

Impact of blindness onset on the functional organization and the connectivity of the occipital cortex

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Contrasting the impact of congenital versus late-onset acquired blindness provides a unique model to probe how experience at different developmental periods shapes the functional organization of the occipital cortex. We used functional magnetic resonance imaging to characterize brain activations of congenitally blind, late-onset blind and two groups of sighted control individuals while they processed either the pitch or the spatial attributes of sounds. Whereas both blind groups recruited occipital regions for sound processing, activity in bilateral cuneus was only apparent in the congenitally blind, highlighting the existence of region-specific critical periods for crossmodal plasticity. Most importantly, the preferential activation of the right dorsal stream (middle occipital gyrus and cuneus) for the spatial processing of sounds was only observed in the congenitally blind. This demonstrates that vision has to be lost during an early sensitive period in order to transfer its functional specialization for space processing toward a non-visual modality. We then used a combination of dynamic causal modelling with Bayesian model selection to demonstrate that auditory-driven activity in primary visual cortex is better explained by direct connections with primary auditory cortex in the congenitally blind whereas it relies more on feedback inputs from parietal regions in the late-onset blind group. Taken together, these results demonstrate the crucial role of the developmental period of visual deprivation in (re)shaping the functional architecture and the connectivity of the occipital cortex. Such findings are clinically important now that a growing number of medical interventions may restore vision after a period of visual deprivation.

Keywords: crossmodal plasticity; blindness; functional specialization; functional integration; dynamic causal modelling

Abbreviations: SCCB = sighted control matched to congenitally blind group; SCLB = sighted control matched to late blind group

Introduction

How specific brain regions attain, maintain and modify their functional tuning regarding the processing of specific stimuli has long fascinated researchers in the field of developmental neuroscience. Indeed many have attempted to separate the 'built-in' functional specialization of a specific region from the response properties that are shaped by perceptual experience.

One of the most striking demonstrations of experience-dependent plasticity comes from studies of congenitally blind individuals in whom the occipital cortex massively changes its functional tuning to support non-visual perceptual and cognitive functions (Bavelier and Neville, 2002). Importantly, these plastic changes appear to be compensatory in nature because they have been shown to correlate with improved abilities in the remaining senses (Amedi *et al.*, 2003; Gougoux *et al.*, 2005). This conclusion is further supported by studies showing that the transient disruption of occipital activity induced by transcranial magnetic stimulation impairs non-visual functions of congenitally blind individuals (Cohen *et al.*, 1997; Amedi *et al.*, 2004; Collignon *et al.*, 2007, 2009a, b).

In sighted individuals, a fundamental characteristic of the occipital cortex is domain specialization, wherein identifiable functional areas specialize in a particular aspect of vision (Zeki *et al.*, 1991). Recent experiments have provided evidence that the occipital cortex of the congenitally blind might follow a division of computational labour similar to the one observed in the sighted (Collignon *et al.*, 2009b; Ricciardi and Pietrini, 2011; Reich *et al.*, 2012). For instance, right dorsal occipital regions, which are known to be preferentially involved in the processing of the spatial relations among visual objects in sighted individuals (Haxby *et al.*, 1991), are preferentially activated during tasks involving the spatial processing of non-visual inputs in congenitally blind individuals (Renier *et al.*, 2010; Collignon *et al.*, 2011b). Such studies have shed new light on the 'nature versus nurture' debate regarding brain development: whereas the recruitment of occipital regions by non-visual inputs in the congenitally blind highlights the ability of the brain to reorganize itself due to experience (nurture influence), the observation of specialized cognitive modules in the occipital cortex of congenitally blind, similar to those observed in the sighted, highlights the intrinsic constraints imposed to such plasticity (nature influence) (Collignon *et al.*, 2012; Dormal and Collignon, 2011).

Is there a limited time window in which these plastic changes can occur? Neurophysiological reorganizations were first thought to be relatively limited after childhood. This idea mainly derived from a series of pioneering studies in the 1960s demonstrating that early monocular deprivation had a dramatic and irreversible impact on the organization of ocular dominance columns in primary visual cortex, whereas such deprivation had virtually no effect when it occurred later in life (Hubel and Wiesel, 1970). These classical studies established the existence of time-limited epochs of stimulus exposure-induced plasticity, named 'critical periods' (Wiesel and Hubel, 1965). The vast majority of the studies investigating blindness-induced crossmodal plasticity have been conducted with individuals deprived of sight early in life, and

the few studies that explored the persistence of crossmodal plastic changes in late-onset blind individuals have provided inconsistent results. Whereas some have shown auditory or tactile recruitment of occipital regions in individuals that acquired blindness later in life (Buchel, 1998; Burton, 2003; Voss *et al.*, 2006), others have suggested the existence of a critical period beyond which little or no functional (Veraart *et al.*, 1990; Cohen *et al.*, 1999; Sadato *et al.*, 2002; Sanchez-Vives *et al.*, 2006) or structural (Noppeney, 2007; Jiang *et al.*, 2009) reorganization is possible. Consistent with the latter hypothesis, a recent study showed that bilateral middle occipito-temporal regions (hMT+ /V5 as defined by a visual motion localizer in a sighted group) responded to moving sounds in congenitally blind but not in sighted, or in late-onset blind individuals (Bedny *et al.*, 2010). However, due to the region of interest (for hMT+ /V5) approach of the study, the authors did not address whether more 'global' crossmodal reorganization could be observed in the late-onset blind and, furthermore, whether functional selectivity for moving sounds could be observed outside of this region of interest. Here, we explored whether crossmodal plastic changes could be observed in the occipital cortex of late-onset blind individuals and if such putative crossmodal occipital recruitment follows organizational principles similar to the ones observed in sighted individuals, as previously demonstrated in the congenitally blind. We characterized brain responses of a late-onset blind group when processing either the pitch or the spatial attributes of identical sounds and compared them with a group of matched sighted control subjects as well as with previously reported findings in congenitally blind subjects performing the same task (Collignon *et al.*, 2011b).

Another key question relates to how non-visual information reaches the reorganized occipital cortex of blind individuals. Recently, Klinge *et al.* (2010) astutely used dynamic causal modelling of signals acquired with functional MRI and demonstrated stronger cortico-cortical connections from primary auditory cortex to primary visual cortex in congenitally blind compared with sighted controls, whereas no significant differences were found concerning the thalamo-cortical connections [from medial geniculate nucleus to primary visual cortex (V1)]. These results suggest that plastic changes in cortico-cortical connectivity play a crucial role in relaying auditory information to the primary visual cortex of early-onset blind individuals. However, two additional important questions remain to be investigated. First, it is unclear whether V1 activation in the congenitally blind is driven by changes in direct 'feed-forward' long-range connections between primary temporal and occipital cortices or if they are rather driven by changes in indirect 'feed-back' connectivity from temporal to multisensory parietal regions to occipital cortex. Second, it is equally unclear how the age at blindness onset might influence such changes in the connectivity patterns with occipital areas. We therefore used dynamic causal modelling to investigate whether auditory activations of primary occipital cortex in the congenitally blind and late-onset blind are more likely due to reorganization in direct (feed-forward) rather than in indirect (feed-back) cortical pathways.

To summarize, the goal of the present study was: (i) to contrast the crossmodal recruitment of occipital regions by sounds when sight is lost before or after the development of the visual system; (ii) to test whether such putative crossmodal plasticity in the

occipital cortex of the late-onset blind shows some level of functional specialization similar to the one observed in the congenitally blind; and (iii) to explore how auditory information flows into the occipital cortex of congenitally blind and late-onset blind individuals.

