

Functional specialization for auditory–spatial processing in the occipital cortex of congenitally blind humans

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The study of the congenitally blind (CB) represents a unique opportunity to explore experience-dependant plasticity in a sensory region deprived of its natural inputs since birth. Although several studies have shown occipital regions of CB to be involved in nonvisual processing, whether the functional organization of the visual cortex observed in sighted individuals (SI) is maintained in the rewired occipital regions of the blind has only been recently investigated. In the present functional MRI study, we compared the brain activity of CB and SI processing either the spatial or the pitch properties of sounds carrying information in both domains (i.e., the same sounds were used in both tasks), using an adaptive procedure specifically designed to adjust for performance level. In addition to showing a substantial recruitment of the occipital cortex for sound processing in CB, we also demonstrate that auditory–spatial processing mainly recruits the right cuneus and the right middle occipital gyrus, two regions of the dorsal occipital stream known to be involved in visuospatial/motion processing in SI. Moreover, functional connectivity analyses revealed that these reorganized occipital regions are part of an extensive brain network including regions known to underlie audiovisual spatial abilities (i.e., intraparietal sulcus, superior frontal gyrus). We conclude that some regions of the right dorsal occipital stream do not require visual experience to develop a specialization for the processing of spatial information and to be functionally integrated in a preexisting brain network dedicated to this ability.

blindness | cross-modal plasticity | ventral-dorsal auditory streams | modularity

When the brain is deprived of its natural sensory inputs, it can rewire itself, showing an impressive range of plastic changes (1). Early visual deprivation thus provides an exceptional model to explore the role of sensory experience in shaping the functional architecture of the brain. Based on a number of studies comparing brain activity of congenitally blind (CB) and sighted individuals (SI), the current prevailing view is that visual deafferentation results in a reliable recruitment of the occipital cortex for nonvisual sensory processing to compensate for the challenging condition that is visual deprivation (2).

Although such findings highlight the brain's remarkable ability to rewire its components, questions remain about the functional organization of the occipital cortex in CB. An important characteristic of the visual cortex in SI is domain specialization wherein specific functional activity has been found in anatomically identifiable regions (3, 4). Our main question was, therefore: does the occipital cortex of CB process the colonizing nonvisual stimuli in a global manner or does it do so using some functional modularity similar to what is observed in SI, with precise regions involved in specific cognitive functions?

Several studies have reported that the occipital cortex of CB responds quite indifferently to a variety of cognitive tasks, suggesting that some common factors (i.e., attentional) rather than specific cognitive processes may contribute to the unselective

occipital activity observed in this population (5–8). In contrast, other studies do suggest that distinct regions of the visually deprived occipital cortex may show functional specialization that is to some extent comparable to what is known in SI (9). In SI, visual information is thought to be processed along two distinct (but interacting) pathways: (i) a ventral stream flowing from the primary visual cortex to the infero-temporal cortex and involved in the analysis of object properties (“what” pathway), and (ii) an occipito-parietal stream devoted to the analysis of the spatial relationship between objects (“where” pathway) (10, 11). Alternatively, another perspective on dorsal and ventral visual processing streams rather considers them to be involved in the control of object-directed actions and object recognition, respectively (12). Interestingly, recent studies in CB have reported task-specific responses in ventral (13–16) and dorsal (17–22) occipital streams in response to “what” and “where” nonvisual processing. For example, Renier et al. (22) have recently found that the middle occipital gyrus (MOG) is preferentially activated by the spatial processing of nonvisual inputs.

In the present study, we used functional MRI (fMRI) to measure brain responses of CB and SI when they processed either the identity (pitch) or the spatial (position in azimuth) attributes of exactly the same sounds; two core auditory abilities that allow us to make sense of the acoustic environment. This allowed for equal sensory input in both tasks, with only the instructions differing between the two. Additionally, using a psychophysical staircase paradigm, we ensured a level of complexity that was similar across tasks and subjects. This paradigm allowed us to precisely investigate whether specific processes map onto specialized subregions of the occipital cortex in CB and whether these regions maintain a modular organization similar to what is observed in SI.

Results

Behavioral results are presented in *SI Text* and show no differences between the groups.

Ventral–Dorsal Auditory Streams. We first tested whether our paradigm allowed us to observe a dissociation between a ventral and a dorsal network for the pitch and spatial processing of sounds, respectively, as previously suggested (23, 24). A conjunction analysis (investigating what is jointly activated in both groups) revealed that the spatial processing of sounds, compared with pitch processing, elicited significantly larger brain responses in a right-sided dorsal network (including the superior frontal

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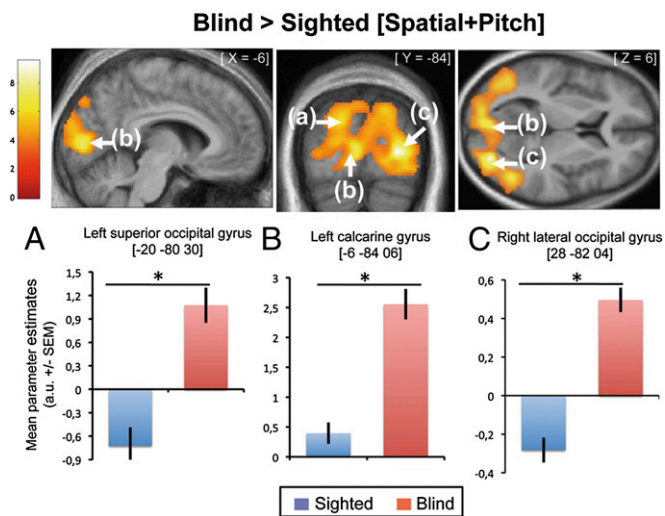


Fig. 2. Auditory cross-modal plasticity in the blind. *Upper:* Activations obtained from contrasts testing the main effects of group independently of condition [Blind > Sighted] \times [Spatial + Pitch]. Functional data are displayed ($P_{\text{uncorrected}} < 0.001$) over a horizontal, a coronal, and a sagittal section of the mean structural image of all subjects normalized to the same stereotaxic space. *Lower:* Mean activity estimates (arbitrary unit \pm SEM) associated with sound processing (Spatial + Pitch) in the sighted (blue) and blind (red) groups for the three main activity peaks obtained with this contrast.

serve in the primary visual cortex of CB seems equal in both tasks, supporting the notion that “early” areas of occipital cortex in the CB (e.g., V1/V2) support more generalized functions (28, 29). However, we also demonstrate that occipital regions involved in auditory spatial discrimination partially differ from those involved in auditory pitch discrimination (Fig. 3).

