SPATIAL AND TEMPORAL PERCEPTION IN SENSORY DEPRIVATION

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SPATIAL AND TEMPORAL PERCEPTION IN SENSORY DEPRIVATION

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Table of Contents

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EDITORIAL
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Editorial: Spatial and Temporal Perception in Sensory Deprivation

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Editorial on the Research Topic

Spatial and Temporal Perception in Sensory Deprivation

The Research Topic aimed at providing new insights into the impact of sensory deprivation on spatio-temporal abilities and their subtending cortical circuits. The Research Topic attracted a wide range of submissions across the spectrum of this theme, and overall, all the submitted papers fall within one of the following topic contributions: (a) papers identifying impaired/preserved abilities after a sensory loss/deprivation; (b) papers investigating cortical plasticity and reorganization mechanisms following sensory loss/deprivation; (c) papers presenting newly developed tools to assess and/or train spatial impairments resulting from sensory loss/deprivation. With this editorial, we intend to discuss the findings of the submitted contributions within the broader context of the literature on the theme by considering the three above-mentioned main contribution categories.

IMPAIRED VS. PRESERVED PERCEPTUAL FUNCTIONS AFTER SENSORY LOSS/DEPRIVATION

Overall, five out of the six papers in this category demonstrated that sensory loss/deprivation leads to perceptual and sensorimotor impairments rather than preserved abilities. Wu et al. demonstrated that long-term abnormal binocular visual experience causing intermittent but recurrent eye misalignment (intermittent exotropia) alters distance stereoscopic acuity (Hatt et al., 2007; Zhou et al., 2019), thus impairs three-dimensional depth perception. The Authors demonstrated that patients with intermittent exotropia require longer times for optimal stereoacuity, arguing that more extended temporal integration might be caused by a longer time needed for binocular cells to integrate the signals from two eyes. This new finding sheds light on the importance of including the temporal dimension of stimulus presentation in stereopsis assessment and rehabilitation training. Luo et al. demonstrated that a clinical condition characterized by progressive visual acuity decrease and progressive peripheral visual field loss (retinitis pigmentosa) affects general visual information processing and specific visuo-spatial and visuo-attentional capabilities.

Similarly, Martolini et al. demonstrated that children with impoverished visual experience from birth (low vision) acquire the ability to represent space based on external frames of reference ("allocentric") rather than on body-centered cues ("egocentric") much later compared to sighted peers. Such finding is in line with previous evidence showing that vision is necessary to guide the development of spatial abilities (Thinus-Blanc and Gaunet, 1997; Eimer, 2004; Iachini and Ruggiero, 2010; Pasqualotto and Proulx, 2012; Cappagli and Gori, 2016; Voss, 2016; Cappagli et al., 2017) and that long-term early-onset visual impairment might compromise such development. Scotto et al. reported that short-term sensorimotor deprivation causes impairments in motor

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control by disrupting the spatiotemporal structure of the pointing movements performed after the deprivation. More specifically, they showed that when healthy individuals immobilize their right limb for 24 h, not only their overall motor performance decreases as previously shown (Huber et al., 2006; Moisello et al., 2008; Bassolino et al., 2012; Bolzoni et al., 2012), but also both early and late kinematic parameters (corresponding to feedforward and feedback processes of motor control, respectively) are altered. This evidence indicates that short-term sensorimotor deprivation alters motor control both at an early step (feedforward control), impairing the ability to predict future actions' sensory consequences, and at a later step (feedback control), and the ability to correct reaching movements toward the target. Since visual cues strongly influence feedback control of movements (Sarlegna et al., 2004, 2007; Saunders and Knill, 2004; Sarlegna and Sainburg, 2009), future research should investigate whether visual feedback during movement can overcome the motor impairments observed after prolonged limb immobilization.

Sharp et al. demonstrated that congenital deafness impairs the development and maintenance of overt oculomotor behavior, suggesting that a hearing impairment can affect the non-deprived visuo-motor domain. Contrary to the other studies presented above, which investigated intra-modal consequences of sensory loss/deprivation, this study directly assessed the link between auditory experience and the development of visual functions. Such evidence corroborates recent hypotheses suggesting the existence of cross-sensory integration and calibration mechanisms (Gori et al., 2010; Morrone, 2010; Gori, 2015; Dekker and Lisi, 2020), thanks to which the most accurate sensory modality for a specific task (e.g., hearing for temporal discrimination) dominates and guides the development of the others. According to this view, it might be hypothesized that hearing would have a role in the control of eye movements. This finding fits well within the literature demonstrating altered eye movement control in the deaf (Bottari et al., 2012). Further studies should investigate how auditory loss impacts crossmodal reorganization in terms of functional change (Cardin et al., 2020). The only study that revealed preserved abilities after sensory deprivation is the one by Chen et al., showing that short-term visual deprivation in one eye does not impair the ability to judge the temporal synchrony of visual stimuli presented after the deprivation in dichoptic and monocular conditions. Contrarily to previous behavioral and electrophysiological/neuroimaging studies showing that monocular deprivation causes a shift in perceptual ocular dominance (Lunghi et al., 2011; Zhou et al., 2013, 2014; Kim et al., 2017; Başgöze et al., 2018; Min et al., 2018) and increased response of the deprived eye vs. a decreased response of the non-deprived eye (Lunghi et al., 2015a,b; Zhou et al., 2015; Chadnova et al., 2017; Binda et al., 2018), this study indicates that such kind of visual deprivation does not influence the temporal processing of visual information. Factors such as the type of task (e.g., binocular rivalry vs. phase combination), the assessed perceptual domain (e.g., spatial vs. temporal processing), and the duration of visual deprivation might underlie such discrepancy.

CORTICAL PLASTICITY AFTER SENSORY LOSS/DEPRIVATION

Sensory loss or deprivation typically induces significant reorganization in sensory cortices (Rauschecker, 1995; Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010; Ricciardi and Pietrini, 2011). It has been argued that crossmodal plasticity may take the form of functional preservation, where cortical regions preserve their function but adapt to process sensory input in a different modality. Or it can result in functional change, where cortical regions change also their function, typically switching from sensory processing to higher order cognition (Cardin et al., 2020). Such plastic reorganization often subtends compensatory mechanisms, which can enable even normal or close-to-normal perceptual abilities. Scurry et al. investigated possible differences between early deaf and typical hearing individuals in a visual-tactile temporal judgment task. Differences in performance were expected, since audition is believed to provide a necessary framework for developing sensitivity to temporal information (Burr et al., 2009; Conway et al., 2009). Surprisingly, the two groups did not differ in their temporal order perceptual performance. However, deaf participants showed enhanced EEG signal strength in both visual and tactile components compared to sighted controls, which indicates compensatory recruitment of auditory and visual areas for visuo-tactile temporal processing. Scurry et al. reported that multisensory areas, such as the right posterior superior temporal sulcus (pSTS), undergo compensatory plasticity. In particular, early deaf individuals showed larger activation of the pSTS compared to healthy controls during tactile motion processing. This activation, which is not accompanied by increased directional tuning, suggests the presence of a more distributed network of neuronal populations involved in tactile motion processing as a consequence of early auditory deprivation. However, in line with the principle of functional preservation, no greater activation of the primary auditory cortex (PAC) was found: audition is predominant in processing temporal features, and visual and tactile temporal tasks lead to PAC activations in the blind (Auer et al., 2007; Bola et al., 2017). This study shows that PAC maintains its temporal processing involvement after a sensory loss without being involved in processing spatial–rather than temporal–tactile aspects. Glick and Sharma demonstrated that early stage mild-moderate age-related hearing loss is associated with cross-modal recruitment of auditory, frontal and prefrontal cortices during visual tasks, suggesting functional changes induced by hearing loss. Significantly, more extensive recruitment of the auditory cortex by vision correlates with more significant hearing loss and lower perceptual and cognitive performance. Moro et al. showed that partial visual deprivation, such as the early loss of one eye, can induce a neuronal reorganization of circuits typically dedicated to binocular vision, resulting in increased brain activation for audio-visual stimuli.

Unfortunately, such cross-modal cortical reorganization can also result in maladaptive outcomes. This process can happen either due to early-onset sensory deprivation or when sensory deprivation or decline occurs later in life. Maladaptive changes led by long-term plasticity are reported by Amadeo et al., who showed that late blind individuals with long time blindness duration present behavioral performance and cortical activations analogous to those shown by early blind individuals. In these participants, temporal cues activate circuits typically responding to spatial cues in both sighted individuals and blind participants with shorter blindness duration. In other words, after many years of blindness, late blind participants start relying on temporal information to build spatial representations, as it happens in early blind individuals (Gori et al., 2013). The fact that many years of late sensory deprivation/decline can lead to maladaptive outcomes highlights the importance of introducing rehabilitation strategies soon after the onset of sensory loss/decline. Notably, the research from Glick and Sharma demonstrates that few months of clinical treatment with hearing aids at an early stage of hearing loss can induce a reversal in the observed cross-modal reorganization of the cortex, accompanied by improved behavioral performance.

NEW TOOLS TO ASSESS AND TRAIN SENSORIMOTOR FUNCTIONS AFTER SENSORY LOSS/DEPRIVATION

Perceptual impairments following sensory loss/deprivation, such as spatial deficits resulting from visual deprivation, posit the necessity to develop and adapt clinical assessment and training tools to meet the sensory loss population's needs. Specifically, specific tools for visually impaired children are less systematically used and spread than those designed for adults (Gori et al., 2016; Elsman et al., 2019). The need for such solutions has been extensively reported in the literature, but the communication between scientific findings and technological development can still benefit from investigations aiming at developing clinical settings and training strategies. Aprile et al. provided a review of standardized and non-standardized tools in use to assess spatial cognition in visually impaired children by employing other sensory modalities than vision, such as haptic/proprioception and audition. By highlighting the limitation in visual impairment dedicated tools, the Authors mainly focused on the lack of formal and informal assessment methods, and promoted the validation of large-scale application of newly developed tools in the context of pediatric visual impairment.

Tivadar et al. investigated mental rotation abilities in blind participants with a digital haptic technology, which was previously tested with sighted participants. In contrast to sighted participants, visually impaired participants generalized training among letters suggesting the involvement of supramodal processes. In the case of visual loss, such functions can be trained to allow blind participants to make better use of more conceptual than sensory-specific encoding strategies to solve tasks requiring the spatial manipulation of mental representations. Morelli et al. presented a longitudinal study reporting a detailed example of a multisensory rehabilitation intervention leading to improved spatial cognition in a visually impaired child (from 9 months to 11 years of age). The Authors highlighted how early and timely intervention is fundamental to sustain and promote neuropsychomotor development in visual impairment. Rehabilitation is often aided by technological solutions that may improve spatial perception and cognition based on the remaining senses. In this context, sensory substitution devices (SSDs) can effectively enhance spatial competence, such as navigating through space independently. As pointed out in this research topic and in the literature (Cuturi et al., 2016), assessing the blind population is often neglected in technological development. Jicol et al. scrupulously tested potential improvements in spatial navigation tasks with two SSDs: the vOICe (Meijer, 1992), which exploits auditory information and the BrainPort (Bach-y-Rita and Kercel, 2003), which provides participants with tactile information on their tongue about the navigated environment. In one experiment, results from sighted participants showed that the combined use of both SSDs provides no improvement, likely because of task difficulty and sensory overload. In another experiment focusing on integrating auditory and self-motion information in sighted and blind participants, only the latter takes advantage of the vOICe device while navigating on the basis of egocentric and allocentric information.

Chebat et al. provided a comprehensive review on the use of SSDs in the acquisition of spatial competence and brain reorganization in case of blindness. The Authors discuss the brain correlates of spatial navigation strategies and support the notion that a modal processing of space can aid spatial navigation in blind individuals. Regarding future research directions on SSDs, the Authors suggest deepening the study of SSDs employment during the first years of development when brain plasticity is most and great improvement may be expected (Röder et al., 2020; Röder and Kekunnaya, 2021). However, not only SSDs but also everyday technologies might foster spatial cognition in the context of sensory deprivation. Holmer et al. tested whether gaming habit with computer and console games influences visuo-spatial control in deaf individuals. Although gaming experience did not influence hearing individuals performance, deaf individuals benefitted from gaming experience compared to deaf non-gamers, likely by improving visuo-spatial attentional control in the peripheral visual field.

AUTHOR CONTRIBUTIONS

IS, LC, and GC wrote the manuscript. IS, LC, ME, MG, and GC revised the manuscript. All authors contributed to the article and approved the submitted version.

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Optimal Stereoacuity Reveals More Than Critical Time in Patients With Intermittent Exotropia

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Synopsis: Both optimal stereoacuity and integration time to achieve that are impaired in patients with intermittent exotropia. The deterioration of stereoacuity is more revealing since it correlates well with exotropia control score.

Background: Despite the periodic misalignment of two eyes, some intermittent exotropia (IXT) patients exhibit normal stereoacuity, particularly when evaluated with static tests. It is not clear if the temporal integration process of stereopsis is altered in IXT patients, thus warranting further research.

Methods: IXT patients (n = 29) and age-matched normal controls (n = 36) were recruited. Static stereopsis was measured with the Titmus stereoacuity test. In computer-generated random dots tests, stereoacuity was measured with a stimuli presentation duration varying from 100 to 1,200 ms. And the relationship between stereoacuity and stimuli duration was fitted into a quadratic model. Optimal stereoacuity was achieved when fitted curve flattened and the critical integration time was the duration needed to achieve optimal stereoacuity.

Results: IXT patients were not found to differ significantly from control subjects under the Titmus test, while the Random Dots stereotest showed significantly worse optimal stereoacuity and significantly longer critical integration time. Multiple regression analysis showed that age ($R = -4.83$; $P = 0.04$) had statistically significant negative correlation on the critical integration time, age ($R = -6.45$; $P = 0.047$) and exotropia control scores ($R = 60.71$; $P = 0.007$) had statistically significant effects on optimal stereoacuity.

Conclusion: The temporal integration for stereopsis is impaired in IXT patients, requiring longer critical integration time to achieve elevated optimal stereoacuity.

Keywords: intermittent exotropia, stereopsis, temporal integration, optimal stereoacuity, critical time

INTRODUCTION

Stereopsis is the finest form of binocular visual processing, in which the image disparity between two eyes is extracted to achieve depth perception (Blake and Wilson, 2011). Stereopsis in humans is absent at birth, emerges around 3 months of age and gradually reaches adult levels around 5 years of age (Aslin, 1977; Fox et al., 1980; Birch et al., 1982; Birch et al., 1985; Giaschi et al., 2013). It is common knowledge that binocular vision adapts to natural occurring disparities, for what concerns stereopsis (Sprague et al., 2015; Gibaldi et al., 2017) and binocular coordination (Gibaldi and Banks, 2019). Due to the high level of neural plasticity in early life, abnormal binocular visual experience often can quickly disrupt this developmental process (Wiesel and Hubel, 1963; Birch et al., 1998).

Intermittent exotropia is a condition in which one or two eyes occasionally deviate outward. It accounts for the majority of exotropia reported worldwide (Govindan et al., 2005), and affects approximately 1 in 30 preschool-aged children in China (Pan et al., 2016). During misalignment, decorrelated binocular inputs impair the normal development of binocular vision. However, due the intermittent nature of exotropia, both eyes are not always misaligned. During alignment, correlated binocular inputs promote the development of binocular vision. Therefore, IXT patients show an understandably wide range of binocular deficits, from having no binocular fusion to normal stereopsis (Lee et al., 2014). Distance stereoacuity has been used clinically to evaluate binocular control, with decreasing stereoacuity indicating increased severity of IXT (Mohney and Holmes, 2006; Holmes et al., 2007; Hatt et al., 2007). Stereoacuity is also used as an index to determine the optimal time for corrective surgery (Holmes et al., 2011).

In previous studies, stereopsis was mostly measured using static stimuli, such as the Titmus test, TNO test (Mix, 2015), where subjects were allowed to view the stimulus as long as they preferred. Although vision involves the processing of both spatial and temporal information, the temporal aspect of stereopsis has been studied little in IXT patients. In normal subjects, stereoacuity improves with viewing duration and often reaches optimal levels at around 100 ms (Harwerth et al., 2003). Those with strong sensory ocular dominance tend to have longer critical integration time (Tmin) to reach similar levels of stereoacuity than those with balanced eyes (Wu et al., 2018). With mismatched binocular inputs during misalignment, it is natural to think that the Tmin would be longer in IXT patients, but this has not been tested before. The only related study reported opposite findings. Using computer-generated stimuli, (Harwerth et al., 2003) reported unchanged Tmin despite impaired stereoacuity measured with Gabor patches and random dots (RD). The study's relatively small sample size and history of corrective surgery in strabismic subjects make IXT population inferences difficult (Harwerth et al., 2003). There was also a lack of information provided about ocular deviation and eye position control. Therefore, new studies are warranted to address this question.

The aim of this study is to investigate whether Tmin is longer in patients with IXT. If that is the case, determining whether the changes in Tmin are closely correlated with exotropia control scores or ocular deviation could support future clinical evaluation.

MATERIALS AND METHODS

Subjects

A total of 29 IXT patients were recruited from Changsha Aier Eye Hospital (Changsha, China). The inclusion criteria were: 1) best corrected visual acuity for each eye ≥ 20/20, 2) anisometropia ≤ 1D, 3) basic type IXT, 4) possessing stereopsis indicated by synoptophore, 5) no previous surgical or non-surgical treatment for IXT other than refractive correction and 6) no history of ocular surgery or trauma. Thirty-six normal subjects, who were patients at the same hospital for refractive error examination, served as controls. The control inclusion criteria were: (1) best corrected visual acuity for each eye ≥ 20/20, (2) anisometropia ≤ 1D, (3) no strabismus, and (4) no history of ocular surgery or trauma. Written informed consent was obtained from all subjects and/or their parents (for those younger than 18 years of age) after providing an explanation of the study's nature and possible consequences. The protocol for the study was approved by the Institutional Review Board of Aier Eye Hospital Group and followed the tenets of the Declaration of Helsinki.

Fusion, divergence and convergence were evaluated with a model synoptophore (Clement Clarke International Ltd., London, United Kingdom). Near stereoacuity was tested using a Titmus stereogram (Stereo Optical Co., Inc., Chicago, IL, United States) and the RD stereotest. For IXT patients, exotropia control was measured using the Office Control Score (Mohney and Holmes, 2006), which ranges from 0 (phoria, best control) to 5 (constant exotropia, worst control), and ocular alignment was assessed at a distance of 6 m using the prism and alternative cover test (Ansons and Davis, 2014).

The RD Stereotest

The RD stimuli for testing stereopsis was programmed using commercial software (MATLAB, version 2012Rb; MathWorks, Natick, MA, United States) (Wu et al., 2018). The visual stimuli were presented on a CRT screen (Trinitron CPD-E200, 17 inches, 43.18 × 32.39 cm, 1024 × 768 resolution; 105 Hz; Sony Corporation, Tokyo, Japan), with Gamma correction for linearity, against a uniform background (50 cd/m^2). The monitor was viewed at a distance of 115 cm. Each eye viewed a pattern of RD subtended 3.3° × 3.3°. Using a double stereoscope, the subjects' left and right eyes viewed fixation marks (**Figure 1A**) in the center of each half of the screen, where the half images of the RD would be presented. The fixation marks were an upward-pointing and downward-pointing "T" for the left and right eyes, respectively. Subjects adjusted the mirrors to fuse the two symbols, and were allowed to begin their trial only when they saw a complete square box with a cross in the center. For each trial, the subjects were instructed to determine whether the central square (1° × 1°) was standing in front of the background or falling behind the background. For a fixed presentation duration, the amount of disparity varied for each trial and the disparity threshold was measured using a 3-down 1-up staircase algorithm

(**Figure 1B**). The initial stimulus values were 400 aresec. The decreasing/increasing rate was 30% before the first reversal, and 15% afterward. Each staircase ended when it reached six reversals and the values from the last four reversals were averaged as the final stereo threshold.

Stereoacuity was measured with different RD presentation durations, including 100, 200, 400, 600, 800, 1,000, and 1,200 ms. It is worth noting that on a stimulus presentation duration of 100 ms, the display in the current study with a frequency of 105 Hz would provide a mismatch of up to ±4.8 ms. The stereo thresholds (th) versus viewing durations were fitted into a quadratic model of $th = h0 * sqrt(t^{-2} + Tmin^{-2})$, where th was the stereoacuity at a given presentation duration (t), $h0$ determined the vertical height of the function, $Tmin$ was the critical time constant at which the stereoacuity no longer changes (the optimal stereoacuity, Dmin). **Figure 2** shows the stereo threshold as a function of viewing duration for a normal subject (**Figure 2A**) and an IXT patient (**Figure 2B**).

Data Analyses and Statistics

Statistical analyses were performed using the R programming package (version 3.2.2[1]; The R Foundation, Vienna, Austria). The Shapiro–Wilk test was used to test the normality of data. The data of each subject's age, refraction, fusion, divergence, convergence and ocular alignment followed normal distribution; therefore, a mean and standard deviation were used for description and a T-test was used for comparison. The data of each subject's Titmus stereoacuity and exotropia control score did not follow normal distribution; therefore, a median and range were used for description and a Kolmogorov–Smirnov test was used for comparison. A chi-square test was used to compare gender difference. Multiple parameter linear regression was used to explore the correlation between Tmin/Dmin and several possible parameters. Differences of $p < 0.05$ were defined as statistically significant.

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[1] http://www.R-project.org

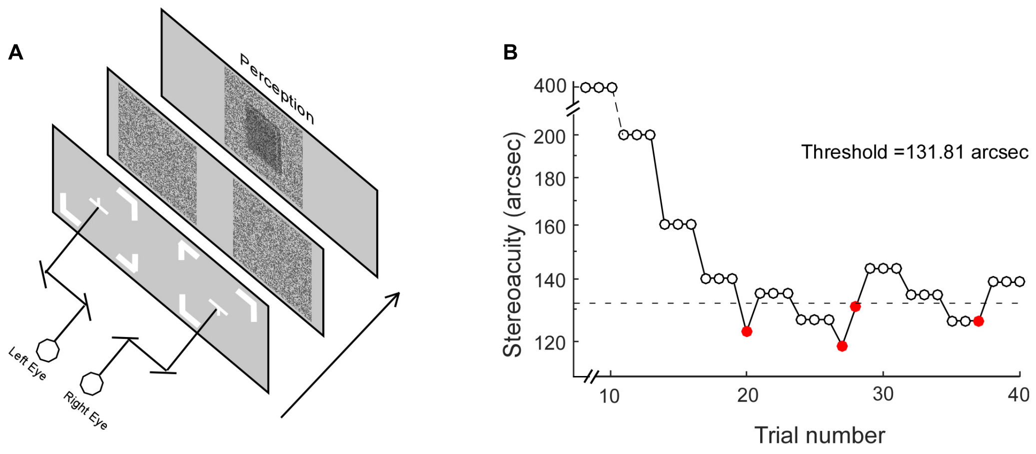

FIGURE 1 | The Random Dot test. **(A)** Stereoacuity was measured with different stimulus presentation durations, including 50, 100, 200, 400, 600, 800, 1,000, and 1,200 ms. **(B)** For each stimulus presentation duration, the stereo threshold was measured with a staircase procedure. Open and closed red circles represent correct and incorrect responses, respectively. The dotted line represents the final stereo threshold averaged from the last four reversals.

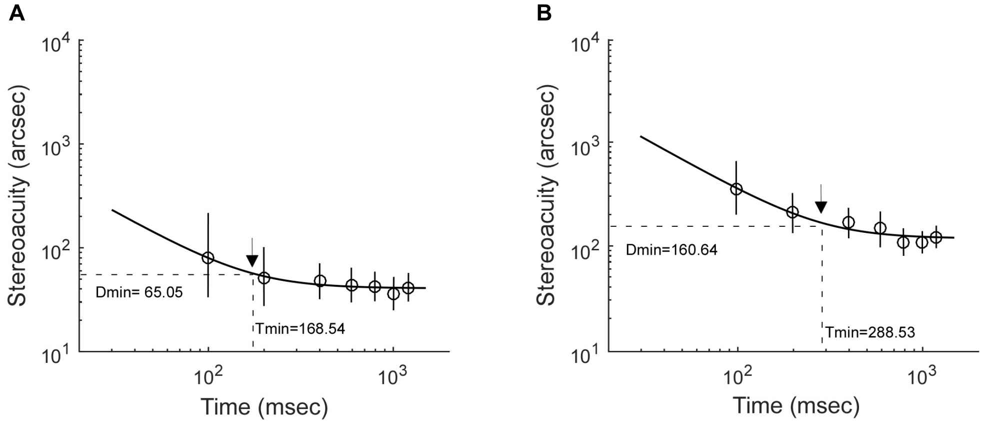

FIGURE 2 | Examples illustrating how stereoacuities change with stimulus presentation durations. **(A)** A control subject. **(B)** An IXT patient. The black arrow indicates the location of optimal stereoacuity (Dmin) and the critical integration time (Tmin) required to achieve it.

RESULTS

Twenty-nine IXT patients (14 males, 48.28%) and thirty-six control subjects (17 males, 47.22%) were recruited during the period of August 2018 to April 2019. There was no significant difference in gender, age, refraction, fusion, divergence or convergence between the IXT and control groups (**Table 1**).

For the Titmus test, IXT patients (median: 80 arcsec, range: 20–320 arcsec) did not differ significantly from control subjects (median: 80 arcsec, range: 20–160 arcsec, KSSTAT = 0.17, $p = 0.71$). For the RD test, the relationship between Tmin and Dmin in the control subjects and IXT patients has been plotted in **Figure 3A**. Dmin for IXT patients was 192.55 ± 120.31 arcsec, significantly worse than the control group (81.18 ± 39.55 arcsec, $t = -5.22$, $p < 0.01$; see **Figure 3B**). Tmin for the IXT group was 234.86 ± 77.79 ms, significantly longer than the normal group (180.01 ± 90.72 ms, $t = -2.58$, $p = 0.01$; see **Figure 3C**).

To further explore how Tmin and Dmin were affected by IXT characteristics, the relationship between Tmin and Dmin, ocular alignment and exotropia control score has been summarized in **Figure 4**. Multiple regression analysis showed that age ($R = -4.83$; $P = 0.04$) had statistically significant negative correlation on Tmin, age ($R = -6.45$; $P = 0.047$) and exotropia control scores ($R = 60.71$; $P = 0.007$) had statistically significant correlation on Dmin.

DISCUSSION

In this study, we found that Dmin is more than doubled in IXT subjects, while Tmin only increases by roughly 30%. The age had statistically significant negative correlation on Tmin and Dmin. Moreover, Dmin is closely associated with exotropia control scores while Tmin is not.

Comparison to Existing Studies

The finding of increased Dmin in our study agreed with many previous studies reporting that stereoacuity is impaired in persons who have abnormal visual experience early in life (Hatt et al., 2007; Zhou et al., 2019). However, the increased Tmin does not agree with early studies. According to Harwerth et al. (2003), Tmin remained constant despite elevated Dmin. This disagreement may be due to several reasons. In the previous study, 12 monkey subjects and two human subjects with microstrabismus were examined. Among the monkey subjects, nine experienced alternating defocus to induce strabismus from 3 weeks to 9 months of age, and three had surgically induced esotropia for an unknown period of time (Harwerth et al., 2003). In our study, all 29 IXT subjects had not received corrective surgeries. The natures of the abnormal binocular experience also differ. During the period of alternating defocus rearing, the eyes never receive clear images simultaneously, although the eyes might still be aligned. For IXT patients, images from both eyes are clear, but mismatched. The two human subjects included in Harwerth's study were diagnosed with microstrabismus, making a direct comparison to results from IXT patients difficult.

TABLE 1 | Patient characteristics in control subjects and IXT patients.

Characteristic	Control subjects (*n* = 36)	IXT patients (*n* = 29)	Statistic value	*p*-value
Gender (Male:Female)	17:19	14:15	<0.01	0.57^a
Age (Years old)	16.78 ± 5.73	16.41 ± 6.13	0.25	0.81^b
Refractive error (Diopter)	−2.86 ± 2.30	−1.87 ± 2.40	−1.69	0.10^b
Fusion (Prism diopter)	29.56 ± 8.89	27.66 ± 8.19	0.89	0.38^b
Divergence (Prism diopter)	−7.28 ± 1.95	−6.93 ± 3.35	−0.52	0.60^b
Convergence (Prism diopter)	22.28 ± 8.51	20.72 ± 8.04	0.75	0.46^b
Ocular alignment (Prism diopter)	–	−36.38 ± 19.27	–	–
Exotropia control score	–	2(1–4)	–	–

$^a\chi^2$ *test.* ^{b}*t-test.*

Previous studies have proved that stereopsis emerges around 3 months of age and gradually reaches adult levels around 5 years of age in normal visual development (Aslin, 1977; Fox et al., 1980; Birch et al., 1982; Birch et al., 1985; Giaschi et al., 2013). In the current study, all the IXT patients were more than 5 years old, however, negative correlation of age were still found on Tmin/Dmin. The onset age of IXT is usually from one to 4 years old (Clarke et al., 2007; Buck et al., 2009),we speculate that perhaps the intermittent decorrelated binocular inputs delays and prolongs the development of stereopsis. To clarify the specific mechanism, it may be necessary to analyze the onset age, duration and severity of IXT. Since these characteristics of IXT are often vague, so we may need to conduct further research in the future.

Stereopsis and Development

Three-dimensional depth perception relies in part on the binocular fusion of horizontally disparate stimuli presented to the left and right eye, visual disparity is encoded in the cortex. Binocular neurons in V1 of awake monkeys are selective for absolute, not relative, disparity (Cumming and Parker, 1999). Higher visual areas, such as V2, V3, V4, and MT, are more engaged with stereoscopic processing than the primary visual cortex (Skrandies, 2001).

Compared with psychophysical methods, visual evoked potentials (VEP) based on cortical neuron electrophysiological records can more objectively reflect the process of stereo information processing. Based on dynamic random dots stereograms (dRDS), studies show that the stereoscopic VEP activity amplitude of patients with impaired binocular integration decreases significantly (Wesemann et al., 1987; Skrandies, 1995). There is a strong correlation between electrophysiological changes and perceptual impairment measured by psychophysical methods (Skrandies, 2009). In addition, previous studies have also found that binocular VEP summation in stereo deficient adults is much lower than normal adults (Shea et al., 1987).

The visual impairments are often caused by abnormal visual input during the early stages of visual system development (Hadad et al., 2015). Amblyopia is the most common disorder of spatial visual development, which often associated with the presence of strabismus, refractive errors, or form

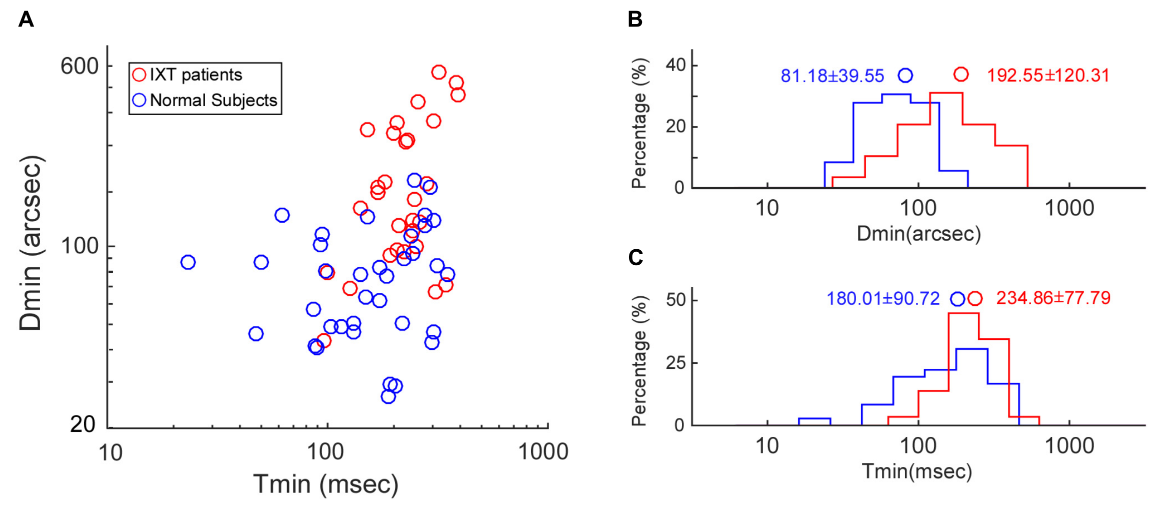

FIGURE 3 | Population data on Dmin and Tmin. **(A)** Scatter plot showing the relationship between Tmin and Dmin in the control subjects (blue dots) and the IXT patients (red dots). **(B)** Histogram showing the distribution of Dmin in the control subjects (blue bars) and the IXT patients (red bars). **(C)** Histogram showing the distribution of Tmin in the control subjects (blue bars) and the IXT patients (red bars). Circles represent the mean values.

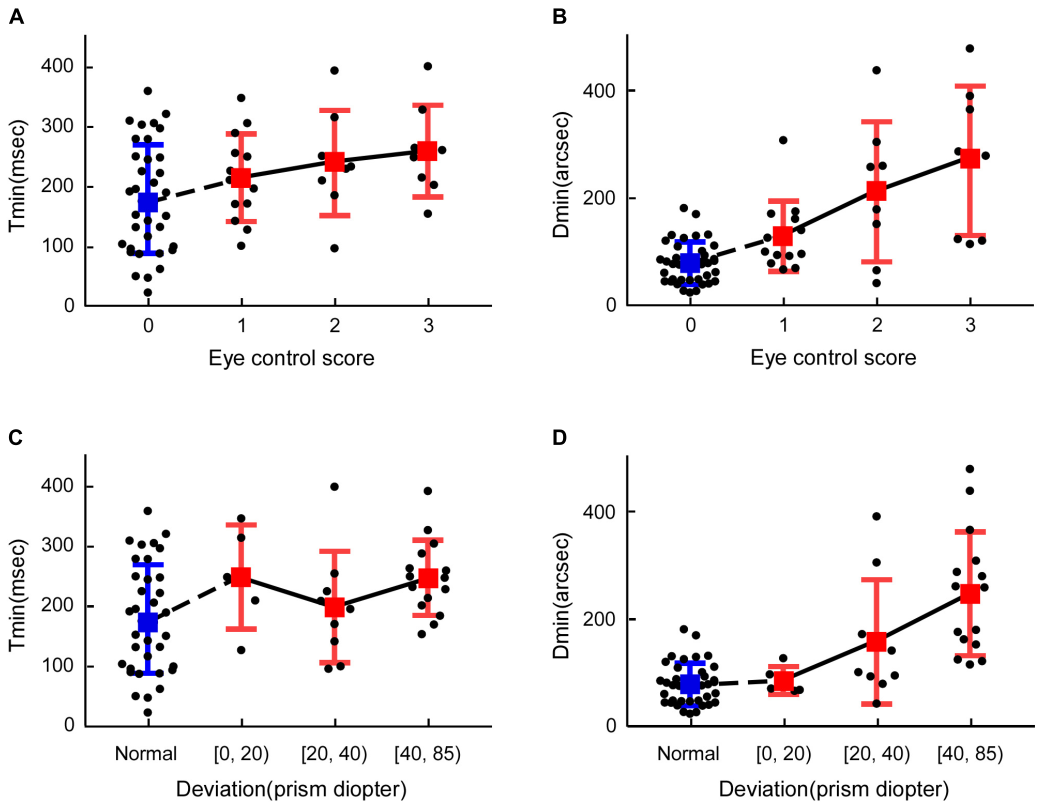

FIGURE 4 | Comparisons between Dmin, Tmin, exotropia control score and ocular deviation. **(A)** Tmin vs. exotropia control score, **(B)** Dmin vs. exotropia control score, **(C)** Tmin vs. ocular alignment, **(D)** Dmin vs. ocular alignment. The blue marker represents the control subjects, and the red marker represents the IXT patients.

deprivation early in life. Amblyopes suffer not only from sensory deficits, but also from deficits not simply explained by low-level considerations, like second-order processing, contour integration, temporal, spatial and/or capacity limits of attention, and motion (Levi et al., 2015). Although IXT patients have normal visual acuity, intermittent abnormal visual input may also cause similar visual impairments, further studies are warranted.

Dmin, Tmin, and Ocular Control

Dmin correlated well with exotropia control score. Worse exotropia control scores indicate that eyes are more frequently misaligned and have shorter periods of exposure to correlated binocular images (Mohney and Holmes, 2006), larger deviations caused large shifts in monocular images during the misaligned phase, creating greater disconcordance between binocular signals, which led to a greater loss of binocular neurons (Smith et al., 1997).

Tmin did not correlate well with ocular control and ocular alignment. At one hand, the imprecise control of vergence position in IXT patients could lead to longer Tmin. When the convergence was carefully controlled, reliable stereoscopic form recognition in random-dot stereograms has been demonstrated for very brief stimulus exposure times (1 ms) (Uttal et al., 1994). Another proof is that, in strabismic amblyopic monkeys, the response latency of V1 neurons dominated by an amblyopic eye is even shorter than that of neurons dominated by a non-amblyopic eye (Bi et al., 2011; Wang et al., 2017). Similarly, the response latency measured with multifocal visually evoked potentials is shorter for an amblyopic eye when compared to a fellow eye. In both studies, the response latencies were measured monocularly with the effect of imprecise control of vergence removed (Greenstein et al., 2008). On the other hand, Tmin is shorter in humans with balanced eyes and significantly longer in subjects with strong ocular dominance (Wu et al., 2018). Therefore, it is not the time need to for information to reach binocular cells, rather the time needed for binocular cells to integrate the signals from two eyes and to extract stereopsis that causes an longer Tmin. It is possible that the variance in ocular dominance in our subjects might have masked the correlation between Tmin and ocular deviation and eye control (Wu et al., 2018). In future studies, we plan to quantify the effect of ocular control, ocular deviation and sensory dominance on IXT patients.

Clinical Applications

Although our study reported significantly longer Tmin values, the relative increment was only 30%. A 50 ms difference would hardly be noticed in clinic, since most clinical stereopsis testing used allow patients sufficient time, usually several seconds, to view printed stimuli. That might explain why so few previous studies addressed the temporal aspect of the stereoacuity test. In the past, most of the training programming have been focusing on how to improve Dmin. It is well established that stereoacuity can be improved after a 3D movie viewing experience (Bridgeman, 2014), and that 3D video game play can improve stereopsis (Li et al., 2018). It is not clear whether temporal integration time is shortened after visual training as those new areas remain unexplored.

With more clinics equipped with electronic visual function test units, precise controlling of the stimulus presentation duration has become practical. It would provide great value to apply both Dmin and Tmin to binocular research. For example, Dmin has long been used as sensitivity index to quantify the ocular control and progression of IXT (Mohney and Holmes, 2006; Hatt et al., 2007; Holmes et al., 2007). The deterioration of stereoacuity usually indicates a necessity for corrective surgery (Uttal et al., 1994). However, stereoacuity repeatability in IXT is quite low, even for measurements taken during the same day (Hatt, 2008). It is not clear if longer Tmin contributes to decreased stability.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Aier Eye Hospital Group. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HW, XL, QX, XZ, LZ, WL, BZ, and ZY conceived and designed the experiments. HW, YT, and QX performed the experiments. HW, XL, YT, QX, XZ, and LZ analyzed the data. XL, WL, BZ, and ZY contributed reagents, materials, and analysis tools. HW, XL, QX, XZ, LZ, BZ, and ZY wrote the manuscript.

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Cortical Neuroplasticity and Cognitive Function in Early-Stage, Mild-Moderate Hearing Loss: Evidence of Neurocognitive Benefit From Hearing Aid Use

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Age-related hearing loss (ARHL) is associated with cognitive decline as well as structural and functional brain changes. However, the mechanisms underlying neurocognitive deficits in ARHL are poorly understood and it is unclear whether clinical treatment with hearing aids may modify neurocognitive outcomes. To address these topics, cortical visual evoked potentials (CVEPs), cognitive function, and speech perception abilities were measured in 28 adults with untreated, mild-moderate ARHL and 13 age-matched normal hearing (NH) controls. The group of adults with ARHL were then fit with bilateral hearing aids and re-evaluated after 6 months of amplification use. At baseline, the ARHL group exhibited more extensive recruitment of auditory, frontal, and pre-frontal cortices during a visual motion processing task, providing evidence of cross-modal re-organization and compensatory cortical neuroplasticity. Further, more extensive cross-modal recruitment of the right auditory cortex was associated with greater degree of hearing loss, poorer speech perception in noise, and worse cognitive function. Following clinical treatment with hearing aids, a reversal in cross-modal re-organization of auditory cortex by vision was observed in the ARHL group, coinciding with gains in speech perception and cognitive performance. Thus, beyond the known benefits of hearing aid use on communication, outcomes from this study provide evidence that clinical intervention with well-fit amplification may promote more typical cortical organization and functioning and provide cognitive benefit.

Keywords: age-related hearing loss (ARHL), cortical visual evoked potentials (CVEPs), visual cross-modal re-organization, hearing aids, speech perception, cognition

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INTRODUCTION

Age-related hearing loss (ARHL), or presbycusis, affects more than 30% of adults over age 50 years and its prevalence roughly doubles with each decade of life, making it the third leading chronic health condition among aging adults (Agrawal et al., 2008). Hearing aids and cochlear implants may restore audibility in ARHL, yet less than 15% of adults who could benefit from hearing aids in the United States use them (Chien and Lin, 2012) and this statistic is even lower (8%) among those adults who could benefit from cochlear implants (Holder et al., 2018). For the small percentage of adults who do seek treatment, treatment is sought out late, typically 7–10 years after initial hearing loss onset (Davis et al., 2007). Access and affordability issues likely complicates the hearing healthcare landscape for aging adults in the United States and there currently exist no best practice guidelines for screening and management of ARHL (Barnett et al., 2017).

Beyond the well-known negative effects of ARHL on communication, quality of life, physical functioning, and psychosocial status, ARHL has also been linked to cognitive decline. For example, large-scale epidemiological studies indicate a strong association between ARHL and risk for mild cognitive impairment and dementia, as well as accelerated decline in cognitive function over time (Lin, 2011; Lin et al., 2011; Thompson et al., 2017; Wei et al., 2017; Zheng et al., 2017; Ford et al., 2018; Loughrey et al., 2018). Though a lack of strong evidence on the long-term protective effects of clinical treatment of hearing loss on cognitive function exists, hearing loss is a potentially modifiable risk factor for cognitive decline (Livingston et al., 2017), warranting further investigation from a public health perspective (President's Council of Advisors on Science and Technology [PCAST], 2015; National Academies of Sciences Engineering and Medicine [NASEM], 2016). One hypothesis explaining the hearing loss-dementia link is that decreased or degraded input to the auditory cortex makes listening more effortful, requiring greater top-down sensory, attentional, and cognitive compensation, which may in turn decrease available resources that can be contributed to other tasks, potentially negatively affecting downstream cognitive function (Pichora-Fuller and Singh, 2006; Schneider et al., 2010; Tun et al., 2012; Pichora-Fuller et al., 2016).

Cross-modal re-organization is a form of cortical compensation observed in deafness and lesser degrees of hearing loss, whereby the auditory cortex is recruited or "re-purposed" by intact visual and somatosensory modalities (Bavelier and Neville, 2002; Strelnikov et al., 2013; Glick and Sharma, 2017). For example, adults with mild-moderate ARHL exhibit more extensive recruitment of auditory cortex during visual motion and face processing tasks relative to NH subjects (Campbell and Sharma, 2014; Stropahl and Debener, 2017). Similarly, vibrotactile stimulation in adults with ARHL elicits more extensive cross-modal neural activity in the auditory cortex (Cardon and Sharma, 2018). Both visual and somatosensory cross-modal re-organization are associated with poorer auditory speech perception outcomes (Campbell and Sharma, 2014; Cardon and Sharma, 2018), but the extent to which these neuroplastic changes influence cognitive outcomes has not been investigated.

In this study, we used high-density electroencephalography (EEG) to record visual evoked potentials (CVEPs) in response to visual stimuli in a group of adults with mild-moderate ARHL and in age-matched normal hearing (NH) controls to assess the relationship between visual cortical neuroplasticity, speech perception and cognitive function. We then fit the group of adults with ARHL with bilateral hearing aids to examine how increased audibility from amplification influenced cortical neuroplasticity, speech perception, and cognitive outcomes.

MATERIALS AND METHODS

Ethics Approval Statement

This study was carried out in accordance with the recommendations of Belmont Report. The protocol was approved by the Institutional Review Board at the University of Colorado Boulder. All subjects provided written informed consent prior to participation in the study in accordance with the Declaration of Helsinki.

Subjects

A total of 41 adults took part in this study (mean age = 64 years, *SD* = 4.68). Subjects were native speakers of English, with no reported neurological impairment and reported normal or corrected-to-normal visual acuity. Thirteen adults comprised the NH control group (mean age = 62.62 years, *SD* = 4.91) and 28 adults comprised the ARHL experimental group (mean age = 65.4 years, *SD* = 4.23). Independent samples t-tests were conducted to confirm that groups did not significantly differ in terms of age [$t(39) = 1.621$, $p = 0.980$] or gender [$t(39) = 0.394$, $p = 0.356$]. It should be noted that it was difficult to recruit subjects in this age-range with normal hearing, likely due to high prevalence of ARHL. None of the ARHL subjects reported hearing aid use prior enrollment in the study.

There was no difference between groups on a variety of known demographic risk factors for hearing loss including smoking [$t(39) = 1.508$, $p = 0.140$], noise exposure [$t(39) = 1.643$, $p = 0.109$], or hypertension [$t(39) = -0.116$, $p = 0.908$]. No subjects reported history of diabetes or clinical depression. The two groups did not differ in terms of education level [$t(39) = -0.975$, $p = 0.335$] or handedness [$t(40) = 1.030$, $p = 0.309$]. As expected with the presence of hearing loss, report of tinnitus was significantly higher in the ARHL group [$t(39) = 4.210$, $p < 0.001$], with 68% ARHL subjects reporting some level of tinnitus. Interestingly, self-report of balance problems was significantly higher in the hearing loss group [$t(39) = 2.030$, $p = 0.049$], with 25% of hearing loss subjects reporting balance disturbances and/or falls in the past year.

Inclusion Criteria

Audiological inclusion criteria for the NH group were defined as pure tone audiometric behavioral thresholds for both ears $\leq$ 25 dB HL from 0.25 to 8.0 kHz, no presence of an air-bone gap ($\geq$15 dB HL at 2 or more adjacent frequencies), and no sign of interaural asymmetry ($\geq$15 dB HL at 2 or more frequencies). Audiological inclusion criteria for the ARHL group was defined as a high frequency pure tone average (HFPTA) (2, 4, 6kHz) > 25 dB HL in both ears, no presence of an air-bone gap ($\geq$15 dB HL at 2 or more adjacent frequencies), and no sign of interaural asymmetry ($\geq$15 dB HL at two or more frequencies). Because pure tone average (PTA) thresholds (0.5, 1, 2 kHz) [$t(39) = -2.44$, $p = 0.81$] and high frequency pure tone average (HFPTA) thresholds (2, 4, 6 kHz) [$t(39) = -1.52$,

p = 0.137] between the right and left ears were not statistically different among subjects, averaged audiometric thresholds across the 2 ears were computed and used for subsequent analyses for each group. Average pure tone air conduction thresholds for each group and corresponding 95% confidence intervals are depicted in **Figure 1**. Average PTA thresholds were 16.5 dB HL poorer in the ARHL group (average = 27.08 dB HL, SD = 10.41) compared to the NH group (average = 10.58 dB HL, SD = 5.23) [$t(39)$ = 5.386, $p < 0.001$]. Average HFPTA thresholds were approximately 33.5 dB HL poorer in the ARHL group (average = 47.44 dB HL, SD = 11.54) compared to the NH group (average = 13.91 dB HL, SD = 3.77) [$t(39)$ = 10.17, $p < 0.001$]. On average, the ARHL group demonstrated a mild sloping to moderate hearing loss and the NH group demonstrated clinically normal hearing thresholds.

Subjects in the ARHL group were required to wear their hearing aids at least 5 h/day for inclusion in 6 months follow-up analyses. Of the 28 ARHL subjects initially enrolled in the study at baseline, a total of 21 subjects (average age = 64.38 years, SD = 4.03) met this criterion. The remaining 7 ARHL subjects were removed from 6 months follow-up analyses due to inability to adjust to hearing aids and/or insufficient hearing aid use (n = 5) (occurring in the first 2 weeks to 3 months after enrollment in the study) or inability to return for 6 months follow-up testing (n = 2).

Hearing Aid Fitting and Verification

Prior to baseline testing, the ARHL group was acutely fit with bilateral receiver-in-the-ear hearing aids from a single manufacturer. The purpose of acute hearing aid fitting was to negate potential confounding effects of audibility on test performance at the baseline evaluation. Hearing aids were programmed in the manufacturer fitting software. Appropriate receiver size (60-power receiver for thresholds < 60 dB HL 0.25–8.0 kHz; 85-power receiver for thresholds ≥ 60 dB HL 0.25–8.0 kHz) and appropriate non-custom acoustic coupling options (open dome, vented, or closed domes) were selected for each ARHL subject based on the degree of hearing loss. Settings for noise reduction, microphone mode, noise management, and binaural broadband controls were set to manufacturer defaults. Acoustic feedback reduction algorithms were not applied due to the potential for these algorithms to affect ideal frequency-gain characteristics and to promote generalizability across manufacturers since these algorithms vary between manufacturers. Instead, if significant feedback was present, modifications to the acoustic coupling (e.g., selecting a more occlusive dome) were made to prevent acoustic feedback.

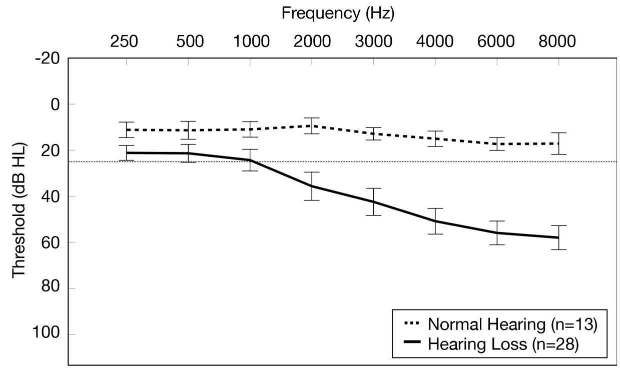


FIGURE 1 | Average pure tone air conduction thresholds for the normal hearing group and age-related hearing loss group. Average pure tone air conduction thresholds across the two ears (0.25–8.0 kHz) are displayed for the normal hearing group (n = 13) (dashed line) and the group with mild-moderate age-related hearing loss (n = 28) (solid line). Frequency (Hz) is displayed on the horizontal axis and pure tone air conduction thresholds in decibels hearing level (dB HL) are displayed on the vertical axis. The dotted line on the y-axis indicates the clinical cutoff for normal hearing thresholds (25 dB HL). The bars display 95% confidence intervals at each threshold for each group.

Probe-microphone measures were performed to verify hearing aid fittings for the ARHL subjects using the Audioscan probe-microphone verification system. Hearing aid gains were adjusted to meet NAL-NL2 prescribed targets between 0.25 and 4.0 kHz for soft (55 dB SPL), medium (65 dB SPL) and loud (75 dB SPL) speech inputs. Maximum Power Output (MPO) was also measured with a swept tone stimulus to approximate uncomfortable loudness levels (UCL). Probe microphone measurements were ± 5 dB of NAL-NL2 targets from 0.25 to 4.0 kHz for all ARHL subjects, indicating adequate audibility. The average difference between actual and prescriptive gain for the 65 dB SPL input was 1.76 above NAL-NL2 targets for the right ear (SD = 2.58) and + 0.96 dB above NAL-NL2 targets for the left ear (SD = 3.16) from 0.25 to 4.0 kHz.

Hearing Aid Follow-Up and Data Logging

The ARHL group returned for routine hearing aid maintenance checks and data logging approximately 2 weeks, 1, 3, and 6 months post-treatment in order to ensure hearing aids were functioning properly and to document average daily hearing aid use using the manufacturer fitting software. At the final 6 months follow-up visit, cumulative usage time over each visit computed for each subject. Only those ARHL subjects who wore their hearing aids for minimum of 5 h/day (n = 21) were included in final 6 months follow-up analyses. Average hearing aid use in these subjects ranged between 5.10 and 14.02 h/day (mean = 9.84 h/day, SD = 2.96).

Cortical Visual Cortical Evoked Potential Testing

Cortical visual evoked potentials (CVEPs) were measured for NH and ARHL subjects in an unaided condition using 128-channel high-density EEG (GSN-Hydrocel 128, Electrical Geodesics, Inc.). CVEPs were recorded using NetStation 5 software (Electrical Geodesics, Inc.) at a sampling rate of 1000 Hz with a band-pass filter set at 0.1–200 Hz. Subjects were seated in an electro-magnetically shielded sound booth and CVEP responses were elicited via a visual motion stimulus (radially modulated grating or star-circle pattern), providing the percept of apparent motion. The visual stimulus was adapted from Doucet et al. (2006) and used in several previous studies in our laboratory (Campbell and Sharma, 2014, 2016; Sharma et al., 2016). Three hundred trials were presented (150 star, 150 circle stimulus presentations) at an inter-stimulus interval of 495 ms and pre-stimulus interval of 100 ms (595 ms recording window). Subjects were instructed to focus on the black dot in the center of the pattern without shifting their gaze. Stimuli were presented via E-Prime 2.0 stimulus presentation software and displayed on a flat screen LCD television at a viewing distance of approximately 42 inches.

Cortical Visual Evoked Potential Waveform Analysis and Current Density Source Reconstruction

CVEP data for each subject were pre-processed offline by applying a high-pass filter (1 Hz). Continuous data were segmented around the stimulus presentation recording window and data were exported from NetStation 5 to Matlab^{TM} (The MathWorks®, Inc.) via EEGLab (Delorme and Makeig, 2004), where baseline correction (to the 100 ms pre-stimulus recording window), bad channel rejection (± 100 μV), bad epoch rejection, re-referencing (to the common average reference), and down sampling (from 1 to 0.25 kHz, to reduce processing time) were performed. Average CVEP responses for each subject were then computed by averaging CVEP responses across several electrodes corresponding to cortical regions of interest (ROIs) on the scalp: Occipital (E71, E76, E70, E75, E83, E74, E82), right temporal (E110, E104, E109, E103, E93, E86, E98, E102, E108), and left temporal (E35, E40, E41, E36, E45, E46, E47, E42, E52) ROIs. ROIs were selected *a priori* based upon previous studies where differences in cortical activation patterns were observed in adults with mild-moderate ARHL using this same stimulus (Campbell and Sharma, 2014) and evidence from previous neuroimaging studies (PET, fMRI, intracranial CVEP recordings) in typical subjects (Dupont et al., 2003; Bertrand et al., 2012; Kellermann et al., 2012) using the same or similar visual motion stimuli. After computing average CVEP responses for each subject across each ROI, peak latencies and amplitudes were extracted for statistical analyses. Peak latency and peak amplitudes were defined at the midpoint of the peak for each CVEP waveform component (P1, N1, P2). Individual waveforms were averaged together to create a grand-averaged waveform for each group (NH and ARHL) at baseline and for the ARHL at 6 months follow-up.

Group cortical source localization analyses were then performed on CVEP data. An independent components analysis (ICA) was applied to pre-processed CVEP data for each subject to identify spatially fixed and temporally independent components underlying each component (P1, N1, P2) in the CVEP response according to the timeframe in which the component occurred (Makeig et al., 1997; Delorme et al., 2012). ICA components accounting for the greatest percent variance for each of the CVEP component were kept, while remaining ICA components were regarded as artifact/noise and discarded. The ICA-pruned CVEP data for individual subjects were then exported from Matlab^{TM} into Curry7^{TM} Neuroimaging Suite (Compumedics Neuroscan^{TM}), where cortical source modeling was performed. Here, grand average ICA-pruned CVEP waveforms for the NH group at baseline and the ARHL group at baseline and 6 months follow-up visits were computed. Current density source reconstruction (CDR) was performed to visualize group and treatment differences in cortical activation patterns. To achieve this, a second ICA was performed on the grand averaged data for each group to identify components with the highest SNR. A head model was then created and standardized using the boundary element method (BEM) (Fuchs et al., 2002). Next, CDRs were computed via standardized low-resolution electromagnetic tomography (sLORETA). sLORETA is a statistical method that estimates current densities with low localization error (Pascual-Marqui, 2002; Grech et al., 2008). The resultants CDRs were projected onto an average adult structural MRI (provided by the Montreal Neurological Institute). CDRs are depicted by a graded color scale (F-statistic) indicating the statistical likelihood of cortical activity in each region. This described protocol has been used in our laboratory to observe changes in visual cross-modal plasticity in adults and children with hearing loss at the single-subject and group level (Campbell and Sharma, 2014, 2016; Sharma et al., 2015, 2016; Cardon and Sharma, 2018).

Speech Perception in Noise Testing

Auditory speech perception in noise was measured in an unaided condition for NH group and ARHL groups at baseline and in an aided condition in the ARHL group at 6 months follow-up visit using the QuickSIN^{TM} test. The QuickSIN^{TM} is a standardized assessment of sentence-level auditory speech perception in background noise (Etymotic Research, 2001; Killion et al., 2004). Two randomly selected recorded lists of 6 sentences (5 key words per sentence) were presented in the context of 4-talker babble noise. Stimuli were presented in a binaural condition via a speaker located at 0° azimuth at a level of 60 dB SPL (conversational speech level). The sentences in each list varied in signal-to-noise ratio (SNR), beginning at 25 dB SNR (easiest) for the first sentence and decreased in 5 dB steps with each subsequent sentence (most difficult). The test is scored in terms of the dB SNR loss, or the dB SNR required for the subject to score 50% of the words correct (threshold), relative to NH adult listeners, with a lower score indicating better auditory speech perception in noise performance and a higher score indicating poorer auditory speech perception in noise performance.

The Arizona Auditory-Visual (AzAv) test was administered for assessment of auditory-visual speech perception in noise (Dorman et al., 2016). The test was administered in an unaided condition at baseline for NH group and in an aided condition at baseline and 6 months follow-up visits for the ARHL group in order to negate potential confounding effects of audibility on test performance. The AzAv was adapted from sentence materials in Macleod and Summerfield (1987, 1990) and developed using methodology of Spahr et al. (2012) in creation of the AzBio, a routinely used auditory-only clinical assessment of speech perception in background noise. The AzAv has been validated in NH and cochlear implanted adults in a series of previous studies reported in Dorman et al. (2016). The test contains 10 lists, with each list comprised of 15 sentences (3 key words per sentence). Sentences spoken by a target talker are presented in the context of multi-talker babble. The test was administered in a binaural condition via a speaker located 0° azimuth, with target sentences presented at a level of 60 dB SPL (conversational speech level). Visual (lip-reading) stimuli were presented on an LCD television at a viewing distance of approximately 42 inches. Several practice lists were first administered in an auditory-only condition, varying the SNR in 2 dB increments (starting at the SNR determined by the QuickSIN^{TM} test) to determine the level at which the subject repeats approximately 40–50% of words correct (to prevent ceiling effects). Next, 2 randomly selected lists were presented in an auditory-only condition and 2 randomly selected lists were presented in an auditory-visual condition. Performance on the AzAv test is scored in terms of visual (lip-reading) benefit, by subtracting average performance (in percent key words correct) in the auditory-only condition from the auditory-visual condition, providing a percent benefit score from the addition of visual (lip-reading) cues.

Cognitive Testing

Cognitive tests were administered in an unaided condition for the NH group and in an aided condition for the ARHL group at baseline and 6 months follow-up visits to negate potential confounding effects of audibility on test performance for the ARHL group. Testing was conducted in a quiet room for all participants to prevent negative effects of noise on test performance for all subjects (Dupuis et al., 2015). The cognitive measures selected probe several cognitive sub-domains: Global cognitive function (Montreal Cognitive Assessment – MoCA) (Nasreddine et al., 2005), executive function (Behavioral Dyscontrol Scale II – BDS-2) (Grigsby and Kaye, 1996), processing speed (Symbol Digits Modalities Test – SDMT) (Smith, 1982), visual working memory (Reading Span Test – RST) (Daneman and Carpenter, 1980; Rönnberg et al., 1989), and auditory working memory (Word Auditory Recognition and Recall Measure) (WARRM) (Smith et al., 2016). The aforementioned sub-domains and associated neuropsychological tools were selected based on theoretical predictions about which sub-domains would be most affected by ARHL and previous investigations where impairments were observed in ARHL subjects (Lin, 2011; Lin et al., 2011, 2013; Loughrey et al., 2018). Test-retest reliability over repeated testing of each cognitive measure is described in the Discussion section.

Subjective Hearing Aid Outcome Measures

To validate hearing aid outcomes in the ARHL group at the 6 months follow-up visit, the Client Oriented Scale of Improvement (COSI) (Dillon et al., 1997), the International Outcome Inventory for Hearing Aids (IOI-HA) (Cox et al., 2002, 2003), and the Satisfaction with Amplification in Daily Living (SADL) scales (Cox et al., 2003) were administered. These questionnaires are routinely used in the clinical setting and provide valuable information regarding self-perceived benefit and satisfaction with hearing aids. The COSI measure asks hearing loss subjects to identify and rank in order up to 5 specific listening situations where they hope to see improvements with hearing aids before hearing aid fitting. Subjects then rate the degree of change in hearing ability on 5-point scale (1 = worse, 2 = no difference, 3 = slightly better, 4 = better, and 5 = much better) and their final hearing ability on a 5-point scale (1 = hardly ever, 2 = occasionally, 3 = half the time, 4 = most of the time, and 5 = almost always) in each of these self-identified listening situation after hearing aid fitting. An averaged degree of change score and final ability score is computed across these listening situations (Dillon et al., 1999). While the COSI is not a standardized measure, it probes situations perceived to be most important to each individual. The IOI-HA is a standardized 7-item survey that targets several different outcome domains: Daily use, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life. ARHL subjects were asked to provide a rating for each item on a 5-point scale (1 = severe, 2 = moderately-severe, 3 = moderate, 4 = mild, 5 = none), where a lower score indicates poorer outcome and a higher score indicates higher outcome for each item (Cox and Alexander, 2002; Cox et al., 2002, 2003; Kramer et al., 2002; Noble, 2002; Stephens, 2002). The SADL is a standardized 15-item survey targeting elements most important to patient satisfaction. Subjects are asked to indicate the relative importance each item on a 7-point scale. The questionnaire was administered at the 6 months post-treatment assessment visit. The questionnaire yields a global satisfaction score as several sub-scores across the following domains: Positive effects, service, negative features, and personal image (Cox and Alexander, 1999, 2001). An average score was calculated for each sub-score category by summing ratings for each item in that category and dividing by the total number of items in that category. A global score was also computed by averaging ratings across all items and dividing by the total number of items.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 25. Histograms, Q-Q plots, and significance tests (Shapiro–Wilk test, Levene test) were first computed to assess potential violation in assumptions of normality and homogeneity of variance for all variables. Visual inspection and outlier analyses were also performed.

Two-tailed independent sample *t*-tests were used to assess differences in the cortical, speech perception, and cognitive outcome variables between NH group and ARHL group at baseline. A series of two-tailed, paired samples sample *t*-tests were applied to assess pre-post treatment effects with hearing aids on cortical, speech perception, and cognitive variables in the ARHL group at the 6 months follow-up visit. Because multiple comparisons were made to assess CVEP (P1, N1, P2) latencies across the different 3 ROIs, a Bonferroni correction was applied (alpha error divided by number of tests) to reduce chance of Type I error, reducing the alpha level from $\alpha = 0.05$ to $\alpha = 0.017$. The same correction was applied for assessing CVEP (P1, N1, P2) amplitudes across the 3 ROIs.

To assess the association between CVEP latencies, speech perception, cognitive performance, and degree of hearing loss within the group of adults with ARHL at baseline and at 6 months follow-up, Pearson's correlation coefficients were computed. Because comparisons were made between the 3 different CVEP components and cognitive outcome measures, a Bonferroni correction was applied during these analyses to reduce chance of Type I error, reducing the alpha level from $\alpha = 0.05$ to $\alpha = 0.017$.

RESULTS

Group Differences in Cortical Visual Evoked Potential Latencies and Amplitudes at Baseline

Plots of the grand average CVEP waveforms for the NH and ARHL groups across the occipital, right temporal, and left temporal ROIs are depicted in **Figure 2**. CVEP responses in the NH and ARHL groups are marked by the presence of all 3 obligatory P1, N1, and P3 CVEP components. Morphological patterns are similar to the findings reported in Campbell and Sharma (2014) using the same stimulus in a smaller group subjects with NH and mild-moderate ARHL. Independent samples *t*-tests indicated no significant differences in P1, N1, or P2 peak latencies or amplitudes between the NH and ARHL in the occipital or left temporal ROI. However, significant differences in P1, N1 and P2 peak latencies were observed in the right temporal ROI ($\alpha < 0.0055$ level). Relative to the NH group, the ARHL group exhibited significantly earlier P1 [$t(39) = -4.65$, $p < 0.001$], N1 [$t(39) = -5.36$, $p < 0.001$], and P2 CVEP latencies [$t(39) = -3.42$, $p = 0.001$] in the right temporal ROI (**Table 1**). Large effect sizes (Cohen's *d*-values) were observed for the P1 ($d = 1.66$), N1 ($d = 1.82$), and P2 ($d = 1.21$) components.

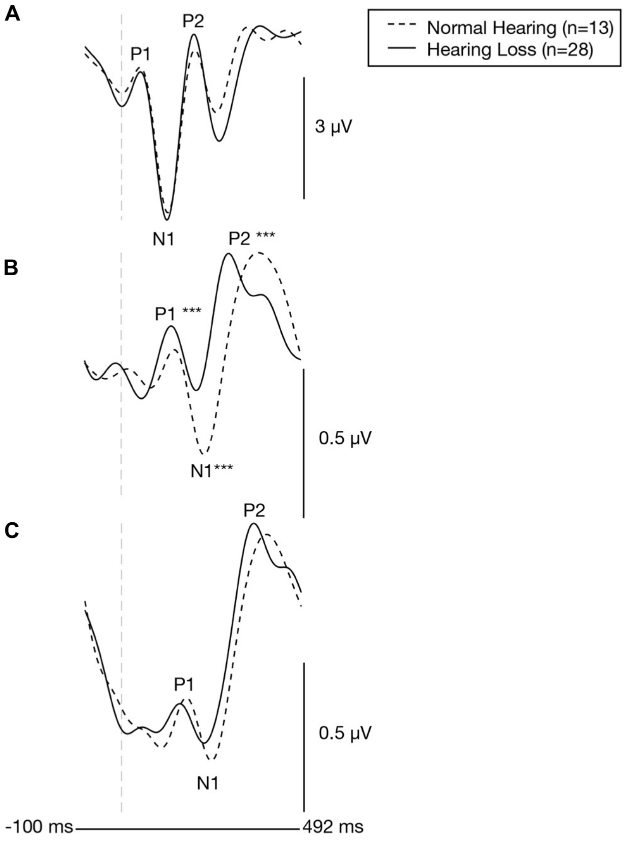


FIGURE 2 | Baseline group differences in cortical visual evoked potentials across an occipital, right temporal, and left temporal region of interest. Grand-averaged CVEP waveforms for the normal hearing group ($n = 13$) and the age-matched group of adults with early-stage, age-related hearing loss ($n = 28$) are depicted for the occipital region of interest **(A)**, the right temporal region of interest **(B)**, and left temporal region of interest **(C)**. Time (milliseconds) is displayed on the horizontal axis and amplitude (µV) is displayed on the vertical axis. Asterisks show level of significance (***$p \leq 0.001$) for differences in CVEP latencies between the two groups. The hearing loss group showed significantly earlier CVEP P1, N1, and P2 latencies over the right temporal region compared to the normal hearing group.

Group Differences in Cortical Visual Evoked Potential Current Density Source Reconstruction Patterns at Baseline

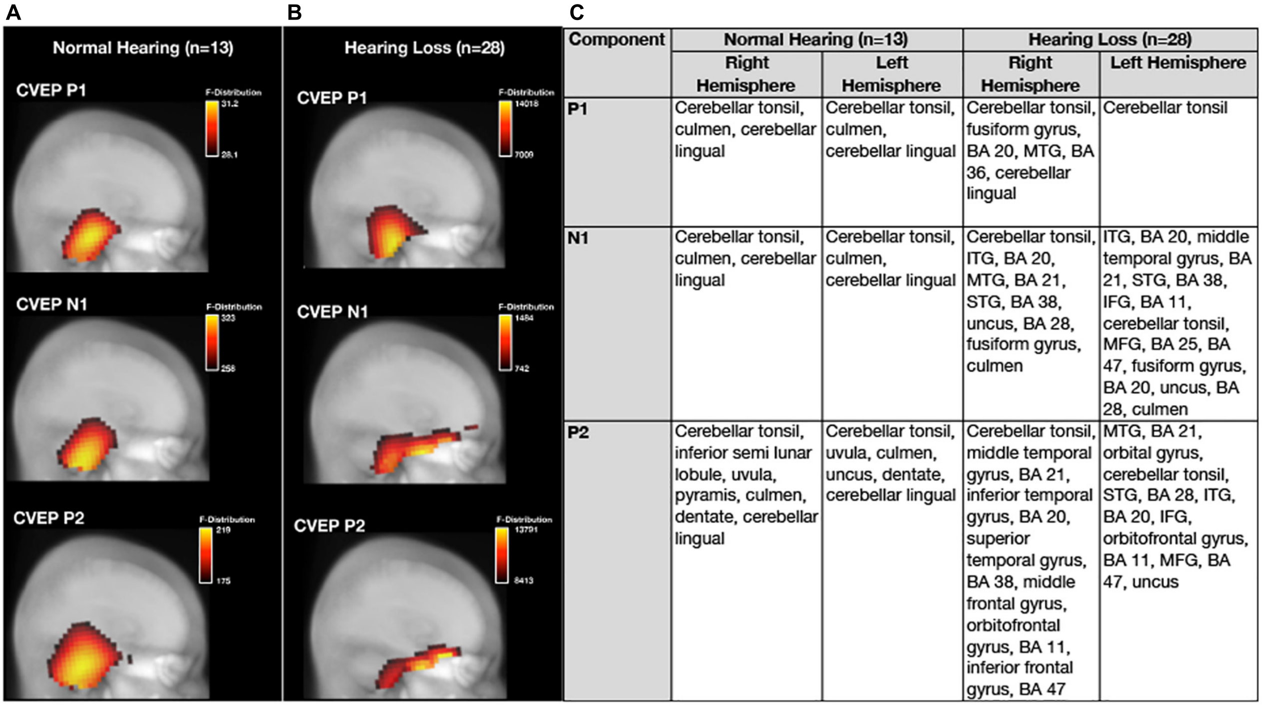
Average baseline CDRs for the NH and untreated ARHL groups are depicted for each CVEP component (P1, N1, and P2) in **Figure 3**. 3D CDRs are displayed on a Maximum Intensity Projection (MIP) (a 2D depth-buffered MRI), providing visualization of the voxels with the highest likelihood of activation. The gradient color scale to the right of each figure indicates the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density computed via sLORETA. **Table 1** lists the cortical regions of activity for each component in the CVEP response in order of highest to lowest likelihood of activation.

As can be observed in **Figure 3**, the visual motion stimulus elicited activity in bilateral occipital and cerebellar cortical regions for all CVEP components in the NH group. These cortical sources are similar to those reported in fMRI and PET studies using similar visual motion stimuli to ours (Dupont et al., 2003; Kellermann et al., 2012) and a previous intracranial CVEP study using the same visual motion stimulus as ours (Bertrand et al., 2012). In the ARHL group, the visual motion stimulus elicited activation over bilateral occipital and cerebellar regions for the P1 CVEP component. For the N1 and P2 component, occipital and cerebellar cortical activation was observed in addition to activation of regions of the auditory cortex (e.g., superior, middle, and inferior temporal gyrus), evidence of visual cross-modal re-organization in the mild-moderate ARHL group. Evidence of cross-modal re-organization as evidenced by activation of regions of auditory cortex to the same visual motion stimulus has been previously reported by Campbell and Sharma (2014) in a group of adults with mild-moderate hearing loss. Further, in addition to evidence of cross-modal recruitment of auditory cortex in the ARHL group at baseline, the ARHL group also exhibited pre-frontal and frontal cortex (orbital gyrus, inferior frontal gyrus, and middle frontal gyrus, predominately in the left hemisphere) activity for the later N1 and P2 CVEP components at the baseline evaluation.

TABLE 1 | Baseline cortical visual evoked potential latencies over a right temporal region of interest.

Component	Average latency (ms)		Standard deviation		95% confidence interval		Statistic *t*(39) (*p*-value)	Effect size (Cohen's d)
	NH	**ARHL**	**NH**	**ARHL**	**NH**	**ARHL**		
P1	128	99	15.62	19.1	118–137	92–106	−4.65, (< 0.001)	1.66
N1	175	134	20.38	24.42	163–187	124–143	−5.36, (< 0.001)	1.82
P2	242	203	24.62	38.42	228–258	188–218	−3.42, (0.001)	1.21

Average peak latencies, standard deviations, 95% confidence intervals, statistical significance values, and effect size are provided for the age-related hearing loss (HL) (n = 28) group and the normal hearing (NH) group (n = 13) in a right temporal region of interest. Significantly earlier P1, N1, and P2 latencies are observed in the HL group.



Component	Normal Hearing (n=13)		Hearing Loss (n=28)	
	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere
P1	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, fusiform gyrus, BA 20, MTG, BA 36, cerebellar lingual	Cerebellar tonsil
N1	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, ITG, BA 20, MTG, BA 21, STG, BA 38, uncus, BA 28, fusiform gyrus, culmen	ITG, BA 20, middle temporal gyrus, BA 21, STG, BA 38, IFG, BA 11, cerebellar tonsil, MFG, BA 25, BA 47, fusiform gyrus, BA 20, uncus, BA 28, culmen
P2	Cerebellar tonsil, inferior semi lunar lobule, uvula, pyramis, culmen, dentate, cerebellar lingual	Cerebellar tonsil, uvula, culmen, uncus, dentate, cerebellar lingual	Cerebellar tonsil, middle temporal gyrus, BA 21, inferior temporal gyrus, BA 20, superior temporal gyrus, BA 38, middle frontal gyrus, orbitofrontal gyrus, BA 11, inferior frontal gyrus, BA 47	MTG, BA 21, orbital gyrus, cerebellar tonsil, STG, BA 28, ITG, BA 20, IFG, orbitofrontal gyrus, BA 11, MFG, BA 47, uncus

FIGURE 3 | Baseline group differences in cortical source activation patterns elicited by visual motion stimuli. Baseline Current density source reconstructions (CDR) for the P1, N1, and P2 cortical visual evoked potential components for the normal hearing group (*n* = 13) are depicted in **(A)** and CDRs for the hearing loss group (*n* = 28) are depicted in **(B)**. 3D current density source reconstructions obtained via standardized low-resolution brain electromagnetic tomography (sLORETA) are projected on a 2D depth-buffered structural magnetic resonance image (Maximum Intensity Projection), providing visualization of the voxels with the highest likelihood of activation. The color scale to the right of each figure shows the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density. **(C)** Describes regions of cortical source activity for each CVEP component, including Brodmann areas (BA), for the normal hearing and age-related hearing loss group by rank in order highest to lowest likelihood of activation (F-statistic).

Group Differences in Speech Perception in Noise at Baseline

Average baseline auditory speech perception scores and corresponding 95% confidence intervals for the NH and ARHL groups are depicted in **Figure 4A**. QuickSIN^{TM} scores were significantly poorer in the hearing loss group compared to the NH group at baseline [$t(39) = 3.703$, $p = 0.001$]. Scores indicated a mild deficit in background noise (3–7 dB SNR) in the ARHL group (average = 5.89 dB SNR loss, *SD* = 4.55) and normal performance (0–3 dB SNR) in the NH group (average = 0.92 dB SNR loss, *SD* = 2.31) (Killion et al., 2004). Average speech perception in noise scores on this test in the hearing loss group are comparable to results in adults with similar degree of sensorineural hearing loss reported in previous studies (Killion et al., 2004; Wilson et al., 2007) and are consistent with the mild-moderate range of hearing loss in our ARHL study sample.

Average baseline visual (lip-reading) benefit scores on the auditory-visual speech perception in noise scores for the NH and ARHL groups are shown in **Figure 4B**. Average benefit from visual cues on the AzAv test across the NH and ARHL groups was 37.21% (*SD* = 10.24) and there was no significant difference in performance between the NH and ARHL groups [$t(39) = 0.517$, $p = 0.608$], indicating that adults with early-stage (mild-moderate) hearing loss do not derive greater relative benefit from visual (lip-reading) cues compared to age-matched NH control subjects. This finding is comparable to previously

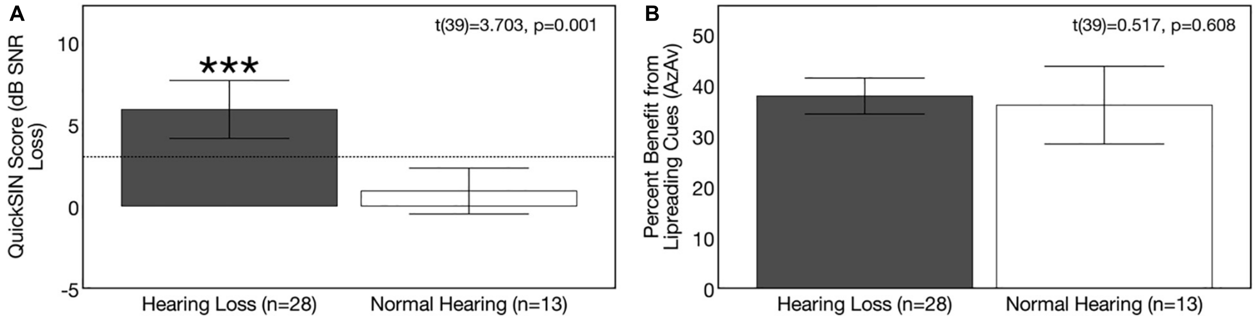


FIGURE 4 | Baseline group differences in speech perception in noise. Average scores on speech perception measures in the age-related hearing loss group (*n* = 28) are depicted in gray and average scores for the normal hearing group (*n* = 13) are depicted in white. Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (***$p \leq 0.05$). **(A)** Depicts average binaural auditory speech perception in noise scores (QuickSIN^{TM}). Scores are plotted in terms of the dB signal-to-noise ratio loss (dB SNR), representing the dB SNR required for the participant to score 50% of words in a sentence correct relative to normal hearing listeners. A higher score indicates poorer auditory speech perception in noise performance. The dotted line indicates the cutoff score (3 dB SNR) for normal function in background noise. The hearing loss group performed significantly poorer on the QuickSIN^{TM} test. **(B)** Depicts average benefit from visual (lipreading) cues on a binaural auditory-visual speech perception in noise test (AzAv). Scores indicate the percent difference score in an auditory-only condition relative to an auditory-visual condition, where a higher score indicates greater benefit from the addition of visual (lip-reading) cues. No significant difference was observed between groups in terms of lip-reading benefit.

reported visual benefit using the same AzAv test materials in cochlear implant recipients, where average benefit from visual cues was 32–44% (Dorman et al., 2016) in studies of older adult listeners using similar auditory-visual speech perception measures (Cienkowski and Carney, 2002; Sommers et al., 2005). The relative benefit from visual (lip-reading) cues described in our study is also comparable to benefit described in younger adult populations under acoustically degraded listening situations (Sumby and Pollack, 1954; Grant and Seitz, 2000; Schwartz et al., 2004; Ross et al., 2007).

Group Differences in Cognitive Function at Baseline

Average results on cognitive measures and corresponding 95% confidence intervals are depicted in **Figures 5A–E**. At baseline, the ARHL group performed significantly poorer than the NH group across all cognitive sub-domains: Global cognitive function, executive function, processing speed, visual working memory, and auditory working memory. Average global cognitive score (MoCA) was 1.69 points lower in the ARHL group (mean score = 24.93, SD = 2.80) compared to the NH group (mean score = 26.62, SD = 1.193) and this difference was statistically significant [$t(39) = -2.074$, $p = 0.045$]. Executive function scores (BDS-2) were 3.06 points lower in the ARHL group (mean score = 20.79, SD = 2.80) compared to the NH group, and this difference was also statistically significant [$t(39) = -3.087$, $p = 0.004$]. The ARHL group (mean score = 43.96, SD = 7.42) performed 7.81 points poorer on the processing speed measure (SDMT) compared to the NH group at baseline, and this difference was significantly significant (average score = 51.77, SD = 6.06) [$t(39) = -3.310$, $p = 0.002$]. Percent recall scores on the visual working memory task (RST) were 6.92% poorer in the hearing loss group (average recall score = 39.61%, SD = 10.81) compared to the NH group (average recall score = 46.53%, SD = 7.25) [$t(39) = -2.091$, $p = 0.043$]. Percent recall scores on the auditory working memory task (WARRM) were 11.39% poorer in the ARHL group (average recall score = 71.52%, SD = 13.36) compared to the NH group (average recall score = 82.01%, SD = 5.69) [$t(39) = -2.937$, $p = 0.006$, $\alpha < 0.01$]. Together, these results suggest a negative impact on cognitive function even in mild hearing loss.

Correlation Between Cortical Visual Evoked Potential Latencies and Behavioral Measures in Untreated, Age-Related Hearing Loss at Baseline

To evaluate the association between visual cortical cross-modal re-organization and behavioral outcomes, we correlated baseline CVEP latencies in ARHL group over the right temporal ROI to auditory performance (degree of hearing loss and auditory speech perception in noise), functional dependence on visual cues, and cognitive function.

Correlations between P1 CVEP and degree of hearing loss for the ARHL group are depicted in **Figure 6A**. A significant negative correlation was observed between HFPTA and P1 ($r = -0.672$, $p < 0.001$), N1 ($r = -0.741$, $p < 0.001$), and P2 ($r = -0.572$, $p < 0.001$) CVEP latencies in the right temporal ROI in the ARHL group at baseline, suggesting that more extensive cross-modal re-organization is apparent in greater degrees of hearing loss. This result is consistent with findings from Stropahl and Debener (2017) where degree of hearing loss and strength of visual cross-modal re-organization in the auditory cortex to visual stimuli were significantly associated in a group of adults with mild-moderate ARHL.

Correlations between CVEP P1 latency and auditory speech perception is shown in **Figure 6B**. A significant negative correlation was observed between auditory speech perception in noise on the and right temporal ROI CVEP peak latencies for the P1 ($r = -743$, $p < 0.001$), N1 ($r = -0.643$, $p < 0.001$),

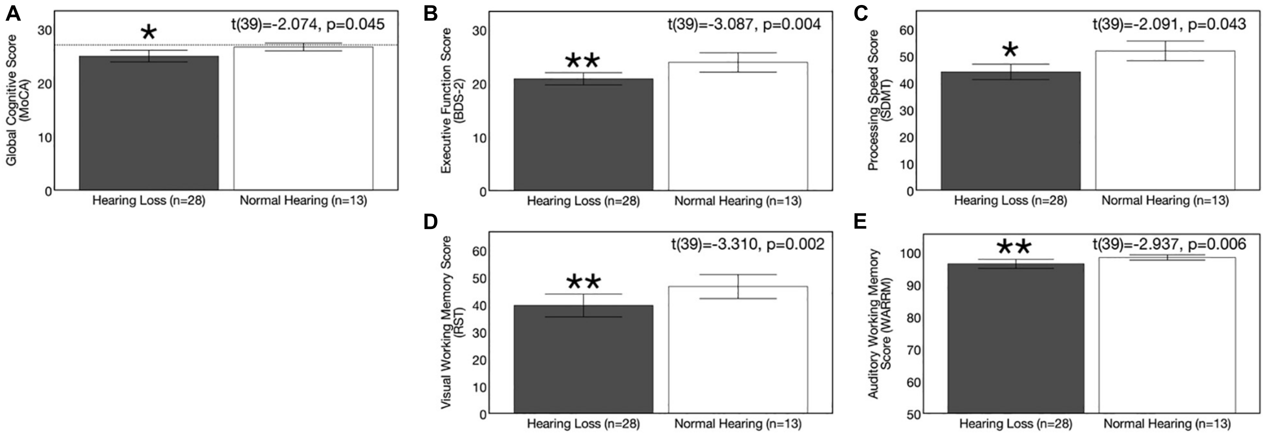


FIGURE 5 | Baseline group differences in cognitive function. Average scores on cognitive measures in the age-related hearing loss group (n = 28) are depicted in gray and average scores for the normal hearing group (n = 13) are depicted in white. Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (**$p \leq 0.01$, *$p \leq 0.05$). **(A)** Depicts average global cognitive function on a screening measure (MoCA) for mild cognitive impairment. Higher scores in indicate higher global cognitive function, out of a total score of 30 points. The dotted reference line on the y-axis indicates the cutoff score ($\leq$ 27) indicating risk for mild cognitive impairment. **(B)** Shows average executive function score (BDS-2). Higher scores in indicate better executive functioning, out of a total score of 27 points. **(C)** Depicts average processing speed score (SDMT). Higher scores in indicate faster processing speeds in a timed, 90 s digit-symbol matching task. **(D)** Shows average visual working memory score (RST) in percent words correctly recalled. Higher scores indicate higher visual working memory performance in a dual-task paradigm. **(E)** Displays average auditory working memory score (WARRM) in percent words correctly recalled. Higher scores indicate higher auditory working memory performance in a dual-task paradigm. The hearing loss group performed more poorly than the normal hearing group across all cognitive outcome measures assessed. Note: Cognitive testing in the hearing loss group was administered in an acutely aided condition to negate confounding effects of audibility on cognitive performance.

and P2 ($r = -0.532$, $p < 0.001$) in the untreated ARHL group. This finding suggests that earlier CVEP latencies, considered an index of more extensive visual cross-modal re-organization of auditory cortex, are associated with poorer auditory speech perception performance. This finding is consistent with previous studies in deaf adults (Doucet et al., 2006; Buckley and Tobey, 2011; Sandmann et al., 2012; Strelnikov et al., 2013; Chen et al., 2016) deaf children (Lee et al., 2001; Campbell and Sharma, 2016), and adults with mild-moderate hearing loss (Campbell and Sharma, 2014).

No significant was observed between CVEP latencies and dependence on visual (facial) cues in the ARHL group at baseline for any of the CVEP components [P1 (r = 0.070, p = 0.724), N1 ($r = -0.123$, p = 0.532), P2 ($r = -0.41$, p = 0.837)]. While a significant association between visual cross-modal neuroplasticity and benefit from visual cues has been reported in deaf adults (Stropahl et al., 2015; Stropahl and Debener, 2017), our results do not show this same tendency in mild-moderate hearing loss. Based on this finding, it possible that visual cross-modal recruitment of auditory cortex may be related to auditory deprivation itself, rather than enhanced auditory-visual integration, at least in the early stages of hearing loss. This finding is consistent with Stropahl and Debener (2017), where visual (lip-reading) benefit for auditory-visual speech perception was not correlated with strength (amplitude) of visual evoked potential responses to facial stimuli in adults with mild-moderate sensorineural hearing loss.

Correlations between right temporal P1 CVEP latency and performance on the global cognitive function (MoCA), executive function (BDS-2), processing speed (SDMT) and auditory working memory (WARRM) tasks are shown in **Figures 7A–D**, respectively. Earlier P1 CVEP latency, considered an index of cross-modal re-organization, was associated with poorer global cognitive function (r = 0.391, p = 0.011) (**Figure 7A**), executive function (r = 0.391, p = 0.010) (**Figure 7B**), processing speed (r = 0.397, p = 0.010) (**Figure 7C**), and auditory working memory (r = 0.379, p = 0.015) (**Figure 7D**). There was no association between P1 CVEP latency and performance on the visual working memory (RST). The P1 CVEP component is heavily modulated by attention (Hackley et al., 1990; Luck et al., 1990; Gazzaley et al., 2008; Zanto et al., 2010). Thus, it is possible that the correlation between these variables may reflect alterations in top-down modulation of attention. If auditory deprivation induces compensatory changes in visual attention, this may reduce available cortical resources available for other downstream cognitive tasks (Broadbent, 1954; Norman and Bobrow, 1975; Lavie and Tsal, 1994; Lavie, 1995; Rees et al., 1997; Lavie and de Fockert, 2003, 2005; Lavie et al., 2004). While not directly addressed in this study, the unexpected activation of frontal and pre-frontal cortex to visual motion stimuli in the untreated ARHL group (**Figure 2**) may similarly reflect a shift in attentional and/or cognitive resources for cortical sensory processing in mild-moderate ARHL.

Effects of Hearing Aid Use on Cortical Visual Evoked Potential Latencies and Amplitudes

Plots of the grand average CVEP waveforms for the ARHL group (n = 21) at baseline and at 6 months post-treatment

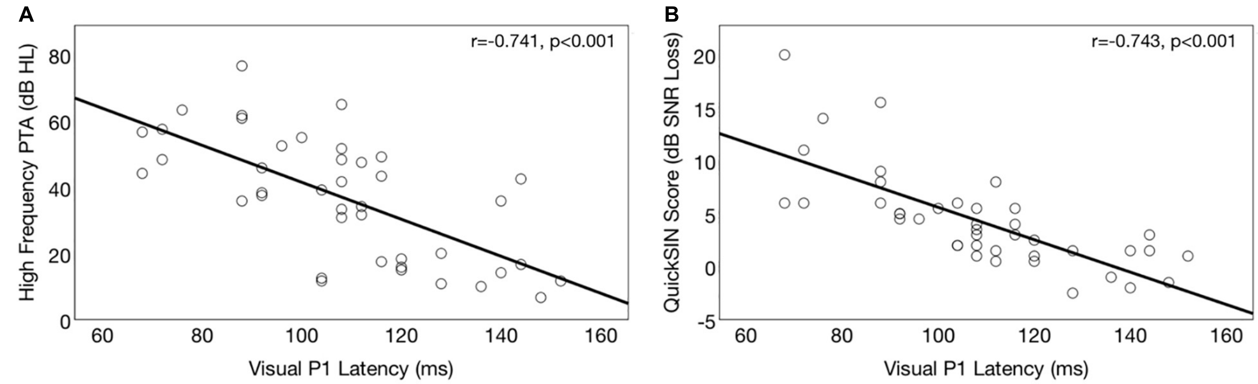


FIGURE 6 | Association between baseline cortical visual evoked potential latencies (CVEP) and auditory function in the hearing loss group. **(A)** Depicts correlations between right temporal CVEP P1 peak latency (in milliseconds) and high frequency pure tone average (averaged across the right and left ear) in the ARHL group. A higher pure tone average (measured in dB hearing level, or dB HL) indicates more severe hearing loss. Earlier CVEP latency, considered an index of visual cross-modal re-organization, is associated with more extensive auditory deprivation in the high frequencies. **(B)** Depicts correlations between right temporal CVEP P1 peak latency (in milliseconds) and binaural auditory speech perception in noise (QuickSIN^{TM}) performance for the ARHL group at baseline. A higher QuickSIN^{TM} score indicates poorer performance in background noise. Earlier CVEP latency, considered an index of visual cross-modal re-organization, is associated with poorer auditory performance in background noise.

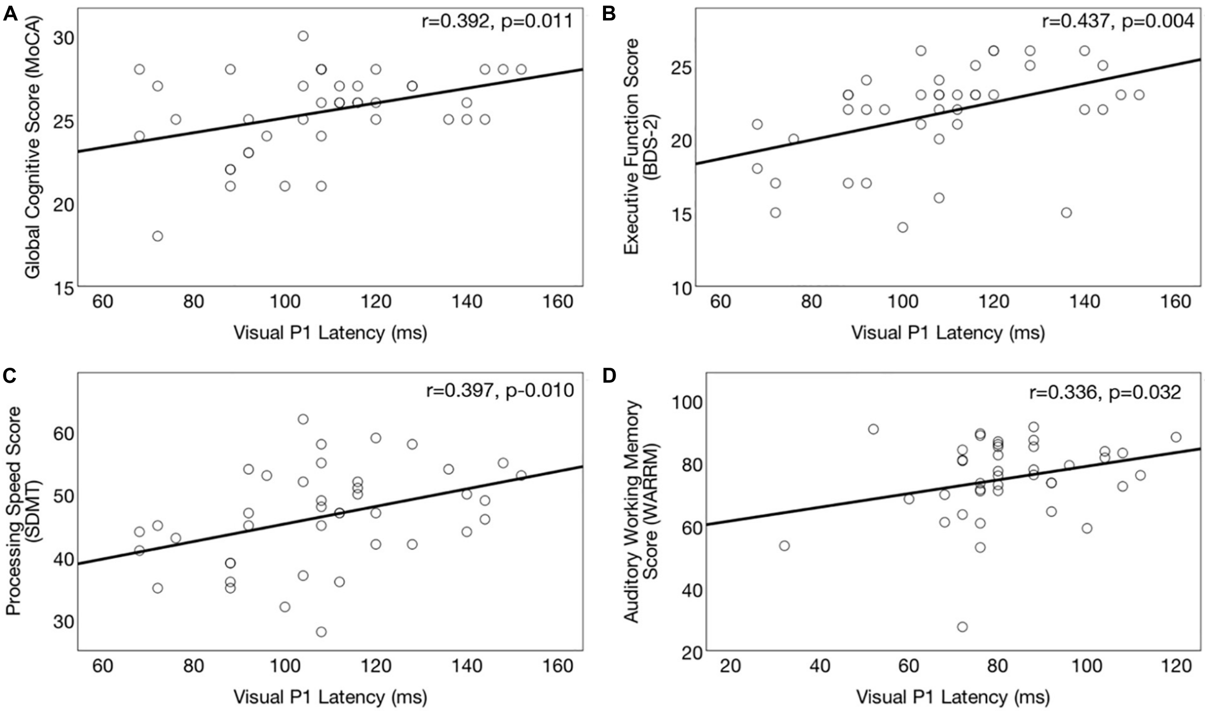


FIGURE 7 | Association between cortical visual evoked potential latencies and cognitive function in the hearing loss group. Significant correlations ($p \leq 0.017$) between right temporal P1 CVEP peak latency (in milliseconds) and cognitive performance across the domains of global cognitive function on the (Montreal Cognitive Assessment) **(A)**, executive function (Behavioral Dyscontrol Scale) **(B)**, processing speed score (Symbol Digits Modalities Test) **(C)**, and auditory working memory (Word Auditory Recognition and Recall Measure) **(D)**. Higher scores on the cognitive measures indicate better cognitive performance. Earlier CVEP latencies, considered an index of visual cross-modal re-organization, are associated with poorer cognitive functioning.

follow-up are depicted for the occipital, right temporal, and left temporal ROIs in **Figure 8**. **Table 2** lists the cortical regions of activity for each component in the CVEP response in order of highest to lowest likelihood of activation for the ARHL group pre-treatment and post-treatment. Paired samples *t*-tests indicated no significant treatment effect hearing aid use on P1, N1, or P2 peak latencies or amplitudes over the occipital or left temporal ROIs ($p > 0.05$). However, significant pre-post

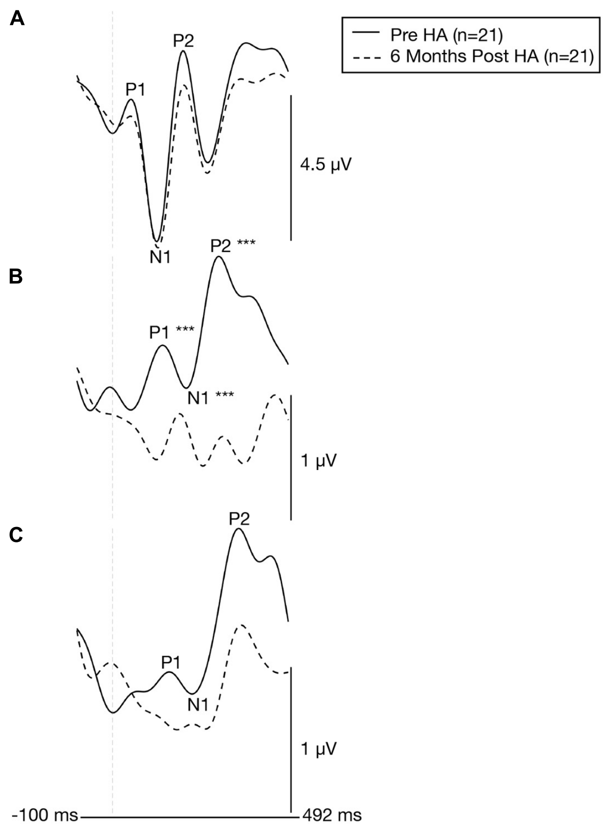


FIGURE 8 | Cortical visual evoked potentials across the occipital, right temporal, and left temporal regions of interest before and 6 months after intervention with hearing aids. Grand-averaged CVEP waveforms for a group of adults with early-stage, age-related hearing loss (n = 21) are depicted for the occipital **(A)**, right temporal **(B)**, and left temporal **(C)** regions of interest before (solid black line) and 6 months after hearing aid use (dashed black line). Time (milliseconds) is displayed on the horizontal axis and amplitude (μV) is displayed on the vertical axis. Asterisks indicate level of significance (***$p \leq 0.001$). The hearing loss group exhibits a significant late ward shift in CVEP P1, N1, and P2 latencies over the right temporal following treatment with hearing aids.

treatment differences in CVEP P1, N1, and P2 latencies were observed in the right temporal ROI. Specifically, the ARHL group exhibited a significant late-ward shift in post-treatment P1 [$t(20) = 4.148$, $p < 0.001$], N1 [$t(20) = 5.193$, $p < 0.001$], and P2 [$t(20) = 4.300$, $p < 0.001$] CVEP peak latencies with moderate to high effect sizes (Cohen's d-values) [P1: $d = 0.78$, N1: $d = 1.21$, P2: $d = 0.82$]. While average post-treatment amplitudes appear visually reduced, this difference was not statistically significant P1 [$t(20) = -0.784$, $p = 0.442$], N1 [$t(20) = -0.476$, $p = 0.639$], P2 [$t(20) = -0.460$, $p = 0.650$]. To our knowledge, no prior studies have evaluated clinical treatment with hearing aids on visual cross-modal plasticity in ARHL. *Post hoc* group comparisons between the NH group evaluated at baseline (n = 13) and the 6 months post-treatment outcomes in the ARHL group (n = 21) indicate no statistical difference in P1 [$t(32) = 1.339$, $p = 0.190$], N1 [$t(32) = 1.010$, $p = 0.320$], or P2 [$t(32) = 0.814$, $p = 0.422$] CVEP latencies over the right temporal ROI, suggesting that restored audibility from hearing aid use may promote more typical cortical visual processing patterns.