Materials and methods

Subjects

Data on four groups of participants were acquired for this experiment: a group of 12 congenitally blind individuals (four females, range 28–56 years old, mean \pm SD = 41 ± 11 years), a group of 12 sighted control subjects matched with the congenitally blind group (SCCB; four females, 26–56 years old, mean = 36 ± 12 years), a group of 10 late-onset blind individuals (eight females, 22–60 years old, mean = 48 ± 11 years), and a group of 10 sighted control subjects matched with the late-onset blind group (SCLB; eight females, 30–60 years old, mean = 49 ± 12 years). Both groups of sighted controls were matched with their respective blind groups for age, gender, handedness, educational level and musical experience. Data on 11 congenitally blind and 11 SCCB subjects have been used in a previous study (Collignon *et al.*, 2011b). All groups were blindfolded throughout the functional MRI acquisition. None of the congenitally blind subjects had ever had functional vision allowing for pattern recognition or visually guided behaviour. In contrast, all subjects in the late-onset blind group had experienced normal functional vision (mean age at blindness onset \pm SD = 36 ± 13 years). At the time of testing, all blind subjects were totally blind or had only rudimentary sensitivity for brightness differences and no pattern vision. In all cases, blindness was attributed to peripheral deficits with no neurological impairment (Supplementary Table 1). All of the procedures were approved by the research ethic and scientific boards of the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR) and the Quebec Bio-Imaging Network (QBIN). Experiments were undertaken with the understanding and consent of each participant.

Task and general experimental design

The experiment was performed as described previously (Collignon *et al.*, 2011b). All subjects were scanned in a single functional MRI run that consisted of 30 successive blocks (20.4 s duration each) separated by rest periods ranging from 6 to 12.4 s (median = 7.34 s) during which the subjects had to alternatively process the spatial or the pitch attributes of the sounds. A short verbal instruction (1300 ms) was delivered 2 s before each block in order to remind the participants whether to focus on pitch or spatial attributes of the sounds. The first condition (spatial or pitch) was counterbalanced across subjects. In the 'spatial' condition, participants had to determine if the second sound of a pair was presented to the left or to the right of the first sound of the pair (the probe), regardless of variations in pitch. In the 'pitch' condition, participants had to determine if the second sound of a pair of sounds was lower or higher-pitched when compared to the probe, regardless of the spatial position. In both conditions and irrespective of the instructions given, the probe was a central 1000 Hz sound (simulating 0° azimuth) lasting 150 ms (10 ms rise/fall times). The target sound always appeared 200 ms after the probe and also lasted 150 ms (10 ms rise/fall times). A 1200 ms response period followed each pair of sounds. Each block, either spatial or pitch, consisted of 12 successive pairs of sounds (Fig. 1A). The same response buttons

(right index and right major) were used in both two-alternative forced choice tasks.

The difficulty level of both tasks was controlled throughout the experiment by adjusting the gap between the probe and the target using a dynamic psychophysical staircase procedure (one-down for a correct response/six-up for an incorrect response) with the subject performance converging at ~80–90% correct. A matrix of 6400 sounds using 40 left and right 'spatial gaps' (created by jointly varying steps of 0.2% interaural level difference with steps of 20 μ s interaural time difference from the probe sound; two primary cues for sound localization in azimuth) and 40 high and low 'pitch gaps' [created using steps of 5 cents (a logarithmic unit of measure used for musical intervals) from the probe sound]. When using the term 'spatial processing of sound' in this experiment, we refer to the ability to lateralize sounds perceived along a line on the horizontal meridian joining the two ears.

The first trial within each block in the spatial and the pitch condition always started with a level of difficulty that was six steps easier than the last trial of the previous block within the same condition (ensuring that a block would never start with a very difficult trial). This staircase procedure ensures equal levels of performance between conditions (spatial versus pitch) for each participant and between participants, so that any task or group differences could not be attributed to differences in terms of performance. In addition, in each pitch block, the target locations of the sounds were determined by the locations of the sounds presented in the preceding spatial block, and vice versa (e.g. pitch in spatial task), so that identical sounds were included in both conditions. This latter aspect ensures that when contrasting the two tasks, no effect can be attributable to differences in the physical attributes of the stimuli.

The experimental run was preceded by a short sound calibration run during which the volume level was adjusted to ensure optimal auditory perception. The task was coded using Cogent2000v1.24 (<http://www.vislab.ucl.ac.uk/cogent.php>) implemented in MATLAB (Mathworks Inc.) and the auditory stimuli were delivered by means of circumaural, functional MRI-compatible headphones (Mr Confon). All auditory stimuli were created using Adobe Audition 2.0 (Adobe Systems Inc.).

Before the functional MRI acquisition, all participants underwent a 30-min training session in a mock scanner (Psychology Software Tools) with recorded scanner noise played in the bore of the simulator in order to familiarize the participants with the functional MRI environment and to ensure that they understood and could perform the tasks.

Behavioural analysis

Performance was analysed using two separate 4 (Group: congenitally blind, SCCB, late-onset blind, SCLB; between-subjects factor) \times 2 (Task: Spatial versus Pitch; within-subjects factors) repeated measures ANOVA; one for accuracy scores and one for reaction times. Moreover, we also performed a simple ANOVA on the auditory-spatial and auditory-pitch resolution level (calculated as the mean gap separating the target from the probe for an entire run) with the factor Group as between-subjects factor.

Magnetic resonance imaging data acquisition and analysis

Functional MRI series were acquired using a 3 T TRIO TIM system (Siemens), equipped with a 12-channel head coil. For full details on recording parameters and preprocessing steps, see the online Supplementary material.

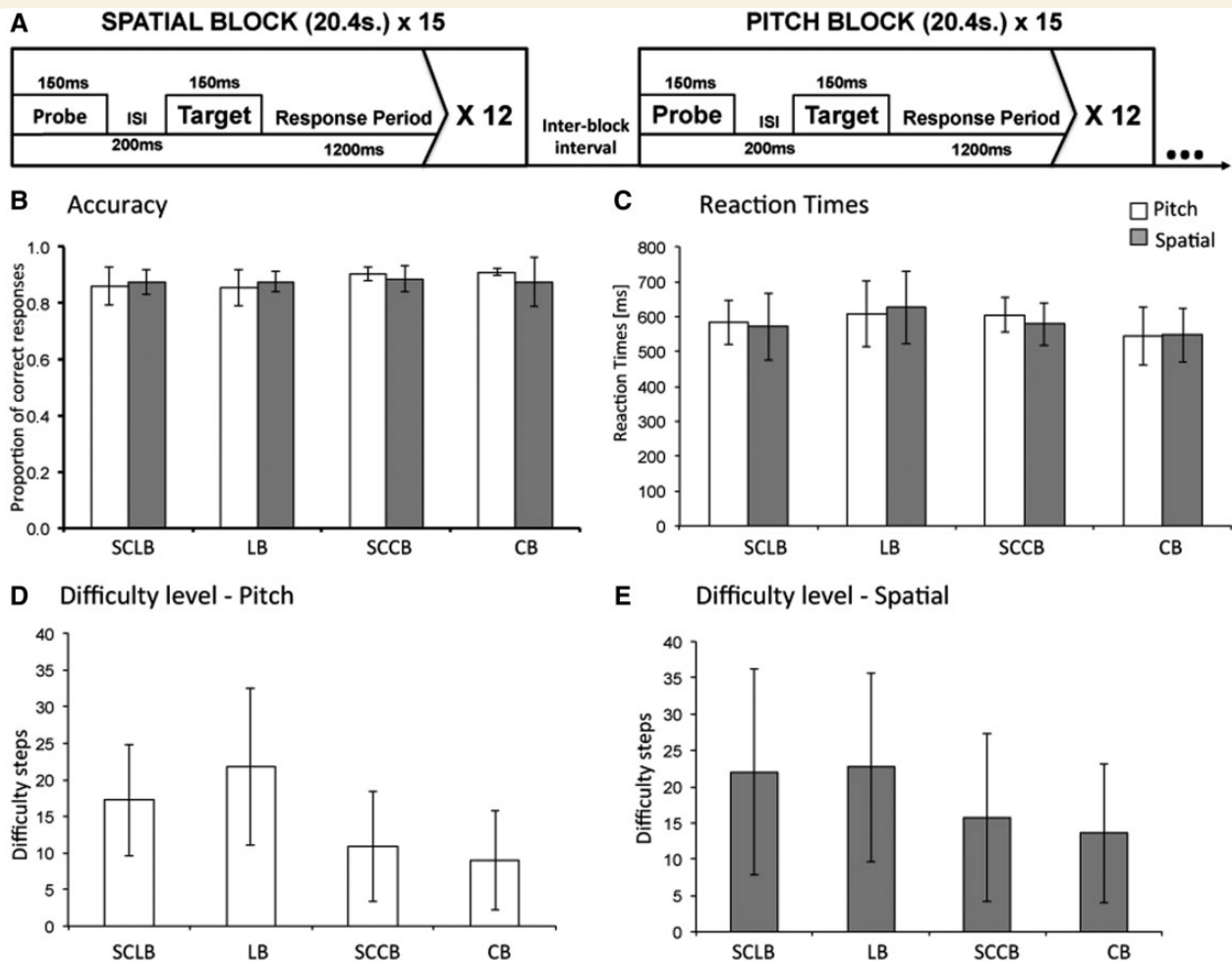


Figure 1 Experimental design and behavioural results. (A) Functional MRI acquisition design. Behavioural performance of the four groups of participants are illustrated for the accuracy scores (B), the reaction times (C), as well as the pitch (D) and the spatial (E) difficulty levels reached in both tasks (D). Error bars denote standard deviation. CB = congenitally blind; LB = late-onset blind; ISI = interstimulus interval.

