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Impact of years of blindness on neural circuits underlying auditory spatial representation

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ABSTRACT

Early visual deprivation impacts negatively on spatial bisection abilities. Recently, an early (50–90 ms) ERP response, selective for sound position in space, has been observed in the visual cortex of sighted individuals during the spatial but not the temporal bisection task.

Here, we clarify the role of vision on spatial bisection abilities and neural correlates by studying late blind individuals. Results highlight that a shorter period of blindness is linked to a stronger contralateral activation in the visual cortex and a better performance during the spatial bisection task. Contrarily, not lateralized visual activation and lower performance are observed in individuals with a longer period of blindness.

To conclude, the amount of time spent without vision may gradually impact on neural circuits underlying the construction of spatial representations in late blind participants. These findings suggest a key relationship between visual deprivation and auditory spatial abilities in humans.

1. Introduction

In our continuously changing world, space representation is one of the hardest problems the brain has to face. Among sensory modalities, vision provides the most detailed information about the spatial configuration of the environment. Indeed, the brain receives high-resolution spatial information directly from the retina, which is coded topographically throughout the visual pathways. During development, vision is important for aligning neural representations of space for different sensory modalities in the brain (e.g. King, 2014; King, 2009). Yet, the role that visual information plays in the development of auditory spatial abilities is still a matter of debate.

Auditory space perception has been extensively studied in early blind individuals but research about late blindness is to date limited (for review, Voss, 2016; Voss, 2013). Actually, late blindness is a natural condition which offers valuable insight into the role of vision on auditory spatial representations. Spatial hearing of late blind subjects (LB) is indeed shaped by the unique combination of visual calibration in childhood and prolonged blindness in adulthood. According to recent data, auditory spatial skills of LB individuals lie somewhere in between those of early blind and those of sighted individuals. It would seem that this group neither benefits from the spatial hearing enhancements observed in early blind subjects, nor does it exhibit any specific perceptual deficits. Unlike early blind subjects, there is no evidence of enhanced monaural localization abilities (Voss et al., 2008, 2011) and LB adults do not show any spatial impairments for audio motion perception on the horizontal axis (Finocchietti et al., 2015), haptic orientation (Gori et al., 2010), auditory distance discrimination and proprioceptive reproduction (Cappagli et al., 2017a). Contrarily to early blind people, LB subjects also succeed in absolute auditory distance estimation (Wanet and Veraart, 1985), locational judgments after a perspective change in small-scale space (Lehtinen-Railo and Juurmaa, 1994), audio shape recognition and navigation tasks (Gori et al., 2017). However, LB individuals are better able compared to sighted people to use spectral cues when localizing sound position in peripheral regions, similarly to early blind subjects (Voss et al., 2004; Fieger et al., 2006). Turning attention to cross-modal plastic changes following late blindness, the literature shows again different results. On the one hand, auditory or tactile recruitment of occipital regions has been observed in LB individuals (Voss et al., 2006; Buchel, 1998; Burton, 2003), suggesting that compensatory mechanisms can be adopted to improve spatial skills even when vision is lost later in life. On the other hand, some studies claim that functional or structural reorganization is almost impossible beyond some critical periods (e.g. Cohen et al., 1999; Sadato et al., 2002; Noppeney, 2007),

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raising doubts about the extent of cross-modal plasticity in the case of late sensory loss. Moreover, some researchers ascribe a central role to blindness onset (e.g. Li et al., 2016; Li et al., 2013), whereas others point out some effects associated with blindness duration (e.g. Wang et al., 2013).

In the light of this background, conclusions about spatial abilities and cross-modal plasticity in LB population remain unclear. To complicate matters, one of the major issues concerning literature on late blindness is the lack of consistency across different studies in classifying blind individuals as early or late blind subjects. A given individual may be arbitrarily categorized as "early blind" in one paper and as "late blind" in others, making comparisons between findings impossible. For instance, some authors classify individuals with onsets of blindness occurring after the age of 5 as LB subjects (Gougoux et al., 2004), whereas others consider 9 years of age as cut-off (Fieger et al., 2006; Bedny et al., 2012) or even 13 years of age (Voss et al., 2008; Sadato et al., 2002; Cohen et al., 1999).

In the present study, we explore audio spatial abilities and neural correlates in a group of late blind participants in order to enrich this research topic and clarify the role of blindness onset and duration. Since late blind individuals experienced both visual exposure and deprivation, investigating their skills and the underlying neural activations allow us to shed light on the relationship between vision and audio spatial perception in humans. Specifically, we test the abilities to compute a spatial bisection task, for which behavioral impairment has been observed in early blind subjects (Gori et al., 2014), and specific occipital modulations in sighted individuals (Campus et al., 2017). The spatial bisection task consists of listening to a sequence of three consecutive, spatially separated sounds, and judging the relative spatial position of the second stimulus. A specific event-related potential (ERP) response has been recently observed in the visual cortex of sighted individuals between 50 and 90 ms after the second sound of the spatial bisection task (Campus et al., 2017). Interestingly, a similar activation was missing after the same acoustic stimuli during the temporal bisection task, which involves the evaluation of temporal intervals between three sounds. The early occipital response observed in sighted people resulted strong and contralateral to the spatial position of the second sound. Thus, the acoustic recruitment of the visual brain seems to be fundamental for audio spatial perception, and lack of vision may affect this spatial processing.

Here, ERPs and psychophysical responses were recorded during spatial and temporal bisection tasks in a group of 12 LB and 12 sighted subjects. Since vision is fundamental for the spatial bisection task (King, 2009; Gori et al., 2012) and LB individuals have been able to see during the first years of life, we expected LB participants with short blindness duration to be similar to sighted subjects. Hence, we expected them to show the contralateral occipital activation between 50 and 90 ms after the second sound of the spatial bisection and a good performance. However, the brain is highly plastic and we hypothesized that prolonged sensory deprivation could gradually affect neural circuits related to the construction of a spatial metric, driving to a weaker occipital activation and a consequent decrease in performance. Our results confirm this hypothesis showing that the duration of blindness impacts on auditory spatial processing, affecting the neural activation associated with behavioral performance in the audio spatial bisection task. As predicted, a short period of blindness is linked to a stronger contralateral occipital activation and a better performance in the spatial bisection task. Contrarily, weaker and not lateralized occipital activation and lower performance are observed in individuals with a longer period of blindness.

2. Materials and methods

2.1. Participants

A group of 12 late-onset blind (LB) subjects (3 females and 9 males) aged between 26 and 68 (mean age ± SD: 50.25 ± 15.85 years) and a group of 12 age-matched ($t_{21.5} = -0.33$, $p = 0.7$) sighted (S) subjects (7 females and 5 males; mean age ± SD: 48.52 ± 13.56 years) were recruited to participate in this study. The onset of blindness ranged from 6 to 51 years (24.75 ± 15.82 years), whereas duration of blindness ranged from 5 to 54 years (25.5 ± 15.29 years). Clinical details of LB participants are summarized in Table 1. All subjects reported normal hearing and no history of neurological, cognitive or other sensory-motor deficits except for total blindness. The research protocol was approved by the ethics committee of the local health service (Comitato Etico, ASL3 Genovese, Italy) and conducted in line with the Declaration of Helsinki. Participants provided written informed consent prior to testing.

