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Title: Changes in thalamocortical connectivity as a potential mechanism of cross-modal plasticity in congenitally blind individuals

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Keywords: cross-modal plasticity, congenital blindness, diffusion tensor imaging, thalamus, cortical thickness

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ABSTRACT

Evidence of cross-modal plasticity in blind individuals has been reported over the past decades showing that non-visual information is carried and processed by classical "visual" brain structures. This feature of the blind brain makes it a pivotal model to explore the limits and mechanisms of brain plasticity. However, despite recent efforts, the structural underpinnings that could explain cross-modal plasticity in congenitally blind individuals remain unclear. Using advanced neuroimaging techniques, we mapped the thalamocortical connectivity and assessed cortical thickness and integrity of white matter of congenitally blind individuals and sighted controls to test the hypothesis that aberrant thalamocortical pattern of connectivity can pave the way for cross-modal plasticity. We described a direct occipital takeover by the temporal projections from the thalamus, which would carry non-visual information (e.g. auditory) to the visual cortex in congenitally blinds. In addition, the amount of thalamo-occipital connectivity correlated with the cortical thickness of primary visual cortex (V1), supporting a probably common (or related) reorganization phenomena. Our results suggest that aberrant thalamocortical connectivity as one possible mechanism of cross-modal plasticity in blinds, with potential impact on cortical thickness of V1.

SIGNIFICANT STATEMENT

Congenitally blind individuals often develop greater abilities on spared sensory modalities, such as increased acuity in auditory discrimination and voice recognition, when compared to sighted controls. These functional gains have been shown to rely on 'visual' cortical areas of the blind brain, characterizing the phenomenon of cross-modal plasticity. However, its anatomical underpinnings in humans have been unsuccessfully pursued for decades. Recent advances of non-invasive neuroimaging techniques allowed us to test the hypothesis of abnormal thalamocortical connectivity in congenitally blinds. Our results showed an expansion of the thalamic connections to the temporal cortex over those that project to the occipital cortex, which may explain, the cross-talk between the visual and auditory systems in congenitally blind individuals.

INTRODUCTION

Cross-modal plasticity can be defined as the adaptive reorganization of the nervous system that occurs after brain damage or disease, integrating both structure and function of two or more different sensorial modalities. In blind individuals this reorganization is often observed as a visual takeover by the auditory and tactile systems (1–6), but it has also been reported involving language (7, 8), olfaction and gustation (9, 10), very often leading to increased abilities and behavioral improvement in the remaining senses. Measured by neuroimaging techniques, recruitment of 'visual' areas in blindness has been reported during auditory (11–15), tactile (3), and linguistic (8) tasks, and correlation with behavioral gains has also been shown (14, 16–19). Moreover, virtual lesions targeted to the 'visual' cortex induced by Transcranial Magnetic Stimulation (TMS) can temporarily impair performance on both auditory (20) and tactile (21, 22) tasks in blind. Altogether, these findings give support to the adaptive role of the cross-modal plasticity involving visual and non-visual sensory coding in blind individuals.

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Despite the accumulating evidences corroborating cross-modal plasticity in blinds, neuroanatomical correlates underling this phenomenon are controversial and may involve a wide range of brain structural changes, including development of new connections and/or unmasking and/or rewiring of the existing ones (23). Indeed, there is no consensus about how and which pathways convey non-visual information to the visual cortex in blinds. Most of the findings about the anatomical underpinnings of cross-modal plasticity and its mechanisms come from studies in animal models of blindness and 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 (24–30). On the other hand, other studies suggest the preservation of geniculocalcarine pathways in blind individuals (31–33), which supports the idea that adaptive plasticity may rely upon the conservation of thalamocortical pathways. In 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 (34–36). Moreover, in addition to the preserved thalamocortical connections, visual cortical areas receive input from auditory and somatosensory nuclei of the thalami in blind mice and opossum (24, 37). 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.

Even though not explaining the cross talk between sensory modalities in humans, blindness-related brain changes have been extensively explored using multiple neuroimaging techniques in the past years. Evidence suggests numerous alterations, including in white matter (WM) and gray matter (GM) of both cortical and subcortical brain regions. Congenitally/early blind individuals often exhibit atrophy of optic chiasm and reduced microstructural integrity of optic radiations and geniculocalcarine tract (33, 38–41), revealed by Diffusion Tensor Imaging (DTI). Also, splenium of corpus callosum, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, which are major WM bundles connecting different cortical areas involved in visual processing and perception, seem to be impacted by the absence of visual input (20, 40, 42–45). Alterations of cortical morphometry in congenitally and early blind individuals are also observed as an increased cortical thickness in the calcarine sulcus, middle temporal gyrus and primary visual cortex (18, 33, 41).

