

Naturalistic stimuli reveal a sensitive period in cross modal responses of visual cortex: Evidence from adult-onset blindness

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ABSTRACT

How do life experiences impact cortical function? In people who are born blind, the “visual” cortices are recruited during nonvisual tasks, such as Braille reading and sound localization. Do visual cortices have a latent capacity to respond to nonvisual information throughout the lifespan? Alternatively, is there a sensitive period of heightened plasticity that makes visual cortex repurposing especially possible during childhood? To gain insight into these questions, we leveraged meaningful naturalistic auditory stimuli to simultaneously engage a broad range of cognitive domains and quantify cross-modal responses across congenitally blind ($n = 22$), adult-onset blind (vision loss >18 years-of-age, $n = 14$) and sighted ($n = 22$) individuals. During fMRI scanning, participants listened to two types of meaningful naturalistic auditory stimuli: excerpts from movies and a spoken narrative. As controls, participants heard the same narrative with the sentences shuffled and the narrative played backwards (i.e., meaningless sounds). We correlated the voxel-wise timecourses of different participants within condition and group. For all groups, all stimulus conditions induced synchrony in auditory cortex while only the narrative stimuli synchronized responses in higher-cognitive fronto-parietal and temporal regions. As previously reported, inter-subject synchrony in visual cortices was higher in congenitally blind than sighted blindfolded participants and this between-group difference was particularly pronounced for meaningful stimuli (movies and narrative). Critically, visual cortex synchrony was no higher in adult-onset blind than sighted blindfolded participants and did not increase with blindness duration. Sensitive period plasticity enables cross-modal repurposing in visual cortices.

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1. Introduction

Studies with people who are blind provide key insights into how experience influences neuronal response properties. In congenitally blind individuals, the occipital lobes, which support visual perception in sighted people, are active during tactile and auditory processing (Collignon et al., 2011; Poirier et al., 2006; Sadato et al., 2002). These “cross-modal”¹ responses are observed in a wide range of tasks, including perceptual tasks such as haptic shape recognition and motion detection, and higher-cognitive tasks, such as Braille reading, solving math equations and auditory sentence comprehension (Amalric et al., 2018; Bedny et al., 2011; Gougoux et al., 2005; Kanjlia et al., 2019; Lane

et al., 2015; Röder et al., 2002; Sadato et al., 1996; Uhl et al., 1991; Wanet-Defalque et al., 1988; Weeks et al., 2000). In people born blind, responses to different cognitive processes are spatially dissociable within visual cortices and sensitive to subtle manipulations of higher-cognitive information, such as grammatical complexity of sentences and math equation difficulty (e.g., Kanjlia et al., 2016). Disrupting activity in early “visual” cortices, by applying transcranial magnetic stimulation to the occipital pole, impairs performance on Braille reading and verb generation tasks, suggesting functional relevance of occipital cortex to nonvisual behavior in this population (Amedi et al., 2004; Cohen et al., 1999; Ptito et al., 2008).

Precisely how blindness enables cross-modal responses remains unclear. A central question is whether cross-modal activity observed in congenital blindness is enabled by sensitive period plasticity (Hensch,

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¹ Consistent with prior literature, we use the term “cross-modal” to indicate visual cortex responses to nonvisual stimuli/tasks. These responses could reflect either sensory processing (e.g., auditory or tactile perception) and/or higher-cognitive operations (e.g., language or mathematical processing).

2004, 2005; Maurer and Hensch, 2012). According to one view, visual cortex has special potential to acquire nonvisual functions during time-sensitive windows of heightened plasticity early in life, so-called sensitive periods. Alternatively, nonvisual responses observed in people who are born blind could reflect latent capabilities of visual cortex that exist in all adults and can be unmasked by vision loss at any age. Examining the response properties of visual cortices in individuals who lost their vision as adults can distinguish between these views. If repurposing is enabled by sensitive period plasticity, then people who lose vision as adults should not show the same cross-modal occipital responses as people born blind.

1.1. Mixed evidence for a sensitive period in visual cortex plasticity

Previous studies comparing individuals that lost their vision at different ages provide some support for sensitive period effects, but the evidence is mixed. On one hand, a number of studies find different responses to nonvisual tasks in congenitally blind as compared to adult-onset blind people (for review see Voss, 2013). For example, in congenitally blind people, visual areas are active during sound localization and motion processing, while such responses are reduced or absent in those who lost vision as adults (Burton et al., 2002a; Cohen et al., 1999; Collignon et al., 2013; Jiang et al., 2016; Sadato et al., 2002). Likewise, a number of studies have found decreased occipital responses during higher-cognitive tasks in adult-onset relative to congenitally blind individuals (i.e., math and language) (Bedny et al., 2012; Burton et al., 2002a; 2002b; Burton and McLaren, 2006; Kanjlia et al., 2019). Some evidence also suggests that occipital responses are only behaviorally relevant in people who were born blind. TMS applied to the occipital pole leads to increased error rates during a Braille reading in congenitally blind but not adult-onset blind individuals (Cohen et al., 1999). There is also evidence that visual cortices of people who are born blind show subtle sensitivity to higher-cognitive information that is absent in people who become blind as adults. For example, only congenitally blind people show enhanced visual cortex activity for grammatically complex sentences over more simple sentence constructions and respond more for complex than simple math equations (Kanjlia et al., 2019; Pant et al., 2020).

At the same time, there is evidence that visual cortices of people who become blind as adults are active during some nonvisual tasks. Büchel and colleagues (1998) observed increased visual cortex activity during Braille reading in blind adults who lost their vision after puberty. Late blind individuals also show responses in occipital cortices during voice recognition (Hölig et al., 2014). Occipital activity was also found in late-blind individuals while making semantic judgments about spoken words and generating verbs, although responses were more anatomically extensive in congenitally blind participants (Burton et al., 2002b; Burton and McLaren, 2006). Both congenitally blind and adult-onset blind individuals show increased resting state correlations between occipital cortices and frontal language areas, although again, these correlations are reduced in individuals who lost their vision as adults, relative to people born blind (Butt et al., 2013; Kanjlia et al., 2019; Sabbah et al., 2016).

There is also an emerging literature suggesting that small but reliable cross-modal responses in visual cortices are observed even in sighted people under some conditions. “Cross-modal” responses in visual cortices of sighted people have been reported during tactile discrimination, haptic exploration of 3-D shapes, and while listening to spoken sentences (James et al., 2002; Merabet et al., 2008; Sathian and Zangaladze, 2002; Seydell-Greenwald et al., 2020). In sighted people, multivariate activity patterns in early visual cortices can distinguish between different natural sound categories (Vetter et al., 2014). Taken together, these findings raise the possibility that early blindness is not necessary for cross-modal responses to emerge in occipital cortices. Thus, the degree to which the timing of experience matters in determining cross-modal responses in visual cortex remains an open question.

1.2. Experiment paradigm

In the current study we leveraged meaningful naturalistic auditory stimuli and inter-subject correlation analysis to test the sensitive period hypothesis in cross-modal plasticity. Naturalistic auditory stimuli, such as spoken narratives and sound excerpts from live-action movies, are intrinsically rich in information across cognitive levels, ranging from low-level perceptual properties (e.g., changes in pitch and volume) to higher-order semantic content (e.g., plot and character intent). These stimuli have been shown to simultaneously engage multiple levels of the neurocognitive hierarchy, including sensory systems and functional networks that are implicated in linguistic processing and narrative comprehension (e.g., Hasson et al., 2015; Lerner et al., 2011). As such, naturalistic stimuli are ideal for testing a broad range of possible responses simultaneously across different populations.