Effects of Hearing Aid Use on Cortical Visual Evoked Potential Current Density Source Reconstruction Patterns

Pre-treatment and 6 months post-treatment CVEP CDRs for the ARHL group are displayed in **Figure 9**. Please note that since stability of cortical sources localization (and SNR) increases with larger subject numbers, all ARHL subjects who were assessed at baseline (n = 28) were compared to the group of ARHL adults who met minimum hearing aid usage criterion 6 months post-treatment with hearing aids (n = 21). While the ARHL exhibited occipital, temporal (e.g., superior, middle, and inferior temporal gyrus), and frontal and pre-frontal cortical activity [e.g., orbitofrontal gyrus, Brodmann area (BA) 11] for the higher-order N1 and P2 CVEP components pre-treatment, there was a post-treatment reduction in auditory cortex recruitment for these components post-treatment, suggestive of a reversal in visual cross-modal re-organization by vision. In addition, post-treatment results indicate a reduction in frontal and pre-frontal cortex activation compared to baseline. Post-treatment CDR results in the hearing loss group are comparable those results observed in the NH group at baseline evaluation (**Figure 3A**).

Effects of Hearing Aid Use on Speech Perception in Noise

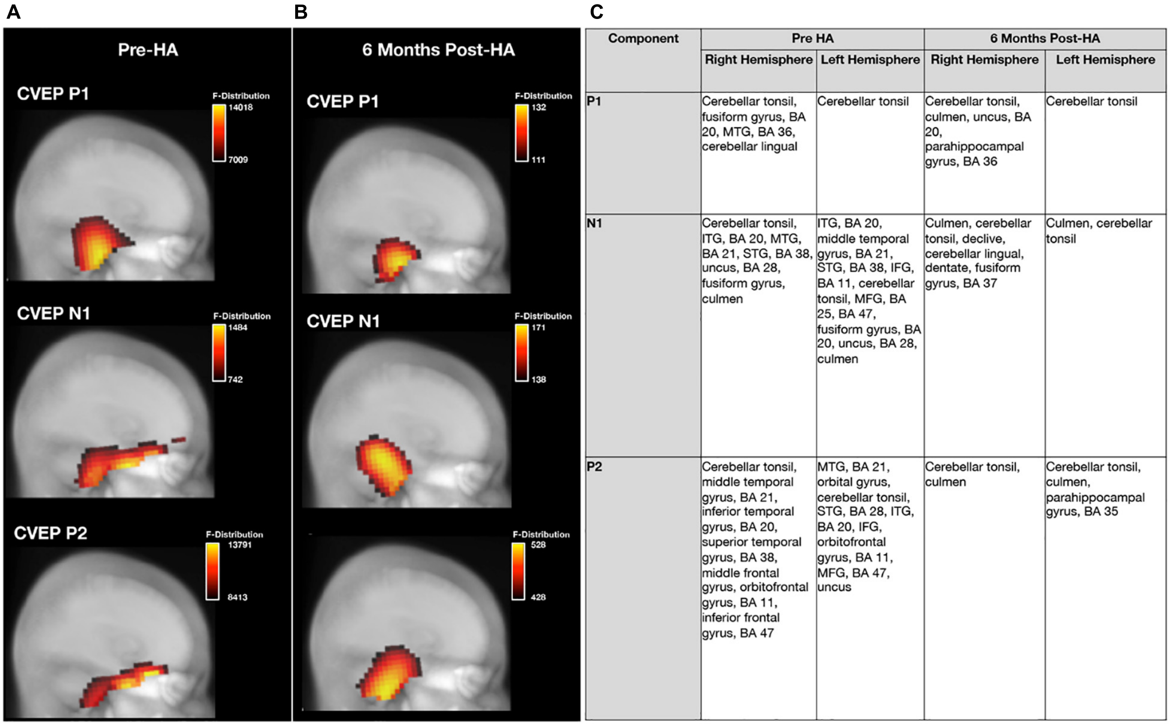
Figure 10A depicts auditory speech perception in noise scores and corresponding 95% confidence intervals in the ARHL group pre-treatment and post-treatment with hearing aids. A significant pre-post treatment improvement in QuickSIN^{TM} score was observed [$t(20) = 4.643$, $p < 0.001$]. While ARHL adults exhibited a mild auditory deficit (3–7 dB SNR) in background noise without hearing aids (average score = 6.05 dB SNR, SD = 5.11), treatment with hearing aids over yielded a 3.6 dB SNR improvement in performance (average score = 2.40 dB SNR, SD = 2.15), with performance comparable to NH adults (0–3 dB SNR).

Figure 10B depicts sentence-level visual (lip-reading) benefit for auditory-visual speech perception in noise (AzAv) at baseline and 6 months follow-up in the ARHL group, as well as corresponding 95% confidence intervals. The ARHL group performed derived similar benefit from visual cues on the AzAv test pre- and post-treatment with hearing aids [$t(20) = -0.203$, $p = 0.841$]. Average benefit from visual cues pre-treatment at the baseline evaluation (acutely aided condition) was 36.93% (SD = 9.69) and average benefit from visual cues at 6 months post-treatment follow-up (aided condition) was 37.66% (SD = 13.92). This finding suggests that hearing aid use does not modify auditory-visual integration in mild-moderate ARHL. However, given that adults with hearing loss did not have an advantage in lip-reading at the pre-treatment baseline compared to NH adults, it was not entirely unexpected that there would be no change in their results after treatment. No correlation was observed between average daily hearing aid use and change in auditory speech perception in noise performance (QuickSIN^{TM}) [$t(20) = -0.148$, $p = 0.523$] or change in dependence on

TABLE 2 | Cortical visual evoked potential latencies over a right temporal region of interest in adults with age-related hearing loss before and after 6 months of hearing aid use.

Component	Average latency (ms)		Standard deviation		95% Confidence interval		Statistic *t*(39), (*p*-value)	Effect size (Cohen's *d*)
	Pre-HA	Post-HA	Pre-HA	Post-HA	Pre-HA	Post-HA		
P1	101	118	19.4	23.78	92–110	108–129	4.15 (<0.001)	0.78
N1	133	166	26.9	27.75	121–145	154–179	5.19 (<0.001)	1.21
P2	196	231	41.18	44.55	178–218	212–252	4.30 (<0.001)	0.82

Average peak latencies, standard deviations, 95% confidence intervals, statistical significance values, and effect size are provided for the age-related hearing loss group pre-treatment and 6 months post-treatment (n = 21). A significant late-ward shift in P1, N1, and P2 latencies are observed with hearing aid use.



Component	Pre HA		6 Months Post-HA	
	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere
P1	Cerebellar tonsil, fusiform gyrus, BA 20, MTG, BA 36, cerebellar lingual	Cerebellar tonsil	Cerebellar tonsil, culmen, uncus, BA 20, parahippocampal gyrus, BA 36	Cerebellar tonsil
N1	Cerebellar tonsil, ITG, BA 20, MTG, BA 21, STG, BA 38, uncus, BA 28, fusiform gyrus, culmen	ITG, BA 20, middle temporal gyrus, BA 21, STG, BA 38, IFG, BA 11, cerebellar tonsil, MFG, BA 25, BA 47, fusiform gyrus, BA 20, uncus, BA 28, culmen	Culmen, cerebellar tonsil, declive, cerebellar lingual, dentate, fusiform gyrus, BA 37	Culmen, cerebellar tonsil
P2	Cerebellar tonsil, middle temporal gyrus, BA 21, inferior temporal gyrus, BA 20, superior temporal gyrus, BA 38, middle frontal gyrus, orbitofrontal gyrus, BA 11, inferior frontal gyrus, BA 47	MTG, BA 21, orbital gyrus, cerebellar tonsil, STG, BA 28, ITG, BA 20, IFG, orbitofrontal gyrus, BA 11, MFG, BA 47, uncus	Cerebellar tonsil, culmen	Cerebellar tonsil, culmen, parahippocampal gyrus, BA 35

FIGURE 9 | Effects of treatment with hearing aids on cortical source activation patterns elicited by visual motion stimuli in age-related hearing loss. **(A)** Depicts current density source reconstructions (CDR) for the P1, N1, and P2 cortical visual evoked potential (CVEP) components for the group of adults with untreated age-related hearing loss assessed at baseline prior to hearing aid fitting (pre-HA) (*n* = 28) and **(B)** depicts average CDRs for the P1, N1, and P2 CVEP components in a sub-group of these adults (*n* = 21) assessed post-treatment after 6 months of hearing aid use (post-HA). 3D current density source reconstructions obtained via standardized low-resolution brain electromagnetic tomography (sLORETA) are projected on a 2D depth-buffered structural magnetic resonance image (Maximum Intensity Projection), providing visualization of the voxels with the highest likelihood of activation. The color scale to the right of each figure indicates the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density. **(C)** Describes regions of cortical source activity for each CVEP component, including Brodmann areas (BA), for the age-related hearing loss group at baseline and 6-month follow-up by rank in order highest to lowest likelihood of activation (F-statistic).

visual cues for auditory-visual speech perception in noise AzAv test: [$t(20) = -0.210$, $p = 0.362$]. Given high homogeneity of average daily hearing aid use among ARHL participants (average = 9.84 h/day, *SD* = 2.96, range = 5.10–14.02 h/day), this is not an unexpected finding.

Effects of Hearing Aid Use on Cognitive Function

Hearing aid use over the course of 6 months resulted in significant improvements in the domains of global cognitive function, executive function, processing speed, and visual working memory (but not auditory working memory). On the global cognitive function measure (MoCA), 71% (*n* = 15) of ARHL adults showed improved performance after 6 months of hearing aid use, 10% (*n* = 2) showed no change in performance, and 19% (*n* = 4) showed decreased performance. On the executive function measure (BDS-2), 90% of subjects (*n* = 19) showed improvement performance, 10% showed no change in performance (*n* = 2), and 0% (*n* = 0) showed decreased performance. On the processing speed measure (SDMT), 81% of subjects (*n* = 17) showed improved performance, 5% showed no change in performance

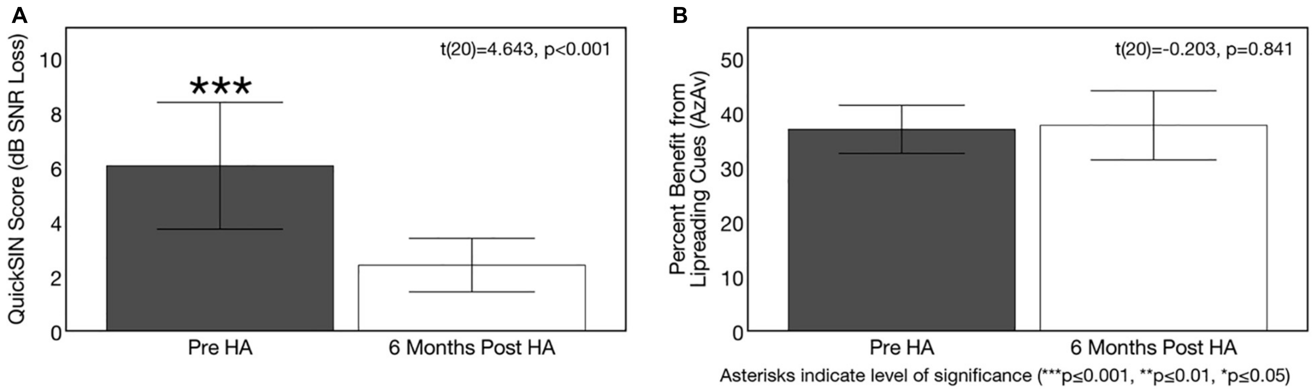


FIGURE 10 | Effects of treatment with hearing aids on auditory speech perception in noise. Average scores on speech perception measures in the age-related hearing loss group pre-treatment (gray) and 6 months post-treatment with hearing aids (Post-HA) (white). Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$). **(A)** Depicts average binaural auditory speech perception in noise scores (QuickSIN^{TM}) before and after hearing aid treatment. Scores are plotted in terms of the dB signal-to-noise ratio loss (dB SNR), representing the dB SNR required for the participant to score 50% of words in a sentence correct relative to normal hearing listeners. A higher score indicates poorer auditory speech perception in noise performance. The dotted line indicates the cutoff score (3 dB SNR) for normal function in background noise. The hearing loss group exhibited significant improvements in auditory speech perception in noise after treatment with hearing aids. **(B)** Shows average benefit from visual (lip-reading) cues on a binaural auditory-visual speech perception in noise test (AzAv). Scores indicate the percent difference score in an auditory-only condition relative to an auditory-visual condition, where a higher score indicates greater benefit from the addition of visual (lip-reading) cues. No significant difference in lip-reading benefit was observed between pre-post intervention test sessions in the hearing loss group.

($n = 1$), and 14% ($n = 3$) showed decreased performance. On the visual working memory test (RST), 71% showed improved performance ($n = 16$), 0% showed no change in performance, and 24% showed decreased performance ($n = 5$). On the auditory working memory test (WARRM), 67% showed improved performance ($n = 14$), 0% ($n = 0$) showed no change in performance, and 33% showed decreased performance ($n = 7$). Pre-post cognitive test results on these cognitive assessments are depicted in **Figures 11A–E**. A 1.62 point improvement in global cognitive function (MoCA) score was observed after 6 months of hearing aid use compared to pre-treatment, which was statistically significant [$t(20) = 2.878$, $p = 0.009$]. Average improvement in executive function (BDS-2) after 6 months of hearing aid use was 3.09 points higher than pre-treatment scores, and this improvement was also significant [$t(20) = 5.253$, $p < 0.001$]. Significant improvements in processing speed (SDMT) by 4.52 points [$t(20) = 4.209$, $p < 0.001$] and visual working memory (RST) by 5.30 percentage points [$t(20) = 4.121$, $p = 0.001$] were also observed after 6 months of hearing aid use. We observed no significant improvement on the auditory working memory (WARRM) measure following treatment with hearing aids [$t(20) = 1.072$, $p = 0.296$].

Further, *post hoc* correlational analyses indicate that reliance on cognitive function is greater in situations where the acoustic speech signal is unfavorable (e.g., unaided) compared to situations where the acoustic speech signal is more optimal (e.g., appropriately aided). For example, the correlations between unaided auditory speech perception in noise (QuickSIN^{TM} score) and performance on the global cognitive function task (MoCA) ($r = -0.37$, $p = 0.018$) and processing speed task (SDMT) ($r = -0.427$, $p = 0.005$) measured at baseline were stronger than the correlations between aided auditory speech perception in noise (QuickSIN^{TM} score) and performance on the global cognitive function task (MoCA) ($r = -0.446$, $p = 0.043$) and processing speed task (SDMT) ($r = -0.292$, $p = 0.199$) measured 6 months after hearing aid use. This finding is consistent with previous studies which show that acoustically degraded speech requires greater cognitive compensation (Rönnberg et al., 2013, 2008; Wingfield et al., 2015). No correlation was observed between average daily hearing aid use and change performance on any of the cognitive tasks (MoCA: [$t(20) = 0.046$, $p = 0.843$]; BDS-2: [$t(20) = -0.11$, $p = 0.618$]; SDMT: [$t(20) = 0.260$, $p = 0.254$]; RST: [$t(20) = 0.143$, $p = 0.535$]; WARRM: [$t(20) = 0.355$, $p = 0.114$]). Given high homogeneity of average daily hearing aid use among ARHL participants (average = 9.84 h/day, *SD* = 2.96, range = 5.10–14.02 h/day), this is not an unexpected finding.

Pre-treatment Cross-Modal Re-organization Predicts 6 Months Post-treatment Auditory Speech Perception Outcomes

Figure 12 shows the correlation between pre-treatment CVEP latencies and post-treatment QuickSIN^{TM} scores in the ARHL group. As shown, there was a significant negative correlation was observed between pre-treatment CVEP latencies in the right temporal ROI and auditory speech perception in noise outcomes for the P1 ($r = -0.743$, $p < 0.001$), N1 ($r = -0.643$, $p < 0.001$), and P2 ($r = -0.532$, $p < 0.001$) components, suggesting that the cross-modal state of the auditory cortex pre-treatment is predicted of 6 months post-treatment auditory speech perception outcomes. No such association was observed

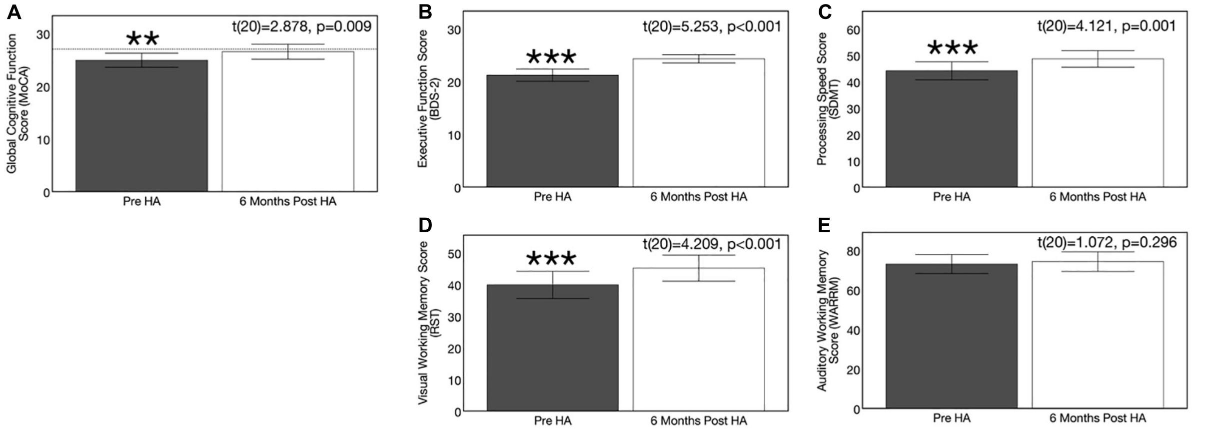


FIGURE 11 | Effects of treatment with hearing aids on cognitive function in age-related hearing loss across 6 months of hearing aid use. Average scores on cognitive measures in the age-related hearing loss group (n = 21) are depicted pre-treatment (gray) and 6 months post-treatment with hearing aids (white). Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.01$). **(A)** Shows average global cognitive function on a global cognitive screening measure (MoCA) pre- and post-treatment. Higher scores in indicate higher global cognitive function, out of a total score of 30 points. The dotted reference line on the y-axis indicates the cutoff score ($\leq$ 27) indicating risk for mild cognitive impairment. A significant improvement in MoCA score was observed post-treatment in the hearing loss group. **(B)** Depicts average executive function score (BDS-2) pre- and post-treatment. Higher scores in indicate better executive functioning, out of a total score of 27 points. A significant improvement in executive function score was observed post-treatment in the hearing loss group. **(C)** Depicts average processing speed score (SDMT) pre- and post-treatment. Higher scores in indicate faster processing speeds in a timed, 90 s digit-symbol matching task A significant improvement in processing speed was observed post-treatment in the hearing loss group. **(D)** Shows average visual working memory score (RST) in percent words correctly recalled pre- and post-treatment. Higher scores indicate higher visual working memory performance in a dual-task paradigm. A significant improvement in visual working memory recall was observed post-treatment in the hearing loss group. **(E)** Depicts average auditory working memory score (WARRM) in percent words correctly recalled pre- and post-treatment. Higher scores indicate higher auditory working memory performance in a dual-task paradigm. No significant improvement in auditory working memory recall was observed post-treatment in the hearing loss group. Note: Cognitive testing in the hearing loss group was administered in the same condition across pre-treatment (acutely aided) and post-treatment (aided) test sessions to ensure similar pre-posttest conditions and to reducing potential confounding effects of audibility on cognitive performance at the pre-treatment visit.

between pre-treatment right temporal CVEP latencies and post-treatment dependence on visual (lip-reading cues) or post-treatment cognitive outcomes across the domains of global cognitive function, executive function, processing speed, auditory working memory, or visual working memory.

Tinnitus status in the ARHL group had no effect on performance outcomes on the QuickSIN^{TM} [$t(20) = 1.027$, $p = 0.318$], AzAv [$t(20) = 0.583$, $p = 0.567$] or on majority of the cognitive tests (MoCA, BDS-2, RST, WARRM) [$t(20) < 1.659$, $p > 0.114$]. Gender had no effect on performance outcomes on the QuickSIN^{TM} [$t(20) = 0.814$, $p = 0.426$], AzAv [$t(20) = 0.175$, $p = 0.062$], or majority of the cognitive tests (BDS-2, SDMT, WARRM) [$t(20) < 0.175$, $p > 0.863$], though females performed slightly better than males on the global cognitive function test (MoCA) [$t(20) = 2.104$, $p = 0.049$] and visual working memory test (RST) [$t(20) = 2.432$, $p = 0.030$] post-treatment. Age was not correlated with performance outcomes on the QuickSIN^{TM} ($r = -0.007$, $p = 976$), AzAv ($r = -0.012$, $p = 0.959$), or majority of the cognitive tests (MoCA, SDMT, RST, WARRM) ($r < 0.358$, $p > 0.111$) in the ARHL group, though older age was correlated with poorer executive function (BDS-2) ($r = -0.645$, $p = 0.002$).

Subjective Self-Report of Hearing Aid Benefit and Satisfaction

Self-report of hearing aid benefit and satisfaction on the COSI, IOI-HA, and SADL is depicted in **Figures 13A–C**, respectively.

On the COSI outcome questionnaire (**Figure 13A**), subjects were asked to identify several listening situations they identified as most important to them at the baseline evaluation, and then were asked to rate their improvement with hearing aids and their final ability with hearing aids in these specific situations on a 5-point scale, with a higher score indicating greater levels of improvement. Average improvement rating with hearing aids was 4.09 (out of 5) ($SD = 0.60$) and average final ability with hearing aids 4.49 ($SD = 0.44$) (out of 5) on the COSI outcome questionnaire, indicating the ARHL group felt they were able to hear most of the time (>75%) with their hearing aids in the specific listening situations they identified as most important to them.

On the IOI-HA outcome questionnaire, ARHL subjects were asked to provide a rating for 7-items assessing daily use of hearing aids, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life at the 6 months follow-up visit. Ratings were provided on a 5-point scale, where a lower score indicates poorer outcome and a higher score indicates higher outcome for each item. Average global improvement rating was 4.33 ($SD = 0.38$), indicating significant benefit from hearing aid use (**Figure 13B**). An additional 8th item on the IOI-HA test probed subject's self-reported hearing difficulty on a 5-point scale (1 = severe, 2 = moderately-severe, 3-moderate, 4 = mild, 5 = none), where a higher score indicates less self-perceived difficulty. Based on the results, the average self-reported difficulty on item 8 of the IOI-HA was

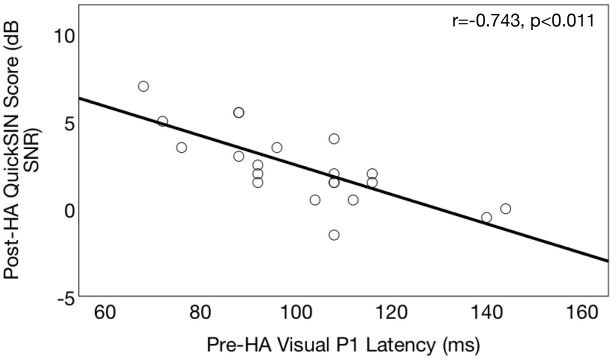


FIGURE 12 | Association between pre-treatment cortical visual evoked potential latencies and post-treatment auditory speech perception in noise outcomes in age-related hearing loss. Correlations between pre-treatment neurophysiological outcomes and post-treatment speech perception outcomes are shown for a group of adults with hearing loss (*n* = 21) who received treatment with hearing aids. Pre-treatment right temporal P1 CVEP peak latency (in milliseconds) is displayed on the horizontal axis and performance 6 months post-treatment binaural aided auditory speech perception in noise performance (QuickSIN^{TM} score) is depicted on the vertical axis. QuickSIN^{TM} scores are plotted in terms of the dB signal-to-noise ratio loss (dB SNR), representing the dB SNR required for the participant to score 50% of words in a sentence correct relative to normal hearing listeners. A higher score indicates poorer auditory speech perception in noise performance. Earlier pre-treatment P1 CVEP latencies (an index of visual cross-modal re-organization) are predictive of poorer post-treatment auditory outcomes.

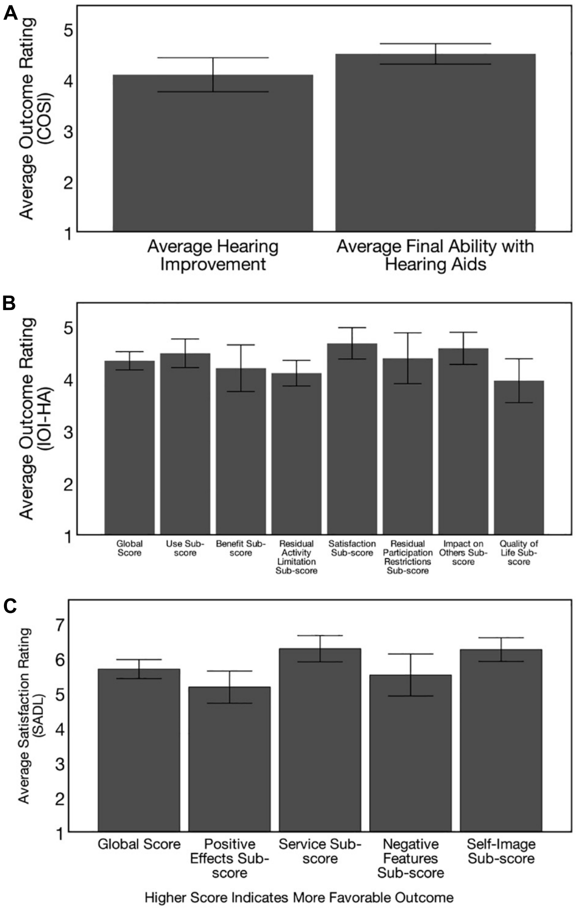


FIGURE 13 | Post-treatment hearing aid outcomes. Outcomes on 3 self-report questionnaires are depicted, with higher scores indicating more favorable outcomes for the adults with hearing loss (*n* = 21) who received treatment with hearing aids. **(A)** Depicts outcomes on the Client Oriented Scale of Improvement (COSI), where subjects were asked to identify 5 specific listening situations where they wanted to see improvement with hearing aids. Six months post-treatment, participants were asked to rate improvement with hearing aids in each of these situations on a 5-point scale (1 = worse, 2 = no difference, 3 = slightly better, 4 = better, and 5 = much better) and their final hearing ability to hear with hearing aids in each of these situations on a 5-point scale (1 = hardly ever, 2 = occasionally, 3 = half the time, 4 = most of the time, and 5 = almost always). Hearing loss participants exhibit improvements with hearing aid use in the listening situations identified as most important to them and can hear "most of the time" (> 75%) in the listening situations identified as most important to them. These results provide subjective data of benefit from clinical treatment of mild-moderate, age-related hearing loss. **(B)** Shows hearing aid Outcomes on the International Inventory of Hearing Aids (IOI-HA), where subjects provided a rating for 7-items assessing daily use of hearing aids, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life at the 6 months post-treatment visit. Average global improvement rating was 4.33 (*SD* = 0.38) and sub-scores were also high, providing subjective evidence of benefit from hearing aid treatment. **(C)** Shows hearing aid outcomes on the Satisfaction with Amplification in Daily Life Questionnaire (SADL), where subjects were asked to provide a rating for 15 items assessing positive effects of hearing aid use, service, negative features, and personal image on a 7-point scale at the 6 months post-treatment follow-up. Average global score was 5.68 (*SD* = 0.60) and sub-scores were also high, indicating high levels of self-perceived satisfaction with hearing aids in early-stage, mild-moderate age-related hearing loss.

3.19 (*SD* = 0.75), indicative of moderate self-reported hearing difficulty in background noise. Average global score across items 1–7 on the IOI-HA was 4.33 (*SD* = 0.38). Average scores across items 1–7 were 4.47 (= 0.60) for the use sub-score, 4.19 (*SD* = 0.99) for the benefit sub-score, 4.10 (*SD* = 0.54) for the residual activity limitation sub-score, 4.67 (*SD* = 0.67) for the satisfaction sub-score, 4.38 (*SD* = 1.07) for the participation sub-score, 4.57 (*SD* = 0.68) for the impact on others sub-score, and 3.95 (*SD* = 9.92) for the quality of life sub-score. These results were compared to normative data in adults with moderate-severe sensorineural hearing loss reporting "moderate" hearing problems on item 8 reported in Cox et al. (2003). Results from our study subjects are comparable these norms across all 7 sub-scores, even though our study subjects had slightly less severe hearing loss. Results provide evidence of real-world effectiveness of hearing aid intervention in the mild-moderate stages of ARHL.

On the SADL outcome measure, the ARHL group was asked to indicate their relative satisfaction with hearing aids across the areas of positive effect, service, negative features, and personal image (**Figure 13C**). Higher scores indicate greater self-perceived satisfaction. Average global score on the SADL was 5.68 (*SD* = 0.60). Average positive effect sub score was 5.15 (*SD* = 1.02), average service sub-score was 6.26 (*SD* = 0.83), average negative feature sub-score was 5.51 (*SD* = 1.32), and average self-image sub-score was 6.24 (*SD* = 0.75). Comparison of our results against normative data reported in Cox and Alexander (2001) indicate global scores and sub-scores falling above the 50th percentile, and service sub-score and negative features sub-scores falling above the 80th percentile for adults with similar degree of hearing loss. Together, results from these hearing aid outcome measures provide evidence of high levels self-perceived benefit and satisfaction from hearing aids in our study sample.

DISCUSSION

Overall, the goal of this investigation was to explore the relationship between cortical visual cross-modal neuroplasticity and speech perception and cognitive outcomes in early-stage ARHL, and to assess treatment effects with well-fit hearing aids on these outcomes. Visual cross-modal re-organization was observed in the untreated ARHL group, as evidenced by earlier CVEP latencies over right auditory cortex and cortical source localization patterns indicating greater probable current densities in auditory cortex to visual motion stimuli. Visual cross-modal re-organization in the ARHL group was associated degree of hearing loss and poorer auditory speech perception outcomes, but not visual (lip-reading) benefit. More extensive cross-modal re-organization in the ARHL group at baseline was also associated with poorer cognitive performance in the domains of global cognitive function, executive function, processing speed, and auditory and visual working memory. As a group, clinical treatment with well-fit amplification reversed cross-modal recruitment of auditory cortex for visual processing in the ARHL group following 6 months of hearing aid use, coinciding with gains in auditory speech perception abilities and improvements in global cognitive function, executive function, processing speed, and visual working memory performance. Further, the cross-modal status of the right auditory cortex at baseline before hearing aid fitting was predictive of 6 months post-treatment auditory speech perception outcomes. To our knowledge, this is the first study to document reversal in visual cross-modal re-organization following clinical intervention with hearing aids, though reversal in cross-modal re-organization has been previously reported in an individual pediatric case of single-sided deafness following clinical intervention with a cochlear implant (Sharma et al., 2016).

Cortical Visual Cross-Modal Neuroplasticity in Mild-Moderate Age-Related Hearing Loss

A main finding from this study was more extensive cross-modal recruitment of auditory cortex by vision in the ARHL group prior to hearing aid fitting. We observed earlier P1, N1, and P2 latencies in the ARHL group relative to NH controls over the right temporal cortex at baseline, and CVEP current density source reconstruction patterns indicating greater cross-modal activity over the auditory cortex. This finding replicates results from a previous high-density EEG study in a smaller group of adults with mild-moderate ARHL using the same stimulus (Campbell and Sharma, 2014) as well as other EEG studies using different visual stimuli (Stropahl and Debener, 2017). Earlier CVEP latencies have been reported in deaf adults and adults with ARHL in previous EEG studies, and are considered an index of visual cross-modal re-organization (Neville and Lawson, 1987; Finney et al., 2003; Fine et al., 2005; Doucet et al., 2006; Buckley and Tobey, 2011; Sandmann et al., 2012; Hauthal et al., 2013; Campbell and Sharma, 2014), where earlier latencies reflect increased synaptic strength and connectivity (Driver and Spence, 2004). Our observations of more extensive visual cross-modal re-organization in the right temporal ROI is also similar to findings from Cardon and Sharma (2018), where there was more extensive cross-modal recruitment of right auditory cortex by the somatosensory modality in adults with ARHL compared to NH controls. Because right auditory cortex has been shown to be more susceptible to atrophy in ARHL (Lin et al., 2014), the deprived auditory cortex may be recruited or 're-purposed' for visual or somatosensory processing. While this phenomenon was once believed to restricted to severe-profound hearing loss (e.g., deafness), our results support a growing body of evidence that even mild auditory deprivation may induce compensatory changes in cortical neuroplasticity (Campbell and Sharma, 2014; Stropahl and Debener, 2017).

Mechanisms of Cortical Visual Cross-Modal Neuroplasticity in Adult-Onset Hearing Loss

Second, results from this study indicate that untreated mild-moderate ARHL is associated with deficits in auditory speech perception in noise and cognitive functioning. The untreated ARHL group exhibited significantly poorer cognitive performance across the domains of global cognitive function, executive function, processing speed, visual working memory, and auditory working memory compared to the NH group at baseline. Poorer global cognitive outcomes in ARHL have been reported in previous cross-sectional studies (Lindenberger and Baltes, 1994; Baltes and Lindenberger, 1997; Gussekloo et al., 2005; Lin et al., 2011, 2013; Deal et al., 2015; Dupuis et al., 2015; Harrison Bush et al., 2015) and cohort studies (Gallacher et al., 2012; Lin et al., 2013; Deal et al., 2015; Hong et al., 2016). Impairments on measures of executive functioning have been previously reported in ARHL cohorts (Gates et al., 1996, 2010; Lin et al., 2013). ARHL is also associated with slower processing speeds (Clark, 1960; Anstey et al., 2001; Valentijn et al., 2005; Lindenberger and Ghisletta, 2009; Lin, 2011; Lin et al., 2011, 2013; Gallacher et al., 2012; Deal et al., 2015, 2017; Bucks et al., 2016) and deficits in working memory (Anstey and Smith, 1999; Hofer et al., 2003; MacDonald et al., 2004; Harrison Bush et al., 2015; Bucks et al., 2016) relative to NH adults. In our study auditory speech perception and cognitive performance was significantly associated with visual cross-modal re-organization, such that earlier latencies (considered a marker of visual cross-modal recruitment of auditory cortex for visual processing) was associated with poorer auditory speech perception and cognitive performance. This finding is consistent with the cognitive load theory (Pichora-Fuller et al., 2016), whereby decreased audibility and/or degraded auditory input in hearing loss taxes the brain, resulting in increased cognitive load, depleting spare capacity for other tasks such as memory.

The pre-frontal and frontal cortex recruitment for visual processing that was observed in the ARHL group at baseline –

which was absent in the NH group – is a new and unexpected finding. Previous studies have found that hearing impaired listeners may exhibit greater frontal cortex activity when processing incongruent audio-visual, auditory, and visual speech stimuli (McGurk Effect), which is presumed to reflect an increase in cognitive effort during auditory-visual integration tasks (Rosemann and Thiel, 2018). Recruitment of frontal and pre-frontal cortex has also been reported in hearing impaired listeners under difficult auditory speech perception tasks such as in background noise (Obleser et al., 2007; Wong et al., 2009). It is also possible that the pre-frontal and frontal cortex activity observed in our ARHL group at baseline may reflect changes in top-down modulatory control. For example, functional interactions between the pre-frontal and visual cortex have been shown to contribute enhance visual processing, and it is presumed that this modulation by prefrontal cortex may enhance visual attention (Gazzaley et al., 2007). Similarly, pre-frontal cortex appears to modulate auditory cortex during speech processing tasks, with more pronounced effects in left compared to right auditory cortex (Park et al., 2015). Thus, hearing loss may alter normal top-down modulatory control by pre-frontal and frontal cortex of sensory cortices. The reduction in frontal and pre-frontal cortex activity in the ARHL post-treatment suggests that hearing aid use may reduce cognitive effort and/or alter top-down modulation of auditory or visual cortex for visual processing.

Potential for Hearing Aid Use to Reverse Visual Cortical Cross-Modal Re-organization and Provide Cognitive Benefit

Notably, as a group our ARHL subjects showed a reversal in visual cross-modal recruitment of auditory cortex within 6 months of hearing aid use. Moreover, this reversal in cross-modal re-organization coincided with recovery in auditory speech perception in noise performance. Performance on cognitive measures in the ARHL group also improved 6 months post-treatment in almost all cognitive sub-domains (global cognitive function, executive function, processing speed, and visual working memory) except for auditory working memory, where test performance approximated performance of the NH control group at baseline. Thus, beyond the known benefits hearing aid use in improving speech perception and communication, our results provide preliminary evidence that hearing aid use may enhance cognitive function.

It is important to emphasize that cognitive assessment at baseline and 6 months follow-up was performed in an aided condition for the ARHL group, reducing the potential confound of audibility on pre-post treatment differences. This study lacked a control group at 6 months follow-up, in order to mitigate this to some extent, we sought to use best clinical practices by choosing cognitive measures with good test-retest reliability over short test intervals. The global cognitive function measure (MoCA) show high test-retest reliability (r = 0.96) with re-test occurring 2 weeks apart (Wong et al., 2009), with slightly lower test-retest reliability (r = 0.75–0.92) over a range of 4-8 weeks or longer (Lee et al., 2008). Test-retest reliability for the executive function measure (BDS-2) is high (r = 0.8) at 8 week and 6 months follow-up intervals (Grigsby et al., 1992, 2002a,b). Test-retest reliability of the SDMT is high (r = 0.7–0.9) when administered over the course of 2 weeks, 1 month, or 2 years intervals (Benedict et al., 2017). High test-retest reliability over minutes (Turley-Ames and Whitfield, 2003), weeks (Klein and Fiss, 1999; Friedman and Miyake, 2004), and months (Klein and Fiss, 1999) is reported for the visual working memory test (RST). High intra-session and inter-session and test-retest reliability ($r > 0.8$) has also been reported for the auditory working memory measure (WARRM) (Smith et al., 2016). However, we cannot rule out potential practice effects since we were unable to test the NH subjects at 6 months.

It is possible that reversal in visual cross-modal neuroplasticity in ARHL may provide an objective marker of treatment benefit. For example, less diffuse cross-modal re-organization has also been reported in deaf adults with good auditory speech perception outcomes following cochlear implantation, while deaf adults with poor auditory outcomes exhibit persistent cross-modal re-organization that persists even years after cochlear implantation (Doucet et al., 2006).

To our knowledge, this is the first study to provide evidence that restored audibility with hearing aids may reverse compensatory changes in cortical resource allocation and promote typical more typical visual sensory processing patterns, coinciding with speech perception benefit and cognitive gains, though other studies indicate neurocognitive benefit from hearing aid treatment in adults with hearing loss. For example, findings from a recent study by Anderson (2019) revealed measurable improvements in working memory after 6 months of hearing aid use in a group of adults with hearing loss relative to NH controls (who showed no change in cognitive performance). Further, cognitive gains in their hearing loss group were associated with P2 cortical auditory evoked potential (CAEP) amplitudes, suggesting that increased auditory input may provide neurocognitive benefit. Our findings are also supported by experimental evidence by Deal et al. (2017) and Karawani et al. (2018a), where hearing aid treatment over longer durations (>6 months) in similar ARHL populations resulted in significant improvements in cognitive function the cognitive domains of global cognitive abilities and processing speed (Deal et al., 2017) as well as improvements in working memory (Karawani et al., 2018b). In addition, long-term neurocognitive benefit has been reported in deaf adult cochlear implant recipients at 6 months and 1 year post post-treatment, where notable gains were observed in the areas of global cognitive function and executive function (Mosnier et al., 2015). These results are in contrast to Nkyekyer et al. (2019), where researchers found no improvement in cognitive function in a group of adults with hearing loss (n = 40) fit with hearing aids and examined over the course of 6 months. However, different cognitive sub-domains were assessed in this study (reaction times, immediate and delayed recall, spatial working memory, and contextual memory), study subjects were almost a decade older than the subjects in our study, and there was limited information provided with regards to the quality of the hearing aid fitting or the duration of hearing aid use during the study. The potential for hearing aid use to provide cognitive benefit may depend on a variety of factors (e.g., age, duration of hearing loss, quality of hearing aid fitting, hearing aid use) or take longer in some patients. Future studies should seek to understand this relationship. It is possible that audiological intervention may only provide neurocognitive benefit if treatment is delivered in a timely manner, before extensive functional and structural neural changes take place.

Interestingly, the extent of visual cross-modal re-organization of auditory cortex pre-treatment (as indexed by earlier cortical visual evoked potential latencies) was predictive of auditory speech perception in noise outcomes 6 months post-treatment. This finding suggests that there may be an upper limit to reversing compensatory changes in cortical resource allocation. That is, recovery of auditory speech perception abilities after clinical intervention may be limited by the extent to which auditory cortex has become “re-purposed” by vision. For the small percentage of adults with ARHL who do seek treatment, treatment is typically sought out late, delayed 7–10 years after the hearing loss onset (Davis et al., 2007). Thus, audiological intervention with hearing aids is likely introduced to a central auditory system that has extensively re-organized after long periods of deprivation, potentially limiting treatment effects of hearing aid or cochlear implants. It is possible that these alterations in visual cross-modal re-organization (or other changes in cortical resource allocation) may contribute to the wide variability in outcomes observed in adults with hearing loss who receive treatment. Extensive central “re-wiring” of the auditory pathways could explain low levels of uptake and use with hearing aids.

Future Directions

This study was not a randomized controlled clinical trial and the NH subjects were not re-tested at 6 months follow-up. At baseline, the untreated ARHL group and NH control group demonstrated clear differences in CVEP latencies, cortical source activation patterns, and cognitive performance. After 6 months of hearing aid use, CVEP latencies significantly increased (right auditory ROI), cortical source activation patterns showed less extensive cross-modal re-organization, and cognitive performance improved in the ARHL group, with measures similar to the NH group at baseline. While preliminary findings from this study supports the idea that early and timely intervention with hearing aids (e.g., in the mild-moderate stages) may provide the best chance of promoting typical cortical sensory functioning and good prognostic cognitive and behavioral outcomes, future randomized controlled trials can provide more robust evidence regarding cortical and cognitive benefit from hearing aid treatment.

Longitudinal follow-up studies are also necessary to understand whether extended hearing aid use (beyond 6 months as reported in our study and previous studies) may modify long-term risk for cognitive decline, including dementia. Currently, there exists no universal screening of hearing loss in the United States and very few adults with clinically significant ARHL use hearing aids or cochlear implants. Research in this area may lead to better tools to diagnose auditory deprivation in its early stages and may also help target optimal timeframes for intervention.

It is important to note that ARHL subjects in our study were fit with well-fit hearing aids (± 5 dB of NAL-NL2 targets measured using probe-microphone measures). ARHL subjects in our study also complied with a high level of daily hearing aid use greater (average = 9.84 h/day, *SD* = 2.96). It is possible that poorly fit devices or low levels of compliance may reduce the efficacy of hearing aids in providing benefit. Future studies should seek to understand how the quality of hearing aid fitting and/or amount of daily hearing aid use may influence auditory, cortical, cognitive outcomes following intervention. Further, while this study focused on group-level differences in baseline auditory, cortical, and cognitive function in NH adults and adults with ARHL, future studies should seek to understand differences in individual characteristics and demographic variables that may affect cortical and cognitive outcomes following intervention for adults with ARHL. Such information may help inform best-practice guidelines and help guide clinical recommendations.

ARHL subjects in our study were fit with hearing aids but received no additional rehabilitation services beyond intervention with hearing aids. Future studies should evaluate whether intervention coupled with additional rehabilitation (e.g., auditory training) may help maximize auditory function once hearing has been “restored.” If the extent of cross-modal re-organization is a limiting factor of post-treatment auditory outcomes, then aural rehabilitation or therapeutic techniques or treatments may help maximize treatment benefit for patients who may be struggling.

The reversal in cross-modal recruitment of auditory cortex by vision and reduction in pre-frontal and frontal cortex activity in the ARHL group after 6 months of hearing aid use suggests that restored audibility from well-fit hearing aids may promote more typical sensory functioning comparable to activity observed in the NH group at baseline. Future studies will aim to examine the role of pre-frontal and frontal cortex activity during sensory processing tasks in ARHL, as it relates to behavioral outcomes of auditory function and cognition. Future studies should also aim to understand how restored audibility with amplification alters top-down attentional or cognitive modulatory control of sensory function.

Finally, our results highlight the potential role of cognitive screening or evaluation in the clinical setting. Currently, only 25% of audiologists incorporate cognitive screening or other special tests into their clinical practice (Anderson et al., 2018). If treatment with hearing aids may provide neurocognitive benefit, then measuring cognitive abilities before and after intervention may provide an additional prognostic indicator or metric by which to evaluate post-treatment outcomes. For example, cognitive assessment tools may help audiologists make better recommendations regarding when a patient should receive intervention or help determine what kind of intervention or rehabilitation plan is ideal. Cognitive assessment may also be used to assess whether a selected intervention or rehabilitation method is providing sufficient benefit. The impact of hearing loss extends beyond the ear, impacting psychosocial function and cognitive function. Greater research resources should be devoted to understanding the larger impact of ARHL on health and wellness.

One of the most remarkable capabilities of the human brain is its capacity for change. As a profession, the field of audiology is beginning to unearth the widespread effects of hearing loss on structural and functional changes in the brain. Ultimately, our clinical interventions (e.g., hearing aids, cochlear implants) the neuroplastic ability for the brain to adapt to restored auditory input. With a more solid understanding of the mechanisms of neuroplasticity in ARHL, our profession may find new and innovative ways to leverage neuroplasticity in order to optimize treatment outcomes for our patients.

DATA AVAILABILITY STATEMENT

All datasets analyzed for this study are included in the manuscript.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board, University of Colorado Boulder. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Both authors of this manuscript contributed to the design of the study, data analysis, interpretation, revision, and review of this manuscript.

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ORIGINAL RESEARCH
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Mental Rotation of Digitally-Rendered Haptic Objects by the Visually-Impaired

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In the event of visual impairment or blindness, information from other intact senses can be used as substitutes to retrain (and *in extremis* replace) visual functions. Abilities including reading, mental representation of objects and spatial navigation can be performed using tactile information. Current technologies can convey a restricted library of stimuli, either because they depend on real objects or renderings with low resolution layouts. Digital haptic technologies can overcome such limitations. The applicability of this technology was previously demonstrated in sighted participants. Here, we reasoned that visually-impaired and blind participants can create mental representations of letters presented haptically in normal and mirror-reversed form without the use of any visual information, and mentally manipulate such representations. Visually-impaired and blind volunteers were blindfolded and trained on the haptic tablet with two letters (either L and P or F and G). During testing, they haptically explored on any trial one of the four letters presented at 0°, 90°, 180°, or 270° rotation from upright and indicated if the letter was either in a normal or mirror-reversed form. Rotation angle impacted performance; greater deviation from 0° resulted in greater impairment for trained and untrained normal letters, consistent with mental rotation of these haptically-rendered objects. Performance was also generally less accurate with mirror-reversed stimuli, which was not affected by rotation angle. Our findings demonstrate, for the first time, the suitability of a digital haptic technology in the blind and visually-impaired. Classic devices remain limited in their accessibility and in the flexibility of their applications. We show that mental representations can be generated and manipulated using digital haptic technology. This technology may thus offer an innovative solution to the mitigation of impairments in the visually-impaired, and to the training of skills dependent on mental representations and their spatial manipulation.

Keywords: blind, low vision, sensory substitution, mental rotation, haptics, digital technology

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INTRODUCTION

A major issue for the visually-impaired is mobility. Visually-impaired and blind individuals have higher risks of unintentional injuries, both at home and in the general environment (Legood et al., 2002; Manduchi and Kurniawan, 2011). Mobility depends on the integrity of our spatial functions, which in turn depend on mental representations that themselves rely on the correct functioning of cortical visual mechanisms (Thinus-Blanc and Gaunet, 1997). Loss of visual functions through visual impairment or blindness can affect the way that mental representations are created, which in turn leads to impairment in multiple functions such as reading, manipulation of objects, or orientation in space (Thinus-Blanc and Gaunet, 1997; Kuyk et al., 2004; Lahav et al., 2012). In fact, visual impairments affect nearly 300 million people globally, with another ∼36 million suffering from complete loss of vision (World Health Organization, 2000). Therefore, studying how mental representations can be established and manipulated in visually-impaired and blind individuals is arguably an important public health issue.

Spatial functions can be supported by visual, tactile, and auditory stimuli (Auvray et al., 2007; Collignon et al., 2007; Lacey et al., 2007a; see Lacey and Sathian, 2012, for a review). Specifically, studies of tactile mental rotation in the blind demonstrate a typical decrease in performance with increasing image rotation (Shepard and Metzler, 1971; Marmor and Zaback, 1976; Prather and Sathian, 2002), consistent with a classic mental rotation effect (Shepard and Metzler, 1971) as found for visual stimuli (Jordan et al., 2001; Thomas et al., 2013; Iachini et al., 2019). This has led to research demonstrating that spatial representations can be achieved in a largely modality-independent fashion (Lacey and Campbell, 2006), engaging a common representational system (Lacey and Sathian, 2012; Masson et al., 2016). The ability of visually-impaired individuals to use tactile information to analyze spatial properties, as well as the modality-independence of spatial skills, have opened new avenues for rehabilitation via sensory substitution. Multiple forms of tactile sensory substitution devices (SSDs), such as the classic Braille alphabet and white cane, but also more novel devices such as the Tongue Display Unit (TDU) (Chebat et al., 2007), focus on rehabilitating functions such as reading and orientation in space. However, such SSDs risk remaining limited in their applications, due to limited libraries of stimuli, persistent training, and restricted accessibility/ergonomics. Moreover, devices such as the TDU or BrainPort (Bach-y-Rita et al., 2005; Arnoldussen and Fletcher, 2012) are invasive (Gori et al., 2016), in that they block the tongue, and that they deliver voltage impulses which, on the long run, might negatively affect the skin through repeated stimulation (Fary and Briffa, 2011), potentially leading to tissue damage and pain (Prausnitz, 1996). New non-invasive applications aiming to digitally render tactile information promise to resolve such issues through digitalization. This digitization of information has led to significant improvements in healthcare, including reduced costs and increased accessibility and reliability of treatments (Noffsinger and Chin, 2000; Dwivedi et al., 2002). Currently, visually-impaired individuals require many training hours together with occupational therapists in order to rehabilitate visual functions such as reading or orientation in space. By contrast, digitizing the delivery method of such therapies would reduce resources for the medical domain, as well as increase patient independence. Thus, patients could train both their tactile perception, as well as their shape and space perception, without the constant supervision of a therapist. In addition, the non-invasive nature of a technology based on ultrasonic vibrations rather than electrical stimulation, such as the one employed in our study does not entail the possibility of negative long-term effects such as those induced by prolonged electrical stimulation.

It has previously been shown that sighted participants can use digital haptics to create and manipulate mental representations of letters (Tivadar et al., 2019). In this study, Tivadar and colleagues tested a group of sighted subjects on a mental rotation task with digitally-rendered haptic stimuli on the same prototype as in the current study. The authors had participants actively explore haptic letters that were simulated on the screen of the tablet, in order to recognize whether these letters were presented in normal or mirrored forms. Critically, these letters could be rotated at four angles (0°, 90°, 180°, 270°), thus obligating participants to engage in mental rotation of the presented stimuli. (Tivadar et al., 2019) results support the fact that participants successfully managed to build mental representations of these digitally-presented haptic letters, that they were then able to rotate so as to correctly determine the form. It has also been shown that mental rotation in the visually-impaired can be supported by tactile stimuli (see Prather and Sathian, 2002, for a review). However, it remains unknown whether visually-impaired and blind individuals can use simulated digital tactile information to build mental representations of objects that they can then also mentally manipulate. In fact, if these digital applications are well-suited to rehabilitate spatial functions, this would highly increase the speed of recovery of such patients. As such, these applications are very promising due to the ease of delivery of digital information, their independence of environment, and the fact that they can easily simulate real-world objects and environments. This in turn supports everyday functions such as localization, mapping, and building internal representations of objects, thus entailing a high translational facility to veridical environments. In addition, being able to create and rotate mental representations of objects based on digital simulated haptic information is an important step in a proof-of-concept for the successful acquisition and manipulation of a simulated haptic space.

In order to investigate whether visually-impaired and blind participants would be able to successfully create and manipulate mental representations of objects, we tested a group of subjects suffering from visual impairments of different types and severities on a mental rotation task, using normal and mirror-reversed digital haptic letters. We chose to have a heterogeneous group in terms of their visual impairment, due to the fact that such applications are aimed at individuals living with various forms of visual impairment. We hypothesized that visually-impaired and blind individuals should show the classic mental rotation effect, as first investigated by Shepard and Metzler (1971), meaning decreasing performance with increasing object rotation. If so, this would mean that participants are able to use digital haptic information to create mental images of 2-D objects, such as letters. Specifically, we expected to see this effect for normal trained as well as new stimuli, contrary to results in sighted (Tivadar et al., 2019), where sighted participants did not perform well with untrained (new) letters. We expect this given higher tactual expertise of visually-impaired and blind participants (Goldreich and Kanics, 2003; Legge et al., 2008; Wong et al., 2011). Similar, yet worse, performance is expected for mirror-reversed stimuli as compared to stimuli presented in their normal form, given previous evidence demonstrating slower reaction times and higher errors with stimuli in their mirrored as compared to normal form (Marmor and Zaback, 1976; Carpenter and Eisenberg, 1978), and the stimulus familiarity effect (White, 1980; Bethell-fox and Shepard, 1988).

METHODS

Participants

Written informed consent was obtained from each participant to procedures approved by the cantonal ethics committee. Fourteen adults (7 women and 7 men; age range 18–64 years, mean ± SD: 40 ± 12.6 years) were tested. Each was compensated 50 Swiss francs for their participation. Ten of the participants were completely blind, and 4 retained some low vision. Most participants were right-handed, only one was left-handed. Regarding Braille literacy, six of them reported good literacy, six of them reported no literacy, and two of them reported little literacy. Most of our participants had an acquired visual impairment or blindness ($N = 10$), and four of them were congenitally blind. Diagnostic visual acuity measurements were transformed into logMAR (Bonavolonta et al., 2010; Patel et al., 2017). Characteristics about patients' demographics and diagnoses are presented in **Table 1**. No participant reported tactile deficits or had a history of or a current neurological or psychiatric illness.

Apparatus

The apparatus was identical to that used in Tivadar et al. (2019). It entailed a 7″ tablet with a 1,024 × 600 pixel touchscreen. The tablet's operating system is Linux-based (Raspbian) and the tablet itself is equipped with a software tool to render and control the presentation of haptic textures. Briefly, the software recodes images in jpeg format into a haptic format using a kit written in C++. Full details of the technique and the haptic rendering are provided in Vezzoli et al. (2016, 2017) and Rekik et al. (2017).

Stimuli

Stimuli were identical to those employed in Tivadar et al. (2019). These were 4 upper-case letters—L, P, F, and G—drawn in Paint (see e.g., Carpenter and Eisenberg, 1978; see also **Figure 1**). We also used Matlab to generate images wherein each letter was rotated 0°, 90°, 180°, or 270° from upright and mirrored. In terms of the conversion from image to haptic rendering, the stimuli appeared centrally and on a white (i.e., blank in terms of haptic rendering) background. All pixels of the letter stimuli were coded with the same haptic texture, based on the Hap2u pre-installed Texture Editor software. The shape of the ultrasonic vibration was a square wave of roughly 2 μm amplitude (see e.g., Sednaoui et al., 2017). This has been shown to produce the most intense and quick reduction of the friction of the screen under the finger; i.e., a "pointy" sensation. Additionally, a "coarse" texture was produced by using a 3,500 μm period of the square wave (see Hollins and Risner, 2000).

Procedure and Task

Likewise, the procedure and task are identical to what is described in Tivadar et al. (2019). All participants completed the experiment within a sound-attenuated, darkened room (WhisperRoom MDL 102126E). All of our participants wore a blindfold as well as noise-canceling headphones (Bose model QuietComfort 2). This was done so as to block any potential residual light and to mask any sounds from the tablet (see also Murray et al., 2005). This may likely minimize any cross-modal facilitation (Lacey et al., 2007b), impeding a recognition of the presence/absence or location of the letters by the sound the tablet made when explored. We would note that while all participants were familiar with letters, no participant was familiar with the haptic tablet or had prior exposure to the haptic stimuli. We instructed participants to explore the tablet with a finger from their dominant hand and to respond with their non-dominant hand. For each letter, the participant was asked to indicate via a computer mouse if it was presented in normal or mirror-reversed manner (left and right buttons, respectively). We explicitly instructed participants to explore the haptic rendering, to identify the letter, and to imagine rotating the letter to upright (0°) so as to judge if the letter was normal vs. mirror-reversed. Stimulus duration was 30 s followed by a 20 second response window. These timings were determined during pilot experiments, where it was evident that participants needed some time to recognize when a stimulus appeared on or disappeared off the screen of the tablet. The ensuing trial was initiated after the response and with the further inclusion of an inter-trial interval ranging 500–1,000 ms. To train the participants with the haptic tablet, we had each of them complete three training blocks, each comprised of 16 trials (2 per condition). During training, a participant was exposed to only 2 of the 4 letters (either L and P or alternatively only F and G). We counterbalanced across individuals the letters to which they were exposed. The pairing of letters was based on their perceptual proximity, which allowed a progressive learning procedure. We trained participants with pairs of letters in this way in order to assess whether effects generalized to untrained stimuli. Prior to exposure to the letter stimuli, we first trained participants to explore the tablet screen via lateral sweeps (Stilla and Sathian, 2008). While we did allow participants to change the finger used for exploring the tablet (to minimize any adaptation or habituation effects), we did not allow for changing hands. We then taught participants to differentiate vertical from horizontal lines. Afterwards, participants completed the abovementioned training blocks. The experimenter (R.I.T.) provided participants with verbal instructions as well as feedback regarding general performance and the accuracy of responses throughout the training session. The testing phase comprised 3 blocks of

TABLE 1 | Patient characteristics and group assignment.

ID	Gender	Age range	Diagnosis	Congenital /acquired	Years of visual impairment	Vision	Residual vision	Visual acuity [logMAR] (right eye; left eye)	Braille	Locomotion	Group of letters trained	Inclusion in analyses
Pat06	F	55–60	Retinitis Pigmentosa & deafness (corrected)	Acquired	14	Blindness	Right eye: 0.03, left eye: 0.03	(1.5; 1.5)	Yes	Cane	2	Y
Pat01	M	60–65	Retinal Vascular Occlusion (L&R)	Acquired	7	Blindness	Total blindness	(3; 3)	Little	Dog	1	Y
Pat15	F	40–45	Congenital retinopathy, both eyes enucleated	Congenital	44	Blindness	Total blindness	(3; 3)	Yes	Cane	1	Y
Pat02	M	25–30	Glaucoma	Acquired	13	Low vision	Visual field <15°, right eye: 0.63, left eye: 0.05	(0.2; 1.3)	No	cane	2	Y
Pat11	F	40–45	Usher Syndrome: Retinitis Pigmentosa, deafness (corrected)	Acquired	7	Low vision	Right eye: 0.16, left eye: 0.16	(0.8; 0.8)	No	Cane	1	Y
Pat14	F	35–40	Optic Nerv Atrophy	Congenital	38	Blindness	Right eye: luminous perception, left eye: hand movements	(2.9; 2.9)	Yes	Cane	2	Y
Pat12	F	40–45	Retinitis Pigmentosa	Acquired	36	Blindness	Luminous perception, shapes	(2.9; 2.9)	No	–	2	Y
Pat13	M	30–35	Optic Nerv Atrophy	Acquired	3	Blindness	Right eye: perception of hand movements, left eye: counts fingers at 1.5 m distance	(2.3; 1.7)	Yes	Cane	2	Y
Pat04	F	30–35	Congenital Glaucoma	Congenital	33	Blindness	Right eye: luminous perception, left eye: total blindness	(2.9; 3)	Yes	Dog	1	Y
Pat09	M	25–30	Lyell syndrome	Acquired	15	Blindness	Right eye: 0.05, left eye: luminous perception	(1.3; 2.9)	No	Cane	1	Y
Pat10	M	25–30	Leber congenital Amaurosis	Acquired	6	Blindness	Right eye: 0.05, left eye: < 0.05	(1.3; <1.4)	Little	Independent	2	N
Pat03	F	55–60	Divergent strabismus, macular hole, cataract (R)	Acquired	6	Low vision	Right eye: 0.2	NA	–	Cane	2	N
Pat16	M	18–20	Leber congenital Amaurosis	Congenital	19	Blindness	Luminous perception	(2.9; 2.9)	Yes	Cane	1	N
Pat08	M	30–35	Usher Syndrome: Retinitis Pigmentosa, deafness (corrected)	Acquired	13	Low vision	Right eye: 0.25; left eye: 0.4	(1.6; 0.4)	No	Independent	1	N

M stands for Male, F stands for female. Training 1 stands for training on the letters L and P, and Training 2 stands for training on the letters F and G.

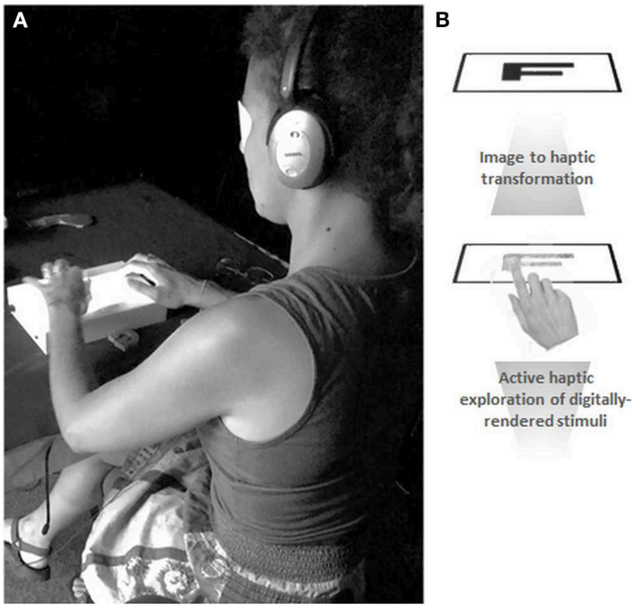

FIGURE 1 | Experimental setup and digital haptic transformation. **(A)** Each subject wore a blindfold and noise-canceling earphones throughout the experiment. This was done to prevent any residual or inadvertent visual input and to mask any audible noise from the tablet. During each trial, the subject could explore the letter stimulus for 30 s with one finger of their dominant hand. They then used their non-dominant hand to respond via a computer mouse whether the letter was upright or mirror-reversed. **(B)** The tablet's pre-installed software development kit translated the image files into haptic renderings. The transformation involves delineating the image in a series of 8 × 8 pixel cells and coding each of the cells into textures, using a haptic library where different textures are defined. Written informed consent was obtained from the individual for the publication of this image.

32 trials, making 96 trials in total per participant [i.e., six trials per each of the 16 combinations of 4 angles (0°, 90°, 180°, and 270°) × 2 conditions (normal/mirror) × 2 training (trained/untrained)]. During the experiment, participants were ecnouraged to take regular breaks between blocks of trials to maintain high concentration and prevent fatigue. The total experiment duration was no longer than 3 h 30 min. Stimulus delivery and behavioral response collection were controlled by Psychopy software (Peirce, 2007).

Behavioral Analysis

We used Matlab to pre-process the data and R (R Core Team, 2018) for analyses. First, we excluded all trials that were classed as missed trials, i.e., trials with RTs over 20 s (15.1% of trials). Any remaining outlier trials were then excluded on a single-subject basis (i.e., for each subject and condition), applying a criterion of the mean ±2 standard deviations around their RTs (2.9% of all trials, see Ratcliff, 1993; Field, 2012). Accuracy means were calculated from the remaining trials. Missing means in certain conditions were replaced with the mean of all subjects for the specific condition (14 cases in total, 8.75% of total data). Upon inspection of Accuracy scores, we found 4 of the 14 patients had a global performance (i.e., across all angles of presentation) for letters in their normal form that was equal to or lower than chance, i.e., $\leq$50% (**Figure 2A**). We excluded these participants. Our final group comprised 10 participants (aged 27–64 years; mean ± SD: 40.7 ± 12.1 years). We compared Accuracy with a 2 × 2 × 4 repeated measures ANOVA with factors Training (trained/untrained), Condition (normal/mirror) and Angle (0°, 90°, 180°, 270°), after not having found a significant deviation from the normal distribution and from homoscedasticity (assumptions tested with Shapiro and Levene tests). Greenhouse-Geiser corrections were applied whenever sphericity was violated. Partial eta-squared is reported as a measure of effect size. As in Tivadar et al. (2019), RTs were not further analyzed as they represented somewhat cued responses, and were not deemed informative as such. More specifically and as described above in the Methods section, participants had to explore the tablet for 30 s before being able to give responses on any given trial. This was done out of practical reasons, in order to ensure correct interaction with the tablet. Therefore, RTs are not representative of the time it took participants to correctly identify the form of a given letter, as even if participants had correctly identified the letter before the 30 s passed, they were not able to respond.

RESULTS

Accuracy

Group-averaged ($N = 10$) accuracy rates are displayed in **Figure 2B**. The 2 × 2 × 4 repeated measures ANOVAs (Training × Condition × Angle) exhibited a significant 3-way interaction (Training × Condition × Angle) [$F_{(3,27)} = 3.28$, $p = 0.04$, $\eta_p{}^2 = 0.27$], and a significant 2-way interaction (Condition × Angle) [$F_{(3,27)} = 3.01$, $p = 0.05$, $\eta_p{}^2 = 0.25$]. There was also a main effect of Condition [$F_{(1,9)} = 7.6$, $p = 0.02$, $\eta_p{}^2 = 0.46$], with generally higher accuracy on Normal than on Mirrored letters. We therefore next conducted two separate 2 × 4 repeated measures ANOVAs (Trained × Angle) for Normal and Mirrored letters. For Normal letters, we observed a significant Trained × Angle interaction [$F_{(3,27)} = 3.81$, $p = 0.02$, $\eta_p{}^2 = 0.30$]. Despite this interaction, the *post-hoc* contrasts comparing accuracy rates for each angle revealed no significant differences between Trained and Untrained conditions (all p's > 0.08; without correction for multiple comparisons). Crucially, however, the within-subjects contrasts revealed a linear main effect of Angle [$F_{(1,9)} = 10.00$, $p = 0.01$, $\eta_p{}^2 = 0.53$]. Participants thus demonstrated typical mental rotation effect (Shepard and Metzler, 1971), i.e., decreasing performance accuracy with increasing angular disparity from upright, for letters presented in their normal form. No significant interactions or main effects were observed for Mirrored letters (F's < 0.9).

We have previously provided a proof-of-concept for sighted subjects with this same protocol as well (Tivadar et al., 2019). We display these data here in **Figure 2C**. In this prior work, we observed a mental rotation effect for trained letters, but not for untrained letters, presented in their normal format. Given that identical paradigms and equipment were used in both studies, we *a posteriori* compared performance across sighted and visually-impaired for the normal format condition, as these were those exhibiting a mental rotation in each group when

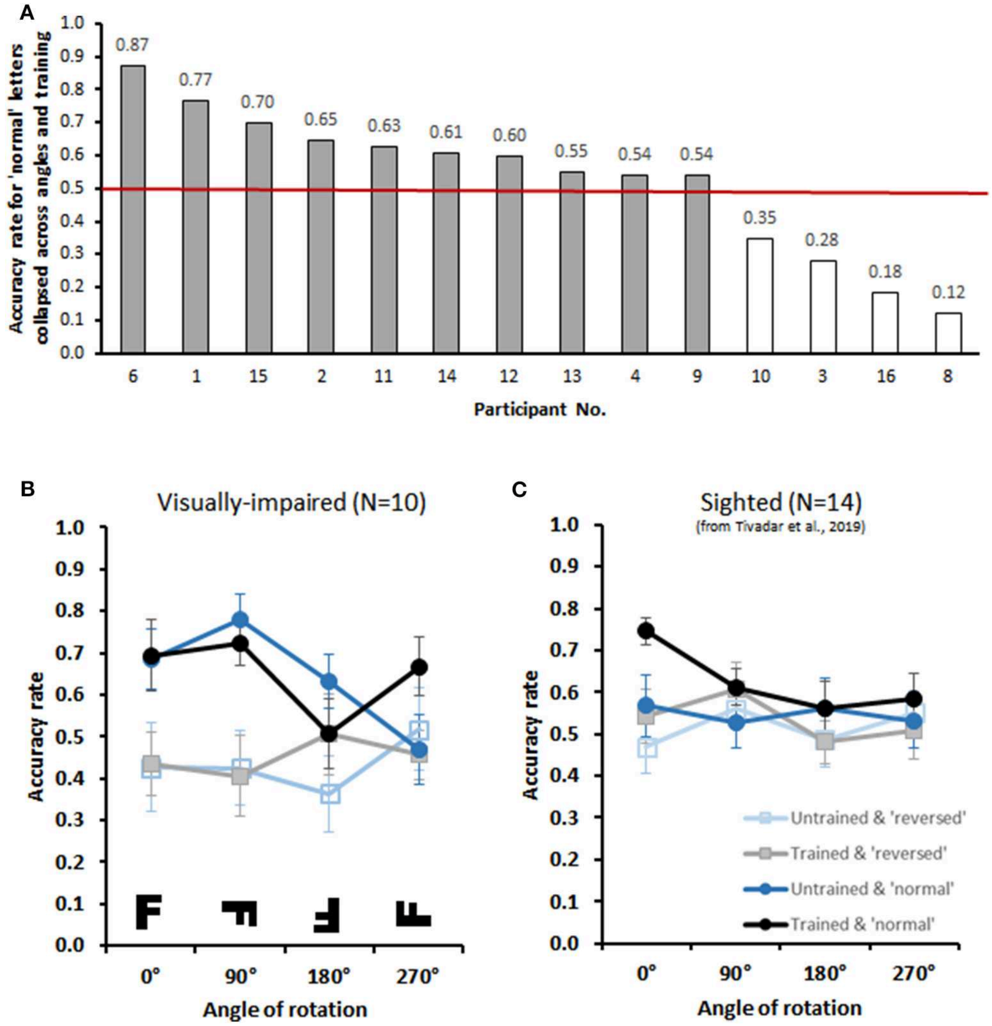

FIGURE 2 | Behavioral Results **(A)** The bar graph displays individual performance (accuracy rates) with trained normal letters collapsed across all angles. The red line indicates chance performance (i.e., 0.50). Participants were included if performance was above chance, resulting in the exclusion of 4 participants. **(B)** The lower graphs display group-averaged performance for upright trained, upright untrained, reversed trained, and revered untrained letters at four orientations (visual versions displayed in the inset) for the group of 10 included participants. There was an archetypical mental rotation effect with upright letters, independently of whether or not they were trained. This was not the case for mirror-reversed letters. **(C)** Comparative data from sighted individuals performing the identical task as originally reported in Tivadar et al. (2019).

studied separately. Specifically, we performed a 2 × 2 × 4 mixed model repeated measures ANOVA with group as the between-subjects factor and Trained and Angle as the within-subjects factors, as described above. The within-subjects contrasts revealed a significant 3-way interaction [$F_{(1,22)} = 6.71$, $p = 0.017$, $\eta_p^2 = 0.23$]. To better understand the basis for this interaction, additional 2-way mixed model ANOVAs were run for trained and untrained conditions separately. For trained letters, there was a linear main effect of angle [$F_{(1,22)} = 6.89$, $p = 0.015$, $\eta_p^2 = 0.24$], as expected, but no significant interaction with group ($p > 0.45$). By contrast, for untrained letters, there was both a linear main effect of angle [$F_{(1,22)} = 9.99$, $p = 0.005$, $\eta_p^2 = 0.31$], as expected, as well as a significant interaction with group [$F_{(1,22)} = 6.93$, $p = 0.015$, $\eta_p^2 = 0.24$]. This overall pattern indicates that visually impaired individuals exhibit greater generalization to untrained letters than their sighted counterparts (**Figures 2B,C**).

DISCUSSION

We provide the first proof-of-concept that visually-impaired and blind individuals were able to use digitally-rendered haptic letter stimuli to create mental representations that they could then spatially manipulate on a task requiring the discrimination of normal vs. mirror-reversed letters. In particular, patients showed the classic mental rotation effect (Shepard and Metzler, 1971), demonstrating decreasing performance with increasing angular disparity, or rotation of the letters, they previously haptically explored. This effect was visible not only for trained letters in their normal but not mirrored format, but also generalized to untrained letters. This is an important result, because it represents a necessary validation of the suitability of digital haptics for the rehabilitation of functions that rely on manipulable mental representations in the visually-impaired.

We furthermore compared the performance of our visually-impaired and blind participants with that of sighted individuals described in our prior published work (Tivadar et al., 2019). In this prior work, using the same device and protocol as here, we observed a mental rotation effect for trained, but not untrained, letters presented in their normal format. The results across the studies differed insofar as visually-impaired and blind individuals exhibited similar performance with both trained and untrained letters, whereas sighted participants showed no evidence for the generalization to untrained letters. It may be that vision (and individual's potential to use visual imagery) deleteriously affects the ability to generalize effects based on haptic-based mental representations from trained to untrained letters. Another alternative, which is not mutually exclusive, is that visually-impaired and blind individuals have greater tactile experience that in turn facilitates the observed generalization. Ample evidence indicates that tactile processing is enhanced by prolonged visual deprivation (Doane et al., 1959; Zubek et al., 1964; Facchini and Aglioti, 2003; Chebat et al., 2007; Wong et al., 2011). However, there is still debate regarding the extent to which short-term visual deprivation can enhance passive tactile discrimination. For example, Wong et al. (2011) observed no enhanced *passive* tactile grating orientation discrimination after short visual deprivation (up to 110 min) of their sighted subjects. By contrast, Facchini and Aglioti (2003), observed enhanced passive tactile grating orientation discrimination after 90 min of blindfolding, and Leon-Sarmiento et al. (2008) observed enhanced discrimination of grating orientations after only 45 min of visual deprivation. Thus, even if we do not assume that blindfolding our sighted participants enhanced their tactile acuity, we suggest, given the above evidence, that visual deprivation impacts tactile discrimination abilities including the ability to form and manipulate mental representations of objects (here letters).

Implications for Models of Perceptual Encoding in the Blind and Visually-Impaired

The fact that visually-impaired and blind participants exhibited mental rotation effects for both trained and untrained normal stimuli might be indicative of an *item-independent* encoding system operating in these individuals, which allows for facilitated transfer between new and learnt stimuli and faster generalization of encoding rules. It was previously proposed that this might be a result of changes in stimulus processing and encoding that are driven by neuroplasticity (Collignon et al., 2006, 2009, 2015). Specifically, it was suggested that the congenitally blind may show different learning strategies from the sighted as a result of allocating more attention to sensory information processing (Pring, 1988; Collignon et al., 2006). In fact, to test the hypothesis that the lack of visual input results in data-driven rather than conceptual encoding strategies, Röder and Rösler (2003) tested memory for environmental sounds in sighted, congenitally-blind and late-blind subjects. They had participants encode sound either in a semantic ("deep") or in a physical ("shallow") fashion, and found that while all three groups profited most from semantic encoding, congenitally blind individuals outperformed the sighted ones on conceptually similar items after encoding (Röder and Rösler, 2003), and age-matched late-blind performed as well as congenitally-blind participants. Such results refute previous beliefs that the blind are less able to use conceptually based encoding strategies (for a discussion, see Thinus-Blanc and Gaunet, 1997), and instead support the hypothesis that the visually-impaired are able to make elevated use of perceptual encoding to aid recognition (Röder and Rösler, 2003; Rokem and Ahissar, 2009). Our results are also consistent with these hypotheses. The lack of differences in performance of our participants between trained and untrained stimuli suggests that once a general schema of stimulus encoding is created, visually-impaired and blind individuals easily transfer the learned concepts to unfamiliar stimuli. The visually-impaired and blind might thus rely more on conceptual item-independent processing (Röder et al., 1997; Collignon et al., 2006; Rokem and Ahissar, 2009) that may help compensate for visual loss.

Implications for Rehabilitation via Sensory Substitution

The multisensory or "supra-modal" nature of object and spatial representations has important implications for rehabilitation applications using sensory substitution in individuals where input from one sensory modality, for example vision, is either impaired or absent. In such cases, both multisensory and cross-modal processes are primary drivers of neuroplasticity in visual areas (Kirkwood et al., 1996; Amedi et al., 2004; Merabet et al., 2005; Pascual-Leone et al., 2005; Murray et al., 2015), which may promote a task-selective and modality-independent re-specialization of these cortical structures (Murray et al., 2016; Amedi et al., 2017). In addition, spatial feature processing does not generally seem to rely on information from a specific modality (Pribram, 1971; Amedi et al., 2001; Pietrini et al., 2004; Struiksma et al., 2009). Lacey et al. (2007b) also demonstrated that such "supra-modal" representations of spatial characteristics are viewpoint-independent, and thus unaffected by object constancy issues (see also Lacey et al., 2009). One implication is that it may prove easier to achieve an "abstract" object representation (Pietrini et al., 2004).It has been repeatedly demonstrated that tactile information specifically can support spatial functions in blind, visually-impaired, and sighted subjects (Marmor and Zaback, 1976; Carpenter and Eisenberg, 1978; Grant et al., 2000; Ptito et al., 2005; Sathian, 2005; Chebat et al., 2007; Wan et al., 2010; Rovira et al., 2011; Vinter et al., 2012).

However, classical devices for conveying tactile information, such as the Braille alphabet, the white cane, and tactile maps, remain limited in the breadth of information they can convey, their accessibility, and their ergonomics (among other considerations) (reviewed in Gori et al., 2016). There are several potential advantages of digital haptics using the finger/hand over technologies such as the BrainPort or TDU delivered to the mouth. For one, digital haptics are completely non-invasive. The abovementioned technologies are not only ergonomically invasive (i.e., the mouth is full), but also use electrical stimulation of the tongue. Second, participants using the TDU needed 9 h of training on a single letter from Snellen's E test (i.e., the letter E) to recognize the letter presented in sizes ranging from 5 to 1.3 cm with 100% accuracy (see Figure 2 in Sampaio et al., 2001). By comparison, our participants needed 45 min to recognize trained and untrained letters in their normal form at a 0° and 90° angle (i.e., 4 letters, size on screen height × length: 4 × 5 cm) with ∼70–75% accuracy. Thus, our method allows faster learning of a wider vocabulary of stimuli. In addition, the renderings via digital haptics allow for rapid and even dynamically changing simulation of a wide variety stimuli (from letters to full spatial maps) that need only to be digitally translated (i.e., coded) into a haptic form. This can be based on pre-programmed libraries or alternatively on real-time image-to-haptics conversation algorithms. Moreover, haptics allow the user a greater degree of control; the device can be explored at the discretion of the individual when they actively explore the tablet with their hand, leaving their mouth (and voice) unobstructed. These collective features may also augment the accessibility of such devices to both children and the elderly alike. However, we would also note that 4 of our 14 patients (i.e., 29%) did not meet our inclusion criterion of greater than chance levels with upright stimuli, independent of their angle of rotation. We can only speculate as to the potential causes and contributing factors. However, it is in our view unlikely that experience with Braille or the etiology of visual impairment has a direct link to performance with the haptic tablet. Both groups included individuals with either congenital or acquired impairments as well as individuals literate and illiterate in Braille. It will be important for further applications of this technology to establish if and how tactile sensitivity and discrimination abilities may underscore abilities to quickly learn to use this device. These points notwithstanding there are a number of promising domains for the application of this technology. One is the transmission of the concept of size-invariance (and perhaps also perspective invariance that can help promote both egocentric and allocentric representations) of haptic stimuli. This is an aspect that requires further exploration.

To date, devices including BrainPort and TDU have shown to be effective for functions ranging from object recognition, including measures of "visual" acuity (Chebat et al., 2007; Arnoldussen and Fletcher, 2012), to tasks requiring actions coordinated with mental representations of the perceived tactile objects (reviewed in Bach-y-Rita and Kercel, 2003). The present results similarly provide evidence that participants were able to understand the shape and even the form that the letters are haptically presented in (i.e., normal vs. mirror-reversed), speaks in favor of the application of digital haptics for simulation of spatial features. This is important, as spatial features rely on internal representations, and are directly related to spatial behaviors (Thinus-Blanc and Gaunet, 1997), such as object manipulation, localization, and spatial mapping. Ongoing work from our laboratory focuses on the applicability of this haptic technology in simulating trajectories modeled on a realistic indoor environment (i.e., an apartment's layout and corridors). Thus, the spatial functions that this technology has the potential to support can be directly extended to independent mobility.

The main innovation from our study is the successful application of a digital method. This is important, as digital rehabilitation methods promise to alleviate the medical field by reducing the necessary resources. Digital haptic stimulation finds applications not only in restoring spatial functions in the blind and visually-impaired, but also for rehabilitation of such functions in participants after sight restoration, for example in sight-restored cataract patients (McKyton et al., 2015). Specifically (McKyton et al., 2015), cataract operated children and young adults demonstrated immense deficits in mid-level visual processing (such as 3D object shapes) after cataract removal, despite intact low-level visual abilities. Using digital haptics, such patients may retrain their deficient spatial skills, in a safe, easy, and cost-effective way. As these representations have a "supra-modal" nature, digital tactile stimulation could aid existing therapy techniques to help patients encode a more abstract object representation. Thus, it is evident that the applicability of digital haptics is very promising for the medical domain.

CONCLUSION

Participants with various forms of visual impairments or blindness were able to use a digital haptic technology to create mental representations of objects. It further suggests that these participants, unlike their sighted counterparts, seem to rely on a more conceptual encoding procedure that is not item-specific, thereby making more use of perceptual information, as well as of a possible multisensory working memory. Our results have important implications for rehabilitation regimes of object-related, spatial and mobility functions using sensory substitution, as well as for virtual simulated sensory perception methods more generally. Thus, our study highlights the merits of using innovative digital technologies as an application in rehabilitation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, MM, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vaudois Cantontal Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RT and MM are responsible for the study concept and design. RT, FA, and JR acquired the data and worked with the participants. CC provided instrumentation and software. The analysis and interpretation of data were carried out by RT and MM. The manuscript was drafted by RT and MM. All authors provided input on revisions to the manuscript. All authors approved the final manuscript.

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BRIEF RESEARCH REPORT
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Congenital Deafness Leads to Altered Overt Oculomotor Behaviors

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The human brain is highly cross-modal, and sensory information may affect a wide range of behaviors. In particular, there is evidence that auditory functions are implicated in oculomotor behaviors. Considering this apparent auditory-oculomotor link, one might wonder how the loss of auditory input from birth might have an influence on these motor behaviors. Eye movement tracking enables to extract several components, including saccades and smooth pursuit. One study suggested that deafness can alter saccades processing. Oculomotor behaviors have not been examined further in the deaf. The main goal of this study was to examine smooth pursuit following deafness. A pursuit task paradigm was used in this experiment. Participants were instructed to move their eyes to follow a target as it moved. The target movements have a possibility of four different trajectories (horizontal, vertical, elliptic clockwise, and elliptic counter-clockwise). Results indicate a significant reduction in the ability to track a target in both elliptical conditions showing that more complex motion processing differs in deaf individuals. The data also revealed significantly more saccades per trial in the vertical, anti-clockwise, and, to a lesser extent, the clockwise elliptic condition. This suggests that auditory deprivation from birth leads to altered overt oculomotor behaviors.

Keywords: deafness, oculomotor abilities, brain plasticity, overt eye movement, pursuit task

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INTRODUCTION

It is well established that oculomotor behaviors depend on both visual and vestibular information, but there is also some evidence that auditory functions are implicated in oculomotor behaviors (e.g., Paulsen and Ewertsen, 1966; Rolfs et al., 2005; Valsecchi and Turatto, 2009; Kerzel et al., 2010; Yuval-Greenberg and Deouell, 2011; Zou et al., 2012). For example, it is well-known that rotating a sound around a subject's head can induce nystagmus (Paulsen and Ewertsen, 1966). Several studies showed that an auditory stimulus can lead to visual saccades toward the source of the sound (Zahn et al., 1978; Zambarbieri et al., 1982; Van Grootel and Van Opstal, 2009) and that the presentation of an auditory stimulus can reduce the rate of saccades (Rolfs et al., 2005; Kerzel et al., 2010; Yuval-Greenberg and Deouell, 2011; Zou et al., 2012). Moreover, one study has shown evidence that gaze position can affect auditory localization accuracy (Maddox et al., 2014) and results from our team suggest that listening or even imagining auditory motion stimulus can induce involuntary eye movements (Landry et al., 2015). Considering the apparent link between auditory input and oculomotor behaviors, one might wonder how the loss of auditory input from birth might influence these motor behaviors.

There are two ways to study oculomotor behaviors. As described by Munoz and Coe (2011), *overt* oculomotor behaviors simply consist of moving the eyes. On the contrary, covert visual selection oculomotor behaviors are more complex. They imply a shift of attention with or without eye movements. All experiments on oculomotor behavior in the deaf have used paradigms that investigate the visual attention aspects of eye movements (e.g., Heimler et al., 2015; Prasad et al., 2015; Jayaraman et al., 2016). Most of these studies demonstrate an increased selective attention for a target in the visual periphery or for a moving target in deaf individuals.

Eye movement tracking enables to extract several components, including saccades and smooth pursuit (Leigh and Zee, 2015). Saccades and smooth pursuit are different and reflect independent processes (saccades: Sparks and Mays, 1990; pursuit: Lisberger et al., 1987). Only one study has measured the ocular performance in the deaf with a classic overt oculomotor behavior task of pro- and anti-saccade (Bottari et al., 2012). Results showed faster saccade latencies and smaller error rates in pro- than anti-saccade trials in deaf, suggesting a possible alteration in the balance between voluntary and reflexive eye-movement. Overt oculomotor behaviors have not been examined further in the deaf. As opposed to saccades, smooth pursuit requires constant regulation by feedback loops (Leigh and Zee, 2015). Smooth pursuit provides a window into processes like movement generation, integrity of combined visual and motor feedback loops and impairment of feedback control (e.g., Robert et al., 2014; Lizak et al., 2016). Here, we aimed to examine smooth pursuit accuracy and saccades in the deaf.

METHODS

Participants

Twenty-four adults participated in the present study. Twelve were deaf, having a severe to profound hearing loss. Nine of these subjects were congenitally deaf. The three other subjects became deaf in infancy, between 2 and 24 months (one from an unknown illness, one from a hereditary condition and one from a premature birth) (age range 18–42, *M* = 29). All participants had a long-term severe-profound sensorineural hearing loss. When they came for the study they had their more recent audiogram with them. These thresholds were used. All audiogram were done within a year pre-study. All but one participant used bilateral hearing aid and used oral language in addition to lip reading. The only participant to use sign language was the one who do not use hearing aid (see **Table 1** for participant characteristics). Twelve control subjects had normal hearing and no otologic problems (age range 18–34, *M* = 26). All subjects had normal or corrected to normal vision. Vision was tested with the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart at a distance of 1.5 meters. The set criterion was 20/20 for each eye either for normal or corrected to normal vision. All participants had completed a post-secondary education. None of the participants from either group had learning disabilities, neurological problems or other known medical conditions. All participants were consenting volunteers and were treated according to Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Medical Research Council of Canada MRRC, 2003). All participants were naïve to the purpose of the experiment.

Eye Movement Recordings

Eye position was acquired non-invasively using a video-based EyeLink 1000 system with a 2000 Hz-upgraded camera (SR Research, Canada). The EyeLink 1000 system records binocular eye position with a sampling rate of 1000 Hz and a spatial resolution of <0.01°. Head movements were restrained by the use of a chin-rest positioned 60 cm from a linearized video monitor (Viewsonic 19″ CRT, 1024 × 768 pixel resolution, 100 Hz refresh rate). A nine-point calibration routine was performed at the beginning of each experimental condition, using the default EyeLink locations. Calibration was repeated if any calibration point was off target by more than 1° or if the average error for all points was above 0.5°. Average calibration accuracy over all participants was 24 min. arc for the central calibration point, and 32 min. arc for the extreme calibration points at the corners of the screen.

Before the beginning of the experiment, proper instructions were presented verbally by the experimenter and displayed on the screen to ensure full understanding of the experimental task by all participants.

Participants were able to clearly understand spoken instructions by using a combination of lip reading and their hearing aids. For the one participant who only communicates using sign language, the instructions were clearly written. The instructions for each condition were presented in writing on the computer screen, allowing all participants to read them. They had as long as they needed to read and understand the instructions, and the experimenter made sure the instructions were understood before the experiment commenced. None of the hearing-impaired participants reported any significant reading difficulty.

Experiment: Pursuit Task

Participants were asked to track a moving 0.5° circular target. Drift correction was achieved by offsetting the target by 10°, with the location dependent on the type of motion presented.

The drift correction target started in a different location depending on the type of motion. For example, for the target moving up/down, left/right, the initial drift correction was at the center of the screen. For the clockwise/anti-clockwise, the target appeared on the left-hand side of the ellipse.

Following the drift correction and a 50 ms blank screen, participants were instructed to move their eyes to follow the target as it moved around the screen in one of four directions: horizontally, vertically, elliptically clockwise, or elliptically counter-clockwise. Moreover, the target moved at one of two velocities (2 or 4 deg/s), resulting in eight conditions repeated three times randomly. Inter-trial interval was self-paced, as the participant had to stare at the fixation marker and press spacebar to initiate the next trial. For an example of raw data for both groups see **Figure 1**.

TABLE 1 | Participants characteristics.

Age al test	Age of deafness	Main Communication mode	PTA (R) (dB HL)	PTA (L) (dB HL)	Hearing Aids	Age of first hearing aid use (years)
21	Birth	Oral	93	55	Bilateral	3
36	Birth	Oral	72	75	Bilateral	24
32	Birth	Oral	85	78	Bilateral	4
18	Birth	Oral	87	85	Bilateral	3
29	Birth	LSQ	113	>113	Ø	Ø
29	2 months	Oral	85	80	Bilateral	2
30	24 months	Oral	78	67	Bilateral	5
27	Birth	Oral	72	70	Bilateral	1–2 months
42	Birth	Oral	58	63	Bilateral	22
25	Birth	Oral	62	82	Bilateral	6
30	Birth	Oral	>105	>105	Bilateral	1
23	3 months	Oral	>98	>98	Bilateral	3

PTA: Pure tone average (500Hz, 1000Hz, 2000Hz).

The position of the target moved depending on task. For up/down, left/right, the target started at the center of the screen (512,384 in X/Y pixel coordinates). In the up/down condition, the target would then move 5° upward, stop, and then 10° downward, stop, and then finally 5° upward to stop back at the center of the screen. Same is true for the left/right condition.

For the elliptical motion, the target moved in the same direction (clockwise or anti-clockwise) forming a circle with a total radius length of 20°. In all cases, the moving stimulus was presented for 10°s. For both of the elliptical condition, the target started at coordinates on the left of the screen (171,384), with the target proceeding to rotate either clockwise or anticlockwise from that position. The parameters of the ellipse were: Amplitude X axis 341 pixels. Amplitude Y Axis 256 pixels. Target was white (RGB = 255,255,255), background was black (RGB = 0,0,0).

Data Analysis

Only the data from the right eye were used. Blink periods were identified using the EyeLink 1000 heuristic filtering algorithm (Stampe, 1993) and were removed. In addition, all samples 200 ms before and after each blink were removed to eliminate the initial and final phases of the blink during which the pupil could be partially occluded. We also removed portions of the data that contained very fast increments and decrements in pupil area (20 units per sample). Martinez-Conde et al. (2006) identified these periods as partial blinks that do not fully occlude the pupil and that are not detected by the Eyelink 1000 algorithm. The remaining eye movement data were analyzed after blink and partial-blink data cleanup.

For the pursuit task, accuracy was measured by calculating an individual's ability to maintain fixation within a 1° radius of the target during the pursuit. This was calculated every 20 samples (i.e., every 20 ms) and percent accuracy was obtained for each trial. The analysis ran using a dynamic region of interest that followed the position of the target on each sample of the eye tracker. Individuals were classified as being accurate if their eye position was within a 1° window around the target during the sample period, or inaccurate if their eye position exceeded the 1° window.

The accuracy (and all subsequent dependent variables) were then entered into a linear mixed effects model. Linear mixed effects models can account for inter-participant and inter-item variation by incorporating random effects in the model design, which is introduced by variation due to individual differences. Their principled methods of modeling heteroskedasticity and non-spherical error variance give linear mixed effects models more power than traditional measures (Baayen et al., 2008). Separate linear mixed effect models on accuracy were completed for each of the four direction (horizontal, vertical, elliptical clockwise, and elliptical counter-clockwise). To predict accuracy, we included one between-subjects factor with two levels (hearing-impaired and controls) and a within-subjects factor of speed with two levels (2 and 4 deg/s) as fixed and random effects—which allowed them to vary across participants. Note we used the Satterwaite method for degrees of freedom. In addition to accuracy, we also calculated mixed effect models with the following dependent variables (1) the number of saccades per trial, (2) saccade latency (time from onset of the stimulus until the first saccade was initiated), (3) saccade amplitude, (4) saccade duration, and (5) average velocity of saccade, for each of the four directions. In addition to the mixed effect models, *post hoc* analysis include Hedges' *g* as an effect size measure appropriate for small sample sizes, and two-tailed Mann-Whitney tests.

We used a linear model because with large samples sizes, the binomial is well approximated by a Gaussian distribution. To confirm this, we assessed the normality of these data using the Shaprio-Wilk test (all $p > 0.05$ indicating these data were not significantly different from a normal distribution). Further, the linearity of the distribution on a quantile–quantile (Q–Q) plot confirmed these data to be normally distributed. After removing blinks, on average 93% of the sample information was retained for use in the analysis.