While brain structural underpinnings of the cross-modal plasticity are still uncertain, well established findings support the idea that blind brain consists in a great model to explore the limits of brain plasticity and investigate its mechanisms. To investigate the anatomical changes induced by the lack of visual stimuli, which in turn may shed light into the mechanisms of cross-modal plasticity in humans, we used advanced neuroimaging techniques based on probabilistic tractography via DTI and brain morphometry to noninvasively assess the thalamic (re)mapping of cortical connections, microstructure of WM and cortical thickness of congenitally blind individuals and sighted controls. Specifically, we tested the hypothesis that the cross talk between different sensory modalities may occur at thalamic level as a remapping of thalamocortical connections and that it would be correlated with the cortical thickness of visual cortex. Our results showed a remapping cortical-thalamic connectivity in congenitally blind individuals as an expansion of the temporal over the occipital anatomical projections from/to the thalamus, when compared to sighted controls. Specifically, congenitally blind individuals showed a reduction of thalamo-occipital connections and the expansion of thalamo-temporal connectivity, co-localizing on visual, auditory and multimodal thalamic nuclei. Moreover, we provide evidence

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suggestive of linked brain mechanisms involved in thalamic remapping and its impact on cortical thickness of primary visual area (V1).

RESULTS

>Changes in White Matter Microstructure

We investigated differences in WM microstructure using TBSS for both fractional anisotropy (FA) and mean diffusivity (MD). Whole brain (threshold-free cluster enhancement (TFCE), corrected $p<0.05$) analysis revealed decreased FA in the major WM structures connecting the occipital cortex, such as the splenium of corpus callosum, bilateral inferior longitudinal fasciculus, bilateral inferior fronto-occipital fasciculus and right superior longitudinal fasciculus (Fig. 1) in congenitally blind subjects, as compared to sighted controls. Whole brain analysis of MD did not reveal significant differences between groups. Analysis restricted to the thalamus revealed decreased FA in congenitally blind individuals mainly in the left thalami, affecting the anterior nucleus, lateral dorsal nucleus, medial dorsal nucleus, ventral anterior nucleus and ventral lateral nucleus, and also right anterior nucleus nuclei, when compared to sighted controls (Fig. 1, highlighted). Right thalamic nuclei that showed increased MD in congenitally blind individuals were pulvinar, medial geniculate nucleus (MGN), anterior nuclei, dorsal nuclei, lateral posterior, medial dorsal, ventral anterior, ventral lateral and ventral posterior. In the left thalamus, congenitally blind individuals showed increased MD in the pulvinar, anterior nucleus, lateral dorsal nucleus and lateral posterior nucleus (Supplementary Fig. S1).

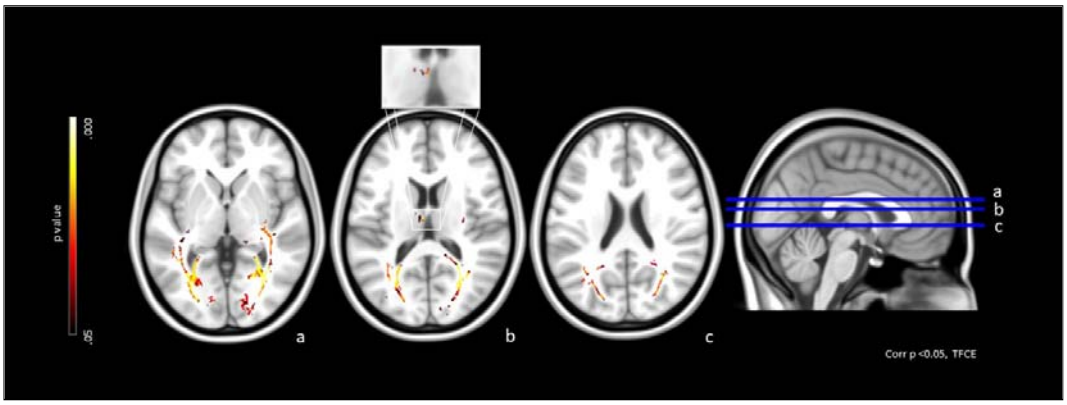

Figure 1. White Matter Changes in Blind Individuals. Whole brain analysis (a, b, c) and region of interest analysis in thalamic areas (b, highlighted area) shows reduced fractional anisotropy (FA) in congenitally blind individuals as compared to sighted controls. Color bar represents p value corrected for multiple comparisons.

> Increased Cortical Thickness

Whole brain comparison of cortical thickness (whole brain analysis, Bonferroni corrected for multiple comparisons, $p=0.05$; Fig. 2) revealed greater thickness of the left primary visual cortex (V1, Brodmann area 17 (BA17), Size= 268.24 mm^2, X=-5.2, Y=-86.4, Z=10.3, MNI) in congenitally blind individuals, as compared to sighted controls. This single cluster was then masked to allow further investigation of thickness

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in each participant. The mean thickness in each group revealed the consistency and homogeneity of the findings. No other cortical region showed between-group differences of thickness.