Functional volumes were preprocessed and analysed using SPM8 [Wellcome Department of Imaging Neuroscience, London, UK, (v4290)], implemented in MATLAB R2008a. Preprocessing included slice timing correction of the functional time series (Sladky *et al.*, 2011), realignment of functional time series, co-registration of functional and anatomical data, spatial normalization to an echo planar image template conforming to the Montreal Neurological Institute space, and a spatial smoothing (Gaussian kernel, 8 mm full-width at half-maximum). After these preprocessing steps, the analysis of functional MRI data, based on a mixed effects model, was conducted in two serial steps, accounting for fixed and random effects, respectively. For each subject, changes in brain regional responses were estimated by a general linear model including responses to the pitch and spatial conditions. These regressors consisted of boxcar function convolved with the canonical haemodynamic response function. The instructions preceding each block were modelled using stick function convolved with the canonical haemodynamic response function and were also included as covariates of no interest together with movement parameters derived from realignment of the functional volumes. High-pass filtering was implemented using a cut-off period of 128 s to remove low-frequency noise and signal drift. Serial correlations were estimated using an autoregressive

(order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

Psychophysiological interaction analyses (Gitelman *et al.*, 2003) were computed to identify any brain region functionally connected to the reorganized occipital regions involved specifically in auditory spatial processing, relative to pitch processing, in congenitally blind (Fig. 4B and Supplementary Table 3). Psychophysiological interaction analyses were conducted to test the hypothesis that functional connectivity between these seed regions and the rest of the brain not only differed between conditions (spatial versus pitch) but was also influenced by the experimental group (congenitally blind > late-onset blind).

In the main effect analysis as well as in the psychophysiological interaction analyses, the resulting set of voxel values for each contrast constituted a map of the *t*-statistic [SPM(T)]. Statistical inferences were performed at a threshold of $P < 0.05$ after correction for multiple comparisons over the entire brain volume, or over small spherical volumes (15 mm radius) located in structures of interest (Supplementary material) (Worsley *et al.*, 1996). We chose to use spheres of 15 mm radius because it was found that the position of the pixel with the highest visual motion-selective significance response within the middle occipito-temporal cortex (corresponding to hMT+ /V5), a region of

main interest in the current study (Fig. 4A), can vary between subjects by as much as 18 mm in the right hemisphere (Watson *et al.*, 1993). Significant clusters were anatomically labelled using the xjView matlab toolbox (<http://www.alivelearn.net/xjview>) or structural neuroanatomy information and probabilistic cytoarchitectonic maps provided in the Anatomy Toolbox (Eickhoff *et al.*, 2007).

Dynamic causal modelling

Dynamic causal modelling is a hypothesis-driven approach (i.e. a technique used to test for a specific set of hypotheses, defined *a priori*) to characterize the causality between the activity of different brain areas and, thereby, to study how information flows in the brain (Friston *et al.*, 2003). Combined with Bayesian model selection, dynamic causal modelling allows for the comparison of competing mechanistic hypotheses of brain connectivity, represented by different network models (Penny *et al.*, 2004). Here, we used dynamic causal modelling and Bayesian model selection to explore how auditory information reaches the occipital cortex of blind individuals. We therefore operationalized our model space based on plausible alternatives. It was recently demonstrated, using dynamic causal modelling, that crossmodal plasticity observed in congenitally blind is more likely to be supported by reorganizations in cortico-cortical connections rather than reorganizations in thalamo-cortical connections (Klinge *et al.*, 2010). We therefore only included cortico-cortical connections in our models (see Shimony *et al.*, 2006 for anatomical support). More specifically, we wanted to test three possible pathways through which auditory input could reach V1: (i) V1 receives auditory input only after it has been processed in 'higher-level' association cortex; (ii) V1 receives auditory input directly from A1, without preliminary processing in associative regions; and (iii) V1 receives auditory input both indirectly from associative regions and directly from A1. Therefore, we used dynamic causal modelling of functional MRI signal to quantify effective connectivity in backward and forward connections at three hierarchical cortical levels (i.e. in temporal, parietal and occipital cortices), during auditory processing in congenitally blind and late-onset blind individuals. In both hemispheres, three regions of interest were considered for our dynamic causal modelling analysis: the primary auditory cortex (A1), the intraparietal sulcus and the primary visual cortex (V1). Based on hypotheses from the literature (Bavelier and Neville, 2002; Pascual-Leone *et al.*, 2005), we constructed seven different models (described below) for each participant, which allowed us to test our hypothesis (Fig. 5).

An important point in dynamic causal modelling analyses with regard to group differences is to use identical brain coordinates for the time series extraction for which significant activations are observed for all groups in order to avoid biasing the estimates of effective connectivity to and from a region (Klinge *et al.*, 2010). Therefore none of the sighted groups were included in the dynamic causal modelling analyses because of the absence of significant occipital activity in SCCB and SCLB for the global processing of sounds (spatial + pitch) (Fig. 2). As a starting point for time series extraction, we used coordinates obtained from the random effects conjunction analysis across both blind groups (congenitally blind and late-onset blind) based on the conjunction null hypothesis, testing for a logical AND (Friston *et al.*, 2005; Nichols *et al.*, 2005). Each region of interest was defined as a sphere of 10 mm radius, centred individually on the local activation maximum closest to each peak of interest from the conjunction analysis (left A1, $-60 -34 14$ mm; right A1, $64 -26 10$ mm; left intraparietal sulcus, $-40 -40 42$ mm; right intraparietal sulcus $42 -38 48$ mm; left V1, $-8 -82 8$ mm; right V1, $22 -98 2$ mm; Supplementary Fig. 4). For each subject, the time series of the activity

for each area was extracted as the principal eigenvariate of the time series of the voxels within the region of interest. These time series were adjusted for subject's movements using the movement parameters as regressors.

Because we had no *a priori* hypothesis about between-hemispheric differences in the way auditory inputs reach the occipital cortex, we built symmetrical models in each hemisphere. In all models, inputs consisted of the auditory stimuli irrespective of the condition (spatial + pitch) that entered the network bilaterally directly in A1. These models were then split into three subsets or 'families' depending on how information flowed from A1 to V1. Family A includes Models 1 and 5, where auditory inputs in V1 rely on indirect 'feed-back' connections between intraparietal sulcus and V1, Family B includes Models 2, 4 and 6 postulating that auditory inputs in V1 rely on direct 'feed-forward' connections between A1 and V1, and Family C includes Models 3 and 7 postulating that auditory inputs in V1 rely on both direct and indirect connections.

The seven dynamic causal modelling models were fitted with the data from each of the 12 congenitally blind and 10 late-onset blind subjects. This provided 154 (22×7) model log-evidence and posterior parameter estimates. The posterior probabilities of each family and model have therefore been estimated separately for each group. Based on the estimated model evidence of each model, random effect Bayesian model selection then calculates the 'exceedance probability', that is, the probability of each model being more likely than any other model (Penny *et al.*, 2004). When comparing model families, all models within a family were averaged using Bayesian model averaging and the exceedance probabilities were calculated for each model family (Penny *et al.*, 2010).

Results

Behavioural results

No difference in performance was observed either between the groups or between the tasks. This was true for both accuracy measures (as expected due to the use of a staircase procedure) and reaction times (Fig. 1B and C), ensuring that functional MRI results would not be biased by behavioural differences.