RESULTS

Figure 2 presents the accuracy measured during the pursuit conditions for the hearing-impaired group (light columns) and the normal hearing control group (dark columns) for each of

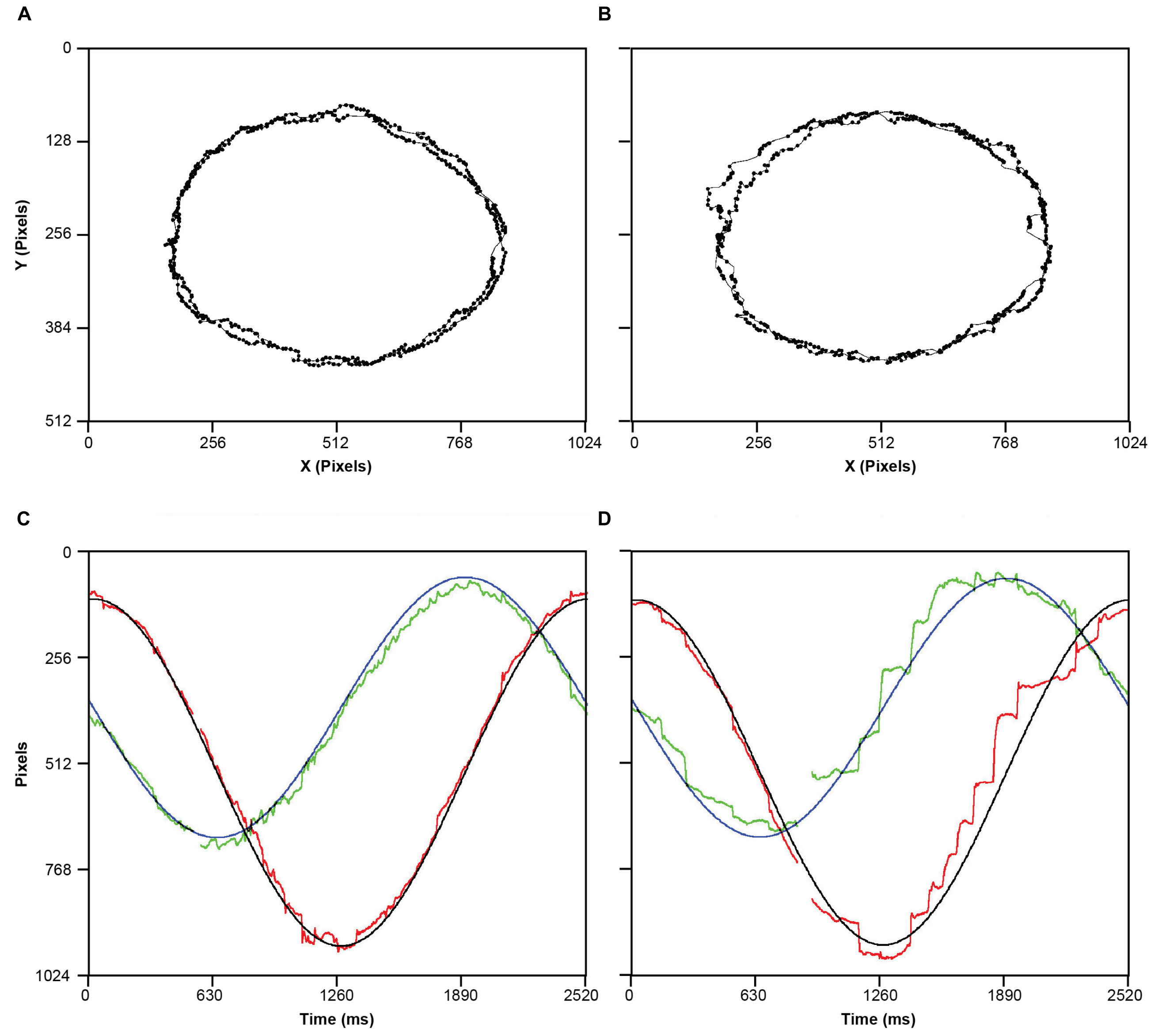

FIGURE 1 | Examples of raw spatial data of eye movements for one control participant **(A)** and one hearing-impaired participant **(B)**. **(C)** a time series representation one cycle of the target elliptical movement in X (Black) and Y (blue) position on the screen, and corresponding tracking eye movements in the X (red) and Y (green). **(D)** Same as C, but for a hearing-impaired participant. Missing data reflect missing samples due to eye blink. Note that all four panels represent the experimental condition where stimulus was moving anti-clockwise at slow speed.

the four pursuit tasks (vertical, horizontal, elliptic clock-wise, and elliptic anti-clock-wise) at two speeds: slow ($2^\circ\ s^{-1}$) and fast ($4^\circ\ s^{-1}$). Accuracy in tracking the target was measured as the percentage of the 10 s trial where the participant-maintained fixation within a 1° radius of the target. The analysis of accuracy in performing the task show significant differences between the groups, $F(1,33) = 11.082$, $p = 0.002$, and between speeds, $F(1,31.2) = 9.507$, $p = 0.004$, but no interaction, $F(1,33) = 0.888$, $p = 0.353$, during the clockwise ellipse task. Likewise, there was a main effect of group, $F(1,33) = 12.34$, $p = 0.001$, and speed, $F(1,30.7) = 15.28$, $p < 0.001$, during the anti-clockwise ellipse task, but no interaction, $\mathrm{F}(1,33) = 2.61$, $p = 0.116$. As seen in **Figure 2**, there was no effect of group, no effect of speed, and no interaction during the horizontal and vertical pursuit task (all $p > 0.1$). *Post hoc* comparisons show a decrease in mean difference in accuracy between controls and hearing impaired participants for the slow clockwise ellipse ($M_{\mathrm{diff}} = -15.440$ [95%CI −25.544, −5.976], Mann Whitney $U = 118$, $p = 0.009$, Hedges' $g = -1.175$ [95%CI −1.928, −0.256]) and slow anticlockwise ellipse ($M_{\mathrm{diff}} = -17.382$ [95%CI −26.884, −8.3], Mann Whitney $U = 122$, $p = 0.004$, Hedges' $g = -1.375$ [95%CI −2.137, −0.502]).

We also analyzed different measurements that affect eye movement during pursuit task, specifically number, duration, latency, amplitude and velocity of saccades. For the average number of saccades (see **Figure 3**) performed in the anti-clockwise ellipse task, there was a main effect of group $F(1,32.7) = 6.047$, $p = 0.019$, and speed $F(1,17) = 37.284$, $p < 0.001$, but no interaction, $F(1,33) = 0.505$, $p = 0.482$. There was also a main effect of speed in the clockwise condition $F(1,32.1) = 65.77$, $p < 0.001$, and a main effect of group, $F(1,28.3) = 8.83$, $p = 0.006$. Interestingly (given the results of the task accuracy) there was a main effect of speed, $F(1,19.2) = 80.662$, $p < 0.001$, for the vertical pursuit task, but no main effect of group, $F(1,11.2) = 1.694$, $p = 0.219$. In the horizontal condition, there was a significant main effects of speed, $F(1,13.7) = 62.02$, $p \leq 0.001$, but not group, $F(1,5.2) = 2.80$, $p = 0.115$. In addition, the analysis did not show any significant interaction (all $p > 0.1$) between group and speed in any of the four pursuit tasks. For all other eye movement measures (average of saccade amplitude, latency until the first saccade, duration and velocity of the saccades), the mixed effect models showed no main effect of group for all conditions (vertical, horizontal, elliptic clock-wise, and elliptic anti-clock-wise: $p > 0.1$).

Focusing on ellipse tracking results, using the *post hoc* analysis we observed that for the fast clockwise ellipse tracking task, there is a significant increase in the number of saccades by the hearing impaired group in comparison to the control group ($M_{\text{diff}} = 7.38$ [95% CI 2.762, 13.736], Mann Whitney $U = 32$, $p = 0.002$, Hedge's $g = 1.02$ [95% CI 222, 1.62). Similarly, we find a similar increase in number of saccades for the hearing impaired group in the slow anti-clockwise condition ($M_{\text{diff}} = 5.435$ [95% CI 2.021, 9.6], Mann Whitney $U = 34$, p = 0.003, Hedges' $g = 1.09$ [95% CI = 0.337, 1.82]).

DISCUSSION

In the present study, eye movements were tested in a group of hearing-impaired individuals who are deaf since early infancy using a pursuit task. The findings indicate that hearing-impaired participants were less accurate at maintaining target fixation than the control group for the more complex motion in the elliptical tasks. However, hearing-impaired participants performed the

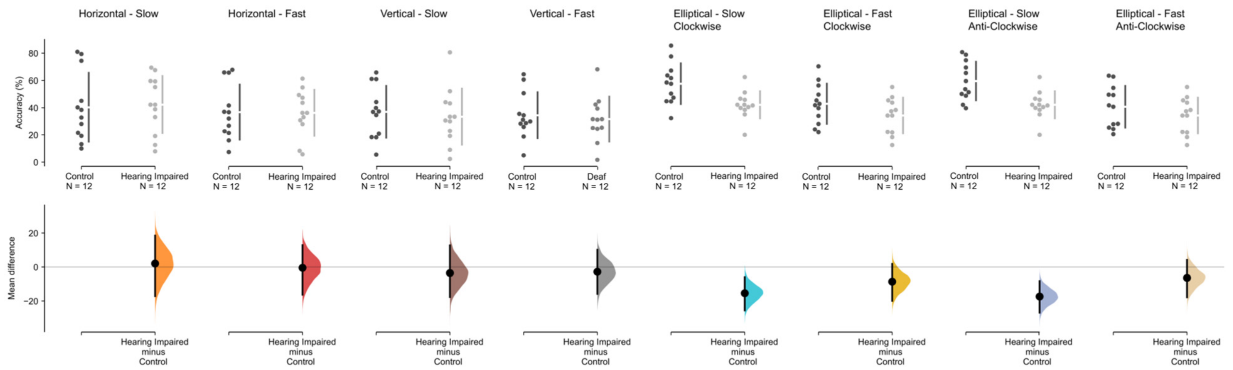

FIGURE 2 | Accuracy results for the pursuit conditions for the hearing-impaired group (light gray) and the control group (dark gray). The mean difference for accuracy (% time on target) for all eight conditions are shown in the above Cumming estimation plot. The raw data is plotted on the upper axes; each mean difference is plotted on the lower axes as a bootstrap sampling distribution (5000 bootstrap samples were taken; the confidence interval is bias-corrected and accelerated). Mean differences are depicted as dots; 95% confidence intervals are indicated by the ends of the vertical error bars.

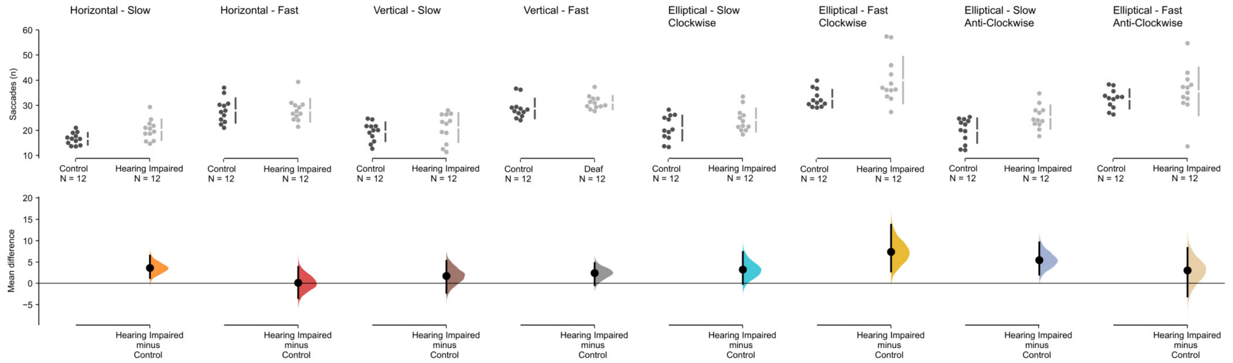

FIGURE 3 | Saccade results for the pursuit conditions for the hearing-impaired group (light gray) and the control group (dark gray). The mean difference for the number of saccades for all eight conditions are shown in the above Cumming estimation plot. The raw data (number of saccades) is plotted on the upper axes; each mean difference is plotted on the lower axes as a bootstrap sampling distribution (5000 bootstrap samples were taken; the confidence interval is bias-corrected and accelerated). Mean differences are depicted as dots; 95% confidence intervals are indicated by the ends of the vertical error bars.

same as the controls in the linear motion tasks. The results also indicate that, compared to a control group with normal hearing function, individuals with impaired hearing show a reduced ability to track a target in the elliptical conditions, and made more saccades per trial in the vertical, anti-clockwise, and to a lesser extent, clockwise elliptic conditions at both of the tested speeds. These results suggest that deafness has an impact on the development or maintenance of overt oculomotor behaviors.

Several studies suggest that deprivation of a sensory modality can alter the development of other modalities (Bavelier and Neville, 2002). Cerebral plasticity following deafferentiation can lead to adaptive or maladaptive behavioral changes (Merabet and Pascual-Leone, 2010). In the deaf individual, several studies suggest better performance for a few visual abilities, including visual detection in the periphery (for a summary see Bavelier et al., 2006). However, such specific improvement in performance has not been found in other sensory systems or processes. In regard to the motor system, auditory deprivation appears to lead to maladaptive behavioral changes. Indeed, deafness generally leads to decreased performance on general dynamic coordination, balance, ball catching, reaction times, speed of movement execution and motor learning (e.g., Wiegersma and Velde, 1983; Gayle and Pohlman, 1990; Siegel et al., 1991; Hartman et al., 2011). Our results are in accordance with the general notion that hearing has an important role in the emergence and maintenance of motor processing.

Since eye movements are simpler than other movements in many ways, the oculomotor system provides an ideal opportunity to investigate the brain mechanisms underlying visually guided movement (Lisberger et al., 1987). Nevertheless, despite a relatively large number of studies, most results are contradictory and it is unclear what the effects of auditory deprivation are on visual orienting, for example (for a review see Dye and Bavelier, 2013). Some studies suggest that when visual periphery and central visual field are simultaneously stimulated, deaf individuals are able to further divide more efficiently their visual attention resources in opposition to control participants (Dye et al., 2009). Many experiments showed that deaf individuals are more readily distracted by non-pertinent distracting elements, especially when those elements appear in the peripheral vision field (Proksch and Bavelier, 2002; Chen et al., 2006). All of these studies aimed to investigate complex attentional processes or pursuit of visual stimuli in the periphery and assessed exclusively visual attention orienting, neglecting whether overt oculomotor behavior may also change in deaf people.

Surprisingly, the covert visual selection aspect of visual oculomotor behaviors has been further investigated than the overt aspect. The study of Bottari et al. (2012) is the only one to date to have measured the ocular performance with a classic overt oculomotor behavior task of pro- and anti-saccade. Results of this study suggest a possible alteration in the balance between voluntary and reflexive eye-movement orienting, shorter saccade latencies and smaller error rates were found in pro-saccade trials rather than in anti-saccade trials in both populations. However, the effect was substantially larger in deaf than hearing participants. Our results confirmed those of Bottari et al. (2012), suggesting that movement generation is altered in the deaf, but we extended the latter by suggesting that combined visual and motor feedback loops, and feedback control, which can be assessed with smooth pursuit (Lizak et al., 2016), is also impaired in this population. Taken together, these data suggest that early auditory input is essential for the normal development of the mechanisms underlying the control of eye movements.

The homogeneity of the group present in this study, in terms of severity, age of onset, progression, and etiology should be taken into consideration when interpreting the present findings. All participants had a severe or profound hearing loss (see **Table 1** for details). The majority of the participants had a hearing impairment from birth while only three became impaired prelingualy, namely between the ages of 2 to 24 months. Finally, all but one participant used hearing aids for amplification. Here, the group of participants all had similar onset of hearing loss, duration of hearing loss, hearing aid use, and modes of communication, factors that have been revealed to critically impact plasticity and behavior in the deaf (e.g., Kral and Sharma, 2012). It is to be noted that the overall variance of their results is quite small and is not different than that of the control group. The many characteristics of hearing loss should be examined further in order to reveal which features trigger more oculomotor behavioral alterations. Future research needs to examine the effect of these characteristics, the kind of behavioral alteration, and whether there exists a critical period during which auditory input is required to develop typical oculomotor behaviors.

Finally, vestibular function may also be discussed in relation to the data. Indeed, a large proportion of congenitally deaf individuals have concomitant vestibular impairment (Buchman et al., 2004). Vestibular cells are involved in vestibule-ocular reflexes, which allow us to hold images still on the retina during brief head movements (Müri and Nyffeler, 2008). In our study, participants had their head fixed, so vestibulo-ocular reflexes were not generated during the experiment. However, neurons from the vestibular nucleus are also involved in signaling eye velocity during smooth pursuit (Katz, 2002; Krauzlis, 2004), so they were involved in the pursuit task. Further studies will need to identify the exact impact of auditory deprivation on oculomotor behavior by controlling for vestibular impairment.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by all participants were consenting volunteers and were treated according to Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Medical Research Council of Canada, MRRC, 2003). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS, CT, and DE designed and performed the experiment. All authors wrote the manuscript and discussed the results.

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Short-Term Deprivation Does Not Influence Monocular or Dichoptic Temporal Synchrony at Low Temporal Frequency

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Studies on binocular combination and rivalry show that short-term deprivation strengthens the contribution of the deprived eye in binocular vision. However, whether short-term monocular deprivation affects temporal processing *per se* is not clear. To address this issue, we conducted a study to investigate the effect of monocular deprivation on dichoptic temporal synchrony. We tested ten adults with normal vision and patched their dominant eye with an opaque patch for 2.5 h. A temporal synchrony paradigm was used to measure if temporal synchrony thresholds change as a result of monocular pattern deprivation. In this paradigm, we displayed two pairs of Gaussian blobs flickering at 1 Hz with either the same or different phased- temporal modulation. In Experiment 1, we obtained the thresholds for detecting temporal asynchrony under dichoptic viewing configurations. We compared the thresholds for temporal synchrony between before and after monocular deprivation and found no significant changes of the interocular synchrony. In Experiment 2, we measured the monocular thresholds for detecting temporal asynchrony. We also found no significant changes of the monocular synchrony of either the patched eye or the unpatched eye. Our findings suggest that short-term monocular deprivation induced-plasticity does not influence monocular or dichoptic temporal synchrony at low temporal frequency.

Keywords: monocular deprivation, temporal synchrony, interocular suppression, temporal processing, visual plasticity

INTRODUCTION

Hubel and Wiesel (1963) first demonstrated that visual experience in early life can shift ocular dominance in the feline visual system. For instance, the closure of one eye during the critical period, and hence blocking any form of visual input entering the eye, for a period of days or weeks shifts the eye dominance favoring the non-deprived eye. Monocular deprivation modifies ocular dominance in favor of the non-deprived eye at the expense of the deprived eye. This change was demonstrated both at the functional and structural levels of the ocular dominance columns in V1. They replicated the study in older cats and showed that the adult visual system is not as susceptible to visual experience (Hubel and Wiesel, 1970). This work ushered the belief that neural plasticity peaks immediately after birth and tapers off after the critical period.

Although monocular deprivation can shift the ocular dominance in favor of the non-deprived eye in young animals recent studies of humans have demonstrated that the adult visual system retains some degrees of neural plasticity, albeit of a different form (Levi, 2005; Thompson et al., 2008; Levi and Li, 2009; Lunghi et al., 2011; Clavagnier et al., 2013; Zhou et al., 2013a; Campana et al., 2014). For instance, patching an eye for a brief period of time (from 15 min to 5 h) has been found to shift perceptual ocular dominance in adults *favoring the deprived eye* for only up to 30–90 min (Lunghi et al., 2011; Zhou et al., 2013a; Kim et al., 2017; Min et al., 2018). The shift in perceptual ocular dominance seems to be reciprocal, whereby the deprived eye's contribution to binocular vision strengthens and that of the non-deprived eye weakens. This reciprocal change in perceptual ocular dominance has been demonstrated with psychophysical methods, such as binocular rivalry and combination (Lunghi et al., 2011; Zhou et al., 2013a), for review see Basgoze et al. (2018). Zhou et al. (2014) and Kim et al. (2017) also showed that this deprivation effect could be induced without completely removing visual input in the deprived eye. Moreover, electrophysiological (Lunghi et al., 2015a; Zhou et al., 2015) and neuroimaging studies (Lunghi et al., 2015b; Chadnova et al., 2017; Binda et al., 2018) have also shown the reciprocal shift. To illustrate, Chadnova et al. (2017) reported an increased response of the deprived eye and decreased response of the non-deprived eye after short-term patching using MEG. They postulated that contralateral inhibition – which is known to regulate the contrast gain of each eye prior to binocular combination in a current model of binocular interaction (Meese et al., 2008) – mediates the patching effect (Chadnova et al., 2017). Using electrophysiology, Lunghi et al. (2015a) found that the amplitude of visually evoked potentials in the deprived eye increased whereas those from the non-deprived eye decreased. The strengthening of the deprived eye after short-term patching has been linked to reduced levels of GABA in the primary visual cortex (Lunghi et al., 2015b).

Short-term deprivation in human adults have also been shown to influence monocular visual functions. For example, Zhou et al. (2013a,c) reported that short-term patching increases the contrast sensitivity of the deprived eye and decreases that of the non-deprived eye in both normal and amblyopic observers. Furthermore, Zhou et al. (2017) reported that the changes in monocular contrast sensitivity for chromatically defined stimuli were similar with that for achromatic- defined stimuli after 2.5-h monocular deprivation. Finally, Binda et al. (2018), using fMRI BOLD responses, showed that monocular deprivation can affect selectivity for spatial frequency in V1. They found that the selectivity for high spatial frequencies was enhanced in the previously deprived eye. Although short-term monocular deprivation affects monocular visual functions, the reciprocal nature of these monocular changes suggest that the patching effect is based on binocular interaction.

Most psychophysical studies have measured the patching effect in the context of spatial vision with behavioral measurements such as binocular combination and rivalry. In a phase combination task, fusible horizontal gratings are shown to different eyes. Measurement of the bias in a fused percept can quantify each eye's contribution to binocular vision (Ding and Sperling, 2006; Zhou et al., 2013a). Conversely, two incompatible but orthogonal gratings are shown to different eyes in a binocular rivalry task. By measuring the perceived relative duration of each eye's grating stimulus for each subject, one can quantify the changes in eye dominance after patching (Lunghi et al., 2011). However, different neural mechanisms may be involved in these two psychophysical tasks (Bai et al., 2017; Baldwin and Hess, 2018). For testing monocular functions, gratings with different spatial frequency and different contrast are used to measure the contrast threshold (Zhou et al., 2013a). Although these psychophysical studies have demonstrated the spatial influence of short-term monocular visual deprivation in human adults, they have not shown whether patching influences temporal processing.

One aspect of temporal processing of visual information in the human relates to when an observer determines whether two stimuli are temporally synchronous. Temporal synchrony reflects the dynamic nature of visual processing. It has been shown to be an effective cue for binding and segmenting different signals in the absence of spatial cues (Rideaux et al., 2016). Temporal synchrony threshold, the minimum degree of temporal phase difference that enables observers to determine whether the target is flickering asynchronously in time, has been measured in the normal population (Hess and Maehara, 2011). It has also been used to assess temporal deficits in patients with amblyopia (Huang et al., 2012). Huang et al. (2012) reported that the temporal synchrony threshold of the amblyopic eye is higher than that of the fellow eye. They proposed that temporal processing deficit, rather than the detectability of the target, increases the temporal synchrony threshold in the amblyopic eye. Moreover, Tao et al. (2019) found that the elevation of temporal synchrony threshold in amblyopia was present not only when stimuli was presented to the amblyopic eye (i.e., monocular temporal synchrony) but also when presented dichoptically to amblyopic and fellow eyes (i.e., dichoptic temporal synchrony; or, interocular temporal delay). These findings suggest that there is clinical relevance to studying temporal processing in the human visual system.

In this study, we investigated whether short-term monocular deprivation could influence temporal processing of visual information, namely, the threshold for detecting temporal synchrony. A similar temporal synchrony paradigm was used as the one in the study of Tao et al. (2019). The patching effect was quantified by comparing the threshold for temporal synchrony before and after 2.5 h of monocular opaque patching. Specifically, thresholds for detecting dichoptic temporal asynchrony under dichoptic and monocular viewing were measured. Our results show that monocular deprivation does not influence either monocular or dichoptic temporal synchrony.

MATERIALS AND METHODS

Participants

Ten subjects (23 ± 0.42 years old; four males) with normal or corrected-to-normal vision (logMAR ≤ 0.0) participated in this study. All subjects were naive to the purpose of the study.

Apparatus

We performed our experiments with a Macintosh laptop equipped with Matlab (Mathworks, Natick, MA, United States) and the Psychtoolbox 3.0.14. We dichoptically displayed the stimuli on gamma-corrected head-mounted 3D goggles (Goovis Pro, NED Optics, Shenzhen, China). The OLED goggles had a resolution of 1600 × 900 pixels (corresponding to 46 × 26 degrees) and a refresh rate of 60 Hz in each eye. The maximal luminance of the OLED goggles was 150 cd/m^2.

The temporal response functions (TRFs) of the OLED monitor and Cathode Ray Tube (CRT) monitor are not the same. To address whether the TRF of the used display would confound our experimental results, we used Ito et al. (2013)'s measures of the TRFs for the CRT and OLED monitor (see **Supplementary Figures S1A,B** in the supplementary) to simulate the display outputs and investigate whether the asynchrony signal in our test (i.e., the temporal lag) was varied across different TRFs. Two temporal profiles with a flickering rate of 1 Hz and 100 ms temporal lag were used in this simulation (**Supplementary Figure S1C**). The temporal profiles of the stimuli (**Supplementary Figure S1C**) were convolved with the TRFs for the CRT and OLED monitor (**Supplementary Figures S1A,B**) and the results showed the temporal lag did not change with the tested TRF (**Supplementary Figures S1D–F**). In summary, the temporal lag threshold measured from our experiment did not confound the TRF of the OLED display. In fact, since our psychophysical task relied on the comparison between two dots, it would work on all the dots simultaneously regardless of which screen was used; it would not selectively affect one dot or dots in one eye. Thus, our measure of synchrony would not be limited by the screen response characteristics.

Design

All subjects participated in two experiments. Each experiment had three stages (**Figure 1**): baseline measurement of temporal synchrony before deprivation, monocular deprivation for 2.5 h and measurement of temporal synchrony after deprivation. We deprived the dominant eye [tested by the hole-in-the-card test (Dane and Dane, 2004)] for all subjects with an opaque patch (no transmission contrast or luminance). During patching, the participants performed typical office tasks such as browsing a web or reading.

We used a similar paradigm to Tao et al. (2019)'s study to measure the threshold for detecting temporal asynchrony. In this paradigm, two pairs of Gaussian blobs were presented; one pair flickered synchronously (i.e., reference), and the other asynchronously (i.e., signal). They flickered at a temporal frequency of 1 Hz. The reason why we measured at this low temporal frequency was that a higher temporal frequency of the blobs would reduce precise measurement and this also ensured there were no afterimages. For Gaussian blobs with a temporal frequency of 1 Hz (the contrast of blob is modulated sinusoidal over time), one cycle of the stimuli included 60 frames in 1 s since our display screen had a refresh rate of 60 Hz. Therefore, in this case, the minimum measurement accuracy would be 6 degrees (i.e., 360 degrees / 60 frames). On the other hand, at a higher temporal frequency, one cycle of the stimuli would include less than 60 frames, resulting in poorer measurement accuracy. In addition, we performed a pilot study using a higher temporal frequency of the blobs and found that the observers could not perform the task.

We modulated the temporal phase difference between the asynchronously flickering blobs to manipulate the degree of the asynchrony. The two blobs in each pair were presented diagonally with a separation of 2.46 degrees horizontally and vertically. The center of the two blobs was 4.3 degrees above or below the fixation. Between trials, the standard deviation of each Gaussian blob's size randomly varied from 0.28 to 0.46 degrees, and their luminance contrast varied from 0.4 to 0.8 to prevent participants from using local size or contrast cues to solve the task.

In Experiment 1, we measured the dichoptic temporal synchrony threshold in dichoptic viewing configuration ("Di" as shown in **Figure 2A**), in which both the signal and reference blobs were presented dichoptically to different eyes. In Experiment 2, we measured the monocular temporal synchrony threshold in two additional monocular viewing configurations, i.e., MD (**Figure 3A**): monocular dominant eye (i.e., the assigned patched eye) viewing, where both signal and reference blobs were presented to the dominant eye; MND (**Figure 3B**): monocular non-dominant eye viewing, where both signal and reference blobs were presented to the non-dominant eye. Throughout this paper, we will refer to the three conditions with the abbreviations Di, MD, and MND.

All subjects performed each viewing configuration on a separate day. For each viewing configuration, the temporal synchrony threshold was measured before deprivation and at 0, 10, 20, and 30 min after the 2.5-h of monocular deprivation. An illustration of the experimental procedure is provided in **Figure 1**. Each test session contained 160 trials (eight temporal phase difference × 20 repetitions) in one measure, which took about 5 min to complete. Before each experiment, subjects were asked to perform at least 160 practice trials.

Procedure

A constant stimuli method was used to measure the minimum degree of asynchrony that observers needed to discriminate the signal blobs (i.e., the pair of asynchronous blobs). Eight levels of temporal lag (i.e., temporal phase difference between the pair of asynchronous blobs), ranging from 33.33 to 266.67 ms and a step size of 33.33 ms, were tested for each viewing configuration (i.e., Di, MD, and MND). In each trial, the stimuli were presented for 1 s. Participants were asked to determine whether the position of signal blobs was above or

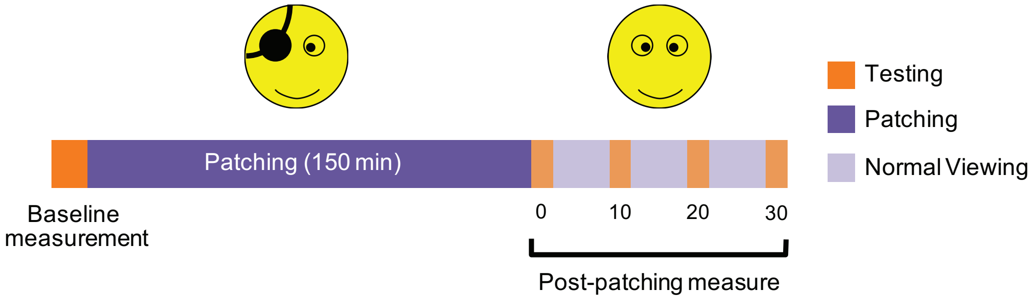

FIGURE 1 | An illustration of the experimental procedure. We deprived one eye for 2.5 h, and assessed the temporal synchrony thresholds at baseline, and 0, 10, 20, 30 min after the finish of the 2.5-h of deprivation.

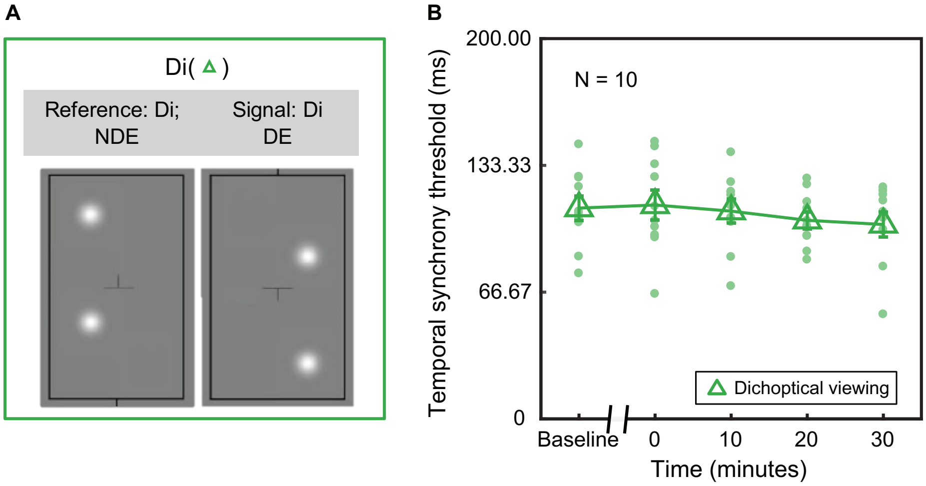

FIGURE 2 | Deprivation effect under dichoptic viewing configuration. **(A)** An illustration of the Di configuration. Both the signal and reference blobs were presented dichoptically to different eyes. **(B)** Dichoptic temporal synchrony threshold in the function of various time points before and after deprivation. Each green dot represents the threshold of each subject. Green triangle denotes the average threshold across ten subjects. Error bars represent standard errors.

below the fixation (two-alternative forced choice, 2AFC). The next trial started 750 ms after the participants' response. The eight levels of temporal lag were tested using an order randomized in various trials.

Data Analysis

For each participant, we derived the psychometric function defined as the proportion correct as a function of the temporal lag. The psychometric function of each configuration at each time point was fitted using Palamedes 1.8.1 (Prins and Kingdom, 2018) based on the following equation:

$$\begin{aligned}\psi(x;\alpha,\beta,\gamma,\lambda) &= \gamma+(1-\gamma-\lambda)F(x;\alpha,\beta)\\ &= \gamma+(1-\gamma-\lambda)[1-exp(-(x/\alpha)^{\beta})] \qquad (1)\end{aligned}$$

where, F (x; α, β) is the Weibull function; x is the temporal lag; α is the threshold; β is a free parameter related to the slope of the function; γ is the guessed rate; and λ is the lapse rate. During our fitting, we set γ at 0.5 and constrained the λ to a fixed value (ranging from 0 to 0.06) for each fitting. A maximum likelihood method was used for deriving the threshold and slope of the psychometric function for each testing time point of each subject.

RESULTS

Experiment 1: Deprivation Effect Under Dichoptic Viewing Configuration (Di)

To assess whether monocular deprivation influences dichoptic temporal synchrony (i.e., the minimum detectable interocular delay), we performed the Di configuration (**Figure 2A**). The averaged and individual temporal synchrony thresholds as a function of time before and after patching are plotted in **Figure 2B**. We conducted a Shapiro–Wilks test to check for normality assumption ($p > 0.05$). Then, a one-way repeated-measures ANOVA was used (one within-subject: time of measurements before and after patching) to check whether the changes in the temporal synchrony threshold induced by monocular deprivation was significantly different relative to the one measured in baseline. One-way repeated-measures

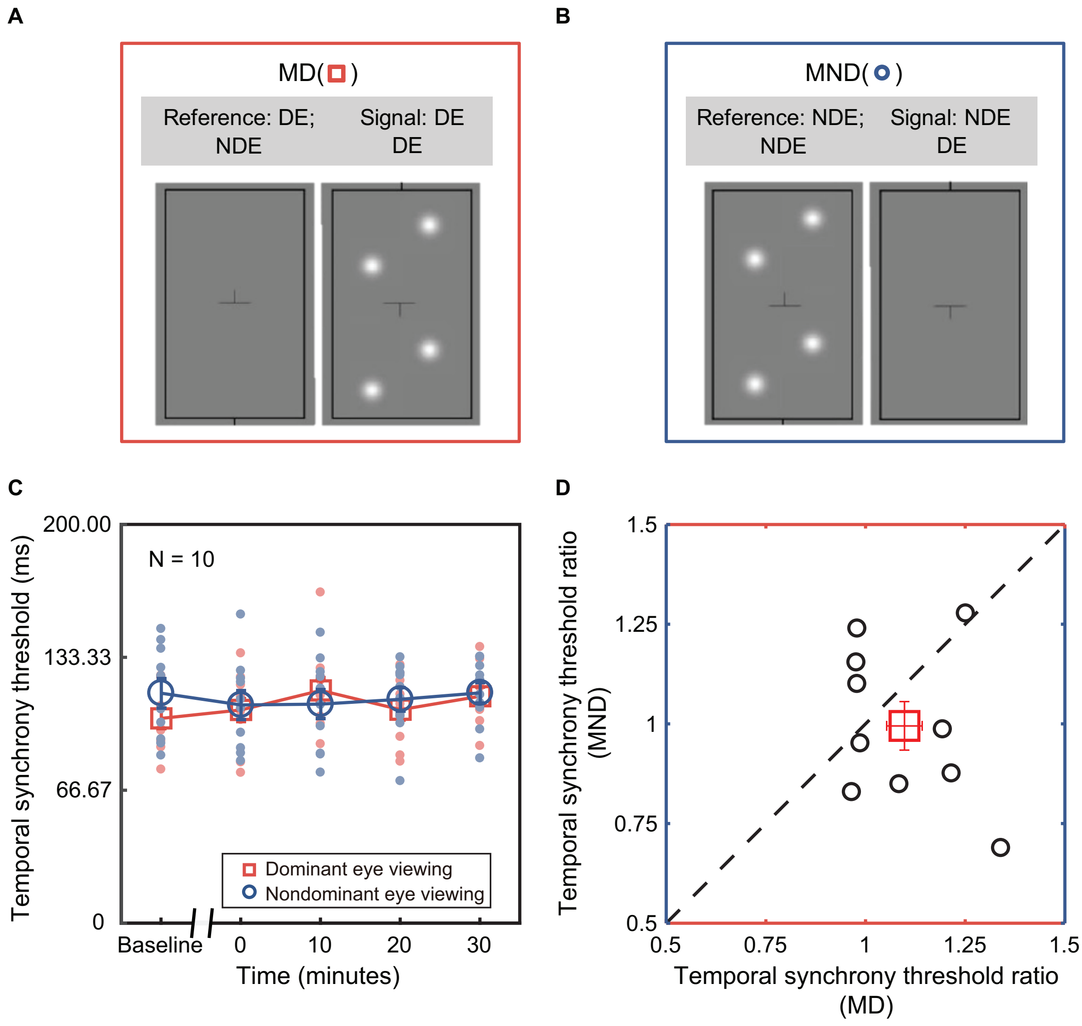

FIGURE 3 | Deprivation effect under monocular viewing configurations. **(A)** Monocular dominant eye viewing (MD). Both signal and reference blobs were presented to the dominant eye (i.e., the assigned patched eye). **(B)** Monocular non-dominant eye viewing (MND). Both signal and reference blobs were presented to the non-dominant eye (i.e., the assigned unpatched eye). **(C)** Monocular temporal synchrony threshold in the function of various time points before and after deprivation. The red plot corresponds to MD configurations, and blue plot to MND. Each dot (blue or red) represents the threshold of each subject. Open symbols (blue circle or red square) denote the average threshold across ten subjects. Error bars (blue or red) represent standard errors. **(D)** Correlation between the changes of monocular temporal synchrony in the deprived eye and non-deprived eye. Error bars represent standard error.

ANOVA showed that the effect of deprivation on the temporal synchrony threshold was not significant [$F(4,36) = 1.464$, $p = 0.233$]. In other words, no significant difference in the dichoptic temporal synchrony threshold was found between before and after patching.

Experiment 2: Deprivation Effect Under Monocular Viewing Configurations (MD and MND)

To assess whether monocular deprivation shifts the threshold for temporal synchrony of one eye – be it the dominant (i.e., the assigned patched eye) or non-dominant eye – we obtained temporal synchrony thresholds in both the MD and MND configurations. The averaged and individual temporal synchrony thresholds as a function of time before and after patching are plotted in **Figure 3C**. One-way repeated-measures ANOVA showed that the effect of deprivation on the temporal synchrony threshold was not significant under either MD [i.e., the assigned patched eye: $F(4,36) = 0.332$, $p = 0.855$] or MND viewing configuration [i.e., the assigned unpatched eye: $F(4,36) = 2.260$, $p = 0.167$]. In short, we found no significant difference in the monocular temporal synchrony threshold before and after patching in both MD and MND configurations.

To further address whether there would be a difference in monocular temporal synchrony threshold between the deprived eye and the non-deprived eye, we conducted an additional two-way repeated-measures ANOVA, with the configuration (two levels) and time point of measurements after patching (four levels) selected as within-subject factors. We found that there was no significant difference between configurations [$F(1,9) = 1.426$, $p = 0.263$] and time points [$F(3,27) = 0.741$, $p = 0.537$]. To better illustrate the relation between the changes of temporal synchrony in deprived eye and non-deprived eye, we divided the value of post-patching tests by the value of baseline to obtain the threshold ratio, and averaged the four post-test ratios. Then we plotted the averaged ratios of non-deprived eye as a function of the average ratios of the deprived eye in **Figure 3D**. There was no significant difference [paired-t test, $t(9) = 1.194$; $p = 0.263$] and no significant correlation ($r = -0.318$, $p = 0.370$) between them.

DISCUSSION

In this study, we investigated whether short-term monocular deprivation could influence temporal processing between the two eyes using a temporal synchrony paradigm. Our results show that short-term monocular deprivation does not affect the dichoptic temporal synchrony threshold in normal observers.

Previous studies – be they psychophysical, neurophysiological or neuroimaging investigations – have reported that short-term monocular deprivation induces neuroplastic changes in the visual system by shifting the perceptual ocular dominance in favor of the deprived eye (Lunghi et al., 2011; Zhou et al., 2013a). Both translucent (20% luminance reduction) and opaque patches (no light transmission or contrast) have been shown to replicate the patching effect (Zhou et al., 2013a). A contrast-gain control model (Ding and Sperling, 2006) has been proposed to underlie the sensory balance between the eyes (Zhou et al., 2013a,b): During patching, the patched eye's contrast-gain would be elevated as a consequence of the loss of visual input. Immediately after patch removal, the previously deprived eye would have its contrast-gain restored to baseline values. Due to the reciprocal nature of the interocular inhibitory circuit (Meese et al., 2006), a reciprocal change would occur for the contrast gain of the non-deprived eye. This explanation is supported by both psychophysical (Zhou et al., 2013a) and neurophysiological studies (Lunghi et al., 2015a,b; Zhou et al., 2015; Chadnova et al., 2017). Assuming that changes in contrast-gain control result in changes in the speed of visual processing, we hypothesized that there may be reciprocal changes in the speed of visual processing in the two eyes after a period of monocular deprivation which might translate to elevated thresholds for temporal synchrony. However, our results show that no significant difference exists between the temporal synchrony thresholds before and after patching when stimuli are either dichoptically or monocularly presented.

Temporal synchrony provides an effective cue for integration and segmentation (Rideaux et al., 2016). Segmentation from temporal synchrony has been shown to be achieved by neurons in the early stage of visual processing (Goodbourn and Forte, 2013). An attenuated and delayed hemodynamic response function in early visual cortex (i.e., reduced synchrony of neural firing) due to abnormal interocular suppression, has been proposed as a possible cause for the temporal synchrony deficits in amblyopia (Farivar et al., 2011; Huang et al., 2012; Tao et al., 2019). Therefore, the processing of temporal synchrony occurs primarily in the early visual cortex. Moreover, electrophysiological studies (Lunghi et al., 2015a; Zhou et al., 2015) have suggested that short-term monocular patching can affect early visual areas, especially primary visual cortex (V1). Also Binda et al. (2018) confirmed that the effect of short-term monocular deprivation was most robust in V1, and moderate in V2, V3 and V4 but absent in V3a and hMT+ via fMRI. However, these studies mainly report the changes of response amplitude after patching rather than those of response timing. An unperturbed temporal synchrony threshold may be the result of little to no influence on the synchrony of neural firing by patching. However, there are multiple functional columns in V1 (Daw, 2006). Therefore, despite our findings of no effect on temporal synchrony detection from patching, it would be inappropriate to conclude that patching minimally affects temporal processing.

Another possible factor is that the patching effect on the temporal processing is too small to be detected by our paradigm. Hess and Maehara (2011) reported that we are surprisingly poor at making temporal synchrony judgements, of the order of 30 milliseconds. Therefore, we performed a power analysis based on the variance from our samples ($n = 10$), i.e., $\sigma_d = 13.414$ for Di configuration, $\sigma_d = 22.054$ for MD configuration, $\sigma_d = 12.835$ for MND configuration. To reach a power of 80%, the effect size would need to be $E = 11.88$ ms, $E = 19.53$ ms, and $E = 11.36$ ms for Di, MD, MND configuration, respectively. Thus, any change in temporal processing that occurs at a finer level than this and that impacts other temporal processes would not have been reflected in our approach using temporal synchrony.

Psychophysical studies on short-term monocular deprivation have shown conflicting results. It seems that findings from one task might not agree with those from other tasks because a specific psychophysical task can target distinct level of spatial processing for visual information. Binocular rivalry and combination tasks have shown different results from identical manipulation of visual information. For example, scrambling the phase of a dichoptic movie in one eye has been shown to elicit the patching effect in a binocular rivalry task (Bai et al., 2017) but not in a phase combination task (Zhou et al., 2014). Also, after short-period patching with a translucent patch, the changes in eye dominance were found to be much stronger and longer-lasting for chromatically defined stimuli than achromatically defined ones in binocular rivalry (Lunghi et al., 2013), whereas the changes were similar for the two kinds of stimuli in binocular combination (Zhou et al., 2017). Baldwin and Hess (2018) used two different masks (parallel vs. cross-oriented) to mimic binocular rivalry and combination. Not finding any correlation between the decrease in detection threshold across the two masks, they concluded that short-term monocular deprivation induces multiple separable effects. We suspect that the task-difference of the patching effect that has been reported in the field of spatial vision might also exist in the temporal vision. Here we tested one specific example of temporal processing, namely temporal synchrony. A future study should investigate whether short-term monocular deprivation affects other aspects of temporal processing in the visual system such as single-event asynchrony judgments, unimodal (visual) or cross-modal (e.g., audio-visual).

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the **Supplementary Data Sheet S1**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Wenzhou Medical University. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YC, SM, FL, JQ, P-CH, RH, and JZ conceived the experiments. YC, ZC, SC, ZW, and CT performed the experiments. YC, SM, ZC, and JZ analyzed the data and interpreted the data. YC, SM, P-CH, RH, and JZ wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.00402/full#supplementary-material

FIGURE S1 | The temporal characteristics for the CRT and OLED monitor. **(A,B)** The temporal response function (TRF) for CRT and OLED. **(C)** The temporal profiles of the stimuli. The solid and dashed lines represent the two stimuli. Two stimuli flickered at 1 Hz and with 100 ms temporal lag. **(D,E)** The temporal profiles convolved with the TRF by using CRT and OLED. **(F)** Temporal lags shown in CRT and OLED. Black column denotes temporal lag we set for two stimuli; red one denotes temporal lag when stimuli appear on CRT display; green one denotes temporal lag when stimuli appear on OLED display.

DATA SHEET S1 | The datasets generated for this study.

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ORIGINAL RESEARCH
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Brain Activation for Audiovisual Information in People With One Eye Compared to Binocular and Eye-Patched Viewing Controls

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Blindness caused by early vision loss results in complete visual deprivation and subsequent changes in the use of the remaining intact senses. We have also observed adaptive plasticity in the case of partial visual deprivation. The removal of one eye, through unilateral eye enucleation, results in partial visual deprivation and is a unique model for examining the consequences of the loss of binocularity. Partial deprivation of the visual system from the loss of one eye early in life results in behavioral and structural changes in the remaining senses, namely auditory and audiovisual systems. In the current study we use functional neuroimaging data to relate function and behavior of the audiovisual system in this rare patient group compared to controls viewing binocularly or with one eye patched. In Experiment 1, a whole brain analysis compared common regions of cortical activation between groups, for auditory, visual and audiovisual stimuli. People with one eye demonstrated a trend for increased activation for low-level audiovisual stimuli compared to patched viewing controls but did not differ from binocular viewing controls. In Experiment 2, a region of interest (ROI) analysis for auditory, visual, audiovisual and illusory McGurk stimuli revealed that people with one eye had an increased trend for left hemisphere audiovisual activation for McGurk stimuli compared to binocular viewing controls. This aligns with current behavioral analysis and previous research showing reduced McGurk Effect in people with one eye. Furthermore, there is no evidence of a correlation between behavioral performance on the McGurk Effect task and functional activation. Together with previous behavioral work, these functional data contribute to the broader understanding of cross-sensory effects of early sensory deprivation from eye enucleation. Overall, these results contribute to a better understanding of the sensory deficits experienced by people with one eye, as well as, the relationship between behavior, structure and function in order to better predict the outcome of early partial visual deafferentation.

Keywords: monocular enucleation, audiovisual processing, multisensory, sensory deprivation, fMRI

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INTRODUCTION

Complete visual deprivation from blindness leads to adaptive changes in other sensory systems. For example, congenitally blind individuals have shorter response times for auditory discrimination tasks (Röder et al., 1999), faster processing of language (Röder et al., 2002), enhanced sound localization (Lessard et al., 1998) and enhanced tactile perception (Sathian, 2000; Goldreich and Kanics, 2003) compared to sighted individuals. These adaptations suggest that underlying physiological changes have occurred within sensory systems to support such behavioral enhancements. It is possible that visual cortex is recruited or reorganized by other sensory systems in the congenitally blind. Neuroimaging studies have shown activation of visual cortex for sensory stimuli normally processed elsewhere in the brain such as audition (Collignon et al., 2009; Merabet et al., 2009), sound localization (Weeks et al., 2000), and tactile perception and Braille reading (Sadato et al., 1996; Cohen et al., 1997; Buchel et al., 1998; Kupers et al., 2007). Not all recruitment or reorganization results in adaptive change as evidence for the disruption of complementary senses when the visual system is compromised also exists. For example, some have shown congenitally blind individuals have decreased sound localization accuracy in the vertical plane (Lewald, 2002), and horizontal plane (Gori et al., 2014) or decreased distance judgment of auditory stimuli (Wanet and Veraart, 1985). Overall, it appears that in the case of complete sensory deprivation, specifically blindness, it is possible for other intact sensory systems to be altered and in some cases, to adaptively compensate for the loss of vision. One might ask whether such neuroplasticity also holds true in cases of partial sensory deprivation, such as the loss of one eye early in life?

Partial visual deprivation from unilateral eye enucleation, the surgical removal of one eye, is a unique model for examining the consequences of the loss of binocularity (see Steeves et al., 2008, for a review). It is unlike other forms of monocular visual deprivation such as cataract or strabismus which leave abnormal binocular input and contributes to competitive binocular interactions. Surgically removing the eye completely eliminates all forms of visual input to the brain from that eye leaving a single stream of information to the visual system and a complete lack of competitive binocular interactions (Steeves et al., 2008). Early monocular enucleation is a useful model of study since the visual system may not have been exposed to abnormal visual input from the removed eye.

Monocular enucleation during postnatal visual system maturation leads to both enhancements and reductions in visual function. These differences in outcome appear to align with whether one is measuring visual spatial ability or visual motion processing and oculomotor systems (reviewed in Steeves et al., 2008; Kelly et al., 2013). Visual spatial ability is largely intact while visual motion processing and oculomotor systems show small deficits. More recently, a number of behavioral studies of people who have only one eye have assessed abilities outside of the visual system, specifically, audiovisual abilities. These studies aimed to investigate what types of accommodations the brain might make across the senses after losing half of its visual input (see Steeves et al., 2008; Kelly et al., 2013).

Within the auditory domain, people with one eye have enhanced sound localization in all locations (within 78 degrees to the left or right of straight ahead) except for the extreme periphery compared to control participants who were binocular viewing, eye-patched or had both eyes closed (Hoover et al., 2012). In terms of audiovisual processing, people with one eye do not show the typical pattern of visual dominance when asked to categorize rapidly presented audiovisual targets, but rather, they show equivalent auditory and visual processing suggesting an enhanced relative weighting to the auditory component of bimodal stimuli (Moro and Steeves, 2012). These results persist even when the temporal load is increased in the same task by asking participants to detect and discriminate auditory, visual, or bimodal repetitions in a one-back task (Moro and Steeves, 2013). People with one eye do not differ in the width of their temporal binding window compared to binocular and eye-patched viewing controls, however, they have longer response latencies relative to controls indicating a longer processing time required for this task. Eye-patched controls' response latencies were intermediate to the two other groups (Moro and Steeves, 2018c). Despite no difference in width of temporal binding window, people with one eye are also less susceptible to the double flash illusion compared to both binocular and eye-patched viewing controls. Furthermore, in that task, people with one eye responded as quickly as binocular and eye-patched viewing controls (Moro and Steeves, 2018c).

People with one eye show no difference in variance of audiovisual localization along the horizontal plane compared to binocular and patched viewing control groups (Moro et al., 2014). However, unlike binocular and eye-patched controls, they take longer to localize unimodal visual stimuli compared to unimodal auditory stimuli (Moro et al., 2014). In terms of audiovisual motion in depth, people with one eye demonstrate the same rate of dynamic visual capture (perception of the direction of an auditory signal to be moving in the direction of the incongruent visual signal despite being asked to respond to the auditory signal alone) (Moro and Steeves, 2018b). Unlike static audiovisual localization, people with one eye have no difference in reaction time or accuracy compared to both control groups for this task (Moro and Steeves, 2018b). Together these audiovisual behavioral studies indicate that perhaps task requirements affect behavioral outcomes for this patient group. Both localization studies used low-level flash and beep stimuli, and people with one eye did not differ in overall performance compared to control groups but did perform slower on tasks with less ecological validity (sounds and images moving along the horizontal plane) (Moro et al., 2014) compared to those moving in depth (Moro and Steeves, 2018b).

To increase ecological validity of audiovisual stimuli, face and voice processing has been studied. People with one eye have increased sensitivity to voices on their own (but not non-human sounds, specifically car horns) in a face-voice and car-horn recognition task (Moro and Steeves, 2019). Perhaps this increased sensitivity to voices compensates for the mild face processing deficits in discriminating feature spacing, the face composite

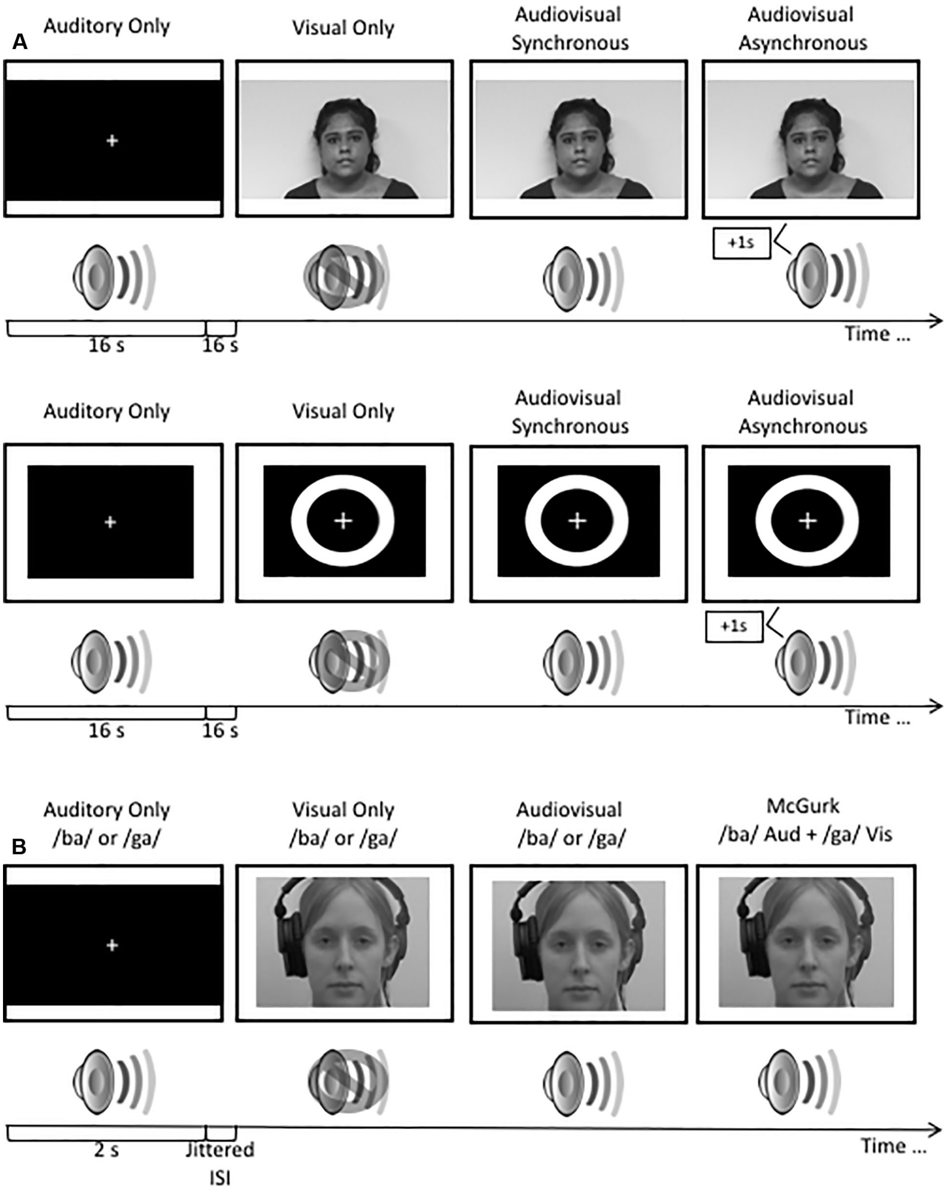

FIGURE 1 | (A) A schematic illustration of the stimuli used in the audiovisual blocked design study. **(B)** A schematic illustration of the presentation of stimuli used in the rapid event related design study. Stimuli used in the rapid event related design study have been previously published (see Quinto et al., 2010; Stevenson et al., 2012; Moro and Steeves, 2018a). All visual stimuli were presented to participants in color.

effect and face processing time that have previously been found (Kelly et al., 2012). Finally, people with one eye perceive the illusory McGurk effect less often than binocular viewing controls (Moro and Steeves, 2018a). Additionally, they have no difference in reaction time compared to both control groups (Moro and Steeves, 2018a). Overall, these behavioral results might suggest forms of behavioral adaptation following the reduction of visual input from one eye early in life.

No other lab has investigated changes in brain structure in people who have had one eye removed early in life. Not surprisingly, significant degeneration of the anterior visual system, including decreased optic chiasm volume and width is found in people with one eye compared to binocular controls (Kelly et al., 2014). People with one eye also have an overall decrease in lateral geniculate nucleus (LGN) volume compared to binocular controls as expected but surprisingly, the LGN volume contralateral to the remaining eye is less reduced likely from recruitment of deafferented LGN cells by the intact eye (Kelly et al., 2014). These findings indicate that subcortical level reorganization of the visual system occurs after losing one eye early in life (Kelly et al., 2014). At a cortical level, a subsequent study revealed that, compared to binocular viewing controls, people with one eye have increased surface area and gyrification in visual, auditory and multisensory cortices (**Kelly** et al., 2015). White matter tracts in the visual and auditory systems of people with one eye were examined using Diffusion tensor imaging (DTI) (Wong et al., 2018, 2019). White matter tracts are greater contralateral to the surgically removed eye in the optic radiations, V1-LGN projections and interhemispheric V1 projections of people with one eye compared to binocular viewing controls, likely a reflection of the differences observed in the LGN volume and optic tract contralateral to the removed eye (Kelly et al., 2014; Wong et al., 2018). Auditory wiring appears more substantial than in controls and, further, the connections between the visual and auditory systems are more intact than expected (Wong et al., 2019). Unlike controls, people with one eye have an asymmetric medial geniculate body (MGB) volume with a larger left than right MGB, regardless of which eye was enucleated perhaps reflecting dominance of left hemisphere in auditory processing (Moro et al., 2015). Taken together, there is moderate cortical, subcortical and wiring alterations of auditory and visual processing following early eye enucleation.

In terms of brain function more recently, our lab found reduced functional activation in people with one eye compared to binocular viewing controls in face-preferential brain regions [left fusiform face area (FFA) and bilateral occipital face area (OFA)] (Kelly et al., 2019). These results complement the mild behavioral face deficits in people with one eye (Kelly et al., 2012). The current study examines audiovisual functional activation in people with one eye compared to binocular and patched viewing controls in two separate experiments. Experiment 1 investigates differences in activation intensity in regions of interest localized by conjunction analysis between groups for low-level audiovisual stimuli and high-level face and voice stimuli. Experiment 2 probes audiovisual regions of interest (ROIs) during the presentation of auditory, visual, audiovisual and illusory McGurk stimuli. We predict that functional activation will reflect our previous behavioral findings, specifically relevant is the absence of a McGurk effect in this group (Moro and Steeves, 2018a). Results from this study will provide a better understanding of how people with one eye process auditory and visual information contributing to better clinical outcomes through cross-sensory accommodations and the promotion of long-term visual health in the remaining eye.

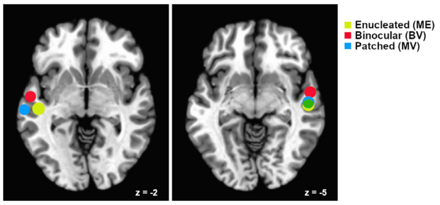

FIGURE 2 | Relative locations of superior temporal gyrus "audiovisual" regions of interest for each participant group. Regions are plotted as spheres (radius = 6 mm) centerd on the mean Talairach coordinates for each group. Left hemisphere regions are shown on an axial slice at Talairach *z* = −2 and right hemisphere regions are shown on an axial slice at *z* = −5. Mean coordinates for the Monocular Enucleation Group (ME) are shown in yellow, Binocular Viewing Controls (BV) in red, and eye-patched Monocular Viewing Controls (MV) in blue. Overlap of the right hemisphere ME and MV regions is shown in green.

MATERIALS AND METHODS

Participants

Monocular Enucleation Group

Seven adult participants who had undergone monocular enucleation (ME) at The Hospital for Sick Children participated in this study (mean age = 34 years, SD = 13 years). All ME participants with one eye had been unilaterally eye

TABLE 1 | Conjunction ROIs containing voxels significantly activated in both participant groups with mean cluster size (SD) and mean Talairach coordinates (STG = superior temporal gyrus, IFG = inferior frontal gyrus).

Groups	Functional ROI	Brain region	Mean cluster size (mm^3)	Mean (SD) talairach coordinates		
				X	Y	Z
BV and ME	Low-level auditory	Right STG	837	56.21 (4.53)	−27.69 (3.27)	8.66 (2.06)
	High-level auditory 1	Right STG	3544	53.27 (5.72)	−21.38 (7.14)	4.06 (3.77)
	High-level auditory 2	Left STG	2038	−55.66 (5.97)	−18.23 (5.43)	3.87 (2.52)
	High-level audiovisual 1	Right STG	6096	55.58 (6.07)	−18.20 (8.98)	4.70 (3.81)
	High-level audiovisual 2	Left STG	2084	−52.74 (6.25)	−16.96 (7.31)	3.95 (2.38)
MV and ME	Low-level audiovisual 1	Right Insula	1398	37.89 (5.06)	19.03 (3.47)	10.34 (2.38)
	Low-level audiovisual 2	Right STG	588	55.45 (2.89)	−27.21 (3.15)	6.67 (2.36)
	High-level auditory 1	Right STG	591	49.66 (3.84)	−16.41 (3.47)	6.20 (1.89)
	High-level audiovisual 1	Right STG	2705	54.68 (5.76)	−12.07 (7.85)	3.53 (3.39)
	High-level audiovisual 2	Left STG	1221	−51.67 (5.18)	−16.82 (7.57)	4.28 (2.46)
BV and MV	Low-level auditory 1	Right Precentral Gyrus	1774	42.07 (3.71)	4.87 (3.51)	33.51 (4.80)
	Low-level auditory 2	Right STG	4061	56.06 (5.69)	−18.91 (7.90)	5.71 (3.99)
	Low-level auditory 3	Left IFG	3010	−59.88 (4.67)	−26.39 (7.98)	6.94 (3.38)
	High-level auditory 1	Right STG	4629	56.85 (6.22)	−13.33 (7.58)	3.29 (3.79)
	High-level auditory 2	Left STG	2408	−55.33 (7.32)	−17.22 (7.42)	4.81 (2.27)
	High-level audiovisual 1	Right STG	5200	56.34 (6.24)	−14.74 (6.86)	2.80 (3.99)
	High-level audiovisual 2	Left STG	4683	−55.83 (6.75)	−17.40 (9.26)	3.09 (3.20)

TABLE 2 | Total number of participants with active ROI, mean (SD) cluster size (mm^3) and mean (SD) Talairach coordinates for experiment 2: rapid event related design.

Group (number with active ROI)	Functional ROI	Mean (SD) cluster size (mm^3)	Mean (SD) Talairach coordinates		
	Audiovisual		**X**	**Y**	**Z**
BV (*n* = 8)	Left	287.22 (255.99)	−53.50 (4.50)	5.50 (15.52)	−7.50 (6.87)
(*n* = 9)	Right	234.88 (146.76)	54.00 (6.99)	9.00 (14.96)	−5.75 (5.50)
MV (*n* = 8)	Left	143.00 (85.20)	−51.50 (7.19)	14.83 (11.14)	−6.50 (6.54)
(*n* = 9)	Right	78.00 (72.63)	60.00 (7.35)	21.75 (10.96)	2.50 (6.80)
ME (*n* = 6)	Left	88.50 (89.03)	−52.00 (3.99)	17.50 (7.75)	−3.50 (2.68)
(*n* = 6)	Right	81.50 (53.74)	46.50 (6.84)	21.50 (8.20)	0.50 (4.52)

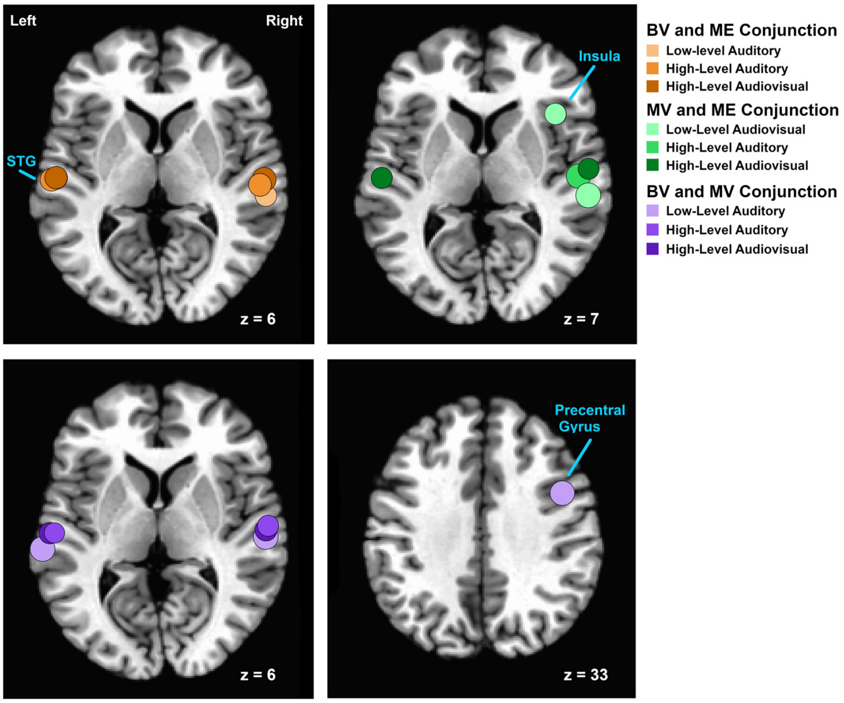

FIGURE 3 | Relative locations of areas isolated using conjunction analyses of functional activation for auditory, visual and audiovisual stimuli between groups. Regions are plotted as spheres (radius = 6 mm) centerd on the mean Talairach coordinates for each pair of groups. Overlapping areas of functional activation for the conjunction analysis between BV and ME groups are shown on an axial slice at Talairach *z* = 6 in shades of orange. Overlapping areas of functional activation for the conjunction analysis between MV and ME groups are shown on an axial slice at Talairach *z* = 7 in shades of green. Overlapping areas of functional activation for the conjunction analysis between BV and MV groups are shown on an axial slice at Talairach *z* = 6 and *z* = 33) in shades of purple.

enucleated (four right eye removed) due to retinoblastoma, a rare childhood cancer of the retina. Age at enucleation ranged from 4 to 60 months (mean age at enucleation = 23 months, SD = 18 months).

Binocular Viewing Control Group (BV)

Ten binocularly intact controls with a mean age of 32 years (SD = 13 years) were tested viewing stimuli out of both eyes.

Monocular Viewing Control Group (MV)

Ten binocularly intact participants, with a mean age of 31 years (SD = 16 years), completed the experiments with one eye patched. Participants' non-preferred eye was patched with a semi-opaque eye covering and translucent tape (five right-eye covered).

All participants (ME, BV, MV) reported normal hearing and normal or corrected-to-normal acuity as assessed by an EDTRS eye chart (Precision Vision$^{\text{TM}}$, La Salle, IL, United States) and wore optical correction if needed. All participants gave informed consent prior to their inclusion in the study, which was approved by York University's Office of Research Ethics.

Stimuli

Audiovisual Blocked Design

Low-level stimuli

Visual stimuli consisted of a white ring on a black background with a visual fixation cross in the center. Each visual stimulus was 17 ms in length. The auditory stimulus consisted of a 3500 Hz pure tone with a duration of 13 ms. Stimuli were repeated eight times per trial for a duration of 2 s. Trials were presented in a block design. Each block consisted of eight trials (16 s/block). Blocks consisting of visual only, auditory only and audiovisual and asynchronous audiovisual (sound was displaced by 500 ms) stimuli were presented (**Figure 1A**). A 16 s interstimulus interval of silence and a blank screen was presented between each block.

High-level stimuli

Visual stimuli consisted of a 16 s video of a female speaker reading an excerpt from a children's story. Auditory stimuli consisted of a 16 s audio clip of the female speaker from the video saying the story aloud in a clear and articulate voice. Audiovisual stimuli consisted of two 16 s videos of the female speaker reading the excerpt with the auditory component of the video either synchronously or asynchronously (auditory presented 500 ms after the visual stimulus) paired with the corresponding video. Participants viewed one repetition per trial. Trials were presented in a block design. Each block consisted of one trial (16 s; **Figure 1A**). A 16 s interstimulus interval consisting of silence and a blank screen was presented after each block.

Rapid-Event Related Design

Visual stimuli consisted of two 2 s videos of a female speaker mouthing the syllables "ba" and "ga," with each presentation containing the entire articulation of the syllable (Quinto et al., 2010; Stevenson et al., 2012; Moro and Steeves, 2018a). Auditory stimuli consisted of 2 s audio clips of the female speaker from the videos saying the syllables "ba" and "ga". Audiovisual stimuli consisted of two 2 s videos of the female speaker saying the syllables "ba" and "ga," paired with the corresponding video, respectively. McGurk illusory stimuli consisted of video footage of the female speaker mouthing the "ga" syllable but paired with the auditory sound clip of the female speaker saying "ba" (**Figure 1B**). Stimuli were presented using a rapid-event related design with jittered interstimulus intervals of variable lengths up to 15 s in order to improve the sampling of the hemodynamic response function (HRF). All stimuli were counterbalanced using OptSeq2 (Greve, 2002). Each stimulus condition was presented 15 times per run.

Procedure

All participants were scanned at York University's Sherman Health Science Research Center with a Siemens MAGNETOM Trio 3T MRI scanner (Siemens, Erlangen, Germany) using a 32-channel high-resolution brain array coil. BOLD (blood-oxygen-level dependent) fMRI imaging was utilized to acquire functional images. An echoplanar imaging sequence with the following specifications was used to obtain functional volumes: 35 contiguous axial slices; in-plane resolution 3 × 3 mm; slice thickness 3.5 mm; TR = 2000 ms; TE = 30 ms; imaging matrix 96 x 96; flip angle 90°; FoV = 192 mm. Following the functional scans, a high-resolution whole brain structural image was obtained with a T1 magnetization-prepared rapid gradient echo imaging sequence. The anatomical imaging had the following parameters: 192 slices; in-plane resolution 1 × 1 mm; slice thickness 1 mm; TR 1900 ms; TE 2500 ms; imaging matrix 256 × 256; flip angle 9°; FoV = 256 mm.

TABLE 3 | Median and interquartile range of the mean beta weight signal in each overlapping area of functional activation for auditory, visual and audiovisual stimuli isolated using conjunction analyses in localizer runs.

Comparison	Functional ROI	Median (interquartile range)	
		BV	**ME**
BV and ME	Low-level auditory	0.62 (0.38–0.72)	0.72 (0.53–0.72)
	High-level auditory 1	0.86 (0.70–0.99)	0.92 (0.80–1.12)
	High-level auditory 2	0.87 (0.74–1.16)	0.99 (0.66–1.28)
	High-level audiovisual 1	0.92 (0.67–1.00)	0.98 (0.92–1.15)
	High-level audiovisual 2	0.98 (0.83–1.24)	1.07 (0.75–1.29)
		MV	ME
MV and ME	Low-level audiovisual 1	0.003 (−0.04–0.07)	0.20 (0.13–0.33)
	Low-level audiovisual 2	0.25 (0.15–0.44)	0.77 (0.61–0.88)
	High-level auditory 1	1.09 (0.66–1.25)	1.05 (0.89–1.25)
	High-level audiovisual 1	0.94 (0.62–1.11)	1.07 (0.91–1.20)
	High-level audiovisual 2	0.69 (0.63–0.88)	0.91 (0.66–1.21)
		BV	MV
BV and MV	Low-level auditory 1	0.06 (−0.004–0.22)	0.09 (−0.02–0.15)
	Low-level auditory 2	0.53 (0.35–0.62)	0.26 (0.22–0.52)
	Low-level auditory 3	0.44 (0.34–0.54)	0.22 (0.14–0.36)
	High-level auditory 1	1.08 (0.95–1.21)	0.97 (0.76–1.07)
	High-level auditory 2	0.84 (0.70–1.10)	0.94 (0.68–1.11)
	High-level audiovisual 1	1.06 (1.01–1.21)	0.96 (0.59–1.10)
	High-level audiovisual 2	0.94 (0.71–1.13)	0.70 (0.68–1.02)

Experimental stimuli were presented using VPixx visual testing software (VPixx Technologies Inc., Montréal, QC, United States) via a 33 × 19.5 cm screen inside of the scanner and noise-canceling headphones (MR Confon GmbH, Magdeburg, Germany). Prior to scanning, sound samples were presented to participants to ensure that the sound pressure level was audible and comfortable. Participants were instructed to press a button on a Current Designs 8-Button Bimanual Curved Lines button box (Current Designs, Philadelphia, PA, United States) whenever they perceived the stimuli to be asynchronous to ensure that they were alert and paying attention throughout the task. Each participant performed in seven experimental runs. Five runs consisted of the audiovisual blocked design stimuli and two runs consisted of the rapid-event related McGurk stimuli. All runs were presented to each participant in counterbalanced order.

Data Analysis

Experiment 1: Audiovisual Block Design Whole Brain and ROI Analyses

During MRI data collection, estimates of head motion (translation and rotation) were viewed in real time in the MRI control room to verify that head movement did not exceed 1 mm in any direction. Participants who exceeded this threshold for head motion repeated imaging runs when necessary. For Experiment 1, analysis of MRI data was performed using BrainVoyager v20.6 (Brain Innovation, Maastricht, Netherlands). Preprocessing of the audiovisual block design functional data included slice time correction followed by motion correction, and linear trend removal. Motion correction used a trilinear/sinc

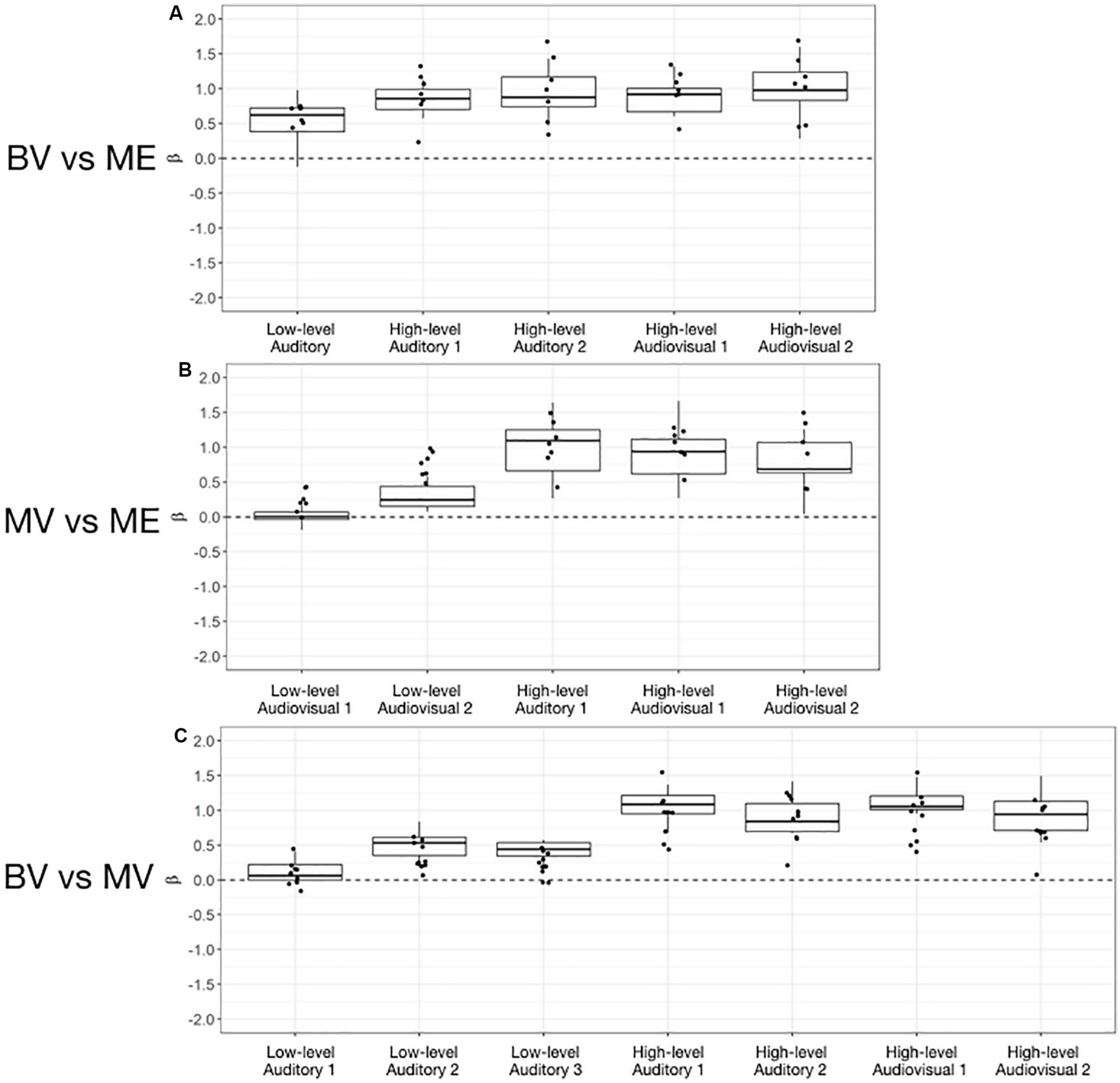

FIGURE 4 | Box and whisker plots of the distribution of peak beta weights for the control groups for the identified auditory, visual and audiovisual ROIs. The horizontal line within each box represents the median of the BV group **(A,C)** and the MV group **(B)**. The boxes correspond to the 25th and 75th percentiles, the whiskers correspond to the 5th and 95th percentiles. Individual data points for the ME group are plotted **(A,B)** and MV group **(C)**.

interpolation method with the first functional volume used as the reference. Plots of head motion estimates and movies of head motion over the course of each functional run were generated and visually inspected to confirm that all experimental runs were free from head movements over 1 mm in any direction and free from obvious hardware-related artifacts. Spatial smoothing was applied to each functional run using a 6 mm full width half maximum isotropic kernel. Functional runs were coregistered with corresponding high resolution T1-weighted anatomical images. Images were transformed from subject-space to Talairach template space.

Design matrices for use in general linear model (GLM) analyses were constructed for each participant using a boxcar design convolved with a hemodynamic response function. Within the design matrices, stimulation timing protocols were used to define separate predictors for each of the eight experimental conditions (i.e., low-level and high-level auditory, visual, synchronous audiovisual, and asynchronous audiovisual stimuli). Non-parametric permutation testing was performed for whole brain group comparisons of each condition using the randomize plug-in for BrainVoyager. Four experimental runs were included in this analysis for each participant (one experimental run was excluded for use as a functional localizer, as described in the following section). Since the randomize plug-in does not support ANOVA testing, comparisons between groups were performed using two-sample unpaired *t*-tests with 1000

TABLE 4 | Median and interquartile range of the mean beta weight signal in each ROI for experiment 2: region of interest analysis.

Group (number with active ROI)	Functional ROI	Mean (Interquartile Range)			
		Auditory	Visual	Audiovisual	McGurk
BV					
(*n* = 8)	Left	0.19 (−0.03–0.39)	0.19 (0.06–0.28)	0.24 (0.11–0.31)	0.007 (−0.05–0.07)
(*n* = 9)	Right	0.16 (0.03–0.29)	0.16 (−0.008–0.22)	0.20 (0.13–0.32)	0.09 (−0.13–0.16)
MV					
(*n* = 8)	Left	0.10 (−0.02–0.23)	0.15 (0.11–0.22)	0.14 (0.06–0.34)	0.13 (0.04–0.31)
(*n* = 9)	Right	0.05 (0.18–0.30)	0.32 (0.03–0.49)	0.15 (0.03–0.36)	0.11 (−0.10–0.31)
ME					
(*n* = 6)	Left	0.27 (0.18–0.43)	0.14 (−0.0004–0.37)	0.21 (0.12–0.38)	0.20 (0.11–0.47)
(*n* = 6)	Right	0.28 (0.19–0.38)	0.09 (0.009–0.28)	0.23 (0.14–0.26)	0.18 (−0.08–0.36)

permutations, threshold free cluster enhancement (TFCE), and FDR thresholding of $q < 0.01$.

To perform region of interest (ROI) analyses, one of the audiovisual block design imaging runs collected from each participant was used as a functional localizer. Group analyses were performed on these localizer runs using multi-subject GLMs computed separately for each of the three experimental groups (i.e., ME, BV, MV). This approach resulted in a group mean map of activity associated with each experimental contrast of interest for each group of participants. Maps to localize the auditory cortex were produced by using activity associated with the unimodal auditory stimuli condition relative to baseline. The visual cortex was localized using activity associated with the unimodal visual stimuli condition relative to baseline. "Audiovisual" regions were isolated by contrasting activity in the synchronous audiovisual condition versus activity in the auditory and visual conditions (i.e., audiovisual > auditory + visual). These group maps were imported into Neuroelf v1.1[1] where conjunction maps were computed for (1) the BV and ME participant groups, (2) the MV and ME groups, and (3) the BV and MV groups to produce ROIs associated with each of the contrasts described above. All voxels included in ROIs had a *p*-value equal to or lower than 0.05 in included groups of participants. This approach was used to help mitigate the possibility of biasing ROI masks toward any one participant group (i.e., to prevent the inclusion of voxels that were only active in one participant group). These ROI masks were then imported back into BrainVoyager where they were applied to analyses of the remaining four functional imaging runs from each participant. Group ROI GLM analyses were performed using these imaging runs, and ANOVAs were used to test for group-related differences in mean beta weight values associated with each region.

Experiment 2: McGurk Region of Interest Analysis

Data associated with Experiment 2 were analyzed using the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). All five audiovisual block design functional runs were used to create region of interest masks for ROI analyses of the McGurk functional imaging runs. Preprocessing of the audiovisual block design runs included slice time correction, coregistration of functional and anatomical images, transformation of images from subject space to Talairach space, motion correction using coregistration of each functional volume to the volume with the minimum outlier fraction, masking of functional data, within mask spatial smoothing using a 4 mm full width half maximum Gaussian kernel, and scaling of intensity values to a mean value of 100. Pairs of volumes where the Euclidean Norm of the motion derivative exceeded 0.3 mm were removed (in practice, this resulted in very few volumes being removed), and motion estimate parameters were included as regressors of no interest to account for motion-correlated variance in the data. In addition, volumes containing greater than 10% outlier voxel fraction were removed (again resulting in few volumes being removed in practice). Stimulation timing for each condition was provided for GLM analyses as described in Experiment 1. Masks of left and right hemisphere superior temporal regions associated with audiovisual processing were created using a conjunction analysis to isolate voxels equally active ($p < 0.05$) in both the Auditory stimuli and Visual stimuli conditions for each individual study participant. These ROIs were applied in analyses of the McGurk stimuli functional runs (see **Figure 2**).

Preprocessing of the McGurk runs was performed as described above for the audiovisual block design runs. For these data, a predictor was defined for each condition (i.e., auditory only, visual only, synchronous audiovisual, and McGurk stimuli) and the timing of each stimulus was used in deconvolution of the rapid event-related structure of these imaging runs. Tent functions for deconvolution analysis were centered at TR times. For each participant, ROI masks (localized using the audiovisual block design runs) were applied to the preprocessed McGurk runs. For each condition, mean beta weights associated with each ROI were extracted for each participant. SPSS was used to perform ANOVA comparisons of mean beta weights between participant groups.

RESULTS

None of the whole brain or ROI analyses performed resulted in any statistically significant differences between any of the

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[1] www.neuroelf.net, RRID:SCR_014147

participant groups tested. Due to the rare patient group involved in this study and the subsequent small sample size, only descriptive statistics are reported. The data reported are the median and interquartile range (IR) mean beta weight signal in each region. The data reports only participants with an active ROI. See **Table 1** (Experiment 1) and **Table 2** (Experiment 2) for each group including mean cluster size and TAL coordinates.

Experiment 1: Whole Brain Analysis

A conjunction analysis on functional localizer runs was conducted to isolate overlapping areas of functional activation for auditory, visual and audiovisual stimuli between groups. The overlapping ROIs localized for each group comparison are depicted in **Figure 3**.

For the BV group ($n = 10$) compared to the ME group ($n = 7$) five ROIs were identified with significant activation in common between groups. These ROIs were applied to the remaining four experimental runs that were not used for ROI localization. People with one eye did not differ in intensity of cortical activation in these common regions of interest compared to binocular viewing controls (see **Table 3**). **Figure 4A** shows that the majority of people with one eye were within the 95% confidence interval (CI) of the binocular viewing control group for all identified ROIs.

For the MV group ($n = 10$) compared to the ME group ($n = 7$) five ROIs were identified with significant activation in common between groups. People with one eye had increased intensity of activation for low-level audiovisual stimuli compared to patched viewing controls (see **Table 3**). **Figure 4B** shows that 5/7 and 6/7 ME participants were above the 95% CI of the MV group for the low-level audiovisual ROIs 1 and 2, respectively.

For the BV group ($n = 10$) compared to the MV group ($n = 10$) seven ROIs were identified with significant activation in common between groups. Patched viewing controls did not differ in the intensity of cortical activation in these common regions of interest compared to binocular viewing controls (see **Table 3**). **Figure 4C** shows that 5/10 MV participants were below the 95% CI of the BV group for the high-level audiovisual ROI.

Experiment 2: McGurk Region of Interest Analysis

A region of interest analysis was conducted for individual functionally localized audiovisual regions in the left and right hemisphere. Intensity of activation was compared between groups for auditory, visual, audiovisual and McGurk illusory stimuli. Median and interquartile range (IR) mean beta weight signal in each region is listed for each stimulus type in **Table 4**.

Left and right audiovisual ROIs were identified for the ME (left, $n = 6$; right, $n = 6$) group, BV (left, $n = 9$; right, $n = 8$) group and MV (left, $n = 9$; right, $n = 8$) group. People with one eye have increased intensity of activation in the left audiovisual ROI for McGurk stimuli compared to binocular viewing controls. Patched viewing controls did not differ in intensity of activation compared to people with one eye. Patched viewing controls have increased intensity of activation in the left audiovisual ROI for McGurk stimuli compared to binocular viewing controls. **Figure 5** (A, B) show that 5/6 people with one eye were outside the 95% confidence interval (CI) of the binocular viewing control group for the McGurk stimuli for the left audiovisual ROI. Panels (C, D) indicate that the majority of people with one eye were within the 95% confidence interval (CI) of the patched viewing control group. Panels (D, E) indicate that the majority of patched viewing controls were within the 95% confidence interval (CI) of the binocular viewing control group.

McGurk Effect Behavioral Analysis

Behavioral performance recorded during the scan session was analyzed. Two of the original 10 MV participants were removed from this data analysis due to performance under chance. A Greenhouse-Geisser corrected ($X^2(2) = 13.383$, $p = 0.001$), 3 × 3 repeated measures analysis of variance (ANOVA) comparing group (ME vs BV vs MV) and McGurk condition ("Ba", "Ga", "Da") revealed a significant interaction, $F(2.719, 29.906) = 6.624$, $p = 0.002$, $\eta_p^2 = 0.376$ and main effect of McGurk condition, $F(1.359, 29.906) = 26.313$, $p < 0.000$, $\eta_p^2 = 0.545$. There was no significant main effect of participant group, $F(2, 22) = 1.043$, $p = 0.369$, $\eta_p^2 = 0.087$. The BV group demonstrated increased perception of the illusory "Da" condition compared "Ba" ($p < 0.000$) and "Ga" ($p < 0.000$). The MV group demonstrated increased perception of the illusory "Da" condition compared "Ba" ($p = 0.000$) and "Ga" ($p < 0.000$). Furthermore, the ME group did not demonstrate an increase in perception of the "Da" condition compared to the "Ba" condition ($p < 1.000$) and the "Ga" condition ($p < 1.000$). Overall these results indicate a replication of the findings of our previous behavioral study (Moro and Steeves, 2018a). **Figure 6** plots the behavioral data for each participant group.

Behavioral Performance and Functional Activation Correlations

We investigated the relationship between the current behavioral McGurk data obtained during the fMRI session for the BV, MV, and ME groups and the current peak beta weight data for left and right audiovisual ROI's with McGurk stimuli. Since both of the control groups (BV and MV) demonstrated a McGurk effect and the patient group (ME) did not, we decided to collapse the data and conduct an omnibus correlation in order to accommodate for the small sample size. Non-parametric Spearman correlations indicate a significant correlation, $r_s(24) = -0.620$, $p = 0.002$ for left audiovisual activation compared to behavioral performance and non-significant correlation, $r_s(22) = -0.114$, $p = 0.615$ for right audiovisual activation to behavioral performance. **Figure 7** plots the behavioral and peak beta weight correlations for the left and right audiovisual ROI.

DISCUSSION

The current study investigated whether people who had one eye surgically removed early in life have altered functional activation for auditory, visual and audiovisual stimuli. In Experiment 1, a region of interest analysis using ROIs localized with group conjunction analyses was conducted to compare overlapping areas of functional activation for auditory, visual and audiovisual

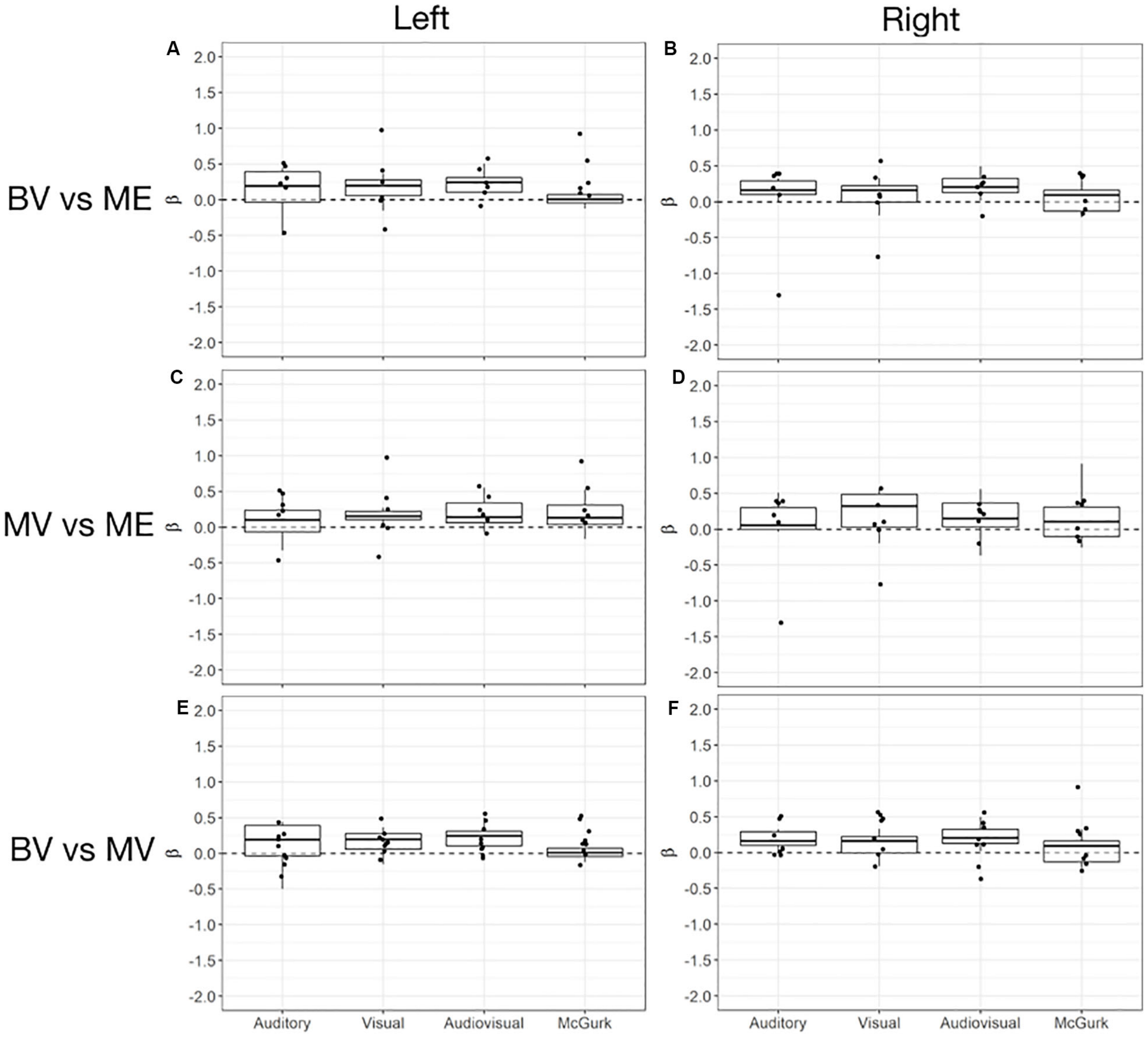

FIGURE 5 | Box and whisker plots of the distribution of peak beta weights for the auditory, visual, audiovisual and McGurk stimulus conditions for the left audiovisual ROI [BV group = **(A,E)**; MV group = **(C)**] and right audiovisual ROI [BV group = **(B,F)**; MV group = **(D)**]. The horizontal line within each box represents the median. The boxes correspond to the 25th and 75th percentiles, the whiskers correspond to the 5th and 95th percentiles. Individual data points for ME group are plotted **(A–D)** and MV group **(E,F)**.

stimuli. When comparing people with one eye to binocular viewing controls five common regions of interest were identified. People with one eye did not differ in intensity of cortical activation in these common regions of interest compared to binocular viewing controls. When comparing people with one eye to patched viewing controls five common regions of interest were identified. People with one eye had a trend for increased intensity of activation When comparing patched viewing controls to binocular viewing controls seven common regions of interest were identified. Patched viewing controls did not differ in the intensity of cortical activation in these common regions of interest compared to binocular viewing controls.

In Experiment 2, a region of interest analysis was conducted for individual functionally localized audiovisual regions in the left and right hemisphere. Intensity of activation was compared between groups for auditory, visual, audiovisual and McGurk illusory stimuli. Both people with one eye and patched viewing controls have a trend for increased intensity of activation in the left audiovisual ROI for McGurk stimuli compared to binocular viewing controls. Patched viewing controls did not differ in intensity of activation compared to people with one eye. Additionally, behavioral performance recorded during the scan session indicates a replication of previous findings (Moro and Steeves, 2018a) where people with one eye do not perceive the McGurk Effect. Correlating behavioral performance on the McGurk task with functional activity yielded a significant negative correlation for the left audiovisual ROI and no significant correlation for the right audiovisual ROI.

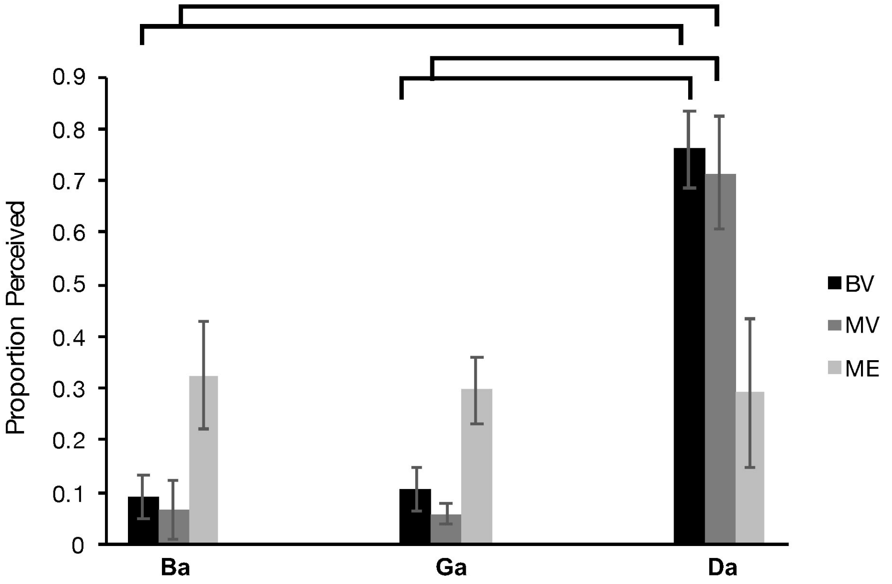

FIGURE 6 | Behavioral McGurk effect perceived (number of times a participant perceived "da" during McGurk trials) for each of the BV (black), MV (gray) and ME group (light gray).