2.2. Stimuli and procedure

Participants sat in a silent room, 180 cm away from the center of an array of 23 speakers spanning ±25° of visual angle (with 0° representing the central speaker, negative values on the left, and positive values on the right; Fig. 1A).

For each trial, three short sounds (namely S1, S2, S3; 500 Hz, 75 ms duration, 60 dB Sound Pressure Level (SPL)) were delivered at three different spatial positions and timings (Fig. 2). The first (S1) and third sound (S3) were always delivered at −25° (i.e. left) and +25° (i.e. right) degrees respectively, with temporal separation fixed at 1.5 s. The second sound (S2) could occur randomly and independently from either −4.50° or 4.50° in space (Fig. 2a), and at either −250 ms or +250 ms in time from the middle of the temporal sound sequence (Fig. 2b). These values correspond to approximately 75% of correct answers for spatial and temporal bisection thresholds evaluated in a preliminary session on 5 subjects. To avoid stereotypical responses, S2 was also presented at 0° and at 0 ms during catch trials. Inter-trial interval was 1250 ± 250 ms.

Subjects performed a spatial bisection task and a temporal bisection task in two distinct randomized blocks. In one block, they judged whether the distance between S1—S2 was smaller or larger than the distance between S2—S3 in the space domain (i.e. spatial bisection). In the other block, they were asked whether the interval between S1—S2 was smaller or larger than the interval between S2—S3 in the time domain (i.e. temporal bisection). Stimuli were identical in blocks, with S2 varying randomly and independently both its spatial position (±4.5°) and its temporal delay (±250 ms). Hence, the only difference between blocks fell on the question, which required subjects the construction of either a spatial or a temporal metric. Blocks consisted of 120 trials for

Table 1
Clinical details of the LB sample (N = 12). The table shows the chronological age at testing, gender, pathology, the age of blindness onset, and years of blindness duration (i.e. number of years spent without vision) for each participant.

Participant	Age	Gender	Pathology	Blindness onset	Blindness duration
S1	26	M	Leber amaurosis	13	13
S2	26	F	Glaucoma	6	20
S3	29	M	Corneal opacity	17	12
S4	45	M	Glaucoma	6	39
S5	49	M	Retinis Pigmentosa	40	9
S6	51	F	Leber amaurosis	46	5
S7	54	M	Chiasmatic glioma	14	40
S8	58	M	Glaucoma	20	38
S9	65	M	Retinis Pigmentosa	38	27
S10	65	F	Retinis Pigmentosa	32	33
S11	67	M	Retinal detachment	51	16
S12	68	M	Glaucoma	14	54

Fig. 1. (A) Setup for auditory spatial and temporal bisection. Subjects listened to a sequence of 3 sounds (S1, S2, S3) delivered from the lower visual hemifield and judged whether the interval between S1—S2 was smaller or larger than the interval between S2—S3, either in space (i.e. spatial bisection) or time (i.e. temporal bisection) domain. **(B) Electrode montage for EEG recording and electrodes considered in EEG data analysis.** In blue, left (C1) and right (C2) central electrodes; in red, left (O1) and right (O2) occipital electrodes.

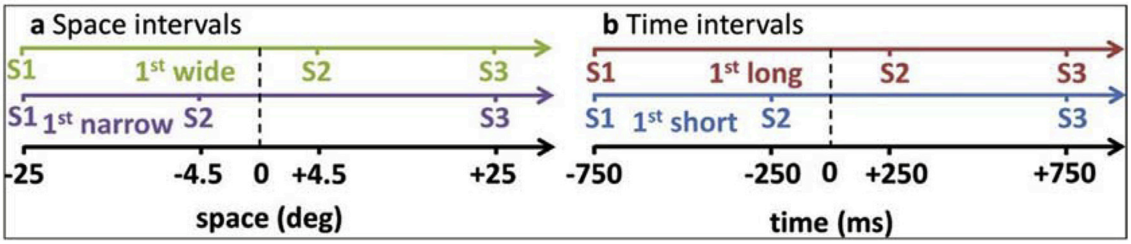

Fig. 2. Experimental protocol for spatial and temporal bisection. For each trial, S1 and S3 were delivered from −25° and +25° respectively, with 0° representing the central speaker, negative values on the left and positive values on the right. S2 could occur randomly and independently from ±4.5° in space (A) and at ±250 ms in time (B) with respect to the physical spatial and temporal midpoints (dashed vertical line). To avoid stereotypical subject responses, S2 was also presented at 0° and at 0 ms during catch trials. For the sake of clarity, in this paper the terms "small" and "large" refer to intervals between sounds irrespectively of space and time, while "narrow" and "wide" in relation to space (A), and "short" and "long" are used in relation to time (B).

each condition (small first interval, large first interval), and there were 15 catch trials. In the spatial bisection task, narrow/wide first interval corresponds to S2 delivered from the left (−4.5°) or right (+4.5°) side of the subject respectively. Temporal separation between sounds was large enough to allow a complete decay of the ERP response. To avoid possible spurious neural responses, subjects were asked to answer using a push-button immediately after S3. We measured execution times (i.e. the time between S3 and button press), and subject performance (i.e. the percentage of correct responses).

For further details about stimuli and procedure see Campus et al., (2017); data used in the study are available upon direct request in agreement with institutional ethics approval.

2.3. EEG data acquisition and pre-processing

High-density EEG was recorded from 64 scalp electrodes using the Biosemi ActiveTwo EEG System (Fig. 1B). Preamplifiers in each electrode were used to reduce noise between the electrode and the amplification/digitization system (BioSemi ActiveTwo, BioSemi B.V. Amsterdam), allowing high electrode impedances. Electrode offsets were kept below 35 mV. The continuous EEG was recorded referenced to a Common Mode Sense (CMS) active electrode and a Driven Right Leg (DRL) passive electrode, which replace the ground electrodes used in conventional systems. CMS and DRL form a feedback loop, thus rendering them references. A first-order analog anti-aliasing filter with a half-power cutoff at 3.6 kHz was applied (see www.biosemi.com). Data were sampled at 512 Hz (2048 Hz with a decimation factor of 1/4) with pass-band from DC to 134 Hz. In order to monitor horizontal eye movements, two additional electrodes were placed at the left and right outer canthi for EOG recording. Thus, trials showing horizontal ocular movements were discarded.