The auditory–pitch resolution level reached was significantly different between groups ($F = 6.4$, $P = 0.001$). Bonferroni *post hoc* tests demonstrated that the auditory–pitch resolution was significantly higher in the late-onset blind compared to the congenitally blind ($P = 0.002$) and sighted controls for the congenitally blind (SCCB) ($P = 0.009$). However, no significant difference was found between the late-onset blind group and sighted controls (SCLB) ($P = 0.99$) (Fig. 1D). These significant effects are probably age-related and thereby support our decision to use two groups of sighted controls appropriately matched with each blind group. The auditory–spatial resolution level reached was not significantly different between groups (Fig. 1E).

Functional magnetic resonance imaging

Auditory recruitment of occipital regions in the late-onset blind and the congenitally blind

To first investigate the effect of early and late visual deprivation on sound processing, we compared the cerebral responses of

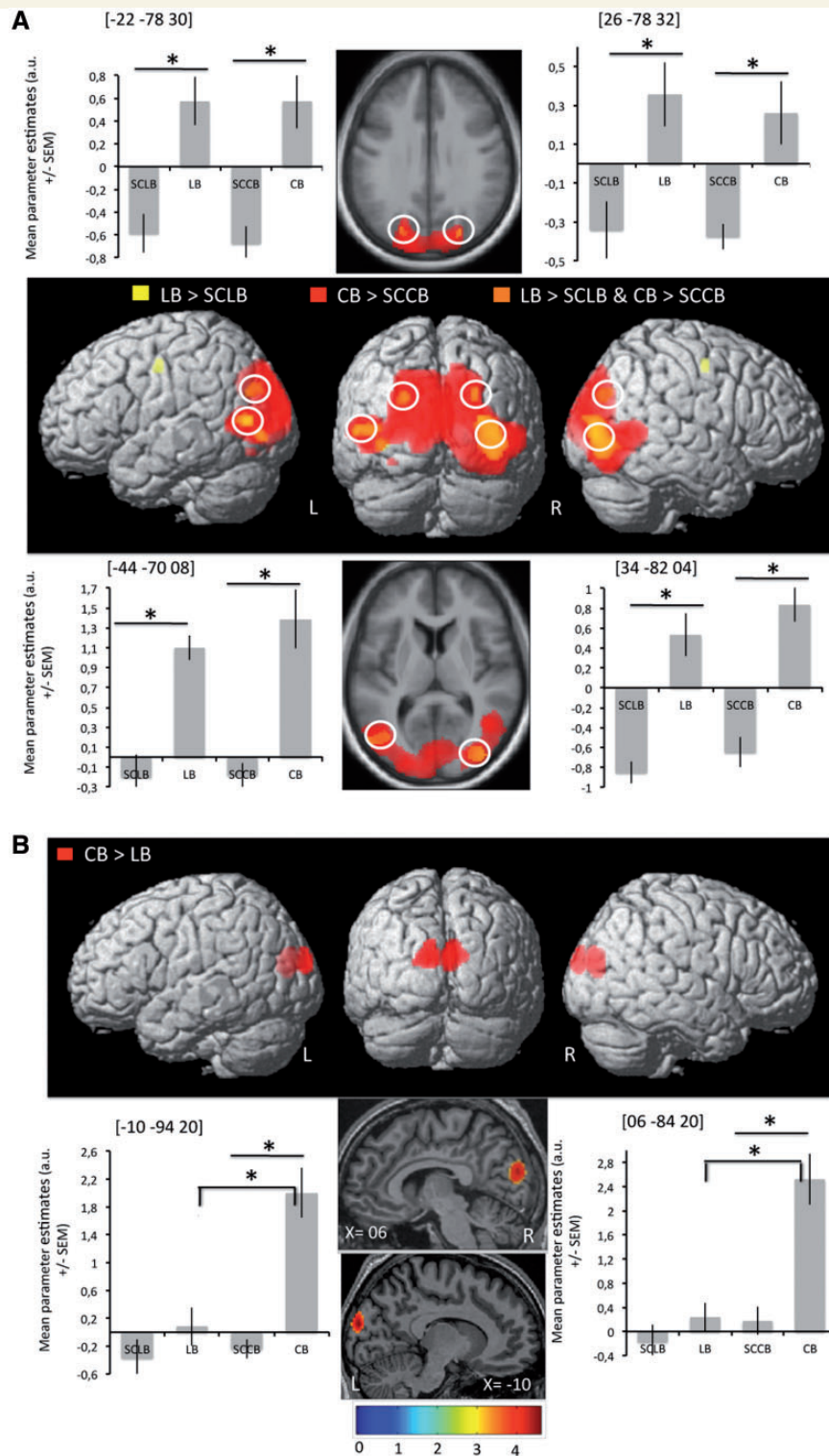


Figure 2 Occipital reorganization in late-onset blind (LB) and congenitally blind (CB) individuals. Results are displayed ($*P_{\text{uncorrected}} < 0.001$) over the mean structural image of all subjects and over a 3D render of the brain. **(A)** Significant differences between each blind group and its respective control group: (congenitally blind > SCCB) \times (spatial + pitch) in red and (late-onset blind > SCLB) \times (spatial + pitch) in yellow. Graphs: mean activity estimates [arbitrary unit (a.u.) \pm SEM] associated with sound processing (spatial + pitch) in the four groups of participants within the four regions obtained with the conjunction (AND) analysis of the two contrasts described above. **(B)** Significant differences between the congenitally blind and late-onset blind independent of conditions: congenitally blind \times (spatial + pitch) > late-onset blind \times (spatial + pitch). Graphs: mean activity estimates (a.u. \pm SEM) associated with sound processing (spatial + pitch) in the bilateral cuneus for the four groups.

congenitally blind versus SCCB and of late-onset blind versus SCLB for both auditory tasks combined (spatial + pitch). These analyses revealed a greater recruitment of occipital regions in response to auditory stimulation in both blind groups compared to their respective sighted control groups. A conjunction (AND) [congenitally blind > SCCB \cap late-onset blind > SCLB] \times [spatial + pitch] analysis indicated that the regions showing crossmodal reorganization in the late-onset blind are in regions where crossmodal reorganization is also observed in the congenitally blind (Fig. 2A, Supplementary Fig. 1 and Supplementary Tables 1.1 and 1.2).

To formally test differences between early and late visual deprivation, we contrasted congenitally blind and late-onset blind brain responses to auditory stimulation [congenitally blind > late-onset blind \times (spatial + pitch)]. This analysis revealed significantly higher bilateral responses in the congenitally blind in a circumscribed region of the cuneus, whereas no responses were significantly higher in the late-onset blind versus the congenitally blind (Fig. 2B, Supplementary Tables 1.3 and 1.4).

In addition, we also assessed whether the number of years of complete blindness would predict the amplitude of the crossmodal responses observed in occipital regions during global sound processing in each blind group separately. Surprisingly, we observed a significant inverse relationship between the number

of years of blindness and activity in several occipital regions in the late-onset blind only (Fig. 3 and Supplementary Table 1.5), suggesting that these occipital regions display more sound-related activity in the first years following deprivation than later on. No significantly positive correlation was observed between the activity level in any occipital voxel and the number of years of complete blindness in the late-onset blind, neither significant positive nor negative correlations were observed in the congenitally blind.