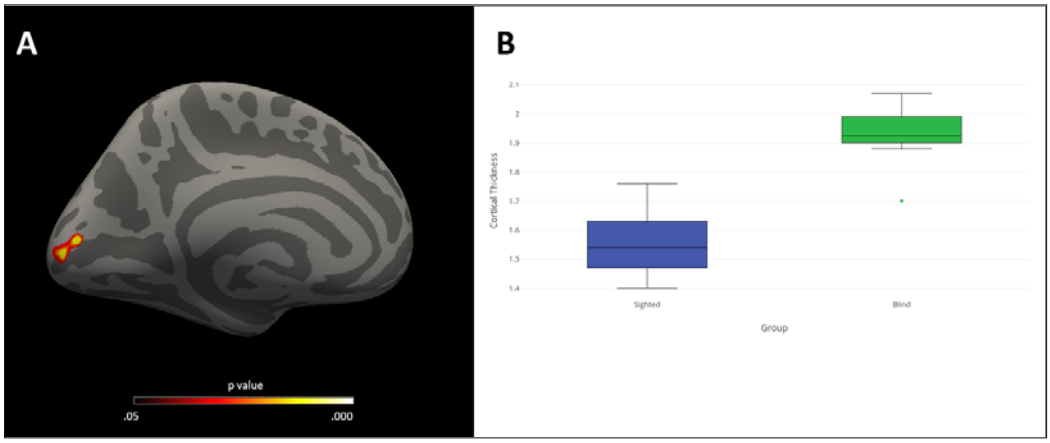

Figure 2. Increased Cortical Thickness in Blinds. (A) Increased cortical thickness in the visual area (BA17) in congenitally blind individuals when compared to sighted controls as a result of a whole brain analysis. Warmer colors denote smaller p value. (B) Box-plot reveals dispersion of cortical thickness in each group, showing highly clustered values.

>Thalamic remapping of cortical connections

The segmentation of the thalami based on tracking probability to six predefined cortical areas (Prefrontal, Motor, Somatosensory, Posterior Parietal, Temporal and Occipital) successfully resulted into six thalamic segments (Fig. 3) in all participants. We extracted the volume (normalized by the volume of the thalami) of each segment and compared them between groups using a mixed effect ANOVA (within-subjects' factors: 'segment' and 'side'; between-subjects factor: 'group'). As a result, main effect of 'segment' ($F(5.90)= 478.222$, $p=0.000$, $\square^2=0.96$) was observed. In addition, there was an interaction effect between 'segment' and 'group' ($F(5.90)= 2.98$, $p=0.015$, $\square^2=0.142$) and 'segment' and 'side' ($F(5.90)= 5.866$, $p=0.000$, $\square^2=0.246$). All other effects were not significant. Simple-effect analysis with Sidak correction for multiple comparisons on the interaction 'segment' and 'group' indicated that sighted controls and congenitally blind individuals significantly differed on the volume of the Occipital segment, being reduced blinds (Fig. 3; Table 1). Further analysis of the interaction 'segment' and 'side' revealed that Frontal, Occipital, Somatosensory and Parietal Posterior segments displayed statistical differences (Table 1, $p<0.05$) in volume between left and right thalami in both groups. Due to non-spherical data, results were corrected using Greenhouse-Geisser correction.

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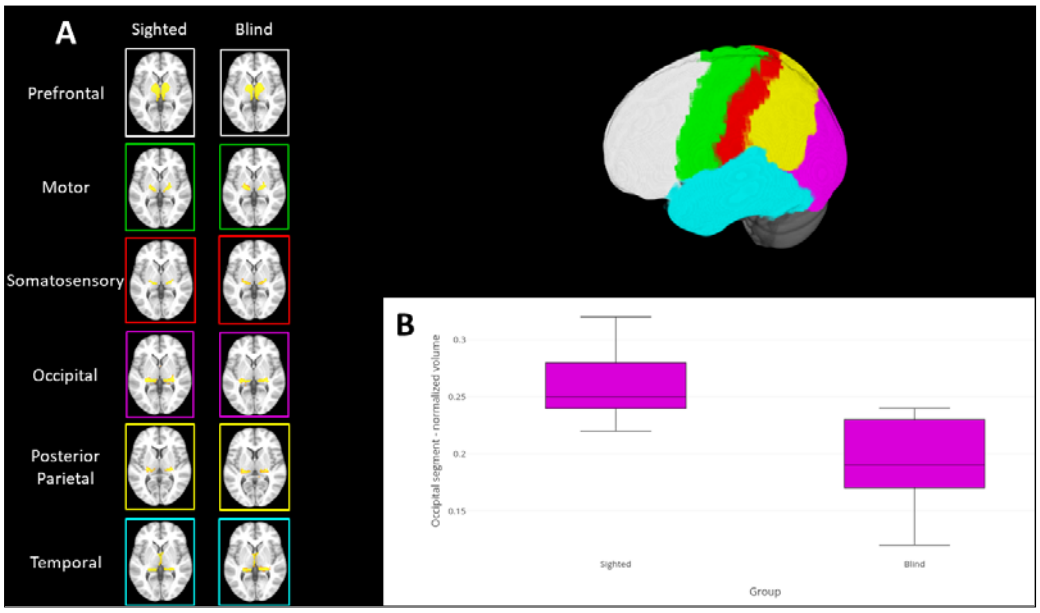