Spatial hearing in CB is shown here to preferentially map onto specialized subregions mainly located in the right dorsal occipital stream. The two primarily activated regions (Fig. 3 and Table 1) are the right cuneus [in the vicinity of what has been described as dorsal hV3/V3A in SI (30)] and the right MOG [in the vicinity of what has been described as hMT+/V5 in SI (31)]. Because these regions have been extensively documented as subserving visuo-spatial/motion abilities in SI (11, 32), we suggest that they might maintain their functional role in CB for the processing of a preserved modality, in this case audition. It is also worth noting that these two regions were also reliably active at an individual level (Table S3). Regarding the right cuneus, our results are in agreement with a previous study of Collignon et al. (17) demonstrating that the application of transcranial magnetic stimulation (TMS) over the right superior occipital gyrus (in the vicinity of the right cuneus/superior occipital clusters observed in the present study; see figure 2 in ref. 17) selectively interfered with sound localization abilities in CB, whereas TMS did not interfere with pitch and intensity discriminations in CB and had no effect on any auditory ability in SI. Regarding the right MOG, our results replicate those of Renier et al. (22), who also found this region preferentially active for the processing of spatial over nonspatial nonvisual stimuli in CB. In our study, the identified MOG was located posterior to the meeting point of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus (region B in Fig. 3), matching the anatomical location of hMT+/V5 in SI (31, 33). Anatomical localization of functional activations based on probabilistic cytoarchitectonic maps as implemented in Anatomy Toolbox (34) and quantifying structure–function correspondences showed that the cluster of interest covered 73% of hMT+/V5 region. Because our spatial task has the potential to induce an apparent motion percept (*Materials and Methods*), further studies should selectively address whether the MOG could be differentially activated by location and motion processing (either real or apparent).

The lingual gyrus, a primary visual region, was also found to be preferentially activated in CB for the spatial processing of sounds, even if to a lesser extent than the dorsal clusters (Table 1). This finding is not entirely unexpected: Gougoux et al. (35) found a similar region to be active during an auditory–spatial task in an early blind group. In the visual domain, the right lingual gyrus has often been reported to be specifically activated during direction/motion discriminations (32, 36, 37). This region may contribute to more “object-like” processing important for extracting spatial position, as postulated by Gougoux et al. (35), although this remains speculative.

None of the brain clusters showing specific activations in CB for the spatial processing of sounds correlated with the spatial resolution level of CB. This may seem puzzling given that a previous study reported that the degree of activation of several foci in the occipital cortex of CB correlated with sound localization accuracy (35). However, the use of an adaptive staircase method, as was the case here, obviously results in the absence of performance differences between subjects. Consequently, the measure used to correlate with brain occipital activity is the “auditory–spatial threshold,” reflecting the mean interaural level difference (ILD) and interaural time difference (ITD) required to discriminate the left or right target from the centrally presented probe (*Materials and Methods*). In addition, computation steps for the spatial perception of sounds in azimuth are mainly processed by the superior olivary nuclei in the brainstem (38). We therefore suggest that the activity in the occipital cortex of CB reflects higher-level perceptual functions rather than the extraction of ILD-ITD cues, which possibly explains the absence of correlation between auditory spatial threshold and occipital recruitment.

The fact that no occipital regions showed preferential activations for the processing of pitch in CB is not so surprising in light of the results of a recent study carried out in deaf cats (39). The authors propose that “supramodal” functions, or attributes that are shared across senses, have a greater potential to engage specific cross-modal plasticity mechanisms after the loss of a sensory input. Indeed, pitch processing, which is specific to audition in contrast to the ability to spatially locate information, which is shared by both vision and audition, may have less potential for specialized cross-modal recruitment of occipital regions in the blind.

Functional Connectivity of the Reorganized Occipital Cortex of CB.

We also demonstrate here that the occipital regions preferentially activated for auditory–spatial processing in CB are part of an extended network of brain areas, including multisensory regions (i.e., inferior parietal lobules, intraparietal sulcus, and superior frontal gyrus; Fig. 3) traditionally considered as important for spatial attention and awareness (40). In fact, most of these regions are activated in both groups, as revealed by the conjunction analysis based on the [Spatial > Pitch] contrast (Fig. 1). Interestingly, we found reliable functional connectivity between the three main peaks of activity located in the right dorsal occipital stream and the posterior superior frontal sulcus (Fig. 3), a region known as the frontal eye field and thought to play a role in the control of spatial attention in SI (41). Strikingly, it has been shown that this region is actively engaged during auditory spatial attention in CB (42). Taken together, these results suggest that the reorganized occipital regions in CB are inherently part of the network involved in auditory localization. Indeed, specific connectivity of precise occipital regions (i.e., dorsal) into an extended brain network wired to serve a specific function (i.e., spatial processing) might constrain the cross-modal reorganization in CB to regions with similar functional specificity. Supporting this hypothesis are the results of a diffusion tensor imaging study showing limited changes in the occipito-parieto-frontal white matter tracts of CB subjects relative to SI (43) and also from a recent study demonstrating that the prefrontal cortex shows massive functional connectivity with the hMT+/V5 area in CB (44).