EEG was filtered between 0.1 and 100 Hz. Transient high-amplitude artifacts from stereotypical (e.g. eye blinks) and non-stereotypical (e.g. movement, muscle bursts) were removed using an automated artifact rejection method named Artifact Subspace Reconstruction (ASR), which is available as a plug-in for EEGLAB software (Delorme and Makeig, 2004; Mullen et al., 2013). ASR uses a sliding window technique whereby each window of EEG data is decomposed via principal component analysis and is compared statistically with data from a clean baseline EEG recording. Within each sliding window, the ASR algorithm identifies principal subspaces which significantly deviate from the baseline and then reconstructs these subspaces using a mixing matrix computed from the baseline EEG recording. In this study, we used a sliding window of 500 ms and a threshold of 3 standard deviations to identify corrupted subspaces. Moreover, channels were removed if their correlation with other channels was inferior to 0.85, or if their line noise relative to signal was more than 4 standard deviations from the channel population mean. Time windows were removed when, after the application of the previously described criteria, the fraction of contaminated channels exceeded the threshold of 0.25. Other parameters were kept as default. EEG data were further cleaned using Independent Component Analysis (Delorme and Makeig, 2004). Specifically, two EEGLAB toolboxes were used, namely SASICA (Chaumon et al., 2015) and IC_MARC (Frolich et al., 2015), keeping all parameters as their default. For component rejection, criteria reported in the corresponding validation papers were followed, mainly based on abnormal topographies and/or spectra. In addition, data were referenced to the average of left and right mastoids.

The ERP analyses followed closely the procedures employed in a prior study investigating auditory spatial metric in sighted participants (Campus et al., 2017), based on the hypothesis that blindness duration could affect the underlying neural circuits. Thus, as in previous work, the present paper focuses on neural responses to the first (S1) and the second sound (S2), for the spatial and temporal bisection tasks separately. In fact, S2 represents the starting point for the development of a metric, whereas S1 can be considered as a control. Neural responses to the third sound (S3) were not taken into account since the last sound could involve more complex mechanisms related to the metric definition, and it could be compromised by behavioral answers.

EEG data were averaged in synchrony with S1 or S2 onsets to compute ERPs, considering a period of 200 ms before S1 onset as a baseline for both sounds. For each condition of the two bisection tasks, a minimum of 50 trials after artifact rejection was required. The total number of trials was around 710 for each condition, approximately 59 per subject; catch trials were not considered. Both correct and incorrect trials were analyzed for two reasons. Firstly, to increase statistical power. Secondly, to investigate the relationship between cortical activation and given response, which reflects the perceived extension of the first interval independently of its real physical extension. Based on our hypothesis (Campus et al., 2017), we focused on electrodes linked to visual and auditory processing (O1 and O2 in occipital areas, C1 and C2 in central areas; Fig. 1B) and on a time window between 50 and 90 ms after each sound. Mean ERP amplitude was computed by averaging the voltage in the selected time window.

ERP waveforms were collapsed across conditions (small first interval, large first interval) and hemisphere of recording (left, right) to obtain ERPs recorded on the contralateral hemisphere and on the ipsilateral hemisphere with respect to stimulus characteristics in space or time. Lateralized ERP responses were calculated as the relative difference between the contralateral and ipsilateral responses. Scalp topographies of mean ERP amplitude in the 50–90 ms time window were realized for each condition (small first interval, large first interval) of space and time bisection tasks.

2.4. Hypothesis-driven analyses

First of all, statistical analysis were conducted to investigate differences in the behavioral performance for the spatial and temporal bisection tasks between S and LB groups. Comparisons between percentage of correct responses were performed with two-way ANOVA, considering group (S, LB) as a between-subjects factor, and task (space bisection, time bisection) as a within-subjects factor. Post-hoc comparisons were conducted with two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction.

Subsequently, we focused on the spatial bisection task for the LB group. After verifying that data fulfilled criteria necessary for regression analyses, a hierarchical regression analysis was conducted to test our main hypothesis. Indeed, we hypothesized that prolonged sensory deprivation could gradually affect neural circuits related to the construction of a spatial metric. Behavioral performance in space bisection (i.e. the percentage of correct responses) was the predicted variable. Based on literature (e.g. Li et al., 2016; Li et al., 2013), a first model (Model 1) considered age of blindness onset as a predictor of behavioral performance. Then, a second model (Model 2) entered years of blindness duration (BD) as a second predictor. Finally, in a third model (Model 3) we added also the EEG data. The construction of spatial metric was previously found to be reflected by a specific ERP component which mostly involves a time window between 50 and 90 ms after the second sound (S2) of the spatial bisection task, as well as contralateral occipital electrodes (Campus et al., 2017). Hence, as predictor of neural activity in Model 3 we used the lateralized occipital ERP response in the 50–90 ms time window after S2 of the spatial bisection task. ANOVA was used to evaluate each single model and the difference of explained variance between models.

Since the size of our clinical sample was limited to 12 subjects, for Model 3 we also run a bootstrapping-type multiple regression analysis to verify its validity. Thus, we applied ordinary nonparametric bootstrap using the *boot*() function of the boot package (Canty and Ripley, 2012) in R, keeping all parameters to their default, to investigate whether the performance of LB participants in the spatial task could be predicted from the lateralized occipital ERP response in the 50–90 ms time window, BD and blindness onset. The bootstrapped confidence interval (95%) was based on 1000 replications. This analysis gave us the possibility to verify the stability of the results despite the size of the sample.

Moreover, to investigate the collinearity between BD and the lateralized ERP amplitude in occipital sites in the selected time window we also run a post-hoc linear regression analysis between these two variables.

In order to exclude a role of chronological age on results, the association between years of blindness and biological age was investigated in the group of LB participants with linear regression analysis, as well as the association in the S group between biological age and lateralized ERP response to S2, and between biological age and performance in the spatial bisection task.

2.5. Data-driven analyses

To provide more support for the time-period choice and the topographic effects associated with S2 in the EEG analysis of the LB group, we also reanalyzed data applying common average reference and performed other data-driven analyses based on average-referenced EEG data. We used Microstate EEGLab toolbox version 1.0 (Poulsen et al., 2018) to perform an analysis based on a timepoint-by-timepoint approach. We performed two separate microstate segmentations, considering space and time bisection separately to identify possibly different processes elicited by the two different tasks. The Topographic Atomize and Agglomerate Hierarchical Clustering (TAAHC) method was adopted. In TAAHC, the user does not have to pre-set the number of clusters. It starts out with all EEG samples having their own cluster and then one cluster is removed at a time. Each iteration of the algorithm consists of finding the “worst” cluster, removes (atomises) it and then reassigns each of its members to the cluster it is most similar to. This process is then continued until there are only two clusters remaining (or a pre-set minimum number of clusters; we kept it to the default of two). The “worst” cluster is defined as the cluster that has the lowest sum of correlations between its members and prototype. We selected and aggregated data across subjects by concatenating the grand average ERPs. We segmented grand average ERPs into microstates and applied a temporal smoothing to the solution by setting a minimum duration of 10 ms for microstate segments to last. To decide the amount of clusters, we checked goodness fit of microstate segmentations by considering Global explained variance (GEV) and Cross-validation criterion (CV); then we made a qualitative decision based on these measures and the quality of the topographical maps of the microstates. All other parameters were kept at their default.