Inter-subject correlation (ISC) analysis furthermore provides a natural measure of the extent to which the same brain region serves a similar cognitive role across different individuals (Hasson, 2004; Hasson et al., 2008). In such analyses, each participant's activity timecourse serves as a model for the other participants. In sighted people, a host of previous fMRI studies have found that listening to the same naturalistic stimulus induces correlated brain activity across people in multiple functional networks, including low-level auditory areas and high-level semantic networks (Lerner et al., 2011; Simony et al., 2016). Cross-subject temporal synchronization indicates that, in a given brain area, responses are time-locked to characteristics that fluctuate over the course of the stimulus presentation. For example, each time there is spoken language in the stimulus, activity will systematically rise at the same time across listeners in brain areas associated with language processing. Analogously, activity in early auditory cortices synchronizes to fluctuations in acoustic properties, e.g., volume. In order for synchrony to emerge in a given cortical location, the same time-varying stimulus features must drive activity in a similar way across different people.

Systematically varying the content embedded in temporally extended stimuli can further provide clues to the stimulus features that drive brain responses across different cortical networks. For example, activity in high-level cognitive areas, such as the precuneus, prefrontal and lateral temporal regions, becomes synchronized when different people listen to temporally extended meaningful stimuli, such as audiobooks and spoken narratives, but not meaningless stimuli, such as backwards speech. By contrast, low-level auditory areas are synchronized by meaningless and meaningful stimuli alike (Hasson et al., 2015; Honey et al., 2012). We can therefore ask, what type of stimuli, if any, synchronize visual cortices across congenitally blind, adult-onset blind and sighted participants.

Two studies have recently used naturalistic stimuli to elicit synchrony in visual cortices of congenitally blind people. Using magnetoencephalography, Van Ackeren et al. (2018) found that in congenitally blind but not sighted people, inter-subject activity in foveal V1 increased while participants listened to brief passages from audiobooks, relative to unintelligible speech. We likewise recently found that while listening to naturalistic auditory stimuli (sound excerpts from popular live-action movies and a spoken narrative) during fMRI, early and higher-order visual cortices are more synchronized across congenitally blind than blindfolded sighted individuals (Loiotile et al., 2019). Critically, visual cortex synchrony among congenitally blind adults only emerged for meaningful naturalistic stimuli but not for meaningless backwards speech. The same meaningful stimuli also synchronized higher-cognitive networks in fronto-parietal and fronto-temporal cortices in both sighted and congenitally blind adults. In contrast, meaningless sounds (e.g., backwards speech) synchronized low-level auditory cortices but not the visual cortices of congenitally blind adults. This finding suggests that in people who are born blind, visual cortices are sensitive to meaningful and cognitively complex information embedded in auditory narratives. Furthermore, the reliable inter-subject correlations indicate that this reorganization systematically localizes to similar occipital regions

across congenitally blind people (Loiotile et al., 2019; Musz et al., 2022).

It is worth noting that, consistent with the idea that some cross-modal information reaches visual cortices even in sighted people, Loiotile et al. (2019) found some degree of synchrony in visual cortices of blindfolded sighted adults. However, this synchrony was weak, relative to the congenitally blind group, and not equally selective for meaningful stimuli. Thus, some cross-modal information reaches visual cortices even in sighted people, but these responses are quantitatively and qualitatively distinct in congenital blindness.

In the present study, we leveraged naturalistic meaningful sounds and inter-subject correlation analysis to test whether auditory responses in visual cortices follow a sensitive period. We compare responses to the same meaningful naturalistic stimuli, as well as meaningless control stimuli, across adult-onset blind, congenitally blind and blindfolded sighted people. To our knowledge, no prior study has measured responses to such stimuli in people with adult-onset blindness.

1.3. Hypotheses

If cross-modal responses in visual cortex can be unmasked by blindness at any age, then we would expect visual cortex synchrony in adult-onset and congenitally blind individuals to be similar to each other and different from blindfolded sighted people. In other words, like congenitally blind adults, adult-onset blind individuals might show high synchrony for meaningful auditory stimuli, i.e., audio-movies and narratives, but not meaningless auditory stimuli, i.e., backwards speech. This result would suggest that in both populations, visual cortices respond to meaning-related properties of naturalistic auditory stimuli, although not necessarily the exact same properties. Such a result would provide evidence against sensitive period effects in blindness. An alternative possibility is that visual cortex synchrony in adult-onset blind individuals is just as robust as in congenital blindness but less selective, that is, observed not only for meaningful but also for meaningless auditory stimuli. This would suggest that *selective* repurposing is restricted to a sensitive period. Finally, if sensitive period plasticity is necessary to enable repurposing, we would expect synchrony in adult-onset blind people to be reduced relative to people who are congenitally blind and no different from those who are sighted. Such a result would support the hypothesis that sensitive period plasticity enhances responses to nonvisual information in visual cortices.

To test among these possibilities, we measured brain responses while participants from three vision groups (blindfolded sighted, congenitally blind, and adult-onset blind) listened to naturalistic auditory stimuli, including 5–7 minute long excerpts from three popular live-action movies and a spoken narrative. Participants also listened to semantically degraded versions of the spoken narrative, one in which the linguistic content was preserved but the coherent plot line was removed (by shuffling the individual sentences in the narrative), and a version that lacked linguistic content but retained some of the low-level acoustic features (by playing the narrative in time-reverse format). We then tested for synchronized activity across vision groups and across stimulus conditions, both in visual cortex and throughout the brain.

2. Methods

2.1. Participants

Twenty-two sighted (S, 4 males), fourteen adult-onset blind (AB, 5 males) and twenty-two congenitally blind (CB, 8 males) participants contributed data to this study (Table 1). All participants were blindfolded during testing. All blind participants reported having at most minimal light perception at the time of the experiment, and had vision loss due to pathology at or anterior to the optic chiasm, and not due to brain damage (Table 2). Sighted participants reported normal or corrected-to-normal vision. Participants with adult-onset blindness became blind after the age of 19 (mean = 38.1, SD = 13.9, min = 19,

Table 1

Participant demographic information and vision loss history summary for the congenitally blind (CB), adult-onset blind (AB) and sighted (S) groups. Duration of blindness is calculated by subtracting age at testing from age at which the current level of vision was reached for the AB group, and age at time tested for the CB group.

Group	Sample size	N Females	Age	Blindness onset (Mean years)	Blindness duration (Mean years)
CB	22	14	43.5 (SD = 16.9)	–	43.5 (SD = 16.9)
AB	14	9	54.3 (SD = 9.7)	38.0 (SD = 13.8)	16.4 (SD = 10.6)
S	22	18	42.7 (SD = 13.8)	–	–

Table 2

Etiology summary for the congenitally blind (CB) and adult-onset blind (AB) groups showing causes of blindness.

Group	Blindness etiology	Participant number
CB	Retinopathy of Prematurity	8
	Leber Congenital Amaurosis	7
	Optic nerve hypoplasia	3
	Retinitis Pigmentosa	1
	Unknown	3
AB	Glaucoma	3
	Retinitis Pigmentosa	3
	Diabetic retinopathy	2
	Trauma	2
	Optic nerve neuropathy	1
	Stevens-Johnson syndrome	1
	Uveitis	1
	Autoimmune disorder	1

max = 57) and were blind for an average of eighteen years after reaching their current level of vision loss (SD = 10.8, min = 6, max = 40) (see Table A.1 for demographic information). Average age of participants in the AB group was greater than both the CB, $t(34) = 2.33, p = .03$ (AB: mean = 54.3 years, SD = 9.7; CB: mean = 43.5, SD = 16.9), and S groups $t(34) = 2.86, p = .01$ (S: mean = 42.7, SD = 13.8), which were matched to each other. Control analyses were performed to test for effects of age. Data from the sighted participants and congenitally blind participants were previously published (Loiotile et al., 2019; Musz et al., 2022).