Blind > Sighted [Spatial>Pitch]

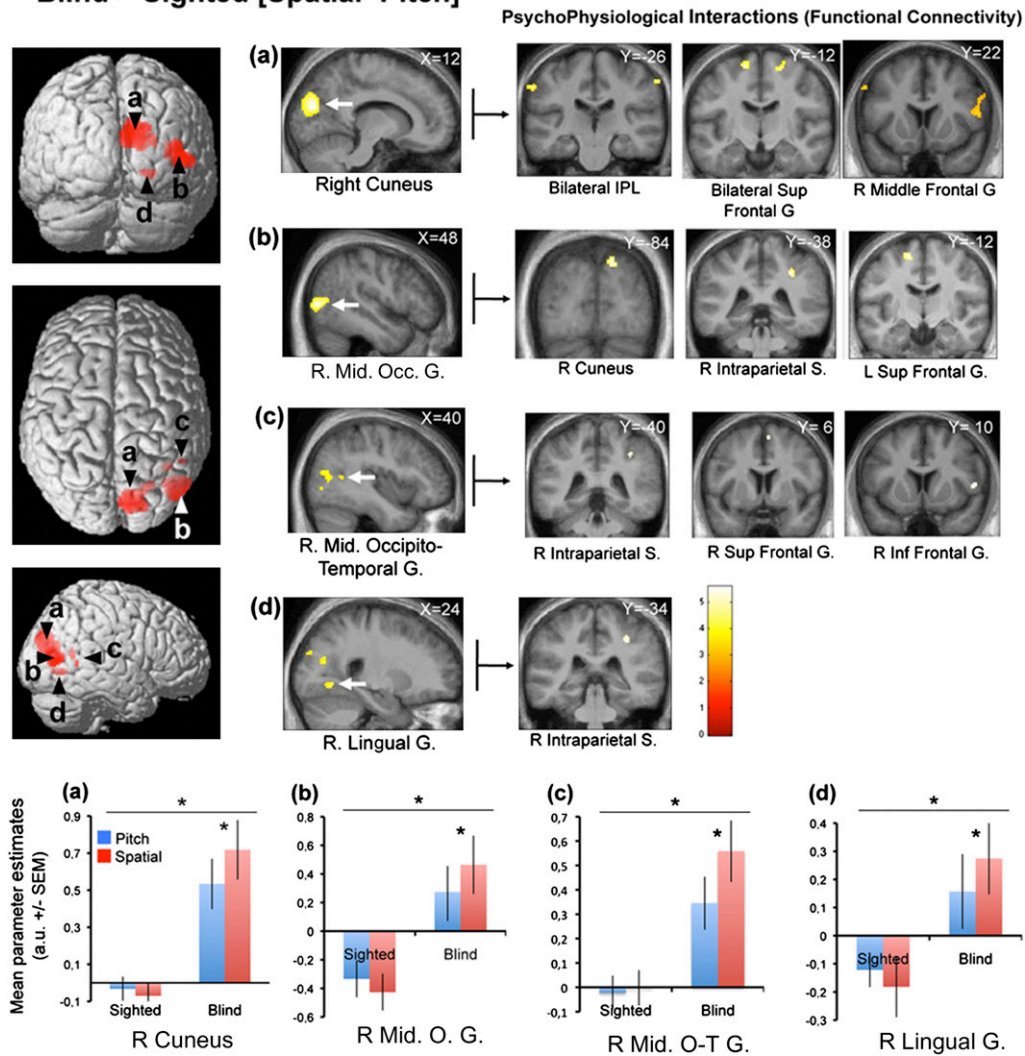


Fig. 3. Network for the spatial processing of sounds in CB subjects. (Left) Activations obtained from the contrast testing which regions are specifically dedicated to the spatial processing of sounds in blind subjects: [Blind > Sighted] \times [Spatial > Pitch]. Functional data are overlaid ($P_{\text{uncorrected}} < 0.001$) over a 3D render of the brain and over sagittal sections of the mean structural image of all blind subjects normalized to the same stereotaxic space. (Lower) Mean parameter estimates (arbitrary unit \pm SEM) associated with the processing of pitch (blue) or spatial (red) attributes of sounds in the sighted and the blind groups for the four main activity peaks. (A) The right cuneus. (B) The right middle occipital gyrus. (C) The right middle occipito-temporal gyrus. (D) The right lingual gyrus. Right: Psychophysiological interaction results using the four activity peaks as seed areas.

Mechanisms. These findings raise questions regarding the developmental mechanisms through which auditory inputs massively invade occipital regions in CB. In early life, the brain is sculpting itself on the basis of experience, with some synaptic connections eliminated and others strengthened (45). The human occipital cortex undergoes such changes in synaptic density during its normal development (46). After a peak of development ending approximately at the age of 8 mo, approximately 40% of the synapses of the visual cortex are gradually removed to reach a stable synaptic density at approximately the age of 11 y (45). It has been suggested that the maintenance of normally transient intermodal connections may underlie, at least in part, the plastic changes observed in CB (2, 9, 47). Moreover, recent anatomical studies showed direct connections between auditory and visual cortical regions in adult sighted monkeys (48, 49), suggesting that some intermodal connections might not be pruned in early infancy. In the present study, as previously observed (26), we found clusters of deactivation in the occipital cortex of sighted subjects during sound processing (Fig. S1). Because both activations and deactivations by nonvisual tasks

indicate the presence of nonvisual input in the occipital cortex of sighted individuals (22), these observations suggest that connections between auditory and visual cortices (48) may subserve cross-modal inhibition and/or multisensory integration in the early stages of sensory processing in individuals without visual deprivation (50, 51). In the absence of competitive visual input during development, these connections may provide the pathways for occipital processing of auditory inputs after visual deprivation.