Moreover, focusing on the neural activity elicited by S2 of the spatial task we used the RAGU Matlab Toolbox (Koenig et al., 2011) to conduct a topographic analysis of covariance (TANCOVA), considering the extension of the first interval of the space bisection task as factor with two levels (narrow first interval, wide first interval) and blindness duration as covariate. The TANCOVA allowed us to further investigate the association between BD and EEG activity, by combining covariance analysis and resampling methods to overcome the issue of multiple testing across EEG channels. Instead of the lateralized ERP response (i.e. contralateral - ipsilateral channels), in the TANCOVA we considered ERP response of each channel to perform a lower level analysis. Considering as factor the extension of the first interval allowed us to account for the lateralization effect, as the level “narrow” corresponded to stimuli provided from the left, and the level “wide” corresponded to stimuli provided from the right of the subject. In this way, the TANCOVA provides a complementary investigation of how BD affected the lateralization of the ERP responses at different latencies and scalp topographies.

3. Results

3.1. Results of hypothesis-driven analyses

The two-way ANOVA performed to investigate differences in the behavioral performance demonstrated a significant interaction ($F_{1,22} = 5.09$, $p = 0.03$, Generalized Eta Squared = 0.1) between group (S, LB) and task (Space, Time). As shown in Fig. 3, although a significant difference between the two tasks ($t_{11} = 6.38$, $p = 0.0001$), all sighted participants succeeded in both the spatial bisection (percentage of correct responses mean ± SD: 88.5 ± 2.2%; execution times mean ± SD: 0.94 ± 0.13 s) and temporal bisection tasks (percentage of correct

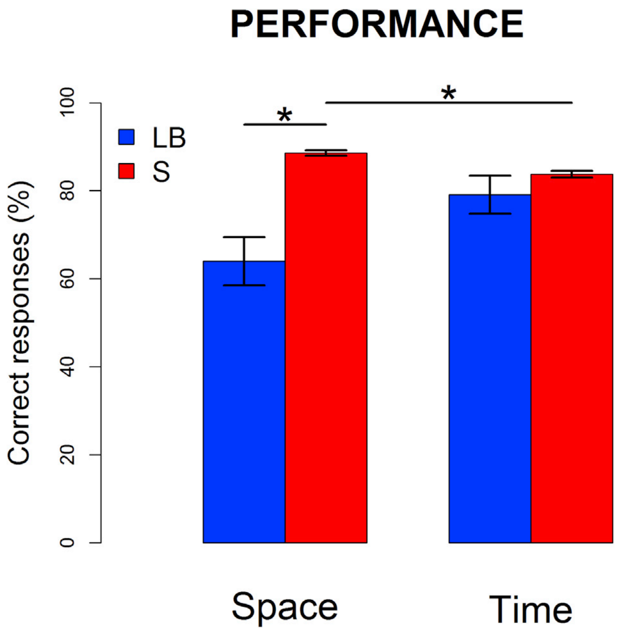

Fig. 3. Performance (mean ± standard error) for spatial (left) and temporal (right) bisection tasks in LB (blue) and sighted (red) subjects. All S participants were able to perform the tasks, with a significant higher performance in spatial bisection. LB participants show significantly lower percentage of correct responses compared to sighted participants in spatial but not temporal bisection. *$p < 0.001$ after Bonferroni correction.

responses: 83.7 ± 2.7%; execution times: 0.95 ± 0.12 s), confirming previous results (Campus et al., 2017). Turning attention to the LB group, post-hoc t-tests revealed that their performance in temporal bisection (percentage of correct responses: 79 ± 15%; execution times: 0.55 ± 0.19 s) did not differ neither from temporal performance of sighted participants ($t_{11.7} = 1.07$, $p = 0.6$), nor from their own performance in the spatial bisection (percentage of correct responses: 64 ± 19%; execution times: 0.74 ± 0.37 s; $t_{11} = -1.71$, $p = 0.2$). However, in the LB group percentage of correct responses for space bisection was significantly lower compared to that of S group ($t_{11.28} = -4.46$, $p = 0.002$), ranging from chance level (49%) to excellent (95%) across LB subjects.

Here, we focused on LB participants and specifically on their occipital neural activation 50–90 msec after S2 of the spatial task to test the hypothesis that blindness duration (BD) could affect the neural circuits underlying auditory spatial metric (Campus et al., 2017). Stated that data fulfilled criteria necessary for regression analyses (i.e. the residuals were normally distributed and homoscedastic, the errors were independent and the relationships linear), we performed a hierarchical regression analysis with performance in the spatial bisection task as predictive variable. Based on literature, Model 1 considered age of blindness onset as first predictor and revealed that behavioral performance is not predictable from this clinical variable (for the model: $R^2 = 0.02$, $F_{1,10} = 0.2$, $p = 0.7$; for age of onset: coefficient estimate = 0.2 ± 0.4, $p = 0.7$). ANOVA showed a significant improvement of the fit from Model 1 to the Model 2 in which BD was added as a second predictor ($F_{1,9} = 84.9$, $p = 0.00002$). According to Model 2 ($R^2 = 0.8$, $F_{2,9} = 18.4$, $p = 0.0007$), behavioral performance is better predicated by years of BD rather than age of onset (for age of onset: coefficient estimate = −0.4 ± 0.2, $p = 0.06$, for BD: coefficient estimate = −1.2 ± 0.2, $p = 0.0002$). Moreover, the improvement reached by adding the neural data in Model 3 ($F_{1,8} = 12.2$, $p = 0.007$) revealed an impact on the performance of the lateralized ERP amplitude in occipital areas. In Model 3 ($R^2 = 0.9$, $F_{3,8} = 33.3$, $p = 0.00007$), both age of onset and the lateralized ERP amplitude are significant predictors (for age of onset: coefficient estimate = −0.5 ± 0.1, $p = 0.008$, for lateralized ERP amplitude: coefficient estimate = 16.7 ± 4.6, $p = 0.007$), while BD not anymore (coefficient estimate = −0.4 ± 0.2, $p = 0.1$).

Since BD is a significant predictor in Model 2 but not in Model 3, in which neural activation was simply entered as predictor, BD and the lateralized ERP amplitude likely explain the same portion of variance. To test the collinearity between these two variables, we also run a post-hoc linear regression analysis (see Fig. 4). There exists a strong significant association between BD and lateralized ERP amplitude in the selected time window (for the model: $R^2 = 0.8$, $F_{1,10} = 36.5$, $p = 0.0001$, for BD: coefficient estimate = −0.05 ± 0.008, $p = 0.0001$), supporting the idea that the early lateralized occipital activation mediates the effect of years of blindness on performance. Thus, a biological variable (i.e. the neural response) seems to be a mediator of the effect of a clinical variable (i.e. blindness duration) on a behavioral variable (i.e. space bisection performance).

For Model 3, we also re-analyzed data with a bootstrapping-type multiple regression analysis to further verify its validity in our small sample ($N = 12$). This analysis confirmed previous ones, showing that lateralized ERP amplitude (95% $CI_r = [8.3, 35.9]$) and, even though less significant, blindness onset (95% $CI_r = [-0.8, -0.06]$) were able to predict the behavioral performance. Even in this case, BD did not result in a significant predictor (95% $CI_r = [-1.4, 0.2]$), likely due to its collinearity with lateralized ERP amplitude. Thus, our analyses suggest that the early activation in contralateral occipital sites could be considered as a neural correlate of audio space bisection skills, and it is strongly influenced by years of blindness duration.