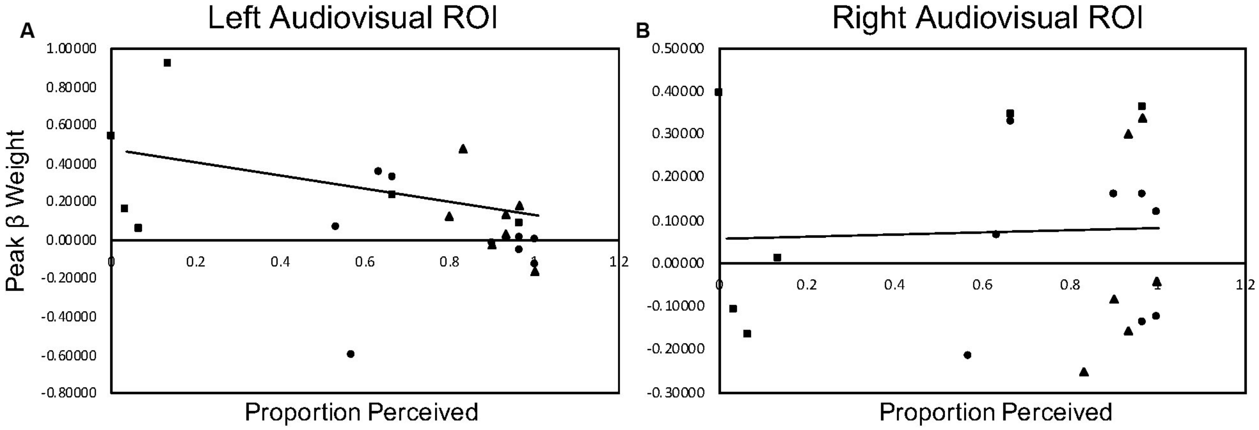

FIGURE 7 | McGurk behavioral performance during scan sessions correlated with peak beta weight activation in the left (column **(A)**) and right (column **(B)**) audiovisual ROI during McGurk trials. The BV group is represented with a circle marker, the MV group is represented with a triangle marker and the ME group is represented with a square marker.

The current analyses indicate that in common areas of activation people with one eye and binocular viewing controls do not differ in intensity of activation despite previously observed audiovisual behavioral (Moro and Steeves, 2012, 2013, 2018a,b,c, 2019; Moro et al., 2014) and structural (Kelly et al., 2014, 2015; Moro et al., 2015; Wong et al., 2018, 2019) differences. The lack of difference in activation intensity between these two groups provides evidence that behavioral differences can nonetheless exist in the absence of functional differences.

In contrast, intermediate behavioral performance has been observed for eye patched controls where they fall in between that of people with one eye and binocular viewing controls (Moro et al., 2014; Moro and Steeves, 2018a,b,c, 2019). Consistent with this, the present neuroimaging study indicates functional differences between people with one eye and patched viewing controls. Specifically, people with one eye have a trend toward increased activation intensity in common regions for low-level audiovisual stimuli compared to patched viewing controls. This indicates that short term partial visual deprivation from wearing an eye patch may have a more negative effect on functional activation than long term partial visual deprivation from unilateral eye enucleation. Previous research on monocular deprivation in binocular viewing participants indicates the presence of neuroplasticity in the visual cortex even after short term monocular deprivation through eye patching (see Castaldi et al., 2020 for review). For example, evidence of strengthened cortical excitability after short term monocular deprivation (Lunghi et al., 2015) and enhanced BOLD V1 activation for high spatial frequency stimuli (Binda et al., 2018). These results are restricted to V1, V2, V3, and V4 while not present in V3a and hMT+ (Binda et al., 2018). Results of the current study may indicate that outside of the visual cortex, a decrease in activation intensity may be present. We have speculated that the previously observed intermediate behavioral performance may be the result of binocular inhibitory interactions from wearing an opaque eye patch (Steeves et al., 2004) and may be reflected by reduced functional activation when temporarily wearing an eye patch. Further studies investigating the relationship between behavior and function, within both visual and audiovisual processing regions in long and short term partial visual deprivation should be considered.

A popular tool for studying the mechanisms underlying multisensory integration is the McGurk effect. Susceptibility to the illusion is often inconsistent and shows inter-subject variability possibly due to different cognitive processes that are being used (Beauchamp et al., 2010; Alsius et al., 2017). Its neural substrates have been examined and increased activation of the left STS has been correlated with greater perception of the McGurk effect (Nath and Beauchamp, 2012). Further, clinical populations show differences in their perception of the McGurk effect. People with amblyopia have a reduced susceptibility to the McGurk effect that persists with both binocular and fellow eye viewing (Narinesingh et al., 2014). People with one eye perceive the McGurk effect less often than binocular viewing controls (Moro and Steeves, 2018a). These results have been replicated with the behavioral data obtained during scan sessions in our current study. The present neuroimaging findings indicate people with one eye have a trend toward increased activation intensity for McGurk stimuli along the STS compared to binocular viewing controls. These results are unexpected since behaviorally this group has a much weaker McGurk effect. Since increased activation in the left STS has been shown to be associated with increased perception of the McGurk effect (Nath and Beauchamp, 2012) we expected that the decreased perception of the McGurk effect would be associated with a trend toward decreased activation. The present findings instead show an inverse relationship, as illustrated with a significant negative correlation between behavior and level of brain activity in the left audiovisual ROI. This negative correlation is driven by participants with one eye and indicates that the activation in the left audiovisual ROI for these participants was higher than that reported by the control participants. This finding suggesting perhaps that other cortical regions contribute more heavily to the perception of the McGurk effect in this patient group. It is also possible that the trend toward increased activation may be associated with reorganization of neurons typically dedicated to binocular vision or the remaining eye activating for removed eye, resulting in overall increased activation. These results should be interpreted with caution, however, since the small sample size investigated in this study is not ideal to conduct correlational analyses.

Additional studies examining individual differences that relate brain structure, function and behavioral performance, specifically in sensory deprived individuals should be investigated. As is typical in studying patients with rare diseases, our study was limited due to the rare patient group of people who had one eye surgically removed early in life due to childhood retinoblastoma. It is challenging to obtain a normalized and sufficiently large sample size to conduct inferential statistics and as such to lessen these limitations each patient was sex- and approximately age-matched with participants in both control groups.

In conclusion, the growing body of evidence demonstrates that a number of perceptual accommodations, as well as, structural and functional brain changes occur across the senses in people who have lost one eye early in life. These adaptations likely serve to mitigate the loss of binocularity during early brain development through altered sensory processing compared to binocular and patched viewing controls.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by York University Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Author contributions by SM include conceptualization, formal analysis, investigation, methodology, visualization, writing (original draft). Author contributions by DG include analysis methodology, visualization, writing. Author contributions by JS include conceptualization, methodology, funding acquisition, project administration, resources, supervision, writing (review and editing).

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The Impact of Vision Loss on Allocentric Spatial Coding

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Several works have demonstrated that visual experience plays a critical role in the development of allocentric spatial coding. Indeed, while children with a typical development start to code space by relying on allocentric landmarks from the first year of life, blind children remain anchored to an egocentric perspective until late adolescence. Nonetheless, little is known about when and how visually impaired children acquire the ability to switch from an egocentric to an allocentric frame of reference across childhood. This work aims to investigate whether visual experience is necessary to shift from bodily to external frames of reference. Children with visual impairment and normally sighted controls between 4 and 9 years of age were asked to solve a visual switching-perspective task requiring them to assume an egocentric or an allocentric perspective depending on the task condition. We hypothesize that, if visual experience is necessary for allocentric spatial coding, then visually impaired children would have been impaired to switch from egocentric to allocentric perspectives. Results support this hypothesis, confirming a developmental delay in the ability to update spatial coordinates in visually impaired children. It suggests a pivotal role of vision in shaping allocentric spatial coding across development.

Keywords: visual impairment, spatial frame of reference, allocentric reference frame, egocentric reference frame, spatial perception

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INTRODUCTION

The ability to locate targets in the environment is a critical aspect of spatial information processing, and consequently, it has been extensively considered a milestone for space development (Lew et al., 2000; Vasilyeva and Lourenco, 2012; Cappagli and Gori, 2019). The cognitive representation of space is given by the reciprocal relationships between entities in the environment. It is strongly dependent on the perspective assumed by the perceiver, namely the frame of reference that allows us to keep track of and continuously update objects' position in space. While the *egocentric* or *subject-centered* perspective references spatial objects' locations to the perceiver's own body, the *allocentric* or *object-centered* frame of reference refers to objects' locations based on external landmarks, such as objects other than the body (Klatzky, 1998; Foley et al., 2015).

Empirical evidence suggests that allocentric spatial coding is promoted by the ability to combine perceptual experiences of an environment (Nardini et al., 2009; Vasilyeva and Lourenco, 2012) and by visual experience across development (Thinus-Blanc and Gaunet, 1997; Pasqualotto et al., 2013). Understanding the context in which egocentric instead of allocentric frames of reference need to be chosen (and vice-versa) depends on the capacity to integrate different spatial coordinates systems to encode space. Research has shown that adults typically employ a spatial strategy based on the integration of egocentric and allocentric frames of reference [e.g., Nadel and Hardt (2004)]. Contrarily, children start to integrate the two reference frames only around 6 years of age (Nardini et al., 2006; Bullens et al., 2010); see also (Nardini et al., 2008). This result is evident even if egocentric and allocentric representations coexist already before that age (Newcombe and Huttenlocher, 2003; Nardini et al., 2006). Indeed, it has been shown that typically developing children attempt to locate objects using allocentric landmarks within 1 year of age. While from 8.5 months of age they rely on adjacent landmarks (cue learning) to find non-visible targets (Piaget and Inhelder, 1967; Acredolo, 1981), they start to rely on distal landmarks (place learning) at the age of 12 months (Lew et al., 2000). This finding suggests a developmental acquisition of allocentric capabilities. At 24 months of age, toddlers show the ability to rely on distal cues (Newcombe et al., 1998), consolidating the consciousness of relations between distal landmarks throughout childhood (Rieser and Rider, 1991; Overman et al., 1996; Nardini et al., 2009; Vasilyeva and Lourenco, 2012). Nonetheless, switching-perspective abilities rely on the capacity to efficiently integrate egocentric and allocentric frames of reference, which is still not mature until 8 years of age (Nardini et al., 2008).

Several studies have demonstrated that vision plays a relevant role in the acquisition of spatial knowledge. Indeed, vision not only permits to perceive multiple stimuli at the same time (Foulke, 1982; Thinus-Blanc and Gaunet, 1997; Merabet and Pascual-Leone, 2010; Pasqualotto et al., 2013; Iachini et al., 2014), but it also allows to acquire the ability to code spatial information in allocentric coordinates. At the cortical level, visual experience seems to shape the architecture of cortical spatial maps by providing the most accurate spatial information (Maurer et al., 2005; Lepore et al., 2009; Ruotolo et al., 2012). As a consequence, visual loss may significantly affect an adequate spatial representation of the external world (Ungar et al., 1995; Bigelow, 1996; Cattaneo et al., 2008; Koustriava and Papadopoulos, 2010). In line with this view, it has been demonstrated that visually impaired adults tend to code space mainly through an egocentric perspective, probably because they rely on sensory modalities other than vision, that is based on body landmarks (i.e., touch; Cattaneo et al., 2008; Pasqualotto et al., 2013). Furthermore, the absence of vision prevents the ability to solve spatial tasks that require the use of allocentric cues (Millar, 1994; Thinus-Blanc and Gaunet, 1997; Cattaneo et al., 2008; Merabet and Pascual-Leone, 2010; Pasqualotto and Proulx, 2012; Schmidt et al., 2013; Iachini et al., 2014). It also impacts on the ability to update flexibly and combine different (egocentric/allocentric) reference frames in response to environmental changes – i.e., switching-perspective skills (Cornoldi et al., 1991; Nadel and Hardt, 2004; Vecchi et al., 2004; Burgess, 2006; Harris et al., 2012). Ruggiero et al. (2018), for instance, evaluated how congenitally blind adults performed a switching-perspective task based on the memorization of haptic spatial stimuli. Their work demonstrated that congenitally blind individuals showed relevant difficulties in switching from external (allocentric) to body-centered (egocentric) frames of reference, but not vice-versa. These findings suggest that normally sighted and individuals with a visual impairment might differently encode spatial information from an early age, especially when visual deprivation negatively impacts on multisensory integration capabilities, upon which spatial competence is based (Thinus-Blanc and Gaunet, 1997; Cappagli et al., 2015; Vercillo et al., 2016). Nonetheless, very little is known about the development of switching-perspective abilities in visually impaired children. Ochaíta and Huertas (1993) suggest that normally sighted and visually impaired children acquire a coherent sense of space, respectively, at 14 and 17 years of age. This can be explained by the fact that visual deprivation results in a lack of sensorimotor (visuo-motor) feedback that delays locomotor development (Fraiberg, 1977; Landau et al., 1984; Fazzi et al., 2002), which has been indicated as a fundamental step for spatial competence development (Bremner et al., 2008). Similarly, other studies indicate that, along with locomotor delays, visually impaired children manifest deficits in performing mental spatial tasks, as mental rotations of the self (perspective-taking; Huttenlocher and Presson, 1973; Millar, 1976; Papadopoulos and Koustriava, 2011; Koustriava and Papadopoulos, 2012), or objects/configurations (Huttenlocher and Presson, 1973; Penrod and Petrosko, 2003; Papadopoulos and Koustriava, 2011). Understanding whether and how visually impaired children develop switching-perspective abilities would be fundamental to increase knowledge about the role of vision in spatial development. Indeed, to date it is still unclear whether the complete (such in the case of blindness), or the partial (such in the case of visual impairment) loss of vision would differently affect the ability of children to acquire an allocentric coding of space.

In the present work, we assessed whether the ability to switch from egocentric to allocentric coordinates is compromised by a partial loss of vision that produces an impoverished visual experience during childhood. We hypothesized that children with an atypical visual experience during development (visually impaired) would rely more heavily on egocentric coordinates and, thus, would show an impairment in task conditions requiring a mental update of spatial configurations according to their new perspective.

To test our hypothesis, we assessed the ability of children with typical and atypical visual experience to switch from an egocentric to an allocentric representation of space in the visual domain. Both visually impaired and normally sighted participants were asked to reproduce a spatial configuration of visual stimuli in four conditions that differed in their reliance on visual input, to understand if vision is crucial to acquire switching-perspective abilities. More specifically, participants were asked to change their physical position in space and mentally rotate the spatial configuration seen according to their new coordinate system to accomplish the task.

MATERIALS AND METHODS

Participants

Normally sighted and visually impaired children between four and nine years of age were enrolled in the study. Normally sighted children were recruited from local schools, visually impaired children were recruited from a local hospital (IRCCS Mondino Foundation, Pavia, Italy) based on their visual acuity (VA). The visual deficit was defined through specific tests following the "International Statistical Classification of Diseases and Related Health Problems" [ICD-10 (World Health Organization [WHO], 1993)], which defines moderate to severe visual impairment as a condition characterized by VA comprised between 0.5 and 1.3 LogMAR [Logarithm of the Minimum Angle of Resolution, defined as $log_{10}(M_{inimum}A_{ngle}R_{esolution})$]. Only visually impaired children presenting with best corrected binocular VA in the range 0.5–1.3 LogMAR were recruited (see **Table 1** for clinical details of participants). All distance VA measurements were carried out at a testing distance of 3 m. To control for cognitive development, visually impaired children undertook the verbal scale of the "Wechsler Preschool and Primary Scale of Intelligence" (Wechsler, 2012), and the "Wechsler Intelligence Scale for Children" (Wechsler, 2014) according to their chronological age. Only children presenting adequate cognitive development were recruited. Neither visually impaired nor normally sighted children reported additional sensory, musculoskeletal, neurological disabilities, or impairments related to colors discrimination. All normally sighted children had binocular best corrected VA of 0.0 LoGMAR or better. Twenty-seven normally sighted (mean age: 6.56 ± 1.80 years) and fifteen visually impaired (mean age: 6.33 ± 1.72 years) children participated in the study. Both visually impaired and normally sighted participants were divided into three groups, according to their age range: 4-to-5 years old (five visually impaired, nine normally sighted), 6-to-7 years old (six visually impaired, ten normally sighted), and 8-to-9 years old (four visually impaired, eight normally sighted). The study was approved by the local Ethical Committee and written informed consent was provided by participants' parents, in accordance with the Declaration of Helsinki.

TABLE 1 | Clinical details of visually impaired participants.

Participant	Age range	Pathology	Visual Acuity (LogMAR)
#1	4–5	Left Micropthalmia and Bilateral Coloboma	1.00
#2	4–5	Nystagmus	1.00
#3	4–5	Retinal Dystrophy	1.00
#4	6–7	Retinopathy	1.30
#5	8–9	Microphtalmia	1.00
#6	6–7	Aniridia	1.30
#7	6–7	Nystagmus	1.00
#8	8–9	Retinal Dystrophy	1.00
#9	4–5	Albinism	0.82
#10	6–7	Bilateral Microphtalmia and Coloboma	1.30
#11	4–5	Optic Nerve Hypoplasia	1.30
#12	8–9	Retinal Dystrophy	0.82
#13	6–7	Nystagmus	0.50
#14	8–9	Optic Nerve Hypoplasia	1.00
#15	6–7	Retinopathy	1.00

The table shows the age range at test, the pathology, and Visual Acuity (VA) expressed in LogMAR scale at a distance of 3 m of visually impaired participants.

Procedure

A switching-perspective task was administered to all participants. Participants sat in the experimental room with the setup positioned in front of them on a table. The setup consisted of two 30 × 30 cm plastic boards, whose layout represented a grid with intersecting embossed straight vertical and horizontal lines used to separate boxes, on which colored coins (red, blue, and yellow) were positioned (**Figure 1A**). The boards were realized in such a way that children with visual impairment could visually discriminate stimuli by relying on high contrast colors (colored coins on high contrast background). Before the beginning of the task, the experimenter showed the participant a configuration with an increasing number of coins to let the child familiarize with the task. The task procedure comprised two phases: (a) a demonstration phase, during which the experimenter asked the participant sitting next to him/her to look at a configuration presented on the experimenter's board; (b) a reproduction phase, during which the participant was asked to reproduce on his board the configuration of the coins shown in (a) by assuming one out of four different spatial positions. During both phases, participants were allowed to look at the experimenter's configuration as many times as they needed to reproduce it. Depending on the number of coins in the configuration presented by the experimenter in the demonstration phase (a), the task assumed three levels of difficulty (**Figure 1B**): (1) one coin, for the simplest level;

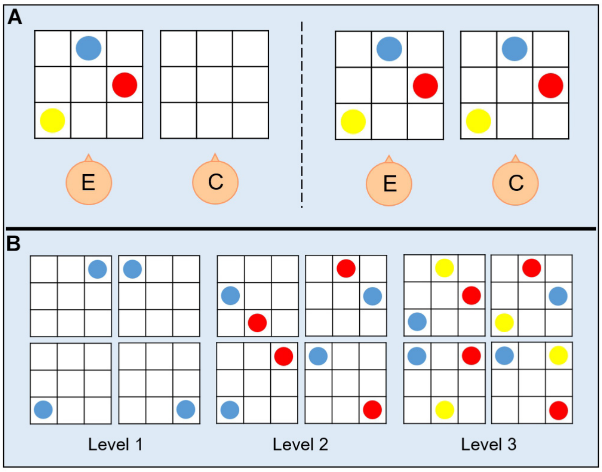

FIGURE 1 | (A) Procedure for the switching-perspective task. On each trial, the experimenter (E) showed to the child (C) one out of twelve possible configurations of colored coins on a plastic board made of nine boxes (left panel) and immediately after the child was asked to reproduce the same configuration on his own plastic board in front of him (right panel). **(B)** Trials for each condition of the task. The switching-perspective task comprised 48 trials that differ with respect to the level of difficulty, namely to the number of coins that constituted the configuration to be reproduced (from one to three coins, respectively, for the easiest and the hardest levels).

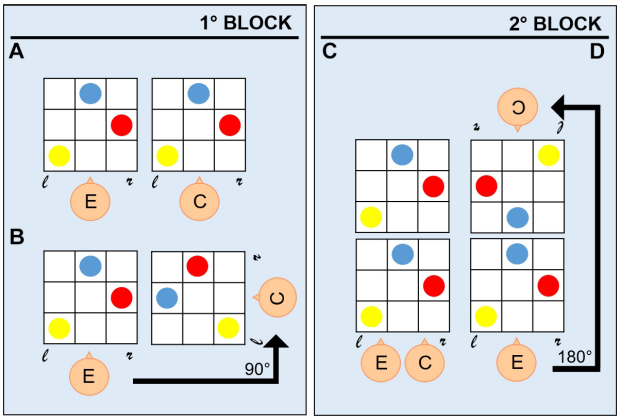

FIGURE 2 | Egocentric and allocentric conditions. Four conditions were administered to participants in two separate blocks: each block comprised both an egocentric **(A,C)** and an allocentric **(B,D)** condition. In the first block (left panel), the allocentric condition **(B)** resulted from a 90° rotation respect to the egocentric condition **(A)**. In the second block (right panel), the allocentric condition **(D)** resulted from a 180° rotation respect to the egocentric condition **(C)**. *E: experimenter; C: child; *r*: right; and *l*: left.

(2) two coins, for the intermediate level; and (3) three coins, for the hardest level. Configurations were presented to the participant in random order concerning the level of difficulty. The participant could assume four spatial positions during the reproduction phase (b), which defined the four conditions of the switching-perspective task: (1) egocentric condition, with the participant sitting next to the experimenter (0° rotation degrees) and the two boards lying next to each other (**Figure 2A**); (2) egocentric condition, with the participant sitting next to the experimenter (0° rotation degrees) and the two boards lying one above the other (**Figure 2C**); (3) allocentric condition, with the participant sitting rotated 90° degrees to the experimenter position and the boards positioned in front of them (**Figure 2B**); (4) allocentric condition, with the participant sitting rotated 180° degrees to the experimenter position and the boards positioned in front of them (**Figure 2D**). The four different spatial conditions defined two reference frames (egocentric vs. allocentric). The main goal of such manipulation was to asses the participants' ability to switch from an egocentric to an allocentric frame of reference. The task procedure comprised two blocks of trials. To randomize the presentation of egocentric and allocentric spatial positions, each block comprised one configuration with participants sat next to the experimenter and one configuration with participants sat rotated to the experimenter. The first block (**Figure 2**, left panel) comprised trials with positions (1) and (3), the second block (**Figure 2**, right panel) included trials with positions (2) and (4). The total amount of trials performed by each participant was 48 (twelve trials per four spatial positions, four trials for each level of difficulty). The whole experiment was performed on the same day in about 1 h, and short breaks were allowed at any time during the session.

Data Analysis and Statistics

The accuracy in the task was measured to quantify the spatial ability to switch from an egocentric to an allocentric frame of reference in children with and without visual impairment. We computed a correctness score, as follows:

$$CS = \frac{\sum_{i=1}^{N} ncr}{N}, \tag{1}$$

where *CS* stands for "Correctness Score," *ncr* stands for the *n*umber of *c*orrect *r*esponses for each of the four task conditions defined by the position assumed by the participant during the reproduction phase (egocentric – 1, egocentric – 2, allocentric – 3, allocentric – 4, and see **Figure 2**), and *N* stands for the number of repetitions per condition (12 trials). Responses were considered as correct (trial score = 1) when the participant accurately reproduced the configuration presented by the experimenter during the demonstration phase, despite the spatial position assumed during the reproduction phase and thus despite the confounding visual feedback of the whole scene. For instance, while in the egocentric conditions children can rely on the visual feedback of the scene to copy the layout configuration, in the allocentric conditions they had to mentally rotate the board layout (90° in condition 3, 180° in condition 4) to place the coins correctly according to the configuration presented (see a comparison of conditions 1/2 and 3/4 in **Figure 2**). Therefore, correct responses for the two egocentric conditions (**Figures 2A,C**) were considered as egocentric responses because correct reproduction was based on egocentric coordinates, while correct answers for the

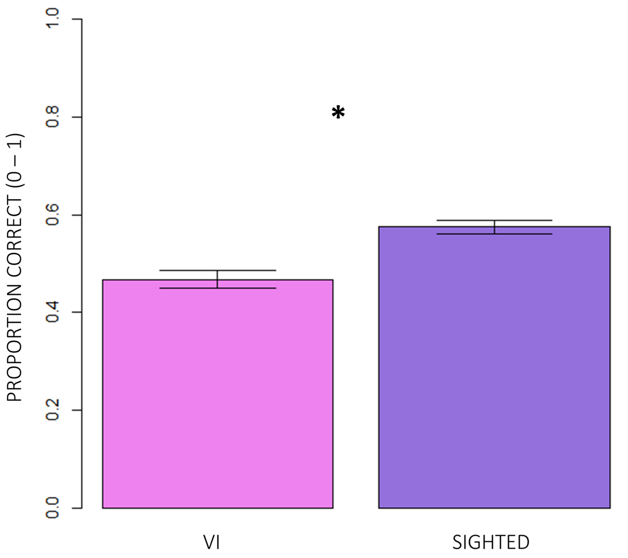

FIGURE 3 | Comparison of correctness of responses between visually impaired and normally sighted participants. The inter-groups analysis showed that visually impaired (VI) children significantly performed significantly worse than normally sighted children (RSS = 5.13, iter = 5000, $p < 2e{-}16$; and Bonferroni: $p = 0.00$), independently of the age group participants belonged to and of the difficulty of conditions.

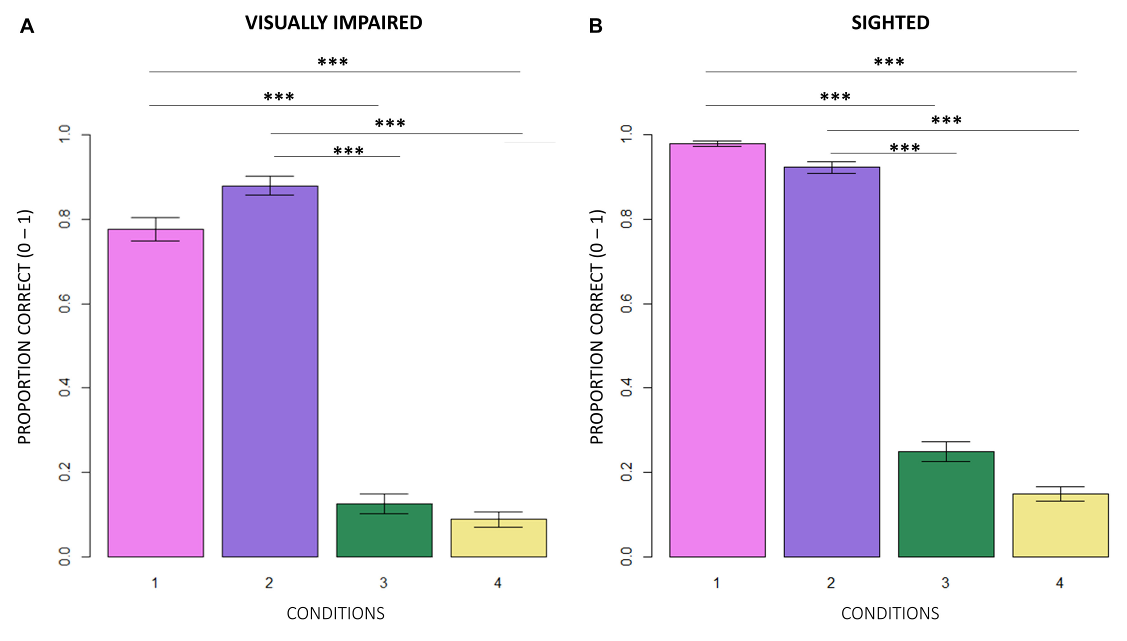

FIGURE 4 | Intra-group comparison between conditions. **(A)** In egocentric conditions (1, 2), visually impaired participants scored significantly higher in correct responses than in allocentric conditions (3, 4; RSS = 71.50, iter = 5000, $p < 2e–16$; and Bonferroni: 1 vs. 3 = 1 vs. 4 = 2 vs. 3 = 2 vs. 4: $p = 0.00$). **(B)** Normally sighted participants obtained a similar result in egocentric conditions (RSS = 162.45, iter = 5000, $p < 2e–16$; and Bonferroni: 1 vs. 3 = 1 vs. 4 = 2 vs. 3 = 2 vs. 4: $p = 0.00$).

two allocentric conditions (**Figures 2B,D**) were considered as allocentric responses because correct reproduction was based on the ability to switch from an egocentric to an allocentric frame of reference. Moreover, we computed a score for "specular" and "casual" responses, given when children positioned coins in a mirror-like configuration with respect to the assumed midline and in a way that could not be linked to any of the categories mentioned above, respectively. We evaluated the normal distribution of data applying the Shapiro–Wilk test of normality with the free software R (Free Software Foundation, Boston, MA, United States). Since we verified that data did not follow a normal distribution, we used non-parametric methods for the analysis. Two levels of analysis were performed: an intra-group level, which considered the performance of visually impaired and normally sighted children to investigate developmental trends separately; an inter-groups level, which compared the performance of visually impaired and normally sighted participants. Starting from the intra-group level, we conducted four separate mixed permuted ANOVAs with "*correct,*" "*specular,*" "*egocentric*" (only allocentric conditions), and "*casual*" responses as dependent variables, within-factors "*age groups*" (three levels: 4–5, 6–7, and 8–9), "*coins*" (three levels: One, Two, and Three), and "*conditions*" (four levels: 1, 2, 3, and 4) as independent variables. For the inter-groups level, we performed four separate mixed permuted ANOVAs with "*correct,*" "*specular,*" "*egocentric*" (only allocentric conditions), and "*casual*" responses as dependent variables, between-factor "*subjects*" (two levels: *Visually Impaired*, Normally Sighted), and within-factors "*age groups*" (three levels: 4–5, 6–7, and 8–9), "*coins*" (three levels: One, Two, and Three), and "*conditions*" (four levels: 1, 2, 3, and 4) as independent variables. The permuted Bonferroni correction for non-parametric data was applied in case of significant effects to adjust the *p*-value of multiple comparisons (significant value: $p < 0.05$).

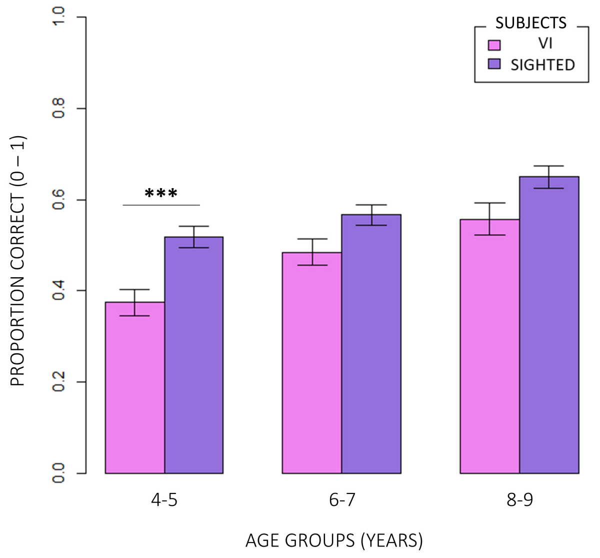

FIGURE 5 | Inter-groups comparison between age groups. Visually impaired participants performed significantly worse compared to normally sighted peers at 4–5 than 6–7 and 8–9 years of age (RSS = 0.21, iter = 5000, $p = 0.0012$; and Bonferroni: 4–5VI vs. 4–5S: $p = 0.00$; 6–7VI vs. 6–7S: $p = 0.06$; 8–9VI vs. 8–9S: $p = 0.10$).

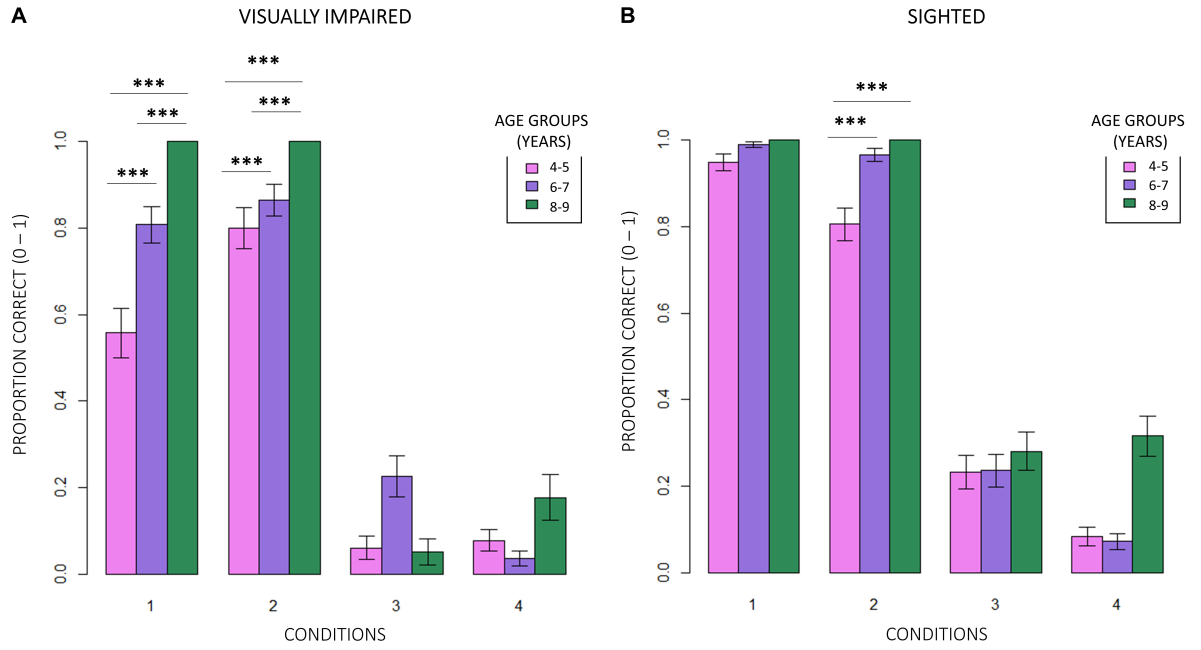

FIGURE 6 | Intra-group evaluation of accuracy among egocentric conditions. **(A)** Visually impaired children showed a strong developmental trend (RSS = 2.09, iter = 5000, $p < 2e{-}16$; and Bonferroni: 4–5_1 vs. 6–7_1: $p = 0.00$; 4–5_1 vs. 8–9_1: $p = 0.00$; 6–7_1 vs. 8–9_1: $p = 0.00$; 4–5_2 vs. 8–9_2: $p = 0.00$; and 6–7_2vs. 8–9_2: $p = 0.00$). **(B)** On the contrary, only 4–5 years old normally sighted participants showed a similar trend, and exclusively in condition 2 (interaction between age groups × conditions; RSS = 0.35, iter = 5000, $p < 2e{-}16$; and Bonferroni: 4–5_2 vs. 6–7_2: $p = 0.00$; 4–5_2 vs. 8–9_2: $p = 0.00$).

RESULTS

Firstly, we compared the correctness of responses between normally sighted and visually impaired participants. **Figure 3** shows that, independent of the age group participants belonged to and of the difficulty of conditions, visually impaired (VI) children significantly reported less correct responses than normally sighted peers (inter-groups analysis; main effect: subjects; RSS = 5.13, iter = 5000, $p < 2e{-}16$; and Bonferroni: $p = 0.00$). The intra-group analysis underlined significant differences between conditions (**Figure 4**). In egocentric conditions (1, 2), correct responses were significantly higher than in allocentric conditions (3, 4) for both normally sighted (main effect: conditions; RSS = 162.45, iter = 5000, $p < 2e{-}16$; and Bonferroni: 1 vs. 3 = 1 vs. 4 = 2 vs. 3 = 2 vs. 4: $p = 0.00$), and visually impaired (main effect: conditions; RSS = 71.50, iter = 5000, $p < 2e{-}16$; and Bonferroni: 1 vs. 3 = 1 vs. 4 = 2 vs. 3 = 2 vs. 4: $p = 0.00$) participants. Moreover, the different effect size between normally sighted and visually impaired children seemed to be related to a development factor (inter-groups analysis; interaction between subjects *x* age groups; RSS = 0.21, iter = 5000, and $p = 0.0012$). In **Figure 5**, visually impaired participants performed significantly worse compared to normally sighted peers at 4–5 than 6–7 and 8–9 years of age (Bonferroni: 4–5VI vs. 4–5S: $p = 0.00$; 6–7VI vs. 6–7S: $p = 0.06$; 8–9VI vs. 8–9S: $p = 0.10$). Starting from these findings, a deeper evaluation of accuracy among egocentric conditions revealed a dependency on age groups (**Figure 6**). Indeed, visually impaired children showed a strong developmental trend (interaction between age groups × conditions; RSS = 2.09, iter = 5000, $p < 2e{-}16$; and Bonferroni: 4–5_1 vs. 6–7_1: $p = 0.00$; 4–5_1 vs. 8–9_1: $p = 0.00$; 6–7_1 vs. 8–9_1: $p = 0.00$; 4–5_2 vs. 8–9_2: $p = 0.00$; 6–7_2vs. 8–9_2: $p = 0.00$), while only 4–5 years old normally sighted participants showed a similar trend exclusively in condition 2 (interaction between age groups × conditions; RSS = 0.35, iter = 5000, $p < 2e{-}16$; and Bonferroni: 4–5_2 vs. 6–7_2: $p = 0.00$; 4–5_2 vs. 8–9_2: $p = 0.00$).

To evaluate a possible influence of the experimental condition on the reproduction of a configuration, we reported the performance across age groups in terms of correct and specular responses scored by the two experimental groups with the use of confusion matrices (**Figure 7**). The levels of gray indicate whether participants reproduced a configuration ("Reproduced configuration", *x*-axis) correctly (dark gray) or specularly (light gray) with respect to the experimenter's configuration ("Target configuration", *y*-axis) in a specific condition. As regards normally sighted children (**Figure 7B**), the number of specular responses resulted higher in allocentric (3, 4) than egocentric (1, 2) conditions, but it gradually reduced with growth. On the contrary, visually impaired participants did not improve their performance by relying more on allocentric frames of reference (**Figure 7A**). Interestingly, at 4–5 years of age, specular responses given by visually impaired children seemed to be higher than normally sighted peers even in the condition 1, where we expected a similar result based on egocentric cues. **Figure 8** confirms that the tendency to reproduce specular configurations in an egocentric condition (1) was significantly higher in 4–5 years old visually impaired than normally sighted participants (inter-groups analysis; interaction between subjects *x* age groups

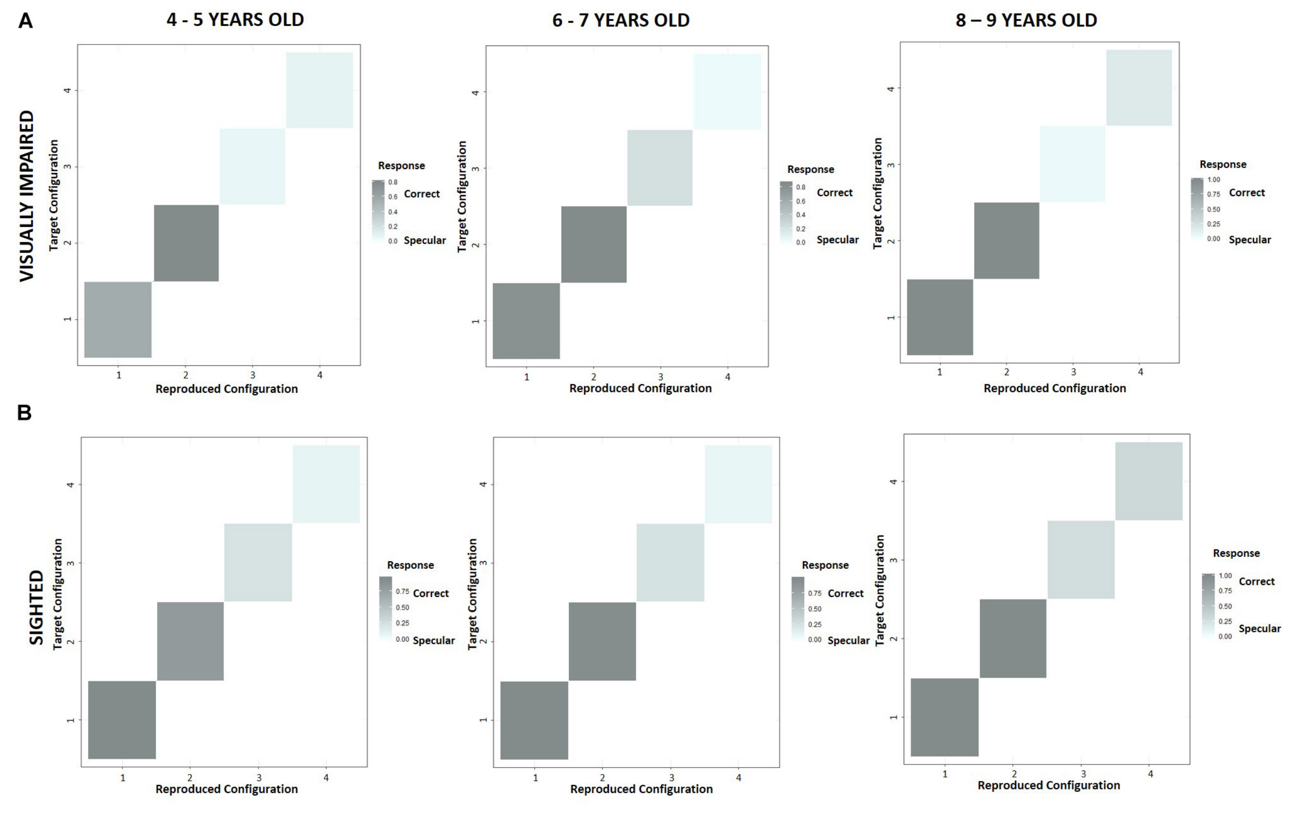

FIGURE 7 | Intra-group performance across age groups in terms of correct and specular responses with confusion matrices. The levels of gray indicate whether participants reproduced a configuration ("Reproduced configuration", *x*-axis) correctly (dark gray), or specularly (light gray) with respect to the experimenter's configuration ("Target configuration", *y*-axis) in a certain condition. **(A)** Visually impaired participants did not improve their performance by relying more on allocentric frames of reference, **(B)** while the number of specular responses given by normally sighted children resulted higher in allocentric (3, 4) than egocentric (1, 2) conditions, gradually reducing with growth.

x conditions; RSS = 0.44, iter = 5000, $p < 2e{-}16$; and Bonferroni: 45VI_1 vs. 45S_1: $p = 0.00$). This result suggests a significant developmental delay in the consolidation process of egocentric spatial competencies in youngest visually impaired children.

Overall, our findings suggested that different developmental abilities to localize spatial stimuli by relying on egocentric and allocentric reference frames depend on the amount of visual experience along with childhood.

DISCUSSION

Several studies indicate that the capability of individuals to integrate egocentric and allocentric frames of reference emerges during the first years of life and typically relies on visual experience. Nonetheless, it is not yet clear when children become able to spontaneously alternate and switch from an egocentric to an allocentric coordinates system depending on task demands and how visual deprivation impacts on this ability. In this work, we tested and verified the hypothesis that children with an atypical visual experience during development (visually impaired) would show a stronger reliance on egocentric frames of reference when a mental update of spatial coordinates was required. In particular, we demonstrated that visually impaired children had more difficulties than typical peers in performing a switching-perspective task. Furthermore, visually impaired children showed a dominance of specular responses (i.e., mirror-like representation of space) at 4–5 years of age in configurations that required an egocentric coordinate system.

Several studies have shown that normally sighted children rely on allocentric cues from an early age. For instance, 3-year-old children can form allocentric representations if provided with environmental cues (Acredolo, 1977, 1978; Acredolo and Evans, 1980; Hermer and Spelke, 1994; Learmonth et al., 2002; Ribordy et al., 2013). They also encode space with egocentric and allocentric coordinates in parallel (Nardini et al., 2006), even if they show a viewpoint-independent perspective only later at five years of age (Nardini et al., 2006). Such findings have been interpreted as the result of cognitive development. Indeed, the first years of life are crucial for the development of executive functions that might play a role in helping children to identify and select the most appropriate spatial strategy according to environmental features (Hermer and Spelke, 1994; Nardini et al., 2008, 2009; Vasilyeva and Lourenco, 2012).

Since vision is crucial for the maturation of spatial cognition (Foulke, 1982; Thinus-Blanc and Gaunet, 1997), the impoverishment of visual feedback can determine impairments in updating spatial coordinates from an egocentric to an allocentric perspective (and vice-versa). Visual impairment can, therefore, produce a developmental delay in spatial planning abilities (Cappagli and Gori, 2016). During development, partial visual deprivation negatively affects the acquisition of spatial competences, resulting in a delay in locomotor and proprioceptive skills (Levtzion-Korach et al., 2000; Bremner et al., 2008). In this work, we found that visually impaired children remained anchored to an egocentric representation of space across ages when they were required to solve the task by using allocentric frames of reference. On the contrary, normally sighted children gradually improved their performance across development, showing an increase in the number of correct responses. This result is in line with previous studies that have reported a deficit of visually impaired children in solving tasks based on the mental rotation of the self (Huttenlocher and Presson, 1973; Millar, 1976; Papadopoulos and Koustriava, 2011; Koustriava and Papadopoulos, 2012) or of the objects (Huttenlocher and Presson, 1973; Penrod and Petrosko, 2003; Papadopoulos and Koustriava, 2011). Recently, it has been hypothesized that the object-centered representation of space cannot be independent of egocentric coordinates (Filimon, 2015). In other words, spatial decisions remained anchored to a purely egocentric spatial reference frame even when spatial locations are referred to external objects. Therefore, it seems that spatial choices are based on a two-steps process. The first step allows to code space in body-centered coordinates, the second step allows relating body-centered to objects-centered coordinates. We can speculate that visually impaired children remained anchored to the first step, being able to code space in egocentric coordinates while not being able to rotate mentally body-centered representation according to the spatial layout. Furthermore, the difficulty in developing allocentric spatial coding skills might be related to different processing of egocentric and allocentric representation at cortical level. Nadel and Hardt (2004) have shown that allocentric and egocentric spatial information are processed in at least partly separate neural networks. Other studies have demonstrated that the activation of the posterior parietal/frontal network and of the posteromedial/medio-temporal cerebral substructures have been reported during egocentric and allocentric spatial coding, respectively (Galati et al., 2010).

Another interesting finding was that visually impaired children manifested a developmental delay in performing the task also from an egocentric point of view. Indeed, in condition 1 (see **Figure 2A**) they produced more specular than egocentric responses at 4–5 years of age, while normally sighted peers correctly maintained the same perspective (egocentric). At the same age, visually impaired children manifest less specular responses in condition 2, which still required an egocentric perspective, even if two boards lying one above the other were presented (condition 1). In this case, the body midline might play a role in the representation of space based on body coordinates. It has been shown that the body midline can be reliable as a body-centered frame of reference when spatially aligned with the coded object (Millar, 1981, 1985), but not in the case of a body midline-crossing spatial task (Millar and Ittyerah, 1992). Moreover, some works have assumed that egocentric spatial coding may also be centered on the eye (Rock, 1997). According to this egocentric dichotomy, results obtained in condition 1 might suggest that visually impaired children tend to refer more on their body midline at early ages to encode body midline-crossing space. In contrast, they mainly refer to their visual residual in case of body midline-aligned space.

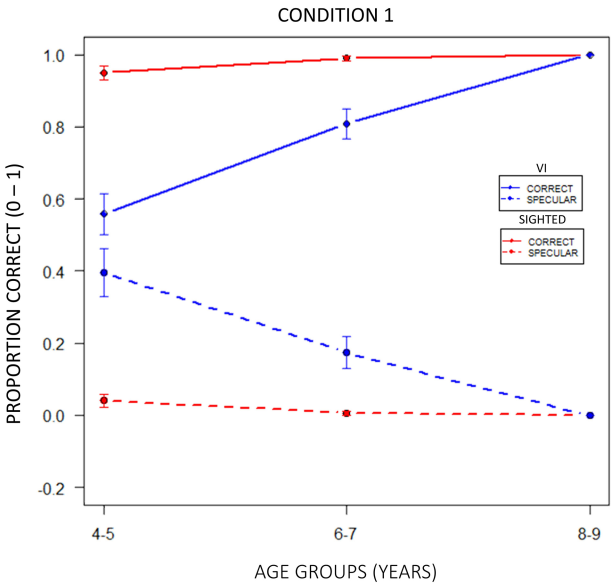

FIGURE 8 | Correct and specular responses in egocentric condition 1. The tendency to reproduce specular configurations was significantly higher in 4–5 years old visually impaired than normally sighted participants (RSS = 0.44, iter = 5000, $p < 2e\text{–}16$; and Bonferroni: 45VI_1 vs. 45S_1: $p = 0.00$). This result might suggest that youngest visually impaired children have a significant developmental delay in the consolidation process of egocentric spatial competences.

To conclude, we evaluated whether visually impaired children acquire allocentric spatial abilities across development similarly to normally sighted children. We defined a switching-perspective task, in which children were asked to reproduce a visual configuration by changing their position in space thus assuming different spatial reference frames. Our work suggests that an impoverished visual experience during development negatively impacts on the development of allocentric spatial coding and the acquisition of a correct body-center perspective in case of body midline-crossing targets. In order to understand whether vision is required to develop spatial competences, future works should assess whether a complete loss of vision from birth, such in the case of congenital blindness, would produce similar or contrasting results. These findings would favor the development of rehabilitative intervention addressed to children's needs.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Pavia Area, Fondazione IRCCS Policlinico San Matteo, Pavia (Italy). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CM, GC, MG, and SS developed the study concept and design. CM and AL collected the data and CM analyzed the data. CM and GC wrote the manuscript. SS and MG provided critical inputs to review the manuscript.

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Short-Term Sensorimotor Deprivation Impacts Feedforward and Feedback Processes of Motor Control

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Sensory loss involves irreversible behavioral and neural changes. Paradigms of short-term limb immobilization mimic deprivation of proprioceptive inputs and motor commands, which occur after the loss of limb use. While several studies have shown that short-term immobilization induced motor control impairments, the origin of such modifications is an open question. A Fitts' pointing task was conducted, and kinematic analyses were performed to assess whether the feedforward and/or feedback processes of motor control were impacted. The Fitts' pointing task specifically required dealing with spatial and temporal aspects (speed-accuracy trade-off) to be as fast and as accurate as possible. Forty trials were performed on two consecutive days by Control and Immobilized participants who wore a splint on the right arm during this 24 h period. The immobilization modified the motor control in a way that the full spatiotemporal structure of the pointing movements differed: A global slowdown appeared. The acceleration and deceleration phases were both longer, suggesting that immobilization impacted both the early impulse phase based on sensorimotor expectations and the later online correction phase based on feedback use. First, the feedforward control may have been less efficient, probably because the internal model of the immobilized limb would have been incorrectly updated relative to internal and environmental constraints. Second, immobilized participants may have taken more time to correct their movements and precisely reach the target, as the processing of proprioceptive feedback might have been altered.

Keywords: immobilization, sensorimotor deprivation, Fitts' task, speed-accuracy trade-off, motor control

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INTRODUCTION

The impact of sensory deprivation has been largely studied to identify behavioral and neural changes following irreversible sensory loss. Over the past decade, such changes have been studied for sensorimotor loss through paradigms involving short-term limb immobilization. Such paradigms mimic the deprivation of motor inputs and outputs that induce maladaptive neural plasticity without compromising brain function (disease-free model; Furlan et al., 2016). Short-term immobilization consists of preventing a body part (often fingers, hand, and/or arm) from moving by means of a splint or a bandage for a period ranging from a few hours to a few days. While several studies have shown that short-term immobilization induced motor control impairments, the origin of such modifications is an open question. Here, a short-term limb immobilization paradigm was used to specify the impact of this sensorimotor deprivation on performance in a Fitts' task. This pointing task specifically required dealing with spatial and temporal aspects (speed-accuracy trade-off) to be as fast and as accurate as possible. The associated kinematic analysis allowed us to assess whether the feedforward and/or the feedback processes of motor control were impacted.

Overall, studies investigating the anatomical cerebral changes following limb immobilization agree on reductions in cortical excitability of the sensorimotor representation linked to the decrease in sensory input and motor output (Facchini et al., 2002; Huber et al., 2006; Avanzino et al., 2011; Burianová et al., 2016). In the same vein, behavioral studies have highlighted the negative immobilization-induced effects on the cognitive level of action. Alterations at the sensorimotor representation level evaluated by means of an implicit motor imagery task were reported following a few hours of arm non-use (Toussaint and Meugnot, 2013; Debarnot et al., 2018). The authors showed that motor imagery processes used to identify the laterality of hand images were slowed down for stimuli corresponding to the immobilized hand. Other studies reported changes in the peripersonal space representation (Bassolino et al., 2012; Toussaint et al., 2018). Using a reachability judgment task, Toussaint et al. reported that the maximum distance at which objects are perceived as reachable was reduced in subjects forced into arm and hand non-use for 24 h. Overall, these studies have shown that representations in the brain are modified with immobilization.

Although functional consequences of immobilization have been demonstrated, these studies did not identify which mechanisms of action were altered. The majority of studies have tested how short-term immobilization impacted out-and-back uncorrected movements toward visual targets (Huber et al., 2006; Moisello et al., 2008; Debarnot et al., 2018). The hand path trajectory of such movements deviated after immobilization, showing that spatial parameters were impacted (Huber et al., 2006; Moisello et al., 2008). Debarnot et al. (2018) added that temporal parameters were also modified during this out-and-back movement following immobilization. They showed that movement time and reaction time were longer than those of Control participants. While these studies demonstrated the impact of immobilization on spatial parameters on the one hand and temporal parameters on the other hand, the associated kinematic analysis was not provided. This analysis was provided in Bassolino et al. (2012) with a reach-to-grasp objects task. The authors showed that the transport phase was impaired following 10 h of immobilization but not the grasping component (Bassolino et al., 2012). To suppress the possible interaction of the grasping component on the transportation phase, we investigated how short-term immobilization impacts the kinematics of a pointing movement (i.e., without a grasping component). A Fitts' task was used to specifically assess how immobilization may modify spatiotemporal aspects of motor control. Therefore, contrary to previously used paradigms with immobilization, the Fitts' task necessitates dealing with speed as well as accuracy (i.e., speed-accuracy trade-off) to reach the target. A kinematic analysis was provided to determine whether the feedforward and/or feedback processes of motor control of the pointing movement were affected. The feedforward model refers to the initiation of early adjustments based on the comparison between the motor commands and the expected outputs (efference copy; Miall and Wolpert, 1996). This feedforward process would be associated with early kinematic parameters (i.e., before peak velocity; Meyer et al., 1982; Elliott et al., 2010). The feedback process corresponds to the correction phase, with an online sensory processing comparing the intended to the current state, and would be associated with later kinematic parameters (i.e., after peak velocity; Meyer et al., 1982; Elliott et al., 2010).

MATERIALS AND METHODS

Participants

Forty-nine right-handed participants (29 men and 20 women; mean age ± SE: 20.0 ± 0.28 years) gave written informed consent prior to the study, in accordance with the 1964 Declaration of Helsinki. The experimental protocol was approved by the ethics committee for research in sciences of physical and sports activities (n°2017250114). All participants reported having normal or corrected-to-normal vision and no neurological or sensorimotor disorders. As we expected, the immobilization effects would disappear within a few trials (Bassolino et al., 2012), and we used a between-subject design. The participants were assigned into one of the two groups (e.g., *Control* or *Immobilized*) and performed either the task with an Index of Difficulty (ID) of *3* or *7* (see section "Procedure"). Fifteen participants constituted the *Control-ID3* group (seven men and eight women; 20.4 ± 0.49 years), twelve were in the *Control-ID7* group (seven men and five women; 20.6 ± 0.49 years), ten were in the *Immobilized-ID3* group (six men and four women; 19.4 ± 0.33 years), and twelve were in the *Immobilized-ID7* group (nine men and three women; 19.6 ± 0.41 years).

Apparatus

The pointing task was performed on a MacBook Pro Retina (OS X 10.11.6 El Capitan 2.5 GH Core i5) with a screen of 13.3 inches (900 × 1440 pixels) refreshed at 60 Hz. This laptop included an 8.6 cm × 10.5 cm trackpad with a resolution of 400 CPI sampling at 125 Hz. Instructions, stimuli and data from the pointing device were handled using a custom-built application written in C++ using Qt and Libpointing (Casiez et al., 2011). The gain between the trackpad and the visual cursor was set to 1: what was seen on the screen corresponded to what was done on the trackpad.

Procedure

The task consisted of horizontal 2D pointing (either left to right or right to left; **Figure 1**) using Fitts' paradigm (Fitts, 1954). The cursor corresponded to a vertical line of 1 pixel width (0.2 mm), and the target was a rectangle of a length corresponding to the

FIGURE 1 | Experimental setup. Subjects were asked to perform a pointing task: They slided their right index on the laptop trackpad to move the visual cursor (white line) into the target (green rectangle).

screen height and a width (W), which was manipulated with the task's ID. The ID integrates both the W and the Distance (D) from the starting point to the target's center as follows: *ID* = Log2(2D/W). Here, D was set to 8 cm, and W was either 2 or 0.125 cm, defining an ID of 3 or 7, respectively. The participants in the two groups (*Control* and *Immobilized*) were assigned to either *ID3* or *ID7* conditions (between-subject design; see section "Participants").

In an illuminated room, the participants sat in a chair adjustable in elevation. They were approximately at 50 cm faced to a laptop. The experimenter placed their forearm on the table perpendicular to the laptop, in a comfortable position. The joints were not restrained, and the pointing mainly consisted of a wrist movement (i.e., abduction when pointing from the left and adduction when pointing from the right). Talcum was applied on the participant's finger before the experiment to reduce dampness and allowed an easy finger slide on the trackpad. This talcum was reapplied whenever the participants needed it. For each trial, the participants were instructed to explore the trackpad with the right finger to find the starting position on the trackpad (left or right border). When the position was reached, the word "calibration" was displayed on the screen. The trial was launched if the finger was static at this specific location for 0.5 s. The trial started with the simultaneous appearance of the cursor and the visual target: The participants could then start the pointing whenever they were ready. The required movement was to point the visual target as precisely and as accurately as possible with a smooth and continuous movement on the trackpad. The participants had to avoid stopping before or after the target. After a period of 0.5 s static in the target, the visual stimuli disappeared, and the trial stopped. The trial direction alternated between rightward and leftward. The vision of the arm was not restrained.

The experiment was composed of two sessions of 40 trials on 2 consecutive days (*Pre* and *Post* tests). The first session (*Pre*) also included a training of 20 trials to familiarize the participants with the task prior to data recording. The *Pre* session lasted 40 min. Immediately after this first session, the participants in the *Immobilized* group had their right arm immobilized with a rigid splint (DONJOY "Comfort Digit"; DJO, Surrey, United Kingdom) that firmly maintained the wrist and three fingers (index, middle, and ring). An immobilization vest (model DONJOY "Immo Axmed") restraining right shoulder, arm and forearm movements was also used to ensure that the participants kept their arm at rest as much as possible during the 24 h of immobilization. The *Immobilized* group also wore actimeters (ActiGraph wGT3X-BT) on the wrist of both hands to verify if they had complied with these instructions. The actimeters recorded the activity level (in counts/min) with ActiLife software (ActiLife v6.11.8, Pensacola, FL, United States).

Twenty-four hours after the first session, both groups returned and performed the second session of 40 trials (*Post*). For the *Immobilized* group, the *Post* test was performed immediately after splint removal by the experimenter. The *Post* session lasted 15 min.

Data Processing

For the Immobilized group, a quantitative check of the activity amount was performed through the recording of both arms with actimeters. During the 24 h immobilization period, 638 ± 59 counts/min were recorded for the right immobilized hand and 2795 ± 115 counts/min were recorded for the left non-immobilized hand (see Toussaint and Meugnot, 2013 for a similar procedure). ANOVA performed on the actimeter values confirmed that the level of manual activity was higher for the left hand than for the right hand [$F_{(1,21)} = 525.5$; $p < 0.001$].

Position data from the trackpad were low-pass filtered with a dual-pass, no-lag Butterworth filter (cutoff frequency: 10 Hz; order: 2). The data were then derivated to compute the finger velocity used to determine the Movement Time (MT) of the pointing. The MT corresponds to the period between the movement onset and offset, which were defined when the velocity reached above and below 5% of Peak Velocity (PV), respectively. We further assessed the impact of immobilization with the analysis of pointing corrections. Although the participants were instructed to point the target with a "*smooth and continuous movement*," some movements were stopped (velocity below 5% of PV) before or after the target. We computed the percentage of trials where corrections appeared (i.e., the correction rate). Movement kinematics were also analyzed to further determine the impact of immobilization on the motor *impulse phase* and online *correction phase*, associated to feedforward and feedback processes, respectively. Modifications in the *impulse phase* were assessed through the analysis of the time of acceleration (AT; time from movement onset to PV). In addition, the time of deceleration (DT; time between PV and movement offset) was associated with the *correction phase* with online corrections (Meyer et al., 1982; Elliott et al., 2010). DT includes the deceleration period of the first submovement (from PV) as well as the period lasting for all potential additional submovements.

Bassolino et al. (2012) found that the influence of immobilization in a reach-to-grasp task did not last more than a few trials. Therefore, we first assessed whether differences appeared over trials by comparing the means of each eight successive blocks of five trials. Repeated-measures ANOVAs were then conducted using a mixed design with two between-subjects factors: *Group* (*Control* vs. *Immobilized*) and *ID* (3 vs. 7) and two within-subjects factors: *Session* (*Pre* vs. *Post*) and *Block* (1–8). A simple effect of Block appeared but no significant interactions were revealed between the *Block* and the *Group* or the *Session* on all the dependent variables. The analyses were then conducted on the mean of the 40 trials. *Post-hoc* tests (Newman-Keuls) were performed when necessary, and the level of significance was set at 0.05 for all statistical analyses.

RESULTS

Kinematic Profiles

Figure 2 depicts velocity profiles for representative trials in the Control and Immobilized groups. As classically shown, the *ID* seemed to modify pointing kinematics: *ID7* was associated with a lower PV, longer MT and more corrections than *ID3*. In addition, **Figure 1** suggests that the *Immobilized* participants exhibited a longer MT and a lower PV in the *Post* session than in the *Pre* session, regardless of the ID. These observations were statistically tested with mean comparisons of selected kinematic parameters.

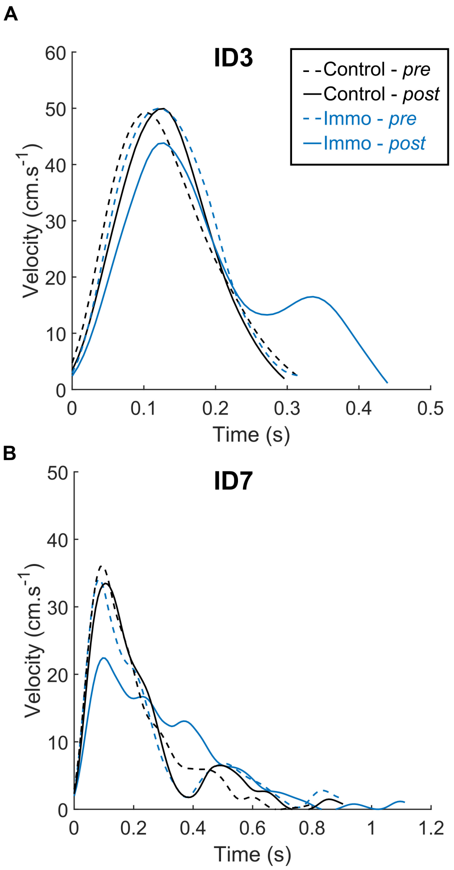

FIGURE 2 | Velocity profiles from representative trials for the *Control* and *Immobilized* (*Immo*) participants who performed in either the *ID3* **(A)** or *ID7* **(B)** condition. Dashed lines represent session *Pre,* and full lines represent session *Post*. Regardless of the *ID*, the *Immobilized* participants exhibited longer MT and lower PV in the *Post* session than in the *Pre* session.

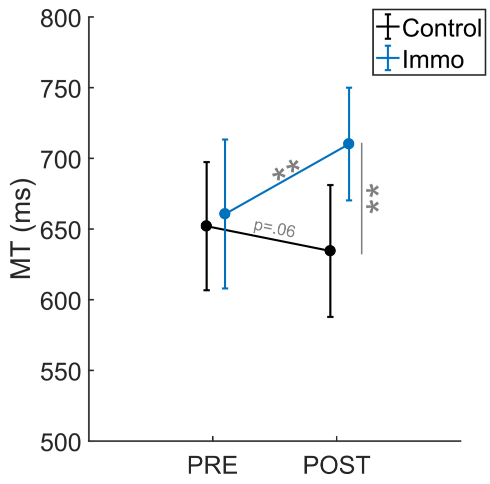

FIGURE 3 | Movement Time (MT) relative to the Session (*Pre* vs. *Post*) for the *Control* and *Immobilized* (*Immo*) groups. $^{**}p < 0.01$. Error bars denote standard error.

Movement Time and Corrections

The repeated-measures ANOVA *Group* × *ID* × *Session* for MT revealed an effect of *ID* [$F_{(1,45)} = 349.0$; $p < 0.001$] as well as an interaction *Group* × *Session* [$F_{(1,45)} = 10.4$; $p < 0.001$]. Overall, the MT was shorter in the *ID3* than in the *ID7* condition (367 ± 12 ms vs. 970 ± 32 ms, respectively). No significant effect of Group [$F_{(1,45)} = 1.6$; $p = 0.21$], Session [$F_{(1,45)} = 2.4$; $p = 0.13$], Group × ID [$F_{(1,45)} = 0.0$; $p = 1.00$], Session × ID [$F_{(1,45)} = 0.2$; $p = 0.62$] nor Group × ID × Session [$F_{(1,45)} = 2.0$; $p = 0.17$] appeared. **Figure 3** depicts the *Group* × *Session* interaction. The *Control* and *Immobilized* groups differed between the *Pre* and *Post* sessions. For the *Immobilized* group, the MT increased between the *Pre* and *Post* sessions (661 ± 70 ms vs. 710 ± 73 ms, respectively; $p < 0.01$). In contrast, for the *Control* group, the MT did not increase between the *Pre* and *Post* sessions and either exhibited a trend toward a decrease (666 ± 64 ms vs. 639 ± 62 ms; $p = 0.06$).

The analysis of corrections (under- and overshoots) revealed an effect of ID [$F_{(1,45)} = 26.9$; $p < 0.001$] with a higher correction rate for ID7 than ID3 (2.0 ± 0.6% vs. 14.1 ± 2.5%). No significant effect of Group [$F_{(1,45)} = 0.9$; $p = 0.35$], Session [$F_{(1,45)} = 0.1$; $p = 0.70$], Group × ID [$F_{(1,45)} = 0.5$; $p = 0.50$], Session × ID [$F_{(1,45)} = 0.0$; $p = 0.95$], Session × Group [$F_{(1,45)} = 0.0$; $p = 0.87$] nor Group × ID × Session [$F_{(1,45)} = 0.7$; $p = 0.42$] appeared. Therefore, the analysis failed to show an effect of immobilization on corrections.

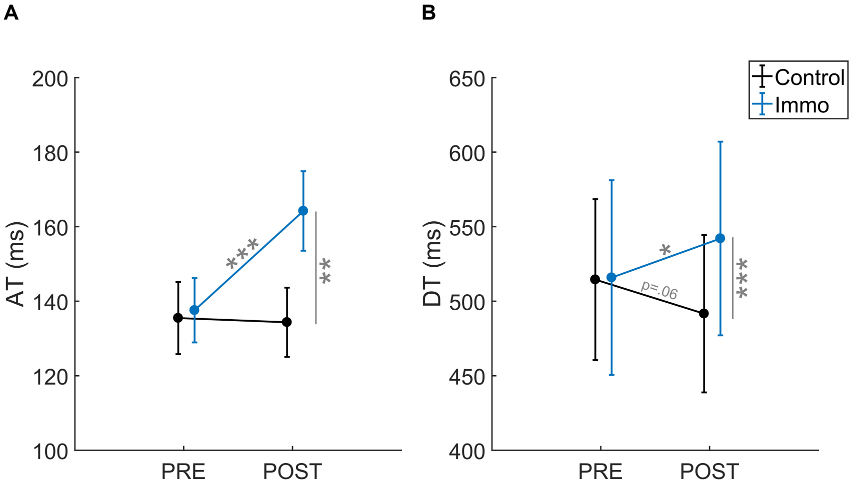

FIGURE 4 | (A) Acceleration Time (AT) and **(B)** Deceleration Time (DT) relative to the Session (*Pre* vs. *Post*) for the *Control* and *Immobilized* (*Immo*) groups. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Error bars denote standard error.

Acceleration and Deceleration Time

The Acceleration Time (AT) corresponds to the absolute period between the movement onset and the PV. This parameter is associated with the impulse phase of motor control reflecting the planning process of the movement. The analysis showed an effect of *ID* [$F_{(1,45)} = 34.6$; $p < 0.001$], *Session* [$F_{(1,45)} = 9.7$; $p < 0.01$] and a *Group* × *Session* interaction [$F_{(1,45)} = 11.5$; $p < 0.01$]. No significant effect of Group [$F_{(1,45)} = 2.5$; $p = 0.19$], Group × ID [$F_{(1,45)} = 0.1$; $p = 0.73$], Session × ID [$F_{(1,45)} = 0.9$; $p = 0.35$] nor Group × ID × Session [$F_{(1,45)} = 1.4$; $p = 0.25$] appeared. Therefore, the AT was shorter at *ID3* (113 ± 4 ms) than at *ID7* (172 ± 11 ms). Moreover, the *post-hoc* analysis of the interaction showed that the *Control* and *Immobilized* groups differed between the *Pre* and *Post* sessions (**Figure 4A**). For the *Immobilized* group, the AT increased between the *Pre* and *Post* sessions (138 ± 9 ms vs. 164 ± 11 ms, respectively; $p < 0.001$). For the *Control* group, the AT did not increase between the *Pre* and *Post* sessions (136 ± 10 ms vs. 134 ± 9 ms; $p = 0.86$).

The Deceleration Time (DT) corresponds to the absolute period between the PV and the end of the movement. This parameter is associated with the homing phase of motor control reflecting online movement corrections (e.g., Woodworth, 1899; Meyer et al., 1982). The analysis showed an effect of ID [$F_{(1,45)} = 553.1$; $p < 0.001$] and a *Group* × *Session* interaction [$F_{(1,45)} = 9.3$; $p < 0.01$]. No significant effect of Group [$F_{(1,45)} = 1.2$; $p = 0.27$], Session [$F_{(1,45)} = 0.0$; $p = 0.83$], Group × ID [$F_{(1,45)} = 0.6$; $p = 0.43$], Session × ID [$F_{(1,45)} = 0.0$; $p = 0.88$] nor Group × ID × Session [$F_{(1,\ 45)} = 0.7$; $p = 0.42$] appeared. Again, the DT was shorter at ID3 (242 ± 9 ms) than at ID7 (790 ± 23 ms), and *post-hoc* analysis of the interaction showed that the *Control* and *Immobilized* groups differed between the *Pre* and *Post* sessions (**Figure 4B**). For the *Immobilized* group, the DT increased between the *Pre* and *Post* sessions (516 ± 65 ms vs. 542 ± 65 ms, respectively; $p < 0.05$). For the *Control* group, the DT did not increase between the *Pre* and *Post* sessions and exhibited a trend toward a reduction (514 ± 54 ms vs. 492 ± 53 ms; $p = 0.06$).

Further analyses were conducted to determine what caused the modifications in the temporal parameters (i.e., MT, AT, DT). More precisely, we computed the peak acceleration, velocity and deceleration to determine whether those modifications occurred at an early or late stage.

Peak Velocity, Peak Acceleration, and Peak Deceleration

We analyzed how fast the pointing movements of the participants were. The analysis of Peak Velocity (PV) revealed an effect of *ID* [$F_{(1,45)} = 66.3$; $p < 0.001$] and a *Group* × *Session* interaction [$F_{(1,45)} = 13.3$; $p < 0.01$; **Figure 5A**]. No significant effect of Group [$F_{(1,45)} = 0.1$; $p = 0.77$], Session [$F_{(1,45)} = 3.0$; $p = 0.09$], Group × ID [$F_{(1,45)} = 0.4$; $p = 0.53$], Session × ID [$F_{(1,45)} = 0.5$; $p = 0.50$] nor Group × ID × Session [$F_{(1,45)} = 0.3$; $p = 0.57$] appeared. First, the PV was higher at ID3 (49.5 ± 2.0 $cm.s^{-1}$) than at ID7 (28.4 ± 1.9 $cm.s^{-1}$). In addition, the *post-hoc* analysis of the interaction showed that the PV in the *Immobilized* group decreased between the *Pre* and *Post* sessions (41.5 ± 3.2 $cm.s^{-1}$ vs. 35.6 ± 2.7 $cm.s^{-1}$, respectively; $p < 0.01$). No difference was found for the *Control* group between the *Pre* and *Post* sessions (514 ± 2.7 $cm.s^{-1}$ vs. 492 ± 3.0 $cm.s^{-1}$; $p = 0.06$). A trend appeared in the *Post* session between the two groups ($p = 0.07$).

The analysis of Peak Acceleration (PA) revealed an effect of ID [$F_{(1,45)} = 52.6$; $p < 0.001$] and a *Group* × *Session* interaction [$F_{(1,45)} = 10.3$; $p < 0.01$; **Figure 5B**]. No significant effect of Group [$F_{(1,45)} = 1.6$; $p = 0.21$], Session [$F_{(1,45)} = 2.2$; $p = 0.15$], Group × ID [$F_{(1,45)} = 2.0$; $p = 0.16$], Session × ID [$F_{(1,45)} = 1.6$; $p = 0.21$] nor Group × ID × Session [$F_{(1,45)} = 0.0$; $p = 0.90$] appeared. As with the PV, the PA was higher at ID3 (634 ± 40 $cm.s^{-2}$) than at ID7 (306 ± 31 $cm.s^{-2}$). In addition, the *post-hoc* analysis of the interaction showed that the PA in the

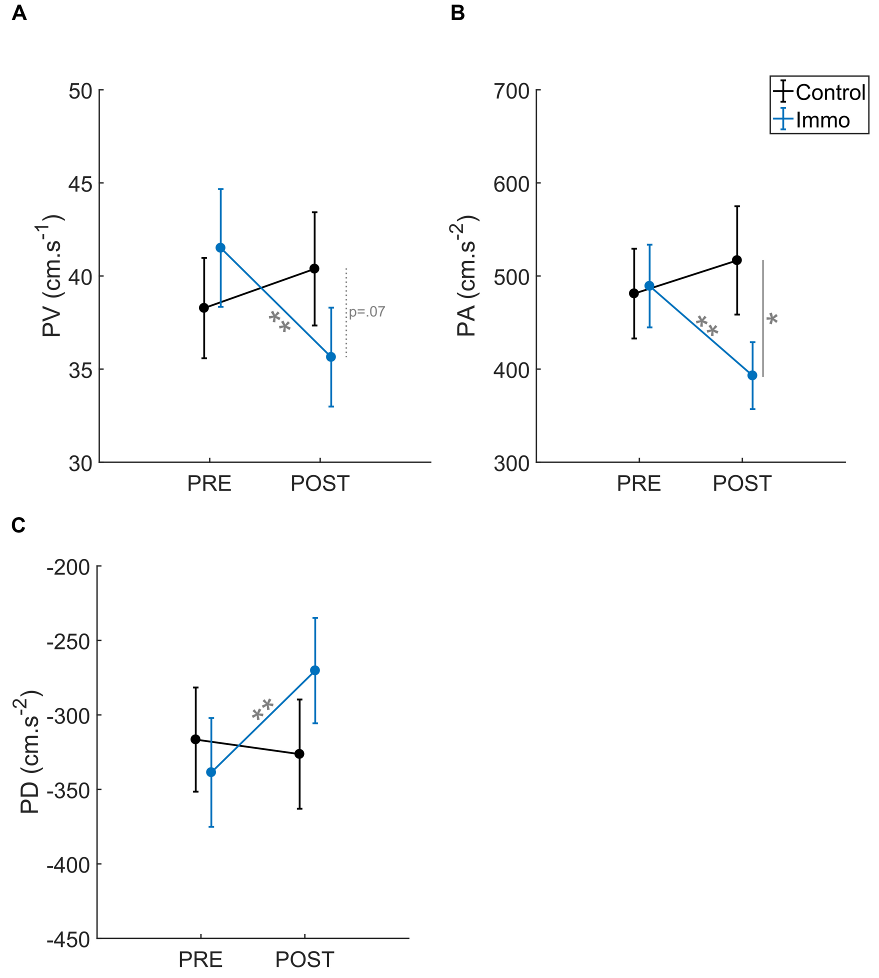

FIGURE 5 | (A) Peak Velocity (PV), **(B)** Peak Acceleration (PA), and **(C)** Peak Deceleration (PD) relative to the Session (*Pre* vs. *Post*) for the *Control* and *Immobilized* (*Immo*) groups. *$p < 0.05$; **$p < 0.01$. Error bars denote standard error.

Immobilized group decreased between the *Pre* and *Post* sessions (489 ± 44 cm.s^{-2} vs. 393 ± 36 cm.s^{-2}, respectively; $p < 0.01$). No difference was found for the *Control* group between the *Pre* and *Post* sessions (481 ± 48 cm.s^{-2} vs. 517 ± 58 cm.s^{-2}; $p = 0.19$). Finally, the *Pre* and *Post* sessions differed between the two groups ($p < 0.01$).

The analysis of Peak Deceleration (PD) revealed an effect of ID [$F_{(1,45)} = 57.6$; $p < 0.001$] and a *Group* × *Session* interaction [$F_{(1,45)} = 6.4$; $p < 0.01$; **Figure 5C**]. No significant effect of Group [$F_{(1,45)} = 0.3$; $p = 0.61$], Session [$F_{(1,45)} = 3.6$; $p = 0.06$], Group × ID [$F_{(1,45)} = 0.8$; $p = 0.37$], Session × ID [$F_{(1,45)} = 1.0$; $p = 0.31$] nor Group × ID × Session [$F_{(1,45)} = 0.1$; $p = 0.72$] appeared. As PA, the PD was also higher at ID3 (−438 ± 29 cm.s^{-2}) than at ID7 (−188 ± 21 cm.s^{-2}). In addition, the *post-hoc* analysis of the interaction showed that the PD in the *Immobilized* group decreased between the *Pre* and *Post* sessions (−339 ± 37 cm.s^{-2} vs. −270 ± 35 cm.s^{-2}, respectively; $p < 0.05$). No difference was found for the *Control* group between the *Pre* and *Post* sessions (−317 ± 35 cm.s^{-2} vs. −326 ± 37 cm.s^{-2}; $p = 0.60$) or between the *Pre* and *Post* sessions between the two groups ($p = 0.14$).

DISCUSSION

Here, we tested how short-term immobilization modified behavioral responses. More precisely, we tested whether the feedforward and/or feedback processes of pointing movements were affected by 24 h of arm non-use. We first showed that immobilization had an impact on sensorimotor control with lengthened movement time without damaging accuracy. This decrease in movement time seemed to result from a global slowdown: The acceleration and deceleration phases were both longer and were associated with lower peak acceleration, velocity, and deceleration. Therefore, immobilization appeared to modify sensorimotor control in such a way that the full spatiotemporal structure of the pointing movements differed.

First, our data confirmed that immobilization leads to a decrease in motor performance (Huber et al., 2006; Moisello et al., 2008; Bassolino et al., 2012; Bolzoni et al., 2012). Such declines in pointing performance have been shown to arise from changes in joint coordination around the deprived segment (Moisello et al., 2008; Bassolino et al., 2012). When the immobilized participants were instructed to make out-and-back straight movements without correction, an increase in the hand-path area amplitude and variability appeared (Huber et al., 2006; Moisello et al., 2008; Bassolino et al., 2012). When the task integrated spatial constraints for trial validation, immobilization rather induced temporal impairments, such as an increase in movement time. Therefore, Bassolino et al. (2012) showed an increase in movement time for a reach-to-grasp task where spatial constraints were defined (i.e., the object reaching movement to perform the grasping) during the five first trials. Here we found that this increase in movement duration could last longer for a pointing task as we did not find an interaction between the immobilization and the trial repetitions. Therefore, no reactivation of the process of proprioceptive inputs would appear contrary to the results of Bassolino et al. (2012). Albeit, here the movement amplitude was reduced and required a less complex motor control than a reach-to-grasp task involving multiple joints from the arm, the hand and the digits. In addition, spatial corrections (stops before or after the target) were not amplified with immobilization, as Fitts' paradigm requires finishing the movement in the target position, and we instructed the participants to perform a "*smooth movement*." Therefore, the participants would lengthen their movement rather than doing several sub-movements to reach the target. In addition, we hypothesized that the behavioral consequences of immobilization would be modulated by task difficulty. Therefore, we expected a higher impact with ID7 than ID3 because motor planning and control is more complex. While we found the classic effect of ID on the kinematic parameters, no statistical interaction appeared with the immobilization factor. The lack of proprioceptive cues would be sufficiently strong to affect any movement, as also suggested by the work of Medina et al. (2009) on a deafferented patient (JDY). In this study, the difference in movement time between controls and JDY would not appear to be modulated by the tested ID (i.e., 4, 4.5, and 5.5) of the pointing task.

Before debating what immobilization changed for feedforward and/or feedback processing, we have to discard the possibility that changes arising from peripheral structures declined. Indeed, immobilization leads to modifications in muscle contractile properties (from slow to fast fiber type) and motor units. However, such transformations appeared after several weeks of immobilization (Desaphy, 2001; Seki et al., 2001a,b; Zanette et al., 2004). In contrast, short-term immobilization (less than 3–4 days) do not impact muscle and nerve properties (Facchini et al., 2002; Huber et al., 2006; Moisello et al., 2008). Therefore, modifications of motor behavior in the present study cannot be attributed to changes in muscle structure following short-term immobilization.

Here, we showed that immobilization impacted both early and late movement kinematics. Since Woodworth's two-component model, kinematic parameters before the peak velocity are associated with *feedforward control* and those after are associated with the *feedback control* (Meyer et al., 1982; Elliott et al., 2010). On the one hand, we showed that immobilization lengthened acceleration duration as well as decreased peak acceleration. Early kinematics modifications have been shown to reflect the use of internal models, i.e., a representation of the action and its sensory consequences (e.g., future states of the arm at the end of pointing; Wolpert et al., 1995). Based on these feedforward inputs of the limb, predictions of the future states are compared to the current state which allow for early corrections (Wolpert et al., 1995; Desmurget and Grafton, 2000; Wolpert and Ghahramani, 2000). Our results suggested that the feedforward control was impacted, probably because the internal model of the immobilized limb would be incorrectly updated. In daily life, the internal model of the limb is continuously updated through motion (see Wolpert and Ghahramani, 2000). During the 24 h of immobilization, motor commands of the limb were largely reduced. Consequently, efference copy as well as dynamical proprioceptive cues could not have been used to maintain or calibrate the internal model with the limb dynamics relative to the environment. Such a decrease in feedback would lead to an altered prediction of the sensory consequences of the action before its execution. Studies with deafferented patients have previously shown that proprioception was critical to update internal models of limb dynamics (Sainburg et al., 1995; Sarlegna et al., 2006; Medina et al., 2009).

On the other hand, our results suggested that immobilization also modifies the feedback control of the pointing: A lengthened deceleration duration as well as decreased peak deceleration were observed. These results suggested disruptions in the process of proprioceptive cues correcting the movement online. This is in line with recent studies (Huber et al., 2006; Weibull et al., 2011; Ngomo et al., 2012; Rosenkranz et al., 2014; Opie et al., 2016), which found a decrease in excitability in the somatosensory areas representing the previously immobilized arm: The proprioceptive cues were less processed, as well as the tactile cues (i.e., decrease of tactile discrimination; Weibull et al., 2011). Therefore, immobilized participants would take more time to correct their movement to precisely reach the target, as the processing of proprioceptive cues might be altered. Visual cues would be particularly used to compensate for this deficit, notably with the online visual comparison between the cursor and the target position. This feedback control of the pointing movement throughout vision was shown to start later than the proprioceptive one (Sarlegna et al., 2004; Saunders and Knill, 2004), which could explain the increase of the correction phase duration. This hypothesis is supported by neurophysiological data which showed that the decrease in cortical excitability of the somatosensory areas of the immobilized limb is associated with a sensitivity increase of the other sensory inputs (Rosenkranz et al., 2014). Further experiments would be necessary to specifically isolate how visual cues impact sensorimotor control after immobilization.

Although functional consequences of immobilization have been demonstrated in the past, the impact of immobilization on the motor control processes has not been fully elucidated. Contrary to previously used paradigms with immobilization, we used a Fitts' task which necessitates dealing with spatiotemporal constraints (i.e., speed-accuracy trade-off). Thanks to a spatiotemporal kinematic analysis, we specifically assessed the impact of sensorimotor deprivation on the motor control processes. For the first time, we showed early and late kinematic changes following a short period of limb non-use, which may be caused by the modification of feedforward as well as feedback processes. Even if these results would have to be extended to a broader population, such as the elderly people, they may have implications in rehabilitation and health care. Everybody has been or will be immobilized during his/her own lifetime due to an accident (e.g., broken limb) or for external reasons (e.g., long travel, prolonged bed rest). The understanding of the sensorimotor consequences of such short-term immobilization thus appeared of particular interest.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee for research in sciences of physical and sports activities (n°2017250114). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS, AM, and LT conceived and designed the research. CS and GC set up the experiments. LT performed the experiments. CS analyzed the data and prepared the figures. CS and LT interpreted the results of the experiments and drafted the manuscript. CS, AM, LT, and GC edited and revised the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Efficiency of Sensory Substitution Devices Alone and in Combination With Self-Motion for Spatial Navigation in Sighted and Visually Impaired

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Human adults can optimally combine vision with self-motion to facilitate navigation. In the absence of visual input (e.g., dark environments and visual impairments), sensory substitution devices (SSDs), such as The vOICe or BrainPort, which translate visual information into auditory or tactile information, could be used to increase navigation precision when integrated together or with self-motion. In Experiment 1, we compared and assessed together The vOICe and BrainPort in aerial maps task performed by a group of sighted participants. In Experiment 2, we examined whether sighted individuals and a group of visually impaired (VI) individuals could benefit from using The vOICe, with and without self-motion, to accurately navigate a three-dimensional (3D) environment. In both studies, 3D motion tracking data were used to determine the level of precision with which participants performed two different tasks (an egocentric and an allocentric task) and three different conditions (two unisensory conditions and one multisensory condition). In Experiment 1, we found no benefit of using the devices together. In Experiment 2, the sighted performance during The vOICe was almost as good as that for self-motion despite a short training period, although we found no benefit (reduction in variability) of using The vOICe and self-motion in combination compared to the two in isolation. In contrast, the group of VI participants did benefit from combining The vOICe and self-motion despite the low number of trials. Finally, while both groups became more accurate in their use of The vOICe with increased trials, only the VI group showed an increased level of accuracy in the combined condition. Our findings highlight how exploiting non-visual multisensory integration to develop new assistive technologies could be key to help blind and VI persons, especially due to their difficulty in attaining allocentric information.

Keywords: navigation, visual impairment and blindness, sensory substitution device, audiotactile, spatial cognition, egocentric, allocentric, multisensory integration

INTRODUCTION

Our world, built by the sighted for the sighted, poses significant challenges for the estimated 252 million visually impaired (VI) individuals worldwide (Bourne et al., 2017). Furthermore, visual impairments and blindness have been estimated to drastically increase in the next 30 years leading to approximately 4 million (when only considering the United Kingdom) living with sight loss (Future Sight Loss, 2009, pp. 43–44).

The eyes are our window to where we are and what is around us in the environment. Vision, with its higher spatial resolution, normally provides the most reliable information when it comes to spatial tasks in general, and to navigation specifically. Evidence that vision dominates other senses during spatial tasks comes from developmental studies. These studies show that children use visual information to calibrate (teach) other sensory cues during spatial tasks (e.g., Gori et al., 2008, 2010, 2012; Petrini et al., 2016) and also show that children have difficulties discounting or ignoring visual information even when it is irrelevant for the task (Innes-Brown et al., 2011; Downing et al., 2015; Petrini et al., 2015). In spatial navigation, vision is so relevant that it can influence even how humans find their way in the dark back to a previously seen location (Tcheang et al., 2011; Petrini et al., 2016). For example, a study using immersive virtual reality showed that, after being presented with conflicting visual information, adult sighted participants used a representation combining visual and self-motion cues to find their way back to the start in darkness (Tcheang et al., 2011).

However, when vision is absent or less reliable (e.g., in a poorly lit environment), our reliance on other sensory cues such as sound becomes essential. This holds especially true for blind individuals who need to mostly or completely rely on other sensory cues to perform daily tasks (e.g., locating a person by his/her voice). Navigation is a particularly important but demanding task for blind individuals as they not only have to find their way by using less reliable spatial information but they also have to avoid collision with a huge number and variety of obstacles in the environment (e.g., objects, people, and animals). Several studies have demonstrated how visual experience is essential for the typical development of spatial cognition and navigation abilities (Pasqualotto and Proulx, 2012). This, however, is not true for all kinds of navigation but it seems to be specific to navigation tasks that require an allocentric (i.e., a spatial representation built on the relative position of objects in the environment), rather than an egocentric (i.e., a spatial representation built on the subject's own position in the environment), representation of space (Pasqualotto et al., 2013; Iachini et al., 2014). For example, Iachini et al. (2014) reported that congenitally blind participants, when compared to late blind and sighted participants, found it difficult to represent spatial information allocentrically, but not egocentrically, during a large-scale space navigation task. Accumulating evidence of this type has prompted the development of numerous types of technological aids aimed to help individuals with visual deficits during navigation requiring allocentric representation (i.e., in large-scale environments).

Among these technological approaches, sensory substitution devices (SSDs) have received a great deal of interest in the last few decades. SSDs are noninvasive technologies that exploit the ability of the brain to adapt and to process the lost sensory information (vision) through the other unaffected senses (e.g., "seeing through the ears"; Bach-y-Rita et al., 1969; Meijer, 1992). SSDs are not only noninvasive and much cheaper than other alternatives (e.g., sensory restoration devices) but are also better suited for use with different types of visual deficits, including congenital blindness. This is because they do not require a developed visual system and/or any previous visual knowledge (Proulx et al., 2014a).

A freely available SSD is The vOICe, which uses an image-to-sound conversion algorithm which receives input from a camera and transposes it into 1-s auditory "soundscapes" (Meijer, 1992). The vOICe algorithm transforms visual images by scanning them from left-to-right, converting them into grayscale, and subdividing them into pixels. Each pixel is then converted into sound (or "sonified") based on its luminance, horizontal position, and vertical position. High luminance pixels sound louder than low luminance pixels, pixels on the left of the visual field are played before those on the right, and pixels at the top have a higher pitch than those at the bottom (Meijer, 1992).

The vOICe has been demonstrated to allow VI individuals to access visual information through audition, allowing object recognition and localization (Auvray et al., 2007). However, The vOICe is limited as users find it difficult to distinguish between multiple objects which are vertically aligned, as it is difficult to distinguish between the pitches of sounds which are played simultaneously (Brown et al., 2015). Similarly, due to the nature of the left-to-right scanning that creates soundscapes, it is difficult to process horizontally aligned objects simultaneously, as their respective sounds are played at different junctures. Nevertheless, the benefit of The vOICe cannot be understated, as it confers superior spatial resolution to all the other tactile-visual sensory substitution systems (e.g., BrainPort; for details see Bach-y-Rita and Kercel, 2003; Haigh et al., 2013; Proulx et al., 2014a).

An alternative SSD is the BrainPort, a visual-to-tactile aid. This device operates by transforming images into a pattern of electrical stimulation delivered *via* an electrode array that sits atop the tongue (Bach-y-Rita and Kercel, 2003). The device is used by exploring this electrode pad, thus objects can be processed theoretically in parallel (Arditi and Tian, 2013), and users might have no difficulty in distinguishing between vertically aligned objects. In addition, the BrainPort confers a superior temporal resolution to The vOICe, although its spatial resolution is inferior (Bach-y-Rita and Kercel, 2003).

That The vOICe and BrainPort each seem to have strengths where the other has weaknesses raises the question of whether the unaffected sensorimotor ability (e.g., self-motion) could be integrated with one or even both of these simultaneously during spatial navigation. Optimal concurrent use of two or more SSDs would be reliant on multisensory integration, the process by which information from different senses is combined to form a holistic percept (Stein et al., 2009). Thus, concurrent use of multiple SSDs could allow multisensory integration of incoming information, whereby the advantages of each device compensates for the respective limitations of the other (Shull and Damian, 2015). Or the use of these devices concurrently with another sensorimotor ability could increase precision and accuracy during spatial navigation by integrating these multiple information sources in absence of vision.

The ability to use a multimodal representation of space in blind individuals when navigating their environment, however, has not received support in persons with restored vision through a retinal prosthesis. Garcia et al. (2015) examined the ability of a group of adult patients with ARGUS II retinal prosthesis to use the restored visual information to navigate a simple two-legged path. The patients, an age-matched control group and another younger control group, had to retrace a two-legged path (two sides of a triangle they previously experienced) in one task and go back to the start point after walking the same two-legged path in another task (i.e., they had to complete the triangle by walking as precisely as possible the remaining third side). Before reproducing the path or completing the triangle, participants could walk (by being guided) the two-legged path with either an indirect visual landmark or no visual landmark. Garcia et al. (2015) showed that, in contrast to sighted individuals, these patients did not use a combined representation of visual and self-motion cues when navigating (when reproducing the path or completing the triangle) but relied entirely on self-motion (Garcia et al., 2015). Thus, it appears that a multimodal representation of space (a single and coherent representation of space obtained by integrating the restored visual information with self-motion) was not formed in these blind individuals.

This stands in contrast to existing evidence from neuroscience, which suggests that congenitally blind individuals can recruit visual areas when recognizing sounds, shapes, and movements through SSDs (De Volder et al., 1999; Poirier et al., 2007), in addition to areas, such as parahippocampus and visual cortex, that are essential for successful spatial navigation in sighted individuals (Kupers et al., 2010). A possible explanation is that blind individuals may usually form a non-visual multimodal representation of space with the unaffected sensory information (e.g., sound and self-motion). In that case, using the restored visual information would be detrimental rather than helpful as the possible representation of space with the restored visual information (with a far lower resolution than typical vision) is poorer than a non-visual multimodal representation of space. Consequently, forming a multisensory representation of space and benefitting from it could be possible for VI and blind individuals when using non-visual information as provided by the SSDs. That blind and VI individuals may use a non-visual multisensory representation of space to increase their accuracy and precision is supported by recent findings showing that an audiotactile map (delivered through a touchpad) was more efficient than either a tactile only map or only walking during a navigation task (Papadopoulos et al., 2018).

The ability of blind/VI and sighted blindfolded individuals to use SSDs (Chebat et al., 2011, 2015; Maidenbaum et al., 2014; Kolarik et al., 2017) efficiently during spatial navigation, even after a short training, is well-known. For example, Chebat et al. (2011) showed that congenitally blind participants had an enhanced ability to detect and avoid obstacles compared to blindfolded sighted when using a tongue display unit (TDU), and Chebat et al. (2015) showed that congenitally blind, low vision, and late blind individuals could achieve the sighted (non-blindfolded) performance in a real and virtual maze after few trials with the EyeCane (a device that uses sound and vibration to deliver information about distances). Chebat et al. (2015) also showed that participants could improve their spatial perception and form a cognitive map through the learning experience afforded by the EyeCane. However, what remains unclear is whether the formation of a cognitive map combining non-visual information can speed up learning and provide better precision and accuracy to VI and blind users. Understanding whether the integration of different non-visual cues can improve VI spatial navigation has both important theoretical and applicative significance. On the one hand, it has important implications for the development, training, and application of existent and new aids for the blinds. On the other hand, it could bring support to a convergent model of spatial learning (Schinazi et al., 2016) in the blind and VI, by showing that even when using less effective cues for navigation, blind and VI can learn to perform as well as sighted by increasing their precision through non-visual multisensory integration.