Figure 3. Connectivity-Based Segmentation of The Thalamus. (A) Thalamic areas showing greater connectivity to each chosen cortical area in sighted controls (left column) and congenitally blind individuals (right column). The color of each frame denotes the according cortical area shown in the upper right (B) Occipital segments showed statistical difference in normalized volume between groups (p<0.000, Sidak correction for multiple comparisons).

Table 1. Comparison of thalamic segments

Segment	Side	Blind		Sighted	
		Mean Volume	SD	Mean Volume	SD
Frontal[§]	L	0,3725	0,02767	0,3648	0,03262
	R	0,3967	0,04581	0,3953	0,03987
Occipital* [§]	L	0,1024	0,01754	0,142	0,02843
	R	0,0852	0,02821	0,1172	0,02176
Temporal	L	0,2728	0,03825	0,2529	0,03291
	R	0,2601	0,05413	0,2313	0,03795
Motor	L	0,1162	0,01777	0,108	0,108

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	R	0,1216	0,0121	0,1139	0,01159
Somatosensory§	L	0,07	0,01953	0,062	0,00891
	R	0,0577	0,01568	0,0612	0,01252
Posterior Parietal§	L	0,0661	0,02038	0,02038	0,02247
	R	0,0787	0,02404	0,0812	0,02685

*Segments that showed significant (p<0.05) between-group differences after simple-effect analysis of the interaction 'segment' and 'group'
§ Segments that showed significant (p<0.05) side differences after simple-effect analysis of the interaction 'segment' and side'
Sidak correction for multiple comparisons was applied. L= left thalamus; R= right thalamus

To investigate whether congenital blindness alters the pattern of connectivity between thalamus and cortex, we conducted a nonparametric group comparison (TFCE, corrected $p<0.05$) of the thalamic segments. The analysis revealed that the thalamic segment connecting to the occipital cortex and to temporal cortex significantly differed between groups (Fig. 4). Thalamo-occipital projections showed decreased connectivity in congenitally blind individuals, when compared to sighted controls, in the left lateral posterior nucleus, bilateral pulvinar, right lateral geniculate nucleus (LGN), right MGN. On the other hand, congenitally blind individuals showed increased thalamic connectivity to the temporal cortex in the bilateral LGN, bilateral pulvinar, right MGN, right lateral dorsal nucleus and right medial dorsal nucleus (Fig. 4). Comparison of thalamic connectivity to the Prefrontal, Motor, Somatosensory and Posterior Parietal cortices did not yield significantly differences (TFCE, corrected $p< 0.05$) between groups. Further investigation using looser thresholds (TFCE, corrected $p< 0.1$; Fig. 5) for exploratory purposes revealed that the same portion of the thalamus including bilateral pulvinar, bilateral LGN, left lateral dorsal nucleus and right MGN displayed opposite results depending on the targeted cortical area in the congenitally blind individuals: increased connectivity to the temporal cortex and decreased connectivity to the occipital cortex, which points to the direct takeover of the thalamo-temporal on the thalamo-occipital connectivity in blinds.

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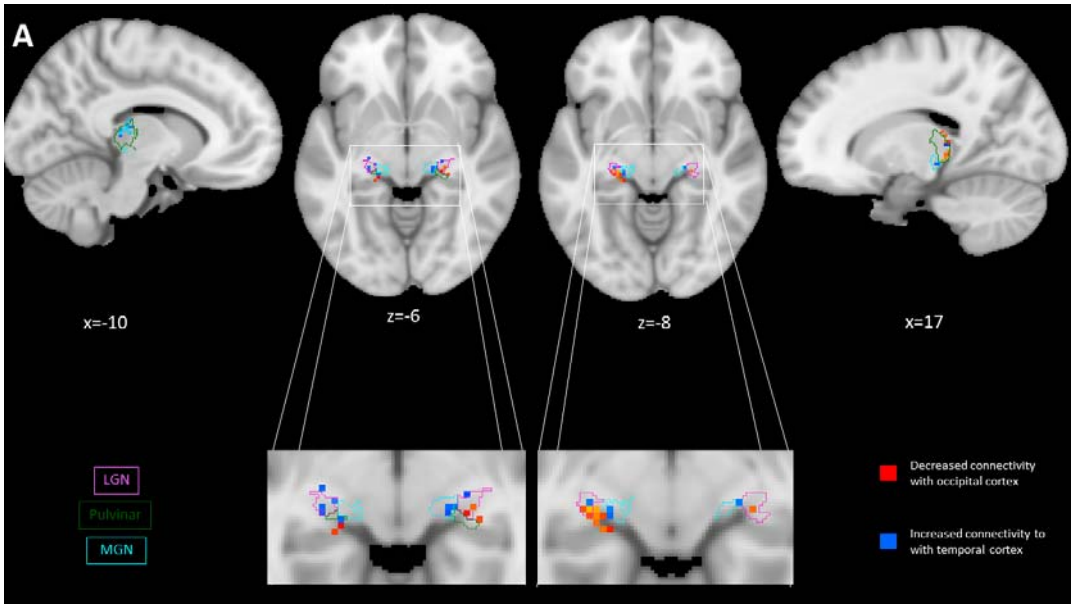