To isolate the effect of BD on neural correlates associated with the construction of spatial metric, we also conducted some analyses considering the chronological age of participants. First of all, BD is not associated with biological age in the LB group (for the model: $R^2 = 0.2$, $F_{1,10} = 3.05$, $p = 0.1$, for age: coefficient estimate = 0.47 ± 0.27, $p = 0.1$). Second, in the group of sighted subjects, we revealed neither a significant association between age and performance in the spatial bisection task (for the model: $R^2 = 0.0004$, $F_{1,10} = 0.004$, $p = 0.9$, for age: coefficient estimate = −0.003 ± 0.05, $p = 0.9$), nor a significant association between age and the lateralized occipital ERP amplitude in 50–90 ms time window after S2 of the spatial bisection task (for the model: $R^2 = 0.004$, $F_{1,10} = 0.04$, $p = 0.84$, for age: coefficient estimate = −14.7 ± 71,

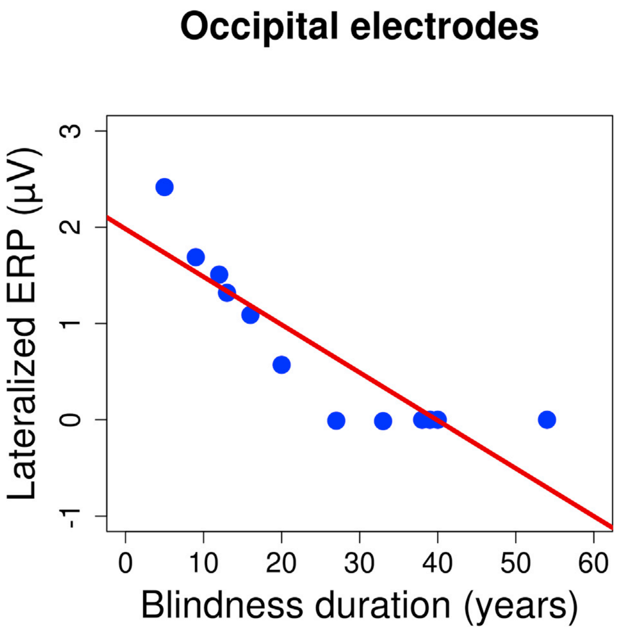

Fig. 4. Results of the linear regression analysis between BD and neural response in the LB group. Years of blindness duration (BD) negatively correlate with lateralized (i.e. contralateral – ipsilateral to S2 position) ERP amplitude in 50–90 ms time window after S2 for the spatial bisection task.

p = 0.84).

Since according to statistical analyses BD linearly affects neural circuits associated with spatial metric, for illustrative purposes, the median of BD (23.5 years) has been arbitrarily used to split the sample in order to represent graphically the different neural activation between those who had been blind for a shorter period of time (i.e. short BD) and those who had been blind for many years (i.e. long BD). Fig. 5 shows the scalp maps of the mean ERP amplitude in 50–90 ms time window when S2 was presented from either +4.5° or −4.5° in space independently of timing (±250 ms) during the spatial bisection task. Specifically, scalp maps are realized separately for the group of sighted subjects (Fig. 5A), individuals with a short BD (Fig. 5B) and with a long BD (Fig. 5C). A positivity involving central and contralateral temporal areas is always evident, likely linked to auditory cortical processing and thus in line with previous literature (Naatanen and Picton, 1987; Campus et al., 2017). However, the physical position of S2 elicits a specific occipital ERP response in sighted people and in the individuals with the shorter BD which is not so evident in subjects with the longer BD. As suggested by statistical analyses, subjects who have been blind for a short period show a strong contralateral occipital response to S2, similarly to sighted individuals. However, occipital ERP response proves to be dramatically attenuated and not contralateral to the stimulus position in participants with a long BD. As regards S1 of the spatial bisection task, as expected (Campus et al., 2017) there is simply an unspecific central response and a contralateral temporal activation in all participants (see Fig. S1 in Supplementary material).

Similarly, ERPs elicited by S2 at occipital and central electrodes during the spatial bisection task are reported in Fig. 6 for subjects with short and long BD.

As regards the occipital ERP response to S2 (Fig. 6A), only subjects with short BD show waveforms very similar to those of sighted individuals described in Campus et al. (2017). Indeed, only individuals with short blindness duration exhibit a prominent positivity between 50 and 90 ms specifically in contralateral electrodes. In contrast, the 50–90 ms occipital ERP component of the other subjects is strongly reduced and also appears in ipsilateral electrodes. Moreover, the auditory-evoked contralateral occipital activation (ACOP; Feng et al., 2014, Mcdonald et al., 2013) results more pronounced and contralateral in individuals with the short BD, whereas it is lower and not lateralized in respect to the stimulus position in the individuals who have been blind for a longer period of time. ACOP has been previously observed in sighted individuals between 250 and 400 ms. As in Campus et al. (2017), a P140 selective for S2 but not lateralized appears in both groups, although it is more pronounced in the one with short BD. Typical auditory ERP response is observed for both groups in central areas (Fig. 6B).

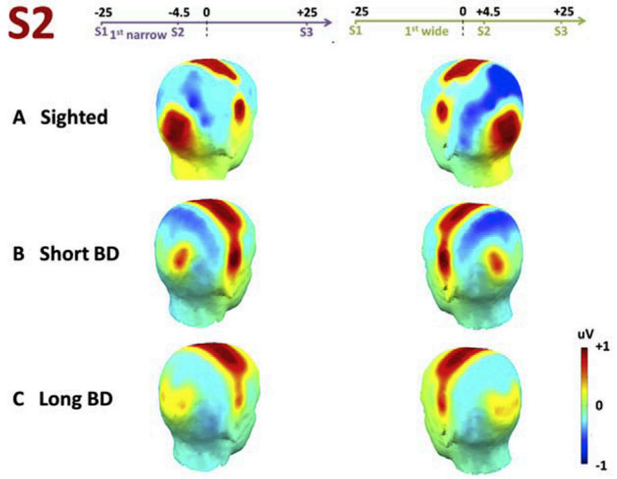

Fig. 5. Scalp maps of the mean ERP amplitude in the selected time window (50–90 ms) after S2 of the spatial bisection task. S2 was presented in space from either - 4.5° (i.e. narrow first interval; see left panel) or +4.5° (i.e. wide first interval; see right panel) independently of timing (±250 ms). Only for the sighted group **(A)** and for individuals with shorter BD **(B)** a strong positivity emerges after S2 in occipital areas contralateral with respect to the physical position of the sound. In individuals with longer BD **(C)** the occipital activation results attenuated and not lateralized with respect to the S2 position in space.

Turning our attention to time bisection performed as control experiment, Fig. 7 represents the scalp maps of the ERP amplitude in the selected time window (50–90 ms) after S2, realized separately for the sighted group (Fig. 7A), individuals with a short BD (Fig. 7B) and those with a long BD (Fig. 7C). Although BD has a linear effect on results, the median of BD (23.5 years) has been again arbitrarily used to split the sample for a graphical reason. ERP scalp topography is shown for S2, when it was presented at either +250 ms or −250 ms independently of space (±4.5°). Only a positivity involving central and temporal areas occurs, related to auditory processing (Campus et al., 2017; Naatanen and Picton, 1987). Interestingly, stimuli in space and time bisection tasks were identical, just the question is different. Thus, S2 location varied in the space domain (+4.5°/-4.5°) even when subjects were judging temporal intervals, but this aspect was not able to elicit an occipital response during time bisection task. Scalp maps of the ERP amplitude in the selected time window (50–90 ms) after S1 of the temporal bisection task are reported in Fig. S1 of Supplemental materials.