Here, we examine this possibility by first testing whether combining a vision-to-sound and a vision-to-tactile information as provided by two SSDs can enhance navigation performance in a group of blind-folded sighted participants. Next, we tested whether combining the information from one SSD with existing and unaffected senses (e.g., self-motion and proprioception) can improve navigation precision and accuracy in a group of blind-folded sighted participants and a group of VI individuals. To test the formation of a cognitive map, we asked participants to perform the navigation task (walking to a target location) in darkness after experiencing the environment under different conditions (e.g., with an SSD or with self-motion). To test whether there was an increase in accuracy and precision (when combining either information from different SSDs or from one device and the available self-motion information), we used a maximum likelihood estimation (MLE) framework (i.e., we compared the reduction in variability for the measured combined condition to that obtained for each sense separately and to the reduction in variability predicted by the MLE; Ernst and Banks, 2002). Under the MLE framework, we expect to see a significant reduction in performance variance (or reduced uncertainty) as predicted by the model when the variance for the unimodal conditions (e.g., when using the two SSDs in isolation) are similar, or in other words when the reliability of the cues to be integrated are similar. Hence, the tasks used here were chosen to be fairly easy and straightforward to assure that a similar level of performance with different devices could be achieved.

In Experiment 1, we examine whether a non-visual multisensory representation of space can improve the navigation performance of a group of sighted blindfolded individuals when using a tactile or auditory SSD (i.e., The vOICe or the BrainPort) or the two together (The vOICe and BrainPort) in an egocentric and allocentric aerial map task. Aerial maps are the most common representations provided to people for building layouts and cities, and blind persons have been shown to benefit from a tactile aerial representation when navigating an unfamiliar environment

(Espinosa et al., 1998), probably because it removes the lack of depth perception as a barrier for VI individuals. Furthermore, a survey representation which encodes external and unfamiliar information of the environment (like in an aerial or map-like view) is more severely affected by lack of vision when compared to route (serial)-based representation (Tinti et al., 2006). Hence, we used an aerial map task to assess the efficiency of different SSDs alone or in combination. We chose this task also based on recent evidence that the use of audiotactile maps to build cognitive spatial representations are more efficient than using only a tactile map or walking in an unfamiliar environment (Papadopoulos et al., 2018). We hypothesized an improved performance (reduced variance) on a distance estimation-based navigation task when participants explored aerial maps using The vOICe and BrainPort together than when using either of these devices in isolation. We also hypothesized an increase in accuracy with a number of trials for all the conditions.

In Experiment 2, we examine whether a non-visual multisensory representation of space can improve the navigation performance of a group of sighted and a group of VI blindfolded individuals when using self-motion or The vOICe or the two together in an egocentric and allocentric spatial navigation task. We hypothesized an improved performance (reduced variance) on the navigation task using The vOICe and self-motion together than when using either The vOICe or self-motion in isolation, especially for the VI group. We also hypothesized an increase in accuracy with a number of trials for all the conditions, especially for the VI group.

EXPERIMENT 1

Method

Participants

Thirty students (15 males and 15 females), aged 18–22 (M = 20.38, SD = 0.924), from the University of Bath, UK, participated in the experiment. Due to technical problems, some of the trials for three participants were not saved correctly and thus we had to exclude these participants. Hence, the data for twenty-seven participants were included in the analysis. Twenty-five were self-reportedly right-handed. All participants had normal vision and audition and were naïve to The vOICe, BrainPort, and the laboratory where the experiment took place. Participants were reimbursed £5 for their time. All participants provided informed consent and were debriefed. The experiment was approved by the University of Bath Psychology Department Ethics Committee (Ethics Code 16:180).

Apparatus

The experiment took place in an 11 m × 7 m laboratory. Two configurations of four target points (each 50 cm × 50 cm) were marked on the floor of the laboratory (see **Supplementary Figures S1, S2**), one for training and one for the experimental procedure. These configurations were based on studies by Garcia et al. (2015) and Petrini et al. (2016).

The laboratory was equipped to record motion tracking data, using a Vicon Bonita system consisting of eight infrared cameras (see **Figure 1B**), which tracked five reflectors on the motion tracking helmet, to which a blindfold was attached (see **Figure 1C**). The Vicon system was controlled through a Python 3.0 script using Vizard libraries. A remote for controlling the script was used to control tracking for each navigation trial (see **Figure 1D**).

The BrainPort device consists of three parts: camera glasses, the processor unit, and the Intra-Oral Device (IOD). A laptop connected the BrainPort's software (vRemote) to the live feed from the camera glasses to display the settings and allow correct positioning of the stimuli. Auditory stimuli were played from the same laptop *via* Philips stereo headphones. The headphones we used were open in the sense that participants could still hear sounds in the room to some extent, as well as their own footsteps. This was done so as to replicate as closely possible to a real environment which will have noises (information normally used by the blind and VI). These noises were always kept constant though throughout the conditions of the study so as not to add a confounding variable. Previous literature suggests that a head-mounted camera performs better than a hand-held camera while using The vOICe for navigation purposes (Brown et al., 2011). As a result, we designed a helmet with a blindfold (Mindfold Eye Mask) and reflectors used for motion tracking attached. A USB camera (ELP 480P webcam with 120° view) was mounted to the middle of the blindfold (see **Figure 1C**). The USB webcam was connected to a mini-PC (1.3 Ghz Intel Atom processor, 1 GB RAM) running Windows XP and The vOICe (Meijer, 1992). Participants used Philips SHS 5200 neckband headphones to listen to the soundscapes.

We used the default settings of The vOICe algorithm aside from changing the zoom to 2×. This enabled participants to observe the objects separately, group them two by two or

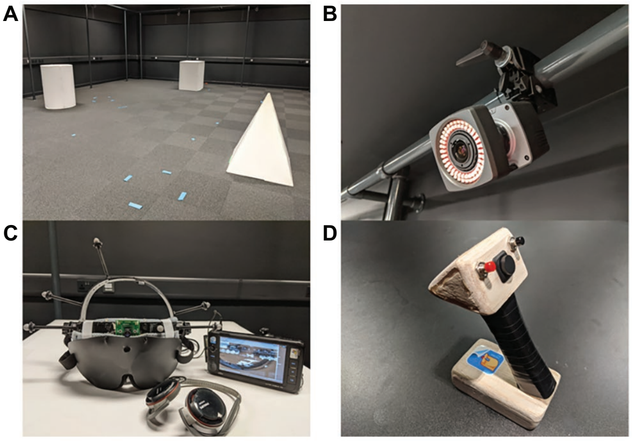

FIGURE 1 | (A) The arrangement of the three objects in the Virtual Reality (VR) Lab as viewed from the start point. **(B)** A Vicon Bonita infrared camera is shown. A system comprising of eight identical cameras was used to obtain three-dimensional (3D) coordinates of the participants' head location. **(C)** The helmet that was constructed for the task; incorporating the blindfold, camera, and trackers. The helmet is wired to a mini PC which runs The vOICe algorithm and plays back the soundscapes through a pair of headphones. **(D)** The remote that was constructed to trigger, stop, and forward trials of tracking from the Vicon tracking system.

explore them all at the same time. The experiment took place in the Virtual Reality (VR) Lab (11 m × 7 m). The three-dimensional (3D) objects developed for the study were a cylinder, a cube, and a four-faced pyramid of the same height (60 cm; see **Figure 1A**). We used different shapes intentionally as we wanted the soundscapes returned by The vOICe to be different so as to replicate more closely real environments where various objects are available. However, the three objects had similar dimensions as they had the same width and length.

Materials

Experimental Stimulus Design

Aerial perspectives of the training and experimental point configurations marked on the laboratory floor were digitally recreated to scale using AutoCad (Version 21.0, AutoDesk, Inc., Mill Valley, California, United States). These were the "aerial maps," with each target and the start point being indicated by a white square on a black background (see **Supplementary Figure S2**). All stimuli were transformed into soundscapes using The vOICe's image sonification algorithm (Meijer, 1992) at the following settings: 2-s scan rate, normal contrast, and foveal view off. A5 sized prints of all stimuli were placed in front of the BrainPort camera and were explored *via* the IOD at the following settings: zoom 33°, invert off, contrast high, lighting low, tilt 25°, and lock off. This ensured that the visual information being transformed by both devices was congruent to ensure that multisensory integration was not prevented (Schinazi et al., 2016).

Training Stimulus Design

The training stimuli consisted of a set of four lines and five sets of circles (all white on a black background), which occupied approximately the same visual area (see **Supplementary Figure S3**). The stimuli were produced in the same fashion and using the same settings as the experimental stimuli.

Conditions

The conditions of the experimental procedure comprised of two unimodal conditions: The vOICe only (vOICe) and BrainPort only (TDU), and one bimodal condition: The vOICe plus BrainPort (vOICeTDU). In each condition, the same aerial map was delivered, and 10 wayfinding task-pairs were completed. Thus, in total, every participant completed 60 wayfinding tasks, based on the same target configuration. The order of wayfinding tasks was counterbalanced among trials and conditions. This was done to minimize a potential confound of participants learning the configuration of target points over subsequent conditions.

Navigation Tasks

Each wayfinding task-pair comprised of an egocentric task and an allocentric task. In the egocentric task, participants navigated directly to target 3 from the start point (**Figure 2**). In the allocentric task, participants navigated from the start point to target 1 and then to target 3 (**Figure 2**). The experimenter oriented participants toward their first target they were to navigate to prior to commencing each task.

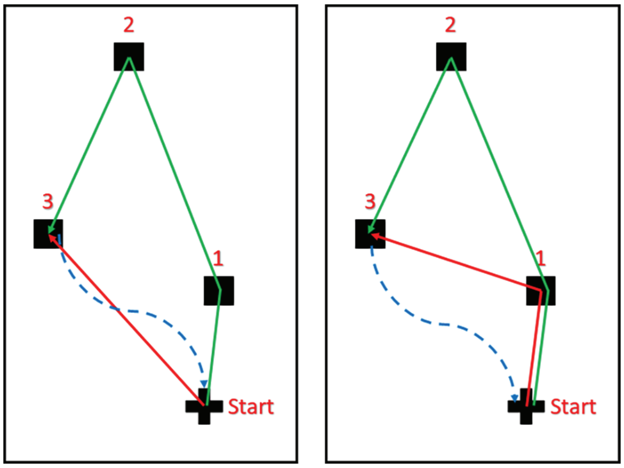

FIGURE 2 | The egocentric **(left panel)** and allocentric **(right panel)** navigation tasks. Objects are represented by the black squares and the cross represents the starting point of the navigation trial. The solid green lines represent the encoding phase in which participants were guided starting from the start point to Object 1, then Object 2, and finally to Object 3. The dashed blue lines represent the scrambled routes used to take participants back to the start point after the encoding phase (green line). The solid red lines represent the routes participants had to navigate in darkness following the encoding phase (red continuous lines).

Participants' motion during the wayfinding tasks was tracked: commencing once they were ready to begin each task and terminating once they announced that they had reached the target location. They were then returned to the start point *via* an indirect route to discourage them from trying to estimate the distance between their final position and the start point from the route the experimenter took them rather than the SSD(s).

Procedure

The study consisted of three phases: basic training, active training, and the experimental procedure. Prior to the study, the experimenter collected demographic information from the participants (age, handedness, and gender). They were then blindfolded to prevent viewing the interior of the laboratory.

Basic Training

Upon beginning the study, participants were trained to use the two SSDs. This procedure utilized the training stimuli. The device that participants were trained with first was counterbalanced in an ABAB fashion. First, the experimenter would explain the mechanisms of action of both SSDs. Then, for each training stimulus, the experimenter either played the auditory file for The vOICe or placed the relevant printed stimulus in front of the BrainPort camera, for 10 s. Participants were asked to use the relevant device to identify and count the lines or circles that were presented to them. The question was left open-ended, so the likelihood of participants correctly identifying the stimulus by chance was negligible. If the stimulus was identified, training would progress to the next stimulus. If not, feedback was provided, and the mechanism of action of each SSD was explained again. This process continued until participants were able to identify and count all training stimuli.

Active Training

The purpose of the active training was to give participants a sense of the scale, how the distances between the target points they experienced using the SSDs equated to physical distances. The active training mirrored the three experimental conditions in terms of the utilized exploration methods (vOICe, TDU, or vOICeTDU) and was counterbalanced mirroring the experimental procedure.

This procedure utilized the aerial map of the training target configuration (**Supplementary Figure S2**), which was delivered *via* the SSDs. Participants were instructed to explore the training aerial map *via* the SSD(s) for as long as required to identify and localize all points. Before each practice trial, participants were told that they would be taken to the starting point and oriented in the direction in which they would need to move initially (depending on whether they were doing an egocentric or an allocentric task). They were then told to walk as far as they needed and turn as much as they needed to reach the target point. During this practice phase, participants received feedback, that is, if they made a mistake in estimating distance or angle then the experimenter would correct them and tell them whether they had over/underestimated. This was done at each target location and for both distance and rotation, and thus, for the allocentric task, participants received feedback after the first (Object 1, see **Figure 2** right panel) and second target (Object 3, see **Figure 2** right panel), while for the egocentric task feedback was received for the only target used for the task (Object 3, see **Figure 2** left panel). They would then complete two trials of the navigation task, one allocentric and one egocentric with the order counterbalanced. At the end of active training, participants were led outside the laboratory for a 5-min break.

Experimental Procedure

Each experimental condition was identical, the only difference being the SSD the participants used to explore the aerial map. This procedure utilized the experimental target configuration and respective aerial map (**Figure 2** and **Supplementary Figure S2**). Upon beginning a condition, participants used the device(s) specified by the condition to explore the aerial map for 10 s (this was an arbitrary time limit enforced to standardize stimulus exposure). That is, participants used the different devices (depending on the condition at hand) to scan the room before attempting the navigation task, while during the navigation task only self-motion was used. When using both devices together, alignment between the two signals was controlled by the participant by activating the BrainPort as soon as The vOICe information started, so that the two devices started to deliver information at approximately the same time. The decision to let the participants control for the start of the BrainPort was taken to better approximate a real condition in which the user would have control on what device to use and when. They would then complete two trials of the navigation task, one allocentric and one egocentric with the order counterbalanced, using self-motion. Upon completing both trials, participants were led back to the SSD apparatus, and they used the device(s) for the given condition for another 10 s, and then completed another pair of navigation trials. This process was repeated until 10 pairs of navigation trials were completed. Once a condition was completed, participants were led outside the laboratory and had another break. The process was then repeated for the remaining two conditions. Once participants had completed the navigation tasks, they were taken outside the laboratory and debriefed, gave final consent, and were paid, thus concluding the experiment.

Results

Individual Estimates

The tracked coordinates obtained through the Vicon system were processed using MATLAB (Version R2018b, The MathWorks, Inc.) and Psychtoolbox command Library (Brainard, 1997; Pelli, 1997). For each participant's end positions (when the participant decided he/she arrived at the object's target position), a bivariate normal distribution was fitted (**Figure 3**), which enabled the estimation of x mean, y mean, x variance, and y variance. The FASTCMD algorithm (Rousseeuw and Driessen, 1999), as implemented by the MATLAB Libra toolbox (Verboven and Hubert, 2005), was used for a robust estimation of these values, with the assumption of 1% aberrant (outlier) values (i.e., a value of 0.99 for the alpha parameter). For each participant, a single variable error was computed by using the sum of the variance of x and y directions of the fitted bivariate distribution (black ellipses in **Figure 3**). Secondly, a measure of constant error was calculated as the distance between the center of the fitted bivariate distribution (center of the black ellipses in **Figure 3**) and the correct position for the target object (Object 3). Variable error is expected to reduce when participants are able to combine multiple modalities and in line with the MLE model (Ernst and Banks, 2002; Alais and Carlile, 2005; Cheng et al., 2007; Van der Burg et al., 2015; Noel et al., 2016). On the other hand, constant error represents a systematic navigational bias. That is, it reoccurs over multiple trials and is consistent. Constant error is expected to reduce when less biased information is available.

Group Analysis

The variable error estimates (obtained as size of the individual ellipsis for each condition, see **Figure 3**) and the constant error estimates (obtained as the distance of the center of each individual ellipsis from the correct target position, point 0,0 in **Figure 3**) were tested to determine whether they were normally distributed. As the majority of conditions did not meet the assumption of normal distribution (Shapiro-Wilk, $p < 0.05$), we used Wilcoxon tests to examine differences between conditions (e.g., vOICeTDU vs. vOICe) within each group, and Mann Whitney U tests to compare the two groups' performances in each condition. We then used Pearson's correlation analyses (as assumption of linearity was met) to determine whether the number of trials (from 1 to 10) was associated with changes in constant error (i.e., accuracy), in other words, whether there was a decrease in error (or increase in accuracy) with increased

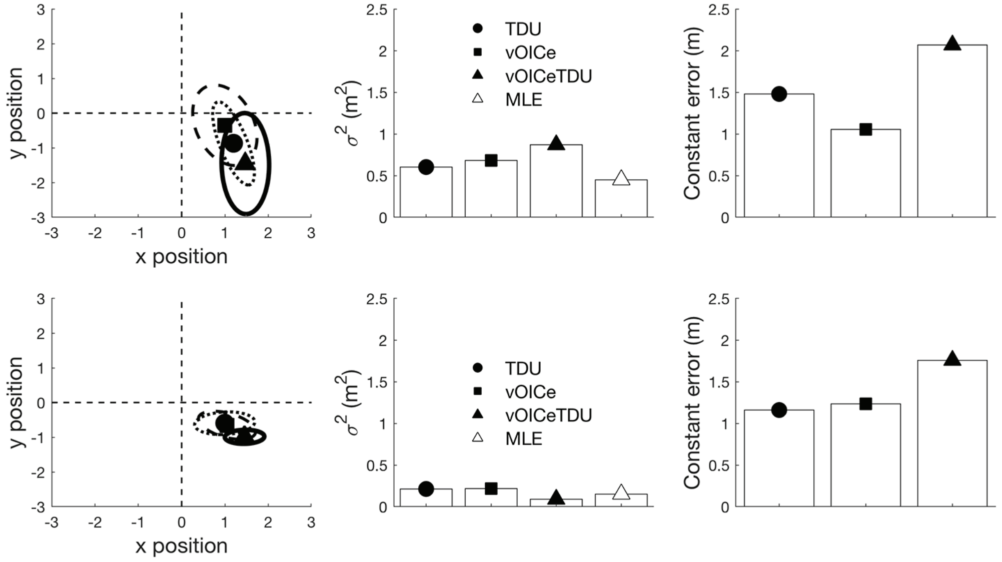

FIGURE 3 | The locations at which the participant stopped relative to the true target position (0,0 in the **left panel**) was used to derive the individual variable error (the area of the ellipse) and constant error (the distance from the center of the ellipse to the target location) for each task (allocentric and egocentric) and each condition (vOICe, TDU, and vOICeTDU) separately. The unit for the *x* and *y* position is in meters. Individual estimates for vOICe, tongue display unit (TDU), and vOICeTDU conditions for the allocentric task are shown in the **top panel**, while for egocentric task, the estimates are shown in the **bottom panel** for the same participant. The triangle labeled maximum likelihood estimation (MLE) (white) in the **central panels** refer to the variability predicted by the MLE model for the combined condition (vOICeTDU). The predicted estimate (MLE) was calculated for each subject, and then averaged, by entering the individual vOICe (σ_{vOICe}) and TDU (σ_{TDU}) measure of variable error into the equation $\frac{\sigma^2_{vOICeTDU}=\sigma^2_{vOICe}\sigma^2_{TDU}}{\sigma^2_{vOICe}+\sigma^2_{TDU}}$.

number of trials. For directional hypotheses, the reported results are one-tailed.

Figure 4 (left panels) shows the results for the variable error in the allocentric (top panels) and egocentric (bottom panels) tasks. Wilcoxon tests were used to compare the variable error between the bimodal (vOICeTDU) and the unimodal conditions (vOICe and TDU) and between the measured bimodal (vOICeTDU) and the predicted bimodal (MLE) conditions separately for the allocentric and egocentric tasks. The analysis showed no significant difference between vOICeTDU and the unimodal (vOICe and TDU) conditions for both tasks, $Z \leq -0.953$, $p \geq 0.170$, one-tailed. There was, however, a significant difference between vOICeTDU and MLE for both tasks ($Z \geq -2.463$, $p \leq 0.014$) indicating that the level of variability for the bimodal condition was not accurately predicted by the MLE model.

A similar analysis was performed on the constant error measures (**Figure 4** middle panels), and it showed no significant difference between vOICeTDU and TDU for both egocentric and allocentric task ($Z \leq -1.410$, $p \geq 0.079$, one-tailed) and a significant difference between vOICeTDU and vOICe in the allocentric task ($Z = -2.440$, $p = 0.007$, one-tailed), indicating higher accuracy and less bias with The vOICe alone, but only a trend in the egocentric task ($Z = -1.600$, $p = 0.055$, one-tailed).

Finally, we examined whether sighted participants showed any learning effect across the 10 trials within each sensory condition (vOICe, TDU, and vOICeTDU) for allocentric and egocentric task separately. Thus, Pearson correlations (given the data linearity) were used to analyze whether the average constant error decreased with an increase in number of trials, i.e., whether participants' accuracy increased with practice. For the allocentric task, as shown in **Figure 4** top right panel, a significant association between decrease in error and increase in trial number was found for the TDU condition ($r = -0.863$, $p < 0.001$, and one-tailed) but not for the vOICeTDU ($r = -0.182$, $p = 0.308$, and one-tailed) and vOICe condition ($r = 0.424$, $p = 0.111$, and one-tailed). In addition, vOICeTDU accuracy performance as a function of trials did not correlate with either the performance in The vOICe or TDU alone ($r \leq 0.039$, $p \geq 0.458$, and one-tailed). For the egocentric task, as shown in **Figure 4** bottom right panel, a significant association between decrease in error and increase in trial number was found for the TDU condition ($r = -0.795$, $p = 0.003$, and one-tailed) and for The vOICe condition ($r = -0.881$, $p < 0.001$, and one-tailed), but not for the vOICeTDU condition ($r = -0.499$, $p = 0.071$, and one-tailed), although the combined condition did show a trend in this direction. Finally, vOICeTDU accuracy performance as a function of trials significantly correlated with both the performance in The vOICe or TDU alone ($r \geq 0.594$, $p \leq 0.017$, and one-tailed). This suggested that in the egocentric task the changes in accuracy in the bimodal condition (vOICeTDU) was driven by changes in accuracy for both The vOICe and TDU condition alone.

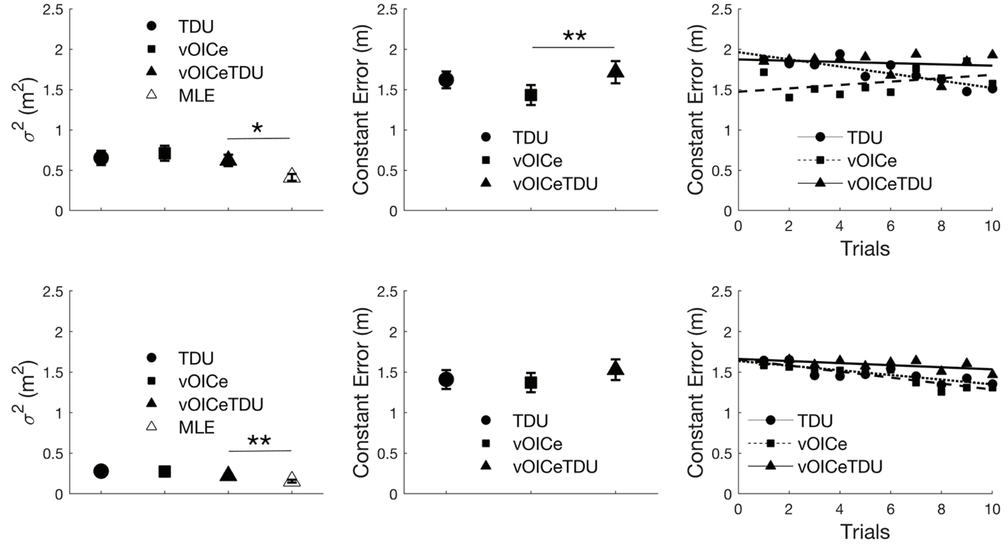

FIGURE 4 | Average variable error **(left panel)**, constant error **(middle panel)**, and relation between average constant error and number of trials **(right panels)** for the allocentric **(top panels)** and egocentric **(bottom panels)** task. vOICe = vOICe condition alone; TDU = BrainPort alone; vOICeTDU = vOICe + TDU. The marker labeled MLE (in white) in the **left panel** refers to the reduction in variability predicted by the MLE model. How MLE was calculated is explained in **Figure 3** caption. Please see **Supplementary Figure S4** for boxplot with median and interquartile range (IQR) measures. $^{**}p < 0.01$; $^{*}p < 0.05$. Error bars represent the standard error of the mean.

EXPERIMENT 2

Method

Participants

Experiment 2 had 32 sighted right-handed participants take part, with equal numbers of males (16, mean age of 23.4 and *SD* = 5.17) and females (16, mean age of 23.1 and *SD* = 2.70). Six VI participants were also recruited for the study (see **Table 1** for participant details). All participants had normal hearing and sighted participants had normal or corrected-to-normal vision as assessed by self-report. They had no prior experience of The vOICe and never been to the VR Lab where the experiment took place. Participants were paid £20 for their time. Ethics approval was granted by the Psychology Research Ethics Committee of University of Bath (ethics reference 16-180).

Apparatus

The apparatus was the same of that in Experiment 1; however, here only The vOICe was used.

Conditions

Three different conditions were utilized, The vOICe only (vOICe), self-motion only (SMO), and vOICe and self-motion combined (vOICeSMO). For the 32 sighted participants, we counterbalanced the tasks order, so that only 11 participants performed the combined vOICeSMO condition at the end. Since the aim of the study was to examine whether sighted and VI participants could use The vOICe when navigating to a target and whether they could benefit from using The vOICe with self-motion together, we tested the six VI participants with a task order for which the combined vOICeSMO condition was always at the end. This was necessary to allow for familiarization with The vOICe and self-motion tasks alone before testing for their combination. Hence, we compared the performance of the six VI to that of the 11 sighted that also had the combined vOICeSMO condition at the end. The data for all 32 sighted are presented as a reference for the 11 sighted to show if any difference emerged due to differences in task order.

Every condition defines the way participants were allowed to explore the objects and learn their physical locations. In vOICe, they stood at a marked location (the start point) and scanned the room and the objects with The vOICe but without moving. In SMO, participants were guided to each object in order (from Object 1 to 2 and then 3) while The vOICe was muted, and brought back to the start point *via* a scrambled path (Garcia et al., 2015; Petrini et al., 2016). In vOICeSMO, participants were guided to each object in the same order as SMO while The vOICe was on and brought back to the start point *via* a scrambled path (see **Figure 2**).

Navigation Tasks

We had two main navigation tasks: an egocentric navigation task, in which participants were asked to directly walk to Object 3 from the start point, and an allocentric navigation task, in which participants were asked to walk to Object 3 through the position of Object 1 (see **Figure 2**). For all conditions, the path to Object 3 either directly or indirectly was unfamiliar as during the encoding phase they were guided through the path formed by all three objects. Participants' motion during the navigation tasks was tracked: motion tracking started once the participant was ready to start either the egocentric or allocentric task and stopped once they announced that they reached the target location. They were then guided back to the start point from where they stopped *via* a scrambled

TABLE 1 | Clinical and demographic information for blind and low vision child participants.

Participant	Sex	Age	Age of onset	Diagnosis	Visual acuity (right eye; left eye) [logMAR]	Vision status
VI1	Female	18	Birth	Bilateral retinoblastoma, cataract, right enucleation	R -; L = 2.8	Congenitally blind
VI2	Male	21	Birth	Congenital bilateral cataracts (until 9 years), glaucoma, retinal detachment		Congenitally blind/sight restored
VI3	Female	18	6 years	Retinitis pigmentosa	R > 1.8; L > 1.8	Early blind
VI4	Male	61	11 years	Stargardt disease	R = 2.8; L = 2.8	Late blind
VI5	Female	20	12 years	Stargardt disease	L = 0.8; R = 0.8	Low vision
VI6	Female	49	41 years	Pathological myopia, choroidal neovascularization	R = 1.1; L = 0.8	Low vision

path and this motion was not recorded (**Figure 2**). Every time they explored the objects in a given condition, the objects were then removed from their locations before participants completed the navigation tasks. The order of the tasks (allocentric or egocentric) was counterbalanced after each trial and each participant completed 60 navigation tasks in total during the experimental phase (10 for egocentric task and 10 for allocentric task for vOICeSMO, vOICe, and SMO). For example, during a vOICeSMO trial, participants would be guided from Object 1 to Object 2 to Object 3 with both self-motion and The vOICe on during the encoding phase, then they would be guided back to the start point following a scramble path from Object 3, and finally the objects were removed and the testing phase would start. During the testing phase participants would be asked to either walk to Object 3 directly from their start position (egocentric task) or to walk to Object 3 through Object 1 position (allocentric task).

Experimental Procedure

Participants were initially welcomed to the Crossmodal Cognition Lab, where after reading an information slip and signing the consent form, they completed a brief demographics survey. Later, they observed an online presentation about the main principles of The vOICe algorithm with examples of simple and complex shapes and their sonifications. The third phase of the theoretical training consisted of a quiz containing 10 questions: each question had one soundscape and four multiple choice 2D simple shapes such as a white triangle on a black background. Participants were asked to pair the soundscape with the correct image. After each question, they were given a brief feedback on whether they had correctly answered the question. Immediately after the quiz, participants were introduced to the tracking helmet. This pre-experimental phase took around 30 min. Participants were then accompanied to the VR Lab, and were asked to wear the tracking helmet with the blindfold just before entering. The practical training to familiarize participants with using The vOICe in localization tasks involved 2 phases: room and object exploration and navigation training.

The practical training began with an accommodation phase where the three objects were placed in different locations on the floor and participants were guided through the room to explore the three objects and the room with The vOICe. Participants were further informed on how the soundscapes change with respect to the location of the object – i.e., while getting closer to or away from an object. This part of the practical training took around 15 min.

The navigation training mirrored the three experimental conditions in terms of the utilized exploration methods (vOICeSMO, vOICe, and SMO). However, the three objects and the start point were placed at different locations than in the main experiment. The order of the conditions during the practice for a specific participant was the same as in the actual experiment. This part of the training took around 30 min.

Main Experiment

During the main experiment, each object encoding condition (vOICeSMO, vOICe, and SMO) was followed by either the egocentric or allocentric task during which participants navigated to the object target with only the self-motion information. Five-min breaks were offered after each condition, in which participants were taken out of the lab and allowed to take off the helmet. The main experiment took approximately 1 h and 30 min.

Results

Individual Estimates

The individual estimates were obtained in the same way as described in Experiment 1. **Figure 5** gives an example of variable and constant errors for a VI and a sighted participant.

Sighted Group

Figures 6, 7 (left panels) shows the results for the allocentric and egocentric tasks, respectively. Wilcoxon tests were used to compare the variable error between the bimodal (vOICeSMO) and the unimodal conditions (vOICe and SMO) and between the measured bimodal (vOICeSMO) and the predicted bimodal (MLE, because estimated through the MLE model) conditions separately for the allocentric and egocentric tasks. The analysis showed no significant difference between vOICeSMO and the unimodal (vOICe and SMO) conditions for the allocentric task, $Z \leq -1.075$, $p \geq 0.141$, and one-tailed (despite a reduction in variable error for vOICeSMO when compared to the two unimodal conditions, see **Figure 6** top left panel). There was, however, a significant difference between vOICeSMO and MLE ($Z = -2.901$, and $p = 0.004$), indicating that the reduction in variability for the bimodal condition was not accurately predicted by the MLE model. The same results were found for the

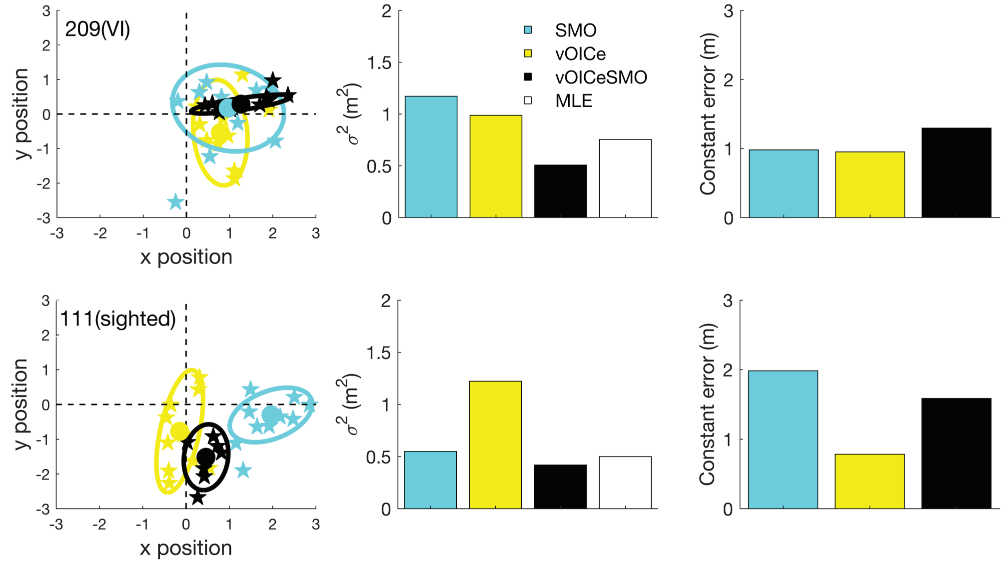

FIGURE 5 | The locations at which the participant stopped relative to the true target position (0,0 in the **left panel**) was used to derive the individual variable error (the area of the ellipse) and constant error (the distance from the center of the ellipse to the target location) for each task (allocentric and egocentric) and each condition (vOICe, SMO, and vOICeSMO) separately. The unit for the *x* and *y* position is in meters. Individual estimates for self-motion (SMO), vOICe, and self-motion + vOICe (vOICeSMO) conditions for the allocentric task are presented for a VI participant in the **top panels** and for a sighted participant in the **bottom panels**. The predicted estimate (MLE) was calculated for each subject, and then averaged, by entering the individual vOICe (σ_{vOICe}) and self-motion (σ_{SMO}) measure of variable error into the equation $\sigma^2_{\text{vOICeSMO}} = \frac{\sigma^2_{vOICe}\sigma^2_{SMO}}{\sigma^2_{vOICe}+\sigma^2_{SMO}}$.

egocentric task (vOICeSMO vs. vOICe and vOICeSMO vs. SMO: $Z \leq -0.777$, $p \geq 0.218$, and one-tailed; SSDMO vs. MLE: $Z = -3.255$, $p = 0.001$, see **Figure 7** top left panel). A similar analysis was performed on the constant error measures (**Figures 6, 7** left middle panel) and showed no significant difference between vOICeSMO and the unimodal conditions vOICe and SMO for both allocentric and egocentric tasks (allocentric: $Z \leq -1.085$, $p \geq 0.139$, and one-tailed; egocentric: $Z \leq -0.764$, $p \geq 0.222$, and one-tailed).

Finally, we examined whether sighted participants showed any learning effect across the 10 trials within each sensory condition (vOICe, SMO, and vOICeSMO) for allocentric and egocentric tasks separately. Pearson correlations were used to analyze whether the average constant error decreased with an increase in number of trials, i.e., whether participants' accuracy increased with practice. For the allocentric task, as shown in **Figure 6** bottom left panel, a significant learning effect was found for The vOICe condition ($r = -0.627$, $p = 0.026$, and one-tailed) and marginally for vOICeSMO ($r = -0.547$, $p = 0.051$, and one tailed), but not for SMO ($r = -0.336$, $p = 0.171$, and one-tailed). In addition, whereas vOICeSMO and vOICe also correlated positively ($r = 0.669$, $p = 0.017$, and one-tailed), vOICeSMO and SMO did not ($r = 0.378$, $p = 0.140$, and one-tailed), indicating that the increased in accuracy (or decrease in error) with trials in the bimodal condition (vOICeSMO) was driven by a learning effect and increased accuracy for The vOICe only condition.

For the egocentric task, as shown in **Figure 7** bottom left panel, a significant learning effect was found for The vOICe ($r = -0.916$, $p < 0.001$, and one-tailed), the vOICeSMO ($r = -0.761$, $p = 0.005$, and one-tailed), and SMO ($r = -0.717$, $p = 0.010$, and one-tailed). Similar to the allocentric task, vOICeSMO and vOICe conditions also correlated positively ($r = 0.745$, $p = 0.006$, and one-tailed), while vOICeSMO and SMO did not ($r = 0.528$, $p = 0.058$, and one-tailed), indicating that in both tasks the increased accuracy in the bimodal condition (vOICeSMO) was driven by a learning effect and increased accuracy for The vOICe only condition (vOICe).

Sighted and Visually Impaired

Here, we report the results for the visual impaired group and for the sighted group that performed the two tasks with the same order of the visual impaired. We always tested the visual impaired group with the vOICeSMO (the combined condition) at the end while counterbalancing across participants the order of the other two conditions (vOICe and SMO). This was because of the small number of participants and because we were interested in examining whether any improvement with both sensory information (vOICe and self-motion) was possible for the VI in such a short session with The vOICe. Hence, below, after presenting the results for the VI group alone, we present the results for the 11 sighted participants that had the same task order as the visual impaired group and then compare these two groups' performances.

Visually Impaired

Figures 6, 7 (right panels) shows the results for the allocentric and egocentric tasks for the six VI participants. Wilcoxon tests

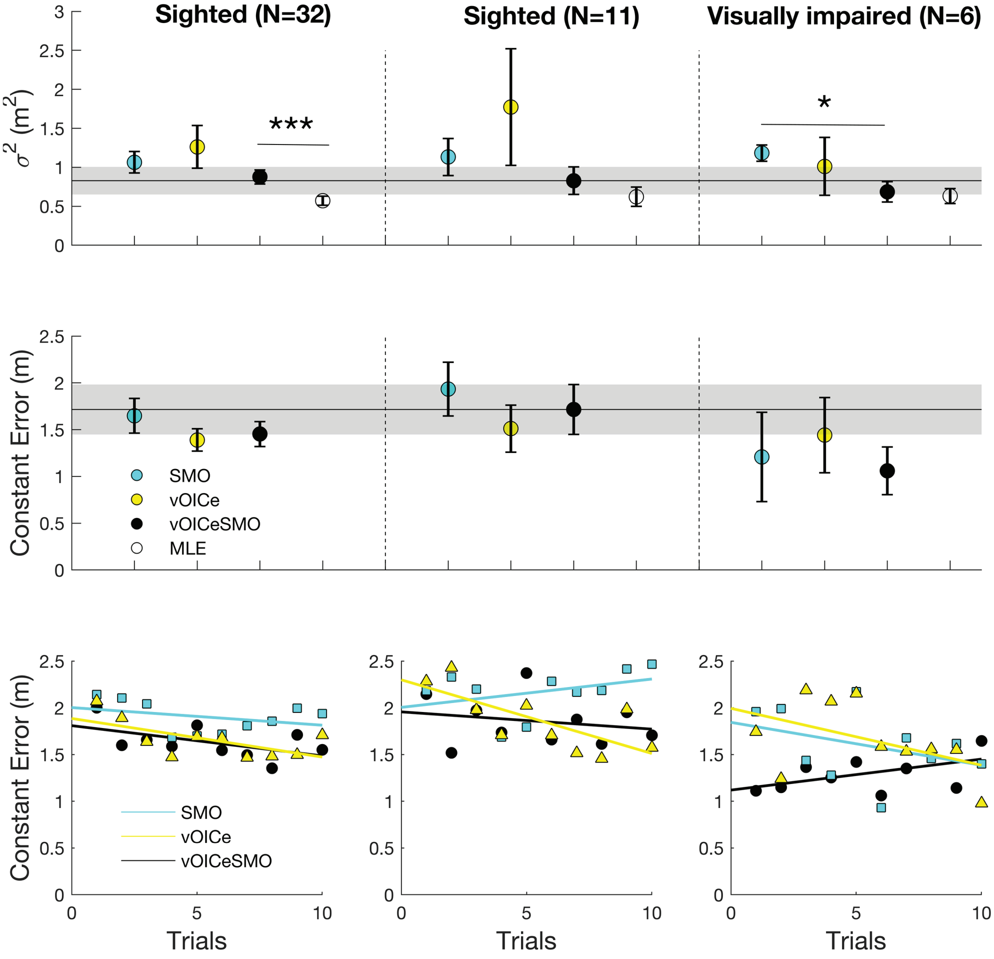

FIGURE 6 | Average variable error **(top panels)**, constant error **(middle panels)**, and relation between average constant error and number of trials **(bottom panels)** for the allocentric task. Average results for the entire sighted group (*N* = 32; **left panels**), the sighted group that performed the task with the same order of the visually impaired (VI) group (*N* = 11; **middle panels**), and the VI group (*N* = 6; **right panels**). vOICe = vOICe condition alone; SMO = self-motion alone; vOICeSMO = self-motion + vOICe. The marker labeled MLE (in white) in the **top panels** refers to the reduction in variability predicted by the MLE model. How MLE was calculated is explained in the **Figure 5** caption. Error bars represent the standard error of the mean, and the shaded dark line represent the combined measure (vOICeSMO) for the eleven sighted **(middle panels)** as a reference to both the combined conditions of the entire sighted group and of the VI group. ***$p < 0.005$; *$p < 0.05$. Please see **Supplementary Figure S5** for a boxplot with median and IQR measures.

were used to compare the variable error between the bimodal (vOICeSMO) and the unimodal conditions (vOICe and SMO), and between the measured bimodal (vOICeSMO) and the predicted bimodal (MLEl) conditions separately for the allocentric and egocentric tasks. The analysis showed no significant difference between vOICeSMO and vOICe conditions for the allocentric task, $Z = -1.363$, $p = 0.086$, and one-tailed, while showing a significant difference between vOICeSMO and SMO ($Z = -1.992$, $p = 0.023$, and one-tailed). Additionally, no significant difference between vOICeSMO and MLE was found for this group ($Z = -0.631$, $p = 0.528$), indicating that the reduction in variability for the bimodal condition was well predicted by the MLE model. The results for the egocentric task returned a significant difference between vOICeSMO and vOICe, $Z = -1.753$, $p = 0.04$, and one-tailed, and between vOICeSMO and SMO, $Z = -1.782$, $p = 0.037$, and one-tailed, but no significant difference between vOICeSMO and MLE: $Z = -0.315$, $p = 0.752$ (see **Figure 7** top right panel). This suggested that the VI group were able to reduce variability and improve their performance by integrating The vOICe information with self-motion as predicted by the MLE model. To examine whether the age of onset for the visual loss or the severity of the visual impairment (measure of visual acuity) correlated with the multisensory benefit shown by the VI group, we ran two linear regression analyses with the multisensory benefit as an outcome. We calculated the multisensory benefit as the difference in variable error between the combined condition (vOICe and self-motion) and the best unimodal condition (i.e., the condition that had the lower variable error between The VOICe alone or self-motion alone). Both regression analyses returned a non-significant result [age of onset: $F(1,4) = 0.77$, $p = 0.795$; visual acuity: $F(1,3) = 0.506$, $p = 0.528$].

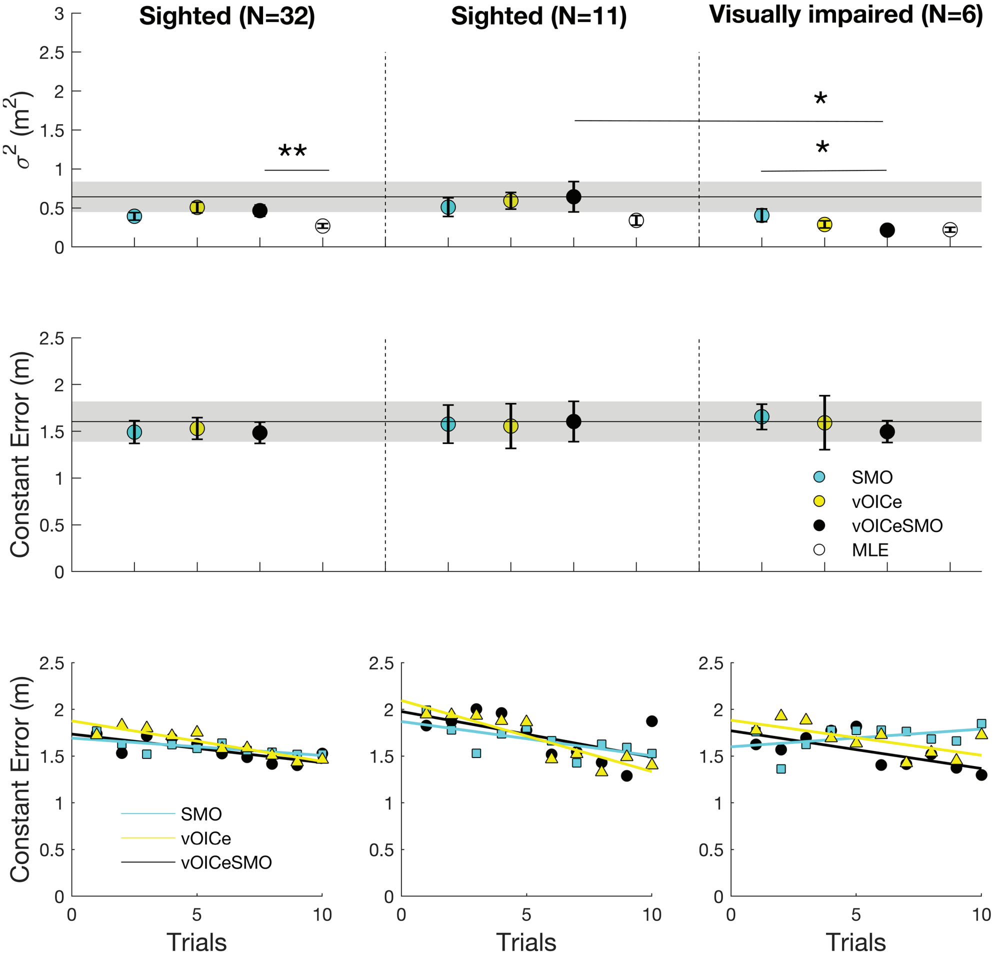

FIGURE 7 | Average variable error **(top panels)**, constant error **(middle panels)**, and relation between average constant error and number of trials **(bottom panels)** for the egocentric task. Average results for the entire sighted group (*N* = 32; **left panels**), the sighted group that performed the task with the same order of the VI group (*N* = 11; **middle panels**), and the VI group (*N* = 6; **right panels**). vOICe = vOICe condition alone; SMO = self-motion alone; vOICeSMO = self-motion + vOICe. The marker labeled MLE (in white) in the **top panels** refers to the reduction in variability predicted by the MLE model. How MLE was calculated is explained in **Figure 5** caption. Error bars represent the standard error of the mean, and the shaded dark line represent the combined measure (vOICeSMO) for the 11 sighted **(middle panels)** as a reference to both the combined conditions of the entire sighted group and of the VI group. $^{**}p < 0.01$; $^{*}p < 0.05$. Please see **Supplementary Figure S6** for a boxplot with median and IQR measures.

A similar analysis was performed on the constant error measures (**Figures 6, 7** right middle panel) and showed no significant difference between vOICeSMO and the unimodal conditions, vOICe and SMO, for both allocentric and egocentric tasks ($Z \leq -1.572$, $p \geq 0.058$, and one-tailed).

Sighted

Figures 6, 7 (middle panels) shows the results for the allocentric and egocentric tasks for the 11 sighted participants that performed the tasks with the same order of the VI (with vOICeSMO always at the end). Wilcoxon tests were used to compare the variable error between the bimodal (vOICeSMO) and the unimodal conditions (vOICe and SMO), and between the measured bimodal (vOICeSMO) and MLE conditions separately for the allocentric and egocentric tasks. The analysis showed no significant difference between vOICeSMO and the unimodal (vOICe and SMO) conditions for the allocentric task, $Z \leq -1.334$, $p \geq 0.091$, and one-tailed (despite a reduction in variable error for vOICeSMO when compared to the two unimodal conditions, see **Figure 6** top middle panel). These results are equivalent to those of the entire sighted group. No significant difference between vOICeSMO and MLE was found ($Z = -1.512$, $p = 0.130$), although the MLE variable error was smaller than that measured for vOICeSMO. The same results were found for the egocentric task (vOICeSMO vs. vOICe and vOICeSMO vs. SMO: $Z \leq -0.578$, $p \geq 0.281$, and one-tailed; vOICeSMO vs. MLE: $Z = -1.646$, $p = 0.100$, see **Figure 7** top middle panel). A similar analysis was performed on the constant error measures (**Figures 6, 7** middle panel) and showed no significant difference between vOICeSMO and the unimodal conditions, vOICe and SMO, for both allocentric and egocentric tasks (allocentric: $Z \leq -1.156$, $p \geq 0.124$, and one-tailed; egocentric: $Z \leq -0.445$, $p \geq 0.328$, and one-tailed). These results again replicate those of the entire sighted group.

Comparing Visually Impaired and Sighted

Finally, we examined whether sighted participants and VI differed in any of the conditions (vOICe, SMO, and vOICeSMO) for the allocentric and egocentric tasks separately. For the variable error in the allocentric task, the two groups did not differ in all conditions (SMO: $U = 25.000$, $p = 0.421$; vOICe: $U = 25.500$, $p = 0.451$; vOICeSMO: $U = 31.000$, $p = 0.841$). For the variable error in the egocentric task, the two groups did not differ in the unimodal conditions (SMO: $U = 28.000$, $p = 0.615$; vOICe: $U = 15.000$, $p = 0.070$) but did differ in the combined condition (vOICeSMO: $U = 13.000$, $p = 0.044$) with VI performing better than sighted when having both cues (**Figure 7**, top middle and right panels). No significant differences were found for the constant error when comparing the two groups on all conditions ($U \geq 17.000$, $p \geq 0.108$, see **Figures 6, 7** top middle and right panels).

Finally, we examined the difference in learning (decreased accuracy) with the number of trials between sighted and VI by running multiple linear regressions with group and trials as predictors and constant error (accuracy) for each condition as outcome. For the allocentric task (**Figure 6** bottom middle and right panels) in the SMO condition, we found a significant regression equation [$F(2,19) = 7.957$, $p = 0.004$], with an R-square of 0.484. Of the two predictors only "group" contributed to the significant result found ($p = 0.001$). For The vOICe, we also found a significant regression equation [$F(2,19) = 5.596$, $p = 0.014$], with an R-square of 0.397; however, this time only the "trials" predictor contributed to this significant effect ($p = 0.009$). Finally, for the vOICeSMO, we found a similar result to SMO, in that we found a significant regression equation [$F(2,19) = 13.805$, $p < 0.001$], with an R-square of 0.619 with "group" as only contributor ($p < 0.001$).

For the egocentric task (**Figure 7** bottom middle and right panels) in the SMO condition, we did not find a significant regression equation [$F(2,19) = 0.413$, $p = 0.668$], with an R-square of 0.046. For The vOICe, similarly to the allocentric task, we found a significant regression equation [$F(2,19) = 14.855$, $p < 0.001$], with an R-square of 0.636, with only the "trials" predictor contributing to this significant effect ($p < 0.001$). Finally, we found a significant regression equation for vOICeSMO [$F(2,19) = 7.836$, $p = 0.004$], with an R-square of 0.480 and both "trials" ($p = 0.004$) and "group" (although only marginally: $p = 0.051$) contributing to this effect.

DISCUSSION

We set out to explore how well two non-visual senses can be integrated to provide a representation of space that aids navigation in egocentric or allocentric tasks. First, in Experiment 1, we examined in a group of sighted individuals whether using one SSD (The vOICe providing an auditory display and the BrainPort providing a tactile display) or both simultaneously provided better performance in transferring information from a map to a real, 3D space. Both the egocentric and allocentric tasks revealed that the variable error did not reduce in the combined condition and was not well explained by the MLE model (e.g., Ernst and Banks, 2002). Performance for The vOICe on its own was less biased compared to the combined condition for the more difficult allocentric task. Consistent with this, there was no learning effect across trials for The vOICe as there was for the BrainPort. In fact, the constant error for The vOICe starts at a lower value and converges with the other by the end of the 10 trials; in contrast, for the egocentric trials, the constant errors were equivalent at the start and followed a uniform decrease in error across all conditions by the end of the 10 trials. A learning effect occurred for both The vOICe and BrainPort in the egocentric task but not in the combined condition. The lack of multisensory benefit in both tasks and the lack of learning effect for the combined condition in the allocentric task could be a consequence of task difficulty and sensory overload. It is plausible to conclude that learning to use two new devices and their delivered sensory information requires higher sensory and cognitive load than when only one device is used. As learning to use the two devices and then benefitting from their integration may require more time and training, it may be possible that a longer period of learning and use of the two devices together would allow for the multisensory benefit to emerge. An alternative explanation for the lack of multisensory integration as found in Experiment 1 is that the information provided by the two devices is too different (e.g., The vOICe transforms visual images by scanning sequentially from left-to-right while the BrainPort transforms visual information into a pattern of simultaneous electrical stimulation). This mismatch in received information may tell the brain that these cues probably belong to separate events, thus impeding integration. Future studies could test both possible explanations by training participants for a longer time when two or more devices are used and by trying to match the type of information provided by the different devices more closely. To this end, the use of new and improved sensory substitution systems such as the sound of vision (SoV; Caraiman et al., 2017) that uses depth cameras to provide the users with rich tactile and/or auditory information would be optimal. Using a system like SoV would allow for a closer match of tactile and sound information when forming a multisensory spatial representation, thus allowing for a better assessment of multisensory benefit during navigation in blind users. Also using SoV will also help overcome some of the limitations of the SSDs used here, for example, by avoiding the constraints of a tongue display which can limit the user's speech and consequently imped social interaction in real life situations.

In Experiment 2, we examined whether a group of sighted and a group of VI individuals could integrate two senses in a navigation task, namely self-motion and the auditory SSD (The vOICe) in an egocentric and an allocentric spatial navigation task. For the sighted group, there was no improvement in the combined condition compared to the unimodal conditions. The sighted showed a decrease in constant error across trials with The vOICe and the combined condition in both allocentric and egocentric tasks, and they had an increase in accuracy for SMO in the egocentric task. Interestingly, improvement in the combined condition correlated with that in The vOICe condition, suggesting that the performance with The vOICe was driving the improvement in the combined condition. Given a longer period of learning, perhaps this could have resulted in a significant reduction in variability in the allocentric task. However, the variable error in the egocentric task was suggestive of good performance and thus indicative of a ceiling effect that might have limited any improvement.

The VI participants in Experiment 2 had a reduction in variability for the combined condition in both egocentric and allocentric tasks; the combination of The vOICe and self-motion was significantly different than self-motion alone in the allocentric task, and the combination was better than both unimodal conditions in the egocentric task. The MLE model predictions did not differ from the combined condition; this indicates that the MLE model predicted performance well and that the VI did benefit from combining The vOICe auditory display and self-motion into a multisensory representation even with such a short period of training and testing.

The multiple regression analyses provided converging evidence that both allocentric and egocentric tasks showed a difference in group performance across trials for the combined condition, such that there was a learning effect. For both tasks, there were no group differences in The vOICe only condition, in that both sighted and VI improved with number of trials. In the allocentric task, though, the group effect was driven by the fact that the VI had a starting error that was much lower for the combined condition than the unimodal condition, unlike the sighted. In contrast, the egocentric task resulted in different performance between the VI and the sighted, with both groups showing improvement but the VI showing greater improvement. Finally, the two groups differed for self-motion in the allocentric task because the VI improved their performance with the number of trials while the sighed did not. Hence, the VI seem to be able to benefit more from the non-visual multisensory representation of space and even self-motion alone. However, in the egocentric task, VI did not improve in the self-motion condition, while sighted did. Finally, in the allocentric task the combined condition for the VI was already better (had lower constant error) than the unimodal conditions from the start (the first trial).

A significant quantity of research and development has been dedicated to The vOICe, demonstrating it allows successful object recognition and localization (Auvray et al., 2007) and offers superior spatial resolution in comparison to other SSDs (Proulx et al., 2014b). However, there is a comparative paucity of research demonstrating the efficacy of The vOICe in the context of spatial navigation. In contrast, the BrainPort has been demonstrated to convey inferior spatial resolution, but superior temporal resolution to The vOICe (Bach-y-Rita and Kercel, 2003), and (perhaps as a result of this) has demonstrable success in assisting VI navigation (Chebat et al., 2011, 2015). Nevertheless, depth perception remains a critical stumbling block for both devices. The first experiment removed the lack of depth perception as a limiting factor for navigation performance by using aerial maps; however, the results indicated that such information was better encoded and utilized when delivered by one device alone rather than both in combination.

Why might these devices not show evidence of optimal integration? Ernst and Banks (2002) Bayesian integration model suggests that optimal integration is better achieved when multiple sensory inputs have similar reliability; additionally, the Convergent Active Processing in Inter-Related Networks (CAPIN; Schinazi et al., 2016) theory postulates that in the blind in absence of the visual modality, other cues receive greater weights than they would have if vision was available (Millar, 1994). Hence, CAPIN postulates that in blindfolded sighted individuals the weights remain unchanged with vision receiving more weight than the other remaining cues. Hence, the lack of multisensory benefit in blindfolded sighted individuals in both experiments could be attributed to this inability to reweight the non-visual information based on the temporarily lack of vision. Furthermore, while audition contributes to a pictorial concept of space, Millar (1994) suggests that haptics exert the greater influence; therefore, information delivered *via* the auditory modality using The vOICe may have been attributed lower reliability than that from the BrainPort, preventing integration. However, our results for the variable error in Experiment 1 show that this explanation is unlikely as the two devices allowed for the same level of reliability, and further, The vOICe did have a lower constant error when compared to the BrainPort. Hence, we believe that the length of training/learning (10 repetitions for conditions) was just not enough to result in an integrated spatial representation using the two devices.

It was striking that, in Experiment 2, learning object locations through The vOICe provided similar precision (variable error) in navigation as self-motion, particularly considering the relatively short training (1 h) participants received. Results for the sighted individuals indicated no significant benefit in navigation precision in the combined condition, in neither type of spatial representation. This is in line with a body of research which suggested that cue competition, rather than integration, may occur in navigation tasks when a level of discrepancy is perceived among the cues (Tcheang et al., 2011; Garcia et al., 2015; Petrini et al., 2016). That is, although sighted individuals could use both cues in isolation with a similar level of precision, they probably discard the information afforded by The vOICe (which is less familiar) and relied on self-motion (given the high level of familiarity and that self-motion is what they were using to walk to the target object).

A significant difference was found between allocentric and egocentric variable error values, with egocentric navigation being more precise. This effect was expected, and in line with previous literature (e.g., Pasqualotto et al., 2013; Adame et al., 2014; Iachini et al., 2014), because in the allocentric navigation participants had to estimate two distances and infer the turning angle between two objects, unlike in egocentric navigation where they estimated one distance in a straight line. Moreover, this difference is indicative of the efficiency of the current design in testing both egocentric and allocentric spatial representations. This is the first study to test The vOICe in navigation tasks, previous research only assessing object recognition or object-locating tasks (Poirier et al., 2007; Proulx and Harder, 2008; Ptito et al., 2008). Even more, to our knowledge no study up to date has investigated in a controlled environment the efficiency of The vOICe in comparison to self-motion. Arguably our participants had much more extensive experience in navigating with SMO (walking in darkness), as opposed to navigating with The vOICe. Furthermore, studies using The vOICe have employed significantly more extensive training, with Auvray et al. (2007) providing 15 h, Amedi et al. (2007) providing 40 h of directed training, and Ward and Meijer (2010) examining its use after several months of usage. The current study thus provides a strong evidence that The vOICe can be effective even with a very short period of training. Although, this result is novel in showing the efficiency of The vOICe for navigation with minimal training, it adds to the existing evidence showing that several SSDs (e.g., EyeCane and tongue unit displays) can aid spatial navigation with a short period of training ranging from few minutes to few hours (Chebat et al., 2011, 2015; Maidenbaum et al., 2014; Kolarik et al., 2017). Moreover, the present findings demonstrate that participants are able to transfer spatial information gathered with The vOICe into self-motion information, since in one condition the spatial representation of objects was learned with The vOICe but the recall was tested with self-motion alone. This supports the idea that participants tend to feed in information acquired through any modality into a multisensory cognitive map pertaining spatial representations of the environment (Tcheang et al., 2011; Schinazi et al., 2016), which they can subsequently use in navigation.

The improvement in performance with number of trials when using The vOICe alone can be indicative of increased decoding abilities in participants. This assumption is supported by studies showing that after extensive training, visual-to-audio sensory substitution can determine instantaneous visual images of the scanned environment (Auvray et al., 2007; Ward and Meijer, 2010; Kim and Zatorre, 2011). In other words, users of SSDs can shift from effortful processing of the new sound information to automatically creating visual images by listening to the soundscapes (Brown et al., 2011). It is known that as high effort processing of navigation cues shifts to automatic processing, the pressure on cognitive resources also decreases (Loomis et al., 2002; Klatzky et al., 2006; Picinali et al., 2014). Therefore, cognitive resources required for processing each modality could decrease with practice, which leaves scope for integration. This is especially relevant for the more complex allocentric task, since decoding more complex sensory information equates to a higher cognitive load (Klatzky et al., 2006). To assess whether optimal integration of self-motion and The vOICe information can be achieved in sighted individuals with further practice, future studies could use the task presented here but with a higher number of trials.

Although a multisensory representation of space and the use of the VOICe and self-motion together did not result in a benefit for the sighted individuals, it did for the VI group. The VI group was able to reduce their variability and increase their precision when using The vOICe and self-motion together despite the very short period of training and low number of repetitions for each sensory condition. The use of a non-visual multimodal representation of space by blind people (Schinazi et al., 2016) is consistent with evidence from neuroscience, which suggests the brain does not process sensory information rigidly but re-organizes when a sensory ability is lost (De Volder et al., 1999; Poirier et al., 2007; Kupers et al., 2011). Our results are also in line with recent findings that show how using an audiotactile map to navigate the environment is more efficient for blind individuals than a tactile map and only walking (Papadopoulos et al., 2018). Hence, the present findings demonstrate that VI and blind persons can optimally integrate (Ernst and Banks, 2002) the new information coming from The vOICe with the available information from self-motion into a richer multisensory cognitive map than when using only self-motion. This brings support to the convergent model of spatial learning (Schinazi et al., 2016) in the blind and VI, by showing that even when using less effective (when compared to vision) cues for navigation, blind and VI can learn to perform as well as sighted by increasing their precision through non-visual multisensory integration.

A limitation to the generalization of the findings reported here, however, is the small sample size of VI individuals, and its heterogonous composition (i.e., different onset of visual impairment or blindness and severity of the condition). These limitations are not uncommon (e.g., Gaunet and Thinus-Blanc, 1996; Kupers et al., 2010, 2011; Gagnon et al., 2012; Chebat et al., 2015; Garcia et al., 2015; Kolarik et al., 2017) and the decision to include participants with different types of visual impairment was driven by the necessity to determine the level of generalization of our findings. That is, we wanted to examine whether different types of visual impairments could benefit from using The vOICe with self-motion when navigating to a target location. Additionally, the onset and severity of the visual impairment did not correlate with the benefit achieved by the participants in the combined condition, and overall, the variability among visual impaired participants' performances was low. Hence, our findings do show that integrating The vOICe information with self-motion during both egocentric and allocentric navigation can benefit persons with different durations and types of visual loss. Another limitation of the present study is the use of a controlled and relatively simple navigation task. Although our findings are promising they require further testing in the complex world outside the laboratory setting or alternatively by using virtual reality environments to simulate complex real situations (e.g., Chebat et al., 2015; Caraiman et al., 2017). In line with this limitation, it would be good for future studies to also obtain measures of performance time (Caraiman et al., 2017) in addition to error and variance to examine whether the availability of two cues together can rapidly speed up the navigation and way finding task. Hence, further studies will be able to assess if the found multisensory benefit in VI persons shown here can extend to daily life tasks and situations and to speed of performance.

Drawing on these findings, the applicability of The vOICe during navigation for the blind and VI population seems very promising. Firstly, the current study showed that both egocentric and allocentric information can be learned by using The vOICe soundscapes to form a rich cognitive map that can subsequently be used to navigate the environment. Moreover, it shows that VI and blind individuals can learn to integrate The vOICe soundscapes and self-motion more readily than sighted, because they usually outperform sighted individuals when using either of these cues during spatial representation encoding and navigation tasks (Tinti et al., 2006; Schinazi et al., 2016). This means that the benefit of using The vOICe alone and in combination with self-motion during spatial navigation can be achieved rapidly in VI and blind individuals with minimum training, hence removing one of the main barriers for the adoption of these SSDs in everyday life. This novel finding is promising in defining a new way to aid the blind population and further our understanding of spatial cognition after sensory loss. In fact, our results highlight how exploiting non-visual multisensory integration to develop new assistive technologies could be key to help the blind and VI persons especially due to their difficulty in attaining allocentric information (Pasqualotto et al., 2013; Schinazi et al., 2016).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Psychology Research Ethics Committee (PREC), University of Bath. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KP, MP, TL-E, EO'N, SL-S, and CJ developed the study idea and the study design. CJ, TL-E, MS, and SL-S recruited and tested participants. KP, SL-S, and CJ analyzed the data. All authors contributed to the writing of the paper.

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SUPPLEMENTARY MATERIAL

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COMMUNITY CASE STUDY
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A Multidimensional, Multisensory and Comprehensive Rehabilitation Intervention to Improve Spatial Functioning in the Visually Impaired Child: A Community Case Study

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Congenital visual impairment may have a negative impact on spatial abilities and result in severe delays in perceptual, social, motor, and cognitive skills across life span. Despite several evidences have highlighted the need for an early introduction of re-habilitation interventions, such interventions are rarely adapted to children's visual capabilities and very few studies have been conducted to assess their long-term efficacy. In this work, we present a case study of a visually impaired child enrolled in a newly developed re-habilitation intervention aimed at improving the overall development through the diversification of re-habilitation activities based on visual potential and developmental profile, with a focus on spatial functioning. We argue that intervention for visually impaired children should be (a) adapted to their visual capabilities, in order to increase re-habilitation outcomes, (b) multi-interdisciplinary and multidimensional, to improve adaptive abilities across development, (c) multisensory, to promote the integration of different perceptual information coming from the environment.

Keywords: visually impaired children, multisensory, rehabilitation, development, cognition, spatial cognition

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INTRODUCTION

Spatial cognition is a multifaceted concept that involves a variety of skills based on the acquisition of knowledge about spatial relationships among entities in the surrounding environment. More specifically, it entails the ability to understand and internalize the representation of the structure, entities, and relations of space with respect to one's own body (Thinus-Blanc and Gaunet, 1997; Vasilyeva and Lourenco, 2010). The development of spatial competence is essential for perceptual, motor and cognitive development (Newcombe and Huttenlocher, 2000; Newcombe and Learmonth, 2009; Vasilyeva and Lourenco, 2012) and the construction of our own identity (Proulx et al., 2016). Indeed spatial functioning is crucial not only for activities such as localizing stimuli and navigating in the environment, but also for cognitive skills such as perspective-taking, and provides an essential foundation for everyday functioning (Newcombe and Learmonth, 2009; Vasilyeva and Lourenco, 2012).

Studies showed that many spatial abilities (i.e., localization) develop in the very first months of life and are heavily influenced by sensory experience (Gavin et al., 2011). For instance, there is evidence that vision plays a pivotal role in spatial development (Thinus-Blanc and Gaunet, 1997; Eimer, 2004). Therefore, one prediction can be that early visual deficit may interfere with different aspects of psychomotor competence and spatial functioning (Reynell, 1978; Elisa et al., 2002; Dale et al., 2017). Even though some studies reported no noticeable differences in terms of spatial performance between sighted and blind people (Ashmead et al., 1998; Ittyerah et al., 2007), other studies indicate that visual experience significantly influences the acquisition of spatial competence (Cattaneo et al., 2008). For instance, several works have shown that visually impaired people may manifest deficits in specific spatial skills (Cattaneo et al., 2008; Koustriava and Papadopoulos, 2012; Pasqualotto and Proulx, 2012), especially when the visual disability is congenital and results in a total loss of visual acuity (Ellemberg et al., 1999; Maurer et al., 2007; Hadad et al., 2015; Hadad et al., 2017). Moreover, such spatial impairments can have life-long implications, negatively impacting on independent mobility and/or social and work inclusion (Shah et al., 2020). For example, visually impaired people can manifest difficulties in assuming different perspectives, understanding other people's mental states and emotions, judging others' trustworthiness (Ferrari et al., 2017), even if mixed results are reported in literature (Bednya et al., 2009; Ma and Han, 2011). It is well known that children with a visual disability may manifest a lack of "initiative" due to the absence of visual feedback emerging primarily at the motor level (Adelson and Fraiberg, 1974; Elisa et al., 2002), then also affecting communication, relational (Fazzi et al., 2007; Fazzi et al., 2019; Chokron et al., 2020) and cognitive levels (Fraiberg, 1968; Fraiberg et al., 1996). For instance, during typical development locomotion facilitates the acquisition of constancy of objects through the visual experience of spatial concepts such as orientation and perspective (Bigelow, 1992). Instead, motor development might be delayed in visually impaired children due on one hand to the difficulty of conceiving an object as existing in space, since for the blind child the ability to search for an object precedes and facilitates locomotor development (Fraiberg et al., 1996; Fazzi et al., 2011; Papadopoulos and Koustriava, 2011) and, on the other hand, to the lack of the physiological feedback to the vestibular and proprioceptive system mediated by vision (Prechtl et al., 2001). Overall, such behavioral findings indicate that visual impairment may have a negative impact on psychomotor and spatial development and result in severe delays in adaptive abilities across childhood. Also, some neurophysiological studies showed that a reduced visual input significantly impacts the functional organization of the cortical visual system during infancy (Hubel and Wiesel, 1977; Blakemore, 1991; Price et al., 1994), supporting the general view that visual experience might be important for perceptual and cognitive development. In the absence or reduction of vision, an early intervention appears to be necessary to foster overall development and encourage independence and social inclusion. This can be made with the involvement of a multi-disciplinary professional team and the direct engagement of caregivers, thus supporting the child not only in the healthcare setting but also in the various contexts of life (Rainey et al., 2014).

BACKGROUND AND RATIONALE

The World Health Organization (World Health Organization, 2017) estimated that in 2015 252.6 million people worldwide were visually impaired, of whom 36 million were classified as blind, with an estimate of 19 million children below the age of 15 years were visually impaired (1% of the total population in this age group), of whom 1.4 million had irreversible blindness (0.08% of the total population in this age group).

In the previous paragraph, we highlighted that visually impaired people can manifest difficulties in the development of spatial competence (Cattaneo et al., 2008; Koustriava and Papadopoulos, 2012; Pasqualotto and Proulx, 2012), especially when visual experience is compromised from birth (Ellemberg et al., 1999; Maurer et al., 2007; Hadad et al., 2015; Hadad et al., 2017). Even though the visual system influences significantly spatial information supplied by other modalities (Spence and Driver, 2012), spatial knowledge relies also on other sensory modalities such as touch, proprioception, kinesthesia, and audition (Millar, 2012). Such findings would argue in favor of early adoption of integrated intervention strategies when dealing with a congenital visual impairment, to promote perceptual and cognitive development and also social cognition through multisensory activities (Berardi et al., 2015; Purpura et al., 2017). Indeed, training intact sensory modalities such as audition and touch from an early age is essential to help the child building a relation with the environment and dialoguing with caregivers and peers. Recent evidence have shown that multisensory experiences such as audio-motor training activities performed from an early age can support the development of spatial abilities in the visually impaired child (Cappagli et al., 2017b, 2019). Moreover, other evidence demonstrated that early non-visual spatial experiences can influence spatial acuity in visually impaired people: more specifically, the earlier children start an orientation and mobility training, the more accurate their space perception is across life-span (Fiehler et al., 2009). Finally, a growing body of literature has shown that echolocation, namely the ability to orient in space by relying on self-produced echoes, may improve the general sense of auditory space in blind people (Kolarik et al., 2014; Vercillo et al., 2014), suggesting that spatial competence can be acquired through alternative non-visual senses. In this regard, a recent article (Norman and Thaler, 2019) supports this view by demonstrating that in blind echolocators the functional topography of the occipital cortex is used to map sensory input from an atypical modality for a directly analogous task-specific purpose (sound localization).

Nonetheless, a very recent review (Elsman et al., 2019) revealed that rehabilitation interventions for the visually impaired are rarely adapted to children's visual capabilities and very few studies have been conducted to assess their short-term and long-term efficacy. Therefore, there is the need to determine which interventions are effective and evaluate their effectiveness to increase functioning, participation, and quality of life in visually impaired children. We argue that the lack of homogeneous results on rehabilitation techniques is due not only to the use of a variety of outcome measures (many of which were not specifically developed for children with visual impairment) but also to the implementation of rehabilitation programs that do not differentiate intervention activities based on the visual and developmental profile of children. Taking into consideration the nature and the degree of the visual disability as well as the developmental profile and additional disabilities would result in an individualized therapeutic approach aimed at boosting perceptual, motor, cognitive, and socio-emotional potentials from an early age across different contexts of everyday life (Sonksen, 1997).

With this aim, we propose an integrated model of intervention that is: (a) multi-interdisciplinary, because it is based on the contribution of different professional figures (child neuropsychiatrists, neuropsychomotor therapists, ophthalmologists, orthoptists, psychologists, speech therapists, orientation and mobility trainers); (b) multisensory, because it proposes activities encouraging visually impaired children to integrate different perceptual information coming from the environment; (c) individualized, because activities are based on the visual and developmental profile of child; (d) multidimensional, because re-habilitation goals rely on a parallel collaboration of professionals and caregivers in the different contexts of life. The proposed intervention, in the context of overall development promotion, is intended to train spatial abilities as well as perceptual, motor, relational, and cognitive abilities linked to the acquisition of spatial competence, by assuming that the latter drives the acquisition of fundamental high-order skills such as perspective taking and problem-solving (Newcombe and Learmonth, 2009).

METHODOLOGICAL ASPECTS

In this work, we describe a re-habilitation intervention characterized by its diversification based on the visual and developmental profile by reporting the case of M., a visually impaired child enrolled in this approach for ten years (June 2009–June 2019), from the age of 9 months. This work has been carried out at the Center of Child Neurophthalmology of the IRCCS C. Mondino Foundation of Pavia, a national reference clinic for the diagnosis of visual disturbances and the re-habilitation of the child with visual impairment.

Targeted Population

The Center of Child Neurophthalmology of the IRCCS C. Mondino Foundation (Pavia, Italy) deals with different types of visual disorders, from both a diagnostic and re-habilitative perspective. Our re-habilitation intervention is based on three steps (**Figure 1**):

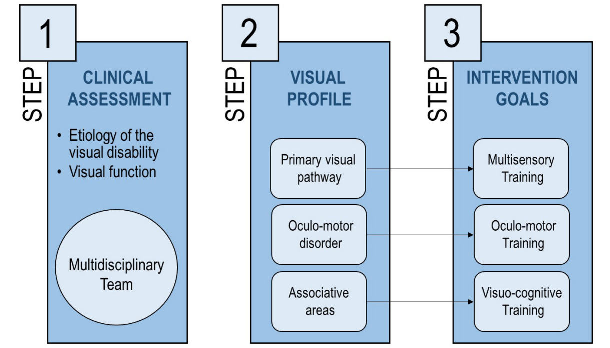

FIGURE 1 | The interventional approach proposed in the current manuscript, described in three steps aiming at identifying the most suitable rehabilitation approach based on visual deficit.

1. At first admission, a comprehensive clinical assessment is performed to identify the clinical profile of the patient (etiology of the visual disability, functional vision, developmental profile, and neuropsychiatric aspects);
2. Depending on the clinical profile of the child, the most damaged visual subsystem is defined: (a) primary visual pathway, affecting visual perception (e.g., in retinal dystrophies), (b) oculo-motor system, conditioning ocular motility (e.g., in oculo-motor apraxia and nystagmus), (c) associative visual areas, regarding visuo-cognitive skills (e.g., in cerebral palsy);
3. Re-habilitation goals and strategies are defined considering the most damaged visual subsystem and the developmental profile of the patient, together with possible comorbidities.

Case Study

We present the case of M., a child affected by a congenital disorder of the primary visual pathway, specifically retinal dystrophy (Leber Congenital Amaurosis), diagnosed at the age of 5 months on the basis of a poor vision from birth, abnormal eye movements, macular atrophy attenuated retinal vessels, and severely reduced scotopic and photopic electroretinogram and abnormal Visual Evoked Potentials (De Laey's criteria; Fazzi et al., 2003). He was enrolled in our re-habilitation intervention since his first admission at our clinic (9 months of age). At admission, we performed clinical and instrumental evaluations (i.e., electrophysiological exams, EEG, and brain MRI) to specifically define the visual impairment and investigate possible comorbidities and syndromic forms of retinal dystrophy. Neurophthalmological examination showed sluggish pupillary reactions, nystagmus, roving eye movements, and a deficit of fixation and pursuit that improved with the addition of sound; fundus oculi examination confirmed the presence of macular atrophy and attenuated retinal vessels; no refractive errors were also reported. Binocular grating acuity (Teller Acuity Cards (Teller et al., 1986)) testable only at the distance of 38 cm, was of 0.60 cy/deg, revealing severe perceptual deficit with residual close-up visual acuity; contrast sensitivity, evaluated with Hiding Heidi Low Contrast Face Test (Chen and Mohamed, 2003), was also altered (close-up response only for high contrast stimuli). Oculo-digital signs such as "eye-pressing" were present. Central Nervous System involvement was excluded, along with other comorbidities. A panel gene testing confirmed the diagnosis of inherited congenital non-syndromic retinal dystrophy involving NMNAT1 gene.

Neurological examination was normal except for mild aspecific hypotonia, frequently described in severely visually impaired children (Fazzi et al., 2005b). The child had good relational competences and attention span for his age, with some degree of emotional stress, expressed through motor hyperactivity and emotional lability, probably due to the necessity to adapt to the environmental requests. Head control and sitting position were acquired, rolling over was rarely observed and improved with the aid of auditory stimulus. Reaching and grasping of objects were performed only with audio-tactile integration, and subsequent occasional integration of visual information. The child functionally used both hands and showed a preference for specific textures. Neuropsychomotor development, evaluated by Reynell-Zinkin Scale (RZS) (Reynell, 1978), was characterized by a slight decline in the area of environment exploration and expressive language.

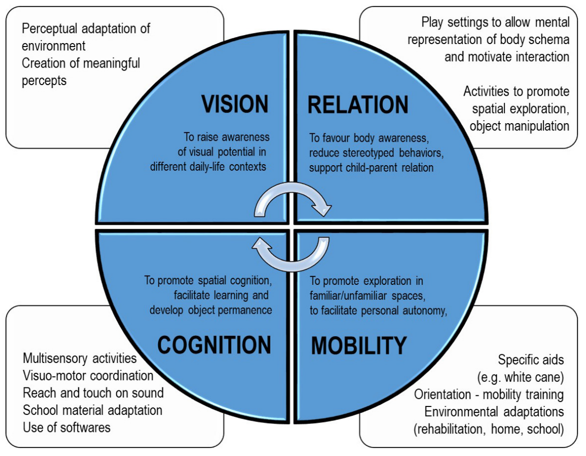

FIGURE 3 | Summary of the main rehabilitation activities for each domain considered (vision, cognition, mobility, and relation) for the patient M., affected by a deficit in the primary visual pathway with residual close-up visual acuity.

Re-habilitation Strategies and Results

Based on clinical assessment, the re-habilitation intervention was focused on the observed developmental fragilities and visual profile (see **Figure 2** for a general description of re-habilitation goals, **Figure 3** for a more specific description of intervention strategies and **Table 1** for a detailed description of re-habilitation activities based on age and developmental goals). During all the re-habilitation process, the intervention also considered the child's developmental profile and the main difficulties that a visually impaired child can encounter compared to sighted children, according to the literature on both typical and visually impaired children development and relying on our experience (Adelson and Fraiberg, 1974; Fraiberg et al., 1996; Cappagli and Gori, 2016; Vercillo et al., 2016; Cappagli et al., 2017a; Fazzi et al., 2010). We will illustrate the case study by presenting the main re-habilitation strategies and results for each developmental stage (9 months to 3 years; 3 to 6 years; 6 to 11 years) defined as "critical windows" for acquiring fundamental perceptual and cognitive abilities in the typical development (see **Figure 2** and **Table 1**).

Training sessions took place twice a week until 3 years of age, once per week in the 3–6 years old period, and twice per month during school age. A periodic neurological and developmental evaluation (every 6–8 months) was performed to tailor re-habilitation activities step-by-step, based both on "standardized" methods and on qualitative observations mainly focusing on the most frequently impaired domains in visually impaired children (e.g., motor initiative, relation, and expressive language). Our comprehensive assessment, both from a qualitative and quantitative perspective, included socio-emotional, relational, and adaptive skills. At the beginning of the intervention and until 3 years of age, a standardized evaluation was made with RZS (Reynell and Zinkin, 1975), a developmental tool for visually impaired children; when the child grew older and was able to sustain more structured evaluations, cognitive evaluations were performed, generally once per year, and based on available standardized tests, such as Wechsler Scales (Wechsler, 2002; Vaughn-Blount et al., 2011); other tests used to evaluate specific domains were the NEPSY-II (Brooks et al., 2010), the Developmental Test of Visual Perception (Brown and Hockey, 2013), batteries to assess learning skills (specifically developed for Italian population), and other non-standardized tests such as topological, figure recognition, and categorization tasks created and performed by our therapists. Results were periodically gathered and discussed in team meetings in order to evaluate the outcome and define the goals of future intervention.

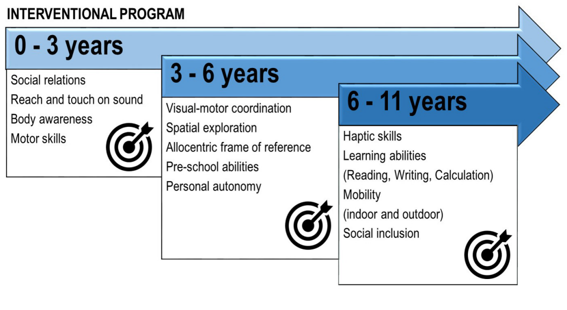

FIGURE 2 | Summary of the main rehabilitation goals for the patient M., affected by a deficit in the primary visual pathway with residual close-up visual acuity, according to his chronological age.

A fundamental aspect of our re-habilitation approach is that it entails activities related not only to the clinical setting but also to the home setting, introducing environmental adaptations transposed in the child's everyday environments, from the perspective of a multidimensional approach. Psychological support for parents is proposed, focused on the acceptance of child's disability and the promotion of the ability to understand his needs and his modalities of expression (e.g., signs of emotional distress expressed with stereotyped behaviors and oculo-digital signs), to support the parent–child relationship. Parents are also asked to actively participate in the training sessions so that they can see the activities and be explained how to talk and play with the child in different contexts. For example, they are taught

TABLE 1 | Re-habilitation activities performed according to developmental age (0–3 years old, 3–6 years old, and 6–11 years old) and perceptual and cognitive domains.

Age	Developmental goal	Re-habilitation activities
0–3	**Functional vision and multisensoriality** Promotion of body awareness and functional use of sensory modalities	• Visual environmental adaptations (e.g., setting with highly contrasting colors and illuminated objects) • Multimodal inputs (objects with emphasized visual, tactile and sonorous features, such as balls with a bell inside, drums, soft puppets made of different cloths)
	Socio-emotional cognition Promotion of parent–child relationship, communication, functional use of language and reduction of stereotyped behaviors, motivation to explore the external world	• Creation of a play environment with the parent who acts as a "mediator" in all the activities • Games based on physical contact and vocal communication to recognize emotions • Tactile exploration of the parent's face (discrimination and identification of the different parts, also through residual vision) • Interactive games with the parents (e.g., the child and the parent/therapist have to exchange an object after naming it; the parent/therapist presents objects by using alternative sensory channels (sound and touch) • Symbolic play (e.g., through interactive invention of short stories, symbolic use of objects)
	Sense of self Promotion of proprioception as baseline for motor development and construction of bodily self	• Play activities in which the parent/therapist positions a vibrating or sonorous object on a visible (e.g., hand) or not visible (e.g., neck) body segment of the child and the child is asked to find and remove it • Denomination activities in which the child is asked to name the body part on which a vibrating or sonorous objcet is placed, in order to develop verbal knowledge of different body parts (the activity can become reciprocal with the child positioning the object on a parent's body segment)
	Cognition (including spatial cognition) Promotion of sensorimotor intelligence, reach and touch on sound, object permanence, mental imagery	• Activities in which an object is only presented by sound or touch, motivating the child to reach and grasp it • Gradual exposure to different objects with integrated use of sight (if possible), touch (through bimanual exploration) and hearing: ◦ objects commonly used in everyday life ◦ objects with specific or peculiar audio-tactile characteristics ◦ bi-dimensional and tri-dimensional objects with different shape, texture, dimension, weight and presented at progressively greater distances and in different spatial positions • Games based on picture puzzles construction in which pieces are actively searched in a visually adapted environment • Exposition to spatial language
	Motor development Promotion of gross-motor (postural control and crawling, walking) and fine-motor (grasping and manipulating abilities) functions	• Perceptually adapted (visually contrasted, multisensory) and spatially organized (safe and circumscribed) environments: the play corner is characterized by sonorous-tactile elements (e.g., tactile tiles and differently textured cloth), delimited by pillows or smooth, soft furniture • Activities in which the child is motivated to reach lights/shapes/sounds on colorful panels on a wall or has to search objects guided by the voice of the parent, promoting independent exploration while keeping a distance from the caregiver
3–6	**Spatial cognition and visuo-motor coordination**	• Praxic-construction tasks with adapted materials (e.g., recreation of a shape by assembling the pieces in which the shape was cut, 2D and 3D puzzles, tangrams) • Block design: free and structured (i.e., from a model) assembling and deconstruction, during storytelling activities • Play activities in which the child has to place small objects in a line or create a geometrical shape • Training of spatial transformation with ego- and then allocentric frame of reference (e.g., reproduction of a configuration of objects on a board by assuming different spatial positions) • Training on opposite spatial concepts (on top of/under, tall/short, in front of/behind) applied both in relation to the child's position and to the objects' positions (for example, the child has to find a ringing object on his right, and then to move and stop in front of the object) • Training on visuo-spatial exploration: identify differences in the spatial layout of similar images, analyze the details in a figure, recognize different orientations of lines • Comprehension of auditory stories based on topographical information • Visual and visuo-tactile (with contrasted and embossed materials) activities with bi-dimensional and tri-dimensional objects in order to foster the development of perceptual and cognitive abilities such as: ◦ topographical reasoning ◦ spatial orientation ◦ reproduction of 3D, 2D, and graphic models • Software based on visual and auditory inputs
	Pre-school abilities Promotion of visuo-cognitive skills, memory, sustained attention	• Visual and visuo-tactile (with contrasted and embossed materials) activities with bi-dimensional and tri-dimensional objects in order to foster the development of perceptual and cognitive abilities such as: ◦ bimanual exploration of objects ◦ recognition / detail analysis ◦ semantic categorization ◦ drawing activities • Auditory activities in order to reinforce mnestic and attentional skills related to sonorous stimuli in the environment: ◦ detection (e.g., listening to sounds and then verbalizing the number of sounds) ◦ discrimination (e.g., distinguish different sounds presented together)

(Continued)

TABLE 1 | Continued

Age	Developmental goal	Re-habilitation activities
		○ memory (e.g., auditory memory game) ○ identification (e.g., listening to a sequence of sounds or words and verbalize the listening order) • Material adaptations (highly contrasted paper sheets, with well-defined margins and tactile references to help spatial organization of the sheet)
	Mobility and personal autonomy Promotion of the ability to move around and be autonomous in everyday routines to improve social inclusion	• Environmental adaptations (in the training setting, at home, at school, if possible) • Motor activities based on tactile and/or sonorous references to improve walking fluidity and speed • Motor training based on identification of position landmarks in a natural environment and construction of the first cognitive maps • Introduction of self-protection techniques (pre-cane) and use of external reference points to orient in novel environments (e.g., windows, lights, and doors) • Promotion of music and sports with peers
6–11	**Haptic and visuo-cognitive skills** Promotion of visuo-tactile integration, tactile discrimination	• Activities with the use of tiflologic cards with embossed spacing and the use of an awl to train the ability to organize points in the space and pursue a gradual exposure to Braille code
	Spatial cognition Promotion of the ability to switch from egocentric to allocentric frames of reference in different contexts	• Prosecution of the activities described for age 3-6 with progressively more complex activities and requests • Spatial and topological organization tasks • Visual-spatial training with exercises based on translations, rotations, overturning of geometric and plane figures
	Learning abilities Promotion of school inclusion and learning	• Environmental adaptations (illumination, first-line lifted desk, and bookrest) • Adapted materials integrating visual and tactile features: graphic cards with enlarged numbers and letters, high target-background contrast, thick margins • Specific cross-modal software for reading and writing (e.g., training of decoding abilities, accuracy, and speed through tachistoscopic presentation of single words and timed reading of brief texts) • Specific cross-modal software for calculation, geometry, auditory attention and memory (e.g., sound detection, discrimination and identification activities, auditory memory games, listening to texts followed by a quiz on the text content) • Provision and training of low vision aids: ○ digital audio-books ○ computer screen reading software ○ tablets computer-based Assistive Technologies (with applications such as screen magnifiers, optical character recognition and text-to-speech conversion) • Teaching of braille code • Compensatory tools (personalized reading and writing materials, such as notebooks with embossed margins and spacing, textbooks with clear and dimensionally adapted letters and line-spacing) • Dispensatory strategies (avoid copying from blackboard, use of capital letters only)
	Mobility, personal autonomy, and social inclusion Promotion of the ability to move indoor and outdoor and acquisition of personal autonomy and activities with peers	• Training in the use of self-protection techniques (introduction of white cane) • Map design: training in the memorization of previously performed routes which are verbalized and then redesigned on a rubber surface with an awl • Training in adaptive abilities for everyday life (e.g., to get dressed properly, to prepare school backpack, to use a phone...) in order to spend more time at school and/or with peers • Promotion of music and sports with peers

to interact with the child through physical contact and vocal communication, respect the time the child needs in the mutual interactions and in response to specific requests, give the right level and kind of input. Specific games based on sound and touch are showed to the parents so that they can reproduce them at home, together with environmental adaptations (see **Table 1**). When the child begins to spend a large amount of time at school, teachers are involved in the re-habilitation process as well, with periodic meetings to discuss the best strategies to promote social inclusion and learning.

From 9 Months to 3 Years of Age

Strategies

The first step of the intervention was directed at promoting sensorial experience and overall development, with a focus on relational, neuromotor and cognitive aspects. These goals were pursued with the creation of highly "socializing" play settings, in which activities based on the use of the voice or tactile perception or emphasizing visual information regarding human face were proposed. Parents were trained to establish a dialogue with the child, using different sensory inputs and catching signs of emotional distress which could interfere with the relational and spatial experience, making object relations less meaningful. The environment was perceptually adapted with the introduction of sensorial panels and audio-tactile objects so that the child could become more conscious of the environment itself and motivated to move and explore his personal (space occupied by the body) (Vaishnavi et al., 1999) and peri-personal (space surrounding our body within the reach of our limbs) (Làdavas et al., 1998) dimensions. Particular attention was dedicated to the ability to locate and grasp an object after sonorous/tactile input and the acquisition of the object permanence: this competence, known as "Reach and touch on sound" (Fazzi et al., 2011), seems to serve also as an organizer of gross-motor experience. The use of chromatic contrasts and lively colors helped the child to become aware of his residual visual function and optimize its integrated use with the other sensory modalities. Particular attention was dedicated to sensory inputs beneficial to the construction of body schema, intended as an on-line representation of the body in terms of posture and its extension in space (Head and Holmes, 1911; Holmes and Spence, 2004). For example, one of the activities proposed was based on the physical contact of audio-tactile objects on various parts of the child's body associated with the denomination of the body segment; the child was asked to search the object on his body and on the parent's body, during simple reciprocal activities (see **Table 1**, "Socio-emotional cognition" and "Sense of self").

At the age of 18 months, after almost 1 year of treatment, we noticed a positive change in awareness and integrated use of different sensory modalities, better functional use of exploration strategies with a prompt ability to find objects and people in the environment and a slight improvement in binocular grating acuity evaluated by Teller Acuity Cards (4.7 cy/deg) at the same distance of 38 cm. Altered contrast sensitivity was confirmed by Hiding Heidi Low Contrast Face Test (high contrast stimuli perception only); no refractive errors were reported. Also, social participation and communicative intentionality were improved, as shown by the reduction of restlessness and oculo-digital signs. Some degree of inattention was still observed during tasks requiring prolonged listening or use of visual-tactile information. RZS confirmed a slight decline in the sensory-motor and language areas but a developmental setback was not observed. From 18 to 36 months of age, the intervention focused on the improvement in the functional use of haptic information and on object manipulation, in order to strengthen exploration, recognition, sensorial semantic categorization, and topological relationships. We then proposed activities of haptic exploration to discriminate different textures (smooth/rough, stiff/soft, etc.), shapes (square, circle, etc.), dimensions, weights, and other physical attributes of objects. Play settings were adapted to be spatially organized and present deep symbolic meaning: we included objects with a meaning for the child to help him recognize them and motivate him to use them in a functional way, possibly fostering the parent-child relationship. In an interactive and entertaining setting, active exploration was stimulated with the use of real objects, placed in different space plans, and through verbal guidance also exposing the child to spatial language (e.g., spatial location words like "up" or "down," deictic terms like "here" or "there," dimensions, shape terms, spatial orientations, etc.). This use of language seems to help to elicit more spatial language production and to build later skills such as the ability to do spatial transformations and analogies (Verdine et al., 2019) and it is recommended also in parent-child interactions. Playing with toys that incorporate shapes (e.g., shape sorters), labeling them, and discussing shape properties may be among the earliest spatial experiences parents provide (Verdine et al., 2016).

Results

After 1 year of training, clinical observation revealed a positive change in the child's close-up visual and behavioral performances, at least partially due to the physiological maturation of the visual system, sustained by an adaptation of the sensory experience to foster the use of residual visual function. Above all, we observed improvement in ocular motility and coordination, improvement in the functional residual vision and good abilities to locate visual targets even in the absence of sound-tactile facilitation in a visually adapted environment (e.g., with the use of highly contrasted patterned panels), and at a near distance. M. used these skills to explore the surrounding environment functionally: in particular, crawling and postural passages were easier when the space of action was reduced and perceptually adapted. Furthermore, residual vision was functionally used even in grasping: after locating objects by relying on the visual feedback, he integrated various sensory information (sound, touch, and sight) to explore them. We also noticed a good progression in gross motor function, and the motor milestones (i.e., standing and walking) were reached as expected compared to sighted peers.

From 3 to 6 Years of Age

Strategies

In this phase, intervention was particularly focused on the promotion of autonomy and the acquisition of pre-school abilities, with specific attention to visual-motor coordination and spatial exploration. When M. was four years old, some difficulties emerged involving visuo-tactile and visuo-motor integration, probably reflecting impairments in visual monitoring and fatigability in the use of visual information, which caused delays in the development of fine-motor skills. The lack of visual-motor integration also negatively interfered with the activities of daily living, making it difficult to acquire personal autonomies. The re-habilitation approach was then readapted to the child's needs and the main goal in this phase was to strengthen different sensorial functions to sustain cognition and learning and to promote autonomy through orientation and mobility training in broader spaces, also with the development of social skills as an endpoint (see **Table 1**). The main strategy to reach these goals was the training of multisensory integration. We trained auditory attention through activities of detection (e.g., asking the child to pay attention to and verbalize the number of sounds presented), discrimination (e.g., asking the child to distinguish different sounds of increasing number and complexity, also using a sort of "memory" game with sounds), identification (e.g., inviting the child to listen to a sequence of sounds and/or words and verbalize the type of the stimuli). Some activities were based on the integration of visual and tactile exploration, to train recognition, association, categorization abilities and learn spatial relations (topological and topographic) and action planning, always sustained by the therapist-use of language to mediate knowledge. These visual-tactile spatial tasks were particularly useful for the future learning of braille code, geometric and graphic abilities. Some cognition enhancement games were also used, based on logic and short stories listening and comprehension tasks. From the perspective of a multidimensional approach, an important aspect of intervention in this phase was the introduction of devices and strategies to adapt the environment and material to the sensory characteristics of the child (for example, the use of a reading desk, the spatial organization of paper also with the use of tactile marks) during graphic tasks at home and/or at kindergarten. Training on orientation and mobility was also introduced. This training was based both on a play setting with the therapist and on the intervention of a personal autonomy instructor focusing on daily life necessities. The general aim was to improve the ability to locate objects in the space by using the child's body as a reference (for example, asking the child to take the ringing object at his right) and then using the surrounding space as reference (i.e., asking the child to move and stop in front/behind the object). The environment was adapted by creating spatial paths with tactile, visual and/or sonorous landmarks. Autonomy and adaptive skills were promoted by training the child to recognize and locate landmarks in the natural environments and to use protection techniques, such as the use of a pre-cane in wide and crowded places.