Functional specialization for the spatial processing of sounds in the occipital cortex of the congenitally blind but not of the late-onset blind

In a recent study, we demonstrated that some regions of the right dorsal occipital cortex are specifically dedicated to the spatial processing of sounds in the congenitally blind (Collignon *et al.*, 2011b). In the present experiment, we investigated whether this functional specialization for auditory-spatial processing in the occipital cortex is triggered by visual deprivation itself or is rather tributary to the loss of sight early in life. The group (congenitally blind > SCCB) \times condition (spatial > pitch) interaction analysis revealed significant differences in activity in the right cuneus, the right middle/superior occipital gyrus and the right middle occipito-temporal gyrus

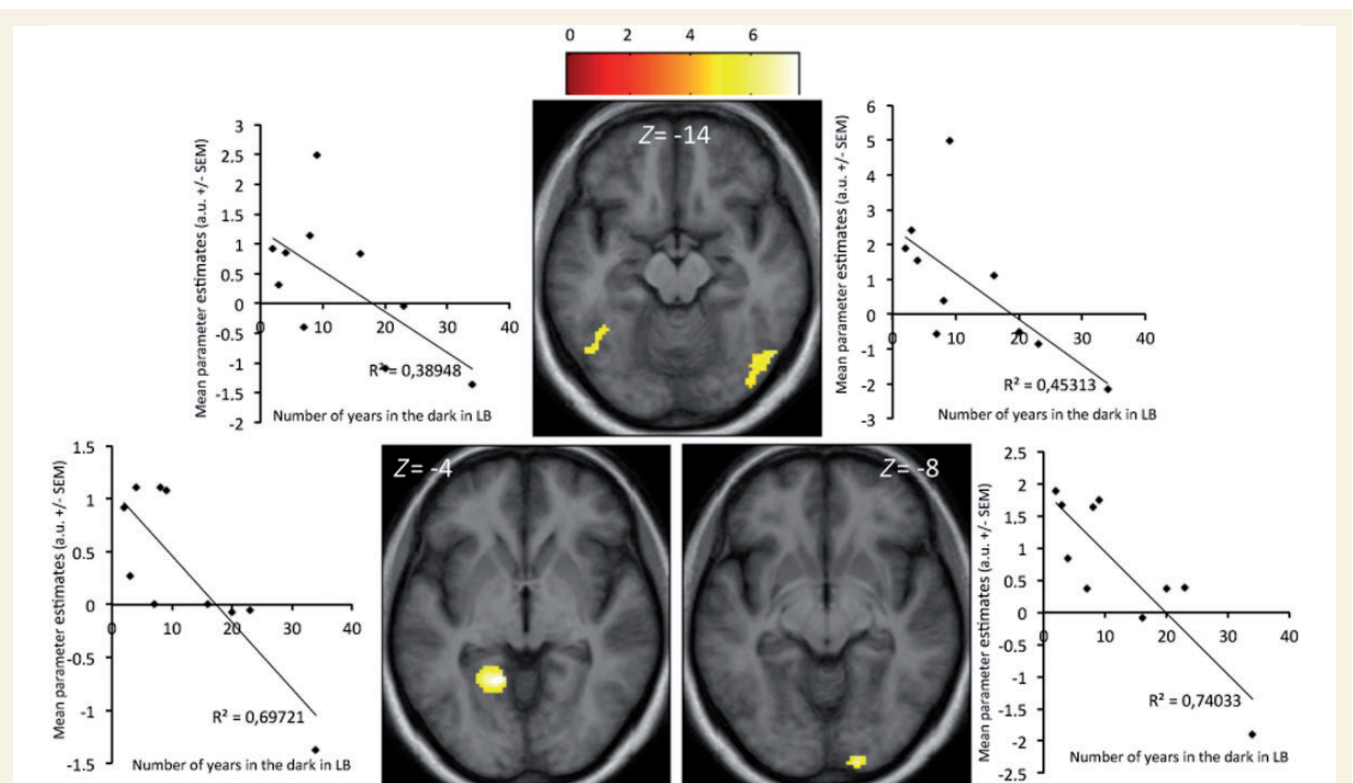


Figure 3 Regression analysis between cerebral activity triggered by the global processing of sounds (spatial + pitch) and the number of years of total blindness in the late-onset blind (LB). Sound-related responses in the left inferior occipital (*top*), the right inferior occipital (*upper panel*), the left lingual/anterior V1 (*bottom left*), the right lingual/posterior V1 (*bottom right*) regions are all negatively correlated with the number of years of blindness in the late-onset blind. Graphs: correlation plots of the blood oxygen level-dependent sound-related estimated responses in these regions against the number of years of total blindness. Each data point represents a single subject of the late-onset blind group.