3.2. *Results of data-driven analyses*

The EEG microstate analysis confirmed the homogeneity of ERP response during the selected time-window by identifying a microstate around 50–90 ms after S2 for both the spatial (see MS4 in Fig. 8A) and the temporal (see MS3 in Fig. 8B) bisection tasks. Specifically, four clusters were obtained for the spatial bisection task, which isolate an early response (i.e. MS4 in Fig. 8A), a response around 100–200 ms (i.e. MS1 in Fig. 8A) likely reflecting a N1b component (Naatanen and Picton, 1987), a cluster around 250 ms (i.e. MS2 in Fig. 8A) possibly related to a P2 component, and a cluster between 250 and 400 ms (i.e. MS3 Fig. 8A) likely reflecting an ACOP (Feng et al., 2014, Mcdonald et al., 2013) or other late cognitive processes.

Moreover, in support of the specific influence of BD on occipital cortical activity during this specific time window, we performed a TANCOVA considering the ERP response to S2 of the spatial bisection task. TANCOVA revealed a significant interaction ($p < 0.05$ during the whole 50–90 ms interval) between BD and the extension of the first interval during the space bisection task (i.e. the distance between S1 and S2; narrow/wide first interval corresponds to S2 delivered −4.5° or +4.5° respectively). The interaction firstly involves a time window approximately between 50 and 90 ms (Fig. 9 left panel) and occipital together with temporal electrodes (Fig. 9 right panels).

EEG data with common average reference for the LB group are reported in Supplementary Materials (see Figs. S2–S4). In occipital sites, similar electrophysiological responses emerges compared to mastoid-referenced data, while a more pronounced activation is evident in temporal area when a common average reference is used. This is likely reflecting the involvement of the mastoid electrodes in auditory processing.

4. Discussion

Recent studies have suggested that early blindness negatively affects spatial bisection abilities (Gori et al., 2014; Finocchietti et al., 2015). In sighted people, who are able to compute spatial bisection, the construction of the spatial metric necessary for spatial bisection task elicits early activation of the visual cortex (Campus et al., 2017). In the present work, we investigate how audio spatial perception is shaped by vision studying neural circuits and performance during space and time bisection tasks in late blind individuals. In particular, our aim is to understand the

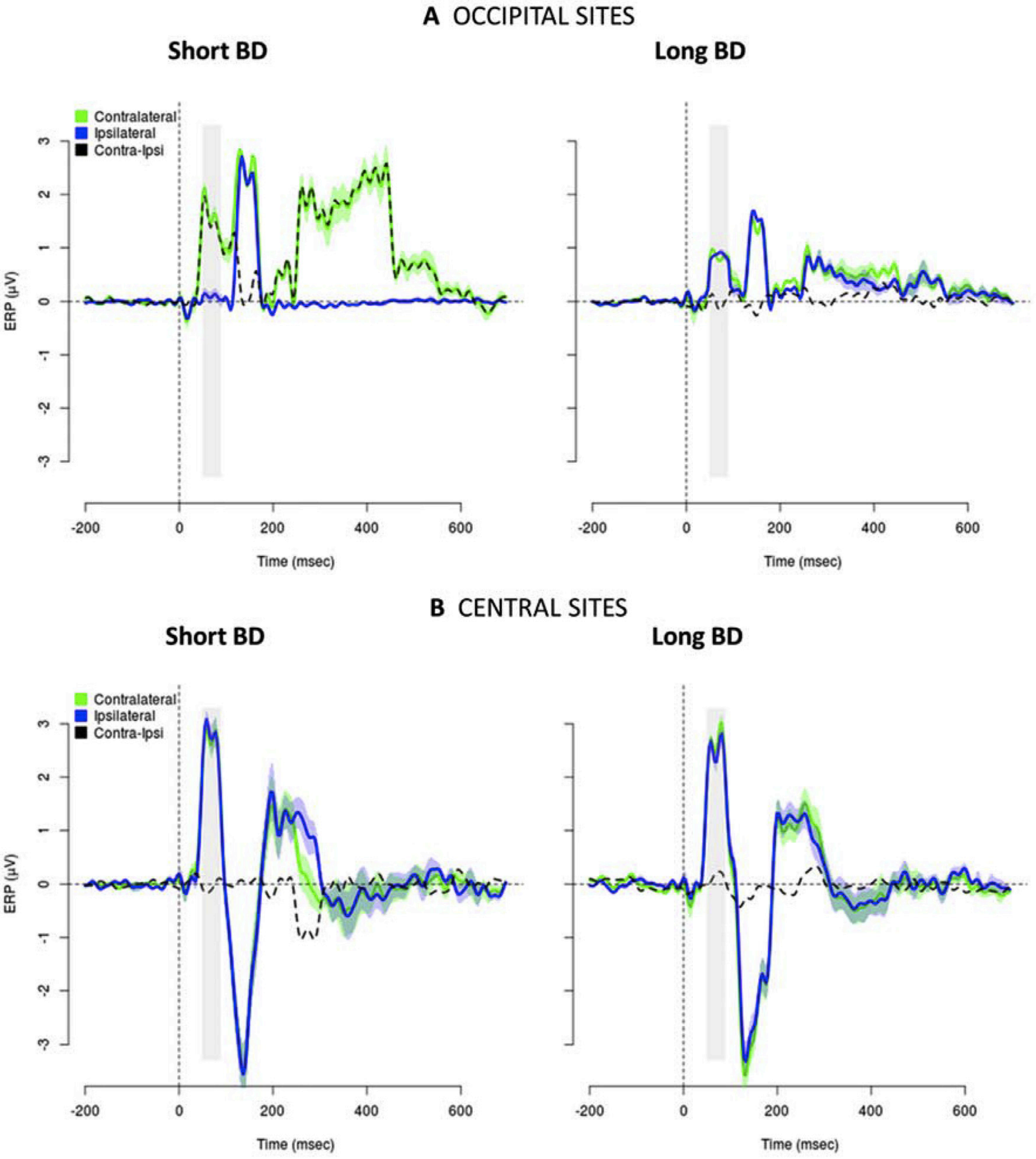

Fig. 6. ERPs (mean ± SEM) elicited by S2 during space bisection task in occipital (A) and central (B) areas, realized separately for subjects with short (left) and long (right) BD. In blue, ERPs collapsed over occipital/central scalp sites contralateral to the side of S2 presentation. In green: ERPs collapsed over occipital/central scalp sites ipsilateral to the side of S2 presentation. In black, contralateral minus ipsilateral difference amplitude. On the x-axis, t = 0 is sound onset. The shaded area delimits the selected time window (50–90 ms).

extent to which late blindness affects the cortical activation of visual areas supposed to modulate spatial metrics.