Klinge et al. (52) recently used dynamic causal modeling of an fMRI dataset to investigate the effective connectivity underlying auditory activations in the primary visual cortex of CB. They found clear evidence for stronger corticocortical connections from primary auditory cortex to primary visual cortex in the blind compared with sighted controls, whereas their results regarding thalamocortical tracts (from medial geniculate nucleus to V1) were inconsistent. These results suggest that plastic changes in corticocortical connectivity probably play a crucial role in allowing auditory information to elicit the participation of the primary visual cortex of blind individuals.

Table 1. Functional results summarizing the main effect of group

Area	Cluster size	x (mm)	y (mm)	z (mm)	Z	P
Group effect [Blind > Sighted] × [Spatial + Pitch]						
Right lateral occipital gyrus	9,289	28	−82	4	5.79	0.000*
Left calcarine gyrus	—	−6	−84	6	5.02	0.010*
Left superior occipital gyrus	—	−20	−80	30	4.80	0.024*
Group × task interaction [Blind > Sighted] × [Spatial > Pitch]						
Right cuneus [†] (≈hV3/V3A)	740	12	−80	22	4.28	0.001
Right superior occipital gyrus ^{††} (≈hV3/V3A)	—	24	−70	20	3.41	0.001
Right middle occipital gyrus ^{††} (≈hMT+/V5)	390	48	−76	6	4.20	0.001
Right lingual gyrus [‡]	538	24	−48	−8	3.74	0.011
Right lingual gyrus ^{††}	—	24	−60	−4	3.49	0.014
Right middle occipito-temporal gyrus ^{††} (≈hMT+/V5)	15	40	−56	12	3.27	0.018
Group-by-task interaction [Blind > Sighted] × [Pitch > Spatial]						
No significant responses						

Brain activations significant after correction over the entire volume (*) or over small volume of interest (small-volume correction).

[†]Cluster not affected by an inclusive mask ($P = 0.001$) of the [Blind] × [Spatial > Pitch] contrast, indicating that the [Blind > Sighted] × [Spatial > Pitch] interaction effect was driven selectively by differences observed in blind subjects.

[‡]Cluster not affected by an exclusive mask ($P = 0.05$) of the [Sighted] × [Spatial > Pitch] contrast, further indicating that the reported interaction effect was driven by differences observed in the blind subjects.

[§]Clusters not surviving an inclusive mask ($P = 0.001$) of the [Blind] × [Spatial > Pitch] contrast, thus not driven selectively by the spatial processing of sounds in blind subjects.

Conclusion. The present study sheds light on mechanisms of cross-modal plasticity by demonstrating that domain specialization, wherein specific functional processing is found to involve specific cortical regions (3), seems to be a ubiquitous property of the occipital cortex, even when deprived of its “natural” inputs since birth. In particular, we have shown that the spatial processing of sounds in CB is performed in specific occipital regions overlapping areas well known to process the spatial attributes of visual inputs in SI. These results suggest that the dorsal stream innately designates its computational role for processing space independently of sensory developmental experience. Moreover, because these reorganized regions are part of an extended brain network, the maintenance of their functional specificity may help a colonized area to keep its functional role within a system of multiple cortical regions. We therefore postulate that cross-modal plasticity in CB allows nonvisual processes to find a “neuronal niche” into a set of circuits that perform functions that are sufficiently close to the ones required by the remaining senses (9, 22).

Materials and Methods

Subjects. Eleven CB [four female, age range 28–56 y (mean ± SD, 36 ± 13 y)] and 11 SI [four female, age range 26–56 y (mean ± SD, 39 ± 11 y)] participated in the study. Both groups were blindfolded throughout the fMRI acquisition and were matched for age, sex, handedness, educational level, and musical experience. None of the blind subjects had ever had functional vision allowing pattern recognition or visually guided behavior, and all were totally blind except for one who had only rudimentary sensitivity for brightness with no pattern vision. In all cases, blindness was attributed to peripheral deficits with no neurological impairment (Table S4). For all subjects, pure-tone detection thresholds at octave frequencies ranging from 250 to 8,000 kHz were within normal limits in both ears. All of the procedures were approved by the research ethic and scientific boards of the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal and the Quebec Bio-Imaging Network. Experiments were undertaken with the understanding and written consent of each subject.

Task and General Experimental Design. Subjects were scanned in a single fMRI session using a block design. The run 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. The duration of the rest blocks were jittered between the start of the sampling of brain volume images relative to the start of the task blocks. This method was used to avoid time-locked sampling whereby all brain images would be acquired at the same time points. A short verbal instruction (1,300 ms) was delivered 2 s before the start of each block to instruct participants which task they would have to carry out (spatial or pitch). The starting condition (either spatial or pitch) was coun-

terbalanced across subjects. In the “spatial” condition, participants had to determine whether the second sound of a pair was left- or right-sided compared with a constant central probe sound, regardless of the variation in pitch of these sounds. In the “pitch” condition, participants had to determine whether the second sound of a pair was lower- or higher-pitched compared with the same probe sound, regardless of the position of these sounds. Therefore, in both conditions and irrespective of the instructions given, the probe was a central sound (simulating zero degrees azimuth) of 1,000 Hz with a 150-ms duration (10-ms rise/fall times). The target sounds always appeared 200 ms after the probe and also had a 150-ms duration (10-ms rise/fall times). It is worth noting that, in the spatial blocs, the presentation in rapid succession of two spatially separate auditory stimuli can induce the perception of auditory movement, a phenomenon called “apparent motion” (53). Each pair of sounds was separated by a 1,200-ms response period. Each block, either spatial or pitch, consisted of 12 successive pairs of sounds (Fig. S2). 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 scan by adjusting the gap between the probe and the target using a dynamic psychophysical staircase procedure (one-down for correct response/six-up for wrong response), with the subject performance converging at ≈90% correct. Given the age heterogeneity of the participants and the age-related decline in spatial or pitch acuity, the staircase procedure adjusted the pairings to generate equal task difficulty for all subjects. Moreover, the target locations in a new pitch block were determined by the locations obtained in the preceding spatial block, and vice versa (e.g., pitch in spatial task), so that the same sounds were included in both conditions. This methodology ensures that when contrasting the two tasks, no effect can be attributable to the difference in difficulty level or to difference between physical attributes of the stimuli between the two tasks.