2.2. Stimuli

Participants listened to six audio clips, each five to six minutes in duration. Three of the audio clips were excerpted from popular live-action movies (*Blow-Out*, *The Conjuring*, and *Taken*). These Audio-Movie clips were chosen because they are engaging, suspenseful, and easy to follow, and could therefore facilitate a shared interpretation and experience across participants. The three other audio clips were versions of the same 6-min excerpt of a live comedy sketch ("Pie-Man"). The intact version was presented in its original format. The "Sentence-Shuffle" version was created by splicing and shuffling the sentences from the intact version, thereby retaining intelligible sentences but removing the coherent plotline. The "Backwards Speech" version was created by playing the excerpt in time-reverse format, such that it lacked any intelligible content. In addition, subjects also participated in a resting state scan, during which no stimuli were presented and participants were instructed to relax and stay awake. All stimuli are available for download at the Open Science Framework: <https://osf.io/r4tgb/>

2.3. Procedure

During fMRI scanning, participants listened to each sound clip, with one clip presented during each of six scanning runs. Prior to scanning, we confirmed that each participant had not previously seen the movies that the clips were sourced from. Clips were presented in pseudo-random order, where each presentation sequence for an AB participant was yoked to a corresponding S participant and CB participant. Participants were instructed to pay attention and listen carefully, as they would have to answer questions about the plot details of each sound clip at the end of the experiment. Immediately before each scanning run, participants were read a brief prologue that provided context for the upcoming sound clip. The presentation of each sound clip was preceded by 5 s of rest and followed by 20–22 s of rest. These rest periods were excluded from all analyses. Due to time constraints, one sighted participant and four AB participants did not complete the resting state scan.

Following fMRI scanning, participants immediately received an orally-presented post-scan questionnaire composed of five multiple choice questions for the comedy sketch and each movie clip (see Table A2 for behavioral performance by subject group). We included data from all participants in all reported brain analyses. While the mean scores for the AB group were consistently lower than the scores for the

CB and S groups, post-hoc t-tests revealed that these differences were not statistically significant (all $p > .05$). In order to most closely match the sample size and behavioral performance of the AB ($n = 14$) and CB ($n = 22$) groups, we repeated all brain analyses in a subset of CB participants ($n = 14$) whose behavioral performance mostly closely matched the AB group (Table A2). Brain results for the subset CB group are qualitatively similar to the results that include all CB participants (Fig. 1).

Auditory stimuli were presented over Sensimetrics MRI-compatible earphones (<http://www.sens.com/products/model-s14/>) at the maximum comfortable volume for each participant. To ensure that participants could hear the softer sounds in the auditory clips over the scanner noise, a relatively subtle, low-frequency sound (RMS amplitude = 0.002, frequency = 3479) was played to participants during acquisition of the anatomical image; all participants indicated hearing the sound via button press. Participants were told to press a button at any point during the scanning session if they could not hear the contents of the sound clips over the noise of the scanner. In such cases, we ended the scanning run, re-adjusted the audio volume, and performed additional sound checks. The scanning run and corresponding sound clip were then restarted.

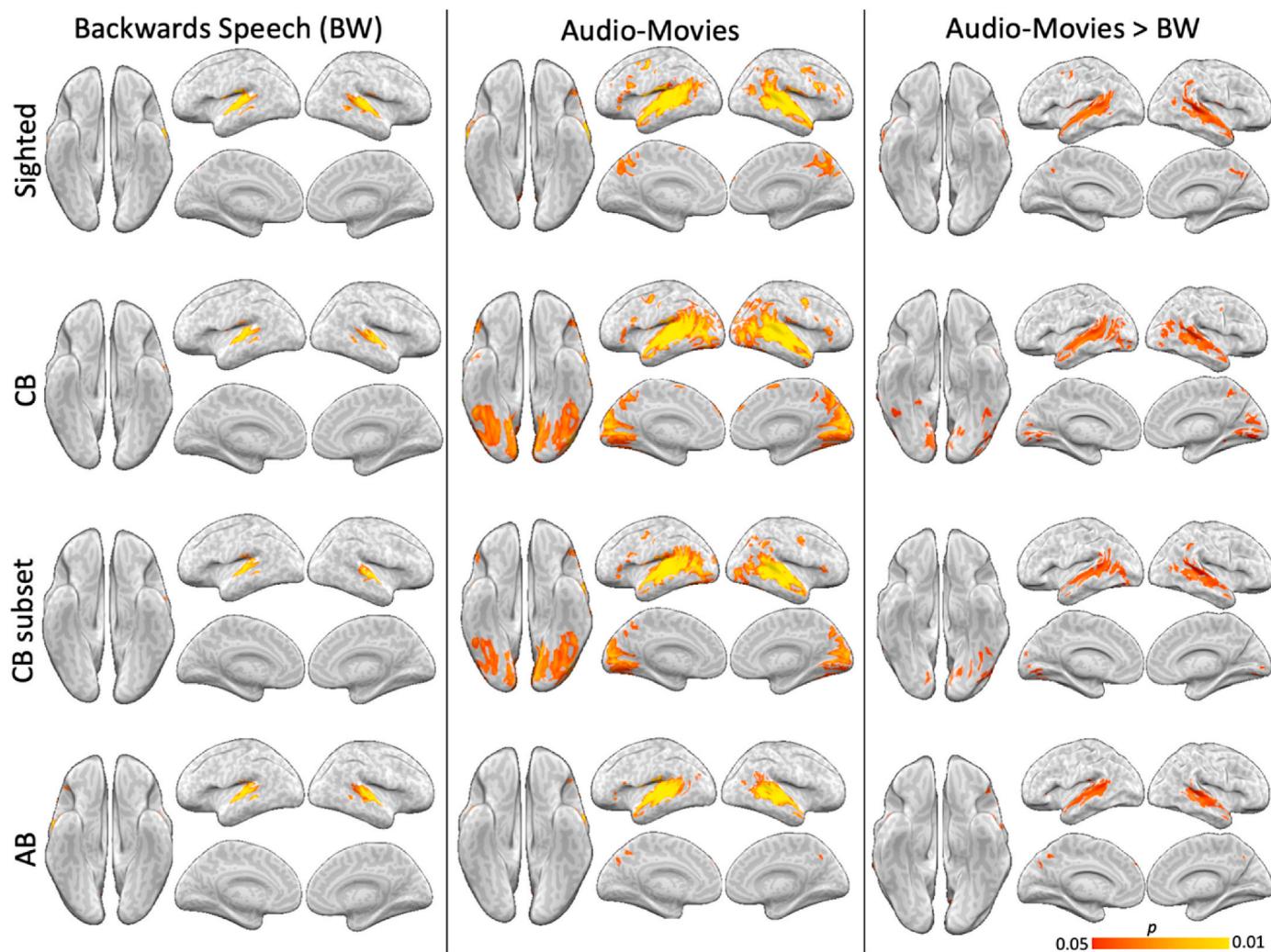


Fig. 1. Whole-brain inter-subject correlation (ISC) reliability maps for the Backwards Speech stimulus (BW), the Audio-Movie stimulus, and the contrast of Audio-Movies versus BW in each subject group, voxel-wise corrected for multiple comparisons at $p < .05$. Voxel-level synchronization is shown within the sighted (S) group; the congenitally blind (CB) group; a subset of the CB group (CB subset) that matches the size of the adult-onset blind (AB) group (both $n = 14$); and the AB group (See Supplemental Figure E1 for between group correlations.).