According to our results, years of visual deprivation in LB people gradually influence neural correlates associated with the performance in the auditory spatial bisection task. Subsequent to a period of visual experience, subjects who have been blind for a shorter period of time exhibit the contralateral occipital response to the second sound similarly to sighted individuals (Campus et al., 2017), and are able to perform the spatial bisection task. However, years without vision drive to a weaker and widespread occipital response to the second sound of the spatial bisection task, and to a lower spatial performance. Specifically, the hierarchical regression analysis highlights such a strong association between duration of blindness (BD), ERP responses and percentage of correct responses. The early occipital ERP response in the hemisphere contralateral to the second stimulus position mediates the effect of the amount of time spent without vision on the performance in the spatial task. Thus, the reduced laterality of the occipital activation associated with many years of blindness seems to be the explanation for the behavioral deficit reported with psychophysical methods. Studies of LB individuals have received less attention than those of early blind individuals and evidence accumulated over the years about late blindness remains vague (for review, Voss, 2016; Voss, 2013). Our data add an interesting new perspective which sheds light on the ambiguity encompassing LB research.

Since the construction of a spatial metric is compromised in early blindness (Gori et al., 2014), the similarity between neural circuits and competences of LB individuals with short BD and sighted people suggests that an early visual experience is necessary and sufficient to fully develop

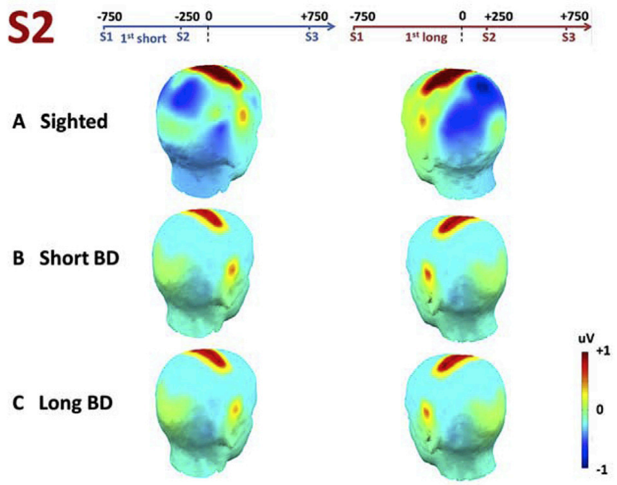

Fig. 7. Scalp maps of the mean ERP amplitude in the selected time window (50–90 ms) after S2 of the temporal bisection task. S2 was presented at either −250 ms (i.e. short first interval; see left panel) or +250 ms (i.e. long first interval; see right panel) in timing, independently of space (±25°). A central and temporal activation is observed for all participants: the sighted group **(A)**, individuals with shorter BD **(B)**, and individuals with longer BD **(C)**.

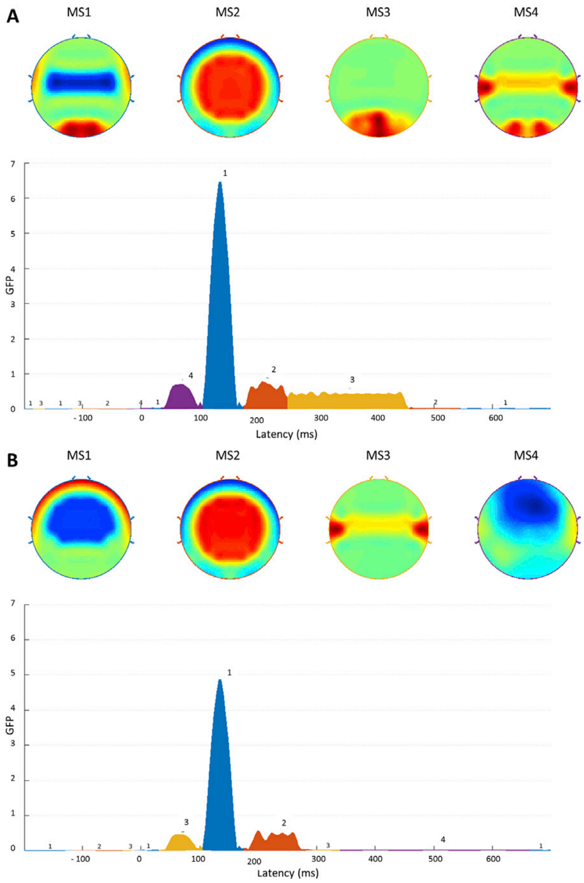

Fig. 8. Results of the microstates segmentation for the ERP elicited by S2 in the spatial (A) and temporal (B) bisection tasks. For both the spatial and the temporal tasks a microstate is identified approximately encompassing the time window considered in this study (50–90 ms after the stimulus; see MS4 in A and MS3 in B).

neural areas involved in complex representations of space. Numerous works have reported similar skills between sighted and LB individuals, asserting that the LB group displays neither the enhancements nor the impairments recorded in early blind adults (e.g. Gori et al., 2010; Wanet and Veraart, 1985). Even though only few of these studies report details about the BD of participants, it is worth noting that where specified LB subjects did not spend a long period without vision - i.e. median of BD = 14 years (Finocchietti et al., 2015); BD < 4 years (Gori et al., 2010); median of BD = 10 years (Gori et al., 2017), mean BD = 22 years (Iachini et al., 2014). Their preserved performance compared to early blind people reported in this and previous studies strengthens the notion that visual information during the first years of life is essential in calibrating auditory space representation in the brain (King, 2014; Finocchietti et al., 2015; Cappagli et al., 2017b).

Yet, one of our main insights of the present work concerns the significant impact of years of blindness on auditory spatial perception. The decrease of the contralateral occipital activation with progressive blindness duration suggests that strategies and neural circuits underlying the construction of spatial metrics are strongly affected by the absence of vision through long-term neural plasticity. Neural changes associated with BD could be related to a general atrophy of the visual cortical system, resulting in less connectivity between the auditory and visual systems. Several other studies have revealed an effect of BD on neural networks underlying spatial processing in the LB population. Collignon et al. (2013) described a negative association between sound-related activity in several occipital regions and years of blindness. In a work by Wang et al. (2013), fractional anisotropy values of corpus callosum show a trend of negative correlation with BD in LB humans. In line with these data, a study investigating cross-modal plasticity in deaf subjects revealed that with progressive deafness duration, the visual activation in the superior temporal cortex decreases and speech perception skills decline (Lee et al., 2007). Differently, Tao et al. (2015) found a positive correlation between BOLD responses in the left middle occipital gyrus and BD, and Qin et al. (2015) reported that the short- and long-range functional connectivity densities (FCDs) of the V1 are reduced in LB subjects compared to early blind individuals, but the short-range FCD of the left V1 positively correlates with BD in the LB group.