Figure 4. Differences in The Pattern of Thalamocortical Connectivity in Blinds Compared to Controls. Cold (dark blue to light blue) colors denote voxels of decreased connectivity to the occipital cortex and hot (red to yellow) colors denote increased connectivity to the temporal cortex in congenitally blind individuals, when compared do sighted controls. Green, cyan and pink colors outline the pulvinar, the medial geniculate nucleus and the lateral geniculate nucleus.

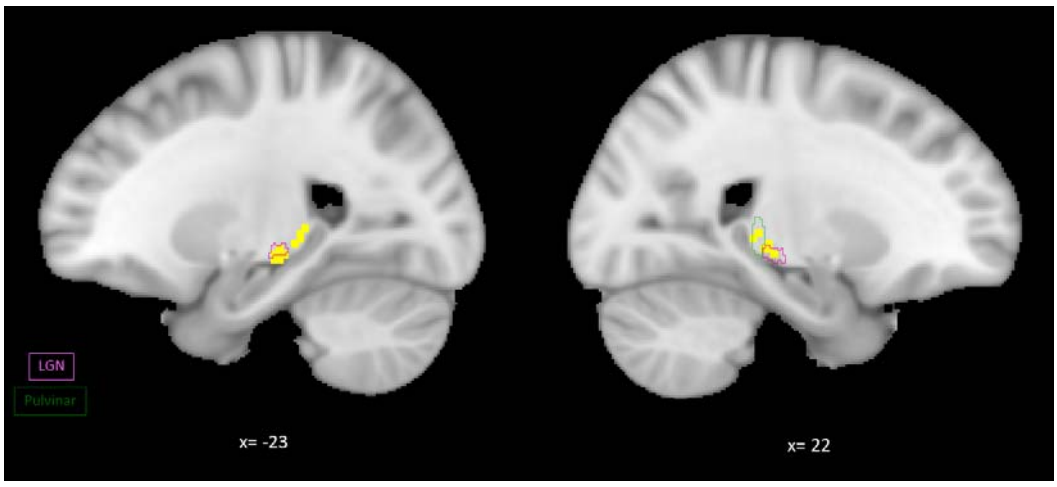

Figure 5. Graphical overlap showing opposite results between groups. Yellow voxels depict thalamic areas showing both increased connectivity with temporal cortex in congenitally blind individuals (congenitally blinds > sighted controls) and decreased connectivity with occipital cortex in sighted controls (sighted controls > congenitally blinds). Dark green and pink areas represent pulvinar and lateral geniculate nuclei (LGN). Looser threshold ($p<0.1$) applied for exploratory purposes.

> Correlation reveals common mechanisms

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To further explore whether there is a direct occipital takeover by temporal projections, we correlated the volume of Occipital and Temporal segments in all participants. We found a negative correlation (Pearson's R=-0,667, *p*=0.001), showing that the greater the Temporal segment the smaller the Occipital one (Fig. 6A). We also tested the hypothesis that visual input plays a pivotal role in the cortical thickness of V1. Correlation of the normalized volume of the left Occipital segment and left cortical thickness of V1 among all participants pointed to an increase of cortical thickness with decreased amount of occipital projections from/to the left thalamus (Pearson's R=-0,559, *p*=0.01; Fig. 6B). Scatter plot reveals highly clustered results, which highlights the consistency of the findings.