Results

At three and a half years old, the child used and integrated visual information with auditory and tactile information for the exploration of the environment and/or objects and located visual targets in the peri-personal space even in the absence of audio/tactile facilitation. This visual competence was used effectively by the child to direct his movements in space. In the exploration and knowledge of close objects, we observed an improved functional use of touch: he showed good skills in bimanual coordination and systematic exploration both to recognize and discriminate the shapes and structures of objects and to analyze topological relationships between them. The overall positive evolution was confirmed by Wechsler Primary and Preschool Intelligence Scale (WPPSI-III) where M. reached a verbal index of 131 and performance index of 106 (total intelligence quotient: 122), showing an adequate spatial competence. The same competences were also measured qualitatively: the child manifested good capabilities of exploring small and familiar environments by using landmark location abilities (for example, the lights coming from windows) and memory skills. Neuro-visual examination showed the persistence of roving eye movements and nystagmus, poor visual fixation and discontinuous smooth pursuit at near. Testing with LEA single symbols (Hyvärinen et al., 1980) confirmed severe low vision (2/10 for near distance, no answers for far distance); other findings were altered contrast sensitivity (evaluated with Hiding Heidi Low Contrast Face Test and LEA symbols) and color perception (Color Vision Test Plates For The Infants) (Lee et al., 1997), and absent stereopsis (Lang Stereotest) (Lang and Lang, 1988); visual field was clinically difficult to evaluate also for his age. Appropriate lenses were prescribed for the evidence of a refractive error (hypermetropia and astigmatism). At 6 years of age, continuous improvements were observed within psychomotor development. Concerning the posturo-motor organization, the ability to walk, run, go up and downstairs and perform postural passages with good motor fluidity and autonomy was acquired. He acquired the ability to move in unknown environments, preferentially using auditory information (i.e., adult's voice) as a guide, although he also used visual information (visual location) functionally, using spatial landmarks such as light points and/or bright color furnishings. Manual organization in bimanual tasks also appeared well modulated even though slow.

From 6 to 11 Years of Age

Strategies

In this phase, the intervention had the main goal of developing and sustaining reading, writing, geometry and math skills together with personal autonomy. Re-habilitation was then focused on supporting visual-spatial perception connected with visuo-cognitive skills (e.g., translations, rotations, and overturning of geometric and plane shapes – see **Table 1** for details). Moreover, it was directed on promoting the enhancement of basic reading-writing skills, increasing decoding accuracy and speed through the use of graphic cards with special features (enlarged numbers and letters with high target-background contrast, different materials, thick edges, adapted bookrest), video writing programs with vocal synthesis and iconographic representation, tachistoscopic presentation of single words, timed reading of small passages, and graphic material. Empowerment of functions such as sustained attention, spatial memory both with visual and auditory tasks, and visuo-cognitive abilities was performed through the use of visuo-tactile materials or specific software. Also, activities of sound discrimination and identification were required, along with prolonged listening and auditory memory tasks. At the same time, haptic competence was continuously enhanced through activities of tactile discrimination, categorization, spatial and topological organization and tactile-kinesthetic memory, also to facilitate the learning of the braille code considering that severe low vision remained stable over time. M. successfully learned to use braille, either to read and write (using a typewriter and, subsequently, a computer). Concerning mathematical competence, activities aimed at enhancing the visual-spatial orientations for the correct reading-writing of numbers and signs and an adequate numerical queuing were proposed; for the learning of math, the child used traditional printed, highly contrasted material (black/white) with enlarged numbers and a low-vision calculator. With the collaboration of school operators and the tiflologist, in agreement with the family, we introduced compensatory (personalized reading and writing materials) and dispensatory (e.g., avoid copying from the blackboard, use of capital letters for writing) tools and strategies to facilitate the learning process. At the same time, we proposed activities to foster spatial cognition both in indoor and outdoor environments along with personal autonomy, with a subsequent positive outcome on social aspects. This was done by improving the protection techniques, developing strategies to remember every-day routes (e.g., by redesigning them with the rubber surface after verbalization by the child) and introducing the use of a white cane at the age of 9 years old, as soon as the child was ready to accept and functionally use it.

Results

At nine years of age, in the context of visual-tactile exploration used for visuo-cognitive tasks (consistent with the objectives of the re-habilitative intervention implemented since school age), the child was able to complete construction tasks, such as block design, and recognize spatial relationships and orientations. In our opinion, the acquisition of an allocentric frame of reference, according to which locations are described using object-to-object relationships independently from the subject's point of view (object-centered representations), may represent a sign of good outcome in terms of spatial competence. Allocentric capabilities were trained and evaluated, for example, during tasks in which the child had to reproduce the spatial configuration of textured coins on a board by assuming different spatial positions (see **Table 1**). Concerning personal autonomies, the child appeared to employ useful strategies to move with bodily awareness in the environment, paying attention to find the visuo-spatial points of reference useful for orientation in different contexts (room, refectory, corridor, and classroom) and to perform more direct spatial paths. Also, personal autonomy and effectiveness in using the white cane to move outdoors improved: the child showed good capabilities of managing to carry out medium-length and complex routes with minimum assistance and good ability to orientate in space.

At the time of writing of this work, M. is 11 years old. When he was first tested with Wechsler Intelligence Scale for Children at the age of six years old, his global intelligence quotient was in the range of typical development with a quite disharmonic profile showing adequate scores for verbal and working memory tasks and borderline scores in the Perceptual Reasoning and Processing Speed Index. In the last cognitive evaluation, his profile fitted perfectly in the typical range with a harmonic profile and good results in Perceptual Reasoning Index, demonstrating an improvement in visual-spatial abilities; the decline in Processing Speed Index may be due to fine-motor slowness related to the visual deficit (**Figure 4**). From the emotional perspective, M. has always shown good coping and relational abilities, and no signs of isolation or passivity have ever been observed.

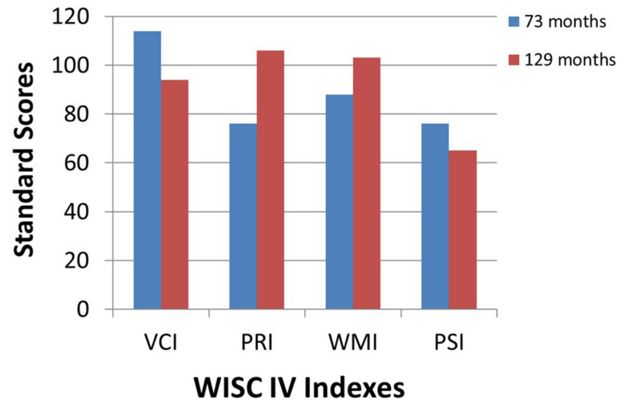

FIGURE 4 | First (73 months) and last (129 months) cognitive assessment of the patient M. with the Wechsler Intelligence Scale for Children (WISC-IV). VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index.

DISCUSSION

In the present work, we presented a paradigmatic case of our re-habilitation program based on a multi-interdisciplinary, multidimensional and multisensory approach for children affected by a visual impairment causing difficulties in spatial development. In fact, it is widely accepted that the lack of early visual experience may have a negative impact on the development of spatial abilities as well as motor skills and mobility (Fraiberg, 1968; Morrongiello et al., 1995; Prechtl et al., 2001; Sonksen and Dale, 2007). Moreover, some studies (Aggius-vella et al., 2017; Purpura et al., 2017; Cuppone et al., 2018) showed how the use of other senses may help blind and low vision children to reach developmental milestones which would otherwise be difficult to achieve, such as object permanence (Elisa et al., 2002; Fazzi et al., 2011), which is one of the main goals of our early re-habilitation. With this work, we argue that our approach may facilitate the acquisition of the ability to adapt to environmental requests, particularly important in the context of spatial cognition. Recent studies have confirmed that multisensory re-habilitation approaches may help the child to move independently in the environment and encode spatial and socially relevant information (Aggius-vella et al., 2017; Cappagli et al., 2017b). Moreover, several evidences have demonstrated that multisensory protocols are more effective than training protocols based on unisensory stimulus regimes due to preexisting congruencies of information coming from the different senses (Shams and Seitz, 2008). This is confirmed by studies suggesting that multisensory-integrated re-habilitation methods could be effective for children with sensorial impairment (Purpura et al., 2017). In line with this view, a very recent article has shown that hemianopia can be rehabilitated with an audio-visual training procedure based on spatiotemporal concordant stimuli, stressing the benefits of multisensory stimulation (Dakos et al., 2020). Overall, such findings could be explained in terms of "crossmodal plasticity," defined as the possibility that sensory deprived regions become responsive to the remaining modalities (in the case of visually deprived people, auditory and tactile modalities) (Dormal et al., 2012) and consequently support the notion that functional specializations of cortical sensory areas is modality-independent. In other words, the positive outcomes of our re-habilitation approach could be at least partially based on the notion that multisensory stimulation (e.g., audio-visual) trains visual cortices to preserve their typical specializations, e.g., to respond to spatial-related stimulation, ultimately further strengthening the emerging proposal that brain organization is driven by specific sensory-independent computations rather than by specific unisensory-inputs as classically conceived (Pascual-Leone et al., 2005; Heimler et al., 2015 Amedi et al., 2017).

Our re-habilitation approach strongly relies on these concepts and adapts to the nature and degree of the child's visual impairment. In the first months of life, multisensory information (auditory and tactile) enhance the experience and motivation of the child to explore the surrounding space, laying the foundation for the use and training of the other senses to support vision. As reported in some studies (Vercillo et al., 2016; Cappagli et al., 2017b), the use of multisensory experience may help to develop spatial skills that would be otherwise compromised by the lack of visual experience. Also, if a residual visual function is present (as in the case of child M.), visual-haptic and visual-auditory activities may be useful to promote the integration of vision and implement perceptual development (Gori, 2015). Multisensory information is used in order to promote body perception that is a fundamental component of environmental knowledge related to movement and orientation in space (Koustriava and Papadopoulos, 2012) and might be impaired in congenitally blind subjects (Parreira et al., 2017). Moreover, relational activities with the therapist and the caregiver can have a fundamental role in our early re-habilitation, since emotional and relational aspects are strictly connected also to spatial cognition (Proulx et al., 2016), even though these aspects go beyond the scope of this article and have not been examined. The activities proposed in our intervention are intended to foster the development of spatial awareness, visuo-motor and visuo-cognitive abilities and learning skills, especially concerning geometry and mathematics. Multisensory experience is not only provided via specific re-habilitation activities in the clinical setting but also promoted through adaptations of the child's everyday environments and activities, according to the International Classification of Functioning, Disability and Health approach (WHO, 2010). As neuropsychomotor development progresses, our re-habilitation work is enriched by the introduction of orientation and mobility training, aimed at promoting autonomy through functional exploration of space (Tinti et al., 2006). In this domain, an important milestone is the ability to switch from an egocentric to an allocentric frame of reference – the first regarding object location in reference to oneself, the second regarding an object location in reference to another object (Klatzky, 1998). Studies showed that visually impaired people tend to use an egocentric frame of reference, confirming the difficulties in the development of normal spatial cognition in blind people (Pasqualotto and Proulx, 2012; Ruggiero et al., 2018), which makes it mandatory an early training in this area (Fiehler et al., 2009; Fiehler and Rösler, 2010) that can be performed through the use of sensory modalities other than vision.

In conclusion, children with a congenital visual impairment can partially or completely lack a sensory experience that is essential for spatial development. Indeed, among sensory modalities, vision is the most pervasive one because it guides the maturation of the very first mental representations about space (Thinus-Blanc and Gaunet, 1997; Eimer, 2004; Pasqualotto and Proulx, 2012). Spatial events can be perceived in a syncretic or "gestaltic" way through vision, which allows the subject to acquire a whole series of information about their shape, dimensions, color, and contrast. Consequently, visual experience shapes the nature and the structure of space, motivating the infant to initiate exploratory activities in the surrounding environment (Kestenberg, 1979). For this reason, pieces of evidence suggest that the visual system has a central role in coordinating all the other perceptual-sensory systems and in guiding actions in space (Duffy, 1978; Fazzi et al., 2005a), raising questions about how to intervene on these aspects.

LESSONS LEARNED AND RECOMMENDATIONS

In the last decades, there has been a raise of interest for visual disability, not only for what concerns enhancements and impairments in spatial knowledge due to the lack of visual experience but also for what concerns the development and the introduction of specific re-habilitation interventions to improve quality of life of visually impaired people. Nevertheless, there has been a simultaneous lack of studies assessing different rehabilitation approaches and outcome measures (Elsman et al., 2019). Moreover, standardized primary (e.g., regarding visual functioning or general perceptual skills) and secondary (e.g., functional status, quality of life, social, and working inclusion) outcome measures are currently not available for the visually impaired population. To our knowledge, only one study (Finocchietti et al., 2019) proposed a first possible goal standard test to evaluate spatial impairment in visually deprived children. In this sense, the use of technological devices could be extremely helpful for visually impaired children in order to reach rehabilitation goals, especially in the field of mobility and autonomy, as it has been shown in some recent works (Cappagli et al., 2017b, 2019).

CONCLUSION

The case of M. demonstrated that an early multisensory and multidimensional re-habilitation can play an important role in the promotion of overall neuropsychomotor development in children with congenital visual impairment without Central Nervous System involvement. Spatial cognition development can particularly benefit from early activities proposed in an enriched environment promoting body knowledge, object permanence and space exploration through multisensory experience. Nevertheless, specific outcome measures, besides randomized controlled trials (RCTs), are needed to confirm our empirical and anecdotal evidences.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the patient's parents for the publication of this case report, including any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FM, GA, GC, and SS contributed to study conception, design, and manuscript writing. AL and FD are directly involved in the rehabilitation process, and contributed to data collection and manuscript writing. GC, MG, and SS contributed to critical manuscript revisions and final approval of the submitted version. All authors contributed to the article and approved the submitted version.

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REVIEW
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Spatial Competence and Brain Plasticity in Congenital Blindness via Sensory Substitution Devices

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In congenital blindness (CB), tactile, and auditory information can be reinterpreted by the brain to compensate for visual information through mechanisms of brain plasticity triggered by training. Visual deprivation does not cause a cognitive spatial deficit since blind people are able to acquire spatial knowledge about the environment. However, this spatial competence takes longer to achieve but is eventually reached through training-induced plasticity. Congenitally blind individuals can further improve their spatial skills with the extensive use of sensory substitution devices (SSDs), either visual-to-tactile or visual-to-auditory. Using a combination of functional and anatomical neuroimaging techniques, our recent work has demonstrated the impact of spatial training with both visual to tactile and visual to auditory SSDs on brain plasticity, cortical processing, and the achievement of certain forms of spatial competence. The comparison of performances between CB and sighted people using several different sensory substitution devices in perceptual and sensory-motor tasks uncovered the striking ability of the brain to rewire itself during perceptual learning and to interpret novel sensory information even during adulthood. We discuss here the implications of these findings for helping blind people in navigation tasks and to increase their accessibility to both real and virtual environments.

Keywords: multisensory, spatial cognition, vision, touch (haptic/cutaneous/tactile/kinesthesia), sensory substitution, brain plasticity, congenital blindness, navigation

INTRODUCTION

Several different mechanisms influence the development of the congenitally blind brain. Neuroimaging techniques show that brain structures devoted to vision are greatly affected (Kupers and Ptito, 2014; Fine and Park, 2018; Singh et al., 2018), and that the extensive use of the remaining senses (e.g., touch or/and audition) helps blind people to develop a set of impressive skills in various cognitive tasks, probably due to the triggering of neural plasticity mechanisms (Schinazi et al., 2016). These enhanced behavioral performances are correlated to brain plasticity using various types of SSDs (Chebat et al., 2018a). Brain modifications are triggered by sensory deprivation and later by the training of the other senses, for example through the use of SSDs to "perceive" visual information. We perceive our environment using all of our senses in parallel, creating a rich multisensory representation of space (Chebat, 2020), but how does the complete lack of vision impact spatial competence and spatial learning? In this paper, we review the plastic changes that occur in the brain of CB that are triggered by SSDs use.

SENSORY SUBSTITUTION DEVICES (SSDs)

SSDs translate visual cues into tactile or auditory information. SSDs consist of three components: a sensor, a processing unit that converts the visual cues using a specific code and algorithm, and a delivery system to transmit the tactile or auditory information. SSDs differ in terms of their respective approaches, codes or algorithms for capturing and sending information, and also in terms of their specific components, but they all aim to transmit visual information via another sense. For example, SSDs use different kinds of sensors to capture visual information, either from a camera (Bach-y-Rita et al., 1969; Meijer, 1992; Bach-y-Rita and Kercel, 2003; Ptito, 2005; Chebat et al., 2007a; Mann et al., 2011; **Figures 1A,F,I** for images of the camera set-ups used for the TDU, EyeMusic, and vOICe) or sonic (Kay, 1974), ultrasonic (Shoval et al., 1998; Hill and Black, 2003; Bhatlawande et al., 2012) and infrared sensors (Dunai et al., 2013; Maidenbaum et al., 2014c; Stoll et al., 2015). The means to deliver the information to the user can also vary greatly. In the case of the Tongue Display Unit (TDU) (Bach-y-Rita et al., 1969; Bach-y-Rita and Kercel, 2003; **Figures 1A–C**), the image captured by a camera is translated and coded onto an electro-tactile grid which "draws" an image on the tongue of the user (**Figure 1C**). In the case of the EyeCane (Maidenbaum et al., 2014c), distance information is received from an infra-red sensor and delivered to the hand and ears through the frequency of vibrations or sounds (**Figures 1D,E**). The EyeMusic (Abboud et al., 2014; **Figures 1F–H**) and vOICe (Meijer, 1992; **Figure 1I**) also rely on a camera for visual information but the algorithm codes the images into sounds, and in the case of the EyeMusic, different musical instruments code for different colors in the image.

Despite these differences, SSDs all use a form of code to translate visual information that must be actively integrated by the user. This process, called distal attribution (Auvray et al., 2005) requires the reinterpretation of what seems like random stimulation into a coherent, visual percept through sensori-motor feedback (Chebat et al., 2018a). This form of reinterpretation of visual information has often been likened to a kind of learned synesthesia (Ward and Wright, 2014). The use of these devices to transfer visual information, via the tactile, auditory or vibratory channels, coupled with complete congenital sensory deprivation leads to training-induced recruitment of brain regions that were typically considered purely visual (Ptito, 2005; Amedi et al., 2007; Proulx et al., 2016). Although the phenomenological sensations reported by CB during the use of these devices is similar to vision (Chebat et al., 2018a), these devices cannot approximate the complexity and resolution of vision *per se*. Thus, the resulting sensations are very different from vision in the sighted, and cannot genuinely replace a missing sense for all of its functions (Moraru and Boiangiu, 2016). This is also true for task specific sensory independent regions according to the task being completed (Kupers et al., 2010a; Matteau et al., 2010; Ptito et al., 2012; Striem-Amit et al., 2012a,b; Abboud et al., 2015; Maidenbaum et al., 2018). SSDs have not become widespread in their general use by the blind population (Loomis et al., 2010; Elli et al., 2014), for various practical reasons (Chebat et al., 2018a). In order for an SSD to be widely accepted by the a visually impaired public, it needs to meet many several criteria, such as general use (for many tasks), facility of use, cost and be worth the learning process in terms of the visual information it can afford in real time (Chebat et al., 2018a). From the point of view of navigation, several of these devices have great potential in improving navigation competence and strategies used by blind people during navigation. We review these concepts in the following sections.

SENSORY DEPRIVATION, BRAIN PLASTICITY, AMODALITY AND SPATIAL COGNITION

A large part of the cortical mantle is dedicated to vision. In the macaque, about 55% of the entire cortex is in some way responsive to visual information, and in humans it is about 35%. This cortical space is by no means wasted for people who are blind from birth, and can be recruited in a variety of cognitive and spatial tasks using the remaining intact senses. Indeed, the recruitment of primary visual areas by other sensory modalities has been known for quite some time in CB (Kupers and Ptito, 2014). This process, known as *amodality* (Heimler et al., 2015; Chebat et al., 2018b) enables the recruitment of brain areas in a task specific, sensory independent fashion (Cohen et al., 1997). The recruitment of task-specific brain nodes for shapes (Ptito et al., 2012), motion (Saenz et al., 2008; Ptito et al., 2009; Matteau et al., 2010; Striem-Amit et al., 2012b), number-forms (Abboud et al., 2015), body shapes (Striem-Amit and Amedi, 2014), colors (Steven et al., 2006), word shapes (Striem-Amit et al., 2012a), faces (Likova et al., 2019), echolocation (Norman and Thaler, 2019), and tactile navigation (Kupers et al., 2010a; Maidenbaum et al., 2018) is thought to represent mechanisms of brain plasticity (Fine and Park, 2018; Singh et al., 2018) for specific amodal recruitment (Ptito et al., 2008a; Chebat et al., 2018b; see **Figure 2**). The recruitment of the brain areas via SSDs not only shows that it is possible to supplement missing visual information, but that the brain treats the SSD information as if it were real vision, in the sense that it tries to extract the relevant sensory information for each specific task we are trying to accomplish (i.e., motion, colors, navigation, and other tasks illustrated in **Figure 2**). How do brain plasticity and amodality influence spatial perception in people who are blind from birth? Since, vision is quite important for active navigation (McVea and Pearson, 2009; Ekstrom, 2015; Jeamwatthanachai et al., 2019), how essential is it for the development of spatial abilities and the neural networks that support these abilities?

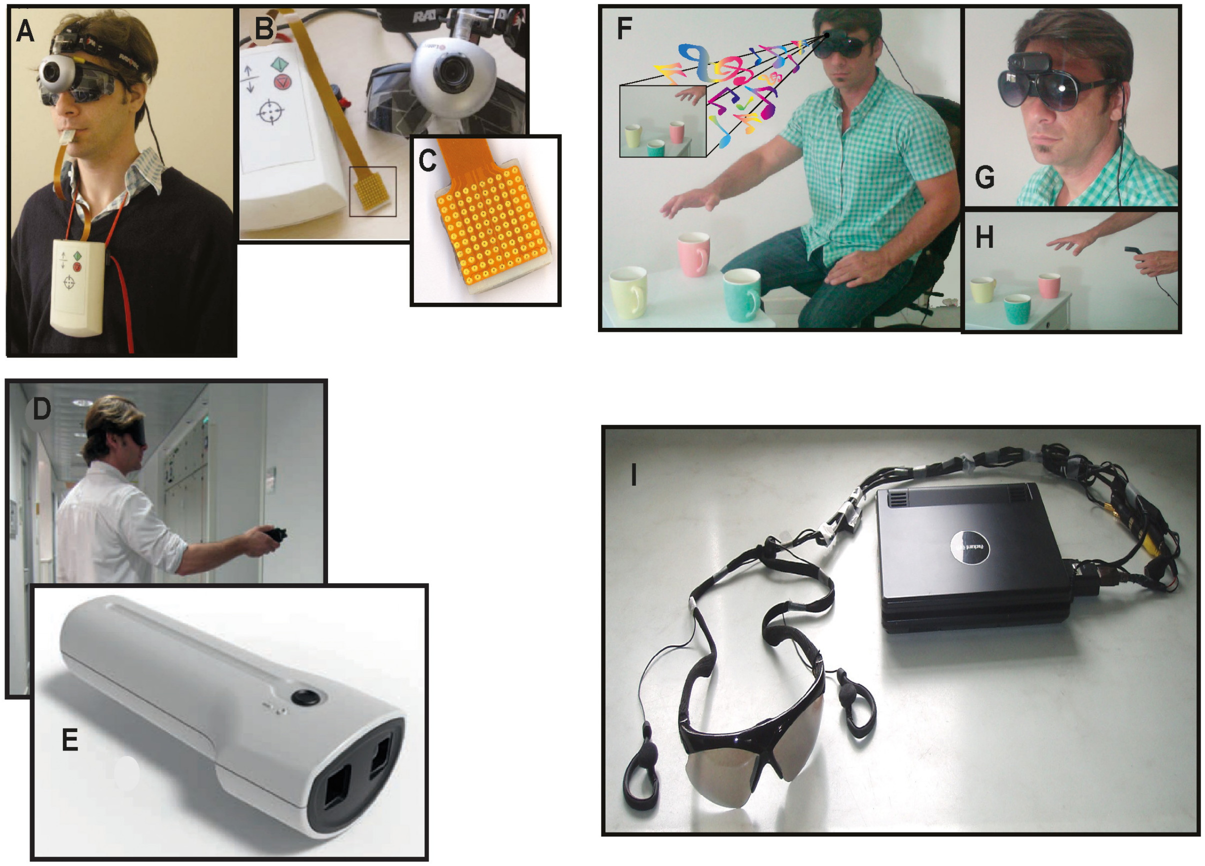
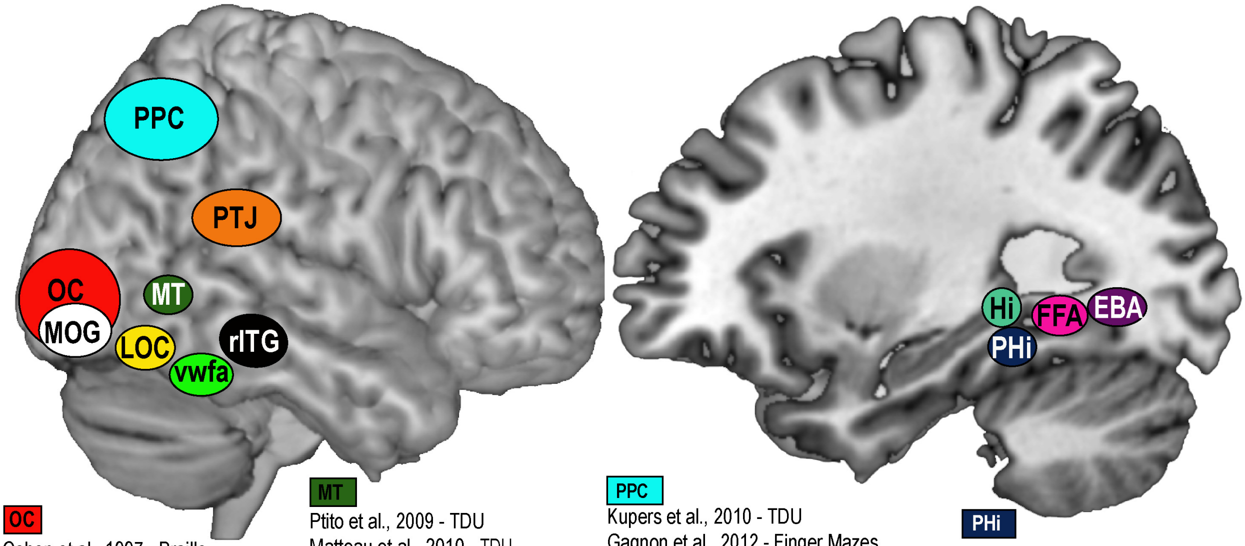


FIGURE 1 | Sensory Substitution Devices (SSDs). Examples of the experimental setup for several different sensory substitution devices. **(A–C)** The Tongue Display Unit (TDU). **(A)** The camera mounted on a pair of blindfold-glasses. **(B)** The entire setup with camera, image converter box, and tongue grid. The box, which is worn on the chest, controls the intensity of the electrotactile stimulation. **(C)** The tongue grid. Applied to the tongue, it delivers a tingling sensation through the electrodes. **(D)** A participant holding the EyeCane that delivers vibrations and sounds to indicate the distance to an object. **(E)** The sensors of the EyeCane and device. **(F)** The EyeMusic experimental setup with headphones and camera. **(G)** The head mounted camera of the EyeMusic. **(H)** The EyeMusic converts colors into different sounds, enabling the recognition of the red apple among the green ones. **(I)** vOICe apparatus. Converts visual images into soundscapes (Meijer, 1992).

Animals can use either visual, tactile (Pereira et al., 2007), olfactory (Save et al., 2000), vestibular (Etienne and Jeffery, 2004), or auditory (Ulanovsky and Moss, 2008) cues to navigate (Rauschecker, 1995). Indeed, prolonged visual impairment improves auditory spatial acuity in ferrets (King and Parsons, 2008). Humans on the other hand have mostly relied on the visual sense to navigate, and vision is considered as the most adapted spatio-cognitive sensory modality (Foulke, 1982). Vision is a capital tool to form cognitive maps (Strelow, 1985). The more these cues are salient in terms of color, or shape the easier they are remembered, and the more precise is our representation of the environment (Appleyard, 1970). Vision is thus helpful for spatial representations, and also for obstacle avoidance. When approaching an obstacle, visual cues guide foot placement by constantly updating our distance with the obstacle (Patla, 1998; Patla and Greig, 2006) and adapt our locomotive behavior according to the circumstance (Armand et al., 1998; MacLellan and Patla, 2006). Certain auditory and tactile spatial abilities are also compromised by the lack of visual experience (Zwiers et al., 2001; Gori et al., 2014). For example, CB individuals show auditory and proprioceptive spatial impairments (Cappagli et al., 2017), deficits in auditory spatial localizations (Gori et al., 2014), and in encoding spatial motion (Finocchietti et al., 2015). It is the lack of visual information that leads to differences in the normal development and alignment of cortical and subcortical spatial maps (King and Carlile, 1993; King, 2009) and appropriate integration of the input from the remaining sensory modalities (Cattaneo et al., 2008; Gori et al., 2014). In addition, most of the neuronal networks responsible for spatial tasks are volumetrically reduced (**Figure 3**; Noppeney, 2007; Ptito et al., 2008b) compared to the sighted, including the posterior portion of the hippocampus (Chebat et al., 2007a; Illustrated in **Figure 6A**), which suggests that the taxing demands of learning to navigate without vision drives hippocampal plasticity and volumetric changes in CB (Chebat et al., 2007a; Ptito et al., 2008a; Leporé et al., 2010). Furthermore, there is a cascade of modifications involving other non-visual brain structures that undergo anatomical (Yang et al., 2014), morphological (Park et al., 2009), morphometric (Rombaux et al., 2010; Tomaiuolo et al., 2014; Aguirre et al., 2016;



OC
Cohen et al., 1997 - Braille
Ptito et al., 2005 - TDU
Renier et al., 2005 - TVSS
Amedi et al., 2007 - vOICe
Merabet et al., 2009 - vOICe
Matteau et al., 2010 - TDU
Collignon et al., 2011 - Sounds
Thaler et al., 2011 - Echolocation
Striem-Amit et al., 2012b - vOICe
Arnott et al., 2013 - Echolocation
Crollen et al., 2019 - Arithmetic

MT
Ptito et al., 2009 - TDU
Matteau et al., 2010 - TDU
Striem-Amit 2012b - vOICe

MOG
Renier et al., 2010 - Spatial Task
Arnot et al., 2013 - Echolocation
Collignon et al., 2011 - Sounds

LOC
Amedi et al., 2007 - vOICe
Striem-Amit et al., 2012b - vOICe
Matteau et al,., 2012 TDU

PPC
Kupers et al., 2010 - TDU
Gagnon et al., 2012 - Finger Mazes
Thaler et al., 2011 - Echolocation

PTJ
Halko et al., 2014 - Audio Navigation

rITG
Abboud et al., 2015 - EyeMusic

vwfa
Reich et al., 2011 - vOICe
Striem-Amit et al., 2012a - vOICe
Sigalov et al., 2016- - vOICe

PHi
Milne et al., 2015 - Echoes
Kupers et al., 2010 - TDU Spatial Task
Gagnon et al., 2012 - Finger Mazes

Hi
Gagnon et al., 2009 Finger Mazes

EBA
Striem - Amit & Amedi., 2014 - vOICe

FFA
Fairhall et al., 2017 - Voices

FIGURE 2 | Brain Amodality and Task specificity via SSDs. A schematic representation of task specific sensory independent recruitment of brain areas via SSDs, or other codes (Braille, echolocation, etc.). Placement of brain areas are approximative. PPC, Posterior parietal cortex; OC, Occipital Cortex; MOG, Medial Occipital Gyrus; LOC, Lateral Occipital Gyrus; MT, Medial Temporal; VWFA, Visual Word Form Area; rITG, Right Infero-Temporal Gyrus; PTJ, Parietal Temporal Junction; PHi, Parahippocampus; Hi, Hippocampus; FFA, Fusiform Face area; EBA, Extrastriate Body Area.

Maller et al., 2016), and functional connectivity (Heine et al., 2015) alterations.

Despite these anatomical changes, visual experience is not necessary for the development of topographically organized maps of the face in the intraparietal cortex (Pasqualotto et al., 2018), or for the ability to represent the work space (Nelson et al., 2018). CB can form mental representations of the work space via haptic information as efficiently as sighted people, indicating that this ability does not depend on visual experience (Nelson et al., 2018). People who are congenitally blind are capable of avoiding obstacles (Kellogg, 1962; Chebat et al., 2011, 2020), integrating paths (Loomis et al., 2012), remembering locations (Chebat et al., 2015), and generating cognitive representations of space (Passini et al., 1990; Thinus-Blanc and Gaunet, 1997; Fortin et al., 2006; Chebat et al., 2018a,b). As a consequence, CB maintain the ability to recognize a familiar route and represent spatial information (Marmor and Zaback, 1976; Kerr, 1983; Passini et al., 1990; Loomis et al., 1993; Thinus-Blanc and Gaunet, 1997; Fortin et al., 2006; Leporé et al., 2009). Moreover, CB can even perform better than their blindfolded sighted counterparts in certain spatial tasks (Rieser et al., 1980; Passini et al., 1990; Loomis et al., 1993; Thinus-Blanc and Gaunet, 1997) and navigate by substituting vision with echolocation (Supa et al., 1944; Teng et al., 2012; Kolarik et al., 2017), tactile information (White et al., 1970; Kupers et al., 2010a; Chebat et al., 2011, 2015, 2017), or even proprioceptive information (Juurmaa and Suonio, 1975). Interestingly, neonatal visual deprivation does not impair the cognitive representation of space. Instead, when substituting visual information by the tactile or auditory modality via SSDs, similar performances are observed in CB compared to sighted participants (Chebat et al., 2018a). CB are therefore able to navigate efficiently using either audition (Maidenbaum et al., 2014b,c,d; Chebat et al., 2015; Bell et al., 2019) or touch (Chebat et al., 2007a, 2011, 2020; Kupers et al., 2010b). They can locate objects (Auvray and Myin, 2009; Chebat et al., 2011), navigate around them (Chebat et al., 2011), and even perform as well (Chebat et al., 2015, 2017) or better than the sighted in certain spatial tasks (Loomis et al., 1993; Chebat et al., 2007b, 2015, 2017). These abilities can be further improved with training (Likova and Cacciamani, 2018). For instance, spatial knowledge can be acquired by CB individuals by using sound cues while playing video games and transferred to the real world (Connors et al., 2014). Using the EyeCane (**Figures 1D,E**), congenitally blind participants can learn real and virtual Hebb-Williams mazes as well as their sighted counterparts using vision (Chebat et al., 2015; **Figures 4A,B**). When learning an environment in the virtual

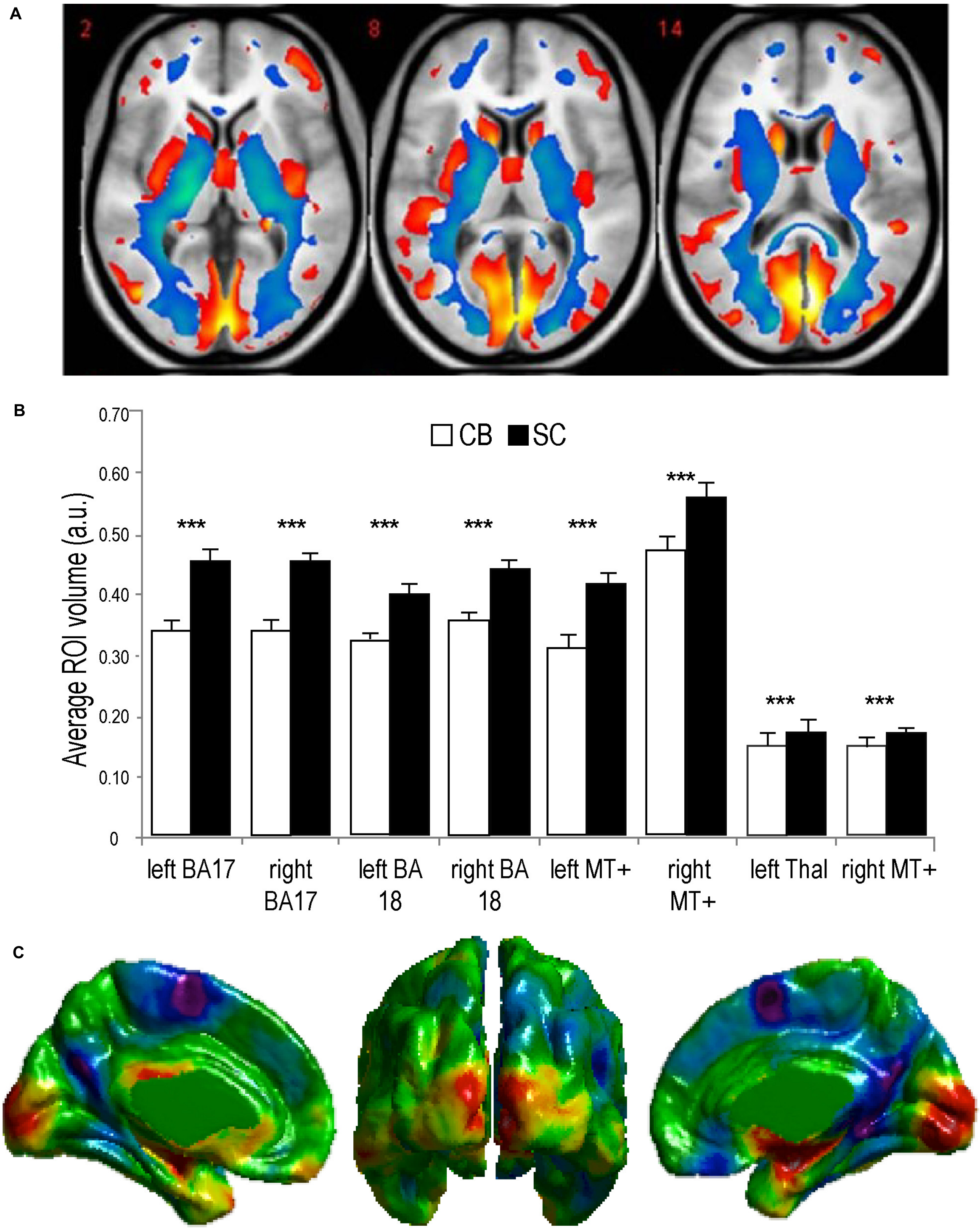


FIGURE 3 | Anatomy of the visual system in congenital Blindness. **(A)** Voxel-based Morphometry results illustrate reductions in white matter projections (blue) and visual cortices (red). **(B)** Bar charts summarize the volumetric reductions in various visual cortical regions for congenitally blind (CB) and sighted controls (SC) (adapted from Ptito et al., 2008b). **(C)** Cortical thickness measurements indicate a thicker visual cortex in CB (adapted from Kupers and Ptito, 2014). ***$p < 0.001$.

world CB participants are able to create a mental map of this environment which enables them to resolve the maze in the real world more efficiently, and vice versa. Moreover, they can transfer the acquired spatial knowledge from real to virtual mazes (and conversely) in the same manner as the sighted (**Figures 4C,D**; Chebat et al., 2017).

Taken together, these results indicate that even if certain specific spatial abilities are deficient in the case of congenital blindness, the resulting deficit in navigation still remains purely perceptual (Vecchi et al., 2004; Amedi et al., 2005), and not as previously suggested a cognitive deficit (von Senden, 1932).

NAVIGATION: STRATEGIES FOR ACQUIRING SPATIAL KNOWLEDGE

Navigation is the ability to find our way in the environment (Sholl, 1996; Maguire et al., 1999) and requires several distinct, yet interrelated skills. Navigation is associated with different perceptual, cognitive and motor networks for path integration, wayfinding or obstacle avoidance and detection. For navigation through the environment, animals and humans alike must translate spatial information into cognitive maps that they compare with an internal egocentric representation (Whitlock et al., 2008). Animals can use strategies to navigate using olfactory indices (Holland et al., 2009), more complex egocentric strategies like the integration of paths based on proprioceptive cues (Etienne and Jeffery, 2004), or strategies relying on complex cognitive maps based on the spatial relation that objects have with one another (O'keefe and Nadel, 1978). Allocentric frames of reference are an abstract coordinate system enabling one to navigate from point to point, whereas an egocentric one does not (Klatzky, 1998).

Several types of labyrinths and mazes (Hebb and Williams, 1946; Barnes et al., 1966; Morris, 1984) and many other variants, including virtual mazes (Shore et al., 2001) have been used to understand the process by which people resolve spatial problems. The Morris maze has particularly been used (Cornwell et al., 2008), often to test the navigational ability of human subjects and its neurological substrates (*see: section on neurological substrates of navigation*). There is, however, a large inter-subjects variability in navigational performances (Wolbers and Hegarty, 2010), that can be attributed to the type and variety of strategies used when navigating. A navigational strategy is defined as a set of functional laws used in order to reach a spatial goal. It influences the way we interact with the environment and our representation of space. In other words, cognitive maps are largely dependent on the employed navigational strategies. Experienced navigators

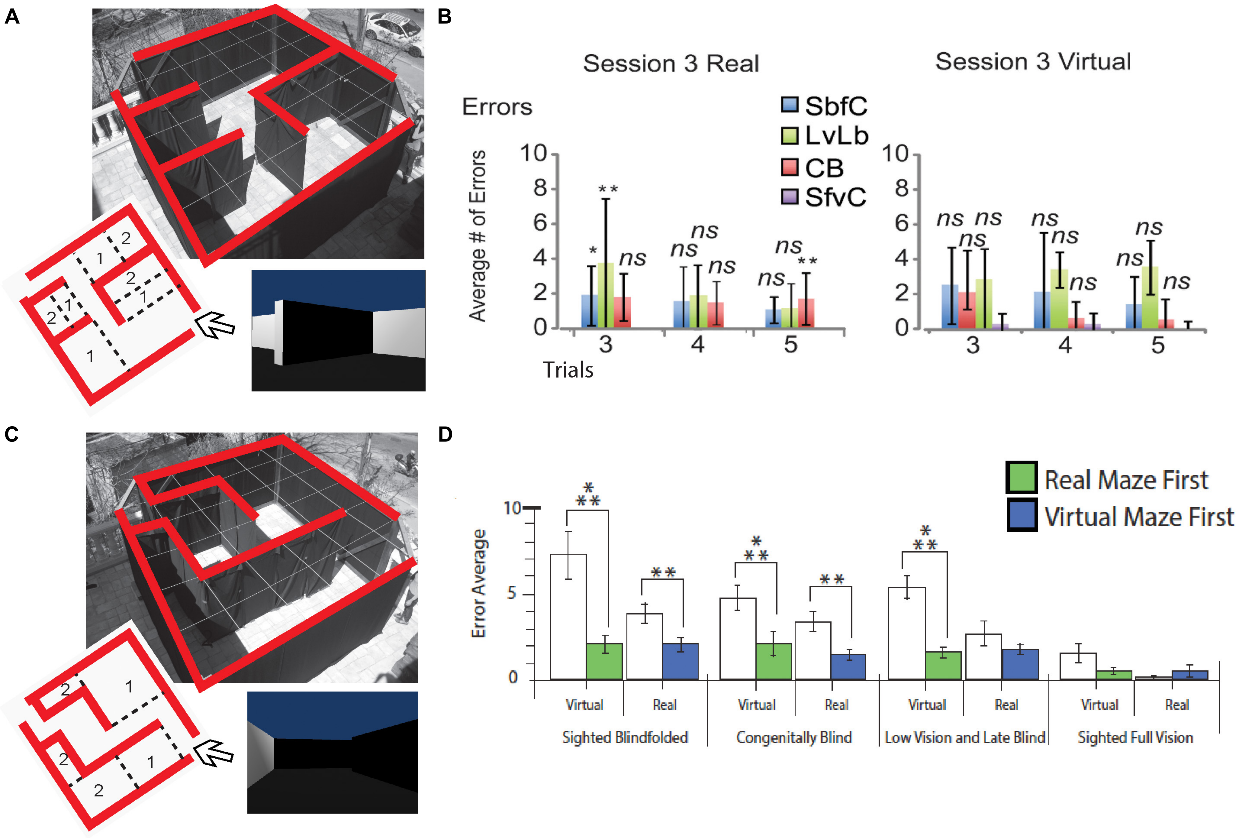


FIGURE 4 | Behavioral Studies. Schematic representation of behavioral studies using the EyeCane. **(A)** A Hebb Williams maze configuration used to test participants' ability to learn a configuration over several days of training in real and virtual environments. **(B)** Behavioral results showing performance for CB, sighted blindfolded controld (SbfC), low vision and late blind participants (LvLb), and sighted full vision controls (SfvC). On the third day of training, there is mostly a lack of statistical difference with the performance of the sighted using vision. **(C)** A Hebb Williams maze configuration used for testing the transfer of spatial knowledge between real and virtual environments and vice versa. **(D)** Behavioral results showing the transfer of spatial knowledge between real and virtual environments and vice versa for CB, and LB (adapted from Chebat et al., 2015, 2017). $^*p < 0.05$ and $^{**}p < 0.01$.

are usually better (Hegarty et al., 2006) since they employ more diverse strategies (Kato and Takeuchi, 2003; Blajenkova et al., 2005), and they are more flexible concerning the strategy to be adopted (Saucier et al., 2003). O'keefe and Nadel (1978) identified different strategies in the behavior of rats while exploring the environment in a Morris water maze. These strategies include the exploration of a novel environment as well as the detection of changes in an already familiar environment, and the ability to make detours or create shortcuts. In sighted humans, three major orientation strategies have been identified using the same paradigm (Kallai et al., 2005). They are characterized by a set of behaviors while looking for a platform in an open space. 1. *Thigmotaxis* (following the wall and approaching the platform); 2. *Turning in circles* (wandering around in circles); 3. *Visual scans* (turning in place to change their view-point); 4. *Enfilade* (accomplishing a quick scan and moving directly to the platform).

In blindness, research on orientation and mobility have identified a series of strategies used in navigation and the exploration of non-familiar environments reminiscent of what has been reported in sighted people (Geruschat and Smith, 1997). Hill et al. (1993) asked blind and low vision participants to explore an open space, find four objects and remember their emplacement. The movement of participants was recorded, quantified and categorized into different strategies. Certain of these strategies apply specifically to people with low vision, and others to blind individuals. Strategies were assigned to five categories for blind participants (Schinazi et al., 2016). 1. *Perimetry* (searching for objects by moving alongside the walls, or the perimeter of the room); 2. *Perimetry toward the center* (moving in concentric circles from the periphery toward the center of the room); 3. *Grid* (exploring the space in a systematic grid-like fashion); 4. *Cyclical* (moving directly from one object to the next); 5. *Perimetry to the object* (moving from the periphery toward the object).

The differences in strategies employed by sighted and blind people reflect the restrictions imposed on navigation without sight; there is no fundamental difference between the strategies employed by the blind and sighted, the only notable difference is that blind people cannot perform visual scans to find their targets, they must rely on encoding of stimuli using egocentric rather than allocentric, coordinates (Röder et al., 2008; Pasqualotto and Proulx, 2012). Although these strategies encourage an egocentric representation of space, and visual experience facilitates allocentric representations (Pasqualotto et al., 2013), it is also possible to achieve an allocentric representation of space without vision. The last two strategies, *cyclical* and *perimetry to the object*, that require an allocentric representation, can only be used by blind people once they have become familiar with the environment using the other strategies.

NEURAL CORRELATES OF NAVIGATION

Sighted people often accomplish tasks of navigation with the greatest ease, like for example going to a well-known destination, or to avoid obstacles in a crowded hallway. This seemingly effortless behavior is in fact the result of the interaction of a complex network of brain regions integrating information from visual, proprioceptive, tactile and auditory sources which translate into the appropriate behavior (Tosoni et al., 2008). The brain takes into consideration information from various senses simultaneously and accomplishes a multitude of operations to enable someone to find their way or step over an obstacle. The hippocampal and parietal cortices are two regions that are traditionally viewed as being related to spatial tasks (Poucet et al., 2003) since they are involved in the processing (Rodriguez, 2010) and in the encoding (Whitlock et al., 2008) of high level spatio-cognitive information, which is crucial for navigation.

The Hippocampus

The hippocampus is part of the medial temporal lobe and is implicated in spatial memory. In the adult monkey, a lesion to the hippocampus results in a deficiency in spatial learning (Lavenex et al., 2006), and in humans, its enlargement predicts learning of a cognitive map (Schinazi et al., 2013), which confirms its functional role in navigation. When implanting electrodes into the medial temporal lobe of rats that can freely move in a maze, pyramidal cells in the hippocampus respond preferentially when the animal is in a precise place (O'Keefe and Dostrovsky, 1971). These place cells, which are mostly found in the posterior part of the hippocampus (O'Keefe and Speakman, 1987; Burgess and O'Keefe, 1996), are organized in functional units that represent space (O'keefe and Nadel, 1978). They are at the origin of cognitive maps of the environment. Space is cartographied using a matrix of pyramidal cells that respond preferentially to places having been already visited (O'Keefe and Burgess, 2005). These maps are allocentric (O'Keefe, 1991) and use the limits of traversable space of their environment (O'Keefe and Burgess, 2005). These cells are also found in the primate (Matsumura et al., 1999) and can represent the position of objects and landmarks of the environment (Rolls and Kesner, 2006). These place cells can also adjust their response according to changes in the environment (Lenck-Santini et al., 2005) and the position of objects in a labyrinth (Smith and Mizumori, 2006). In addition, the prefrontal cortex (PFC) also seems to be sensitive to places, like hippocampal cells (O'Keefe and Dostrovsky, 1971).

In addition to place cells, there also exists populations of cells that are coding for the heading direction (Taube et al., 1990; Oler et al., 2008). Path integration requires that the animal constantly updates its direction during its movements through its trajectory. These cells that code for the direction of an animal are found in the subiculum (Taube et al., 1990), in the striatum (Wiener, 1993) and in the posterior parietal cortex (Chen et al., 1994). These cells compose a sort of internal compass that allows the animal to monitor its direction while traveling.

The Parahippocampal Complex

The human parahippocampus is composed of the entorhinal and perirhinal cortex. This structure surrounds the hippocampus, and the entorhinal cortex is one of the important sources of projection to the hippocampus. It is also implicated in navigation (Aguirre et al., 1996). The entorhinal cortex is composed of Brodmann area 28 and is situated alongside the rhinal sulcus. The grid cells

(Hafting et al., 2005) recorded in the dorsal part of the entorhinal cortex respond preferentially in an organized way and code the environment in the form of a grid. They have receptive fields that are sensitive to different parts of the environment, which are divided in quadrants, like a grid. In opposition to place-cells of the hippocampus, the entorhinal grid-cells code the environment in a geometric fashion (Moser et al., 2008). The hippocampus and the entorhinal cortex cooperate to allow for navigation and we know that this system, when lesioned, perturbs this function (Parron et al., 2006). Indeed, sighted human patients with lesions to the parahippocampus are incapable of learning a new route (Hublet and Demeurisse, 1992; Maguire, 2001). In fact, a case study demonstrates that a lesion to the hippocampus has an effect mostly on the allocentric representation of a path (Holdstock et al., 2000). The parahippocampal area is also involved in the recognition of visual scenes used to navigate (Epstein and Kanwisher, 1998; Epstein et al., 2007). By representing an image of visual scenes to participants in an fMRI scanner, there is an elevation of blood flow in the parahippocampus, leading to the coining of this region as the parahippocampal place area (PPA).

It was later discovered that cells that are sensitive to places are also found in the retrosplenial cortex (RS) (Epstein, 2008). Although RS and PPA are both sensitive to the recognition of visual scenes for navigation, they have complementary, yet different roles (Epstein et al., 2007). The PPA would be more involved in the recognition of scenes, namely the representation of a particular one during navigation, whereas, the retrosplenial cortex serves to situate that scene in the environment. This type of scene recognition is used during navigation to transmit information (an egocentric representation) to a representation of this place on a map (allocentric). The interaction of these two zones during navigation could therefore serve to transform egocentric information of the environment into an allocentric one (Epstein, 2008). These landmarks that are so important for the formation of cognitive maps are coded in the parahippocampus in order to be recognized in their context and by the retrosplenial cortex to be situated in space.

The Parietal Cortex

The parietal cortex allows for several different functions. The anterior part of the parietal cortex is responsible for the integration of somatosensory information (Tommerdahl et al., 2010), and the posterior part (PPC) is implicated in multimodal integration of spatial information (Cohen, 2009), that is used to explore personal space (Mountcastle et al., 1975). PPC is also involved in spatial navigation (Seemungal et al., 2008). Lesion studies in the parietal cortex in rodents (King and Corwin, 1993) and primates (Weniger et al., 2009) demonstrate deficits in the processing of egocentric information: animals cannot integrate a path (Save et al., 2001). The PPC is part of the dorsal visual stream (Mishkin et al., 1983), and enables the perception of movement and the planification of our own movement (Goodale and Milner, 1992). The transformation of our own allocentric representation into a representation centered on the self to plan our movement in space takes place in the PPC (Buneo and Andersen, 2006). In monkeys, neural activity in the parietal cortex is sensitive to the direction of a learned trajectory (Crowe et al., 2004a), and these cells are activated when the animal tries to solve a maze (Crowe et al., 2004b). A recent model on the role of the parietal cortex suggests that it would interact with the hippocampus to select a more appropriate route between two points (planification), and produces a representation that is egocentric of the environment to guide movement between those two points (execution) (Nitz, 2009). Moreover, the parietal cortex interacts with the frontal cortex for the planification and decision making).

Clinical studies also show the importance of the parietal cortex in navigation and spatial representation in general (De Renzi, 1982a,b). Lesions in parietal regions in humans can lead to spatial disorientation (Hublet and Demeurisse, 1992), meaning an inability to find one's way in the environment, and in some occasions even spatial (Vallar and Calzolari, 2018) or personal neglect (Committeri et al., 2018). fMRI studies showed that the parietal cortex is activated multiple times during the navigation process (Spiers and Maguire, 2006). Medio-Parietal regions play an important role in analyzing movement in immediate space and parietal regions play a role in the opacification of movement in space that is not visually accessible (Spiers and Maguire, 2006). This explains why lesions in the parietal lobe interfere with movement in personal space (spatial neglect) and in navigational space (topographical disorientation) as well. Studies using tactile mazes found that the parietal cortex is essential for the acquisition of spatial memory and the planification of movement (Saito and Watanabe, 2006). Indeed, in this task, participants use their parietal cortex only in the encoding of the goal phase of the task, meaning the encoding of the exit and the planification of movement to reach it.

NEURAL ACTIVITY ACCORDING TO THE TYPE OF NAVIGATION STRATEGY

Using fMRI, the hippocampus in humans has been shown to be implicated in navigation (Ghaem et al., 1997). When participants try to solve a maze while in the scanner, the recorded activity is stronger in the right hippocampus (Maguire et al., 1997; Gagnon et al., 2012). Many studies have involved the hippocampus in topographic memory of places (Burgess et al., 2002) and allocentric representations (O'Keefe, 1991; Holdstock et al., 2000). A study demonstrated that the modulation of the interaction between the hippocampus and frontal or parietal regions depends on the type of strategy used in navigation (Mellet et al., 2000). Indeed, it is confirmed that the cortical activity in navigation tasks depends on the ability and strategies used by participants (Ohnishi et al., 2006). In addition, the cerebellum has also been linked to navigational tasks (Rondi-Reig et al., 2014).

There are also differences between men and women according to the strategy used to navigate (Grön et al., 2000). Men and women do not employ the same strategies when navigating, and men perform in general better than women (Astur et al., 1998). These differences are attributable to the fact that men employ strategies that are mostly allocentric and that women use more egocentric strategies to navigate (Sandstrom et al., 1998). BOLD responses differ when the mental navigation of maps are allocentric or from an egocentric viewpoint of a route

(Mellet et al., 2000). Indeed, positron emission tomography (PET) shows that the hippocampus on the right side and the fronto-parietal network are recruited for both egocentric and allocentric representations (Galati et al., 2000; Zaehle et al., 2007). The PPA is activated bilaterally only for egocentric tasks. Using fMRI, different activations for egocentric and allocentric navigations are also found, but with certain nuances (Shelton and Gabrieli, 2004). In a fMRI study, Holdstock et al. (2000) reported that the hippocampus is more activated by allocentric tasks, and confirmed previous data reported in humans and animals (O'Keefe, 1991). In this study, the authors show that a parietal network is involved in navigation in both conditions, but that the frontal region is only present in the egocentric condition. It was found that participants that performed well in spatial tasks use allocentric strategies that are positively correlated with the medial temporal lobe (hippocampus). In opposition participants that performed poorly activated the parietal cortex and used more egocentric strategies (Ohnishi et al., 2006).

THE IMPACT OF VISUAL DEPRIVATION ON SPATIAL COMPETENCE: THE CASE FOR THE CONVERGENT MODEL

What happens then when someone is deprived of vision since birth? It is more difficult to gather sensory information in the absence of vision, and that information is harder to interpret, but spatial representations and competence can still be achieved. If sensory information is substituted with a different modality, the convergent model (Schinazi et al., 2016) suggests that spatial competence can be acquired faster (**Figure 5**).

Theories on the Acquisition of Spatial Competence in Blindness

Interestingly enough, as early as 1779, Diderot noted in his *letter on the blind*, the ability of certain non-sighted people to orient themselves in space without the aid of a cane, and that they had a certain innate sense for the perception of obstacles. In 1944, studies at Cornell University (Supa et al., 1944) showed that blind people were capable of detecting obstacles only when they were provided auditory information. The absence of tactile information did not perturb their obstacle detection sense, but the absence of any auditory information was detrimental to their performance. This hypothesis was confirmed by Ammons et al. (1953) who showed that in blind people in whom the auditory input was blocked, there was an inability to perceive obstacles. They concluded that audition was a crucial factor for navigation in blindness. This phenomenon is called echolocation. Blind people still use this technique by tapping their cane on the ground, clapping their hands or making clicking sounds with their tongue to perceive echoes. Kellogg (1962) was the first to quantify this ability. He measured the sensitivity of blind and sighted volunteers to the variation of size, distance and texture of objects perceived only with auditory echoes. He demonstrated that blind people had significantly superior results compared to the sighted in terms of their ability to detect objects, their texture and distance (Kellogg, 1962). These results were reproduced (Strelow and Brabyn, 1982), but it was demonstrated that although the CB outperformed their sighted blindfolded counterparts, their ability was way below that of the sighted using vision.

Theories on the acquisition of spatial competence in blindness can be classified into three main categories, that is either cumulative, persistent or convergent (**Figure 5**; Schinazi et al., 2016). It is evident that without visual cues, the acquisition of spatial knowledge concerning an environment and eventual spatial competence can be impaired, but to what extent? The cumulative model and persistent models hold that errors made when acquiring spatial knowledge, and thus also spatial competence, in an environment leads to further errors that are either persistently or cumulatively further away from the performance of their sighted counterparts having received as much spatial experience in the same environment. The convergent model considers that although it may take more time for CB people to gain spatial information and spatial competence, eventually their spatial competence will converge with that of the sighted. For a long time, the literature on the subject of congenital blindness has entertained the idea that people who are blind from birth were deficient or ineffective in their ability to comprehend space (von Senden, 1932). The deficiency theory proposes (see both the cumulative and deficient model in **Figure 5**) that people who are congenitally blind are either incapable of, or inefficient in their ability to develop mental representations of space and environment. According to this theory, this inability to form efficient cognitive maps is due to the use of tactile, proprioceptive, or auditory cues that are not useful in creating these maps. Blindness leads to a diminution in autonomy because of a deficit in orientation in space and mobility. It is evident that it is harder to navigate without the appropriate information furnished by vision. This inability to navigate alone is of course a handicap that is important for blind people (Loomis et al., 1993), who have difficulty in understanding certain concepts relating to space (Rieser et al., 1980), and in making mental rotations (Ungar et al., 1995; Fortin et al., 2006). Further evidence that would seem to support this view comes from volumetric studies of the hippocampus in CB. The posterior end of the right hippocampus is volumetrically reduced in CB (Chebat et al., 2007a; **Figure 6A**), precisely in the same area that is usually associated with navigation in humans (Duarte et al., 2014). The hippocampus is composed of many different distinct cellular layers (**Figure 6B**), and it is unknown which ones drive the volumetric reductions in CB. Despite these behavioral findings and volumetric differences, people who are blind, even those without any visual experience, are able to represent familiar spaces, and have an overall good understanding of large spaces (Casey, 1978). In opposition to the *deficiency theories* concerning spatial competence acquisition, there are also many different studies that seem to support the *convergent* model of spatial acquisition. For example, CB process spectral cues more efficiently than the sighted (Doucet et al., 2005), and can process auditory syllables more efficiently (Topalidis et al., 2020), have better sound pitch discrimination (Gougoux et al., 2004), are better at locating sound sources

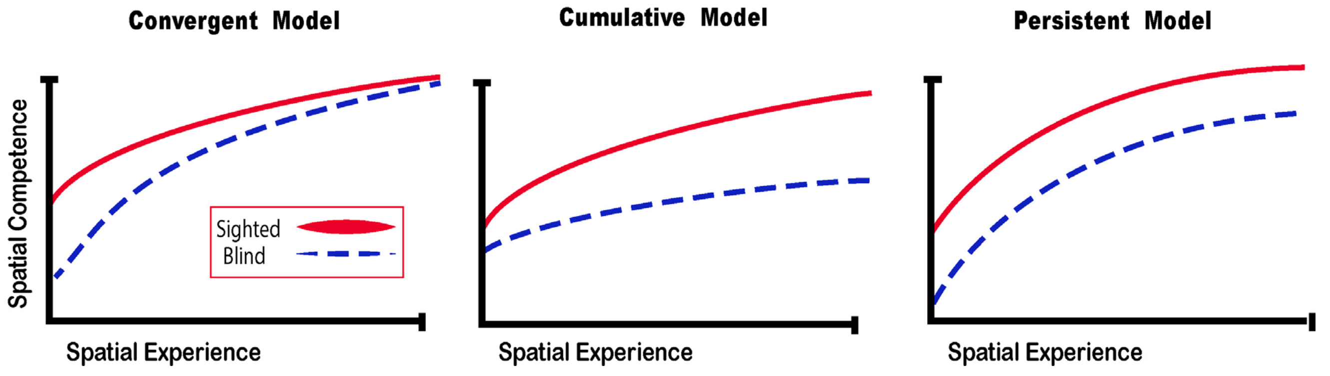


FIGURE 5 | Spatial Competence Acquisition Models for the Blind. The convergent model holds that spatial competence of CB in novel environments eventually reaches the level of the sighted with enough experience. The cumulative model considers that errors made by blind people when exploring space are cumulative, therefore even by acquiring more spatial experience, their spatial competence can never equal that of the sighted. The persistent model projects that errors made by the blind during spatial explorations are persistent and that their spatial competence remains below that of the sighted. In this review, we argue for the convergent model for the acquisition of spatial competence by the blind (adapted from Schinazi et al., 2016).

than the sighted (Lessard et al., 1998), more accurate sound localization than the sighted (Lewald, 2007), improved auditory spatial tuning (Röder et al., 1999), and even supra normal auditory abilities in far space (Voss et al., 2004), possibly by recruiting mechanisms of cross-modal brain plasticity to process auditory information (Collignon et al., 2009). Furthermore, it is possible to form a mental layout of space in a virtual task using echo-acoustic information (Dodsworth et al., 2020). It is therefore not a question of a deficit at the level of the mental representation of space. In an environment that does not enable the advantages of visual navigation (i.e., in a maze where the walls were at arm's length, so that subjects could touch them), the performance of blind subjects was equal to, or even surpassed that of the sighted (Passini et al., 1990; Fortin et al., 2008). Far from being deficient in spatial tasks, nor in their comprehension of space in general, people who are blind may have a different comprehension of space generated by other senses and therefore develop other strategies to represent and configure space (Thinus-Blanc and Gaunet, 1997).

Spatial Perception Strategies and Sensory Substitution Devices

In the same way that the physiology of the brain shapes vision, the engineering of each different SSD sets limitations on the type and quality of visual information available. The angle of the camera-sensor (field of view) for example or nature of the sensor information (distance information vs. contrast information or edges of objects) and the way this information is conveyed, influence how the SSD user explores the environment (Bermejo et al., 2015). Regardless of the type of visual information transferred, or the modality used by the device (tactile or auditory), the distal attribution process is a crucial step in developing strategies when using SSDs (Siegle and Warren, 2010). This process allows the user to attribute an external cause to the sensation provided by the SSD (Hartcher-O'Brien and Auvray, 2014). When this process is complete, the user is able to understand how the information conveyed by the apparatus relates to the representation of the object in space. This leads to the integration and transformation of SSD information into a coherent representation of the world around us (Cecchetti et al., 2016a) allowing blind people to interact with their environment efficiently. Using the vOICe. for example it is possible to recognize and locate objects efficiently (Brown et al., 2011). The strategies developed by blind people when using SSDs to navigate reflects the absence of a cognitive deficiency in representing space (Schinazi et al., 2016). When vision is substituted by tactile or auditory information the type of strategies used by CB and LB resembles the strategies described above used by the sighted, and the spatial updating of auditory scenes mimics the spatial updating of visual scenes (Pasqualotto and Esenkaya, 2016). Indeed, when comparing the strategies used and navigation patterns of sighted and blindfolded sighted participants using the EyeCane in a virtual environment, we find that LB and CB performances can be quite similar to the sighted. The same is true for the paths they use to explore their environments, using a visual strategy to explore real life Hebb-Williams mazes (Maidenbaum et al., 2014b; Chebat et al., 2015). This is surprising given that much of the spatial information is lost when translated into tactile or auditory information (Richardson et al., 2019). It would seem then that even a little spatial information is enough to enable blind people to develop navigation strategies that resemble those employed by the sighted.

Perceptions of Obstacles by Congenitally Blind Individuals

Obstacle avoidance tasks include two separate skills. The ability to understand where the obstacle is in space, and also the ability to walk around it. Pointing tasks have for objective the evaluation of knowledge of participants on directional relations between places. These tasks can help to evaluate the perception of space (Kelly et al., 2004), the perception of movement (Israël et al., 1996; Philbeck et al., 2006) and the spatial memory to plan and accomplish a movement. One can ask the participant to move

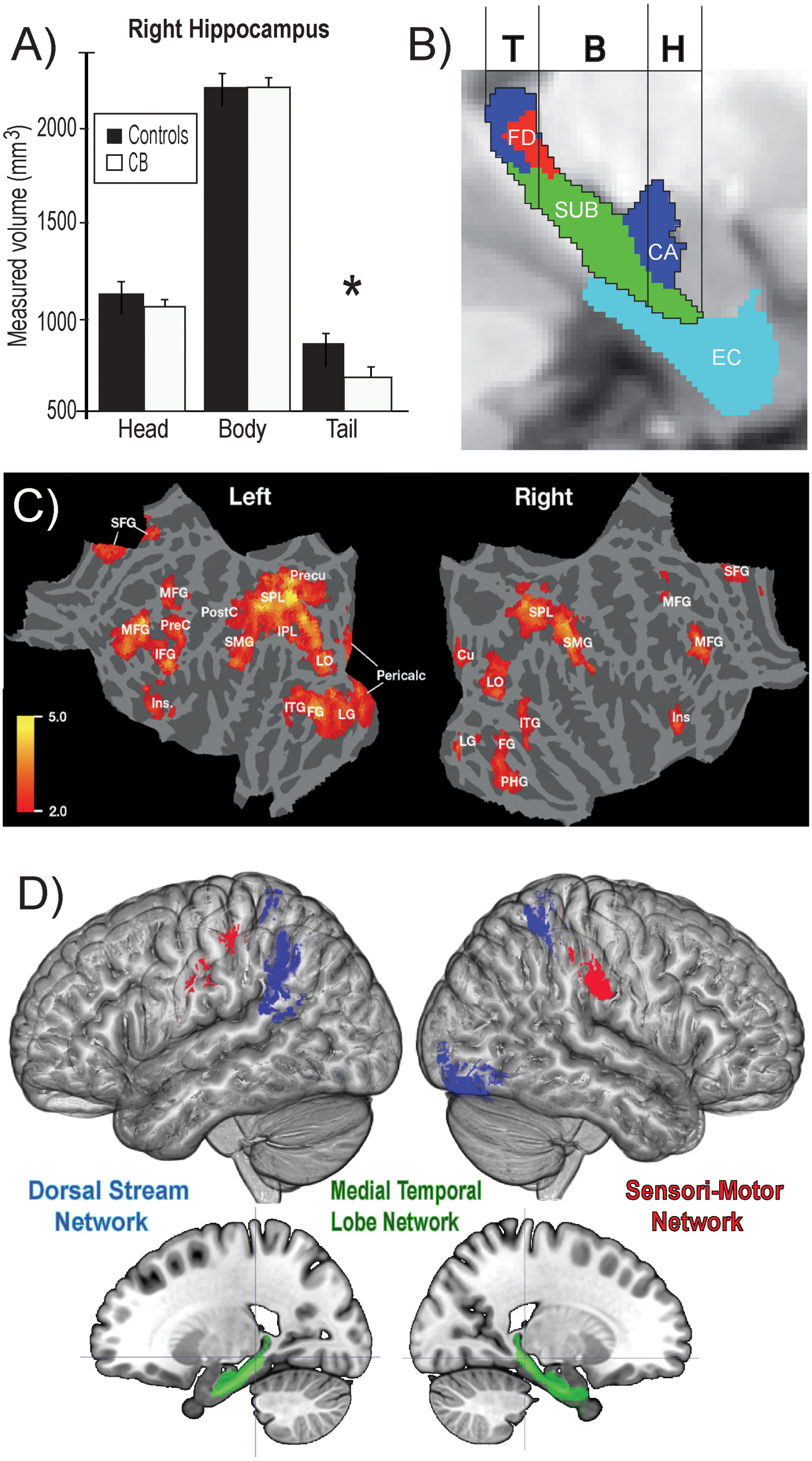


FIGURE 6 | Summary of findings on the neural correlates of navigation in the blind. **(A)** Volumetric reductions in the head of the hippocampus of CB. **(B)** Different cellular layers of the hippocampus according to the head, body and tail segmentation. **(C)** Flat mounts showing recruitment of visual areas for navigation by CB. **(D)** Three networks involved in obstacle detection and avoidance in CB and sighted participants. For avoidance, both CB and SC rely on the dorsal stream network, whereas for obstacle detection SC recruit medial temporal lobe structures and CBs additionally recruit a motor network (adapted from Chebat et al., 2007b, 2020; Kupers et al., 2010a). **p* < 0.05.

actively or passively and point toward the starting point. We can also ask the subject to verbally describe the azimuth toward the goal. Physically pointing implies the contribution of the motor network to accomplish the motor action of pointing as well as the spatial task to find your point of origin. Navigation also implies the ability to move in the environment and avoid obstacles on the path. Obstacles can be very large, like the size of a mountain or a building for example, that one must skirt (circle) to get around, or quite small, like a sidewalk that one must step over. In both cases, this implies being able to locate the obstacle on the path and develop a strategy to keep the goal in mind and reach it despite this obstacle.

Using tactile information, CBs are able to detect and avoid obstacles efficiently using a SSD in a real life obstacle course (Chebat et al., 2007a, 2011, 2020). Indeed, CBs have natural adaptive mechanisms to use tactile information *in lieu* of visual information. Using the TDU, for example, CBs outperform their sighted blindfolded counterparts in different tasks including navigation. Work from our laboratory using the TDU in route recognition demonstrated the recruitment of primary visual areas in CB, but not in sighted blindfolded or in LB (Kupers et al., 2010a; **Figure 6C**). In line with these results, CB participants, LB and blindfolded sighted controls learned to use an SSD to navigate in real-life size mazes. We observed that retinotopic regions, including both dorsal-stream regions (e.g., V6) and primary visual cortex regions (e.g., peripheral V1), were selectively recruited for non-visual navigation after the participants mastered the use of the SSD, demonstrating rapid plasticity for non-visual navigation (Maidenbaum et al., 2018). Moreover, the ability of participants to learn to use the SSD to detect and avoid obstacles was positively correlated with the volumes of a network commonly associated with navigation (Chebat et al., 2020; **Figure 6D**). For avoidance, both CB and SC rely on the dorsal stream network, whereas for obstacle detection SC recruit medial temporal lobe structures and CBs additionally recruit a motor network. These results suggest that the blind may rely more on *motor memory* to remember the location of obstacles (Chebat et al., 2020). Similar results were reported by Gagnon et al. (2010) in a tactile maze where the performance of CBs was significantly higher than that of the sighted controls.

FUTURE PERSPECTIVES OF SENSORY SUBSTITUTION DEVICES

The major conclusion of studies on the blind using SSDs is that navigation is indeed possible without any visual experience. Spatial competence can be achieved by blind individuals partly due to mechanisms of brain plasticity, and amodality. Visual deprivation from birth leads to anatomical volumetric reductions of all components of the visual system, from the retina to the thalamic primary visual relay (dorsal lateral geniculate nucleus) (Cecchetti et al., 2016b), the visual cortex and extrastriate cortices including the ventral and dorsal streams (Ptito et al., 2008b). These structures have been shown to reorganize and develop ectopic projections with other sensory cortices mostly touch and audition (reviewed in Kupers and Ptito, 2014; Chebat et al., 2018b; Harrar et al., 2018). Indeed, CB trained with SSDs activate their primary visual cortex (Ptito, 2005) in a tactile orientation task, and the dorsal visual and ventral streams for tactile motion (Ptito et al., 2009) and the perception of tactile form (Ptito et al., 2012). In line with these findings, another study found retinotopic like maps in the visual cortex of expert blind echolocators, providing further evidence for the task specific organization of the brain (Norman and Thaler, 2019). It seems therefore that CB can compensate for the loss of vision by using other trained senses to invade and recruit the visual cortices. This means that navigational skills are indeed possible through a rewired network of connections that involves the hippocampal/parahippocampal network (Kupers et al., 2010a; Kupers and Ptito, 2014). Furthermore, the use of SSDs could possibly greatly enhance spatial competence in people who are blind by supplementing missing visual information and allowing for the use of more direct exploration of the environment. This would allow blind people to form allocentric representations of space more quickly and efficiently. Indeed, according to a convergent model of spatial competence in CB, by being able to acquire more spatial information in relatively less time via SSDs, CB may be able achieve spatial competence more rapidly.

We conclude here on the future of SSDs and their efficacy for substituting vision in a natural environment. To date, all studies have focused on laboratory settings (Elli et al., 2014) with carefully controlled environments and have furnished encouraging results. However, as all available SSDs suffer from methodological shortcomings from their technology to their adaptability to the environment, it may take a while before we see their widespread use (Chebat et al., 2018a). Current trends investigating the impact of personality traits on SSD use (Richardson et al., 2020) will surely lead to better, more adaptable and customizable devices. Another important question concerns the ideal age to start training with SSDs. Indeed, the developmental aspect is crucial to SSD studies (Aitken and Bower, 1983; Strelow and Warren, 1985), and training children from a very young age could prove to be very beneficial from a behavioral point of view. Most studies using SSDs to explore mechanisms of brain plasticity do so with the training of people well beyond the critical period. Considering that the human brain is much more plastic before the critical period (Cohen et al., 1999; Sadato et al., 2002), it would be very interesting to investigate what congenitally blind children can achieve using SSDs (Strelow and Warren, 1985; Humphrey et al., 1988) compared to sighted adults (Gori et al., 2016). Future studies should also concentrate on studies in acquired blindness in later age, taking into account the onset and duration of blindness. It would also be interesting to investigate the impact of the sophistication (ease of use of devices) and personalization (adapted to each individual) of task specific SSDs.

In order for SSDs to become widespread there is a need to move experiments from the laboratory setting (Elli et al., 2014; Maidenbaum et al., 2014a) to real environments. Also, it would be useful to take advantage of virtual reality to train people with SSDs (Kupers et al., 2010b; Chebat et al., 2015; Baker et al., 2019;

Netzer et al., 2019; Yazzolino et al., 2019; Siu et al., 2020) and explore their ability to transfer spatial knowledge between real and virtual environments (Chebat et al., 2017; Guerreiro et al., 2020). Given that these devices are totally non-invasive compared to other highly invasive techniques like surgical implants (retinal or cortical), efforts should be pursued in developing high quality SSDs that will improve the quality of life of the blind.

ETHICS STATEMENT

Written, informed consent was obtained for the publication of any identifiable data and images.

AUTHOR CONTRIBUTIONS

All authors collaborated for many years on the topic of sensory substitution and cross modal plasticity, contributed equally to the conception, and writing of this review.

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Years of Blindness Lead to "Visualize" Space Through Time

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Spatial representation has been widely studied in early blindness, whereas research about late blindness is still limited. We recently demonstrated that the early (50–90 ms) event-related potential (ERP) response observed in sighted people during a spatial bisection task, is altered in early blind people and is influenced by the amount of time spent without vision in late blind individuals. Specifically, in late blind people a shorter period of blindness is associated with strong contralateral activation in occipital cortex and good performance during the spatial task–similar to that of sighted people. In contrast, non-lateralized occipital activation and lower performance characterize late blind individuals who have experienced a longer period of blindness–similar to that of early blind people. However, the same early occipital response activated in sighted individuals by spatial cues has been found to be activated by temporal cues in early blind individuals. Here, we investigate whether a similar temporal attraction can explain the neural and behavioral changes observed after many years of blindness in late blind people. An EEG recording was taken during a spatial bisection task where coherent and conflicting spatio-temporal information was presented. In participants with long blindness duration, the early recruitment of both visual and auditory areas is sensitive to temporal instead of spatial coordinates. These findings highlight some limits of neuroplasticity. Perceptual advantages from cross-sensory calibration during development seem to be subsequently lost following years of visual deprivation. This result has important implications for clinical outcomes following late blindness, highlighting the importance of timing in intervention and rehabilitation programs that activate compensatory strategies soon after sensory loss.

Keywords: spatial perception, temporal perception, late blindness, EEG, auditory processing

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INTRODUCTION

From birth, infants gradually learn to combine the spatial information arriving from their sensory modalities into a coherent multisensory representation of space (Bremner et al., 2008). The visual modality has a fundamental role in this process, making it possible to obtain an instant and exhaustive representation of the surrounding environment in a single frame (Tinti et al., 2006). Given the importance of visual experience, what happens to spatial representation when visual input is missing is a key question (e.g., Ricciardi et al., 2020).

Spatial representation has been extensively studied in early blindness (for a review, Voss, 2016). Studies reveal conflicting results about spatial performance following early visual loss. On the one hand, blindness can lead to the functional recruitment of visual areas and to enhance the remaining senses (e.g., Gougoux et al., 2004). On the other hand, studies suggest that the lack of visual input negatively affects some additional spatial processing (e.g., Gori et al., 2014). The study of late blindness has often been neglected (for a review, Voss, 2013). Since late blind (LB) people experience visual calibration in childhood and blindness in adulthood, study of their spatial reasoning can deepen our knowledge about the role of visual experience and deprivation on the way in which the brain builds spatial representations. The intersection of visual experience and deprivation leads to peculiar spatial skills and neural correlates, in some cases similar to those of sighted people (e.g., Wanet and Veraart, 1985; Finocchietti et al., 2015b) and in others resembling those of early blind individuals (e.g., Voss et al., 2004; Fieger et al., 2006).

A consistent body of literature on late blindness has focused on the age of blindness onset to investigate critical time windows where visual experience is necessary to develop specific abilities (e.g., Li et al., 2013, 2016). Interestingly, we have recently demonstrated that, in a complex spatial task, years of blindness matter more than the age of onset (Amadeo et al., 2019). Specifically, we observed that neural activation associated with the behavioral performance of LB people during a spatial bisection task was influenced by the amount of time spent without vision (or, blindness duration, BD). The spatial bisection task consists of listening to a sequence of three sounds and judging the relative spatial position of the second sound with respect to the other two sounds. The second sound is crucial to perform the bisection task because it represents the initial point for the construction of a spatial metric. We observed that immediately after vision loss, performance and neural correlates of LB individuals are similar to those of sighted people. They succeed in the task, and exhibit the same early (50–90 ms) contralateral activation observed in the occipital areas of sighted individuals after the second sound of the spatial bisection (Campus et al., 2017). Yet, with years of visual deprivation, spatial bisection skills and neural correlates of LB people become modified. Specifically, after more than 25 years of BD, LB individuals show a weaker and non-lateralized occipital response to the second sound, and an associated lower performance. The same neural pattern of response has been previously observed in early blind people, who are unable to perform the task (Campus et al., 2019).

Furthermore, when early visual experience is lacking, people use a different strategy to represent complex configurations of space (Gori et al., 2018, 2020b). In fact, early blind people are strongly influenced by temporal representations of events when inferring auditory spatial representations. Manipulating spatial and temporal coordinates of sounds during a spatial bisection task reveals this. We created conditions of coherence between space and time by associating a short/long spatial distance between two sounds with a short/long temporal interval between them. With spatiotemporal coherence, the spatial bisection deficit of early blind people disappeared. Moreover, under these conditions, the same early contralateral occipital response observed in sighted individuals was present. Thus, occipital activation selective for the spatial position of the second sound in the spatial bisection task is observed in early blind individuals when temporal cues are informative about space. We also created conditions of conflict between space and time associating a short spatial distance between sounds with a long temporal interval between them, and similarly a long spatial distance with a short temporal interval. When conflicting spatiotemporal information was presented, the behavioral deficit of early blind people increased. Further, at the cortical level, while the early contralateral occipital response was still present in early blind people, its topography was inverted. Namely, the topography appeared based on the virtual position of the second stimulus as defined by its temporal delay. Interestingly, the auditory cortical response of early blind individuals was similarly contralateral to the position of the second sound as indicated by the temporal delay. These results suggest that the same circuits responding to spatial cues in sighted individuals may be sensitive to temporal cues following early visual deprivation. Audition is the most reliable sense for temporal representation (e.g., Burr et al., 2009). It could be that when the visual calibration of the auditory space is missing during childhood (see cross-calibration theory, Burr and Gori, 2012), the auditory modality strongly adheres to the temporal domain. This could result in auditory spatial maps based on a temporal coordinate system when visual experience is missing.

Given that LB individuals with a long BD closely resemble early blind individuals in the spatial bisection task, we tested whether a similar temporal dominance could explain the neural and behavioral changes driven by years of blindness in LB individuals. To this end, we replicated the experimental paradigm previously performed with early blind people with LB participants with different years of BD. Electroencephalographic (EEG) and psychophysical responses were recorded during a spatial bisection task when coherent and conflicting spatiotemporal cues were delivered. As in previous studies (Amadeo et al., 2019; Campus et al., 2019), we performed a temporal bisection task as a control experiment, where the subject evaluated temporal intervals instead of spatial distances between three sounds. Results suggest that BD in LB individuals is associated with a tendency to build spatial maps relying on temporal information during the spatial bisection task.

MATERIALS AND METHODS

Participants

The sample consisted of 12 late-onset (LB) blind individuals [mean age ± standard deviation (*SD*): 50.25 ± 15.85 years; females = 3, see **Table 1** for clinical details], and 12 blindfolded sighted (S) individuals [48.52 ± 13.56 years; *t*-test for age: $t(21.5) = -0.33$, $p = 0.7$]. Age of blindness onset ranged from 6 to 51 (24.75 ± 15.82) years of age, and BD ranged from 5 to 54 (25.5 ± 15.29) years. All blind subjects were completely blind and lacked hearing problems (this was verified prior to testing). Participants involved in the study were the same LB and

TABLE 1 | Clinical details of the late blind participants ($N = 12$).

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

For each participant, data from left to right are chronological age, gender, pathology, age of blindness onset, and years of blindness duration (i.e., number of years spent without vision).

sighted individuals that took part in our previous experiment (see Amadeo et al., 2019). Written informed consent was required prior to participation. The experiment was conducted in accordance with the Declaration of Helsinki, after ethics approval from the local health committee (Comitato Etico Regione Liguria).

Stimuli and Procedure

Participants performed a spatial and a temporal bisection task. They sat in front of a set of free-field speakers placed in the lower visual hemifield. Three stimuli were played at three different spatial positions (**Figure 1A**) and times (**Figure 1B**). Stimuli consisted of sounds with the following characteristics: 500 Hz, 75 ms duration, 60 dB SPL at the subject position. The first sound (S1) was delivered at -25°, while the third sound (S3) was delivered at + 25° (with 0° representing the central speaker, negative values on the left and positive values on the right). The temporal interval between S1 and S3 was fixed at 1.5 s. The second sound (S2) could be played from either -4.5° (left) or 4.5° (right; **Figure 1A**) in space, and independently at either -250 ms or + 250 ms in time (**Figure 1B**; with 0 ms representing the middle of the temporal sequence). These values were chosen based on previous literature (e.g., Amadeo et al., 2019; Campus et al., 2019). The task consisted of evaluating either the spatial distances (spatial bisection) or the temporal intervals (temporal bisection) between the three sounds. Specifically, participants had to answer if the distance/interval between S1 and S2 (i.e., the first distance/interval) was smaller or larger than the distance/interval between S2 and S3 (i.e., the second distance/interval). Presentation order of the spatial and temporal bisection tasks was randomized between subjects. A trial with S2 played from the left (-4.5°) side of the subject (a smaller first distance) is referred to as "narrow" space, while that with S2 played from the right (+ 4.5°) side of the subject (a larger first distance) is referred to as "wide" space. Similarly, S2 played sooner (-250 m) is referred to as "short" time, while S2 played later (+ 250 ms) is referred to as "long" time.

Thus, four conditions were possible: (1) S2 from -4.50° at -250 ms (i.e., *narrowSpace_shortTime*: first distance/interval narrow in space and short in time), (2) S2 from -4.50° at + 250 ms (i.e., *narrowSpace_longTime*: first distance/interval narrow in space and long in time), (3) S2 from + 4.50° at -250 ms (i.e., *wideSpace_shortTime*: first distance/interval wide in space and short in time), and (4) S2 from + 4.50° at + 250 ms (i.e., *wideSpace_longTime*: first distance/interval wide in space and long in time). Exactly the same stimuli were used in the temporal and spatial bisection tasks, and each bisection task consisted of 60 trials per condition (i.e., 240 trials). An S2 was also delivered at 0° and at 0 ms during catch trials (i.e., *equalSpace_equalTime*; number of catch trials = 15). Inter-trial interval was 1250 ± 250 ms. Subjects were instructed to answer by pressing the appropriate button when all the three sounds were delivered, i.e., after S3. The time employed to answer was recorded to ensure participants were engaged in the task. For more information about setup and procedure refer to Gori et al. (2020b).

EEG Data Collection and Preprocessing

We recorded high-density EEG from 64 scalp electrodes with the Biosemi ActiveTwo EEG System (**Figure 1B**). Data were acquired at 2048 Hz and then downsampled to 512 Hz after band pass filtering from DC to 134 Hz. Two additional electrodes were used (left/right outer canthi) to check ocular movements. The EEG was filtered between 0.1 and 100 Hz. To remove stereotypical and non-stereotypical transient high-amplitude artifacts, we applied the Artifact Subspace Reconstruction technique implemented by the EEGLAB plug-in (Delorme and Makeig, 2004; Mullen et al., 2013). We kept all parameters at default values except that we used a sliding window of 500 ms. Independent Component Analysis was used to clean the EEG data (Delorme and Makeig, 2004); specifically, we used SASICA (Chaumon et al., 2015) and IC_MARC (Frølich et al., 2015), two EEGLAB toolboxes. We kept all parameters at their default and referred to validation papers for component rejection. We used the mean of left and right mastoids as reference. For more information about EEG data processing refer to Gori et al. (2020b).

Behavioral and EEG Data Analysis

We wished to test if, with increasing BD, temporal cues during a spatial bisection task alter performance and recruitment of the visual and auditory cortices of LB individuals in a manner similar to that seen in early blind individuals (Gori et al., 2020b). In fact, we previously showed that in early blind people the second sound (S2) of the spatial bisection does not produce the early contralateral occipital activation observed in sighted individuals (Campus et al., 2019). A similar pattern characterizes LB subjects that spent many years without seeing (Amadeo et al., 2019), but not LB subjects that recently lost sight. The lack of this response has been proposed as the neural correlate of a low performance at the task. However, by adding coherent or conflicting temporal cues in the spatial bisection task, we noticed that, in early blind people, the same early occipital response is elicited by temporal cues (Gori et al., 2020b). To test whether the same mechanism characterizes performance and cortical recruitment

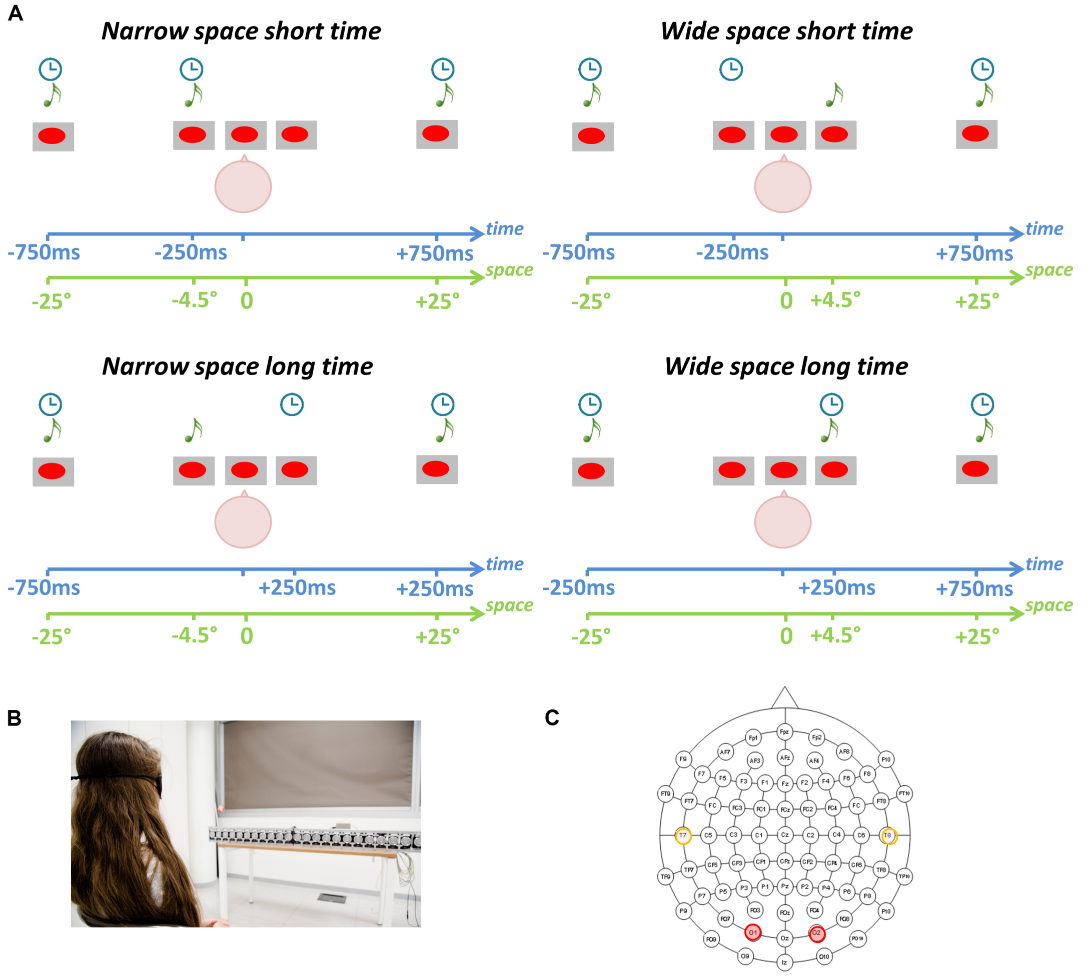

FIGURE 1 | Spatial and temporal bisection tasks. **(A)** Experimental paradigm. Three sounds (S1, S2, S3) were played from three spatial positions and at three different time points. Participants evaluated the relative position of S2 in space (spatial bisection) or time (temporal bisection) with respect to the other two sounds (S1 and S3). Stating that 0° represents the central speaker, S1 was always played from -25° (i.e., left) while S3 was always played from + 25° (i.e., right). Stating that 0 ms represents the halfway point of the trial duration, S1 was always played at -750 ms while S3 was always played at + 750 ms. Based on the condition, S2 was played randomly and independently from ± 4.5° in space and at ± 250 ms. The interaction of spatial and temporal coordinates of S2 leads to four conditions: (i) *narrowSpace_shortTime*: S2 from -4.50° at -250 ms (Top Left); (ii) *narrowSpace_longTime*: S2 from -4.50° at + 250 ms (Bottom Left); (iii) *wideSpace_shortTime*: S2 from + 4.50 at −250 ms (Top Right); (iv) *wideSpace_longTime*: S2 from + 4.50 at + 250 ms (Bottom Right). **(B)** Setup. Participants sat in front of free-field speakers. **(C)** Electrode montage. EEG analyses focused on left (T7) and right (T8) temporal electrodes (orange) and left (O1) and right (O2) occipital electrodes (red).

of LB people with long blindness duration (BD), we added coherent or conflicting temporal cues to the spatial bisection task and focused EEG analyses on the early cortical responses to S2 of the spatial bisection task. We used the responses to S2 during a temporal bisection task as a control to verify that the mechanism is specific to the spatial task.

First of all, statistical analyses were conducted to investigate differences in the behavioral performance (i.e., percentage of correct responses) between S and LB groups in the spatial and temporal bisection task. Prior to perform analyses, logit transformation was applied to percentage of correct responses. For each task (i.e., separately for spatial and temporal bisection tasks), conditions were grouped based on the congruence or incongruence of the spatiotemporal coordinates of S2. This led to two merged conditions: coherent trials (*narrowSpace_shortTime* and *wideSpace_longTime*), and conflicting trials (*narrowSpace_longTime* and *wideSpace_shortTime*). For each bisection task (spatial and temporal), comparisons between percentage of correct responses were done using a two-way ANOVA, with group (S, LB) as a between-subjects factor, and condition (coherent, conflicting) as a within-subjects factor. *Post hoc* comparisons were conducted using two-tailed t-tests, with probabilities treated as significant when lower than 0.05 after Bonferroni correction. If temporal information helps LB people as hypothesized, their performance should be higher in the coherent conditions where temporal cues can be used to correctly perform the task.

At a neurophysiological level, EEG data were averaged encompassing S2 onset. To obtain event-related potentials

(ERPs), we used as baseline a period of 200 ms before the beginning of each trial. After artifact removals, we required a minimum of 40 trials for each of the four spatial and temporal conditions. Catch trials were excluded from statistical analyses. For each ERP the total number of trials was equal to 1410, approximately 59 per subject. Based on our hypothesis (Gori et al., 2020b), we focused our analyses on a time window of 50–90 ms after the sounds, using electrodes involved in visual (O1, O2 in occipital areas) and auditory (T7, T8 in temporal areas) activity (**Figure 1C**). The choice of time window and scalp sites was based on microstate analyses and topographic analysis of covariance conducted in a previous study of spatial bisection skills following late blindness (Amadeo et al., 2019). In addition, we knew from previous studies that spatial bisection skills are reflected by a specific ERP component in the time window between 50 and 90 ms after the second sound (S2) of the task, as well as contralateral occipital electrodes (Campus et al., 2017). To obtain mean ERP amplitude, we averaged the voltage in the selected (50–90 ms) time window.