The experimental run was preceded by a short sound calibration run, during which the volume level was adjusted for each subject so as to ensure optimal auditory perception during scanning. The task was coded using Cogent2000v1.24 (<http://www.vislab.ucl.ac.uk/cogent.php>) implemented in MATLAB (Mathworks), and the auditory stimuli were delivered by means of circumaural, fMRI-compatible headphones (MR Confon).

All auditory stimuli were created using Audition 2.0 (Adobe Systems). A matrix of 6,400 sounds using 40 left and right “spatial gaps” (created by jointly varying steps of 0.2% ILD with steps of 20-μ ITD 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 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 joining the two ears (51).

Before the fMRI acquisition, all participants underwent a 30-min training session in a mock scanner, with recorded scanner noise played in the bore of the simulator to familiarize them with the fMRI environment and to ensure that the participants understood and could perform the tasks.

Behavioral Analysis. Performances in the scanner were analyzed by separately submitting accuracy scores and reaction times to a 2 (Groups: CB vs. SI; between-subjects factor) \times 2 (Tasks: Spatial vs. Pitch; within-subjects factors) repeated-measures ANOVA. Moreover, we also separately submitted the auditory-spatial and auditory-pitch resolution level (calculated as the mean gap separating the target from the probe for an entire run) to a simple ANOVA with the factor Groups (Blind vs. Sighted) as a between-subjects factor. A threshold of $P < 0.05$ was used for assessing the significance of the results. Behavioral results are presented in *SI Text* and show no differences between groups.

fMRI Data Acquisition and Analysis. The fMRI series were acquired using a 3-T TRIO TIM system (Siemens) equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation [time to repetition (TR) 2,200 ms; time to echo (TE) 30 ms; functional anisotropy (FA) 90°; 35 transverse slices; 3.2-mm slice thickness; 0.8-mm interslice gap; field of view (FoV) 192 \times 192 mm²; matrix size 64 \times 64 \times 35; voxel size 3 \times 3 \times 3.2 mm³]. The four initial scans were discarded to allow for steady-state magnetization.

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A structural T1-weighted 3D magnetization prepared rapid gradient echo sequence (voxel size 1 \times 1 \times 1.2 mm³; matrix size 240 \times 256; TR 2,300 ms; TE 2.91 ms; TI 900 ms; FoV 256; 160 slices) was also acquired for all subjects. Functional volumes were preprocessed and analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>; Welcome Department of Imaging Neuroscience, London), implemented in MATLAB R2008a (Mathworks). Preprocessing included the realignment of functional time series, the coregistration of functional and anatomical data, a spatial normalization to an echo planar imaging template conforming to the Montreal Neurological Institute space, and a spatial smoothing (Gaussian kernel, 8 mm FWHM).

Details of the fMRI data analysis can be found in *SI Text*.

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Supporting Information

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SI Text

Behavioral Results. As expected, because of the use of a staircase paradigm, no difference of performance was observed between groups or between tasks (Fig. S1 B and C). Moreover, the simple ANOVA testing the group effect on auditory–spatial and auditory–pitch resolution level did not show a significant between-group effect (Fig. S1D). In the pitch discrimination task, the mean distance between the probe (1,000 Hz, central position) and the target was 27 Hz (± 17 Hz SD) in the sighted group and 16 Hz (± 20 Hz) in the blind group. In the spatial discrimination task, the mean distance between the probe (1,000 Hz, central position) and the target was 276 μ s interaural time difference (ITD) and 2.76% interaural level difference (ILD) (± 198 μ s ITD and 1.98% ILD) in the sighted group and 284 μ s ITD and 2.84% ILD (± 196 μ s ITD and 1.96% ILD) in the blind group.

The lack of performance differences between the two groups may seem puzzling at a first glance, especially regarding the spatial task because several previous studies outlined superior performance of the congenitally blind (CB) over sighted individuals (SI) for this ability (see ref. 1 for a recent review on the topic). However, previous studies showing difference in performance between CB and SI groups in spatial tasks have demonstrated that such differences manifest when sounds are presented monaurally (2, 3) or in the periphery (4). In the present experiment, the spatial task required the lateralization of intracranial sounds perceived along a line joining the two ears (*Materials and Methods*, main text). These sounds lead to a near-centered intracranial perceived location, roughly estimated to the foveal–parafoveal border if we attempt to make a correspondence with 3D sounds (5). This strongly suggests that blind individuals use subtle spatial cues more efficiently than sighted controls, particularly the spectral content of the sound, which is one of the principal remaining cues for localizing a source under a monaural listening condition or for the localization of sounds in the periphery (6). However, in the present experiment intracranial sound locations were obtained by jointly adjusting the ITD and ILD of pure tone. No head-related transfer function, which includes spectral cues, was used because people only had to judge the location of sounds along the azimuth coordinate. Indeed, our absence of better performance in the CB group may be related to this absence of spectral content in the sounds used in the present experiment.