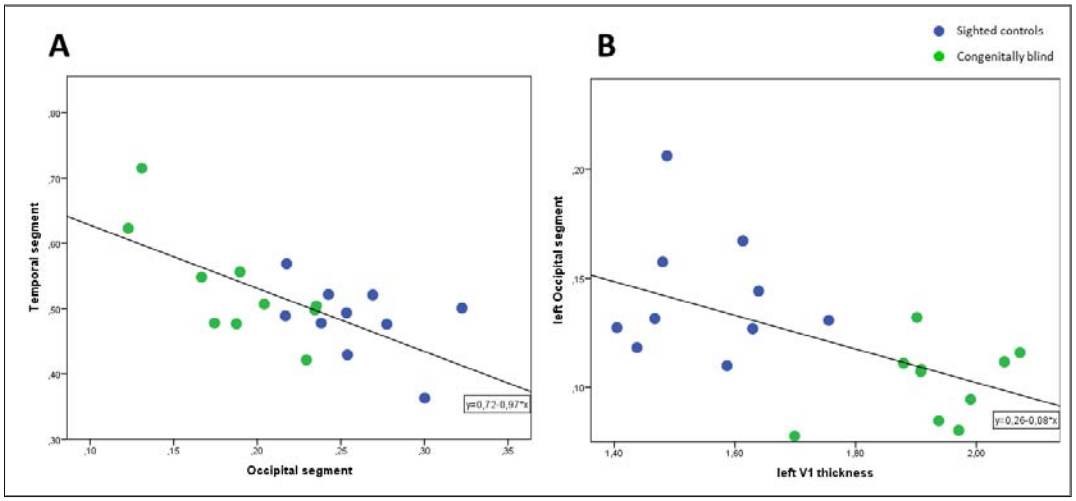

Figure 6. Thalamocortical Connectivity and Changes in the Visual Cortex. Pearson's correlation between the volume of temporal and occipital segments and (B) left occipital segment and cortical thickness of left V1.

Discussion

Supported by animal studies, one of the current hypotheses to explain cross-modal plasticity in blinds is that it relies upon aberrant thalamocortical connections. To test this hypothesis, we used advanced neuroimaging techniques based on DTI and cortical morphometry to perform the connectivity-based segmentation of the thalamus in congenitally blind individuals and sighted controls. Our results suggest that a specific remapping of thalamocortical connections takes place in congenitally blind individuals as a thalamo-temporal takeover of the thalamo-occipital projections, which co-localized in visual, auditory and multimodal thalamic nuclei. In addition, focal impairment of WM integrity, also impacting the thalamus, and increased cortical thickness of left V1 were observed. The correlation between remapping of thalamocortical projections and the cortical thickness of V1 suggests common mechanisms triggered by the absence of visual stimuli, which led to a direct takeover of thalamo-occipital by thalamo-temporal projections that results in greater cortical thickness of V1. Taken together, we provided the first evidence of structural plasticity of thalamocortical connections in congenitally blind individuals, shedding light into the possible mechanisms of cross-modal plasticity and its impact on the visual cortex.

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The connectivity-based segmentation of the thalamus successfully resulted into six different thalamic segments in all participants, which were qualitatively similar between groups and comparable to those segmentations observed in previous studies (46, 47). However, comparison of volume revealed decreased thalamo-occipital connections in congenitally blind individuals. This finding is in line with previous studies that showed volume impairing of the visual system, including the geniculocalcarine pathways (33, 38, 45, 48). Despite interesting, volume comparisons of thalamocortical connectivity have low intrinsic sensitivity, as differences in connectivity may not be reflected as volume changes. To disentangle this, we compared the pattern of connectivity between groups. In agreement to the reduced volume, thalamo-occipital projections also displayed weaker connectivity in congenitally blind individuals. In addition, we observed increased connectivity to the temporal cortex, even though the volume of the Temporal segment did not differ between groups.

Thalamic nuclei that exhibited decreased connectivity to the occipital cortex included bilateral pulvinar and right LGN, whereas those showing increased connectivity to the temporal cortex included bilateral LGN, bilateral pulvinar and right MGN. Superimposing thalamic areas exhibiting decreased connectivity to the occipital cortex to those showing increased connectivity to the temporal cortex revealed direct takeover of thalamocortical connections. This specific remapping occurred in bilateral pulvinar, bilateral LGN, left lateral dorsal nucleus and right MGN. In agreement to this, we found negative correlation between volume of Occipital and Temporal segments, which reinforces the direct relation between both phenomena.

Our findings are in accordance with previous studies that showed an expansion of different sensory territories, including the auditory, on thalamus over deprived visual nuclei (34, 35, 49–51). LGN and MGN are main relays of the visual and auditory systems, respectively, and are often associated with cross-modal plasticity involving the auditory system in animal models of blindness. Animal studies suggest that neurons on the LGN territory convey auditory information to the visual cortex since they receive inputs from the inferior colliculus, a mesencephalic auditory nucleus (24, 35, 37, 52, 53). However, the ectopic projection of inferior colliculus to the LGN and then to V1 is diffuse and disorganized (34, 54), which makes it very unlikely to explain all the phenomenon of cross-modal plasticity in blinds. Rather, thalamo-cortical and cortico-cortical plasticity have been hypothesized as additional mechanisms in which non-visual information reaches visual cortex (23).

Determining the cellular underpinnings of the present results is not straightforward. It is well established that the lack of input impairs correct maturation of the visual system, impacting collaterals elimination of LGN neurons (55–58). The inappropriate maturation of LGN intrinsic organization may pave the way to the invasion of the thalamo-temporal projections instead. In this newly invaded area, in which auditory and visual thalamic neurons coexist with no clear organization, cross-communication among them would result in the auditory activation of the visual cortex, as observed in functional neuroimaging studies (11–15).