We focused on spatial performance and neural correlates of LB participants to investigate the influence of BD years. Since we were interested in how the subject's responses related to the stimuli presented, instead of analyzing overall percentage of correct responses in merged conditions (coherent, conflicting), we analyzed the percentage of trials in which the subject perceived the first distance as wider for each condition (i.e., *narrowSpace_shortTime*, *wideSpace_longTime, narrowSpace_longTime*, *wideSpace_shortTime*). For coherent conditions, a narrow (i.e., S2 delivered from the left) and wide (i.e., S2 delivered from the right) first distance in space corresponded to a short and long first interval in time respectively. However, for conflicting conditions, a narrow and wide first distance in space corresponded to a long and short first interval in time respectively. Therefore, in the conflicting conditions, S2 could be physically delivered from the left (i.e., closer to S1) but temporally closer to S3 (i.e., right; *narrowSpace_longTime*). Alternatively, S2 could be physically delivered from the right (i.e., closer to S3) but temporally closer to S1 (i.e., left; *wideSpace_shortTime*). If participants use the temporal information to perform the task, their performance in the conflicting conditions should be based on the virtual position of the second sound, as indicated by the temporal delay rather than actual spatial distance. Since our hypothesis was that after many years of blindness LB people are attracted by the temporal information, we conducted an analysis of covariance (ANCOVA) with: percentage of trials (logit-transformed) in which subject perceived the first distance as wider as the dependent variable, condition as a factor and BD and age of onset as covariates. Based on literature (e.g., Li et al., 2013, 2016), we decided to include age of onset as a covariate to rule out an effect of this variable on results. Based on our prediction, we expected a significant interaction only between condition and BD. Specifically, during the conflicting conditions, with increasing BD, participants should perceive the first distance as wider when the first interval is longer in time, and actually narrower in space. On the other hand, BD should not influence responses in the coherent conditions where spatial and temporal cues are congruent. Thus, for each condition, we subsequently carried out *post hoc* linear regressions between percentage of trials in which the subject perceived the first distance as wide and BD.

Since the neural correlates of spatial bisection skills are well established, we used a similar approach to investigate whether BD influences the ERP response in occipital and temporal areas during the conflicting conditions. For each electrode (O1, O2, T8, T9), we built an ANCOVA with individual mean ERP amplitude in the selected time window as the dependent variable, condition (*narrowSpace_shortTime*, *wideSpace_longTime, narrowSpace_longTime*, *wideSpace_shortTime*) as a factor, and BD and age of onset as covariates. Again, we included age of onset in to account for the possibility that results could be related to this variable. Subsequently, for each electrode and condition of the spatial bisection task, we performed *post hoc* linear regressions between individual mean ERP amplitude in the 50–90 ms time window and years of BD. Indeed, if after many years of blindness individuals use temporal cues to evaluate spatial distances, the ERP response to S2 in the conflicting conditions (*narrowSpace_longTime*, *wideSpace_shortTime*) should gradually invert its topography. For the sake of clarity, we here explicitly predict results based on the case that with increasing BD, people start to answer using the virtual position of S2 suggested by the temporal delay. Given that typically a cortical response is more contralateral to the physical position of a sound, in the condition *narrowSpace_longTime* (i.e., S2 spatially from the left but temporally closer to S3, which is played from the right), the response in O1 and T7 (ipsilateral to the physical spatial position, but contralateral to the virtual position suggested by the temporal delay of the sound) should increase with BD, while the response in O2 and T8 (contralateral to the physical spatial position, but ipsilateral to the virtual position suggested by the temporal delay of the sound) should decrease. Conversely, in the condition *wideSpace_shortTime* (i.e., S2 spatially from the right but temporally closer to S1, which is played from left), the response in O1 and T7 should decrease with BD, while the response in O2 and T8 should increase. Summarizing, we did not expect any effect of BD in the coherent conditions, as the spatial position and temporal delay give congruent information and all participants should be able to perform the task. Thus, only in the conflicting conditions do we expect that with increasing BD, electrodes physically contralateral to the real spatial position of sounds attenuate their response, while those contralateral to the virtual position suggested by the temporal cues show a higher activation.

Scalp topographies of mean ERP amplitude in the 50–90 ms time window were evaluated for each condition of spatial and temporal bisection tasks. Since BD linearly affects neural circuits associated with spatial bisection skills (see also Amadeo et al., 2019), for illustrative purposes only, the median BD (23.5 years) was arbitrarily used to split the sample to visualize 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). The same approach was used to graphically represent ERPs elicited by S2 at occipital (O1, O2) and temporal (T7, T8) electrodes during the spatial bisection task. To further exclude a role of chronological age on results, we run a linear regression analysis to investigate the association between years of blindness and biological age of LB participants.

RESULTS

Overall, results showed that, with increasing blindness duration (BD) years, temporal cues alter performance and recruitment of the visual and auditory cortices of LB individuals during a spatial bisection task. We previously showed the second sound (S2) of the spatial bisection produces an early contralateral occipital activation in sighted individuals but not in early blind people (Campus et al., 2019) or LB people with long BD (Amadeo et al., 2019). However, by adding coherent temporal cues, the same early occipital response is elicited in early blind people (Gori et al., 2020b). Here, we tested whether coherent temporal cues influence performance and cortical recruitment of LB people with long BD.

Behavioral Differences in Performance

Behavioral differences in performance (i.e., percentage of correct responses after logit transformation) between groups showed a strongly significant interaction between group (LB, S) and condition (coherence, conflict) for the spatial [$F(1, 22) = 15.55$, $p < 0.0001$, ges = 0.25] but not the temporal [$F(1, 22) = 4.47$, $p = 0.05$, ges = 0.06] bisection task (**Figure 2**). For the spatial bisection task (**Figure 2** left), the performance of LB participants in conflicting trials is significantly lower than that of sighted people [$t(11.2) = -4.04$, $p = 0.004$], and their own performance in coherent trials [$t(11) = 4.7$, $p = 0.001$]. Although performance of sighted people decreased in conflicting compared to coherent conditions [$t(11) = 23.5$, $p < 0.001$], their performance was always well above chance (i.e., > 75%, mean ± standard error of the mean (SEM), for coherent trials: 91 ± 0.6%; for conflicting trials: 86 ± 0.5%). In contrast, the performance of LB people in conflicting conditions was drastically reduced (for coherent trials: 87 ± 3%; for conflicting trials: 41 ± 7%). For the temporal bisection task (**Figure 2** right), only a main effect of condition was significant [$F(1, 22) = 11.02$, $p = 0.003$, ges = 0.14], reflecting a slight decrease in performance during the conflicting conditions for both groups [for LB: coherent trials: 89.4 ± 3%, conflicting trials: 70.5 ± 6%, $t(11) = 2.7$, p = 0.04; for S: coherent trials: 85.6 ± 0.6%, conflicting trials: 81.9 ± 0.5%, $t(11) = 14.3$, $p < 0.001$]. Thus, behavioral results suggest that LB individuals are specifically sensitive to the spatiotemporal conflicts during spatial judgments and improve their spatial performance when temporal information is aligned with spatial information. In contrast, the cross-domain conflict or coherence during temporal judgments had a similar, negligible influence in both groups.

Impact of Years of Blindness on Spatial Bisection Performance

To investigate the impact of BD years on spatial bisection performance, we took into account each condition before merging for spatiotemporal coherence and conflict. The ANCOVA with percentage of wide first distance indicated as a dependent variable, condition as factor and BD years and age of onset as covariates, revealed a significant interaction between BD and condition [$F(3, 32) = 11.51$, $p < 0.001$]. No significant effect of age at onset emerged [for the main effect of onset: $F(1, 32) = 0.4$, $p > 0.05$; for the interaction between BD, condition and onset: $F(3, 32) = 0.9$, $p > 0.05$]. Given the significant interaction between BD and condition, we performed *post hoc* linear regressions between the logit-transformed percentage of trials in which the first distance was reported as wider and BD, separately for each condition. For coherent conditions (i.e., *narrowSpace_shortTime* and *wideSpace_longTime*), the percentage of wide first distance responses depended on the actual physical spatial position of the sound, which was congruent with the temporal delay. Thus, percentage of wide first distance was unrelated to BD years in the conditions *wideSpace_longTime* [$r = -0.3$, $p > 0.05$] and *narrowSpace_shortTime* [$r = 0.02$, $p > 0.05$]. However, for the conflicting conditions, the percentage of answer wide first distance responses was influenced by BD years. In the condition *narrowSpace_longTime* ($r = 0.7$, $p = 0.01$, **Figure 3** left), LB individuals with shorter BD (i.e., fewer years of visual deprivation) answered based on the real spatial position of the stimulus (i.e., low percentage of wide first distance), despite the long temporal interval. With increasing BD years (i.e., more years of visual deprivation), LB individuals reported a higher percentage of wide first distances, although the first distance was narrow. Since the first temporal interval was longer, we can hypothesize that this result likely happens because the temporal coordinates of the stimulus trick LB participants with long BD. A similar pattern characterized responses in the other conflicting condition, *wideSpace_shortTime* ($r = -0.8$, $p < 0.001$, **Figure 3** right). In this case, the slope of the relationship is reversed: with increasing BD years, the percentage of wide first distance answers decreases. Since the first temporal interval was shorter in this condition, we can again hypothesize that the lower percentage of wide first distance likely happens because the temporal coordinates of the stimulus trick LB participants with long BD. Therefore, individuals with long BD apparently tend to estimate the first spatial distance based on the time interval between the two stimuli.

Impact of Years of Blindness on Neural Correlates of Spatial Bisection

To confirm behavioral findings, we investigated the effect of increasing years of BD on how the cortical response associated with spatial bisection skills is influenced by temporal information. Spatial bisection skills are reflected by an early (50–90 ms) ERP response in occipital areas contralateral to the second sound position in space (Campus et al., 2017), and also in early responses in temporal scalp sites (Gori et al., 2020b). Thus, we focused on the early (50–90 ms) activation after S2 in both occipital (O1, O2) and temporal (T7, T8) scalp sites. For each occipital (O1, O2) and temporal (T7, T8) electrode, a significant interaction between BD and condition was present for mean amplitude in the 50-90 ms time window after S2 [for O1: $F(3, 32) = 29.25$, $p < 0.001$; for O2: $F(3, 32) = 19.29$, $p < 0.001$; for T7:

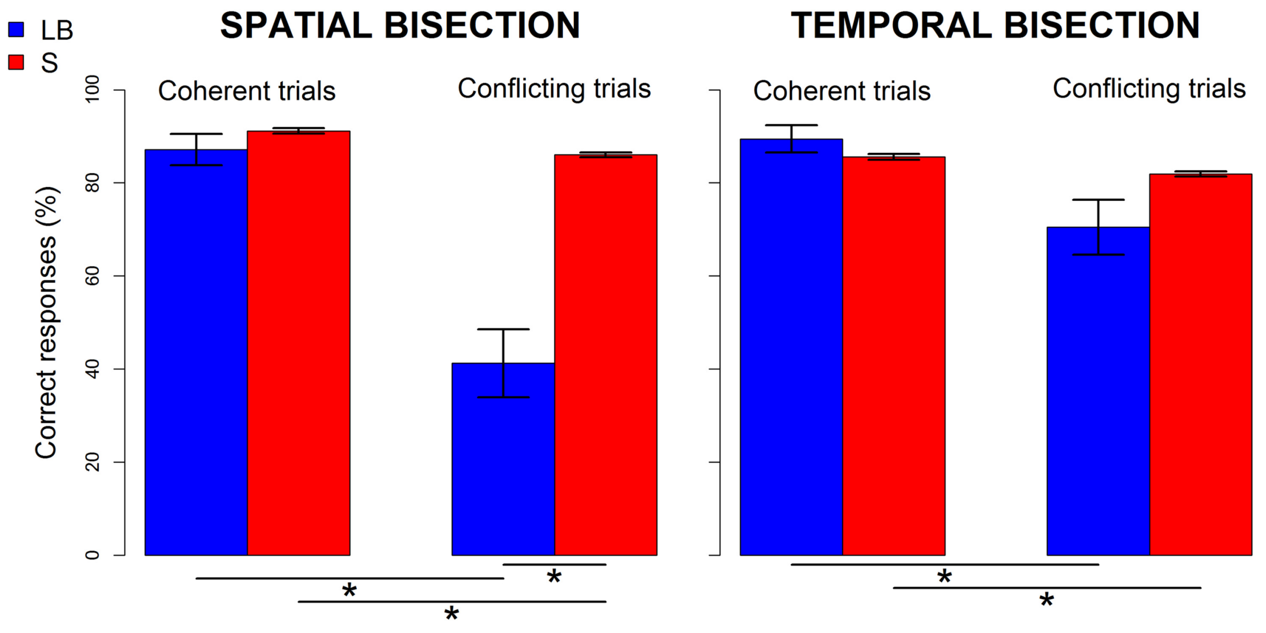

FIGURE 2 | Performance of late blind (LB, blue) and sighted (S, red) individuals in spatial **(left)** and temporal **(right)** bisection tasks. Percentage of correct responses before logit transformation (mean ± SEM) is shown separately for coherent (i.e., *narrowSpace_shortTime* and *wideSpace_longTime*) and conflicting trials (i.e., *narrowSpace_longTime, wideSpace_shortTime*). Stars indicate significant differences ($p < 0.01$).

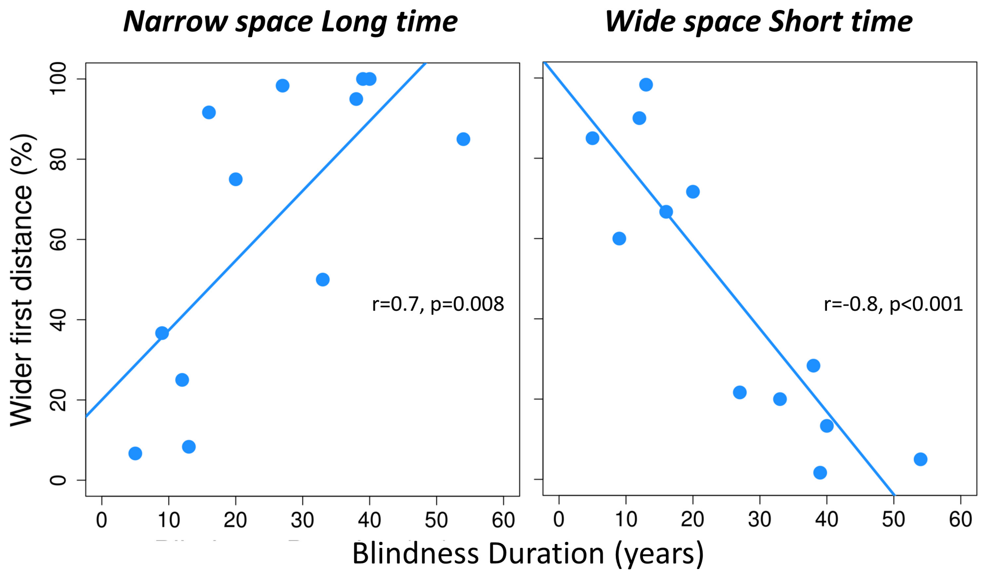

FIGURE 3 | For each conflicting condition of the spatial bisection task, the perceived localization of S2 is plotted against years of blindness duration. For each conflicting condition (*narrowSpace_longTime, wideSpace_shortTime*), percentage of trials in which the first distance is reported as wider (i.e., perceiving S2 as played from the right) is plotted against years of blindness duration. Narrow and wide first spatial distances mean that S2 was played from the left (-4.5°) or right (+ 4.5°) side of participants respectively. Light blue lines indicate significant correlations. For each correlation, we report Pearson correlation coefficient (r) and significance level (p).

$F(3, 32) = 14.4$, $p < 0.001$; for T8: $F(3, 32) = 16.04$, $p < 0.001$]. The interaction between BD, condition, and age of onset was not significant [for O1: $F(3, 32) = 1.54$, $p > 0.05$; for O2: $F(3, 32) = 0.54$, $p > 0.05$; for T7: $F(3, 32) = 1.34$, $p > 0.05$; for T8: $F(3, 32) = 1.79$, $p > 0.05$], as well as the main effect of age of onset [for O1: $F(1, 32) = 0.21$, $p > 0.05$; for O2: $F(1, 32) = 0.27$, $p > 0.05$; for T7: $F(1, 32) = 1.1$, $p > 0.05$; for T8: $F(1, 32) = 0.6$, $p > 0.05$].

As expected, *post hoc* linear regressions indicated that ERP amplitude was not dependent on BD in coherent conditions. However, ERP amplitude was significantly related to BD years in conflicting conditions (see **Figure 4**). In the coherent condition

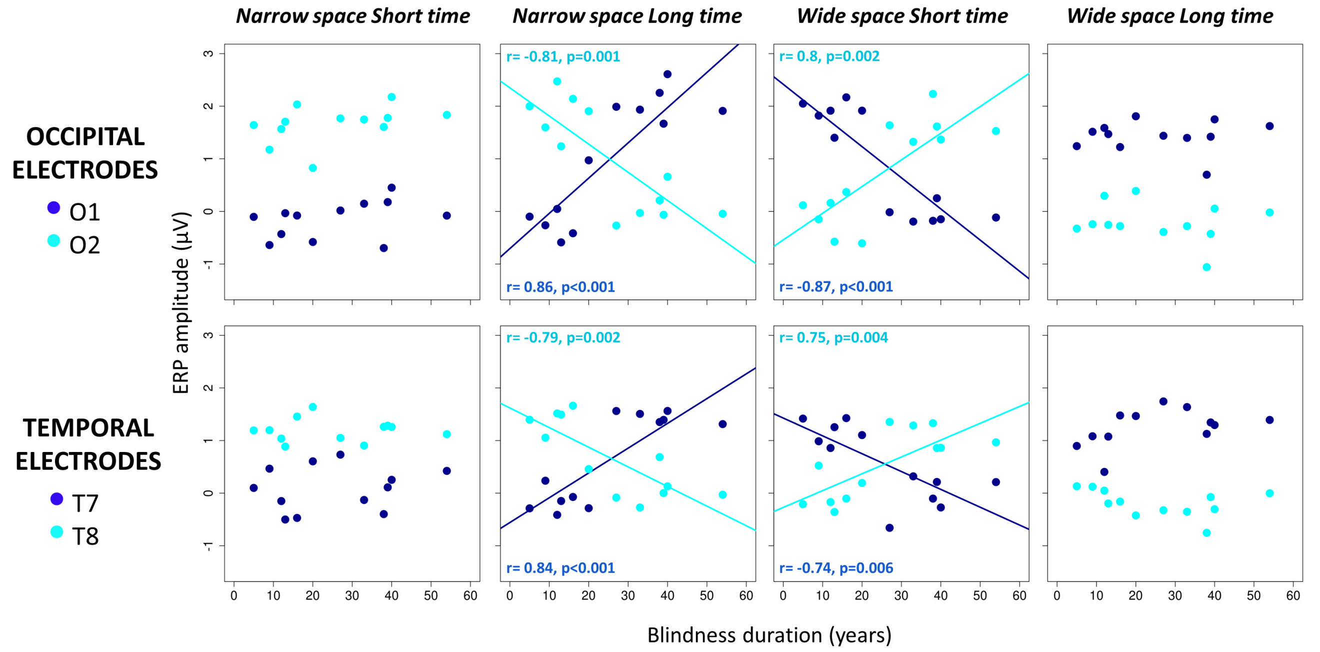

FIGURE 4 | Correlations between years of blindness duration and mean ERP amplitude in occipital **(top)** and temporal **(bottom)** electrodes 50–90 ms after S2 of the spatial bisection task. For each participant and condition (*narrowSpace_shortTime, narrowSpace_longTime, wideSpace_shortTime, wideSpace_longTime*), ERP amplitude in O1/T7 (dark blue) and O2/T8 (cyan) is plotted against years of blindness duration. Lines indicate significant correlations. For each correlation, we report Pearson correlation coefficient (r) and significance level (p).

narrowSpace_shortTime, ERP response in O2 and T8 is higher (see cyan dark blue dots in **Figure 4**), while ERP response in O1 and T8 is lower (see dark blue dots in **Figure 4**), regardless of BD (participants correctly perceived the sound as delivered from the left; for O1: $r = 0.36$, $p > 0.05$; for O2: $r = 0.4$, $p > 0.05$; for T7: $r = 0.17$, $p > 0.05$; for T8: $r = 0.01$, $p > 0.05$). Similarly, in the coherent condition *wideSpace_longTime*, ERP response in O1 and T7 is higher, while ERP response in O2 and T8 is lower, independent of BD (participants correctly perceived the sound as delivered from the right; for O1: $r = 0.01$, $p > 0.05$; for O2: $r = 0.17$, $p > 0.05$; for T7: $r = 0.47$, $p > 0.05$; for T8: $r = 0.39$, $p > 0.05$). In the coherent conditions the spatial and temporal contributions to the correct response are confounded. The conflicting conditions allow us to observe whether the response is aligned with spatial or temporal cues. In the conflicting condition *narrowSpace_longTime*, BD is negatively correlated with ERP amplitude in O2 ($r = -0.81$, $p = 0.001$) and T8 ($r = -0.79$, $p = 0.002$), and positively correlated with ERP amplitude in O1 ($r = 0.86$, $p < 0.001$) and T7 ($r = 0.84$, $p < 0.001$). In the conflicting condition *wideSpace_shortTime*, BD is negatively correlated with ERP amplitude in O1 ($r = -0.87$, $p < 0.001$) and T7 ($r = -0.74$, $p = 0.006$) and positively correlated with ERP amplitude in O2 ($r = 0.8$, $p = 0.002$) and T8 ($r = 0.75$, $p = 0.004$). Thus, the physical position of S2 still elicits a specific occipital and temporal contralateral response in LB subjects that recently lost sight, while after many years of BD the response becomes inverted and ipsilateral. The occipital and temporal sites of LB participants with short BD show activations similar to those found in the coherent conditions, contralateral with respect to the spatial position of S2. Responses of LB participants with long BD in the conflicting conditions are instead ipsilateral to the spatial position of S2. They are contralateral to the perceived virtual position of the sound based on its temporal delay.

To visualize these results, we arbitrarily divided the LB group into two subgroups based on BD median (short BD: BD < median BD, $N = 6$; long BD: BD > median BD; $N = 6$). In **Figure 5**, we report scalp maps of the mean ERP amplitude in the 50–90 ms time window after the S2 of the spatial bisection task, separately for each group (plus sighted individuals) and condition. Similarly, **Figure 6** reports ERP waveforms elicited by S2 in the spatial bisection tasks in occipital (top) and temporal (bottom) scalp sites, separately for each condition and group.

In LB individuals with short BD, early occipital and temporal responses to S2 were high and lateralized based on S2 physical spatial position for both coherent and conflicting conditions (see **Figure 5** center and **Figure 6** blue and orange curves). The left occipital and temporal areas showed a response only when the stimulus was physically from the right side of the participant (i.e., *wideSpace_shortTime*, *wideSpace_longTime*) but not when it was from the left side (i.e., *narrowSpace_shortTime, narrowSpace_longTime*). Symmetrically, the right occipital and temporal areas responded when S2 was played from the left side, and did not respond when it was played from the right side. This pattern resembles that of the sighted group (**Figure 5** top). However, in the long BD group, the same pattern was evident only for the coherent conditions. In coherent conditions, left occipital and temporal areas of LB individuals with long BD (**Figure 5** bottom and **Figure 6** green and violet curves) showed

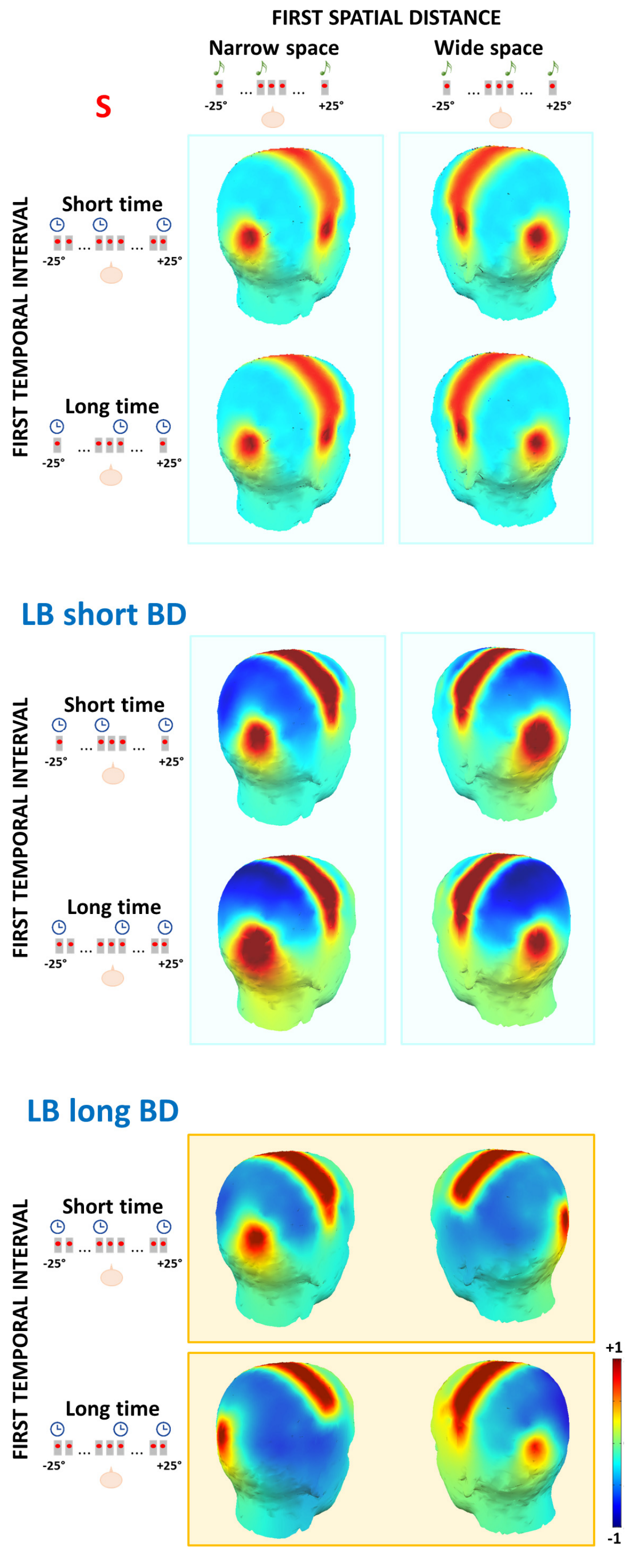

FIGURE 5 | Topography of the mean ERP amplitude in the 50–90 ms time window after S2 of the spatial bisection task, for sighted (S), late blind people with short blindness duration (LB short BD) and late blind people with long blindness duration (LB long BD). The first spatial distance could be narrow *(Continued)*

FIGURE 5 | Continued
(i.e., S2 played from -4.5°; **left panel**) or wide (i.e., S2 played from + 4.5°; **right panel**). The first temporal interval could be short (i.e., S2 played at -250 ms; first row for each group) or long (i.e., S2 played at + 250 ms; second row for each group). The contralateral occipital and temporal activation of sighted and LB with short BD individuals depends on the first spatial distance (i.e., vertical cyan rectangles). The same contralateral occipital and temporal activation in LB with long BD individuals depends on the first temporal interval (i.e., horizontal orange rectangles).

a similarly strong response when the sound was played from the right (*wideSpace_longTime*), and a similarly weak response when the sound was played from the left (*narrowSpace_shortTime*). Symmetrically, the right occipital and temporal areas showed an equally strong response when S2 was played from the left (*narrowSpace_shortTime*), and a similarly reduced activation when it was played from the right (*wideSpace_longTime*). In contrast, during conflicting conditions, LB individuals with long BD had topographically reversed responses compared to LB individuals with short BD. The response was contralateral with respect to the virtual position of the sound, suggested by its temporal coordinate as opposed to its real spatial location. Thus, for long BD subjects, a much stronger activation appeared in the left occipital and temporal areas when S2 was temporally closer to S3 (played from right) but physically played from the left of the subject (*narrowSpace_longTime*), and weaker when the sound was temporally closer to S1 (played from left) but physically played from the right (*wideSpace_shortTime*). Symmetrically, a stronger response emerged in the right occipital and temporal areas when S2 was temporally closer to S1 but physically played from the right side of the subject (*wideSpace_shortTime*), and weaker response was elicited when the sound was temporally closer to S3 but physically played from the left side (*narrowSpace_longTime*). These results suggest that years of blindness influence LB individuals to process spatial signals based on temporal properties.

The 50–90 ms time window is the first one that shows an effect associated with the spatial task. This is evident in **Figure 6**, showing the ERP waveforms elicited in occipital electrodes by S2. In agreement with our previous study (Gori et al., 2020b), a later P140 selective for S2, but not lateralized, appears in both groups independently of the condition. Typical auditory responses appear for all participants in central areas (see **Supplementary Figure S1**).

To exclude the possibility that our result is due to chronological age, we verified a lack of correlation between BD and chronological age for LB participants ($r = 0.48$, $p > 0.05$). Moreover, during the temporal bisection task performed as a control, cortical responses supported the specificity of temporal attraction during complex spatial representation following years of visual deprivation. In the temporal bisection task subjects were asked to evaluate timing presentations of sounds. Under this condition, all LB participants showed typical auditory responses and were not affected by the cross-domain conflict (i.e., only a response in central areas and a response in temporal areas contralateral with respect to the physical location of the stimulus

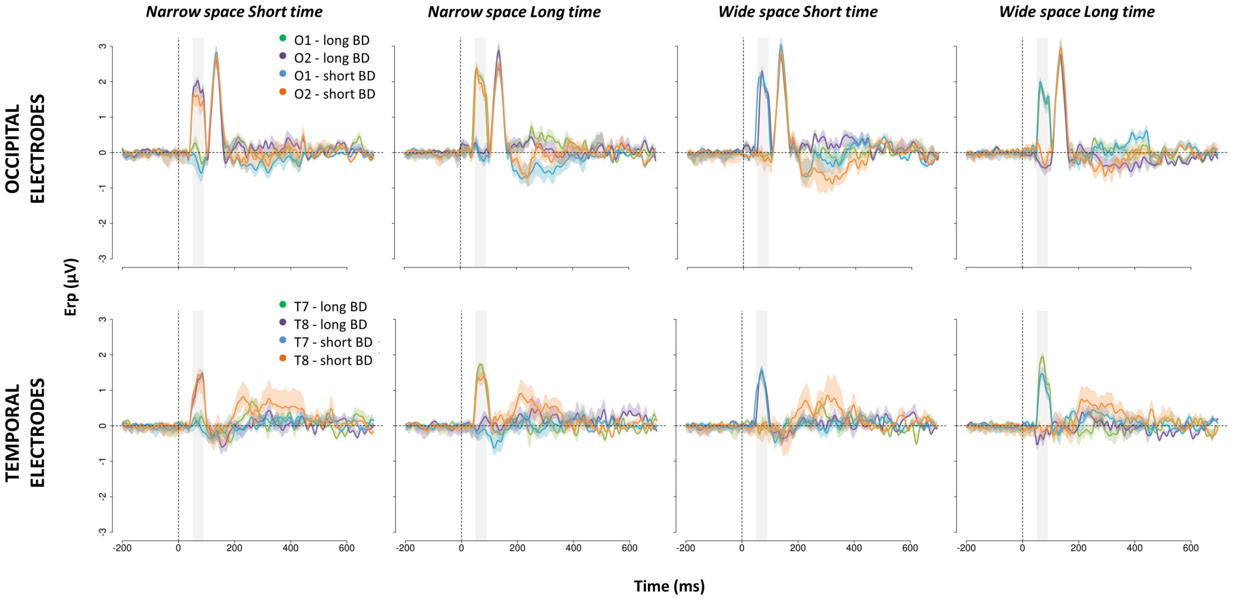

FIGURE 6 | ERPs evoked in occipital **(top)** and temporal **(bottom)** scalp sites by S2 of the spatial bisection task. Waveforms (mean ± SEM) are reported for O1, O2, T7, and T8, separately for LB individual with long (i.e., long BD) and short (i.e., short BD) blindness duration. All coherent (i.e., *narrowSpace_shortTime*, *wideSpace_longTime*) and conflicting (i.e., *narrowSpace_longTime*, *wideSpace_shortTime*) conditions are displayed. In the conditions *narrowSpace_shortTime* and *narrowSpace_longTime* conditions, O1 and T7 are ipsilateral and O2 and T8 are contralateral to the physical location of the sound. In the conditions *wideSpace_longTime* and *wideSpace_shortTime* conditions, O1 and T7 are contralateral and O2 and T8 are ipsilateral to the physical location of the sound. On the *x*-axis, time = 0 ms represents the onset of the sound. The shaded area indicates the 50–90 ms time window.

were observed). In **Supplementary Material**, we report scalp maps in the selected time window (50–90 ms) after the S2 of the temporal bisection task (**Supplementary Figure S2**), and waveforms elicited by the stimulus in occipital (**Supplementary Figure S3** top), temporal (**Supplementary Figure S3** bottom) and central (**Supplementary Figure S1** bottom) scalp sites. For details about waveforms and results in the sighted group, please refer to Gori et al. (2020b).

DISCUSSION

We previously showed that LB individuals with a long history of BD (i.e., > 25 years) do not show typical spatial bisection skills and neural correlates (Amadeo et al., 2019). Indeed, they do not show the early contralateral occipital activation associated with spatial bisection skills in sighted people and LB individuals who have recently lost vision. In this study, we investigated whether different performance and neural correlates of LB people with long BD are due to the use of an alternative strategy to represent space, based on temporal properties of stimuli. As expected, we demonstrate that years of visual deprivation following late blindness gradually lead complex spatial representations to be inferred based solely on temporal properties of events.

The spatial bisection task involves the evaluation of spatial distances among three stimuli, requiring relative comparisons between each pair of stimuli. To succeed at the task, people must understand Euclidean relationships and build sophisticated and well-calibrated auditory spatial maps. In agreement with previous studies (Campus et al., 2017; Amadeo et al., 2019), we confirm that sighted individuals and LB individuals with recent visual loss succeed at the spatial bisection task, and show a specific ERP response in occipital areas, likely involving the visual cortex, between 50-90 ms after the second of the three sounds of the task. The early occipital response is strong and contralateral to the physical spatial position of the second sound, which represents the first step in building a metric in space. More interestingly, we demonstrate that with increasing years of visual deprivation, performance and cortical activation become more influenced by temporal instead of spatial coordinates of the second sound. Indeed, the bisection task naturally combines spatial with temporal representations. The first and the third stimuli identify both a spatial distance and a temporal interval. By independently modulating the spatial and temporal coordinates of the second stimulus, it is possible to deliver signals coherent or conflicting in space and time. Thus, the bisection task allows us to investigate the weight given to spatial or temporal information in solving the task. To create coherent conditions, we associated a short spatial distance between the first and the second stimuli with a short temporal interval, and a wide spatial distance between the first and the second sound with a long temporal interval. To create conflicting conditions, we associated a narrow spatial distance between the first and the second sound with a longer temporal interval, and a wide spatial distance between the first and the second sound with a short temporal interval. A narrow spatial distance between the first and the second sound means that the second sound was physically played from the left side of the participant, while a wide spatial distance means that the second sound was physically played from the right side.

In coherent conditions, LB participants with long BD show a good performance and the same contralateral occipital response as sighted participants. Thus, they show a lateralized occipital activation of the visual cortex opposite to the actual spatial position of the second sound. Hence, by presenting coherent spatiotemporal information, we observe for the first time in LB people with long BD the early occipital response associated with spatial bisection skills. LB people with long BD displayed the response which was absent in our previous study that did not consider temporal information (Amadeo et al., 2019; Campus et al., 2019). Since there was no response when the temporal cues were not considered, and only spatial information was provided, we can suppose that the activation observed is related to the introduction of temporal information coherent with the spatial one. However, coherent conditions do not allow disentangling between the contributions of spatial and temporal information; this requires conflicting conditions. In conflicting conditions, with increasing BD in LB participants, performance and early cortical activation (i.e., 50–90 ms) differ. The response in long BD individuals recalls that of sighted people and blind participants with short BD but with an inverse topography. As BD years increase, left occipital activation emerges for long temporal intervals and narrow spatial distances (i.e., second sound physically played from the left but temporally closer to the sound from the right). Similarly, right occipital activation emerges for short temporal intervals and wide spatial distances (i.e., second sound physically played from the right but temporally closer to the sound from the left). These patterns of response also involve the temporal scalp sites of LB people with long BD.

Thus, our results suggest that occipital and temporal activation shows a lateralization pattern that aligns with the "temporal" position of the stimulus, determined by its temporal delay rather than its spatial coordinate. An impact of auditory temporal features on occipital areas has previously been observed in sighted people (Murray et al., 2016). For example, Bueti and Macaluso (2010) showed that temporal expectations of upcoming auditory events modulate activity in the occipital visual cortex, Romei et al. (2012) found that a single beep can phase-align alpha oscillations to sounds in the occipital cortex, and Cecere et al. (2015) demonstrated a link between an alpha frequency and the temporal window of the flash-beep illusion (Shams et al., 2000). Moreover, we have recently demonstrated that the visually evoked occipital component (C1) appears earlier during a temporal bisection of visual stimuli compared to a spatial bisection of the same stimuli (Amadeo et al., 2020). Within this context, Giard and Peronnet (1999) also revealed that visual cortex activates earlier the in response to synchronous audio-visual stimuli than visual stimuli alone. In the current experiment, the temporal information not only brings about a misperception of the stimulus in the occipital cortices, but also a sensory illusion which tricks the auditory processing at the early stages. In agreement with previous results (Gori et al., 2018, 2020b), the spatial nature of the visual cortices seems to be sufficiently dominant to drag the early activation of auditory cortices involved in the auditory processing of sounds. This is not the first study where sensory illusions are found to trick the early stages of processing of sensory cortices (e.g., Shams et al., 2001; Murray et al., 2002; Ress and Heeger, 2003; Watkins et al., 2006).

The behavioral performance confirms a temporal attraction during the spatial bisection task. Indeed, when we investigated the association between individual performance and years of visual deprivation, we observe that the higher the BD, the more the answer of participants was determined by the temporal cues in the conflicting conditions. These findings enrich previous findings, where we observed that following many years of visual deprivation, LB people gradually become less able to perform the spatial bisection task, and the associated early occipital response gets reduced and non-lateralized (Amadeo et al., 2019). Years of blindness drive to alternative ways of processing complex spatial representations, based on temporal instead of spatial information.

Our results (see **Figures 5**, **6**), suggest that the LB group can be split in two; individuals having less than 20 years of blindness differed from individuals with more than 30 years of blindness. Unfortunately, we do not have enough participants aged 20–30 years old to fully understand the effect of BD on behavioral and neurophysiological parameters, particularly whether the influence is linear. A future experiment should specifically investigate what happens around 25 years after vision loss. Although it is the simplest method, the main reason we used linear regression analysis was for its robustness with respect to noisy or subsampled data. We further felt it unlikely that a drastic change occurs between these years, creating two independent groups. Moreover, other studies investigating LB people indicate years of visual deprivation tend to have a linear effect on certain parameters (Collignon et al., 2013; Wang et al., 2013; Tao et al., 2015). For example, Collignon et al. (2013) demonstrated that years of blindness of LB individuals are linearly associated with sound-related activity in some occipital regions. The effect of blindness duration on spatial representation that we observed is not due to aging. Indeed, in our experiment no association between years of blindness duration and chronological age was observed. In line with literature (Lepore et al., 2010; Li et al., 2013; Wang et al., 2013), we suggest that neural changes may be due to a progressive degenerative mechanisms following a lack of constant visual stimulation, such as structural atrophy and impairment of anatomical connections in the visual cortex.

It is important to mention that LB individuals represent a specific population, and it is difficult to find a large sample within this population without comorbidities or other confounding factors; therefore statistical power is necessarily affected by a small sample size. However, our control experiment confirms the specificity of the temporal attraction during the spatial representation. In the temporal bisection task, the cross-domain conflict only slightly affects the performance of LB participants, similarly to sighted people. Also, in line with our previous experiment (Amadeo et al., 2019), no peculiarities emerge at the cortical level in the conflicting and coherent conditions of the temporal bisection task. Moreover, the effect during the spatial task is not due to mere attention to space. The time window we focused on is very early (50–90 ms), and reflects more sensory rather than cognitive processing. Attention to space, in fact, is expected to weakly affect early ERPs, such as the occipital response of interest (Campus et al., 2017) and the N1 (Roder et al., 1999; Lange et al., 2006).

Results of this study add interesting insights into long-term neural plasticity. Since the construction of complex spatial representations is not compromised in late blind individuals with recent visual loss, visual experience during childhood seems to be important and sufficient for the complete development of complex spatial bisection skills and underlying neural circuits. In line with the cross-calibration theory (e.g., Burr and Gori, 2012), vision has time to solve its important role in calibrating complex auditory spatial representations during development. However, it is worth stressing that LB people with prolonged blindness show the same mechanism that characterizes the occipital and the temporal cortices of early blind people. Early blindness presents the same temporal focus during spatial evaluations in bisection tasks (Gori et al., 2018, 2020b). This suggests that strategies and neural circuits underlying the spatial bisection skills are strongly influenced by prolonged visual deprivation through long-term neural plasticity. Observing that prolonged visual deprivation later in life drives to the same reorganization of visual and auditory cortices as that seen in early visual deprivation provides essential cues about how the brain works. Our results stand against studies claiming that functional or structural reorganization is almost impossible beyond some critical periods (e.g., Cohen et al., 1999; Sadato et al., 2002; Noppeney, 2007). Instead, they are in line with literature showing that compensatory neural mechanisms can be adopted even later in life (e.g., Buchel, 1998; Burton, 2003; Voss et al., 2006; Collignon et al., 2013). However, most studies in this direction support the idea that auditory or tactile recruitment of occipital regions provide improved spatial skills, while our results seem to highlight some potential side effects of neuroplasticity. The auditory recruitment of the occipital brain in spatial bisection is not associated with better performance, but rather underlies an alternative way of building spatial representation.

On the one hand, using temporal information to infer spatial maps can be a useful strategy by which blind people can overcome problems in complex spatial representations. This strategy can be successful from time to time. There are situations in real life where spatial and temporal information is congruent, and this strategy would allow blind people to use unimpaired temporal coordinates to decode auditory spatial maps, facilitating interaction with others. On the other hand, this strategy could be dysfunctional when there is conflicting spatial and temporal information. There are real-life situations, such as accelerations or decelerations of environmental objects, where using temporal information to assume spatial positions would introduce a misperception of the stimulus, impacting one's capability to interact with the environment. Therefore, our findings agree that there is no time window in which plastic changes can occur, cross-modal reorganization can occur even after the full development of the visual system. However, the direction of plastic neural changes is not apparent and does not always lead to successful behavioral outcomes.

Since the strategy adopted by early blind people and LB people with long BD is not always functional, one might wonder why the strategy exists and from where it came. According to the cross-calibration theory (Gori, 2015), during childhood the most reliable sense for a given perceptual property calibrates the other sensory modalities (see Gori et al., 2012). Within this framework, the visual modality, with its high spatial accuracy, is used to calibrate spatial representations of other senses. Similarly, the auditory modality, with its high temporal accuracy, is used to calibrate temporal representations of other senses. Sighted adults and LB individuals with short BD, who have experienced cross-sensory visual calibration during childhood, can build even complex spatial representation in the auditory modality. Early blind people, who did not experience visual calibration during childhood, instead focus on temporal cues (Gori et al., 2018, 2020b). Since after many years of visual deprivation, LB individuals also focus on temporal cues, the perceptual advantages of cross-sensory visual calibration seem to be gradually lost with the lack of visual experience. This result suggests that constant cross-sensory visual calibration may be necessary to maintain its beneficial effects. A hypothesis to explain temporal attraction during spatial representation involves considering the speed of the stimuli. It could be that, during development, the visual system calibrates the auditory sense of space by processing speed. When vision is available, the visual system may facilitate the transference of auditory processing from a temporal to a spatial coordinate system relying on speed processing. When visual inputs are absent, this transfer may not occur (i.e., in early blindness) or may gradually deteriorate (i.e., in late blindness), resulting in auditory maps based only on temporal cues for inferring complex spatial representations (Gori et al., 2020a). Thus, we speculate that, when visual-spatial networks are weakened by long-lasting lack of sensory stimulation, blind individuals assume constant velocity of environmental stimuli, thereby inferring space from time. This idea is supported by the Imputed Velocity Theory (Huang and Jones, 1982), which researchers previously proposed to explain the Tau and Kappa effects (Bill and Teft, 1972; Sarrazin et al., 2007; Kawabe et al., 2010). According to the latter, humans intuitively impute uniform motion to discontinuously displayed successive stimuli.

To conclude, in this work, we show that the long-lasting absence of visual input following late blindness leads to a reorganization of how people build complex spatial representations. After a long amount of time with no vision, a new strategy to represent space emerges, whereby the visual and auditory circuits use temporal information to interpret spatial metrics. Beyond theoretical relevance, the results of the current study have important repercussions for rehabilitation strategies following sensory loss. First, the knowledge that after prolonged blindness the effects of cross-sensory visual calibration are lost highlights the relevance of timing in interventions. People that become blind should be soon involved in early rehabilitation programs to activate compensatory strategies and not to lose perceptual-advantages from previous cross-sensory visual calibration. Long-term plasticity seems to lead to some maladaptive changes. We hypothesize that constant stimulation and training soon after vision loss may prevent them from occurring. For example, timely sensory-motor training such as the one previously validated in blind children (Finocchietti et al., 2015a) could have important effects. Secondly, if blind people benefit from spatiotemporal coherence, there is potential to develop new rehabilitation strategies by providing temporal cues to inform about spatial dimensions. For instance, trainings involving velocity tasks could be planned, where time can be used to infer space (as suggested in the model proposed by Gori et al., 2020a). Coherent temporal cues could be initially associated with spatial cues and then, only gradually, disassociated to promote recalibration. Blind people rely strongly on auditory information to orient themselves in their environments, and various techniques and approaches (e.g., serious games) could be realized to help them by taking advantage of temporal cues to learn about space.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Liguria Region. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant's legal guardian/next of kin for the publication of any identifiable images or data presented in the study.

AUTHOR CONTRIBUTIONS

MG and CC conceived the study and designed the experiments. MA, MG, and CC carried out the experiments and analyzed the data, wrote the manuscript, prepared figures, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.00812/full#supplementary-material

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Increased Right Posterior STS Recruitment Without Enhanced Directional-Tuning During Tactile Motion Processing in Early Deaf Individuals

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Upon early sensory deprivation, the remaining modalities often exhibit cross-modal reorganization, such as primary auditory cortex (PAC) recruitment for visual motion processing in early deafness (ED). Previous studies of compensatory plasticity in ED individuals have given less attention to tactile motion processing. In the current study, we aimed to examine the effects of early auditory deprivation on tactile motion processing. We simulated four directions of tactile motion on each participant's right index finger and characterized their tactile motion responses and directional-tuning profiles using population receptive field analysis. Similar tactile motion responses were found within primary (SI) and secondary (SII) somatosensory cortices between ED and hearing control groups, whereas ED individuals showed a reduced proportion of voxels with directionally tuned responses in SI contralateral to stimulation. There were also significant but minimal responses to tactile motion within PAC for both groups. While early deaf individuals show significantly larger recruitment of right posterior superior temporal sulcus (pSTS) region upon tactile motion stimulation, there was no evidence of enhanced directional tuning. Greater recruitment of right pSTS region is consistent with prior studies reporting reorganization of multimodal areas due to sensory deprivation. The absence of increased directional tuning within the right pSTS region may suggest a more distributed population of neurons dedicated to processing tactile spatial information as a consequence of early auditory deprivation.

Keywords: cross-modal plasticity, early deafness, superior temporal sulcus, auditory cortex, tactile motion

INTRODUCTION

Individuals affected by early sensory deprivation often display enhanced perceptual sensitivities for the remaining modalities. For instance, visual motion detection (Shiell et al., 2014) and visual motion direction discrimination (Hauthal et al., 2013) appear to be superior in early deaf (ED) participants compared to normal hearing (NH). These behavioral changes are typically accompanied by cross-modal reorganization, where brain areas deprived of default sensory input respond to input from the remaining modalities. Prior studies with ED adults report activation of primary auditory cortex (PAC) to peripheral visual stimuli (Karns et al., 2012), during presentation of visual motion (Finney et al., 2001; Fine et al., 2005) and during a visual rhythm matching task (Bola et al., 2017). Other studies report similar cross-modal reorganization of auditory cortex in ED for processing vibrotactile stimuli (Levänen and Hamdorf, 2001; Auer et al., 2007) and during touches to the face (Karns et al., 2012).

Often, cross-modal plasticity follows the concept of functional constancy – deprived cortical areas retain function but shift the type of sensory input (Bavelier and Neville, 2002; Amedi et al., 2007; Saenz et al., 2008; Jiang et al., 2014; Renier et al., 2014). For instance, when presented with both fixed-frequency and speech-derived vibrotactile stimuli, more widespread activity within auditory region was observed in ED participants (Auer et al., 2007). In addition, distinct patterns of activity were observed for a deviant vibrotactile frequency compared to a standard vibrotactile frequency in supratemporal auditory cortex of an ED case study participant (Levänen et al., 1998). Auditory signals normally convey similar temporal and frequency information as vibrotactile stimuli, as evidenced by robust interaction between these two modalities when their frequencies overlap (Crommett et al., 2017; Pérez-Bellido et al., 2017). Indeed, specificity toward vibrotactile frequency demonstrated in the above findings provides evidence of maintained auditory cortex function in ED adults for haptic rather than auditory sensory input.

Along with cross-modal recruitment of primary sensory areas, multimodal regions, such as the posterior superior temporal sulcus (pSTS), are additional targets for compensatory plasticity upon early auditory deprivation because multimodal areas exhibit increased numbers of neurons responsive to intact modalities when one modality is deprived (Rauschecker and Korte, 1993; Meredith et al., 2011). The pSTS is an association area within the superior temporal cortex that normally displays responses to multiple modalities including auditory, visual, and tactile (Beauchamp et al., 2008; Jiang et al., 2015) and is involved in the perception of biological motion (for review see Decety and Grèzes, 1999; Grossman et al., 2000; Grossman and Blake, 2002). Sadato et al. (2004) reported that early deaf (< 2 years), late deaf (> 5 years), and NH individuals all showed activation of the pSTS during visual processing of sign language. However, only ED adults demonstrated increased activity of the middle STS (Sadato et al., 2004), a region normally responsive to voices and audiovisual speech during speech processing (Venezia et al., 2017). Such findings suggest that, in response to early deafness, inherently auditory or multimodal STS areas demonstrate cross-modal reorganization and enhanced activation for the visual modality to retain STS function, in this case linguistic processes. In addition to decoding auditory and visual features of language, the pSTS region is also involved in audiovisual temporal processing (Zhang et al., 2010; Noesselt et al., 2012) and visual motion processing (Beauchamp et al., 2002; Grossman and Blake, 2002; Nelissen et al., 2006). Therefore, it is not surprising that bilateral superior and middle temporal gyri activation was evident in ED adults during a visual rhythm discrimination task (Bola et al., 2017), and STS activation patterns were dependent on the frequency of a vibrotactile stimulus in an ED case study (Levänen et al., 1998).

While these various findings describe how an auditory-deprived brain functionally adapts its organization for visual motion processing, visual temporal processing (i.e., rhythm), and tactile temporal processing (i.e., frequency), changes to cortical processing of tactile motion as a result of early deafness remain untested. The higher-order processing of visual motion cues by the pSTS region, such as preferential activation for articulated vs. unarticulated human motion (Beauchamp et al., 2002), biological vs. scrambled motion (Grossman and Blake, 2002), and dynamic vs. static faces (Pitcher et al., 2011), establishes the pSTS as a likely candidate for cross-modal recruitment during motion processing tasks. Further, STS is responsive to auditory (Lewis, 2000), tactile (Jiang et al., 2015), and visual non-biological motion (Nelissen et al., 2006), allowing for a more salient and representative percept of the target of interest, a useful characteristic as the STS is heavily involved in processing social cues and interactions (Beauchamp, 2015; Deen et al., 2015; Venezia et al., 2017). Therefore, this study was particularly interested in characterizing the pSTS response to tactile motion upon early auditory deprivation.

Besides higher-order multisensory areas, we also wanted to examine any functional cross-modal reorganization of intact primary sensory areas in ED adults as these regions are crucial for processing tactile motion. Haptic motion discrimination and decoding the manner in which a tactile object moves across the skin is a crucial piece of information dictating our perception and understanding of the identity, function, and route of that object. Decoding of tactile motion direction is initiated by stimulation of rapidly adapting and slowly adapting type I afferents, which activate directionally tuned neurons localized within the subregions of macaque SI, specifically areas 3b, 1, and 2 (Pei et al., 2010; for review see Pei and Bensmaia, 2014), similar to the direction sensitivities of visual neurons located within primary visual cortex and MT + (Albright, 1984). Area 1 of SI plays a primary role in motion decoding as a large proportion of area 1 neurons demonstrate strong, coherence-dependent directional tuning, regardless of the type of tactile stimulus (Pei et al., 2010). Comparable to models describing the mechanism of global visual motion perception in MT + (Amano et al., 2009, 2012), the convergence of tactile inputs to area 1 results in a global percept of tactile motion driven by the vector average of the two-dimensional contours comprising the plane of motion and the terminators, all weighted by their respective saliencies and speeds (Pei et al., 2011; for review see Pei and Bensmaia, 2014). The importance of SI in decoding tactile motion was further shown when transcranial magnetic stimulation applied to SI of NH adults resulted in a significant reduction in the ability to discriminate direction of tactile motion (Amemiya et al., 2017). In addition, the feed-forward inputs from SI to SII also contribute to the global percept of haptic features, including motion (Hsiao, 2008). Indeed, in NH individuals, both SI and SII reveal differential responses dependent on the direction of tactile motion stimulation (Wacker et al., 2011). As prior studies suggest reduced specificity for processing intact sensory inputs due to intramodal plasticity and computational efficiency (Gougoux et al., 2009; Stevens and Weaver, 2009; Jiang et al., 2014), it is likely that similar functional reorganization in ED SI/SII underlies processing tactile motion.

In addition to reorganization, cortical regions lacking input from their typical modality (i.e., PAC and auditory input) also undergo changes to tuning properties of their neuronal populations. In the anterior auditory field of ED cats, there was a shift in modality-specific neurons, as well as an increase in the visual and somatosensory neuronal receptive fields compared to NH cats, reflecting wider tuning of these neuronal populations (Meredith and Lomber, 2011), presumably allowing for greater compensation for the lost modality through a wider range of neural excitation. A similar finding in congenitally deaf cats revealed broader tuning of interaural time difference (ITD)–sensitive inferior colliculus neurons providing a probable explanation for the poor ITD discrimination common in cochlear implant users (Hancock et al., 2012; Laback et al., 2015). However, while ED adults exhibited a fivefold increase in multimodal pSTS activation compared to NH adults for directional visual motion, there was no evidence for direction specificity in active voxels (Retter et al., 2019), indicating that neuronal populations within the pSTS region may not demonstrate strong directional sensitivity for motion, or such profiles could not be elucidated with the frequency tagging approach used in that study.

As tuning properties of neuronal populations provide insight into the sensitivity and functional role of their respective cortical areas, an additional goal of the current study was to characterize the directional sensitivities in somatosensory regions and other areas that may exhibit reorganization for tactile processing in ED adults, such as PAC and pSTS region. In terms of tactile motion processing, direction discrimination is mediated by the directional sensitivity of neuronal populations within tactile processing areas (Hsiao, 2008; Pei et al., 2010, 2011; Hsiao and Gomez-Ramirez, 2011). Indeed, directional tuning of neurons within macaque SI displayed increased sensitivity to direction with increased motion coherence, a finding that closely resembled human behavioral performance on a tactile motion discrimination task (Pei et al., 2010). We used a modified population receptive field (pRF) analysis originally developed for retinotopic mapping (Dumoulin and Wandell, 2008) and later adopted for tonotopic mapping in PAC of NH individuals (Thomas et al., 2015) and in human middle temporal complex (hMT^+) of early blind (EB) participants (Huber et al., 2019a,b). pRF estimation allowed for the characterization of tactile direction tuning profiles (directional selectivity and tuning bandwidth) of neuronal populations in areas of interest, specifically somatosensory cortices, PAC, and pSTS.

While we expected increased activation of pSTS for tactile motion in deaf due to the multimodal inputs inherent to this region and the loss of auditory input, we did not expect enhanced directional tuning in the pSTS of ED as Retter et al. (2019) previously reported absence of directional specificity for visual motion by ED despite increased pSTS activation. Indeed, we found enhanced pSTS activation by ED without an increase in the proportion of or changes in the bandwidth of directionally tuned voxels. In addition, we did not see greater activation of PAC by ED in line with our hypothesis based on the functional-constancy theory of cross-modal reorganization. Finally, we hypothesized similar activations of somatosensory areas in both ED and NH adults as this region's primary sensory input is unaffected by early deafness while the tuning bandwidths of neuronal populations in SI and SII may be broadened in ED adults allowing for compensatory profiles of neural excitation. We did not find any differences in SI or SII activation between the two groups, whereas in the ED adults, we found reduced proportions of directionally tuned voxels in SI only.

MATERIALS AND METHODS

Participants

Seven ED with bilateral severe to profound hearing loss (ages 31–55 years; two males; cause and age at onset of deafness are reported in **Table 1**) and 7 age- and gender-matched NH controls (ages 28–54 years) participated in this study. There was no statistical difference in age between the two groups ($t_{12} = 1.04$, $p = 0.32$). Participants were screened for any history of neurological or psychiatric disorders, history of brain injury, antipsychotic medications, and cognitive decline. Participants provided signed informed consent before any experimentation and were financially compensated for their time. Protocols were reviewed and approved by the institutional review board at the University of Nevada, Reno in accordance with the guidelines of the Declaration of Helsinki for research involving human subjects.

Visual Motion Localizer

A visual motion localizer was used to identify pSTS region in all participants over a tactile motion localizer to avoid spurious results (Kriegeskorte et al., 2009; Jiang et al., 2015). Motion localizer scans consisted of blocks of moving and static dots as well as a fixation condition that did not contain any dots. Dots were presented within a circular aperture (radius 8°) with a central fixation cross surrounded by a gap (radius 1.5°) in the dot field. Visual stimuli were generated using MATLAB and PsychToolbox (Brainard, 1997; Pelli, 1997). Visual stimuli were back-projected onto a display located behind the magnet and

TABLE 1 | Demographic information of early deaf participants.

Participant	Age (years)	Handedness	Clinical description	Age at deafness onset (months)	Auditory deprivation (left; right) (dB)
ED1	30–35	R	Fever	15	Total; 85
ED2	45–50	R	Maternal gestational measles	Birth	100; 90
ED3	30–35	R	Cytomegalovirus	12	Total; profound
ED4	40–45	R	Unknown	12	95; 95
ED5	30–35	R	Hereditary	Birth	80; 70
ED6	50–55	R	Unknown	Birth	85; 90–100
ED7	40–45	R	Spinal meningitis	9	Profound; profound

viewed through a mirror attached to the MR head coil. All dots were white presented on a black background. Each dot subtended 0.3° (dot density 1 per degree). To prevent tracking of individual dots, the dots had a limited lifetime of 200 ms. In the moving condition, all dots moved coherently in one of eight directions (spaced evenly between 0° and 360°) with a speed of 8° per second. The direction of motion changed once per second, and the same direction never appeared in subsequent trials. In static conditions, the dots were presented without any motion, and the position of the dots was reset once per second. In fixation conditions, only the fixation cross was presented without any dots. Participants were asked to fixate throughout the scan without performing a task. Each block lasted 10 s during which one of the three visual stimulation conditions (motion, static, or fixation) was presented. Two motion localizer scans were obtained from every participant. Each scan lasted ∼5 min and included 30 10-s blocks.

Tactile Stimulus Design and Procedure

During tactile motion scans, motion was simulated in four main directions (rightward, leftward, upward, and downward) using a small grating surface held within a plastic tube (JVP dome) (Stoelting Co., Wood Dale, IL, United States) consisting of equidistant bar and groove widths equal to 0.35 mm. The JVP dome was manually placed on the center of the participant's right index finger pad by an experimenter, and tactile motion was simulated by the experimenter sweeping the dome across the finger pad in the appropriate direction for a total of 2 s (1 sweep/1 s) (**Figure 1**). As displayed in **Figure 1**, the orientation of the dome was continually adjusted by the experimenter dependent on the direction of motion so that the orientation of the grooves embedded in the dome was perpendicular to the direction of motion. At the groove distance of 0.35 mm, participants were unaware of the dome's orientation (Wong et al., 2011).

Each block of tactile motion contained all four directions. The order of directions was pseudorandomized to include all possible order combinations of tactile motion directions. Each block consisted of 8 s of tactile motion (2 s for each of the four directions of motion) followed by a 4-s baseline rest period (**Figure 1**, top panel). To maintain participant's attention throughout each scan, they were asked to complete a 1-back task. In two of the blocks (7.69%), rather than presenting all four directions, one direction of tactile motion was randomly selected to be repeated (**Figure 1**, bottom panel). Upon perception of this direction repeat, participants were instructed to press a response button with their left hand. Each participant participated in four experimental scans. Each scan lasted ∼5 min and included 26 12-s blocks (including blocks containing the 1-back task). Participants wore an eye mask throughout tactile motion scans to prevent any visual input of the experimenter's movements.

fMRI Data Acquisition

Scanning was performed at the Neuroimaging Facility of Renown Health Hospital in Reno, NV on a 3T Philips Ingenia scanner using a 32-channel digital SENSE head coil (Philips Medical Systems, Best, Netherlands). Three-dimensional (3D) anatomical images were acquired at 1 × 1 × 1 mm resolution using a T1-weighted MPRAGE (magnetization-prepared rapid gradient echo) sequence. Functional images were obtained using a standard echo planar imaging sequence (EPI) with 2.75 × 2.75 × 3-mm voxels. A continuous block design was used (TR = 2 s, TE = 25 ms) for both visual motion localizer and tactile motion scans.

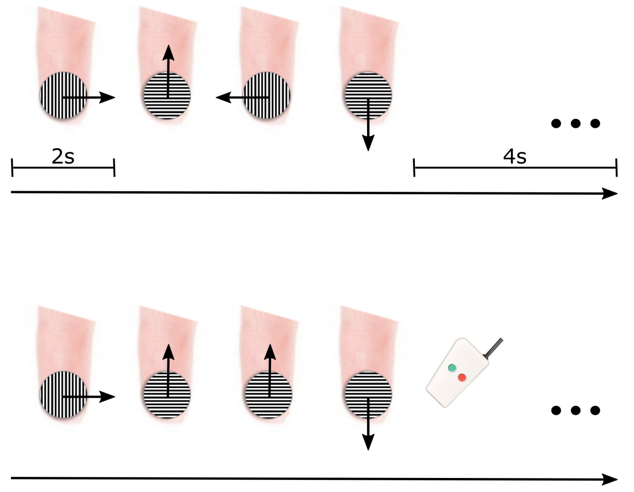

FIGURE 1 | fMRI paradigm for delivering tactile motion. Each 12-s block consisted of all four directions of tactile motion (each direction was simulated for 2 s) followed by a 4-s baseline period (top panel). To ensure participant's attention, two of the blocks had a direction immediately repeated, and participants were instructed to press a button on the response box when they noticed the repeat (bottom panel).

Functional Magnetic Resonance Imaging Data Preprocessing

Data were analyzed using Brain Voyager QX (version 2.8; Brain Innovation, Maastricht, the Netherlands) and MATLAB (Mathworks, Natick, MA, United States). Initially, functional data underwent preprocessing steps that included three-dimensional motion correction (trilinear/sinc interpolation), high-pass filtering including linear trend removal [general linear model (GLM) approach with a design matrix containing a Fourier basis set (sines and cosines for two cycles)] and slice scan time correction (cubic spline). For each participant, preprocessed functional data were coregistered to their corresponding anatomical data. The initial alignment was based on header information from functional and anatomical sessions, and fine-tuning alignment was gradient based. Anatomical and functional data were then transformed into Talairach space (Talairach and Tournoux, 1988).

Functionally Defined pSTS Region

To examine responses in the pSTS region, we functionally defined voxels that showed significant activation, based on a false discovery rate of 0.05 at the cluster level (qFDR < 0.05) averaged across all ED and NH participants to visual motion vs. static condition. However, pSTS recruitment for visual motion

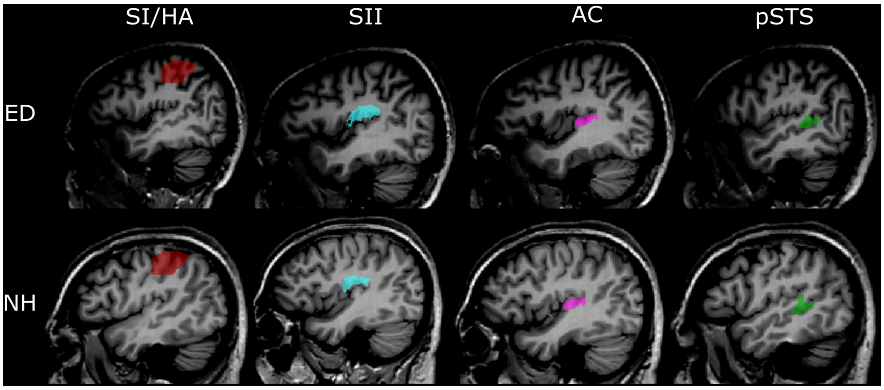

FIGURE 2 | Representative anatomically and functionally defined ROIs. Sagittal views of the four ROIs in the left hemisphere defined using either the functional (pSTS) or anatomical (SI/HA, SII, PAC) criteria are shown in the Talairach volume space of a representative ED (top panel) and NH participant (bottom panel). Red, SI/HA; light blue, SII; pink, PAC; green, functionally defined pSTS.

is primarily evident in ED, not NH participants; thus, this region of interest (ROI) did contain some bias for our ED group. Generous ROIs were created that encompassed superior STG, middle STG, and middle and posterior STS. The group-level pSTS region ROI was applied to individual volume space, and voxels were identified and removed if they encompassed part of the temporoparietal junction (TPJ), lateral fissure, or parietal operculum, resulting in individual pSTS region ROIs. Representative pSTS region ROIs from an ED and an NH participant are shown in **Figure 2**.

TABLE 2 | Talairach coordinates and total voxel number (in functional resolution) for group-defined ROIs.

ROI name	Hemisphere	*x*	*y*	*z*	No. of Voxels
SI/HA	R	32	−40	50	1066
	L	−35	−39f	49	1033
SII	R	49	−19	20	474.8 (43.83)
	L	−48	−18	18	562.3 (26.12)
PAC	R	45	−20	9	212.2 (14.82)
	L	−42	−22	9	192.0 (25.32)
pSTS region (functional)	R	51	−37	11	130.2 (11.81)
	L	−49	−37	6	90.4 (11.49)
pSTS region (anatomical)	R	52	−36	7	259.5 (23.64)
	L	−54	−37	6	246.2 (19.55)

Numbers shown in parenthesis in the no. of voxels column are the SD. The right and left SI/HA ROIs were the same for all participants.

Anatomically Defined ROIs

ROIs were created for primary somatosensory cortex/hand area (SI/HA), secondary somatosensory cortex (SII), and PAC using the Julich probabilistic atlas. We created maximum probability maps (Eickhoff et al., 2006) containing voxels from all subregions for SI, SII, and PAC (**Figure 2**). This procedure ensured no overlap between somatosensory regions or between SII and PAC as voxels could be assigned to only one ROI. Thus, voxels permitted to SII were prevented from also being assigned to PAC and vice versa. ROIs were then transformed to Talairach space and applied to each participant's brain volume. Upon Talairach transformation, however, there was a small overlap between group-level SI and SII ROIs (30 and 31 functional voxels in the right and left hemispheres, respectively), as well as group-level PAC and SII ROIs (42 and 51 functional voxels in the right and left hemispheres, respectively). To ensure separate, non-overlapping SI/SII ROIS and SII/PAC ROIs within the Talairach space, overlapping voxels were removed. To limit the SI area for voxels encoding hand-specific information, the SI region was constrained along the *z* axis (coordinates between 37 and 63; Kitada et al., 2019). Central coordinates of the SI/HA ROIs are shown in **Table 2**.

In addition, structural volumes were used to manually identify and remove voxels from each individual's SII ROI that were located on Heschl's gyrus, along the planum temporale (PT), superior temporal gyrus (STG), or TPJ. Similarly, voxels from individual PAC ROIs were manually identified and removed if they extended beyond Heschl's gyrus or superior temporal gyrus, or if they resided along the parietal operculum. These extra steps ensured that any overlap between SII and auditory cortex did not confound our analyses. Group averaged central coordinates and total number of voxels for SII and PAC ROIs are shown in **Table 2**. Representative SI/HA, SII, and PAC ROIs for an ED and NH participant are displayed in **Figure 2**.

To verify findings from the functionally defined pSTS region, an anatomically defined posterior STS region based on the Atlas of Intrinsic Connectivity of Homotopic Areas (area label 88; Joliot et al., 2015) was also generated and transformed to Talairach space. This atlas-based pSTS ROI also reduced any bias conferred by using a visual motion localizer to functionally define pSTS. The atlas-defined pSTS region was inspected on each individual's volume, and voxels that extended to the TPJ, parietal operculum, or lateral fissure were removed. Group averaged central voxels and total voxel number are presented in **Table 2**. The more anterior functionally defined pSTS region had marginal overlap with the more posterior atlas-based pSTS region in both

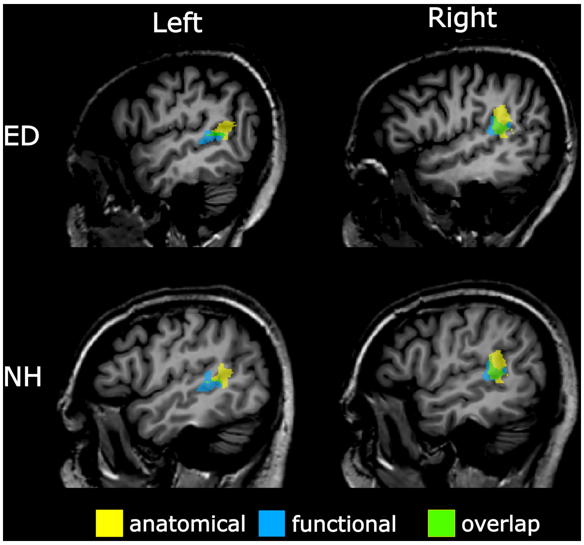

FIGURE 3 | Overlap between anatomically and functionally defined pSTS region. Sagittal view of left (left panel) and right (right panel) pSTS regions defined anatomically via the AICHA (yellow) and functionally via a visual–motion localizer (blue) on a representative ED (top panel) and NH participant (bottom panel). Overlapping voxels between anatomical and functional pSTS regions are displayed in green.

TABLE 3 | Percentage of voxels with significant tactile motion response in ROIs anatomically defined (SI/HA, SII, PAC, and pSTS) and functionally defined pSTS region.

ROI name	Hemisphere	NH	ED
SI/HA	R	29.47% (3.47%)	22.63% (4.84%)
	L	44.39% (5.69%)	35.64% (4.74%)
SII	R	23.76% (3.46%)	27.94% (5.67%)
	L	39.56% (7.03%)	41.57% (5.04%)
PAC	R	7.09% (2.97%)	10.80% (4.35%)
	L	13.07% (4.10%)	18.61% (5.62%)
pSTS region (functional)	R	11.96% (2.52%)	47.68% (7.80%)
	L	10.95% (5.30%)	29.34% (9.08%)
pSTS region (anatomical)	R	9.74% (3.22%)	30.28% (5.35%)
	L	15.10% (6.34%)	17.96% (4.25%)

Numbers represent the group average percentage of voxels within the respective ROI that showed significant activity (qFDR < 0.05) to the tactile motion stimulus vs. baseline. Numbers in parentheses are standard error. Rows represent ROIs.

ED (right: 32.91% ± 2.81%, left: 15.36% ± 4.70%) and NH (right: 33.36% ± 4.16%, left: 14.89% ± 4.80%) as can be seen in **Figure 3**.

General Linear Model Analysis

To quantify differences in the blood oxygenation dependent level (BOLD) response to tactile motion between ED and NH participants, responses to tactile motion vs. baseline were computed for each participant within each ROI. Significant responses were quantified using a threshold of qFDR < 0.05. The proportion of voxels within each ROI with a significant response was reported.

Population Receptive Field Analysis

Voxels within all ROIs were analyzed using methods originally developed for retinotopic mapping (Dumoulin and Wandell, 2008) and later modified for tonotopic mapping (Thomas et al., 2015). Using custom software written in MATLAB, we adapted the pRF analysis for our current experimental stimulus, tactile motion. Briefly, we assumed each voxel within a specified ROI had a one-dimensional Gaussian sensitivity profile (or pRF) centered on the preferred direction of tactile motion. For each voxel, we generated a predicted time-course by convolving the pRF with a general hemodynamic response function (Talavage and Edmister, 2004) and the stimulus sequence. The correlation was estimated between this predicted pRF time-course and the actual functional magnetic resonance imaging (MRI) time-course for each of the four scans, and the maximum correlation value and parameters associated with it were extracted. These best-fitting parameters were used as the initial parameters for a non-linear search algorithm (MATLAB's fminsearch function), which uses unconstrained non-linear minimization to estimate the pRF parameters [center and standard deviation (SD)] that maximize the correlation between the pRF predicted fMRI time-course and the observed BOLD time-course. This procedure was performed for each voxel within the ROI, and the parameters (center and SD) associated with the best-fitting pRF were extracted. The center and SD of the pRF provide estimates for the preferred direction and size of the receptive field for the voxel, respectively. Each direction of tactile motion was assigned a numeric label in a clockwise manner in order to perform the analysis: rightward motion = $\pi/2$; downward motion = π; leftward motion = $3\pi/2$; upward motion = 2π.

To be retained for further analysis, a voxel had to meet all of the following criteria, similar to those used in Thomas et al. (2015) and Huber et al. (2019a,b): (1) The correlation between the observed fMRI-time-course and the predicted time-course was greater than $r = 0.16$; (2) the center of the best-fitting pRF fell within the range of tested directions ($\pi/2$ - 2π); and (3) the SD of the best-fitting pRF fell within a range based on the interval of our numerically labeled directions ($\pi/2$ - $3\pi/2$).

Note that during scanning sessions, tactile motion was simulated by placing the JVP dome on the middle of the index finger pad and moving it in the appropriate direction (**Figure 1**). For the up direction, the dome was moved toward the body away from the fingertip, whereas for the down direction, the dome was moved away from the body toward the fingertip. There is a substantial concentration of tactile receptors at the fingertip compared to the more proximal region of the finger pad while the amount of tactile receptors on the lateral and medial areas of the finger pad is much more equivalent (Johansson and Vallbo, 1979). As described in the "Results," the drastically limited number of voxels displaying sensitivity for the up direction led us to exclude it in subsequent analysis on tuning widths.

Statistical Analysis

Within each ROI, we performed a leave-one-out cross-validation procedure to assess the reliability of our pRF model. For this analysis, we trained the pRF model using all but one

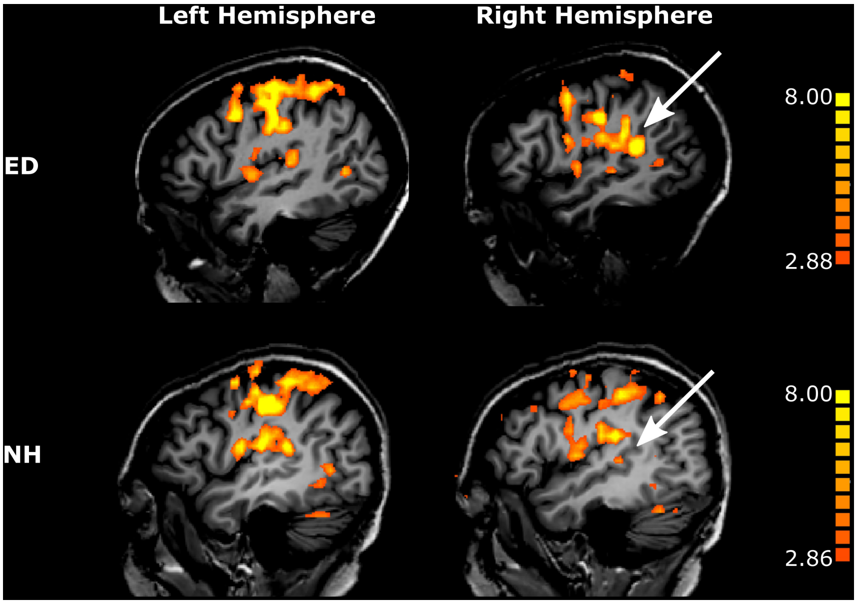

FIGURE 4 | Tactile motion activates right pSTS region to a greater extent in ED than in NH. Voxels with significant activation (qFDR < 0.05) are shown on sagittal sections in the left hemisphere (left column) and in the right hemisphere (right column) for a representative ED (top row) and NH participant (bottom row). White arrows point to right pSTS region.

scan and found the correlation between the predicted and the obtained time-courses for each left-out scan. Voxels with an average correlation of $r > 0.16$ were retained for subsequent analysis and classified as "directionally tuned." These procedures were performed separately within each ROI for each participant.

To determine group differences between the proportions of voxels that showed significant activation during tactile motion and for voxels that demonstrated directional tuning, the non-parametric, Wilcoxon rank sum test was used because the data violated normality assumptions. A Wilcoxon rank sum test was also used to compare activation differences between left and right somatosensory ROIs within each group. However, as parametric assumptions were met for tuning width data, mixed analyses of variance (ANOVAs) were used to evaluate the effect of direction and of group in tuning width estimates. Statistical tests were Bonferroni corrected for multiple comparisons when appropriate. Statistical analysis was performed in R version 1.1.463. In addition, because of limited sample size of $n = 7$ per group, *post hoc* power analyses were performed in G*Power 3.1 software. For our statistically significant findings of increased activation for tactile motion in functionally defined right STS and broader tuning widths in functional and anatomical right STS, *post hoc* power was ≥95.71%.

TABLE 4 | Percentage of voxels that demonstrated significant directional tuning within ROIs anatomically defined (SI/HA, SII, PAC, and pSTS) and functionally defined pSTS region.

ROI name	Hemisphere	NH	ED
SI/HA	R	9.07% (3.03%)	2.84% (0.52%)
	L	15.10% (3.28%)	3.79% (1.10%)
SII	R	7.22% (2.86%)	4.42% (2.04%)
	L	12.18% (3.35%)	5.15% (1.69%)
PAC	R	1.30% (0.67%)	0.99% (0.29%)
	L	2.47% (1.88%)	1.80% (1.06%)
pSTS region (functional)	R	3.93% (1.71%)	10.28% (2.68%)
	L	2.10% (1.20%)	3.31% (2.45%)
pSTS region (anatomical)	R	1.76% (0.52%)	3.96% (1.13%)
	L	2.56% (1.18%)	1.38% (0.54%)

Numbers represent the group average percentage of voxels within the respective ROI that passed our predefined criteria following pRF estimation. Numbers in parenthesis are standard error. Rows represent ROIs.

RESULTS

First, we sought to identify regions that were recruited during simulated tactile motion of the right index finger in our ED and NH groups using GLM. To quantify the extent of activation, we calculated the percentage of voxels that showed significant BOLD activity (qFDR < 0.05) within our functionally defined pSTS region and anatomically defined (SI/HA, SII, PAC, pSTS) ROIs for tactile motion simulation vs. baseline periods. Results from this GLM analysis are displayed in **Table 3** and **Figure 4** and are subsequently referred to as tactile motion responses. We then characterized the directional tuning of voxels within each ROI using a modified pRF model based on the four directions of tactile motion used in this study. Results from our pRF analysis are displayed in **Table 4** and **Figure 5** and are subsequently referred to as directionally tuned responses.

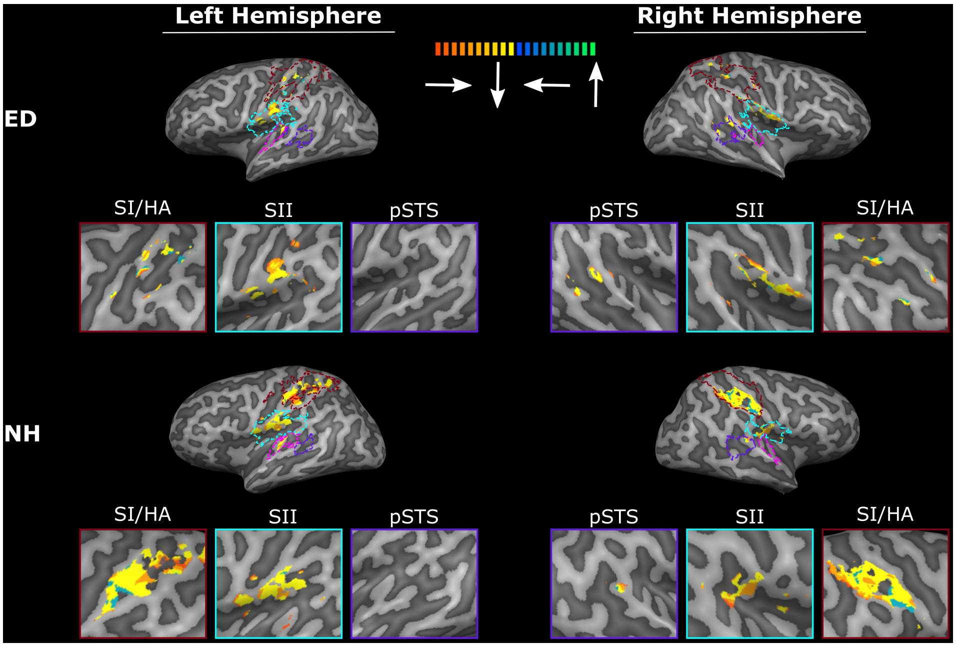

FIGURE 5 | ED and NH participants exhibit similar directional tuning in ipsilateral SI/HA and bilateral SII with minimal tuning in right pSTS region. The best directions within SI/HA (red), SII (blue), functionally defined pSTS region (purple), and PAC (pink) are shown on the cortical surface of a representative ED (top panel) and NH (bottom panel) participant. Direction center values are color-coded along a gradient with right corresponding to red-orange, down corresponding to yellow, left corresponding to blue, and up corresponding to green. All maps are thresholded at $r > 0.16$.

Similar Tactile Motion Response in SI/HA and SII With Reduced Directional Tuning in Contralateral SI/HA in Early Deaf Individuals

As expected, there was no significant difference between ED and NH in the proportion of voxels displaying significant tactile motion response in right SI/HA (Wilcoxon rank sum test, $p = 0.209$) and in left SI/HA (Wilcoxon rank sum test, $p = 0.456$). This finding was consistent for right SII (Wilcoxon rank sum test, $p = 0.710$) and left SII (Wilcoxon rank sum test, $p = 0.456$). As seen in **Figure 4**, there was a trend toward greater activation in the left somatosensory areas compared to right for both ED (right: 22.6% ± 4.84%; left: 35.6% ± 4.74%) and NH (right: 29.5% ± 3.47%; left: 44.39% ± 5.69%), likely due to tactile stimulation of the right index finger, however, this was not significant for either group in SI/HA (Wilcoxon rank sum tests, p's ≥ 0.07) or in SII (Wilcoxon rank sum tests, p's ≥ 0.07).

Next, we sought to examine the directionally tuned response of voxels within these somatosensory areas that are known to exhibit direction selectivity to process tactile motion (Pruett et al., 2000; Pei et al., 2011). While no particular organization for direction specific voxels is evident in either the SI/HA or SII ROIs shown on the surface maps of ED or NH (red and blue outlines on surface and corresponding red and blue boxes in **Figure 5**), the sensitivity of this method is apparent as voxels demonstrating directional tuning to three of the tested directions (right, left, and down) are observed. The absence of directional tuning for the upward direction (and exclusion for analysis) is likely due to the procedural drawback discussed in "Materials and Methods." Briefly, there was reduction of tactile receptors at the proximal part of the fingertip stimulated during the up direction as compared to the distal, medial, and lateral areas of the finger pad stimulated during the down, right, and left directions, respectively (Johansson and Vallbo, 1979). As expected, there was no significant difference between ED and NH in the proportion of voxels within right SI/HA (right: Wilcoxon rank sum test, $p = 0.179$) or SII (right: Wilcoxon rank sum test, $p = 0.318$; left: Wilcoxon rank sum test, $p = 0.128$) that exhibited directional tuning. However, NH had a significantly larger proportion of directionally tuned voxels in left SI/HA as compared to ED (Wilcoxon rank sum test, $p = 0.006$), which survived Bonferroni correction ($p = 0.00625$; 0.05/8).

Figure 6 presents boxplots along with individual data points of the tuning width estimates from the right, left, and down directions for ED and NH groups within various ROIs. A repeated-measures ANOVA was performed with group (ED vs. NH) as a between-participants factor and direction (right vs. left vs. down) as a within-participants factor. It should be noted that not all participants had voxels tuned for all three directions. There was no difference in tuning width estimates between ED and NH groups for the right SI [$F_{(1,\ 32)} = 0.77$, $p = 0.386$], left SI $F_{(1,\ 29)} = 3.15$, $p = 0.087$], right SII [$F_{(1,\ 27)} = 1.08$, $p = 0.307$], or left SII [$F_{(1,\ 31)} = 0.734$, $p = 0.398$] ROIs. Further, there was no effect of direction on tuning width estimates for right SI [$F_{(2,\ 32)} = 1.67$, $p = 0.204$], left SI

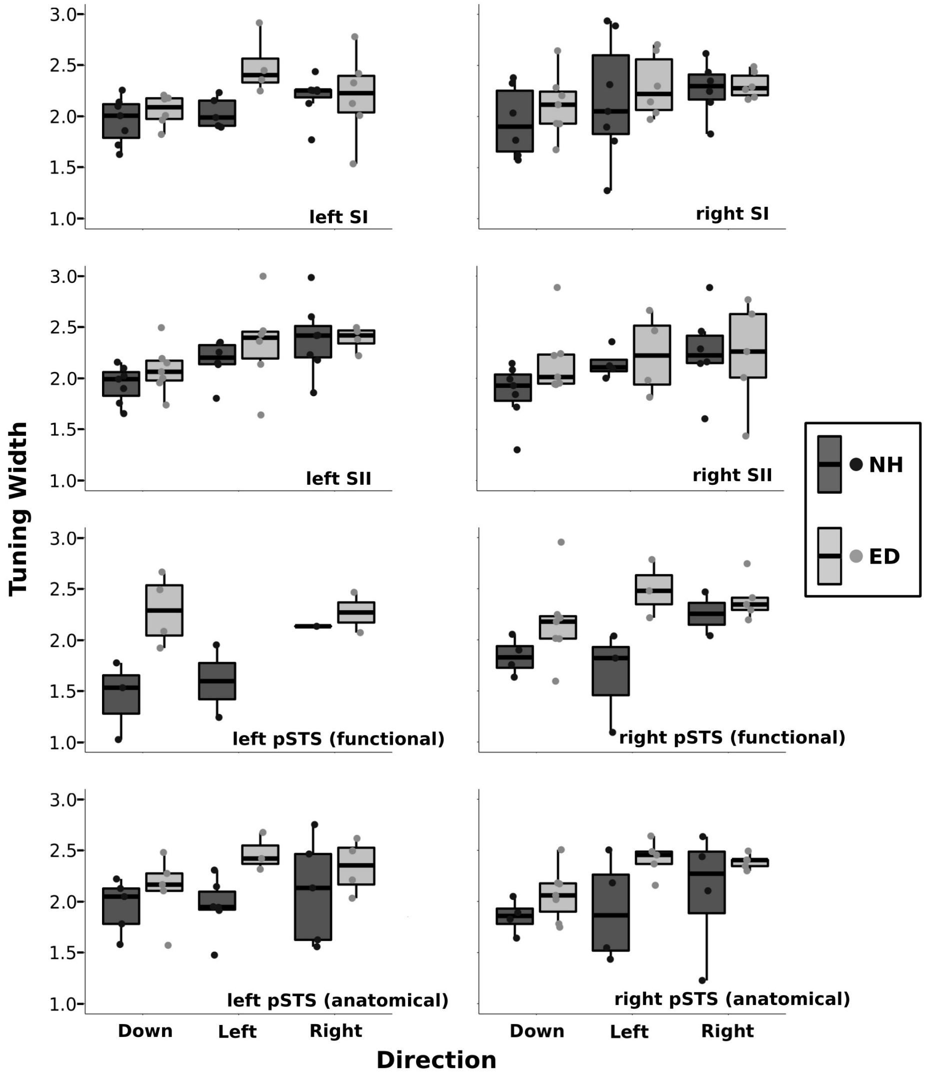

FIGURE 6 | Tuning width estimates are shown separately for down, left, and right directions within the primary and secondary somatosensory ROIs as well as for the functionally and anatomically defined pSTS regions. Boxplots are displayed for each group (NH: dark gray, ED: light gray) where the lower and upper hinges correspond to the 25th and 75th percentiles, and the central bar corresponds to the median. The upper and lower whiskers extend to the largest and smallest, respectively, value no further than 1.5 × the interquartile range. Individual data are also plotted for NH (dark gray circles) and ED (light gray circles).

[$F_{(2,\ 29)}$ = 2,79, $p = 0.077$], or right SII [$F_{(2,\ 27)} = 1.3$, $p = 0.289$]. However, there was a difference in tuning widths based on direction in left SII [$F_{(1,\ 31)} = 5.93$, $p < 0.008$] that survived the Bonferroni-corrected *p*-value of 0.0083 (0.05/6). Follow-up paired *t*-tests using Bonferroni-adjusted *p*-values demonstrate that tuning width estimates for the down direction were narrower than both the right and left directions (*p*'s < 0.018).

Early Deafness Resulted in Greater Recruitment of Right Posterior STS Region for Tactile Motion Processing

While recruitment of the left pSTS region in ED as compared to NH during tactile motion stimulation was not significant (Wilcoxon rank sum test, $p = 0.318$), the right pSTS region exhibited significantly greater tactile motion activity in ED compared to NH using a Bonferroni-corrected *p*-value of 0.00625 (0.05/8) (**Figure 4**) (Wilcoxon rank sum test, $p = 0.001$). This finding cannot be attributed to the size of the right pSTS region as there was no significant difference between groups (Wilcoxon rank sum text, $p = 0.122$). However, as the pSTS ROI was functionally defined with a visual motion localizer and thus may bias toward the ED group (see "Materials and Methods"), we additionally created an atlas-based pSTS ROI (Joliot et al., 2015) to provide a secondary method of comparing tactile motion responses between ED and NH groups. In line with findings from our functionally defined pSTS region, there was no difference between groups in the anatomically defined left pSTS region (Wilcoxon rank sum test, $p = 0.522$). While ED continued to demonstrate greater tactile motion responses in the anatomically defined right pSTS region (Wilcoxon rank sum test, $p = 0.017$), this did not survive multiple-comparisons correction.

A significant number of voxels with direction-selective responses was also observed in functionally defined right pSTS region of the ED group (*mean* = 10.28%, *SE* = 2.68%), but not in the NH group (*mean* = 3.93%, *SE* = 1.71%) as observed in **Figure 5** (purple outline on surface and corresponding purple box). A repeated-measures ANOVA revealed that ED participants had significantly broader directional-tuning bandwidths than NH in functionally defined [$F_{(1,\ 18)} = 9.91$, $p = 0.0056$] right pSTS region. This was further supported by a secondary analysis also showing a significant effect of group in the anatomically defined right pSTS region [$F_{(1,\ 23)} = 6.00$, $p = 0.022$]. However, given the individual variability within the groups, the present findings on comparisons of directional tuning properties within right pSTS region should be interpreted with caution. This is particularly evident in **Figure 6**, which shows a reduced number of tuning width measures within pSTS region ROIs compared to somatosensory ROIs as not every participant exhibited voxels with a significant directionally tuned response for all three directions in pSTS.

A closer look at the ED group reveals that four participants had between 14.62 and 16.95%, whereas three had a more limited proportion of voxels with directional tuning (≤3.79%). In the NH group, one participant showed 13.04% of functionally defined right pSTS region voxels with a directional-selective response, whereas the remaining participants had ≤ 5.60% (two participants had 0%) of functionally defined right pSTS region voxels with significant directional tuning. Interestingly, these same four ED and one NH participants showed the largest proportions of direction-selective voxels within the anatomically defined right pSTS regions, albeit smaller values (4.44–9.14, and 3.17%, respectively), whereas the remainder of ED and NH subjects had minimal proportions of directionally tuned voxels (<2.27% and < 2.84%, respectively). In functionally defined left pSTS region, few participants showed voxels that were tuned to the left (NH: 2, ED: 0), right (NH: 1, ED: 2), and down (NH: 3, ED: 4) directions (**Figure 6**); therefore, no statistical test was conducted comparing groups or tuning widths based on direction in the left hemisphere ROI.

PAC Is Minimally Involved in Tactile Motion Processing as a Consequence of Early Deafness

As is evident in **Figure 4**, PAC showed minimal tactile motion response in both NH (right: *mean* = 7.09%, *SE* = 2.97%; left: *mean* = 13.07%, *SE* = 4.10%) and ED (right: *mean* = 10.80%, *SE* = 4.35%; left: 18.61%, *SE* = 5.62%). While group averages trended toward greater activation in PAC for the ED over NH participants (**Table 3**), this did not reach significance for either hemisphere (right: Wilcoxon rank sum test, $p = 0.653$; left: Wilcoxon rank sum test, $p = 0.535$). In fact, those ED participants who exhibited extant left PAC tactile motion response (4 of 7; > 13%) did not actually reveal activity on Heschl's gyrus, but instead, this activation was closer to the PT region (**Figure 4**). Because of the minimal proportion of voxels showing directionally tuned responses within right and left PAC for both groups (≤2.47%) (see pink outline on surfaces in **Figure 5**), we are hesitant to conclude neuronal populations within PAC that display direction-selective responses to tactile motion.

DISCUSSION

The main aim of the current study was to examine the effects of early auditory deprivation on tactile motion processing. Using a standard GLM approach, we quantified tactile motion response in SI/HA, SII, PAC, and pSTS region. In addition, we employed a modified pRF model to assess tactile motion direction tuning in these areas.

Similar Tactile–Motion Response in SI/HA and SII With Reduced Directionally Tuned Response in Contralateral SI/HA of Early Deaf Individuals

We found no significant difference between ED and NH groups in the proportion of voxels within SI/HA and SII demonstrating significant tactile motion responses. Research on tactile perception typically focuses on how we are able to integrate various cues of an object we are directly interacting with, such as position, orientation, and shape. SI is the first cortical region in this process, while SII typically performs higher-order functions on the cutaneous information (Hsiao and Gomez-Ramirez, 2011). In primates, it has been demonstrated that both regions contain neurons that have various tuning properties for object features such as curvature (Yau et al., 2013), orientation (Thakur et al., 2006), and direction of motion (Pei et al., 2010, 2011). Further, directional modulation of cortical activity within somatosensory areas has been shown in humans (Wacker et al., 2011). There was no significant difference in the proportion of voxels that demonstrated directional tuning between ED and NH in right SI/HA or in bilateral SII. However, NH individuals did exhibit significantly increased proportions of directionally tuned voxels in left SI/HA as compared to ED.

This finding is consistent with previous findings showing reduced activation or feature specificity in non-deprived regions. In normally sighted but not early blind (EB) individuals, direction of auditory motion could be successfully classified by PT, a region normally dedicated to decoding auditory motion information (Baumgart et al., 1999; Warren et al., 2002; Alink et al., 2012), suggesting loss of auditory directional tuning within PT due to early visual deprivation (Jiang et al., 2014). In addition, there was decreased activation of PAC during combined vocal and non-vocal stimulation vs. silence in EB compared to sighted controls (Gougoux et al., 2009). The reduced directional tuning of ED contralateral SI/HA reported in the present study implies similar intramodal plasticity and may suggest an extended network responsible for general and more efficient sensory processing of intact modalities (Gougoux et al., 2009; Stevens and Weaver, 2009). Alternatively, this may reflect additional areas that partially take over the functional role of SI/HA, similar to hMT + in EB individuals wherein classification of auditory motion direction is possible in EB participants (Jiang et al., 2014).