2.4. fMRI data acquisition

Whole-brain structural and functional MRI data were collected on a 3 T Phillips scanner. T1-weighted structural images were collected in 150 axial slices with 1 mm isotropic voxels using a magnetisation-prepared rapid gradient-echo (MPRAGE). T2*-weighted functional images were collected with a gradient echo planar imaging sequences in 36 sequential ascending axial slices with $2.4 \times 2.4 \times 3$ mm voxels and 2-s TR (echo time: 30 ms, flip angle: 70°, field-of-view: 76 × 70 matrix, slice thickness: 2.5 mm, inter-slice gap: 0.5, slice-coverage: FH 107.5, PH direction L/R, first-order shimming).

2.5. fMRI data processing

Preprocessing was performed using FEAT (fMRI Expert Analysis Tool) Version 6.00, part of FSL (<http://fsl.fmrib.ox.ac.uk/fsl>) and included slice time correction using Fourier-space time-series phase-shifting, motion correction using MCFLIRT (Jenkinson et al., 2002), high-pass filtering (140s), and linear detrending. All functional volumes were co-registered and affine transformed to a standard anatomical brain (MNI152) using FLIRT. Functional images were smoothed with a 4 mm FWHM Gaussian kernel and resampled to 3 mm isotropic voxels. The first four and last eight TRs of each scanning run were discarded, corresponding to the rest periods before and after the clips (accounting for delays in hemodynamic response). Analyses were performed in volume space and data were projected onto a cortical surface with NeuroElf for visualization (neuroelf.net).

2.6. Inter-subject correlation analysis

We used inter-subject correlation (ISC) to test whether the same anatomical locations perform consistent functions across individuals. For each vision group and each auditory stimulus, we assessed the degree of stimulus-driven synchronization across individuals at each voxel in the brain. ISC is defined as the correlation of BOLD activity timecourses across participants as they listen to or view a common stimulus (Hasson et al., 2004; Hasson et al., 2010). Within-group ISC (i.e., “reliability”) was calculated as the average correlation at each voxel between that voxel’s BOLD activity timecourse in one individual subject and the average of BOLD timecourse in the remaining individuals in the group. Between-group ISC was calculated as the correlation between the timecourse from each subject in one group (e.g., a participant of the AB group) versus group-average timecourse of the comparison group (e.g., the mean timecourse of the CB group). Subject versus rest-of-group correlations (or subject versus comparison group correlations, for the between-group comparisons) were then averaged together, resulting in one mean ISC value at each voxel. The voxel-level ISC values were then projected to the brain to yield group-level ISC maps. To create mean Audio-Movies synchronization maps, the averaged *r*-value ISC maps for each movie condition were first transformed to Fisher’s *z*-values. The three resulting *z*-maps (one per movie) were then averaged together and subsequently transformed back into *r*-maps.

To evaluate synchrony among subjects for each stimulus condition, the statistical likelihood of each observed ISC value was assessed using a bootstrapping procedure based on phase-randomization, and maps were corrected for multiple comparisons using non-parametric family-wise error rate (Regev et al., 2013). All ISC and statistical analyses were performed with custom software written in MATLAB (MathWorks). The null hypothesis was that the BOLD response timecourse at each voxel in each individual was independent of the BOLD response timecourses in the corresponding voxel of the other individuals (i.e., that there was no inter-subject reliability among individuals). For each scanning run and stimulus condition, we applied a phase randomization to each voxel timecourse by applying a fast Fourier transform to the signal, randomizing the phase of each Fourier component, and then inverting the Fourier transformation (Lerner et al., 2011; Loiotile et al., 2019). This

procedure scrambles the phase of the timecourse but preserves its power spectrum. For each randomly phase-scrambled surrogate dataset, we computed ISC for all voxels in the same manner as for the empirical correlation maps described above. The resulting correlation values were then averaged across all subjects within each voxel, yielding a null distribution of mean ISC values for all voxels.

To correct for multiple comparisons, we retained the highest ISC value from the null distribution of all voxels in a given iteration. This bootstrapping procedure was repeated 1000 times to obtain a null distribution of maximum noise correlation values. We implemented voxel-wise correction to control multiple comparisons across the brain. Familywise error rate (FWE) was defined as the top 5% of the null distribution of the maximum correlation values, which was then used to threshold each veridical map (Nichols and Holmes, 2002). Thus, we rejected the null hypothesis for a particular comparison if an observed ISC value was in the top 5% of all 1000 values in each null distribution (i.e., a one-tailed statistical test). Differences in thresholds across stimulus conditions and subject groups (values ranging from 0.09 to 0.15) reflect variances in the null sampling distributions, due to differences in the degrees of freedom among stimuli (e.g., number of timepoints) and between the sample sizes across groups. To conservatively test whether the visual cortices in the AB group show any synchronization in response to nonvisual stimuli, for each stimulus condition we applied the most lenient threshold from the three subject groups. Results were qualitatively similar to those obtained by using each group’s own criteria.

In order to identify voxels that show an increase in ISC for one stimulus condition over the other within each subject group, we computed the observed difference score in ISC values at each voxel (e.g., Audio-Movies minus Backwards Speech) and then re-calculated these difference scores 1000 times using phase-scrambled surrogate datasets as described above. At each voxel, a *p*-value (one-tailed) was computed by comparing the observed difference score to a null distribution of the 1000 difference scores yielded by the phase-scrambled timecourses. Whole-brain corrections for multiple comparisons were implemented with the same FWE procedures as described above for the within-group contrasts. This same procedure was used to identify voxels that show an increase in ISC in one subject group versus the other, however in this case difference scores were computed between groups (e.g., CB Audio-Movies minus AB Audio-Movies) instead of between stimulus conditions.

2.7. Inter-subject correlation: region of interest (ROI) analysis

We used three bilateral ROIs: primary visual cortex (V1), the early auditory cortex (A1), and higher-cognitive posterior lateral temporal cortex (PLT) (Loiotile et al., 2019). The V1 ROI was sourced from a previously published anatomical surface-based atlas (PALS-B12; Van Essen, 2005). The early auditory cortex ROI was defined as the transverse temporal portion of a gyral based atlas (Desikan et al., 2006; Morosan et al., 2001). A higher-cognitive bilateral PLT ROI was taken from parcels responding to higher-level linguistic content in sighted subjects, defined as responding more to sentences versus non-word lists (Fedorenko et al., 2010). This PLT subregion is sensitive to high-level linguistic information, ranging from word and sentence-level meaning to sentence structure (Bookheimer, 2002).

For each ROI, ISC was computed across participants using each individual’s response timecourse, averaged across all voxels in the ROI. For all comparisons, statistical significance was assessed with the same procedure that was applied to the whole-brain analysis. Namely, *p*-values were computed by comparing each observed ISC value (or ISC difference scores, in the case of between-condition comparisons) to a null distribution of noise correlation values that were created by applying phase randomization to each ROI timecourse. No subsequent multiple comparisons correction were performed. All statistics for factor comparisons (i.e., ROI, group, and/or conditions) were obtained by subtraction of the relevant *z*-transformed ISC values. Fisher’s *z*-

transformed- r values were subsequently transformed back to r (correlation coefficient) values for reporting.