The pulvinar is well known as a higher-order, multimodal thalamic nuclei involved in visual attention that mediates cortical synchronization, regulates corticocortical transmission and connects to associative areas in the frontal, temporal, parietal and visual cortices (59, 60), and also to superior colliculus (for review, see (61). Pulvinar connections to roughly all cortical areas make it a potential candidate to integrate different sensory modalities at associative levels and to pave multimodal plasticity in blinds. Interestingly, studies have shown impairment of pulvinar microstructure and

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volume in human blinds (39, 45). On the other hand, function and anatomy of the lateral dorsal nucleus are not clear, and future studies must address how the absence of visual stimuli impacts it.

Even though the temporal cortex hosts primary and secondary auditory areas in humans, it has several functions that go beyond the auditory domain, including memory (62), visual recognition (63) and categorization (64), and multisensory integration (65). Thus, although thalamic cross-modal plasticity between spared auditory and deprived visual system has been widely reported in both animal models and humans (24, 37, 52, 53), interpretation of our results should also consider the hypothesis of multimodal plasticity, not restricted to the auditory domain.

Over the past years, several authors have described increased cortical thickness in the blind brain (11, 18, 33, 66, 67), which can be explained by the lack of correct pruning during ontogenesis due to reduced input (66, 68, 69). In our study, congenitally blind individuals displayed greater thickness of the left but not the right V1 (BA 17), when compared with sighted controls. Despite increase of cortical thickness in blinds has been reported bilaterally, most prominent results are often reported in the left occipital cortex in right-handers (11, 67), indicating lateralization effects of plasticity in blinds. Indeed, visual cortex is highly lateralized for a wide range of stimuli (70–73). Non-visual tasks, such as spatial and pitch discrimination of sounds (12), voice perception (74) and recognition (15), sound localization (16), syntactic (8) and semantic (7) processing of sentences seem to elicit lateralized activation of visual cortex in blinds, either at right or left hemisphere. In addition, the lateralization of functional connectivity to associative brain areas has also been reported (12, 75). Due to the nature of hemispheric dominance of the visual cortex that differently affects both hemispheres depending on the task, it is hard to precise what aspects of brain plasticity underpin the left lateralization of increased cortical thickness in congenitally blinds. Interestingly, we observed a negative correlation between the volume of the left thalamo-occipital connection with thickness of ipsilateral V1. Since animal evidence suggests input to V1 as a critical part of cortical maturation and pruning (66, 68, 69), at least in the left hemisphere, thalamocortical connections seem to play a role on this phenomenon. However, we did not find evidence of lateralization effects on thalamo-occipital connections in blinds, so we cannot rule out the existence of abnormal connections to right V1 from both cortical and subcortical targets to counterbalance cortical thickness.

We did not find evidence of thalamic remapping of connections to the somatosensory and motor cortices in blinds. 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 most probable connections are taken in account 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 analysis. As a result, 'normal' pattern of thalamic segmentation, due to subtle and unnoticed thalamic remapping, would mask less structured but meaningful connections. Second, despite 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 as 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 (30, 37, 76–78). In humans, indirect measurement based on functional connectivity pointed to direct connections between occipital and auditory cortex (79) and primary somatosensory cortex (80, 81). Moreover, visual cortex of enucleated animals also displays both abnormal corticocortical and thalamocortical connections with somatosensory, auditory and motor areas (24),

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suggesting that both mechanisms may coexist to support cross-modal plasticity in blinds.

In accordance with previous studies that showed decreased FA of WM in blinds (40, 41, 43–45), we observed focal impairment of WM integrity in congenitally blind individuals, impacting most of the occipital connections to the associative cortical areas. Structures showing decreased FA were splenium of corpus callosum, bilateral inferior longitudinal fasciculi, bilateral inferior fronto-occipital fasciculi and right superior longitudinal fasciculus, which are known for their role in processing and integration of visual information. Lower FA values refer to impairment of WM integrity and myelination and are commonly pointed as a biomarker of plasticity in both normal and diseased brain. However, visual input has been shown to be crucial for maturation and refinement of crude initial connectivity of the visual system (68, 78, 82), suggesting that decreased myelination of visual WM tracts in congenitally blind individuals might reflect the lack of maturation of the system rather than axonal degeneration per se. Moreover, the thalamus also displayed reduced integrity in congenitally blind individuals, indicating that microstructural impairment is not restricted to corticocortical bundles. These findings are in line with previous study of Reislev and colleagues (46), that using similar approach of connectivity-based segmentation of the thalamus reported lower FA in the thalamo-occipital and thalamo-temporal connections in both congenitally and late blind individuals. In addition to the reduced FA, previous studies suggest that the lack of visual input also impacts WM volume, compared with sighted controls (33, 39, 43).

