mapping the thalamocortical projections and exploring a possible remapping of thalamic territories and their connectivity pattern to/from the cortex. Thus, one key difference between the present and previous studies is that visual-related thalamic nuclei investigated here were identified using subject-level tractography. Interestingly, the thalamic territory occupied by projections to/from the temporal cortex showed greater volume, whereas those to/from the occipital cortex showed reduced volume in CB individuals compared to the SC, which brings new insights into the thalamic remodeling in congenital blindness. The comparison of thalamic volumes obtained from different approaches, such as probabilistic tractography and VBM, must be explored in future studies considering their technical aspects and biological underpinnings. For example, we employed a probabilistic tractography algorithm to map the connectivity distributions from individual voxels within the thalamus in each participant, while VBM relies on the boundaries between thalamic nuclei (Iglesias et al., 2018).

Even though interesting, volume comparisons of thalamic structures have low intrinsic sensitivity, as differences in connectivity may not be reflected as volume changes. This would be even more tricky since thalamocortical remapping may be presented as both shrinkage and expansions of nuclei territories in a non-homogeneous and distributed pattern. For the first time, we disentangled this by comparing the voxel-wise differences in thalamocortical connectivity between groups, revealing the pulvinar's central role in remapping thalamocortical connectivity. WM connections between pulvinar/lateral posterior nuclei and occipital cortex were decreased in the CB group. On the other hand, increased connectivity to/from the temporal cortex was observed in the pulvinar. These findings suggest a shift in the thalamocortical connections in blind individuals, prioritizing the temporal projections over the occipital ones.

The pulvinar is the largest, higher-order multimodal thalamic nucleus, involved mainly in visual attention (Benarroch, 2015). It displays a wide range of cortical connectivity beyond the visual cortex, roughly to the GM of all lobes and subcortical structures such as the amygdala and superior colliculus (Benarroch, 2015; Leh et al., 2008; Saalmann et al., 2012). Evidence suggests that cortico-cortical integration via pulvinar is an important pathway for transferring visual information between cortical areas (Saalmann et al., 2012; Theyel et al., 2010). Thus, it is reasonable to hypothesize that the pulvinar may become a central player in the dynamics of cross-modal plasticity, possibly by integrating different sensory modalities at associative levels and paving multimodal plasticity in blind individuals. However, the pulvinar typically connects to higher-order areas of the temporal cortex, such as inferior, ventral, and lateral temporal areas, temporo-parietal junction, and mesial temporal cortex (Arcaro et al., 2015; Leh et al., 2008; Rosenberg et al., 2009). Therefore, it is impossible to conclude whether the aberrant connectivity pattern of the pulvinar described here relies on new thalamocortical projections to the temporal cortex or a mechanism of remodeling the preexisting ones.

Hence, the role of pulvinar in cross-modal plasticity needs to be considered and further explored in future studies.

It is worth noting that our findings add new insights to the still-developing literature on thalamocortical connectivity changes in blind humans. Even though Reislev and colleagues (Reislev et al., 2017) have investigated possible differences in thalamocortical connectivity between CB and SC groups, evidence of thalamic remapping has not been found. For the first time using a voxel-wise approach, we reported converging evidence that thalamic projections to/from the temporal cortex are increased as opposed to those to/from the occipital cortex. First, comparisons of the thalamic territory connecting to the temporal and occipital cortices showed increased and decreased volume in the CB group, respectively. Second, the voxel-wise analysis pointed to an aberrant pattern of thalamocortical connectivity involving pulvinar/lateral posterior nucleus, LGN, and MGN, among others. Thus, despite similarities, we used original analysis to describe the impact of congenital blindness on thalamocortical connectivity in humans.