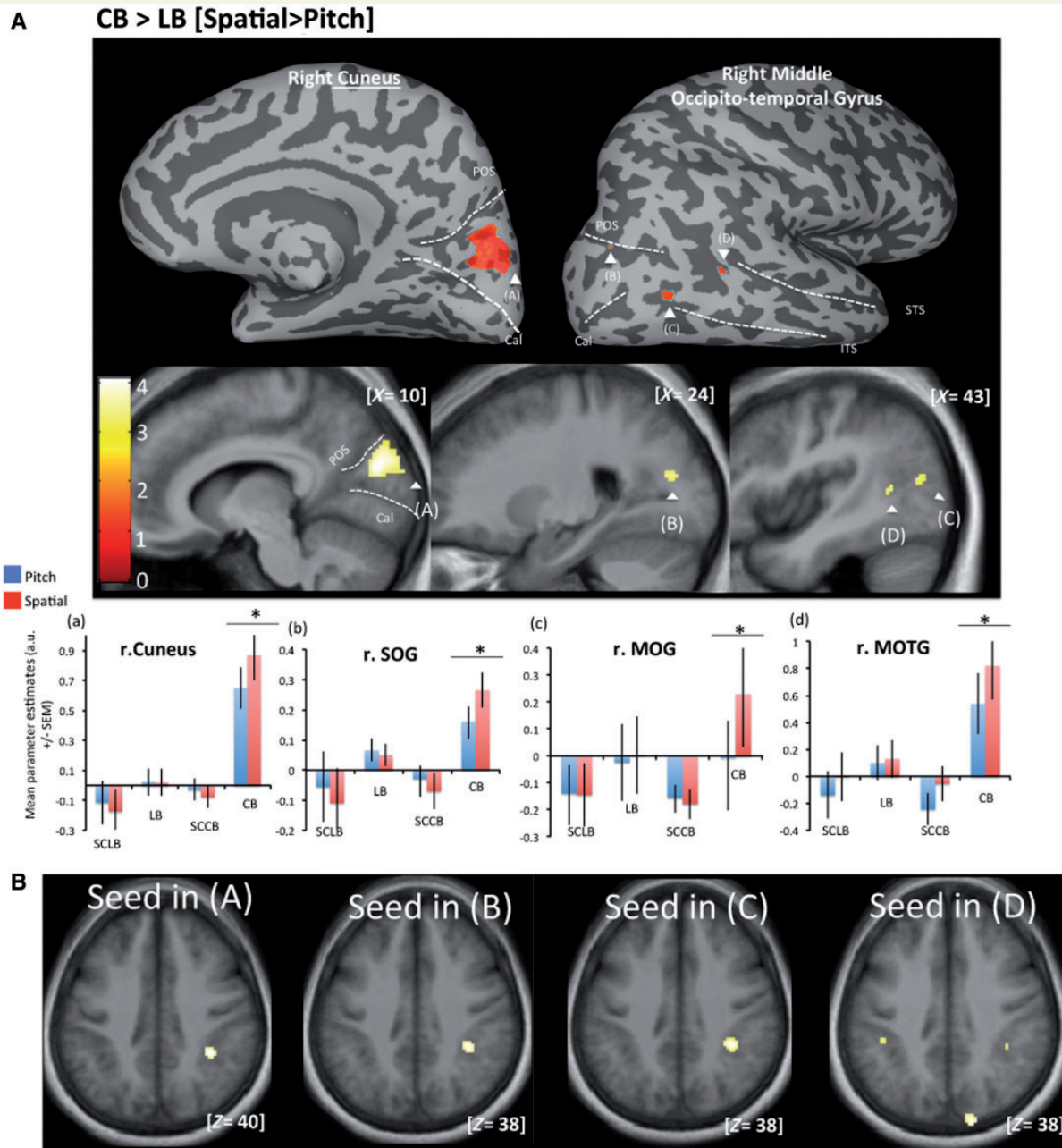


Figure 4 (A) Activations obtained from the contrast testing which regions are specifically dedicated to the spatial processing of sounds in the congenitally blind when compared to late-onset blind: (congenitally blind > late-onset blind) \times (spatial > pitch). Functional data are overlaid ($P_{\text{uncorrected}} < 0.001$) over a 3D render of an inflated canonical brain surface in MNI space (using NeuroLens software) and over sagittal sections of the mean structural image of all blind subjects normalized to the same stereotaxic space. Graphs: mean parameter estimates (a.u. \pm SEM) associated with the processing of pitch (blue) or spatial (red) attributes of sounds in the four groups of participants for the four main activity peaks: (a) The right cuneus (10 – 80 22), (b) The right superior occipital gyrus (SOG: 24 – 74 18), (c) The right middle occipital gyrus (MOG: 40 – 70 14), (d) The right middle occipito-temporal gyrus (MOTG: 44 – 54 08). It is worth noting that clusters (D) do not survive an inclusive mask ($P = 0.001$) of the (congenitally blind > SCCB) \times (spatial > pitch) contrast meaning that some spatial selectivity is found in this region (even if in the form of deactivations) in the SCCB (see Supplementary Fig. 1). (B) Psychophysiological interaction maps revealing stronger functional connectivity in the CB relative to the LB between all seed regions (the right cuneus, the right middle/superior occipital gyrus and the right middle occipito-temporal gyrus) and the right Intra-Parietal Sulcus (IPS) for the spatial processing of sounds as compared to pitch processing. Activity is overlaid ($P_{\text{uncorrected}} < 0.001$ except for seeds in D which is overlaid $P_{\text{uncorrected}} < 0.005$) over sagittal sections of the mean structural image of all blind subjects normalized to the same stereotaxic space.

(Fig. 4 and Supplementary Table 2.1). However, the group (late-onset blind > SCLB) \times condition (spatial > pitch) interaction analysis did not reveal any significant responses (Fig. 4; Supplementary Table 2.2). To further explore whether this functional specialization for auditory spatial processing is dependent on the age of blindness onset, we carried out the group (congenitally blind > late-onset blind) \times condition (spatial > pitch) interaction analysis and observed significant differences in activity in the right cuneus, the right middle/superior occipital gyrus and the right middle occipito-temporal gyrus (Supplementary Table 2.3).

None of the contrasts examining for the functional preference for processing the pitch of sounds (pitch > spatial) revealed significant results in the occipital cortex of any of the groups.

Functional connectivity analyses

Psychophysiological interaction analyses (Gitelman *et al.*, 2003; see 'Materials and methods' section) were computed to identify any brain region functionally connected to the reorganized occipital regions specifically in auditory spatial processing, relative to pitch processing, in the congenitally blind relative to the late-onset blind (Fig. 4B and Supplementary Table 3). Psychophysiological interaction revealed stronger functional connectivity in the congenitally blind relative to the late-onset blind between all seed regions (the right cuneus, the right middle/superior occipital gyrus and the right middle occipito-temporal gyrus) and the right intraparietal sulcus for the spatial processing of sounds as compared to pitch processing (Fig. 4B and Supplementary Table 3). We further observed significant coupling between the right middle/superior occipital gyrus and the right middle frontal gyrus, as well as between the right middle occipito-temporal region, the left intraparietal sulcus and the right cuneus [this region was observed in the contrast (congenitally blind > late-onset blind) \times (spatial > pitch)].

Dynamic causal modelling

A random-effects family-wise inference addressed the connectivity architecture (Fig. 5A) of sound-induced activity in occipital regions in both blind groups and showed that models including direct connections from the primary auditory cortex (A1) to V1 and no connections from intraparietal sulcus to V1 could best explain the V1 responses in the congenitally blind (Family B), whereas in the late-onset blind the preferred family did not include direct connections from A1 to V1 but rather included connections from intraparietal sulcus to V1 (Family A) (Fig. 5B). In addition, a random effects Bayesian model selection showed that the model connecting A1 to V1 and V1 to intraparietal sulcus (Model 6 in Fig. 5A) had a very high probability of evidence in the congenitally blind (Fig. 5C; exceedance probability of 0.79). In the late-onset blind, however, the model connecting A1 to intraparietal sulcus and intraparietal sulcus to V1 (Model 5 in Fig. 5A), with backward connections (Fig. 5C; exceedance probability of 0.49) had the strongest evidence (Fig. 5C).

Discussion

Crossmodal recruitment of occipital cortex for general auditory processing in the congenitally blind and late-onset blind

The study of congenitally blind and late-onset blind individuals represents a unique opportunity to explore brain plasticity mechanisms following radical changes in sensory experience during different developmental periods. We first showed that blood oxygen level-dependent responses elicited by sounds were found in occipital areas in both blind groups, whereas sighted subjects instead mainly showed blood oxygen level-dependent signal decreases in these regions (Fig. 2, Supplementary Fig. 1). This clearly shows that crossmodal reorganization occurs even after the full development of the visual system. This remarkable adult plasticity is exemplified by the results of a specific late-onset blind individual in our sample who suddenly lost his sight (diabetic retinopathy) at the age of 50 and showed extensive crossmodal recruitment of his occipital cortex <2 years after this abrupt onset of blindness (Supplementary Fig. 2).

Our observation that occipital recruitment for auditory processing appeared reduced in the late-onset blind when compared to the congenitally blind (Fig. 2) is in accordance with some previous studies showing similar findings (Cohen *et al.*, 1999; Voss *et al.*, 2008; Bedny *et al.*, 2010, 2012) but strongly contrasts with another study suggesting stronger crossmodal recruitment of primary visual cortex in late-onset blind (Buchel *et al.*, 1998). The only region showing a significantly higher level of activity in the congenitally blind compared with the late-onset blind is the bilateral cuneus (Fig. 2B), a region corresponding to V2d-V3d/V3a (Larsson and Heeger, 2006). In the sighted control (SC), this retinotopic area (Wandell *et al.*, 2007) has been shown to be notably involved in stereoscopic depth perception (Tsao *et al.*, 2003), an ability that is very dependent on early visual experience (Banks *et al.*, 1975; Fawcett *et al.*, 2005). It is therefore possible that the functional tuning of the cuneus might be set early in life, which then restricts crossmodal plasticity when vision is deprived in adulthood. Overall, these results indicate that the late-onset blind do show altered functioning of their deafferented visual cortices but, crucially, the age of blindness onset appears to play an important role in determining which occipital regions will become responsive to auditory processing. Our results therefore demonstrate the existence of region-specific critical periods for crossmodal plasticity.

An intriguing aspect revealed in our study is the negative correlation between sound-related activity in several occipital regions and the total number of years of blindness in the late-onset blind (Fig. 3). Our results point to the existence of an initial imbalance following sight deprivation in what used to be a pre-existing audio-visual network, which then might progressively stabilize following several years of visual deprivation. These results accord with those from a study investigating crossmodal plasticity in deaf humans that showed that visual activation in the left