In summary, the present results provide evidence for direct expansion of the temporal over the occipital thalamic connections in congenitally blind individuals, as compared to sighted controls. We demonstrate that the degree of thalamo-occipital connectivity correlates with cortical thickness of V1, which support the hypothesis that visual input from the thalamus is necessary for correct cortical pruning and thickness. We believe these aberrant thalamic connections to the temporal and occipital cortices can explain, at least in part, how non-visual stimuli are relayed to the 'visual' cortex. However, further investigation will be important to determine the correlation between this structural thalamo-cortical connectivity remapping and its functional counterpart in congenital blinds.

METHODS

>Subjects

This study was conducted in accordance with the ethical standards compliant with the Declaration of Helsinki and has been approved by the Copa D'Or Ethics and Scientific Committee. Ten congenitally blind (mean age: 31.8, standard deviation: 8.7, 6 male) and ten sex- and age-matched sighted controls (mean age: 32.2, standard deviation: 6.66, 6 male) were included in the study. All participants were right handed, braille readers, had no history of neurologic or psychiatric diseases and were not taking brain active medication. Their congenitally blindness resulted from peripheral abnormalities and had no impact on neurologic function, leading to complete blindness except for residual light sensitivity.

>Data Acquisition

Brain imaging was performed at D'Or Institute for Research and Education with a 3T Achieva scanner (Philips Medical Systems, the Netherlands) using an eight-channel

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SENSE head coil. Imaging consisted in a high-resolution 3D T1-weighted image (1mm^3 isotropic, TR/TE (ms) = 7,2 / 3,4, FOV= 240 x 240, matrix = 240, slice thickness = 1mm) and diffusion-weighted (2mm^3 isotropic, no gap, TR/TE (ms)= 10150/60, FOV = 224 x 224, matrix = 112 x 112) with diffusion sensitization gradients applied in 64 noncollinear directions, with a β factor of 1000 s/mm2.

>Data Analysis

Before data preprocessing, the images were visually inspected for excessive movements or artifacts. Diffusion-weighted images were preprocessed and analyzed using FSL toolboxes. In each subject, original data was corrected for the effects of head movement and eddy currents using eddy correct, and a brain masks was created by running bet on one of the B=0 (no diffusion weighting) images. We created FA images using FDT, and then non-brain tissue was removed using BET. All subjects' data were aligned into a common space using the nonlinear registration tool FNIRT, and the mean FA image was created and thinned to create a mean FA skeleton. The FA and MD maps of each subject were projected onto skeletonized FA and the resulting data fed into voxelwise cross-subject statistics using TBSS (83). Whole brain analysis was conducted to find differences in WM properties among groups in major bundles. Also, analyses restricted to the thalami were conducted to reduce number of comparisons and to find subtle but meaningful differences between groups.

Connectivity-based segmentation of the thalamus was also performed using FDT, as described by Behrens (Behrens et al., 2003). Six cortical masks were predefined using Harvard-Oxford atlas: Prefrontal (prefrontal cortex), Motor (precentral cortex) Somatosensory (postcentral cortex), Posterior Parietal (parietal cortex, except for the postcentral cortex), Occipital and Temporal. Both right and left thalami masks were obtained from the subcortical version of the same atlas (Harvard-Oxford subcortical). All masks were registered into the subjects' space using nonlinear registration. After BEDPOSTX, probabilistic tracking was conducted with PROBTRACKX tool, in which the thalamus was defined as seed region, and the six ipsilateral cortical masks as classification targets. Following, proj_thresh was applied to calculate the number of samples reaching each target mask as a proportion of the total number of samples reaching any target mask. Then, find the biggest performed the hard segmentation of each thalamus (left or right) based on its connectivity to each of the six ipsilateral cortical areas. The volume of each segment of the thalamus was normalized by the volume of the ipsilateral thalami in each subject, and was analyzed with SPSS 20.0 (IBM Corporation, New York) using repeated measure analysis of variance (ANOVA). Group analysis of tracking probability was performed by running 5000 nonparametric permutations of each segment in each thalami.

Cortical thickness analysis

The cortical thickness data were calculated from high-resolution 3D T1-weighted gradient-echo images using Freesurfer software (http://surfer.nmr.mgh.harvard.edu/). Preprocessing steps included motion correction, removal of non-brain tissue, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction and surface deformation following intensity gradients.

In order to investigate group differences, we applied the command-line Freesurfer group analysis stream, including correction for multiple comparisons. First, the data from every subject were assembled by: resampling each subject's data onto a common space, spatially smoothing it and concatenating all the subject's resampled and smoothed data into a single file. We defined the design matrix and design contrast comparing both groups, resulting in a t-test analysis of the whole brain. The statistical

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results were, then, submitted to a clusterwise correction for multiple comparisons ($p<0.05$).

Acknowledgements
We thank Marina Monteiro and Ivanei Bramati for the technical support during data analysis. This work was funded by Foundation for Research Support in the State of Rio de Janeiro (FAPERJ), National Council of Scientific and Technological Development (CNPq), the Capes Foundation and intramural grants of the D'Or Institute for Research and Education (IDOR).

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