Functional MRI Analysis. The analysis of functional MRI (fMRI) data, based on a mixed-effects model, was conducted in two serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated by a general linear model including the responses to the pitch and spatial conditions. These regressors consisted of boxcar function convolved with the canonical hemodynamic response function. The instruction preceding each block, movement parameters derived from realignment of the functional volumes (translations in x, y, and z directions and rotations around x, y, and z axes) and a constant vector were also included as covariates of no interest. High-pass filtering was implemented in the design matrix using a cutoff period of 128 s to remove slow drifts from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white-noise model and a restricted maximum likelihood algorithm.

Linear contrasts tested the main effect of each condition ([Pitch], [Spatial], [Spatial > Pitch], and [Pitch > Spatial]) and the main effect of general auditory processing ([Spatial + Pitch])

and generated statistical parametric maps [SPM(T)]. These summary statistics images were then further spatially smoothed (Gaussian kernel 6 mm FWHM) and entered in a second-level analysis, corresponding to a random-effects model, accounting for intersubject variance. One-sample *t* tests characterized the main effect of conditions ([Pitch], [Spatial], [Spatial > Pitch], and [Pitch > Spatial]) in SI and CB groups separately. A conjunction analysis based on a conjunction null hypothesis characterized brain areas jointly activated for the contrasts [Spatial > Pitch] and [Pitch > Spatial] in both groups (CI and SI). Two-sample *t* tests were then performed to identify group effects independent of the condition ([CB > SI] \times [Spatial + Pitch]) and to explore group \times condition interaction effects ([CB > SI] \times [Pitch > Spatial] and [CB > SI] \times [Spatial > Pitch]). Two-sample *t* tests were also performed to investigate group effect for each condition separately ([CB > SI] \times [Spatial]; [CB > SI] \times [Pitch]; [SI > CB] \times [Spatial]; [SI > CB] \times [Pitch]; see Table S5). Main effects of condition in each group were used as inclusive or exclusive masks to identify which group was driving the interaction effects.

The resulting set of voxel values for each contrast constituted a map of the *t* statistic [SPM(T)], thresholded at $P < 0.001$ (uncorrected for multiple comparisons; *Z* threshold of 3.09). Statistical inferences were performed at a threshold of $P < 0.05$ after correction for multiple comparisons over either the entire brain volume or over small spherical volumes (10-mm radius), located in structures of interest. Significant clusters were anatomically labeled using structural neuroanatomy information and probabilistic cytoarchitectonic maps provided in Anatomy Toolbox 1.7b (7) or using a brain atlas for brain regions not covered by this toolbox (8).

Psychophysiological interaction (PPI) analyses (9) were computed to identify any brain regions showing a significant change in the functional connectivity with a seed region (the right cuneus, the right middle occipital gyrus, the right middle occipitotemporal gyrus, and the right lingual gyrus) as a function of the experimental condition ([Spatial, Pitch]) in the CB group. Indeed, PPI analyses were conducted to test the hypothesis that functional connectivity between seed regions and the rest of the brain not only differed between conditions (Spatial vs. Pitch) but was also influenced by the experimental group (CB or SI). In each individual, time-series of activity from the seed area were extracted from the local maxima detected within 10 mm of the peaks identified in the [CB > SI] \times [Spatial > Pitch] contrast. New linear models were generated at the individual level, using three regressors. One regressor represented the condition (Spatial > Pitch). The second regressor was the activity extracted in the reference area. The third regressor represented the interaction of interest between the first (psychological) and the second (physiological) regressor. To build this regressor, the underlying neuronal activity was first estimated by a parametric empirical Bayes formulation, combined with the psychological factor and subsequently convolved with the hemodynamic response function (10). The design matrix also included movement parameters. A significant PPI indicated a change in the regression coefficients between any reported brain area and the reference region, related to the experimental condition (Spatial > Pitch) in CB. Next, individual summary statistic images obtained at the first level (fixed-effects) analysis were spatially smoothed (6-mm FWHM Gaussian kernel) and entered in a second-level (random-effects) analysis using a one-sample *t* test. Inferences were conducted as for the main-effect analysis. PPI carried out in the SI with the same seed areas were used as exclusive masks ($P = 0.05$) to ensure that the pattern of functional connectivity with the seeds

areas that is present in CB is not present in SI. These analyses allow exploration of the functional connectivity between any seed area and the rest of the brain, in CB, during Spatial sound processing compared with Pitch processing.

Finally, in the random-effects analyses, posterior probability maps (PPMs) enabling conditional or Bayesian inferences about regionally specific effects were performed (11). PPMs represent a powerful complementary approach to classic statistical parametric maps inferences (11). This type of analysis allows controlling that one seed area activated in one group (CB) presents a low probability of activation in the other group (SI). This is of particular interest in the case of the present study because it gives a direct measurement of the intrinsic probability of activation in SI of regions showing significantly more activity in CB than SI. PPMs and effect size were computed for the contrasts [Spatial + Pitch] and [Spatial > Pitch] in the CB group to verify that seed areas (using 10-mm volume of interest around activation peaks) obtained with [CB > SI] in these contrasts (the right middle occipital gyrus, the left calcarine gyrus, and the left middle occipital gyrus for [Spatial+Pitch]; the right cuneus, the right middle occipital gyrus, and the right lingual gyrus for [Spatial > Pitch]) have a low probability of activation in the SI group.