To test for group differences in ISC after partialling out variance attributed to participant age, regression analyses were run using participant age to predict participant-level ISC values in a given ROI. Each regression model included data from two subject groups at a time (i.e., AB vs. CB; AB vs. S) to enable pairwise comparisons. The residuals from the regression model were then compared across groups. Group-average differences in these residuals were then computed. To assess statistical significance, these values were compared to a null distribution of group differences in such residual values, which were derived in the same manner but using the phase-randomized timecourses to compute ISC instead.

To assess whether blindness duration among the AB group and the CB group contributes to a participant's timecourse synchrony to other individuals in visual cortex, we correlated each blind participant's duration of blindness with their individual ISC value for the Audio-Movies condition in the V1 ROI. For AB individuals, this correlation was computed two different ways: once using each participant's synchrony to the rest-of-AB-group average timecourse (i.e., within-group ISC) and once using each participant's synchrony to the CB group

average timecourse (i.e., between-group ISC). For the CB group, the correlation was computed between blindness duration (i.e., age) and within-group ISC (i.e., each participant's synchrony to the rest-of-CB group average timecourse).

3. Results

3.1. Whole-cortex analysis

3.1.1. Similar synchrony across groups in non-visual networks

In response to the Audio-Movies stimuli, significant inter-subject synchrony emerged in all three subject groups in several nonvisual brain areas associated with higher cognition. In particular, the Audio-Movie stimuli induced significant ISC across bilateral temporal cortex, including the temporal poles, superior and middle temporal gyrus and the angular gyrus. Synchrony also emerged in the lateral prefrontal cortex and on the medial surface in the precuneus (Fig. 1). As previously reported, synchrony observed in these nonvisual regions was similar across the CB and S groups (Loiotile et al., 2019). The AB group showed reliable ISC in similar higher-cognitive regions, including left precuneus and bilateral lateral temoral cortex, although synchrony among AB

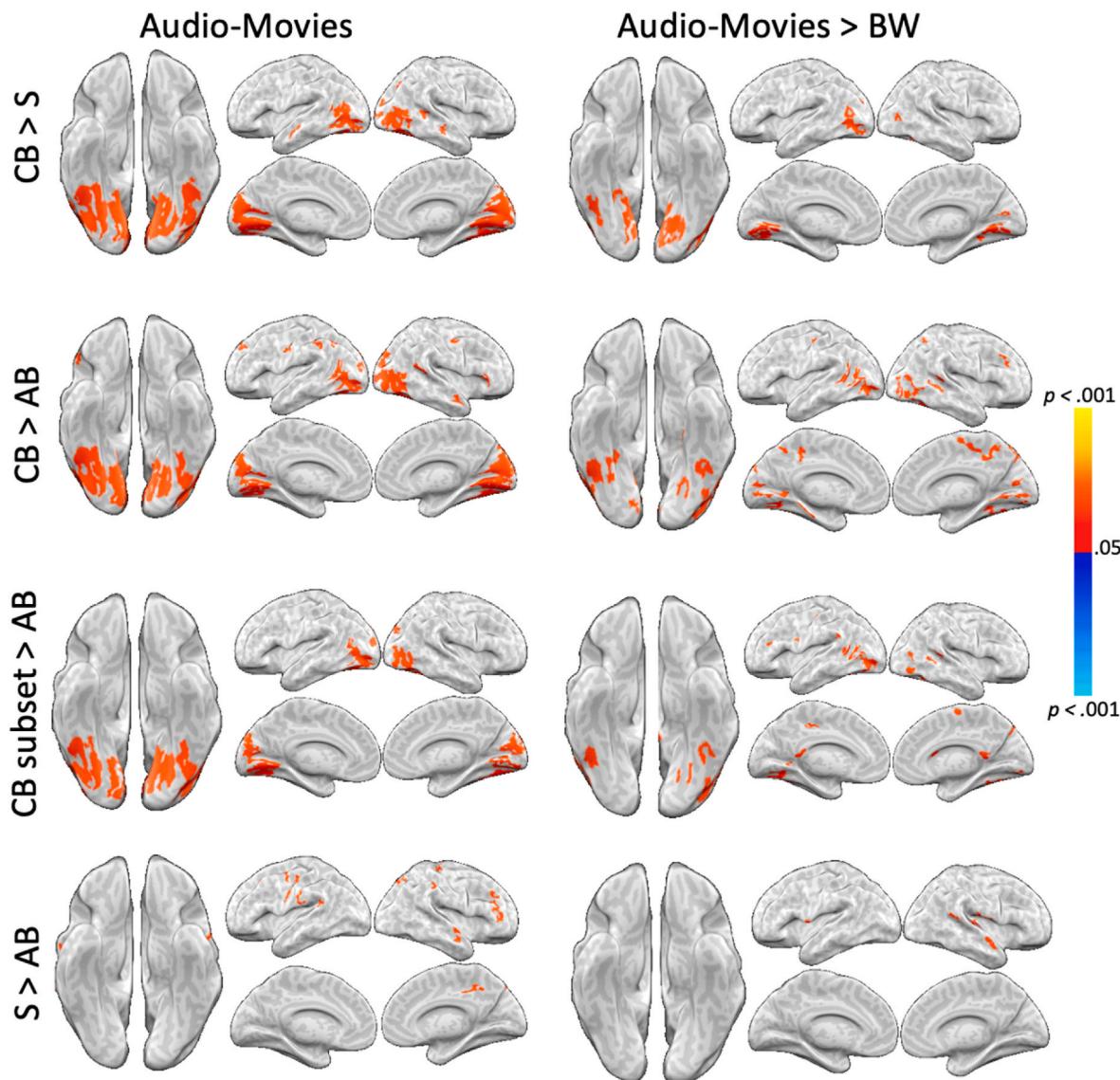


Fig. 2. Between-group maps showing differences in whole-brain, voxel-wise synchrony for the Audio-Movie stimulus and for the contrast of Audio-Movies versus Backwards Speech (BW). All maps voxel-wise corrected for multiple comparisons at $p < .05$. CB: congenitally blind; AB: adult-onset blind; S: sighted.

individuals in these areas was less spatially extensive than in the other groups (Fig. 2).

In contrast to the Audio-Movies, the synchrony induced by the Backwards Speech stimuli was limited to bilateral auditory cortex in all three groups (Fig. 1). In direct comparisons between Audio-Movies versus Backwards Speech, ISC was greater for the Audio-Movies in each group in most of the same regions that showed above-threshold synchrony for the Audio-Movies condition, including bilateral lateral temporal cortex and precuneus. No brain area showed the reverse contrast, with greater ISC for Backwards Speech than Audio-Movies. In addition, there were no differences in ISC among groups for Backwards Speech.

For the intact version of the spoken narrative ("Pie-Man"), the synchrony in nonvisual regions largely matched the results for the Audio-Movies. For all three subject groups, Pie-Man induced synchronized responses in bilateral temporal cortex. For the CB group and the S group, but not the AB group, synchrony also emerged in precuneus and lateral prefrontal cortex (Supplemental Figure B1). In addition, both the CB and AB groups also showed small clusters of reliable ISC along the medial surface of the frontal cortex. This synchrony was bilateral in the CB group and right-lateralized in the AB group.