We did not find evidence of thalamic remapping of connections to the somatosensory and motor cortices, for example, in CB. However, careful interpretation of the results must consider two key points. First, the connectivity-based segmentation of the thalamus used in the present study is a "winner-takes-all" approach in which the most probable connections are considered while the least probable ones are discarded. Hence, plasticity involving somatosensory and motor remodeling of thalamic connections may not have been strong enough to be detected by our methods. As a result, the "normal" pattern of thalamic segmentation would mask meaningful but less structured connections. For example, even though weaker, somatosensory, auditory, and motor thalamic nuclei are connected with V1 in blind opossum (Karlen et al., 2006). In addition, V1 activation following tactile stimulation may be driven by aberrant connections between the ventroposteriorlateral nucleus and LGN in CB individuals (Müller et al., 2019). Second, although we did not intend to assess corticocortical connections between visual and the remaining sensory modalities, this kind of direct connectivity has been reported in animal models of blindness and must be considered a possible mechanism of cross-modal plasticity in humans. In fact, the intermodal connections during ontogenesis seem to be altered by the lack of visual input in animals (Berman, 1991; Bock et al., 2012; Charbonneau et al., 2012; Laemle et al., 2006; Laramée et al., 2014). In humans, indirect measurement based on functional connectivity pointed to direct connections between the occipital and auditory cortex (Klinge et al., 2010) and primary somatosensory cortex (Ioannides et al., 2013; Wittenberg et al., 2004). Moreover, the visual cortex of enucleated animals also displays both abnormal corticocortical and thalamocortical connections with somatosensory, auditory, and motor areas (Karlen et al., 2006), suggesting that both mechanisms may coexist to support cross-modal plasticity in this condition.

In accordance with previous studies that showed decreased FA of WM in CB (Leporé et al., 2010; Ptito et al., 2008; Reislev et al., 2016; Shu, Li, et al., 2009), both voxel-wise and tract-based analysis pointed to the focal impairment of WM integrity in CB individuals. Structures showing decreased FA included optic radiation and parts of the ventral and dorsal streams of the visual system. Lower FA values refer to WM integrity and myelination impairments and are commonly pointed to as a biomarker of developmental changes, axonal degeneration, and plasticity. Indeed, visual input is crucial for the maturation and refinement of early connectivity of the visual system (Bourgeois et al., 1989; Laramée et al., 2014; Sengpiel & Kind, 2002), suggesting that decreased myelination of visual WM tracts in CB individuals might reflect the lack of maturation of the system rather than axonal degeneration per se. Such an insufficient maturation of the visual system also impacts the internal cytoarchitecture of the thalamus (Cooper et al., 1993; Sengpiel & Kind, 2002), which may be presented as decreased FA values (Assaf, 2019; Johansen-Berg et al., 2005; Wang et al., 2020).

The present findings raise intriguing questions that should be addressed in future studies. First, the CB group showed increased structural connectivity between the ventral anterior nuclei and the temporal cortex. Given that most studies focused on exploring abnormal thalamocortical connectivity involving V1, the possible involvement of a motor thalamic nucleus, such as the ventral anterior, deserves further investigation. Importantly, we cannot rule out the existence of intrathalamic connections underlying this finding, as probabilistic connectivity is an indirect method for inferring connectivity. However, evidence from translational studies supporting this hypothesis remains to be shown. Second, our sample of blind individuals includes only CB. Despite similar approaches have targeted both CB and late blind individuals (Reislev et al., 2017), future studies should employ voxel-wise investigation of thalamocortical connectivity in people with acquired blindness to elucidate to what extent the present thalamocortical connectivity changes depend on visual experience.

In summary, the present study corroborates previous findings pointing to the brain of congenitally blind individuals as a model of WM plasticity. For the first time in humans, the remapping of thalamocortical connections involving both unimodal and multimodal thalamic nuclei has been described, which may represent a mechanism of how non-visual stimuli are relayed to the "visual" cortex. Future studies should employ neurophysiologic approaches to correlate these changes with functional plasticity often observed in the absence of visual stimuli from birth.

CONFLICT OF INTEREST

DATA AVAILABILITY STATEMENT

ORCID

Theo F. Marins [ID] https://orcid.org/0000-0002-5017-707X

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