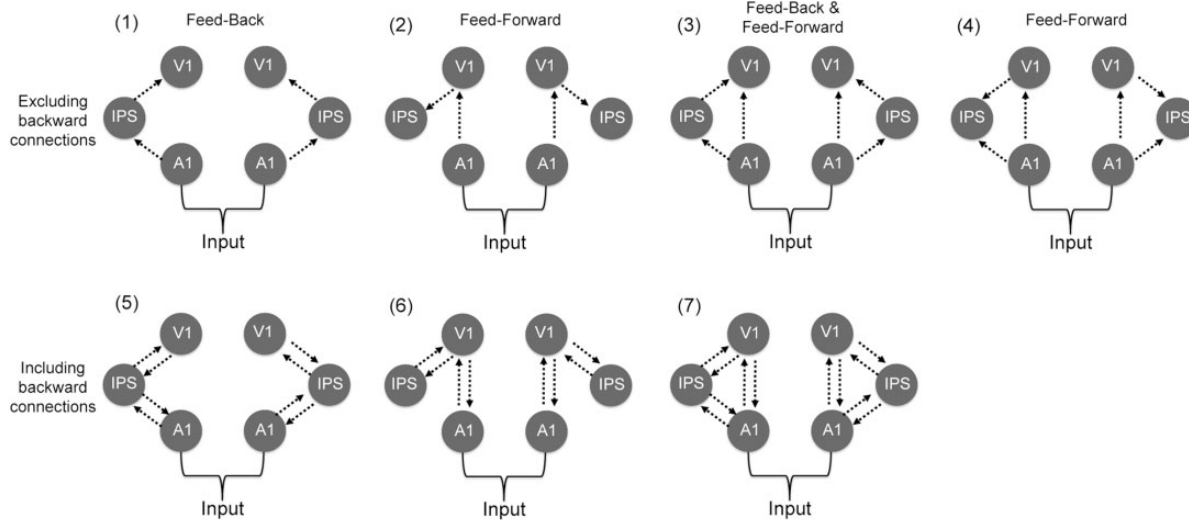
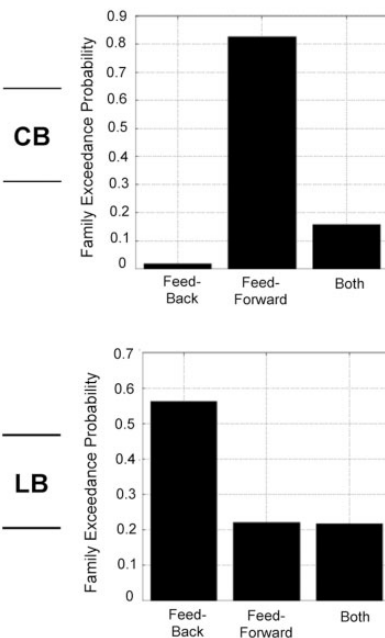
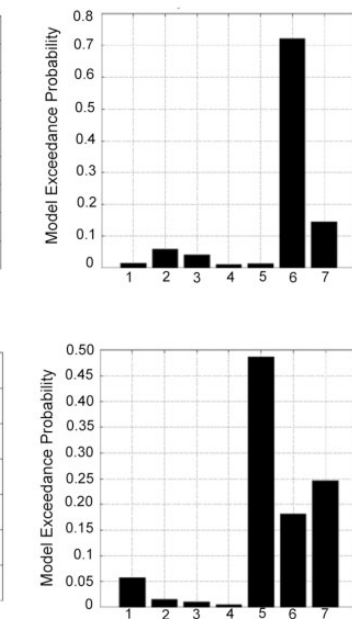
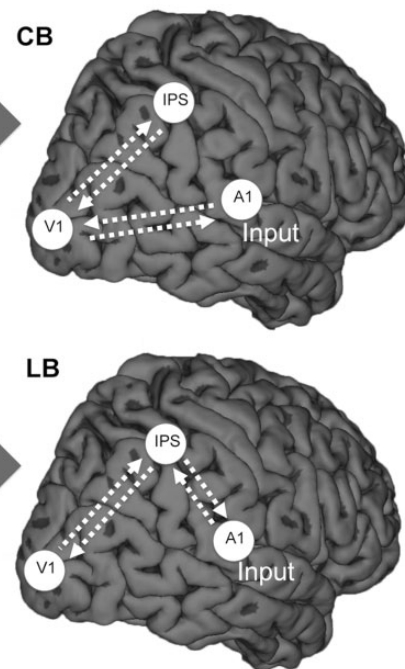
A DCM Models**B Family Inference****C Best Model Inference****D Schema of the pathways best supporting auditory activity in V1 in CB and LB**

Figure 5 Dynamic causal modelling analyses. **(A)** The seven dynamic causal models used for Bayesian model comparison. Each model receives (parameterized) subcortical input at the bilateral A1 sources. **(B)** Family-wise Bayesian model selection was used to establish the best neuronal network architecture in the congenitally blind (CB) and the late-onset blind (LB). In the congenitally blind the best models included direct connections between A1 and V1 and no connections between intraparietal sulcus and V1. In the late-onset blind the best models did not include direct connections between A1 and V1 but rather included connections between A1 and intraparietal sulcus. **(C)** Random effects Bayesian model selection showed that the model connecting A1 to V1 and V1 to intraparietal sulcus (Model 6) best fit the data in the congenitally blind, whereas the model connecting A1 to intraparietal sulcus and intraparietal sulcus to V1 (Model 5) best fit the data in the late-onset blind. **(D)** A schematic representation of how auditory information flows towards V1 in the congenitally blind (CB) and late-onset blind (LB).

posterior superior temporal cortex decreased with increasing deafness duration (Lee *et al.*, 2007).

The neural underpinnings of these observed changes might stem from the concept of homeostatic synaptic scaling, a form

of synaptic plasticity that increases or decreases the strength of all of a neuron's excitatory synapses to rapidly provide stability to neural networks ensuing perturbation in neural activity (Turrigiano, 2008). In blind mice, a rapid and global up-scaling of visual

neurons excitability has been observed following visual deprivation (primarily due to regulation of postsynaptic AMPA-type glutamate receptors), which was speculated to underlie the recruitment of this region for processing previously sub-threshold inputs carrying tactile or auditory information (Goel *et al.*, 2006; Goel and Lee, 2007; Lee, 2012).

On the basis of our data, it may be hypothesized that the crossmodal plasticity observed in the late-onset blind might represent the macroscopic correlate of the homeostatic synaptic plasticity observed at the cellular level in the visual cortex of blind mice (Turriano, 2008). The observation of a negative correlation between sound-related activity in some occipital regions and the total numbers of years of blindness might suggest that, at least for these specific regions, such homeostatic up-scaling of occipital neurons may be an 'initial' reaction to visual deprivation that progressively stabilize with time. However, to the best of our knowledge, no animal study has directly investigated how this homeostatic up-scaling observed in late-acquired blindness evolves across a prolonged period of visual deprivation.

One might also wonder whether the occipital recruitment in the late-onset blind relates to the use of visual imagery processes, which has been shown to activate components of the visual system (Kosslyn *et al.*, 1995). Even if we cannot definitely exclude this possibility, it appears very unlikely. First, previous visual imagery paradigms showing occipital recruitment involved active tasks that explicitly require subjects to intentionally rely on this ability (Kosslyn *et al.*, 2001), which was not the case here. Furthermore, it appears implausible that the late-onset blind group relied on previous visual experience to resolve the task while blindfolded sighted participants did not. It could even be suggested that residual voluntary (imagery) or involuntarily (hallucinations) visual capabilities might actually hinder crossmodal plasticity as the presence of such abilities have been considered to be a good prognostic sign for visual field recovery in partially blind individuals (Tan *et al.*, 2006).

A sensitive period for the development of functionally specific crossmodal reorganization for auditory spatial processing in the occipital cortex of blind individuals

It was recently demonstrated that non-visual recruitment of the occipital cortex follows organizational principles that maintain the functional specialization of the colonized brain regions (Collignon *et al.*, 2009a; Ricciardi and Pietrini, 2011; Reich *et al.*, 2012). This suggests that a specialized region that evolved to perform a specific cognitive operation (i.e. infer the spatial relationship between elements) in the visual domain can be used efficiently by other senses for similar computations in case of early visual deprivation. We demonstrate here that the functional selectivity for the spatial processing of sounds in the right dorsal stream is only observable in the congenitally blind but not in the late-onset blind (Fig. 4A). The concomitant presence of crossmodal activity in the occipital cortex with an absence of functional selectivity has

not been reported in previous studies involving late-onset blind individuals. This strongly suggests the existence of a critical period for such crossmodal functional specialization to occur. Based on these observations, we assume that there is a progressive process in early life, for at least some occipital subregions, of getting gradually a sensory-dependent functional specialization. More specifically, regions corresponding to the right cuneus and the right superior and middle occipital gyrus were selectively recruited for the spatial processing of sounds only in the congenitally blind, in the vicinity of regions (V3d-V3A and hMT+ /V5) that have previously been extensively described as subserving visuo-spatial and visual-motion processing in the sighted (Haxby *et al.*, 1991; Watson *et al.*, 1993).