In contrast to the intact version of Pie-Man, synchrony for the Sentence-Shuffle stimulus condition was limited to the bilateral temporal cortex in each of the three subject groups (Figure B1). In both the CB and the S groups, synchrony in lateral temporal cortex did not extend posteriorly to the angular gyrus or anteriorly to the temporal pole, as was observed for the intact Pie-Man and the Audio-Movies. In contrast, the Sentence-Shuffle and Pie-Man ISC maps for the AB blind group were largely similar.

As expected, the resting state scan did not induce synchrony among individuals in any brain region in any subject group.

3.1.2. Visual cortices of adult-onset blind individuals show no higher synchrony than sighted and lower synchrony than congenitally blind adults

In whole-brain analyses, the AB group, like the sighted group and unlike the CB group, showed no above threshold synchrony anywhere in visual cortices for Audio-Movies. Within the CB group, the Audio-Movies synchronized activity in the bilateral occipital cortices. In the CB group exclusively, reliable ISC spanned the medial, lateral, and ventral surfaces of visual cortex (Fig. 1). This pattern of results was recapitulated in the ISC maps yielded by each individual movie clip (Supplemental Figure B2). Each audio-movie synchronized responses in visual cortices, but only among the CB participants. In contrast, the Backwards Speech stimulus did not induce synchrony in visual regions of any subject group. The direct contrast of Audio-Movies versus Backwards Speech ISC showed that synchrony in the visual cortices was reliably greater for the Audio-Movies, but only for the CB group. This contrast was reliably greater in the CB than in either the S or AB groups (Fig. 2).

Since there were more CB than AB participants, we performed a subset analysis to ensure that difference among groups was not introduced by the difference in sample size. For this analysis, we generated ISC maps using a subset of CB participants of equal size to the AB group (Fig. 1, third row). Like the AB group, the CB subset map showed less spatially extensive synchrony in the higher-cognitive nonvisual regions for the Audio-Movies, relative to the S group and the full CB group. However, unlike the AB group, the CB subset group still showed visual cortex synchrony while listening to the Audio-Movies, and not during Backwards Speech. Thus, group size could not account for visual cortex synchrony differences across CB and AB groups.

3.1.3. Spoken-narrative

The AB group, like the sighted and unlike the CB group, showed no above threshold synchrony in visual cortices during the spoken narrative stimulus. For the CB group but not the S group or the AB blind group, the intact Pie-Man stimulus induced synchronized responses in the bilateral occipital cortices (Supplemental Figure B1). The location and spatial

extent of this synchrony in visual cortex largely matched the above-threshold ISC locations observed for the Audio-Movies. In contrast, the Sentence-Shuffle condition did not induce visual cortex synchrony for any of the three subject groups.

3.2. ROI analysis

3.2.1. Adult-onset blind individuals shows lower V1 synchrony than congenitally blind individuals, and are not different from sighted blindfolded adults

To more closely examine how inter-subject synchrony varied across subject groups and stimulus conditions in V1, we conducted an ROI analysis (Fig. 3). As a point of comparison, we also examined synchrony in early auditory cortices (A1) and language-responsive posterior lateral temporal (PLT) cortex. Since there is a large number of possible comparisons between groups and stimuli, increasing a false-positive risk, we conducted only hypothesis-driven comparisons.

In V1, Audio-Movies elicited less synchrony in the AB group than the CB group ($p < .001$) and no more synchrony in the AB group than the sighted group ($p > .1$). Audio-Movie synchrony for the CB group was significantly greater than the S group ($p < .001$). In tests for group-by-condition interactions, the increase in ISC for Audio-Movies versus Backwards Speech was marginally greater in the CB group than the AB group ($p = .07$), the difference between the AB and S groups was not significant ($p > .1$), and the CB group showed a larger difference than the S group ($p < .01$).

In within-group analyses, Audio-Movies elicited reliable ISC in all three groups (S: $r = .08$; CB: $r = 0.21$, AB: $r = 0.08$, all $p > .001$) and greater ISC than Backwards Speech in all three groups (all $p < .001$). The Backwards Speech condition only showed above-chance synchrony in the CB group ($r = 0.07$, $p = .01$). Participant-level V1 ISC values in response to the Audio-Movie stimuli are shown in Fig. 4 and Supplemental Figure C1.

A similar pattern was observed for the Pie-Man narrative stimulus. In the V1 ROI, the AB group showed lower synchrony than the CB group and did not differ from the S groups ($p > .1$). The CB group showed higher synchrony than the S group (both $p < .001$). Additionally, V1 timecourses for the CB group showed greater synchrony for the intact Pie-Man stimulus versus Backwards Speech ($p < .001$). In contrast, ISC values for these stimuli did not vary for the AB group ($p > .1$) or the S group ($p > .1$). Group-by-condition interaction tests confirm that the difference in ISC values for Pie-Man versus Backwards Speech was smaller in the AB group than the CB group ($p < .001$) and did not differ between the AB group and the S group ($p > .1$). The CB group showed a larger difference relative to the S group ($p < .001$). Finally, in the within-group analysis, reliable ISC emerged for the narrative Pie-Man stimulus in the CB group ($r = .20$, $p < .001$) but not in the AB group ($r = 0.001$, $p > .1$) or the S group ($r = 0.02$, $p > .1$).

For the Sentence-Shuffle stimuli, V1 timecourses were not synchronized for the AB ($r = -0.004$, $p > .1$) or S groups ($r = 0.01$, $p > .1$) but were synchronized above chance for the CB group ($r = 0.11$, $p < .001$). AB synchrony was lower than the CB group ($p < .001$) and did not differ from the S groups, ($p > .1$). CB synchrony was higher than S synchrony ($p < .001$). Both the AB group and S groups showed no differences between ISC values for Pie-Man versus Sentence-Shuffle (both $p > .1$). In contrast, in the CB group, V1 synchrony was greater for the Pie-Man condition than Sentence-Shuffle ($p < .001$).

In the A1 ROI, there was significant inter-subject correlation (ISC) for the Backwards Speech condition in all three groups (S: $r = 0.34$; CB: $r = 0.25$; AB: $r = 0.27$, all $p < .001$), and ISC did not differ by group (all $p > .1$). In A1, Audio-Movies also showed significant ISC in all three subject groups, but ISC for the S group ($r = 0.47$) exceeded both the CB group ($r = 0.37$) and the AB group ($r = 0.36$, all $p < .01$), while the CB and AB groups did not differ from one another ($p > .1$). Tests for group-by-condition interactions revealed that the difference in ISC values for Audio-Movies versus Backwards Speech did not vary among subject