Coordinates of Areas of Interest Used for Spherical Small-Volume Corrections. Literature reporting brain activations related to auditory-pitch or auditory-spatial processing in blind and sighted subjects was considered for selecting coordinates of interest, depending of the contrast of interest. Before performing any small-volume correction (svc), peaks reported in Talairach (Talairach and Tournoux, 1988) space were transformed to Montreal Neurological Institute space using Matthew Brett's bilinear transformation (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>); no coordinates were shifted more than 5 mm). Standard stereotactic coordinates of previously published a priori locations, used for spherical svc, are as follows:

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Table S1. Functional results for the main effect of condition ([Pitch > Spatial] and [Spatial > Pitch]) in conjunction in each group (SI and CB)

Area	Cluster size	x (mm)	y (mm)	z (mm)	Z	P
Conjunction [CB \cap SI] \times [Spatial – Pitch]						
R superior frontal gyrus	1,308	32	0	48	5.34	0.002*
R middle occipito-temporal gyrus	690	48	-54	10	5.31	0.000
R inferior parietal lobule	1,444	52	-40	30	4.95	0.005
R middle frontal gyrus	340	40	56	16	4.29	0.001
R precuneus-superior parietal lobule	385	4	-52	60	4.23	0.001
L inferior frontal gyrus	64	-40	50	-6	3.58	0.01
R insula-R inferior frontal gyrus	107	46	22	-8	3.54	0.024
R middle frontal gyrus	32	44	06	30	3.30	0.025
Conjunction [CB \cap SI] \times [Pitch – Spatial]						
R anterior inferior temporal gyrus	35	44	0	-32	4.24	0.024
L anterior planum polare	405	-24	4	-20	4.15	0.013
L inferior frontal gyrus/insula	90	-46	06	04	4.12	0.002
L posterior middle temporal gyrus	207	-42	-36	02	4.12	0.006
L precentral gyrus	75	-38	-24	66	3.41	0.016
L middle temporal gyrus	21	-48	-22	-12	3.31	0.034

Brain activations significant after correction over the entire volume (*) or over small volume of interest (svc). R, right; L, left.

Table S2. Summary of the PPI analyses (functional connectivity analyses) performed on the [Spatial > Pitch] contrast in CB

Seed area for PPI analyses in CB	Cluster size	x (mm)	y (mm)	z (mm)	Z	P
Right cuneus						
R superior frontal gyrus	31	18	-12	60	3.87	0.005
	—	22	-18	70	3.26	0.028
L superior frontal gyrus	84	-14	-10	64	3.86	0.006
R inferior parietal lobule	25	58	-30	54	3.49	0.021
	—	64	-24	46	3.26	0.027
R middle frontal gyrus	7	56	22	36	3.45	0.037
L inferior parietal lobule	34	-64	-24	40	3.34	0.028
L inferior parietal lobule	7	-66	-22	30	3.23	0.029
R middle frontal gyrus	1	50	38	26	3.13	0.037
R inferior parietal lobule	1	30	-38	40	3.11	0.038
Right lateral occipital gyrus						
R inferior parietal lobule	29	32	-38	38	3.71	0.013
L superior frontal gyrus	66	-16	-12	58	3.70	0.010
R cuneus	42	14	-84	38	3.58	0.014
R cerebellum	17	14	-72	-44	3.26	0.027
Right middle occipito-temporal gyrus						
R inferior frontal gyrus	14	52	10	6	3.24	0.026
R superior frontal gyrus	6	6	6	60	3.21	0.028
R supramarginal gyrus	8	36	-40	42	3.18	0.030
Right lingual gyrus						
R inferior parietal lobule	26	32	-34	42	3.4	0.038

Brain activations significant after correction over small volume of interest (svc). All of the clusters reported in the table are not affected by an exclusive mask ($P = 0.05$) of the PPI carried out in the sighted subjects with the same seeds areas, further indicating that the reported regions present a pattern of functional connectivity with the seeds areas that is present on CB but not on SI. R, right; L, left.

Table S3. Small-volume correction analysis done around the Montreal Neurological Institute coordinate 44, -77, -2, identified as hMT+/V5 by Tootell et al. (1) and coordinate 24, -76, 24, identified as a visuospatial region by Haxby et al. (2)

Subjects	Cluster size	Coordinates			Z	P
		x (mm)	y (mm)	z (mm)		
hMT+/V5 (44, -77, -2)						
CB1	8	46	-66	-12	3.56	0.041
CB2	629	44	-72	12	>8	0.000
CB3	1,255	44	-66	-2	>8	0.000
CB4	42	48	-66	8	4.32	0.003
CB5	4	52	-64	2	4.16	0.007
CB6	—	—	—	—	—	—
CB7	249	36	-76	-10	4.86	0.000
CB8	48	40	-76	-2	3.82	0.021
CB9	245	48	-74	12	4.26	0.004
CB10	27	52	-70	8	4.2	0.004
CB11	—	—	—	—	—	—
V3/V3A (24, -76, 24)						
CB1	264	22	-84	34	5.53	0.000
CB2	678	18	-70	34	6.72	0.000
CB3	1305	24	-86	20	>8	0.000
CB4	4	28	-78	38	3.46	0.05
CB5	673	24	-84	36	7.25	0.000
CB6	—	—	—	—	—	—
CB7	260	16	-74	26	5.45	0.000
CB8	40	32	-88	22	3.57	0.000
CB9	372	38	-80	26	5.76	0.000
CB10	176	36	-82	18	5.3	0.000
CB11	48	22	-66	16	3.67	0.033

Brain activations significant after correction over small spherical volume of interest (15-mm radius), centered on the above-mentioned coordinates.

1. Tootell RB, et al. (1995) Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci* 15:3215–3230.
2. Haxby JV, et al. (1994) The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. *J Neurosci* 14:6336–6353.