The existence of a restricted time window for blindness to lead to functionally specific cross-modal plasticity in right dorsal regions is consistent with previous evidence of early structural (Gogtay *et al.*, 2004; Bourne and Rosa, 2006; Flom *et al.*, 2009) and functional (Elleberg *et al.*, 2002; Fine *et al.*, 2003; Gregory, 2003; Maurer *et al.*, 2005) maturation of these regions. Our results also support the recent findings of Bedny *et al.* (2010) who, focusing on hMT+ /V5, reported that this region reacts more strongly to an auditory condition with higher motion content (approaching footsteps) than to a condition with lower motion content (tones increasing in intensity), in early-onset blind individuals but not in a group of five late-onset blind individuals. In the present study, using a whole brain approach, we extend these findings by showing that despite the presence of crossmodal reorganization in the occipital cortex of both congenitally blind and late-onset blind individuals only the congenitally blind showed functional specialization for the spatial processing of sounds in the right dorsal pathway. The dorsal stream's ability to implement spatial/motion computations on the basis of non-visual inputs appears to be linked to an early developmental epoch. Our results therefore do not support the idea that the functional selectivity for spatial processing observed in dorsal occipital regions in the blind's brain simply arises from the unmasking of 'silent' connections existing in metamodal spatial regions also present in the sighted brain (Pascual-Leone and Hamilton, 2001), as this selectivity should also be observed in the late-onset blind.

What might drive the maintenance of the preferential coding for spatial processing in right dorsal occipital regions in the congenitally blind? It has been proposed that the development of cognitive domain selectivity in the brain is driven by the innate pattern of connectivity a region has with a network of other regions involved in the processing of this specific ability (Johnson, 2011; Mahon and Caramazza, 2011). Using functional connectivity analyses, we show that during the spatial (versus pitch) processing of sounds, the congenitally blind, when compared with the late-onset blind, demonstrate a stronger coupling between right dorsal occipital areas and the intraparietal area (Fig. 4B), which is known to play a major role in visuospatial attention in the sighted's brain (Nobre *et al.*, 1997). Hence, the difference in the functional specialization of the dorsal stream between the congenitally blind and late-onset blind not only resides in a preferential coding for auditory-spatial processing in the congenitally blind, it is also evidenced as an enhanced task-specific connectivity with intraparietal sulcus regions in the congenitally blind. It could therefore be

hypothesized that the observed selectivity for non-visual spatial computations in right dorsal occipital regions in the congenitally blind might arise from its innate pattern of connectivity, notably with the intraparietal sulcus. However, this selectivity is not observed in the late-onset blind, maybe because these circuits have been wired for visuospatial processing during early development. All together, these results suggest that the preservation of occipital functional properties can serve as a guiding principle for cross-modal plasticity only when vision is lost early in life.

The absence of functional selectivity in the occipital cortex of the late-onset blind concomitantly with a negative correlation between the activity of some of these regions and the number of years of blindness leads us to question the functional significance of the crossmodal reorganization we observed in this population. A previous study showed a negative correlation between occipital activity and performance in an auditory spatial task in the late-onset blind, suggesting not only that not all crossmodal recruitment is beneficial, but also that it may even be detrimental to the task at hand (Voss *et al.*, 2006). Cohen *et al.* (1999) applied transcranial magnetic stimulation over the occipital cortex of congenitally blind and late-onset blind individuals and disrupted Braille reading performance only in the congenitally blind but not in the late-onset blind. Together, these results suggest that the crossmodal plasticity observed after the full development of the visual system might neither be specific nor compensatory, in marked contrast to what is seen in the congenitally blind (Wan *et al.*, 2010).

Pathways for crossmodal plasticity in congenitally blind and late-onset blind

Our dynamic causal modelling results suggest that global auditory activity in the occipital cortex of the congenitally blind is best explained by direct feed-forward connections from A1 to V1, whereas in the late-onset blind auditory information appears to rely more on an indirect feedback route from A1 to V1 using parietal regions as a relay (Fig. 5 and Supplementary Fig. 4).

We know from neurodevelopmental studies that following an initial period of exuberant proliferation of synapses, their number is gradually reduced, notably in occipital regions (Huttenlocher and de Courten, 1987; Bourgeois and Rakic, 1993). The elimination of weaker, unused or redundant synapses is thought to mediate the specification of functional and modular neuronal networks (Changeux and Danchin, 1976). Indeed, experiments in kittens have demonstrated that projections from the auditory cortex to the occipital cortex are eliminated either through cell death or retraction of exuberant collaterals during the synaptic pruning phase (Dehay *et al.*, 1988; Innocenti *et al.*, 1988). Importantly, in kittens deprived of vision at birth, these extrinsic connections to the occipital cortex seem to remain (Berman, 1991; Yaka *et al.*, 1999). It is thus plausible that in the absence of competitive visual inputs during the synaptic stabilization phase, a significant number of direct auditory connections to the occipital cortex persist. Although the maintenance of normally transient intermodal connections may underlie, at least in part, the plastic changes observed in cases of congenital loss of sight, this cannot account for the cerebral reorganization observed in the case of late-onset

blindness, where visual deprivation arises in a brain already wired for visual processing. We therefore propose that the reorganizations occurring in people deprived of vision in adulthood alters the pattern of connectivity within the neuro-architectural constraints that are already established (Knudsen, 2004). In line with these assumptions, an elegant study combining PET scan and transcranial magnetic stimulation showed that the application of transcranial magnetic stimulation over the primary somatosensory cortex induced significant activation of the primary visual cortex only in an early-onset blind group but not in late-onset blind or sighted subjects (Wittenberg *et al.*, 2004), consistent with the hypothesis of reinforced direct cortico-cortical connections between primary sensory cortices in early but not in late-onset blind individuals. The idea that crossmodal plasticity in the late-onset blind relies on the reorganization/strengthening of a pre-existing pattern of connections is also supported by studies on short-term visual deprivation where the speed at which changes occur within occipital activity would not allow for the creation of new connections (Merabet *et al.*, 2008). Our observation that a feed-back model best explains auditory activity in the occipital cortex of the late-onset blind might therefore reflect a reorganization of the networks classically involved in 'top-down' phenomena like visual attention (Corbetta and Shulman, 2002), imagery (Kosslyn and Thompson, 2003) or crossmodal influences on primary sensory regions from multisensory convergence zones (Macaluso and Driver, 2005). This, however, does not exclude the possibility that the reorganization of direct connections between A1 and V1 might also mediate some of the sound-induced activity observed in the occipital cortex of the late-onset blind since such pathways have been observed in adult sighted primates (Falchier *et al.*, 2002; Rockland and Ojima, 2003) and humans (Beer *et al.*, 2011).

Conclusion

Our results show that the brain is capable of massive crossmodal reorganization as a result of visual deprivation, but crucially, the expression of this blindness-induced plasticity differs considerably depending on the developmental period during which it occurs. Whereas massive auditory recruitment of the occipital cortex was found in both blind groups, crossmodal activity in bilateral cuneus was unequivocally higher in the congenitally blind than in the late-onset blind, highlighting the existence of region-specific critical periods for crossmodal plasticity. Moreover, regions of the right dorsal stream preferentially active for the spatial processing of sounds in the congenitally blind did not show such functional preference in blind individuals who lost sight later in life. Early sensory experience therefore appears to instruct dorsal occipital neural circuits their sensory-functional preference and allows for their incorporation into a brain network dedicated to the processing of auditory spatial information. Moreover, dynamic causal modelling revealed that different architectures of cortical pathways underlie the auditory activations of primary occipital cortex in congenitally blind (feed-forward) and late-onset blind (feed-back) individuals. We suggest that visual deprivation in early life modifies the architecture of occipital circuits in a fundamental way, whereas the reorganizations that occur in visually deprived adults rather

alters connectivity patterns within the architectural constraints established during normal visual development. Such conceptions recently appeared in studies investigating adults with amblyopia suggesting that the original model of a fixed critical period for plasticity may have exceptions, putatively through latent synapses capable of re-expression in adults (Bavelier *et al.*, 2010; Hess *et al.*, 2010). Our improved understanding of the differential mechanisms of cross-modal plasticity resulting from early versus late visual loss might ultimately help to evaluate the functional outcome of sight restoration (Collignon *et al.*, 2011a), which is of increasing importance since a growing number of medical advances will soon allow it to be a promising option for blind people. Despite the observation of crossmodal plasticity in both blind groups, the quantitative and qualitative differences in the re-organization observed between the congenitally blind and late-onset blind suggest that these changes are more 'epiphenomenal' in nature in the latter group, and therefore might present less of a hindrance to sight restoration procedures compared to when vision is reacquired after early visual deprivation (Fine *et al.*, 2003; Levin *et al.*, 2010; Dormal *et al.*, 2012).

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Supplementary material

Supplementary material is available at *Brain* online.

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