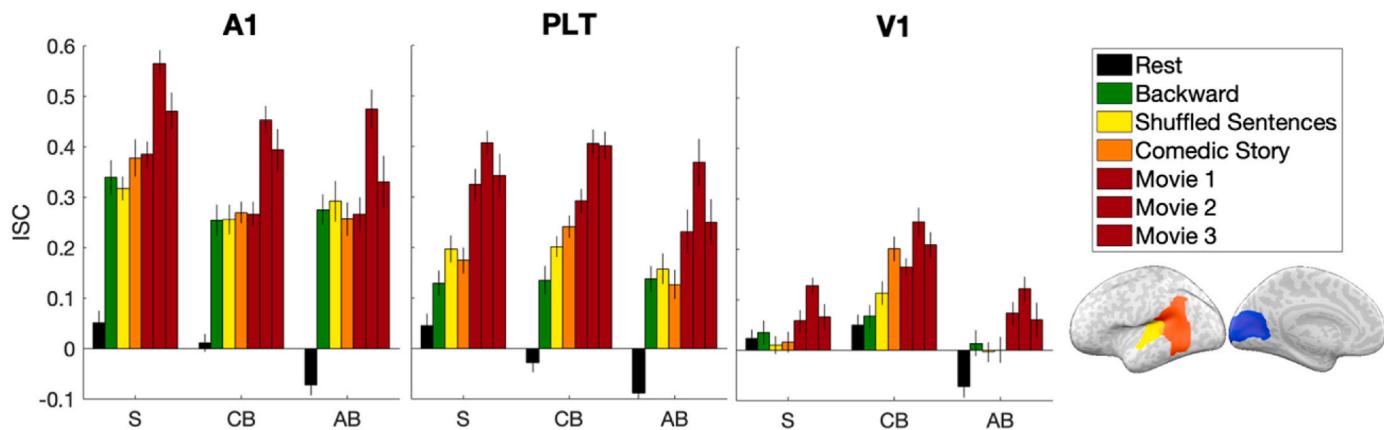


Fig. 3. Left: Within-group ISC values for each region of interest (ROI) and each subject group. Right: ROIs are displayed in the left hemisphere (A1 in yellow; PLT in orange; V1 in blue) but inter-subject correlations are calculated bilaterally. Results for each individual audio-movie appear in the order listed and are shown for illustration purposes only; the reported results for Audio-Movies are averaged across the three movies. Error bars indicate ± 1 SEM. A1 = early auditory cortex; PLT = posterior lateral temporal cortex; V1 = primary visual cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

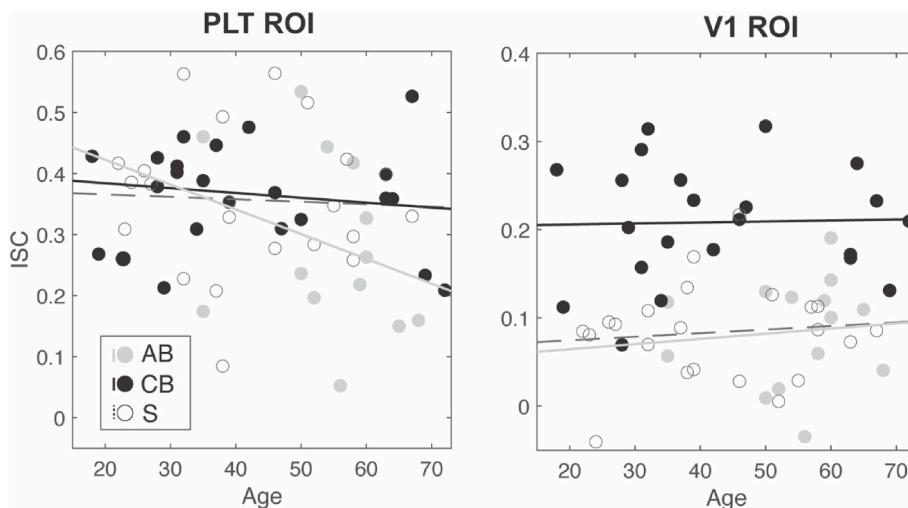


Fig. 4. Relationship between participant age and ISC for the Audio-Movies condition in the PLT ROI (left) and the V1 ROI (right). Trend lines depict the linear relationship between age and ISC in each subject group. Participant age was not strongly correlated with ISC in either PLT (AB: $r = -0.28$; CB: $r = -0.16$; S: $r = -0.04$) or V1 (AB: $r = 0.09$; CB: $r = 0.03$; S: $r = 0.1$).

groups (all $p > .1$).

For the PLT language ROI, synchrony was higher for Audio-Movies than Backwards Speech in all groups (all $p < .001$) but both Backwards Speech and Audio-Movies induced reliable ISC in all groups (Backwards Speech: S: $r = 0.13$, CB: $r = 0.13$, AB: $r = 0.14$, all $p < .001$; Audio-Movies: S: $r = 0.36$, CB: $r = 0.37$, AB: $r = 0.28$, all $p < .001$). Synchrony for Backwards Speech did not vary by group (all $p > .1$). Synchrony for the Audio-Movies was significantly lower among AB participants than the CB group ($p < .001$), and marginally lower than in the S group ($p = .09$). The difference in Audio-Movies synchrony for the CB versus S groups was not significant ($p > .1$). In group-by-condition interaction tests, the difference in ISC values for Audio-Movies versus Backwards Speech was reliably lower in the AB group than in the CB group ($p = .03$), and marginally lower than in the S group ($p = .05$). Upon closer inspection of the data (Fig. 3), the AB group showed lower synchrony than the CB and sighted groups for [Movies 1 and 3](#), but [Movie 2](#) showed equal synchrony across groups in PLT (all group pairwise comparisons $p > .1$).

We performed a follow-up analysis to test whether V1 synchrony was lower in AB participants than CB participants, even for [Movie 2](#), which

was matched across groups in PLT. In the V1 ROI, AB ISC for [Movie 2](#) was significantly lower than the CB group ($p < .01$) and did not differ from the S group ($p > .1$). This analysis shows that ISC in V1 is lower in AB relative to the CB group, even for a stimulus condition that is matched in PLT.

Next, we tested whether age could explain the lower synchrony for Audio-Movies observed in the AB group relative to the other two groups, as AB participants were generally older than both the CB and S participants (see Methods). After partialling out the effect of age, in the V1 ROI, the residual ISC values for the AB group remained significantly lower than CB ($p < .0001$) and did not differ from the S group ($p > .1$) ([Supplemental Figure C1](#)). By contrast, after partialling out age in the PLT ROI, the residual ISC values of the AB group were not different from the S group ($p > .1$) and marginally lower than the CB ($p = .10$). Age was not strongly correlated with ISC values for the AB group in either the V1 ($r = -0.09$, $p > .1$) or the PLT ($r = -0.28$, $p > .1$) ROI (Fig. 4).

Finally, neither the CB group nor the S group showed any reliable synchrony in any ROI during the resting state scan (all $p > .1$). Resting state data were only available for 10 of the 14 AB participants, and in this subgroup the timecourses among AB participants during rest were

negatively correlated in the A1 ROI ($r = -0.07, p < .01$), the PLT ROI ($r = -0.07, p < .05$), and the V1 ROI ($r = -0.09, p < .01$). These results should be interpreted with caution, as they were not predicted and only a relatively small subset of participants contributed resting state data to this analysis.

3.2.2. V1 synchrony differences between CB and AB participants not accounted for by blindness duration

People who are born blind are on average blind for a longer time than people who become blind as adults. It is therefore possible that differences observed between CB and AB groups are related to blindness duration, rather than age of blindness onset. Contrary to this possibility, we found that among AB participants, there was no relationship between blindness duration and V1 ISC values (i.e., each AB participant to the rest-of-group average timecourse) ($r = -.11, p > .1$) or between blindness duration and between-group V1 synchrony with the congenitally blind group (i.e., each AB participant to the CB group-average timecourse) ($r = -.03, p > .1$) (Supplemental Figure C2). This is despite the fact that blindness duration varied considerably within the AB group ($SD = 10.8$, min = 6, max = 40). In addition, the age at which participants lost their vision was not correlated with within-group V1 synchrony ($r = 0.15, p > .1$) or synchrony with the CB group ($r = 0.03, p > .1$).