Table S4. Characteristics of the blind subjects

Subject	Age (y)	Sex	Hand	Residual visual perception	Onset	Cause of blindness	Education	Musical experience
CB1	32	F	R	No	0	Glaucoma	High school	No
CB2	43	M	R	No	0	Glaucoma	University	Yes
CB3	39	M	R	Diffuse light	0	Leber's congenital amaurosis	University	No
CB4	56	F	R	No	0	Retinopathy of prematurity	High school	No
CB5	38	M	R	No	0	Detached retina	High school	Yes
CB6	31	F	R	No	0	Bilateral Retinoblastoma	High school	No
CB7	26	M	R	No	0	Leber's congenital amaurosis	University	Yes
CB8	30	M	R	No	0	Bilateral retinoblastoma	High school	Yes
CB9	46	M	R	No	0	Congenital Cataract	University	Yes
CB10	40	M	R	No	0	Retinopathy of prematurity	University	Yes
CB11	27	F	R	No	0	Retinopathy of prematurity	High school	No

Handedness was evaluated using an adapted version of the Edinburgh inventory (1). CB and SI were classified as "musician" if they currently practice or have practiced an instrument or vocal for more than 2 y on a regular basis (at least 2 h a week). M, male; F, female; R, right handed; L, left handed; A, ambidextrous.

1. Oldfield RC (1971) The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9:97–113.

Table S5. Brain activations ($P < 0.001$, uncorrected) related to the main effects observed in our tasks

Area	Cluster size	x (mm)	y (mm)	z (mm)	Z
Task effect [Spatial > Pitch]					
Sighted					
R inferior parietal lobule	426	68	-32	38	4.27
	—	62	-42	48	3.89
	—	52	-40	32	3.85
R precentral gyrus	64	32	0	48	3.53
R middle occipito-temporal gyrus	28	48	-54	10	3.50
R middle frontal gyrus	15	34	60	8	3.25
Blind					
R middle occipital gyrus	3,179	50	-52	6	5.22*
	—	50	-64	10	4.78*
	—	12	-80	22	4.11
R inferior parietal lobule	283	36	-40	40	3.94
R superior frontal gyrus	43	24	10	68	3.72
R middle frontal gyrus	254	34	2	52	3.66
	—	46	-2	52	3.38
R lingual gyrus	68	24	-66	-2	3.33
Task effect [Pitch > Spatial]					
Sighted					
R central sulcus	128	58	-10	50	4.67*
R posterior superior temporal gyrus	287	46	-30	-6	4.45
R anterior inferior temporal cortex	171	44	-4	-32	3.96
L insula	647	-42	-24	22	3.96
L putamen	—	-20	6	10	3.56
L inferior frontal gyrus (opercular part)	61	-58	-8	16	3.74
L middle/superior temporal gyrus	221	-52	-36	4	3.73
R cerebellum	31	28	-72	-34	3.43
L cerebellum	20	-26	-54	-18	3.35
Blind					
No significant responses					
Group effect [Blind > Sighted]					
Spatial					
R lateral occipital gyrus	11,950	32	-80	-2	6.06*
L calcarine	—	-6	-86	6	4.96*
R lateral occipital gyrus	—	46	-64	8	4.70*
Pitch					
L calcarine	5,474	-6	-84	2	4.95*
L superior occipital gyrus	—	-20	-78	30	4.90*
R lateral occipital gyrus	—	26	-82	4	4.73*
Group effect [Sighted > Blind]					
Spatial					
R middle temporal gyrus	58	64	-8	-14	4.43
R hippocampus	67	24	-22	-10	4.05
R angular gyrus	202	50	-62	38	3.95
Pitch					
R angular gyrus	50	46	-64	46	4.16
R hippocampus	12	26	-40	-4	3.26
Main effects separately					
Spatial in sighted					
L premotor/motor cortex	5,924	-34	-10	52	5.69*
R superior temporal gyrus (A1)	1,119	66	-26	12	5.14*
R cerebellum	939	12	-72	20	5.05*
L superior temporal gyrus (A1)	903	-64	-18	12	4.3
R cerebellum	116	22	-62	-50	4.02
L cerebellum	68	-24	-64	-50	3.66
L cerebellum	132	-28	-64	-26	3.66
L inferior parietal lobule	12	-48	-38	56	3.27
Pitch in sighted					
L premotor/motor cortex	7,081	-6	8	54	5.88*
R cerebellum	1,607	34	-64	26	5.17*
R superior temporal gyrus (A1)	1,227	64	-26	10	5.11*
R inferior frontal gyrus	387	58	14	20	4.56
R precentral gyrus	399	56	2	48	4.31

Table S5. Cont.

Area	Cluster size	x (mm)	y (mm)	z (mm)	Z
R cerebellum	113	22	-64	-50	3.95
L cerebellum	165	-28	-62	-24	3.75
L thalamus/putamen	247	-14	-16	6	3.68
L cerebellum	12	-22	-64	-50	3.23
Spatial in blind					
L cuneus/primary visual cortex (V1)	14,966	-6	-86	6	6.27*
L premotor/motor cortex	8,929	-34	-10	52	5.86*
L intraparietal sulcus	—	-38	-42	48	5.15*
R superior temporal gyrus (A1)	1,561	64	-26	10	5.69*
L superior temporal gyrus (A1)	1,511	-60	-32	12	4.96*
R intraparietal sulcus	398	42	-40	44	4.36
R superior frontal gyrus	181	38	38	28	4.06
L brainstem	21	-6	-22	-8	3.81
R superior parietal lobule	98	30	-56	54	3.45
R brainstem	5	6	-22	-10	3.33
Pitch in blind					
L cuneus/primary visual cortex (V1)	10,453	-6	-84	4	6.26*
L premotor/motor cortex	7,581	-12	-2	62	6.08*
R superior temporal gyrus (A1)	1,624	64	-26	10	5.89*
L superior temporal gyrus (A1)	1,884	-58	-32	12	5.66*
L occipito-temporal gyrus	532	-44	-62	6	4.54
R occipito-temporal gyrus	252	46	-60	6	4.48
R insula	251	32	20	6	4.2
R inferior frontal gyrus	463	58	12	8	4.11
R intraparietal sulcus	81	42	-36	42	3.6
R superior frontal gyrus	22	36	38	28	3.48
L thalamus	26	-14	-16	6	3.39

*Significant after correction over the entire volume at $P < 0.05$.