All the above-mentioned works claim a central role of BD, highlighting both compensation mechanisms and neuroplasticity limits which affect the structural and functional reorganization of the brain even when visual deprivation occurs later in life (for review, Voss, 2013; Dormal et al., 2012). Other research points to the importance of blindness onset in determining LB subjects' abilities and neural activations (Li et al., 2013, 2016). Although we only find a weaker effect of blindness onset on behavioral responses during the space bisection task, our results do not necessarily disagree with previous studies. The onset of blindness may be very compromising when it occurs early in life, but in our sample the earliest onset corresponds to 6 years of age. Early visual inputs set the cerebral architecture underlying spatial functions (Cohen et al., 1997), and the sensitive window for the development of the visual cortex ranges from several months to 10 years after birth for different occipital areas (Lewis and Maurer, 2009; Wattam-Bell et al., 2010). Similarly, the time interval of multisensory integration mechanisms is thought to involve the first 8 years of life (Gori et al., 2008; Gori, 2015). We argue that the age of blindness onset might be specifically impairing when vision loss takes place within the sensitive period, which is not the case in our sample.

We can exclude that our findings concerning BD derive from biological age. Indeed, BD and biological age do no correlate in the LB group, and in sighted people chronological age is associated with neither the occipital neural activation linked to spatial metric nor performance in the spatial bisection task.

Since vision is important for aligning neural representations of space deriving from different sensory modalities (e.g. King, 2014; King, 2009), a possible explanation of our results is that visual deprivation interferes with the remapping of auditory spatial information in the brain. In sighted people, the auditory external frame of reference is anchored to the visual system (Foley et al., 2015). External representations, such as

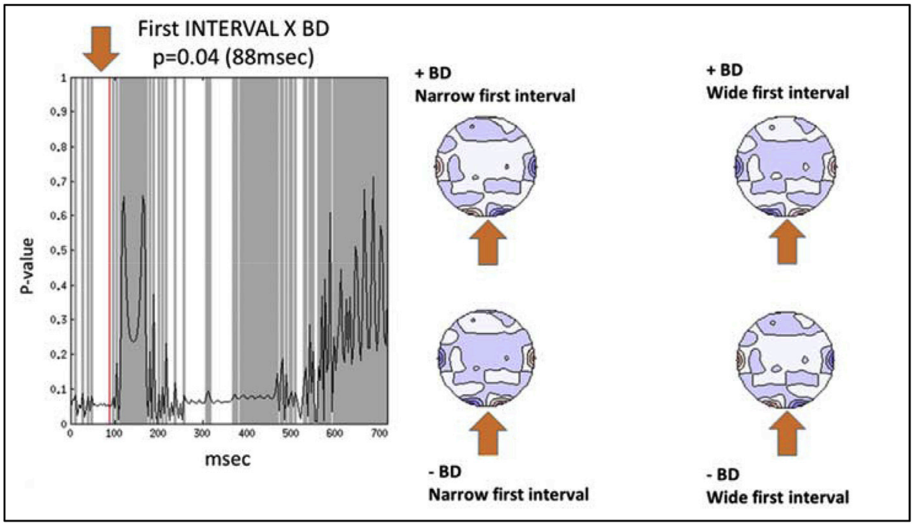

Fig. 9. Results of TANCOVA. A specific interaction emerged between Blindness Duration (BD) and the extension of the first interval (i.e. the distance between S1 and S2). Narrow/wide first interval corresponds to S1 delivered from the left (−4.5°) or right (+4.5°) side of the subject respectively. Left panel: white areas correspond to times where the interaction is significant ($p < 0.05$); the interaction firstly involves a time window approximately between 50 and 90 ms (see the orange arrow). Right panel: the interaction not only involves temporal electrodes (which are expected due to the auditory task), but also occipital electrodes (see orange arrows).

those required by the spatial bisection task, seem to originate from the spatial alignment of auditory and visual signals in oculocentric (eye-centered) coordinates (Pouget et al., 2002; King, 2009; Jay and Sparks, 1984; Cohen and Andersen, 2002). Unlike more traditional sound localization tasks, our experiment requires a spatial judgment which depends on two external auditory landmarks and it is more anchored to an external perception of the surrounding space (Gori et al., 2014). Thus, visual deprivation might impact on the processes related to the codification of the auditory space, driving to an impairment in building external spatial representations. We have recently shown that early blind people use temporal cues to infer spatial coordinates of the environment (Gori et al., 2018). Starting from this, a possible speculation about our results is that prolonged blindness may drive LB people to rely more on other cues, such as temporal instead of spatial coordinates, when building external spatial representations.

Although attention is a difficult issue to rule out completely, we find it an unlikely explanation of our results. Attention to space can be expected to weakly affect early ERPs, such as the observed occipital response or the N1a (Roder et al., 1999; Lange et al., 2006). In this regard, it is important to note that the ERP component which we found to be modulated by years of BD reflects early perceptual effects, far from the late cognitive effects (e.g. attention and expectation) reflected by the ERP component known as ACOP (Feng et al., 2014, Mcdonald et al., 2013). This latter is characterized by a late time window (250–400 ms) and by estimated sources localized to the ventrolateral extrastriate visual cortex (Brodmann's area 19). ACOP is elicited by unpredictable sounds and this is the reason why we observed it after the second sound of the spatial bisection task. Instead, we show that a strong response in the same early time window as a visual-evoked C1 (50–90 ms), with generators involving visual cortex (Campus et al., 2017), appears in individuals with short BD but is drastically attenuated after prolonged visual deprivation. In addition, our results do not seem to originate merely from attentional factors because LB participants on average succeeded at the temporal bisection task, meaning that there was no deficit in attention *per se* in individuals with longer BD.

The influence of BD on spatial bisection neural circuits and abilities might be related to spatial imagery. In recent years, a growing body of research has employed the mental scanning paradigm as a tool to investigate the metric properties of mental spatial images in the blind population (Cattaneo et al., 2007, 2008; Iachini and Ruggiero, 2010; Afonso et al., 2010). Interesting findings of spatial representations in blind individuals emerge from the study conducted by Afonso et al. (2010). They claimed that only blindfolded sighted and LB participants are able to create metrically accurate spatial representations of small-scale spatial configurations by listening to a verbal description or by exploring the configuration haptically. However, late and early blind participants, but not sighted individuals, can generate accurate spatial mental images though locomotor exploration of a full-scale navigable environment. These results highlight that spatial imagery in LB subjects differs from the spatial imagery of both early blind and sighted individuals (Afonso et al., 2010). Spatial imagery is shaped by prior visual experience, and one hypothesis is that it could be subsequently transformed by the amount of time spent without vision, thus influencing performance in spatial tasks. However, we think that our effect cannot only be due to visuo-spatial imagery. Indeed, we found that in sighted individuals and in LB subjects with short BD the second sound of the spatial bisection task selectively elicits an early contralateral neural activation also in auditory temporal regions, which is not linked to visuo-spatial imagery.

5. Conclusions

In conclusion, the main insight of the present study concerns the amount of time spent without vision: blindness duration modulates neural circuits and strategies underlying the construction of spatial metrics in late blind people. The results represent a new step toward understanding the role of vision on spatial perception, and how the brain and complex skills react to sensory deprivation. Moreover, investigating how blind individuals construct space representation is helpful for the development of effective rehabilitative methods to improve spatial abilities. Future research should further explore the effects associated with blindness duration and this parameter could be taken into account as a good candidate to explain inconsistencies in late blindness research.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.01.073.

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