4. Discussion

4.1. Summary of main findings

The present results support the hypothesis that visual cortices are especially capable of developing responses to non-visual information during a sensitive period early in life. Previous studies found that listening to meaningful naturalistic sounds, including excerpts from popular live-action movies and spoken narratives, synchronizes activity in higher-order cognitive networks more so than meaningless stimuli (e.g., backwards speech) (Lerner et al., 2011; Simony et al., 2016). Such synchrony is thought to reflect the common engagement of these higher-cognitive networks by meaningful stimuli across individuals, whether because of the presence of meaningful information or greater attention by participants to meaningful than meaningless stimuli or both (Hasson et al., 2015; Honey et al., 2012). Critically, visual cortices across congenitally blind people are also synchronized more by meaningful than meaningless auditory stimuli, suggesting involvement in higher-order cognitive processing and/or sensitivity to attention to higher-order cognitive information (Loiotile et al., 2019; Van Ackeren et al., 2018).

In contrast, we report here that people who become blind as adults show no more synchrony in visual cortices than blindfolded sighted adults. In adult-onset blind individuals, V1 synchrony did not increase with blindness duration, and no more synchrony is observed for an individual who has been blind for forty years than for another blind for six. Lower shared responses among people who become blind as adults, relative to congenitally blind people, suggests that the human visual cortex has a special capacity to develop cross-modal responses during a sensitive period of development.

The current findings with naturalistic auditory stimuli are consistent with previous studies using traditional experimental task-designs that find reduced or absent cross-modal activity in adult-onset blind individuals (Bedny et al., 2010, 2012; Cohen et al., 1999; Jiang et al., 2016; Kanjlia et al., 2019; Pant et al., 2020; Sadato et al., 2002). Naturalistic stimuli are rich with information across different cognitive levels, ranging from low-level perceptual features (e.g., changes in pitch and volume) to intermediate linguistic properties (e.g., individual words and sentences) to higher-order semantic content (e.g., narrative plot and character intent). None of these features appear to induce synchrony in the AB population. Together with prior literature, our results suggest that responses to auditory stimuli in visual cortices of adult-onset blind individuals are weaker and/or inconsistent across individuals, relative

to people born blind and not different from blindfolded sighted people.

Both the adult-onset blind and blindfolded sighted groups showed reduced synchrony relative to the CB participants, to a similar degree. Nevertheless, region of interest analyses in V1 revealed a low but significant degree of synchrony among blindfolded sighted and adult-onset blind people. This finding is consistent with previously observed responses to nonvisual information in visual cortices of sighted individuals. During visual tasks in sighted people, responses in the occipital lobes are modulated by top-down task demands (Gazzaley et al., 2007; Ruff et al., 2006; Serences and Yantis, 2007; Waskom et al., 2014). Even in the absence of visual input, the visual cortices are recruited when sighted participants engage in mental imagery (Hindly et al., 2015; Hsu et al., 2012; Stokes et al., 2009), and when visual stimuli are anticipated or remembered but not currently present (Kastner et al., 1999; Sergent et al., 2011). Nonvisual stimuli, such as tactile and auditory input, have also been shown to elicit visual cortex activity in sighted people under some circumstances (Facchini and Aglioti, 2003; James et al., 2002; Merabet et al., 2004, 2008; Sathian, 2005; Seydel-Greenwald et al., 2020; Vetter et al., 2014; Voss et al., 2016; Zangaladze et al., 1999). These findings demonstrate that nonvisual input can activate the visual cortices even in sighted adults.

The present results, together with prior literature, show however, that cross modal responses in people born blind are more anatomically extensive and robust, occur under different stimulus conditions, and are more sensitive to subtle cognitive manipulations (e.g., Kanjlia et al., 2016; Lane et al., 2015; Pant et al., 2020). Although a handful of TMS studies suggest the behavioral relevance of visual cortex activity in congenitally blind people, no such evidence exists for adult-onset blind people (Amedi et al., 2004; Cohen et al., 1999; Ptito et al., 2008). Thus, while cross-modal effects are present in visual cortices of all people, early blindness substantially modifies the character of these responses (Collignon et al., 2011; Merabet et al., 2004; Pascual-Leone and Hamilton, 2001; Sathian and Still, 2010; Still, 2008; Wolbers et al., 2011). A key outstanding question concerns how blindness/visual experiences build on a common anatomical blueprint present at birth to enable the distinct functional pattern observed in congenitally blind, as opposed to sighted and adult-onset blind adults.

4.2. Caveats: adult-onset cross-modal responses not ruled out by naturalistic designs

The present findings provide compelling evidence that adult-onset blindness does not enhance shared visual cortex responses for naturalistic auditory stimuli. However, an important caveat is that we cannot rule out is the possibility that some stimuli and tasks would reveal cross-modal responses in people who become blind as adults. Although the space of possible response properties sampled by naturalistic auditory stimuli is relatively wide, it is by no means exhaustive. One kind of manipulation that is lacking in the current study is an explicit task with overt responses. If visual cortices of adult-onset blind people become active during, e.g., decision making or motor function, then a naturalistic listening paradigm would fail to induce such activity. Indeed, several studies have found some activity in visual cortices of adult-onset blind individuals during effortful tasks that involve making on-line decisions. For example, cross-modal activity has been reported when adult-onset blind participants make button presses or verbal responses to indicate semantic judgments in response to individual words and sentences (Aguirre et al., 2016; Burton et al., 2003; Burton et al., 2002b; Burton and McLaren, 2006; Pant et al., 2020). Notably, even when observed, such responses are weaker than those seen in visual cortices of people born blind during the same tasks.

It is also unclear whether responses observed in adult-onset blind people are different from those of people who are sighted. In the current study, the sighted participants wore light-exclusion blindfolds matching them in current visual experience to the blind participants. This was not always the case in prior studies comparing adult-onset blind and sighted

adults. Nevertheless, understanding the role of decision making and motor output in driving cross-modal activity in visual cortex of adult-onset blind and blindfolded sighted people merits further research. Finally, it is worth noting that the current results do not imply that there is no distinctive plasticity or learning occurring in people who become blind as adults, merely that if such plasticity exists, it is different from what is observed in people born blind.

A further element of the present design worth considering is that lack of synchrony among AB participants in our study could reflect individual variability in this population, rather than a lack of cross-modal responses in each individual. Unlike task-based designs, inter-subject correlation analyses, such as this one, rely on activity occurring in relatively similar regions across people. Thus, if entirely different parts of visual cortex are responsive in different adult-onset blind individuals, synchrony would not be observed in the group. The current findings could thus indicate either that there is a sensitive period for developing cross-modal responses to naturalistic sounds, or instead that there is a sensitive period for having anatomical systematicity of such responses across individuals. One way to distinguish between these possibilities in future studies would be to look for correlated responses to repeated listening of naturalistic auditory stimuli within each adult-onset blind individual.

4.3. Summary and conclusions

In conclusion, we report that vision during development severely attenuates shared cross-modal responses in visual cortices. While visual cortices of people born blind show robust synchrony for meaningful naturalistic auditory stimuli, visual cortices of individuals who were sighted during childhood, lost vision as adults and have, in some cases, been blind for decades, remains functionally similar to the visual cortices of people who are sighted. These results support the view that the cognitive flexibility and systematic reorganization of visual cortices is limited by sensitive periods during development.

Author contributions

R.E.L. and M.B. designed research; R.E.L. and E.M. performed research; E.M. and J.C. analyzed data; E.M. and M.B. wrote the first draft of the paper; E.M., R.C., and M.B. edited the paper; E.M. and M.B. wrote the paper.

Data availability

Group-level whole-brain ISC maps for each subject group and each stimulus condition are available for visualization and download on the NeuroVault website at the following URL: <https://neurovault.org/collections/MIXNTFJU/>

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuropsychologia.2022.108277>.

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