Our pRF analysis also provided estimates of tuning width for individual voxels. Across both NH and ED participants, neural tuning for the downward direction of tactile motion was narrower than for right and left directions in contralateral SII. Accurate representations of haptic objects are driven by complex activity patterns and interactions within SI and SII initiated by stimulus-specific activations. SII not only receives tactile information in a feed-forward manner from SI, but also via direct tactile inputs from the thalamus, which are thought to even exceed thalamic inputs to SI (Mackie et al., 1996; Rowe et al., 1996; Tommerdahl et al., 2010). These various inputs likely contribute to the narrow and specific tuning for specific stimulus features, such as motion direction and spatial orientation, underlying the higher-order tactile processing roles of SII neurons (Hsiao et al., 2002). In addition, the increased density of receptors found at the tip of the index finger compared to the medial and lateral areas of the finger pad (Johansson and Vallbo, 1979) likely contributes to the increased sensitivity for the downward direction reported in the present study. This corresponds to prior studies reporting greater directional acuity for proximal/distal vs. lateral/medial motion (Keyson and Houtsma, 1995) and activity modulation in SI and SII for downward vs. upward diagonal direction (Wacker et al., 2011). However, the precise relationship between peripheral sensor distribution and central tuning properties are beyond the scope of this article.

The tuning width of neural populations has also been associated with perceptual abilities. For instance, narrow directional tuning widths of neurons in macaque MT correspond with more precise perceptual discrimination (Purushothaman and Bradley, 2005), and sensitivity of somatosensory neurons in macaque SI and SII is associated with the ability to discriminate the direction of tactile motion (Pei et al., 2010, 2011). There are contradictory findings regarding any behavioral advantages for ED individuals for processing somatosensory information. Some studies report enhanced tactile abilities in deaf, for example, in a suprathreshold change detection task (Levänen and Hamdorf, 2001), but reduced sensitivity in a temporal discrimination task (Papagno et al., 2016). However, other findings report no difference in tactile frequency discrimination (Levänen and Hamdorf, 2001), tactile detection thresholds (Moallem et al., 2010; Heimler and Pavani, 2014), tactile spatial discrimination (Papagno et al., 2016), and tactile motion discrimination (unpublished data). While we found no difference in the tuning widths of voxels within SI or SII between ED and NH groups, future studies are needed to resolve the disparate findings regarding alterations in haptic perception associated with early deafness.

Greater Tactile Motion Response in Right pSTS Region of ED Participants

While there was no difference in the extent of SI/HA and SII recruitment, there was a significant increase in the tactile motion response of functionally defined right pSTS region for our ED group compared to NH. This finding was confirmed using the anatomically defined right pSTS (although this only trended toward significance after Bonferroni correction), suggesting that multisensory areas serve as prime targets for compensatory plasticity. Future studies that define subregions of the STS using anatomical landmarks or using a vibrotactile localizer to functionally define pSTS region would provide additional evidence on the functional role of this cortical area. For instance, Venezia et al. (2017) demonstrated a posterior–anterior map along the STS dedicated for processing distinct aspects of visual, audio, and audiovisual speech. Functional and modality sensitivities of STS subareas in ED could further elucidate the neural substrates involved in cross-modal reorganization for tactile motion processing. Polymodal regions already display neural areas responsive to multiple modalities so that, during sensory deprivation, receptors from intact modalities can compensate for the deprivation by enhancing response strength and expand to involve neurons deprived of their preferred input. Indeed, changes to neural response properties within normally multimodal areas have been shown for sensory deprived cats. The anterior ectosylvian cortex (AEC) of the cat is a multisensory region containing bimodal and unimodal neurons responsive to visual, auditory, and somatosensory cues. Visually deprived cats show an increase in the proportion of neurons within AEC that are responsive to auditory and tactile input (Rauschecker and Korte, 1993). Similar findings have been reported regarding the auditory field of the anterior ectosylvian sulcus in cats. Normally, ∼30% of the entire neuronal population modulate their response upon somatosensory input (Meredith et al., 2006), and another ∼30% alter their response during visual stimulation (Meredith and Allman, 2009), indicating the existence of subthreshold multisensory neurons. When early deafness is induced via cochlear lesions, this area exhibits significant cross-modal plasticity with ∼90% of neurons demonstrating modifications in their modality response profiles, likely due to a release on the sensory specificity of existing neural connections (Meredith and Lomber, 2011).

In humans, the STS region, including the middle and posterior temporal sulci, middle temporal gyrus, and STG, has consistently been identified as displaying multimodal response properties. The pSTS region is necessary in integrating auditory and visual information (Calvert et al., 2001; Noesselt et al., 2007) and also becomes active during vibrotactile (Beauchamp et al., 2008) and tactile motion stimulation (Jiang et al., 2015) in hearing adults. As a result of auditory deprivation, the pSTS region undergoes reorganization (Li et al., 2013) and becomes recruited for visual motion processing (Bavelier et al., 2001; Shiell et al., 2015), visual temporal processing (Bola et al., 2017), and tactile frequency processing (Levänen et al., 1998). To our knowledge, this article is the first to report similar compensatory plasticity in right pSTS region for tactile motion processing in ED. Further, the unilateral response to tactile motion of the pSTS region reported here is consistent with prior studies examining this area for visual processing under early deafness. A similar hemispheric bias for the right pSTS region over the left has been shown in ED for detecting moving over static visual stimuli (Vachon et al., 2013) and in the anterior STS region in response to faces (Weisberg et al., 2012) in early deafness.

Despite a significantly larger proportion of voxels with tactile motion response in the right pSTS region in the ED group, this region does not demonstrate a considerable directional-selective response for all participants. While we did find a significant proportion of voxels exhibiting directional tuning within the right pSTS region on the group level, this was not representative of the individual data (three ED participants had $\leq$ 3.79% of directionally tuned voxels in functionally defined right pSTS region). One possibility for this might be due to a more distributed network of neuronal populations in this region rather than neurons dedicated to processing specific aspects of tactile motion. Indeed, ED individuals do show an effect of attention on activation of pSTS while presented with moving visual dot stimuli (Bavelier et al., 2001). A similar effect may occur in the context of tactile motion. While activation of right pSTS region in ED during tactile motion presentation may reflect increased attention and resources for processing a tactile stimulus, the dispersed number of directionally tuned voxels within pSTS reveals that this region is not necessarily involved in processing discrete features of the tactile stimulus. This is consistent with right pSTS region recruitment for directional vs. non-directional visual motion without specificity for a particular direction in ED adults (Retter et al., 2019). Further, for those individuals with directionally tuned voxels, the ED group displayed significantly broader neural tuning for anatomically and functionally defined right and left pSTS regions regardless of motion direction indicating more global processing of the haptic cue vs. specific processing of motion direction by pSTS. This is further supported when comparing the increased proportion of directionally tuned voxels in the functionally defined right STS compared to the anatomically defined right pSTS for all participants. The functionally defined right pSTS was more anterior and specific to areas also responsive to visual motion in ED, supporting the notion that the functionally defined right pSTS highlights a region that is recruited for supramodal motion processing as a consequence of early auditory deprivation.

Minimal Tactile Motion Response and Directional Tuning in PAC for ED

When presented with visual motion stimuli, a consistent finding is recruitment of auditory cortex in deaf individuals (Finney et al., 2001; Fine et al., 2005). Similar cross-modal plasticity of PAC is revealed during a visual detection task in the peripheral visual field (Scott et al., 2014). These findings fall in line with the enhanced visual processing abilities reported for deaf individuals, specifically greater attention to the visual periphery (Bavelier et al., 2006; Scott et al., 2014) and heightened sensitivity for detecting and discriminating visual motion (Pavani and Bottari, 2012). However, the current results did not find evidence for substantial PAC activation during tactile motion presentation. Further, the minimal activation that was present was not confined to ED participants, and neither group demonstrated directional tuning within PAC.

One major principle guiding cross-modal plasticity is retainment of function (Bavelier and Neville, 2002; Renier et al., 2014), whereby functional reorganization of a sensory-deprived cortical area is guided by computational fitness, or characteristics that will enable the same functional role of the area, also known as functional constancy (Amedi et al., 2007; Saenz et al., 2008; Jiang et al., 2014). The auditory modality is predominant in processing temporal features, and prior studies showing PAC recruitment by ED adults during a visual rhythm task (Bola et al., 2017) and using vibrotactile stimuli (Auer et al., 2007) support the principle of functional constancy. As the current design used spatial features of the tactile stimulus, it is perhaps not surprising that there was no significant recruitment of PAC in the ED group.

Furthermore, the minimal tactile motion response that was seen in PAC was in both groups and was not localized to Heschl's gryus but close to PT. Numerous findings implicate PT in the dorsal auditory pathway and show PT activation for spatial feature processing such as motion and spatial change (Alink et al., 2012; Isenberg et al., 2012; Jiang et al., 2014). Indeed, in early deafness, PT has been reported to be active in the context of visual motion (Finney et al., 2001), and cortical density of the PT was associated with visual motion detection abilities (Shiell and Zatorre, 2017). Future studies should use an auditory motion/spatial localizer to functionally define the PT and explicitly investigate this region's response to tactile motion in ED.

CONCLUSION

The current findings provide evidence for compensatory plasticity within right pSTS region of ED adults for processing tactile motion. However, it is important to note that this finding did not survive multiple-comparisons correction when the anatomical definition of the right pSTS region (corrected p = 0.07) was used, limiting the scope of our results. Future studies that use a vibrotactile localizer, rather than a visual motion localizer as in the current study, to define pSTS region could strengthen evidence for the group difference in activation. In addition, an increase in sample size could reveal a statistical difference for both ROI definitions and would also increase the robustness of present findings. Finally, we acknowledge the potential drawbacks of manual tactile motion simulation by the experimenter including spatiotemporal variability and overall reproducibility. Future replication of the study involving a mechanical device would address these limitations and may reduce the variability found for directional tuning.

Despite the significant increase in tactile motion response of right pSTS region in ED participants, there was no evidence for enhanced directional tuning. The lack of auditory input to the polymodal STS likely drives the increased recruitment of this region, allowing for increased resources allocated to processing tactile motion albeit with reduced tuning to spatial features of the stimulus (i.e., direction). However, this interpretation should be taken with some caution due to the individual variability and the limited directions we simulated manually. Future studies could use a device for automated stimulus presentation, which would allow precise stimulation in a greater number of directions. Another main finding was the reduced directional tuning in contralateral SI/HA of ED despite similar somatosensory area activation relative to NH suggesting that early deafness leads to modified tuning profiles of neuronal populations within intact primary sensory areas. In summary, early deafness leads to cross-modal recruitment of the innately multimodal right pSTS region, despite absence of enhanced directional tuning, and reduced directional sensitivity of intact SI/HA. Taken together these findings suggest that early auditory deprivation results in a more distributed cortical network with a wider response profile for tactile motion processing.

DATA AVAILABILITY STATEMENT

The de-identified raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Nevada, Reno Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FJ designed the experiment. AS and FJ collected the data. AS conducted the statistical analysis with assistance on approach and interpretation from CM, EH, and FJ. AS wrote the manuscript. CM, EH, and FJ critically evaluated the manuscript. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Standardized and Experimental Tools to Assess Spatial Cognition in Visually Impaired Children: A Mini-Review

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The acquisition of spatial cognition is essential for both everyday functioning (e.g., navigation) and more specific goals (e.g., mathematics), therefore being able to assess and monitor spatial cognition from the first years of life would be essential to predict developmental outcomes and timely intervene whenever spatial development is compromised. Several shreds of evidence have indicated that spatial development can be compromised in the case of development with atypical sensory experience such as blindness. Despite the massive importance of spatial abilities for the development of psychomotor competencies across childhood, only a few standardized and experimental methods have been developed to assess them in visually impaired children. In this review, we will give a short overview of current formal (standardized) and informal (experimental) methods to assess spatial cognition in visually impaired children, demonstrating that very few validated tools have been proposed to date. The main contribution of this current work is to highlight the need of *ad hoc* studies to create and validate clinical measures to assess spatial cognition in visually impaired individuals and address potential future developments in this area of research.

Keywords: spatial cognition, visual impaired children, clinical assessment, review, rehabilitation

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INTRODUCTION

Several shreds of evidence have shown that the acquisition of spatial capabilities is fundamental for psychomotor, cognitive, and social development (Newcombe and Huttenlocher, 2000; Vasilyeva and Lourenco, 2012). For instance, it has been suggested that spatial cognition not only is fundamental to navigate and orient in the environment, even with the use of symbolical means such as models or maps (Montello and Raubal, 2012), but also it is linked to perspective taking and problem-solving (Newcombe and Learmonth, 2009). Overall, spatial cognition refers to the knowledge and internal or cognitive representation of the structure, entities, and relations of space (Hart and Moore, 2017). In this sense, spatial cognition can be considered as a component of the broader concept of intelligence and constitutes a relevant element that defines the structure of human intellect, involved both in everyday life skills and in the acquisition of learning abilities (Newcombe et al., 2013). The neuropsychological examination of general intelligence in children and adults typically takes into consideration spatial subtests. For instance, the most recent version of the Wechsler Intelligence Scale for Children includes a subtest (Visual Spatial Index – VSI) that directly assesses visuo-spatial processing. Also, many tests have been developed to specifically assess different aspects of spatial cognition in sighted children, such as visuo-spatial perception, visuo-spatial memory, construct abilities and orientation skills. Such findings suggest that a crucial factor in fostering psychomotor and cognitive development is spatial cognition, which supports the acquisition of fundamental abilities such as reasoning. This argues in favor of the importance of an overall assessment of such abilities to better define the cognitive profile of the child, whether he/she is sighted or visually impaired. In literature, the evaluation of spatial cognition in visually impaired people has led to contrasting results: some work supports the hypothesis of visually impaired people being able to acquire similar spatial competencies to their sighted peers, while several other works have indicated that spatial cognition can be compromised in visually impaired people (Thinus-Blanc and Gaunet, 1997; Pasqualotto and Proulx, 2012; Schinazi et al., 2016; Giudice, 2018). In this sense, the assessment of spatial abilities in this population would be necessary to personalize rehabilitation interventions based on patients' strengths and limitations. Indeed, children with visual impairment may manifest delays in locomotion development (Hallemans et al., 2011) and difficulties in understanding the topographical position of sound sources in space (Fazzi et al., 2011; Cappagli and Gori, 2016; Vercillo et al., 2016) as well as in proprioceptive localization (Cappagli et al., 2017a). Nonetheless, very few standardized tools exist to assess spatial abilities in children with blindness or low vision. The reason could be that most of the conventional spatial tests for typical children are visual and cannot be easily adapted to other modalities (such as hearing or touch) for technical reasons. On the contrary, many research paradigms have been developed to assess spatial cognition in children with none or partial vision, but none of them has been formally validated, except for a single study, to our knowledge, that developed and validated an experimental battery of spatial tests, providing the first gold standard for assessing spatial cognition deficits in visually impaired children (Finocchietti et al., 2019). This study evaluated the reliability of a test battery comprising six spatial tests assessing different spatial competencies (e.g., the ability to estimate the topographical representation of single or multiple sound sources) on a group of thirty aged 6–17 visually impaired children and showed good-to-excellent reliability for all six tests. From a practical point of view, the lack of standardized methods to assess spatial cognition in children with visual impairment results in a lack of outcome measures for rehabilitation interventions, limiting the objective evaluation of children's advancements, as highlighted in a recent review on the topic (Elsman et al., 2019).

STANDARDIZED TOOLS TO ASSESS SPATIAL COGNITION IN THE VISUALLY IMPAIRED CHILD

A range of psychometric tests has been developed for blind or partially sighted individuals. Some of them are based on tests for sighted people, while others have been specifically designed for visually impaired people. Tests developed for adults include, for example, the Cognitive Test for the Blind (Nelson et al., 2002) and the Haptic Intelligence Scale for Adult Blind (Shurrager and Shurrager, 1964). Since this mini-review is intended to summarize only tools designed for visually impaired children, a description of the adult tests goes beyond our purpose.

Regarding the standardized tools to assess spatial cognition in visually impaired children, we highlight some limitations: first of all, the majority of them have been developed as a general intelligence test, with spatial cognition representing only a limited part. Other limitations are the absence of validation measures and the lack of reported evidence about their acceptance rate (Atkins et al., 2012). Moreover, developmental tests to measure general intelligence and/or specific aspects of intelligence (i.e., spatial cognition) in visually impaired children are mostly for children in scholar age (from 6 years old) and lack of standardized norms or have norms that refer to sighted peers (Bauman and Kropf, 1979). Moreover, most of them are based almost exclusively on the assessment of haptic spatial processing, and are used to assess children with different degree of visual impairment: in this sense a low vision child could be disadvantaged, compared to a blind peer, when faced with a test requiring only haptic abilities, not being put in a position to use his/her residual vision.

Below we report a list of the most used standardized tests specifically targeted to measure spatial capabilities or more widely related to general intelligence in visually impaired children (in **Table 1** we summarized the main studies reported below).

Reynell-Zinkin Scales (Reynell and Zinkin, 1975; Reynell, 1978)

This test was designed to assess the motor and mental development of blind or partially sighted children from birth to 5 years of age. The original study (Reynell and Zinkin, 1975) was based on 116 recordings of a heterogeneous population of visually impaired children (blind or partially sighted) with any other disabilities, whose both motor and mental development were assessed. Subsequently, the same authors (Reynell, 1978) used the Reynell-Zinkin Mental Development Scale to assess a more homogeneous population composed of 109 visually impaired children almost without associated disabilities (17 had mild cerebral palsy, 8 had hearing impairment). Nonetheless, no reliability and validity data were available until 1995 (Dote-Kwan, 1995). Vervloed et al. (2000), given the lack of psychometric data in the original version of the scale and the clinical impression that the age norms tended to overestimate the real developmental level of visually impaired children, constructed new age developmental levels. In this study, 82 children aged 0–48 months with low vision without any other disability were included. It was concluded that the Reynell-Zinkin Scales, to evaluate the rate of progress of visually impaired children, should be better administered between ages 1 and 3.5 years old. Also, the authors pointed out that: (a) these new age levels should not be used to compare the separate scales due to the lack of standardized scores; (b) with the new age levels, it was possible to compare the rate of development in similar visual categories. By now, the Reynell-Zinkin Mental Development

TABLE 1 | List of standardized tests to assess spatial cognition in visually impaired children with their main related studies.

Test	Related studies	Visually impaired sample	Functional vision	Age	Comorbidities	Sighted controls (sample size)	Type of analysis	Main result	Limits
Reynell-Zinkin Scale *	Reynell (1978)	109	Blind and partially sighted	0–60 months	17 mild cerebral palsy 8 hearing impairment	Yes (NA)	Comparative quantitative study (visually impaired VS sighted)	A developmental pattern for visually impaired children is outlined with respect to sighted children	- Reliability and validity measures were not provided - Not specifically designed to assess spatial abilities
	Dote-Kwan (1995)	18	Blind	20–36 months	No	No	Pearson product-moment correlation	Strong correlation with Maxfield-Buchholz score	- Small sample size - Limited age range
	Vervloed et al. (2000)	82	Low vision	0–48 months	No	No	Study of item distribution, scale reproducibility, internal consistency, standard errors of measurement, and associations with personal and environmental factors.	New developmental age levels were provided	- Internal consistency of the subscales is not sufficient at all ages for all the subscales
Haptic Test Battery	Ballesteros et al. (2005)	59	Blind and partially sighted	3–16 years	No	Yes (60)	Alpha coefficient for reliability; factor analysis for validity	Good internal consistency, construct validity (six-factor structure) and age sensitivity	- Not specifically designed to assess spatial abilities - Assessment of only haptic spatial processing - No differences between blind and low vision children in test administration nor specific adaptations
Haptic 2-D	Mazella et al. (2016)	69	Blind and low vision	5–25 years	26 out of 69 with cognitive/sensory or neurological comorbidities	Yes (69)	Test-retest reliability; Convergent validity; Discriminant validity	Good sensitivity, reliability and validity. Better suited to assess tactual abilities at 5 to 18 years old	- Not specifically designed to assess spatial abilities - Assessment of only haptic spatial processing - No differences between blind and low vision children in test administration nor specific adaptations - Only one-hand exploratory movements

(Continued)

TABLE 1 | Continued

Test	Related studies	Visually impaired sample	Functional vision	Age	Comorbidities	Sighted controls (sample size)	Type of analysis	Main result	Limits
The Bayley Scales Of Infant And Toddler Development (3rd Edition) **	Bayley (2006)	1700	Typically developing children (standardization sample)	1–42 months	10% with mental, physical and behavioral difficulties	No	Split-half method and coefficient alpha for internal consistency reliability; Factor analysis	Good validity and reliability	- Not specifically designed to assess spatial abilities in visually impaired children - Potential floor inadequacy for lower performing and extremely young children (0–6 months)
	Visser et al. (2014)	19	11 out of 19 with low vision	22–90 months	All 19 children with different degree of motor impairment	No	Comparative quantitative study (standard test VS accomodated test)	No significant different between Low Motor/Vision accommodated version and the standard version. Accommodations showed to be beneficial for a subgroup of children	- No vision adaptation for blind children (i.e., tactual or sonorous) - Small sample size - No data to support the hypothesis of a better performance with the adapted test
Intelligence Test For Visually Impaired Children	Dekker (1993)	155	106 blind children, 49 visually impaired children	6–16 years	No	No	Alpha coefficients and odd-even split-half coefficient for reliability; Factor analysis	Good validity and reliability. Useful to compare braille-educated and print-educated visually impaired children	- Not specifically designed to assess spatial abilities - Assessment of only haptic spatial processing - Separated age-normed tables should be used for children with and without usable vision
The Hill Performance Test Of Selected Positional Concepts	Hill and Hill (1980)	273	Blind	6–10 years	64 with additional disabilities (no further information available)	No	Test-retest method for reliability; Spearman Rank-Order Correlation for validity	Sufficiently reliable and valid	No assessment of spatial concepts other than basic positional concepts

*We included the original study (Reynell, 1978), the first study (Dote-Kwan, 1995) that provided some quantitative data about the validity of the scale and the study (Vervloed et al., 2000) that provided new developmental age levels for the Reynell-Zinkin Scale. **We provided both the standardization study of the third edition (Bayley, 2006) and the pilot study (Visser et al., 2014) that tested specific adaptation for visual and motor disabilities.*

Scale focuses on six developmental areas, each assessed through specific items: social adaptation, sensorimotor understanding, exploration of the environment, response to sound and verbal comprehension, expressive language, and communication. The purpose of these scales is to define, as early as possible, the abilities and difficulties of a visually impaired child to better tailor an appropriate intervention. The assessment of spatial abilities is better represented by the "exploration of environment" scale: the items proposed are intended to progressively assess the ability to explore surfaces and objects encountered during locomotion, orient in a room and explore it through directed locomotion, also using fixed objects (doors, pegs or other furniture) as reference points. Moreover, the subscale "response to sound" gives indication about children' ability to orient to sonorous stimuli in space.

Haptic Test Battery (Ballesteros et al., 2005)

This test has been developed to assess the perceptual and cognitive abilities of visually impaired children without any other known disabilities between 3 and 16 years old using active touch. First designed in 2002, it was subsequently refined (Ballesteros et al., 2005) to examine its reliability and construct validity on 119 schoolchildren (59 blind or visually impaired, 60 sighted). The original battery included twenty sub-tests. The first three sub-tests were adapted from the Luria-DNI neuropsychological battery (Manga and Ramos, 2017). The others explored perception of texture, 2-D raised-line shapes, and 3-D objects, as well as the perception of their spatial orientation, and memory for familiar and for novel objects, recognized in previous studies as major aspects of haptic perception and cognition (Lederman, 1983; Millar, 1986; Ballesteros et al., 1999). Test materials are composed by raised-line, raised-dot, raised-surface shapes and displays, and familiar and novel 3-D objects. At the end of the reliability and validity study, six factors were identified as being explored by the sub-tests proposed. The first one, spatial comprehension, includes seven sub-tests that aim to assess, respectively: (i) the ability of the child to compare different haptic dimensions (shape, size, texture), (ii) to recognize shapes with the same orientation, (iii) to individuate spatial location on a 2D surface, (iv) to classify objects as "symmetric" or "asymmetric" (three subtests), and (v) to recognize "non-sense" 3D objects after an interpolated task (this last sub-test is also included in the "Longer-term coding for new objects" factor). Regarding the statistical influence of age and visual condition, age resulted in being significant in all the subtests, and the visual condition showed to be significant in five sub-tests (in which blind performed better than the sighted group). The authors concluded that all these sub-tests investigate aspects of spatial perception and cognition, resulting in a valid assessment of haptic spatial processing and development. In our opinion, two subtests assessing, respectively, the ability to recognize and localize stimuli on a worksheet and the ability to scan a dot-display (both involved in pre-school ability to read braille) may be useful to evaluate children' spatial abilities, giving the importance of such abilities in the development of good pre-school skills.

Haptic-2D (Mazella et al., 2016)

This is a psychometric test originally designed for visually impaired subjects between 5 and 18 years of age. In the validation study, subjects with additional disabilities were included in the visually impaired group. According to the authors, it is the first test taking a developmental approach to tactual abilities using 2D raised materials only (dots, lines, shapes, patterns, and pictures printed on swell paper). The purpose of the battery is to evaluate tactile functioning in terms of raised-shape processing, sequential scanning and raised-line object identification, thus providing information about essential pre-school and everyday life abilities. The battery is composed of eleven tests divided into five categories: (a) scanning skills, (b) tactile discrimination skills, (c) spatial comprehension skills, (d) short-term memory, (e) picture comprehension. Some of the tests are taken or adapted from Haptic Test Battery (Ballesteros et al., 2005). The two tests included in the spatial comprehension dimension are, respectively, a spatial orientation and a spatial location test. In both tests, the participant is presented with a series of six items, preceded by a practice trial, with the aim of comparing the tactile item with a benchmark stimulus. The authors concluded that the haptic modality can be used in the context of psychometric evaluations for visually impaired or blind children and adolescents, providing a measure of the age-related efficiency of processing of raised materials. According to the authors, the proposed battery has good psychometric properties but shows two major limitations, one referred to the constraints imposed on the exploratory hand movements (most of the tests have to be performed with one hand only), the other referred to the possibility of using non-informative vision during the tests by subjects with low or normal vision. Subjects with additional disabilities were included in the original study group of 138 participants, showing significantly different scores respect to subjects with no additional disorders only in the tactile memory span test.

The Bayley Scales of Infant and Toddler Development (Bayley, 1969)

In its third version, this is an instrument designed to measure the developmental functioning of infants and toddlers and to identify possible developmental delay (Albers and Grieve, 2006). The original Bayley Scales of Infant Development (BSID) was published in 1969 (Bayley, 1969), while the second edition (BSID-II) was presented in 1993 (Bayley, 1993). The Bayley-III is designed to be administered to children between 1 and 42 months of age and is composed of Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior scales. Spatial perception evaluation can be found in the Cognitive and the Motor scales, where visual and tactile exploration and perceptual-motor integration tasks are proposed (e.g., building simple structures, tracing an outline on paper, visual tracking, reaching). The Scale is designed to be used as part of the assessment for children with various disorders and/or disabilities. In 2014 (Visser et al., 2014), a pilot study was conducted based on an adapted version of the test for children with visual and/or motor impairment to increase the construct validity by decreasing the influence of the impairment on the test results. The adaptation was based on the Low Motor and Low Vision accommodated versions of the Dutch Second Edition of the Bayley Scales of Infant Development (Ruiter et al., 2011). The Low Vision adaptations were integrated with the Low Motor adaptations and consisted of slight adaptations in materials and instructions and in the removal of the time limits, allowing children to have more time to explore and identify materials. Children were administered once the Low Motor/Vision accommodated version and once the standard version of the Bayley-III, with an average time interval of 2 weeks between the two administrations. The authors concluded that some of the children with motor and/or visual impairment might benefit from the adaptations, which result in a smoother test administration and valid test results, even though there were no significant data to support the hypothesis that most of the children would score higher with the adapted test.

Intelligence Test for Visually Impaired Children (Dekker, 1993)

This tool was developed to fill the gap between the need to measure intelligence in visually impaired children aged between 6 and 15 years old and the lack of instruments specifically designed for this population. It was designed to include 13 subtests assessing a broad spectrum of abilities, from verbal competencies to reasoning, memory skills, and spatial perception. Regarding the latter, four subtests were identified as underlying, respectively, the Orientation factor ("Map Question" and "Plan Questions") and the Spatial Ability factor ("Block Design" and "Rectangle Puzzles"). Dekker (1993) administered this test to a Dutch-speaking population of children between 6 and 16 years old with "usable" and "no usable" vision. An analysis of the results depending on the grade of visual impairment and the visual education received ("print" or "braille") was performed. Results indicated that low-vision performed better than blind children in spatial and orientation sub-tests. Moreover blind children referred to braille-education at the age of six obtained the lowest scores in the spatial subtests, indicating these two variables have to be taken into consideration when the test is administered.

The Hill Performance Test of Selected Positional Concepts (Hill and Hill, 1980)

This test is based on the "Concepts Involved in Body Position and Space" test developed by the same author (Hill, 1971) to evaluate basic positional concepts in visually impaired children between 6 and 10 years of age. The seventy-two performance items are divided into four parts assessing the abilities to (a) identify positional relationships of body parts; (b) demonstrate positional concepts by moving various body parts to one another; (c) demonstrate positional concepts by moving the body in relation to objects; (d) form object-to-object relationships. The revised test was validated on a sample of 273 American visually impaired children with basic skills regarding motion, body parts knowledge, and receptive language, and was administered by orientation and mobility specialists. The authors did not find a significant difference in performance according to the school placement, nor to the ability to read braille. To our knowledge, no studies were published using this test.

RESEARCH PARADIGMS TO ASSESS SPATIAL COGNITION IN THE VISUALLY IMPAIRED CHILD

In contrast with the very few standardized methods listed above, many experimental paradigms have been developed to investigate spatial cognition in visually impaired individuals, but most of them have been tested only on adults, leading to mixed results (Thinus-Blanc and Gaunet, 1997; Pasqualotto and Proulx, 2012; Voss, 2016; Setti et al., 2018). The criteria generally used by researchers to define experimental paradigms are very different among studies. A useful distinction can be made between locomotion tasks and tabletop tasks, respectively, requiring and not requiring individuals to move in the environment. Both intended to test the ability of participants to build a spatial representation of the setup (Klatzky et al., 1995). It is not the purpose of this work to review all the research paradigms proposed in the literature, but to provide examples of experimental tabletop and locomotion tests designed for visually impaired children that might be taken as a reference for future validation studies. Moreover, it would be useful to link novel validated experimental paradigms to standardized clinical tools in order to provide clinicians and researchers a comprehensive battery of methods to assess spatial cognition in the visually impaired child.

Among tabletop tests, different auditory and haptic spatial competencies have been investigated in visually impaired children. For instance, the ability to understand the spatial relation of three sounds differently positioned in space (Vercillo et al., 2016) and the ability to identify and/or reproduce the spatial position of auditory (Ashmead et al., 1998; Cappagli and Gori, 2016; Cappagli et al., 2017a) or haptic targets (Gaunet et al., 2007; Ittyerah et al., 2007), the ability to switch from egocentric to allocentric spatial frames of reference (Ochaita and Huertas, 1993). Moreover, some research has shown that technological tools such as programmable tactile displays can be used to administer tabletop spatial perception and memory tests to visually impaired children (Leo et al., 2017, 2018). Among locomotion tests, visually impaired children were tested on their ability to detect and avoid obstacles (Ashmead et al., 1989), identify and reach sonorous objects (Bigelow, 1986; Ihsen et al., 2010; Fazzi et al., 2011), make spatial inferences finding new routes between external landmarks (Landau et al., 1984) and navigate in large-scale environments showing evidence of spatial cognitive mapping (Morrongiello et al., 1995).

To our knowledge, only one study validated a battery of experimental spatial tests (BSP, Blind Spatial Perception), providing the first gold standard for assessing spatial cognition deficits in visually impaired children (Finocchietti et al., 2019). A group of thirty children with visual impairments aged 6–17 years old were tested on the BSP comprising the following six spatial tasks: auditory bisection (listen to three sounds and report whether the second sound was closer in space to the first or to the last one presented), auditory localization (listen to one sound and point toward its spatial location), auditory distance discrimination (listen to three sounds and report whether the first or the second presented is closer to their body), auditory reaching (listen to one sound and reach it in space), proprioceptive reaching (repeat a memorized arm movement toward a specific spatial position), and general mobility (walk straight for three meters and come back at their own pace). Test-retest reliability showed good-to-excellent reliability for all six tests, demonstrating that the BSP is a reliable tool to identify spatial impairments in visually impaired children.

CURRENT RESEARCH GAPS AND POTENTIAL FUTURE DEVELOPMENTS

It is well known that visual experience alone and multisensory experience involving visual information is crucial in forming a mental representation of space (Eimer, 2004; Pasqualotto and Proulx, 2012). Research studies suggest that the absence of vision affects the development of specific spatial abilities in visually impaired children (Cappagli and Gori, 2016; Vercillo et al., 2016; Cappagli et al., 2017a) with possible negative consequences on other developmental domains such as social cognition (Hestenes and Carroll, 2000; Lewis et al., 2000). This evidence leads to the hypothesis that rehabilitation programs should include specific multisensory spatial training from an early age (Cappagli et al., 2017b, 2019). Standardized clinical and/or experimental tools to assess spatial cognition in the developing visually impaired child would provide the criteria to identify both spatial challenges and rate of progress and consequently to focus habilitation intervention strategies on areas requiring support. Being able to identify spatial impairments with standardized and validated methods early would increase the benefits of rehabilitation interventions. With this review, we highlighted that very few standardized tools to assess spatial cognition in visually impaired children have been developed. Moreover, the tools developed to date present some important limitations: for example, the poor specificity for spatial cognition (most of them being primarily developed as general intelligence tests), the preeminent use of haptic modality, and the general lack of differentiation between blind and low vision children, not allowing for an adequate exploitation of residual vision. Furthermore, almost none experimental methods have been validated until now. The lack of standard and validated behavioral measures to evaluate spatial abilities in the visually impaired has led to contrasting results in the literature about enhancements and impoverishments of spatial cognition in this population. In this sense, our research group is currently working to develop assessment tools for spatial cognition that can be standardized on a visually impaired pediatric population, also through proper adaptations of the most commonly used tests for sighted children. Moreover, we are also working to increase scientific knowledge about the developmental aspects of spatial cognition in visually impaired children [e.g., Martolini et al. investigates allocentric spatial development in low-vision children (Martolini et al., 2020)].

Overall, with this work we identified two main research gaps that might address future development in this research area:

1. the lack of formal (standardized) tests to evaluate spatial capabilities in visually impaired children and/or the lack of auditory or tactile adaptations of existing standardized tools to assess the same skills in sighted individuals;
2. the lack of informal (experimental) validated methods to determine spatial cognition in the visually impaired pediatric population, especially for what concerns paradigms in the auditory modality.

Potential future developments in this area of research may concern not only the creation of new standardized test for spatial evaluation as suggested in the previous sections, but also the validation and large-scale application of recently developed prosthetic devices to support spatial learning in blind individuals. Indeed, during the recent years, there has been an increasing interest in the development of technological aids to convey spatial information to the blind by means of haptic (e.g., accessible interactive tactile maps for geographical representations) (Ducasse et al., 2018) or auditory (e.g., radio beacons for navigation or sound sensory substitution for obstacle avoidance) displays (Chebat et al., 2017; Strumillo et al., 2017). Such affordable devices have been created to allow visually impaired users to build a mental representation of the surrounding environment, fostering their overall adaptation to real-life situations. Nonetheless, very few of such technological tools have been validated on visually impaired children (Gori et al., 2016), with negative consequences on rehabilitation outcomes. Since it has been shown that technological systems to support spatial learning blind individuals can even determine training-induced plastic changes, it would be promising to expand their use in the visually impaired community. For instance, the validation of technical aids to support the acquisition of echolocation skills would be of fundamental importance for visually impaired individuals, since it has been shown that echolocators can develop sighted-like performance in terms of spatial cognition (Teng et al., 2012; Vercillo et al., 2015). Similarly, it would be interesting to validate systems that support spatial learning in blind children from an early age, since it has been shown that they can foster multisensory development such as the ABBI (Audio Bracelet for Blind Interaction) device (Finocchietti et al., 2015; Ben Porquis et al., 2018).

AUTHOR CONTRIBUTIONS

GA, GC, FM, and SS conceived the manuscript. GA, GC, and FM wrote the article. SS and MG provided critical feedback and contributed to the final approval of the submitted version. All authors contributed to the article and approved the submitted version.

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Electrophysiological Dynamics of Visual-Tactile Temporal Order Perception in Early Deaf Adults

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Studies of compensatory plasticity in early deaf (ED) individuals have mainly focused on unisensory processing, and on spatial rather than temporal coding. However, precise discrimination of the temporal relationship between stimuli is imperative for successful perception of and interaction with the complex, multimodal environment. Although the properties of cross-modal temporal processing have been extensively studied in neurotypical populations, remarkably little is known about how the loss of one sense impacts the integrity of temporal interactions among the remaining senses. To understand how auditory deprivation affects multisensory temporal interactions, ED and age-matched normal hearing (NH) controls performed a visual-tactile temporal order judgment task in which visual and tactile stimuli were separated by varying stimulus onset asynchronies (SOAs) and subjects had to discern the leading stimulus. Participants performed the task while EEG data were recorded. Group averaged event-related potential waveforms were compared between groups in occipital and fronto-central electrodes. Despite similar temporal order sensitivities and performance accuracy, ED had larger visual P100 amplitudes for all SOA levels and larger tactile N140 amplitudes for the shortest asynchronous (± 30 ms) and synchronous SOA levels. The enhanced signal strength reflected in these components from ED adults are discussed in terms of compensatory recruitment of cortical areas for visual-tactile processing. In addition, ED adults had similar tactile P200 amplitudes as NH but longer P200 latencies suggesting reduced efficiency in later processing of tactile information. Overall, these results suggest that greater responses by ED for early processing of visual and tactile signals are likely critical for maintained performance in visual-tactile temporal order discrimination.

Keywords: deafness, temporal processing, cross-modal plasticity, event-related potentials, multisensory perception, temporal order perception

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INTRODUCTION

Natural timing discrepancies between multiple sensory signals inherently relay the source(s) and degree of congruency between those signals. Throughout development, with normal exposure to multisensory events, the brain develops an intrinsic strategy to compensate for the inherent differences in propagation and processing speeds of multimodal information allowing for coherent percepts (for review see Murray et al., 2016). This integrative mechanism is largely driven by sensitivities to the temporal and serial nature of the particular sensory cues. For instance, due to the fact that visual information typically precedes auditory information, individuals are more sensitive to temporal asynchronies for auditory-leading compared to visual-leading information (Conrey and Pisoni, 2006; van Eijk et al., 2008; Cecere et al., 2016). This is also reflected in the asymmetry of the temporal binding windows (Conrey and Pisoni, 2006; van Wassenhove et al., 2007; Powers et al., 2009; Hillock et al., 2011; Stevenson et al., 2012), the period of time within which multiple stimuli are likely to be perceptually integrated, indicating that exposure to patterns of natural temporal delays within multimodal signals is a major driver in fine-tuning this sensitive process. Temporal recalibration of audiovisual (Fujisaki et al., 2004) and visual-tactile (Hanson et al., 2008) stimuli (i.e., the perceptual shift in perceived simultaneity of auditory and visual signals following repeated exposure to a consistent temporal delay between the two cues) emphasizes the flexibility of this integrative process across modalities. Such permeability is crucial for adapting to different external environments and maintaining temporal congruency and subsequent integration across sensory systems. However, absence of sensory input during development may significantly alter temporal discrimination and decoding, particularly if the deficient modality inherently conveys temporal and sequential information (i.e., the auditory system, for review see Conway et al., 2009). Indeed, early deaf adults demonstrated reduced sensitivity for sensory-motor timing and deficits in sensory-motor temporal recalibration for visual stimuli in the central visual field suggesting impairments in perception of sensorimotor causality (Vercillo and Jiang, 2017).

Recalibration of temporal order perception is thought to reflect the brain's interpretation of external signals rather than the physical asynchrony between signals. This notion is supported by findings from auditory-induced cueing of a visual temporal order judgment task where attention toward one of two visual signals (left or right) was induced via an auditory signal prior to either the synchronous or asynchronous presentation of the two visual cues. Participants demonstrated a clear perceptual bias toward the visual signal from the cued location as being presented first, regardless of simultaneous presentation and any latency differences in early visual evoked components (i.e., P100) suggesting that such a perception is not driven by increased visual processing speed (McDonald et al., 2005). However, increased amplitude of the visual P100 did accompany this condition, theorized to reflect enhanced signal strength of the cued visual signal that is interpreted as temporal primacy during later stages of processing (McDonald et al., 2005). Intriguingly, during asynchronous trials, the latency of the early visual P100 component was approximate to the veridical delay between the two visual signals, regardless of participant's perception (McDonald et al., 2005). Activation and connectivity patterns between regions of the prefrontal cortex, insula, and superior temporal sulcus (STS) are likely responsible for higher order processing of both the physical temporal order dynamics of the stimulus pair and the perceptual state of the participants (Noesselt et al., 2012). As the STS is inherently multisensory, absence of a modality induces reorganization of sensory inputs to and connections between primary sensory cortices and this multimodal STS region (Meredith and Lomber, 2011; Meredith et al., 2011) which should subsequently affect temporal order processing.

Auditory input does appear to play a particularly important role in creating refined resolution for temporal processing. The Auditory Scaffolding Hypothesis suggests that early auditory experience provides a necessary framework, or scaffold, to develop sensitivity to temporal information, including serial order, since these properties are fundamental to sound (Conway et al., 2009). In early deaf (ED) adults, tactile duration, but not spatial, discrimination was impaired compared to normal hearing (NH) controls (Bolognini et al., 2011). Compared to spatial discrimination, ED adults also show degraded temporal discriminatory abilities whereas NH did not show different sensitivities between spatial and temporal tasks (Papagno et al., 2016). In a complex temporal bisection task, ED adults demonstrated impaired performance that was eliminated when spatial cues were linked to the temporal differences between stimuli (Amadeo et al., 2019). Performance in these spatially varied temporal bisection tasks did not vary among NH individuals suggesting that early deafness exerts limitations on precise and independent development of temporal processing (Amadeo et al., 2019). Deficits were also found for unisensory visual and tactile simultaneity judgments in ED compared to NH adults (Heming and Brown, 2005) suggesting impaired temporal processing due to early auditory deprivation. Additionally, children with cochlear implants showed deficits in serial learning of visual and auditory information (for review see Pisoni et al., 2016) providing further support for the need of early auditory experience to precisely discriminate serial information of sensory cues.

Alternatively, some studies don't show any deficits in visual or tactile temporal processing abilities of ED individuals and suggest that compensatory mechanisms lead to recruitment of auditory areas by intact modalities enabling normal or even enhanced perceptual abilities. For instance, tactual discrimination thresholds, estimated using stimuli ranging from 2 and 300 Hz, and tactile temporal order discrimination thresholds, estimated from a task discriminating which of two vibrotactile stimuli was presented first, did not significantly differ between ED and NH (Moallem et al., 2010). Similarly, visual temporal order thresholds did not differ between ED and NH, although ED adults had faster response times than NH during a visual temporal order discrimination task (Nava et al., 2008). These findings support unaltered temporal processing in unimodal contexts for early deaf adults.

The conflicting results outlined above were found while assessing unisensory temporal processing abilities, however, as temporal discrepancies between signals significantly affects integrative processes, alterations in multisensory temporal processing are expected in ED adults. The extent of facilitation from audio-tactile simultaneous presentation compared to unimodal presentation was examined in both congenitally deaf cochlear implant (CI) users and late deaf CI users (age of onset 7 years or later) by comparing reaction times for a bimodal stimulus to reaction times for unimodal stimuli (Nava et al., 2014). While both CI groups showed evidence of audio-tactile interaction, measured as multisensory facilitation (i.e., faster reaction time for bimodal compared to unimodal stimuli), only congenital CI users had weaker redundancy gains compared to their age-matched NH controls. Further, there was a significant correlation found in the congenital CI group, not the late deaf CI group, that showed faster tactile reaction times were associated with weaker redundancy gain. Overall, this may suggest that early deafness results in enhanced reliance on the tactile modality, possibly from cross-modal reorganization that strengthens and increases inputs for tactile information. A similar conclusion was found in a recent study that compared evoked neural dynamics of unisensory visual and tactile stimuli to synchronous visuo-tactile stimulation. The latency of the tactile N200 component (defined as the negative peak within 152 – 252 ms after stimulus presentation) was modulated by simultaneous presentation of a visual stimulus in NH only, not ED, suggesting limited multisensory interactions and diminished visual influence over tactile processing in ED (Hauthal et al., 2015). This finding also reflected behavioral results which showed deficits in the extent of multisensory facilitation in ED adults compared to NH (Hauthal et al., 2015). Taken together, this may suggest that ED individuals assign higher reliability to tactile information which would limit the visual system's influence over tactile processing and behavioral redundancy effects would be reduced in the presence of a hyper-salient tactile cue.

Another study that supports the notion of absent early auditory experience modifying multisensory processing and degraded visual influence over somatosensation showed that ED adults had increased susceptibility to a tactile induced double flash illusion compared to NH (Karns et al., 2012). In addition, the strength of the illusion was positively associated with somatosensory activation in primary auditory cortex (PAC) of ED (Karns et al., 2012). The increased likelihood of integrating asynchronous stimuli, as predicted by PAC activity during tactile stimulation, further suggests that the tactile modality primarily drives the integration of asynchronous stimuli underlying these illusory percepts in ED more so than NH. Interestingly, opposing findings were reported in a group of CI users that were tested with an audio-induced double vibration illusion. Only NH participants perceived illusory tactile stimuli when multiple auditory cues were presented, indicative of auditory-tactile interaction in NH but not in CI users (Landry et al., 2013). This finding described CI users that had congenital deafness and CI users that had progressive deafness (onset between 7 to 17 years of age), suggesting that a lack of auditory exposure, regardless of the time period, affects multisensory interactions even following CI implantation (Landry et al., 2013).

Presumably, for multisensory interactions in this auditory-to-tactile direction to occur (not in the tactile-to-auditory direction as show by Karns et al., 2012), early auditory experience is required. These conflicting findings may be indicative of unequal modulations on the remaining modalities as a consequence of absent early auditory experience. In other words, the tactile system of ED individuals seems to exert a greater cross-modal influence than the visual or partially restored auditory system (in the case of CI users). Similar to differential neural dynamics found during a simultaneity judgment task in normal hearing individuals exposed to auditory-leading versus visual-leading stimulus pairs (Cecere et al., 2016), it is likely that different mechanisms drive multisensory binding depending on the leading sensory input and that these mechanisms are differently affected by early sensory experience.

By examining how stimuli from one modality (i.e., visual) modulates the processing of a subsequent stimulus from a different modality (i.e., tactile), effects of early auditory deprivation on the multisensory integration process can be better understood. As precise integration relies on efficient decoding of temporal information between signals, what is the consequence of auditory deprivation on cross-modal influence of temporally disparate signals? Using a visual-tactile temporal order judgment task, this project investigated how information from one modality (i.e., visual) affected the processing of temporally disparate lagging signals from the opposite modality (i.e., tactile) in ED compared to NH. In line with previously reported findings, we would expect reduced influence by leading visual stimuli on tactile processing in ED compared to NH but similar influence on visual processing by leading tactile cues for both groups (Hauthal et al., 2015). When a significant cross-modal influence is exerted on sensory processing of the subsequent stimulus in the pair, we would predict reduced amplitudes of the ERP component (i.e., reduced visual P100 amplitudes in NH compared to ED for tactile-leading visual SOA conditions). As ED have demonstrated larger amplitudes for visual and tactile processing during unisensory detection tasks (Hauthal et al., 2015), we also would expect greater amplitudes in the ED group for the synchronous condition across ROIs. If efficiency of sensory processing is reduced (or enhanced) by early deafness for either visual or tactile modality, we would predict slower (or faster) latencies of the respective ERP components (McDonald et al., 2005). In addition, following the auditory scaffolding hypothesis, we would expect less precise multisensory temporal processes, manifested in worse performance accuracy during the TOJ task by the ED group. This prediction is further supported by previously reported impairments in multisensory interactions for congenital CI users (Nava et al., 2014) and ED (Hauthal et al., 2015) compared to NH. To investigate effects of auditory deprivation on processing multimodal signals, ERP components reflecting sensory processing were compared. Specifically, the influence of a leading stimulus on the early and late components of a subsequent stimulus were investigated across different SOAs between ED and NH within occipital and fronto-central electrodes. Finally, spatial topography differences in early and late stages of sensory processing were examined for both groups.

MATERIALS AND METHODS

Participants

12 early deaf with bilateral, severe to profound hearing loss (M = 41.73 ± 8.45; 5 males; cause and age of deafness onset reported in **Table 1**) and 12 age- and sex-matched normal hearing controls participated in this study. All participants

TABLE 1 | Demographic information on ED subjects.

ID	Age (years)	Handedness	Clinical description	Age at deafness onset (months)	Auditory deprivation (left; right) (dB)
ED1	46–50	R	Hereditary	Birth	90; 90
ED2	40–45	R	Spinal meningitis	9	90; 90
ED3	50–55	R	Unknown	18	105; 110
ED4	40–45	R	Spinal meningitis	4	100; 100
ED5	30–35	R	Hereditary	15	Total; 85
ED6	50–55	R	Unknown	Birth	85; 90–100
ED7	40–45	R	Maternal gestational measles	Birth	100; 90
ED8	50–55	R	Hereditary	Birth	90; 90
ED9	35–40	R	Cytomegalovirus	12	Total; 90
ED10	30–35	R	Unknown	Birth	80; 80
ED11	30–35	R	Unknown	16	120; 120
ED12	36–40	R	Spinal meningitis	18	110; 110

were right-handed and reported normal or corrected-to-normal vision. Participants were screened for any history of neurological or psychiatric disorders, history of brain injury, antipsychotic medications and cognitive decline. Participants provided signed informed consent before any experimentation. All experiment protocols were reviewed and approved by the Institutional Review Board at the University of Nevada, Reno.

Stimuli

The visual stimulus was a 33 ms white circle of 3.5° centered around a fixation cross, presented via the Psychophysics Toolbox using a Display + + system with a refresh rate of 120 Hz (Cambridge Research Systems, Rochester, United Kingdom). The 50 ms tactile stimulus of 50 Hz was generated using the PiezoTac tactor device (Engineering Acoustic, Casselberry, FL, United States). To approximate the same central location as the visual stimulus, the tactile stimulus was always presented to the tip of the participant's right index finger positioned directly below the center of the display.

Experimental Paradigm

Throughout each experimental block, a white fixation cross was presented in the center of the screen on a gray background. During each trial, a visual and tactile stimulus were presented at varying stimulus onset asynchronies (SOAs) where negative SOAs represent tactile-leading conditions and positive SOAs represent visual-leading conditions. Based on pilot data, 7 SOAs were chosen so that 2 were outside of the average TBW (± 250 ms), 2 were within the average TBW (± 30 ms), 2 were at the limit of the average TBW (± 100 ms), and the final SOA of 0 ms was a simultaneous, control condition. Each SOA was repeated 60 times, in a randomized order, for a total of 420 trials separated into 3 experimental blocks.

After the visual-tactile pair was presented, participants were asked to make a temporal order judgment (TOJ) about the 2 signals by pressing "1" on the keyboard for a flash first response and "2" for a touch first response using their non-dominant left hand. To reduce muscle artifacts into the cortical signal, participants waited to enter their response until 800 ms after the second stimulus presentation, indicated when the fixation turned green. Trials were separated by a variable interval between 1000 – 1300 ms.

Behavioral Analysis

Accuracy of temporal order judgments were quantified for all asynchronous conditions. For each individual, the average correct response was calculated for each asynchronous SOA level tested and individual proportions were averaged together across participants within both the NH and ED groups. Individual's proportion of 'visual first' responses were also plotted as a function of SOA value and fit with a cumulative gaussian function. The mean and the standard deviation were estimated from the cumulative distribution as estimates of sensitivity or just noticeable difference (JND) and perceived synchrony or point of subjective equality (PSE), respectively (Weber, 1834; Fechner, 1860; Burr et al., 2009; Scurry et al., 2019). The JND represented the smallest temporal difference between visual and tactile signals that an individual could detect while the PSE represented the perceptual bias of a participant's perception of visual-tactile synchrony. Individual JND and PSE values were averaged across participants within each group.

Electroencephalography Data Acquisition and Analysis

Participants performed the visual-tactile TOJ task while EEG data were continuously recorded from a 128 channel BioSemi Active 2 system (BioSemi, Amsterdam, The Netherlands). In addition to the standard 10–20 electrode locations, this system included intermediate positions. Default electrode labels were renamed to approximate the more conventional 10–20 system (see **Supplementary Figure S1** in Rossion et al., 2015). 4 additional channels recorded electrooculography (EOG) signals, two channels on the lateral sides of each eye to detect horizontal movement and two channels above and below the right eye to detect vertical movement (i.e., blinks). EEG was sampled at a rate of 512 Hz and processed offline using EEGLAB (v.14_0_0b) and ERPLAB (v.6.1.3) with MATLAB R2013b (Mathworks, Natick, MA, United States).

First, EEG data were bandpass filtered from 0.1 to 40 Hz with a second order, non-causal Butterworth filter and re-referenced to the common average reference. Channels were identified for rejection using the TrimOutlier plugin (v.0.17) based on a threshold of ±200 μV. Across participants, an average of 2.8 (± 4.24) channels were rejected and spherically interpolated. Next, epochs of 1200 ms, beginning 200 ms before trial onset (defined as onset of the first stimulus in the visual-tactile pair), were extracted from continuous data. Epochs corrupted by artifacts were identified following visual inspection and an average of 9.00 (± 7.78) trials ($<$2.2%) were rejected across participants. Blink and eye movement artifacts were corrected in the epoched data using Independent Component Analysis (ICA). Event related potentials (ERPs) were calculated for each individual as the average of all epochs within each experimental condition. ERPs were baseline corrected relative to the mean amplitude of the pre-trial interval of 200 ms. ERPs were then averaged across participants within the NH and the ED groups.

To quantify the electrophysiological dynamics of processing a sensory stimulus preceded by a stimulus from a different modality, amplitudes and latencies were extracted for the lagging stimulus of the asynchronous experimental conditions for each participant. Amplitudes were defined as the maxima peak within a pre-defined time window while latencies were estimated as the time to peak onset within the time window. Specifically, amplitudes and latencies of early (P100) visual components were estimated in the 120 – 180 ms window post visual onset, based on Basharat et al., 2018; Setti et al., 2014. To maintain consistency across SOA level, the window shifted based on the SOA (positive SOAs and 0 SOA: 120 – 180 ms; −30 SOA: 150 – 210 ms; −100 SOA: 220 – 280 ms; −250 SOA: 370 – 430 ms). Visual components were examined within a visual region of interest (ROI), defined as the average of ERPs from 12 occipital channels (I1, POI1, O1, POO5, POOz, Oz, OIz, Iz, I2, POI2, O2, POO6) (Setti et al., 2011). A later visual component (N200) was not included after initial analysis showed extremely variable and inconsistent amplitude values across participants for all SOA levels. Amplitudes and latencies of the early (N140) and late (P200) tactile processing components were extracted from time windows defined as 100 – 180 ms and 190 – 250 ms post tactile onset, respectively (Hauthal et al., 2015, 2013). Again, to retain consistency and continuity of the overall group trends, these windows shifted based on the SOA for both tactile N140 components (negative SOAs and 0 SOA: 100 – 180 ms; + 30 SOA: 130 – 210 ms; + 100 SOA: 200 – 280 ms; + 250 SOA: 350 – 430 ms) and tactile P200 components (negative SOAs and 0 SOA: 190 – 250 ms; + 30 SOA: 220 – 280 ms; + 100 SOA: 290 – 350 ms; + 250 SOA: 440 – 500 ms). These estimates were done within a Fronto-Central (FC) ROI made up of the average of 8 channels (Cz, C1h, C2h, FCC1h, FCC2h, FCC1, FCC2, and FCz) and known to reflect somatosensory processing (Ito et al., 2014; Hauthal et al., 2015).

To quantify topographic differences between groups for each SOA level and component, an index known as the global dissimilarity measure (DISS) (Lehmann and Skrandies, 1980) was computed for the same windows used to examine the respective ERP component at the respective SOA level. DISS was estimated as the square root of the mean squared difference between scalp potentials of each electrode which were normalized by their instantaneous global field power (GFP) (Murray et al., 2008). GFP was calculated as the standard deviation of the whole scalp electric field (Murray et al., 2008). DISS provides a topographic index between 0 and 2 where 0 represents homogeneity and 2 represents inversion of the scalp topography (Murray et al., 2008).

Statistical Analysis

As ROIs had unequal number of channels, separate mixed ANOVAs were calculated for each region of interest using the between factor of group (NH vs ED) and the within factor of SOA (7 levels). Due to multiple ANOVAs to investigate differences in both amplitude and latency of visual P100 in occipital, tactile N140 in FC and tactile P200 in FC, the critical alpha level used to determine statistically significant effects will be 0.0167 (0.05/3). As processing of simultaneous visual-tactile events was an additional aspect of investigation, separate independent *t*-tests with a Bonferroni corrected alpha value of 0.0167 (0.05/3) were used to examine differences between ED and NH groups during the 0 ms SOA condition in tactile N140 and tactile P200 components within FC and in the visual P100 component in occipital ROI. Independent *t*-tests were also used to compare PSE and JND values between groups as well as for an *a priori* comparison of components evoked during synchronous presentation of visual-tactile stimuli.

Non-parametric permutation tests were used to quantify the significance of estimated DISS values for each component at the respective SOA levels. Following the commonly used topographic ANOVA (TANOVA) method (Murray et al., 2008), individual subjects were randomly assigned to either the ED or the NH group and new group-averaged ERPs were computed. Then, new DISS values were estimated for each SOA at each of the components as reported in section 2.5. This procedure was repeated for 2500 iterations for each ERP component at each respective SOA level and empirical distributions were generated. If the original DISS estimates fell within an *a priori* defined significance level of 0.05, they were deemed significant.

All statistical analysis was performed in R statistical software.

RESULTS

ED and NH Adults Had Equivalent Performance Accuracy, Temporal Order Sensitivity and Perceived Synchrony

Initially, we quantified the proportion of correct responses for each asynchronous SOA condition within each group (**Figure 1**, left panel). As expected, a mixed ANOVA showed an effect of SOA [F(5,110) = 26.57, $p < 0.001$, $n_p{}^2 = 0.55$] on performance accuracy. Although ED and NH groups did not perform differently overall [F(1,22) = 3.03, $p = 0.10$], there was a significant interaction between group and SOA [F(5,110) = 3.85, $p < 0.01$, $n_p{}^2 = 0.15$]. However, follow up *t*-tests that compared group accuracy performance at each SOA level using a corrected p value of 0.0083 showed that ED did not perform significantly different from NH at any SOA (uncorrected $ps \geq 0.047$). Average

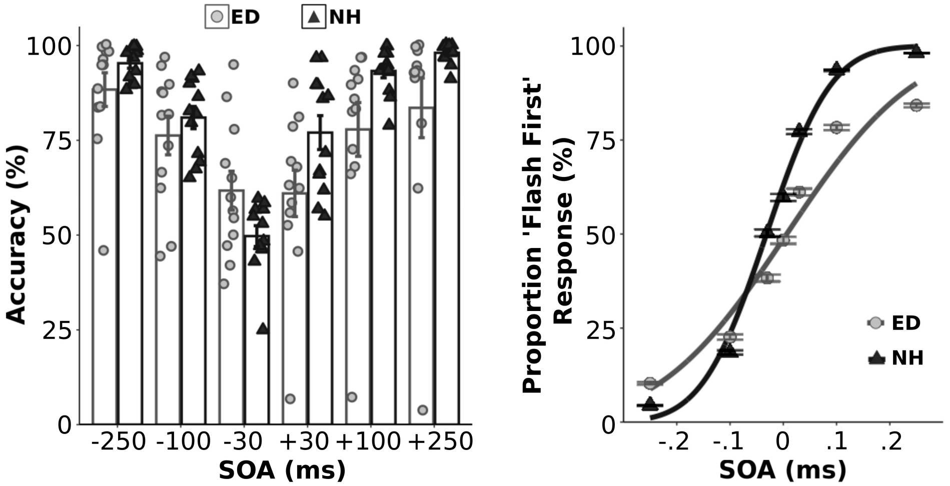

FIGURE 1 | Behavioral performance in the visual-tactile temporal order judgment task. **Left panel:** Group averaged and individual data for behavioral accuracy are plotted for ED (light gray boxes with light gray circles) and NH (black boxes with black triangles) groups for each asynchronous SOA test level. **Right panel:** Average proportion of flash first response at each SOA level along with the fitted cumulative normal distribution is plotted for ED (light gray circles w/light gray line) and NH (black triangles w/black line). **Error bars reflect standard error.

psychometric functions from both groups are displayed in the right panel of **Figure 1**. Two separate independent *t*-tests also revealed that ED and NH groups did not differ in their sensitivity (JND) [t(22) = −0.27, p = 0.79] or point of subjective equality (PSE) [t(22) = 1.69, p = 0.11] for the visual-tactile TOJ task.

Visual and Tactile Components Induced by Synchronous Visual-Tactile Stimulation

As we were interested in differences in the electrophysiological dynamics of simultaneous visual-tactile events between ED and NH adults, *a priori* independent *t*-tests with Bonferroni correction (0.05/3 = 0.017) compared the amplitudes and latencies of tactile N140 and P200 in FC ROI and the visual P100 component within the occipital ROI. Amplitudes of the tactile N140 component were significantly larger in ED compared to NH in FC ROI [t(22) = −3.51, $p < 0.01$, d = 1.43] while amplitudes of the tactile P200 component were comparable between the two groups [t(22) = 1.88, p = 0.07] (see **Figure 2** top left panel). In addition, there was no significant difference between ED and NH latencies of tactile N140 [t(22) = −1.10, p = 0.28] or tactile P200 components [t(22) = 0.84, p = 0.41] in FC ROI. In occipital ROI, ED adults had a significantly larger amplitude for the visual P100 component [t(22) = 2.90, $p < 0.01$, d = 1.19] (see **Figure 3**, top left panel) while there was no group difference for visual P100 latency estimates [t(22) = −0.33, p = 0.74].

Visual Influence on Early and Late Tactile Sensory Processing Components

Group averaged ERPs are shown in **Figure 2** for the 3 visual leading conditions (positive SOAs), and synchronous condition for comparison, for ED (dark gray line) and NH (dark blue line) in FC ROI. The 3 tactile leading conditions were not plotted in the FC ROI as we wanted to demonstrate the change in the somatosensory ERP induced by a preceding visual stimulus. For group average tactile N140 amplitude and latency values across all SOAs, see **Supplementary Table S1**. As observed in the top right panel of **Figure 2**, the amplitudes of the early tactile N140 component were significantly larger for ED compared to NH [F(1,22) = 11.5, $p < 0.01$, n_p^2 = 0.34] and there was a significant effect of SOA [F(6,132) = 15.62, $p < 0.001$, n_p^2 = 0.42]. However, these were qualified by a significant interaction [F(6,132) = 2.41, $p < 0.05$, n_p^2 = 0.10]. Follow up pair-wise comparisons with Bonferroni corrected alpha value of 0.007 (0.05/7) were performed for each SOA to determine which conditions had amplitude differences between ED and NH. For the synchronous and smallest SOA levels (±30), ED had significantly larger tactile N140 amplitudes than NH [t's(22) < −3.51, p's < 0.001, d's ≥ 1.43]. However, there was no group difference at ±100 or ±250 SOAs [t's(22) > −1.77, p's > 0.09].

While there was no group difference in tactile N140 latencies [F(1,22) = 0.01, p = 0.93], there was an effect of SOA [F(6, 132) = 4.31, $p < 0.001$, n_p^2 = 0.16] and a significant interaction [F(6,132) = 2.53, $p < 0.05$, n_p^2 = 0.10]. To explore this interaction *post hoc*, separate *t*-tests were performed for each SOA level. Only at −250 and −100 SOAs did ED have significantly shorter latencies than NH [t's(22) < −2.3, corrected p's < 0.05, d's ≥ 0.94]; there was no latency difference between groups at the other 5 SOA levels [t's(22) < 1.71, p's > 0.10].

For the amplitudes of the tactile P200 component within FC ROI, there was no significant difference between ED and NH groups [F(1,22) = 1.13, p = 0.30] nor a significant interaction between group and SOA [F(6,132) = 1.74, p = 0.12]. However, there was a significant effect of SOA [F(6,132) = 23.5, $p < 0.001$, n_p^2 = 0.52] (see **Figure 2**, bottom right panel) with follow up comparisons showing that the amplitude of the synchronous and −30 SOAs

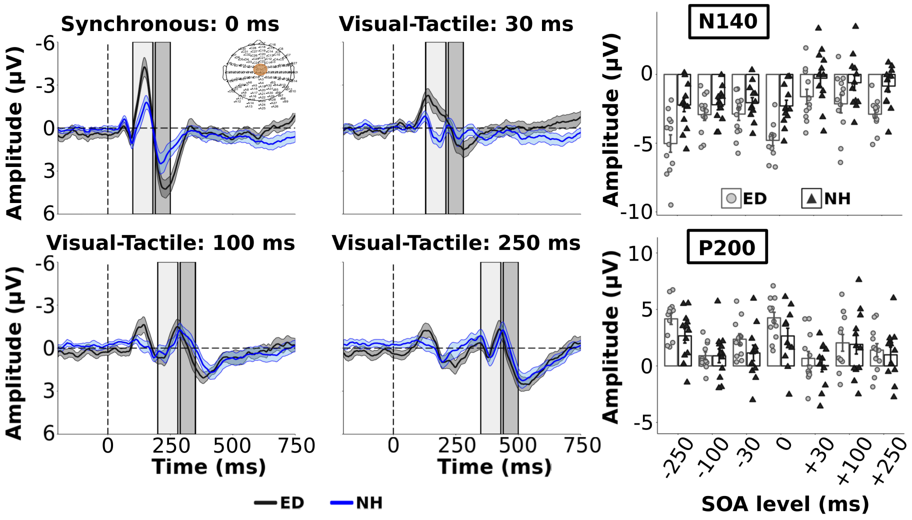

FIGURE 2 | Group average ERPs and tactile components from Fronto-Central ROI. Group averaged ERP waveforms from FC electrodes (ROI shown in **top left panel**) are plotted for ED (gray solid line) and NH (blue dashed line) groups for synchronous and 3 visual-leading conditions. The gray and blue shaded envelopes around the waveforms correspond to the ± SE for the ED and NH group-averaged waveform, respectively. Amplitudes of the tactile N140 and P200 components are shown **(right column)** for group-averaged and individual data from ED (light gray boxes with light gray circles) and NH (black boxes with black triangles) groups extracted from the respective time windows (N140: light gray box; P200: darker gray box) displayed in the ERP plots.

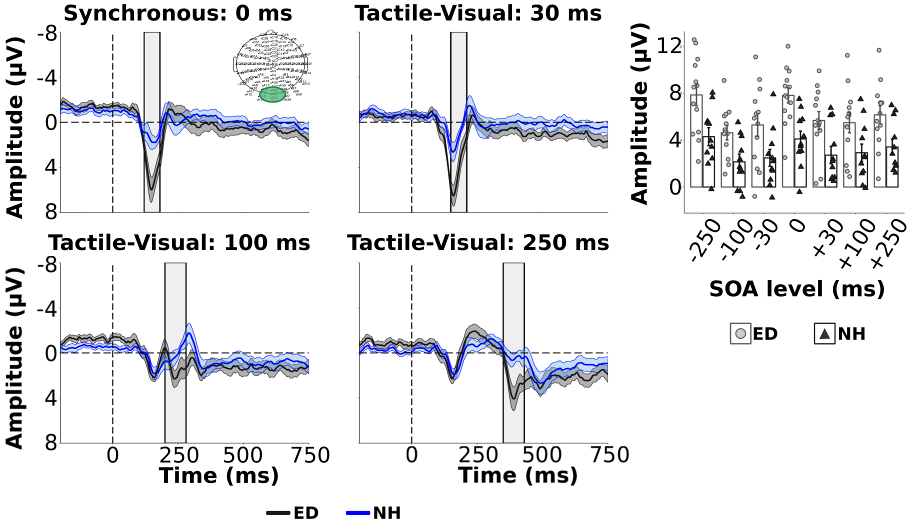

FIGURE 3 | Group average ERPs and visual components from occipital ROI. Group averaged ERP waveforms averaged from electrodes within occipital electrodes (ROI displayed in **top left panel**) are displayed for ED (dark gray solid line) and NH (blue dashed line) groups for synchronous and 3 tactile-leading visual conditions. The gray and blue shaded envelopes around the waveforms correspond to the ± SE for the ED and NH group-averaged waveform, respectively. Amplitudes of the visual P100 component are shown for group-averaged and individual data from ED (light gray boxes with light gray circles) and NH (black boxes with black triangles) groups extracted from the post-stimulus time window relative to the visual cue (shown by light gray box on ERP plots) for each SOA level **(top right panel)**.

were significantly larger than the +30, ±100, and −250 SOAs (corrected p's < 0.002). Further, the +100 SOA had a significantly smaller amplitude than the +250, −30 and −250 SOAs (corrected p's < 0.01, d's ≥ 0.75) but not than the +30 or −100 SOAs ($p > 0.28$). P200 amplitudes did not significantly differ between +30 and +250 ($p = 1.0$) (see **Supplementary Table S2** for group average tactile P200 amplitude and latency values).

ED adults had significantly longer tactile P200 latencies than NH [F(1,22) = 4.90, $p < 0.05$, $n_p{}^2 = 0.18$]. In addition, there was a significant effect of SOA [F(6, 132) = 3.22, $p < 0.01$, $n_p{}^2 = 0.13$] but no significant interaction. Bonferroni corrected pairwise comparisons revealed that the latency in the + 250 SOA was significantly longer than +30, −100 and −250 SOAs (corrected p's < 0.04, d's ≥ 0.81). No other comparisons were significant (corrected p's > 0.06).

Tactile Influence on Visual Sensory Processing Components

Next, we quantified the influence of tactile information on the processing of subsequent visual signals, within occipital ROI, presented at variable delays. While we were more interested in how the tactile stimulus may affect subsequent processing of the visual stimulus, **Figure 3** shows the group averaged ERPs for ED and NH adults across the synchronous and tactile-leading visual conditions (3 negative SOA levels). **Supplementary Table S3** reports group averaged visual P100 amplitude and latencies values for all SOAs. A mixed ANOVA showed that ED group had significantly larger visual P100 amplitudes than NH group [F(1,22) = 10.07, uncorrected $p < 0.01$, $n_p^2 = 0.31$]. While there was no significant interaction [F(6,132) = 0.65, uncorrected $p = 0.69$], SOA level did significantly affect visual P100 amplitudes [F(6,132) = 12.28, uncorrected $p < 0.001$, $n_p^2 = 0.36$]. *Post hoc* comparisons with Bonferroni correction revealed that the visual P100 amplitude induced by the synchronous condition (0 ms) was significantly larger than ± 100 and ± 250 SOAs (corrected p's < 0.01, d's > 1.03) but not ±30 SOAs (corrected p's ≥ 0.30). As expected, amplitudes did not differ between the three visual-leading tactile conditions (+SOAs) (corrected p's > 0.19). However, the visual P100 amplitude was significantly larger for the −30 SOA than both −100 and −250 ms SOAs (corrected p's < 0.001, d's > 1.39).

There was no significant difference between visual P100 latencies estimated from occipital region for ED and NH groups [F(1,22) = 0.33, $p = 0.57$] nor was there a significant interaction [F(6,132) = 1.65, $p = 0.14$]. However, there was a significant effect of SOA [F(6,132) = 5.18, $p < 0.001$, $n_p^2 = 0.19$] with follow up pairwise comparisons using Bonferroni correction revealing that the latency in the −30 SOA condition was significantly shorter than the synchronous (corrected $p < 0.001$, $d = 1.23$) and −100 SOA (corrected $p < 0.05$, $d = 0.78$) but not −250 SOA (corrected $p = 0.26$) nor any of the positive, visual-leading SOAs (corrected $p > 0.09$).

Widespread Distribution of Activity During Visual-Tactile Processing in ED

Scalp topographies are displayed in **Figure 4** for both ED (top row) and NH (bottom row) groups for the tactile N140 components (defined at 100 – 180 ms post-tactile stimulus onset in each VT pair) derived in synchronous and visual-leading tactile (VT) conditions. The ED group reveals more dispersed activity in the fronto-central electrodes compared to the NH group, particularly for the synchronous and + 30 SOAs (see left two panels in **Figure 4**). Global dissimilarity (DISS) was calculated to quantify the topographical similarity between ED and NH at each SOA displayed. A DISS value of 1.08 for the +30 SOA was larger than expected based on the upper 5% confidence limit of the permutation analysis. This finding suggests that the spatial topography between ED and NH was indeed heterogenous while the topographies for 0 ms, +100 and +250 SOAs appear moderately homogenous (DISSs = 0.70; 0.68; 0.71; respectively). Dissimilarity analysis to compare ED and NH spatial topographies during the tactile P200 time window (190–250 ms after onset of tactile stimulus in VT conditions) (**Figure 5**) revealed similar activation patterns between the groups (DISS < 0.68) for all conditions, a finding supported by our permutation analysis.

Finally, mean amplitudes are displayed within the time window of 120–180 ms following the visual stimulus of the respective tactile-leading visual pair in **Figure 6**. The distribution of the positive deflection in the occipital area was observed as more widespread in ED (top row) than in NH (bottom row), particularly in the 30 ms condition as confirmed by a DISS estimate of 0.90 which surpassed our 5% confidence limit used in the permutation analysis. The other conditions induced more similar topographies between groups (DISS < 0.67).

DISCUSSION

Congenital or early loss of auditory input may have severe consequences for subsequent temporal detection and sensitivity. This is particularly important in understanding how perception of multisensory cues is affected, a process heavily dictated by temporal discrepancies between the sensory signals comprising the multisensory event. Visual-tactile temporal sensitivity also distinctly influences perception of body ownership and representation. For instance, susceptibility to the rubber hand illusion [when a participant feels their own hand, hidden from view, being stroked while watching a rubber hand get stroked, they feel as if the rubber hand was their own (Botvinick and Cohen, 1998; Liu and Medina, 2017)] can be predicted from a subject's temporal sensitivity to visual-tactile asynchronies (Costantini et al., 2016). Not only is visual-tactile temporal acuity important for perceived body representation, improved development of sensory substitution devices relies on understanding the affected person's perceptual experience, specifically what affects perception of multimodal synchrony (Kristjánsson et al., 2016). While majority of prior studies examining multisensory processing in ED have primarily relied on simultaneous stimulus presentation, the aim of the current study was to understand how early deafness affected the processing of synchronous as well as asynchronous multisensory signals.

There was no significant difference between ED and NH adults in behavioral performance accuracy, visual-tactile temporal order discrimination sensitivity or perceived visual-tactile synchrony. When the visuo-tactile pair was simultaneous, the ED group had larger amplitudes for early visual (P100) (in occipital electrodes) and early tactile (N140) (in FC electrodes) components. When the two signals were temporally offset from each other, ED had larger amplitudes of the early N140 tactile component within FC ROI for the smallest SOA conditions (± 30 ms) while ED had larger visual P100 amplitudes in occipital ROI across SOA conditions. In addition, ED showed shorter latencies of the tactile N140 component for −250 and −100 SOAs while they demonstrated significantly longer latencies for tactile P200 component across SOA levels. Finally, regardless of group, there was a similar dependence on SOA level for amplitude modulation within all ROIs examined.

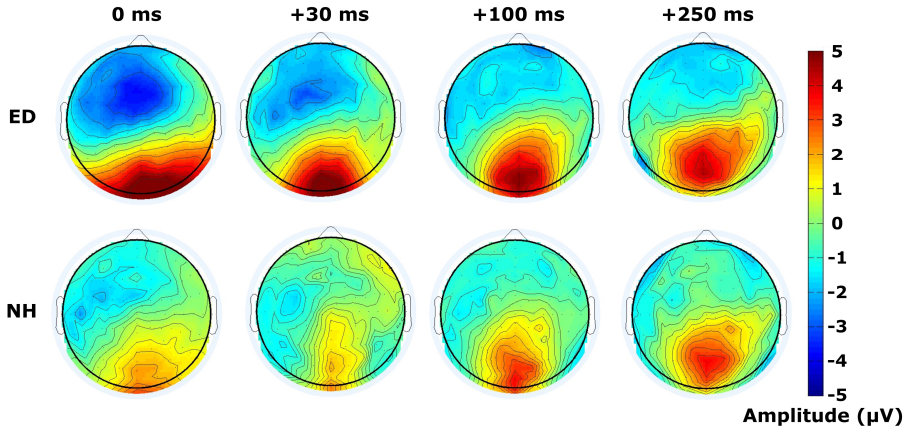

FIGURE 4 | Scalp topography of mean amplitudes for tactile N140 component. Scalp topographies of mean amplitudes within time window designating the tactile N140 component are displayed for ED **(top row)** and NH **(bottom row)** groups, for synchronous and 3 visual-leading conditions (positive SOAs).

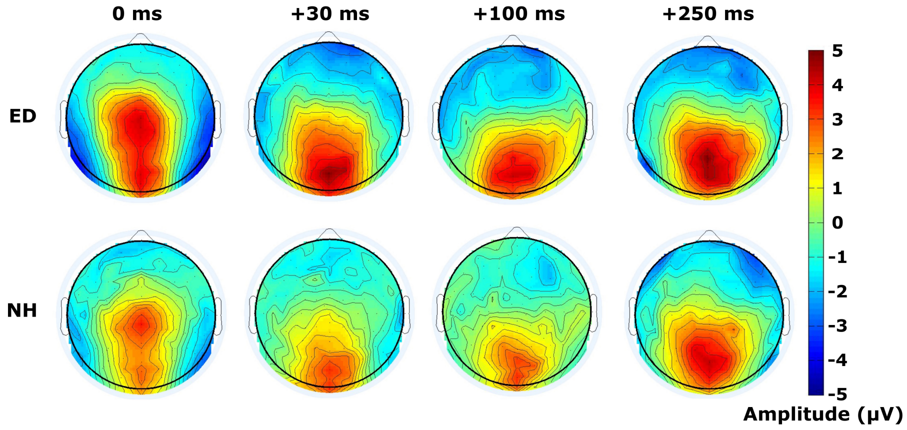

FIGURE 5 | Distribution of activity within tactile P200 time window. Scalp topographies of mean amplitudes within time window designating the tactile P200 component are displayed for ED **(top row)** and NH **(bottom row)** groups, for synchronous and 3 visual-leading conditions (positive SOAs).

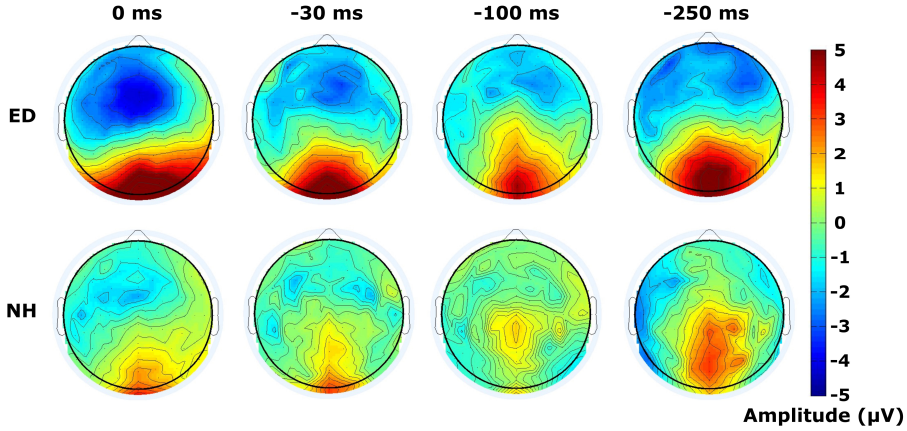

FIGURE 6 | Distribution of activity across scalp within visual P100 time window. Scalp topographies of mean amplitudes within time window defining the visual P100 component are displayed for ED **(top row)** and NH **(bottom row)** groups, for synchronous and 3 tactile-leading conditions (negative SOAs).

The absence of any group differences in behavioral measures was somewhat surprising given prior studies that have shown impaired unisensory temporal order sensitivities (Heming and Brown, 2005; Bolognini et al., 2011) and reduced behavioral gains to multisensory versus unisensory stimuli presentation (Nava et al., 2014; Hauthal et al., 2015). However, findings from the current study as well as a prior study also reporting absence of group differences in sensitivities for discriminating visual temporal order suggest that auditory experience may not be critical for establishing a framework that allows precise discrimination of temporal order across modalities as previously described by the auditory scaffolding hypothesis (Conway et al., 2009). Follow-up studies that incorporate more levels of SOAs as well as additional temporal discrimination tasks, such as cross-modal duration perception (i.e., gap detection), would provide additional evidence that may reveal differences in multisensory temporal order perception and other temporal perceptual abilities in ED.

Despite comparable temporal order perceptual abilities, differences in amplitudes for both visual and tactile components between ED and NH during simultaneous visual-tactile stimulation reveals altered sensory processing due to auditory deprivation. There was a greater amplitude of the visual P100 component in occipital region of ED for the synchronous condition. This finding may be indicative of increased cortical resources dedicated to processing visual information or altered visual processing at early stages in ED. Heightened visual P100 amplitudes in ED measured during a visual detection task predicted reaction times suggesting enhanced unisensory processing in ED (Bottari et al., 2011). Larger amplitudes of early visual components (P110) in ED were also described by Hauthal et al. (2013) in the context of unisensory visual stimulation via alternating checkerboard patterns. One contributing factor offered as an interpretation was recruitment of posterior parietal cortex by ED, either for additional processing of or increased attention toward the visual stimuli (Hauthal et al., 2013). Similarly, while the larger visual P100 amplitudes reported in the present study do not necessarily reveal enhanced processing of the visual stimulus, it is clearly indicative of altered early visual processing in ED during bimodal stimulation.

Early processing of the tactile stimulus showed alterations in FC ROI of ED with greater tactile N140 amplitudes at the shortest SOAs tested (−30, 0, +30 ms). Increased responsiveness in somatosensory electrodes is in line with a previous study that suggested increased cortical excitability in ED for somatosensation (Güdücü et al., 2019), perhaps resulting in enhanced haptic decoding within somatosensory areas. This explanation may also help explain the larger amplitudes of ED only at the most ambiguous SOAs, conditions where greater resources would be necessary to discern the correct temporal order. While electrodes within FC region were selected to investigate somatosensory processing, this area has also previously shown reliable and comparable auditory ERPs across groups (Ponton et al., 2000; Bishop et al., 2007; Setti et al., 2011; Mahajan and McArthur, 2012; Basharat et al., 2018). Therefore, there is likely recruitment of auditory areas by ED for early stages (reflected by N140) of tactile processing, similar to the cross-modal recruitment of auditory cortex by ED for processing vibrotactile (Levänen and Hamdorf, 2001; Auer et al., 2007), visual motion (Finney et al., 2001) and visual rhythm stimuli (Bola et al., 2017). However, without source localization it is difficult to pinpoint the cortical areas leading to the enhanced response found in FC electrodes.

As multisensory integration is thought to occur in early stages of sensory processing within traditionally unisensory areas (Kayser et al., 2005; Schroeder and Foxe, 2005) as well as multimodal areas (Senkowski et al., 2008; Hauthal et al., 2013), both primary and secondary somatosensory regions, auditory areas and multimodal areas along parieto-temporal region could have contributed to the greater N140 amplitudes found in ED. Such an increase in signal strength by additional activated areas would indeed be reflected in larger amplitudes (McDonald et al., 2005). While no group differences of the later P200 tactile component amplitudes were found, ED adults did demonstrate later latencies for this later tactile component. The tactile P200 normally reflects attentional enhancement during sensory processing (Freunberger et al., 2007) and audio-tactile interactions in NH adults (Zumer et al., 2019). Taken together, these findings implicate that signal strength is not affected while speed of later tactile processing is affected by auditory deprivation.

ED adults also had significantly larger amplitudes of the early visual P100 component, regardless of SOA, within occipital ROI. This is likely consequent of cross-modal reorganization dynamics and the resulting increased influence of the tactile modality on visual as a result of early auditory deprivation (Karns et al., 2012; Hauthal et al., 2015). Indeed, tactile modulation of primary visual areas may be due to increased connectivity from somatosensory onto visual networks, as shown in early deaf cats (Stolzberg et al., 2018). Similarly, increased tactile N140 amplitudes from FC electrodes during visual-leading tactile conditions could be due to increased afferent projections from visual and somatosensory areas onto auditory areas (Wong et al., 2015) reflecting a larger amount of cortical resources dedicated to processing tactile stimuli. The widespread distribution of activity visible on the ED scalp topographies across frontal and central electrodes during tactile processing and across occipital electrodes during visual processing also suggests recruitment of additional areas and/or neuronal populations for processing visual-tactile information. However, considering the comparable behavioral performance and sensitivities, modulation of visual-tactile processing is not necessarily indicative of enhanced processing, simply altered and more distributed processing. Additionally, a prior investigation on audio-visual temporal order perception in NH adults theorized that increased amplitudes of early sensory components led to enhanced signal strength associated with the external signal evoking that component and subsequent perceptual bias toward the perceived temporal order of that signal (McDonald et al., 2005). However, the current study shows enhanced signal strength in ED for visual P100 components from all SOA levels and for tactile N140 components at the shortest SOA levels without improved behavioral performance. Therefore, we propose that in the case of early deafness, increased amplitudes and thus signal strength reflect enhanced recruitment of cortical areas to process the stimuli without any temporal primacy effect resulting in similar performance accuracy and sensitivity across groups.

Compensatory mechanisms, such as increased cortical activation, may be largely driven by the haptic modality which is consistent with modality appropriateness, a hypothesis proposing that the sensory modality with greater resolution for the task at hand exerts greater influence in the subsequent processing and perception of the multisensory event. As the tactile modality has a heightened temporal resolution compared to the visual domain (Baumgarten et al., 2017), the tactile cues should be given greater perceptual weight during the present TOJ task. For NH adults, auditory information dominates temporal processing (Walker and Scott, 1981; Welch et al., 1986), however, under absence of audition (i.e., deafness) tactile information becomes the most reliable modality for temporal processing. If the ED group does indeed more heavily weigh tactile information for temporal processing, this could be reflected in the subsequent influence on visual areas. For instance, when tactile preceded visual information, the leading tactile stimulus was likely more salient in ED increasing the reliability and detection acuity needed to perceive temporal order. The earlier latencies found for ED in the −250 and −100 ms (tactile-leading) SOA conditions implies faster processing of the tactile stimulus by ED when there is reduced influence from a visual stimulus, possibly enhancing the saliency of the tactile cue. A similar finding for visual saliency and faster visual processing was reported in ED performing a spatial task, a domain dominated by the visual modality (Heimler et al., 2017). Follow up studies directly manipulating the reliability of visual and tactile signals are necessary to fully understand how saliency of one modality influences processing of the second modality in a temporal order discrimination task. In addition, source localization is required to discern the cortical sources producing these responses measured in FC and occipital electrodes to more fully understand what regions are directly modulated by tactile and visual systems.

One common finding for both groups was the amplitude modulation of tactile components dependent on the SOA. For tactile-leading visual conditions within occipital ROI, the amplitude of the early P100 component was largest for 30 ms condition compared to 100 ms and 250 ms SOA conditions. In a similar study, early sensory processing components of the lagging stimulus in an audio-visual pair showed reduced amplitudes in older versus young adults at the large SOA (270 ms) but not small SOA (70 ms) (Setti et al., 2011). In conjunction with the reduced precision of older adults performing a TOJ task, the authors hypothesized that the lower amplitudes reflect reduced processing of the second signal and integration of the 2 cues at this large delay (Setti et al., 2011). However, a study replicating the design of Setti et al. (2011) showed opposing results (reduced amplitude for young compared to older at the same large SOA – 270 ms) (Basharat et al., 2018). This was interpreted as a reduced ability for older individuals to disengage their attention from the second stimulus as compared to young. In the present study, the reduction of early tactile N140 and early visual P100 amplitudes with increasing SOA was present in both groups. In line with the interpretation of Basharat et al. (2018), this could indicate a reallocation or reduction of cognitive resources in processing the secondary tactile stimulus presented at a later delay for all participants. As behavioral performance also increased with increasing SOA, the larger delay likely improved perceptual resolution to discern temporal order and dedicated processing of the second stimulus wasn't required.

Results presented from this study showcase some alterations to processing visual-tactile stimuli between ED and NH participants. ED adults had larger amplitudes for early visual and tactile processing components estimated from the simultaneous visual-tactile condition suggesting increased cognitive resources for multisensory processing after early auditory deprivation. In addition, ED adults had larger tactile N140 components within FC electrodes at the shortest SOAs (± 30 ms). These findings along with the broader activation patterns observed on the scalp topographies of ED during the early time window post-tactile onset suggest compensatory mechanisms and potential recruitment of auditory areas by ED to process tactile information but not enhanced temporal processing. Future studies probing additional visual-tactile tasks (i.e., detection or spatial tasks) would further determine if cortical processing differences in ED, as reported in our study, are common across global visual-tactile processing or specific to temporal processing. Finally, ED adults also had larger visual P100 components estimated from occipital electrodes for all SOA conditions likely due to cross-modal reorganization of tactile inputs onto visual areas as well as modality appropriateness of the tactile system for temporal processing tasks.

DATA AVAILABILITY STATEMENT

The de-identified raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at the University of Nevada, Reno. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS and FJ designed the experiment and interpreted the data. AS and KC acquired the data and conducted statistical analysis. AS wrote the manuscript. FJ critically evaluated the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.544472/full#supplementary-material

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Evidence of an Effect of Gaming Experience on Visuospatial Attention in Deaf but Not in Hearing Individuals

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Auditory cortex in congenitally deaf early sign language users reorganizes to support cognitive processing in the visual domain. However, evidence suggests that the potential benefits of this reorganization are largely unrealized. At the same time, there is growing evidence that experience of playing computer and console games improves visual cognition, in particular visuospatial attentional processes. In the present study, we investigated in a group of deaf early signers whether those who reported recently playing computer or console games (deaf gamers) had better visuospatial attentional control than those who reported not playing such games (deaf non-gamers), and whether any such effect was related to cognitive processing in the visual domain. Using a classic test of attentional control, the Eriksen Flanker task, we found that deaf gamers performed on a par with hearing controls, while the performance of deaf non-gamers was poorer. Among hearing controls there was no effect of gaming. This suggests that deaf gamers may have better visuospatial attentional control than deaf non-gamers, probably because they are less susceptible to parafoveal distractions. Future work should examine the robustness of this potential gaming benefit and whether it is associated with neural plasticity in early deaf signers, as well as whether gaming intervention can improve visuospatial cognition in deaf people.

Keywords: deafness, sign language, visuospatial attention, executive function, gaming

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INTRODUCTION

Without technical intervention, congenitally profoundly deaf individuals have little opportunity to process sound. As a result, auditory cortex reorganizes to process other types of information, including visual cognition (Cardin et al., 2013, 2018; Ding et al., 2015; Twomey et al., 2017; Holmer et al., 2019; for reviews, see Alencar et al., 2019; Cardin et al., 2020), possibly offering deaf individuals the potential to outperform their hearing peers in this domain (Cardin et al., 2018). However, deaf children sometimes have difficulty achieving expected performance in academic skills, such as reading and math (Qi and Mitchell, 2012), and may not realize their potential as adults (Rudner et al., 2016). Performance on some visuospatial tasks, in particular those tapping into visuospatial perception and attentional processes, have been shown to be altered in deaf individuals (for reviews, see Bavelier et al., 2006; Rudner et al., 2009). In hearing individuals, visuospatial perception and attention have been reported to shift as a function of gaming experience (for recent meta-analyses, see Wang et al., 2016; Bediou et al., 2018; also see, Kristjánsson, 2013; Powers et al., 2013, for critical reviews). One study has also reported improved inhibition control in deaf individuals after playing a first-person shooter game one hour per day for 16 weeks (Nagendra et al., 2017). The aim of the present, cross-sectional, study was to investigate the combined effect of deafness and naturally occurring gaming experience on visuospatial attention.

Changes driven by congenitally deafness seem to be limited specifically to attentionally demanding aspects of visuospatial processing (Bavelier et al., 2006). Visual processing is supported by dorsal and visual neural streams. The dorsal visual stream supports processing of "where" a stimulus is and how it moves while the ventral stream supports identification of "what" the stimulus is. Both "what" and "where" processing becomes attentionally demanding in the presence of task-irrelevant information. Armstrong et al. (2002) reported evidence of an influence of deafness on the function of the dorsal visual stream. Effects of deafness are manifested in altered processing of motion in the visual periphery (Bavelier et al., 2001; Armstrong et al., 2002; Bosworth and Dobkins, 2002; Fine et al., 2005) as well as some aspects of peripheral attention in deaf individuals (Bavelier et al., 2001; Proksch and Bavelier, 2002; Colmenero et al., 2004; Dye et al., 2007; Hauser et al., 2007). In addition, detection of changes outside foveal vision seems to be faster in deaf than in hearing individuals (Loke and Song, 1991; Chen et al., 2006; Dye et al., 2009), suggesting that stimuli outside the fovea are more likely to challenge attentional control in deaf populations, at least when those stimuli are of relevance to solving the task (Bavelier et al., 2006; Belanger and Rayner, 2015). For the ventral stream, Armstrong et al. (2002) showed no effect of deafness, whereas others showed altered effects of deafness in both ventral and dorsal streams (Weisberg et al., 2012; Samar and Berger, 2017). Because the dorsal stream is susceptible to effects of deafness, with increased attentional resources used for processing of stimuli in the periphery, deaf individuals might perform worse than hearing individuals on visual tasks where stimuli outside the fovea need to be suppressed.

Working memory, the active storage of representations for ongoing processing, and attentional control, the selection of stimulus to focus on in processing, limits performance on cognitive tasks (Oberauer, 2019). For the processing of stimulus-rich displays and subsequentially presented stimuli, working memory is recruited and demands on attentional control are high. Although verbal working memory is similar for deaf and hearing individuals (Boutla et al., 2004; Andin et al., 2013), deaf individuals have better visuospatial working memory than hearing peers when assessed on a dynamic sequence tapping task, such as the Corsi Block-Tapping Test (Wilson et al., 1997; Geraci et al., 2008; Lauro et al., 2014). Similar results have been shown with a card-pair matching task (Rudner et al., 2016). This behavioral advantage may well reflect enhanced dorsal stream processing. On a static visual working memory task, however, the performance of deaf individuals has been reported to be worse than for hearing individuals (Lauro et al., 2014). It is likely that this reflects compromised ventral stream processing (cf. Samar and Berger, 2017).

In the Flanker task (Eriksen and Eriksen, 1974), the participant needs to suppress static distractors presented outside the fovea while making a decision on a target stimulus presented in the center of the visual field. Thus, it is a task requiring visuospatial attentional control for selective monitoring of what is visually present (Dye et al., 2007; Unsworth et al., 2015). This means that the Flanker task probably taps both dorsal and ventral visual stream functions and this notion is supported by empirical data (Lange-Malecki and Treue, 2012; Perry and Fallah, 2014; McDermott et al., 2017). A slowing of performance on the task is typically observed as the incongruence between response selection for a target stimulus and flanking distractors increases (Eriksen and Eriksen, 1974; Rueda et al., 2004; Sladen et al., 2005; Dye et al., 2007), indicating a conflict in determining what the target is. The standard task typically has two response keys, corresponding to two different targets, and incongruence is achieved by presenting flanking stimuli that correspond to the non-target response key. In other trials, flanking stimuli are congruent with the target stimulus, which leads to faster responses. The difference in response times between incongruent and congruent trials is an indicator of visuospatial attentional control (Rueda et al., 2004), and with an increase in attentional allocation to stimuli outside the fovea in deaf individuals (Bavelier et al., 2006) as well as altered ventral stream processing (Weisberg et al., 2012; Samar and Berger, 2017), an incongruence effect is likely to be stronger for deaf compared to hearing individuals. Thus, despite superior performance on some tasks related to the dorsal stream, deaf individuals are more distracted by flanking stimuli in a Flanker task than hearing participants (Dye et al., 2007; Dye and Hauser, 2014), irrespective of sign language skill (Proksch and Bavelier, 2002; Dye et al., 2007; also see Bosworth and Dobkins, 2002; Dye et al., 2009). This does, however, align with the notion of changed ventral stream processing in deaf compared to hearing individuals shown in some studies, since the Flanker task poses a challenge in maintaining control of *what* (i.e., ventral) is presented on the screen, rather than *where* (i.e., dorsal) stimuli are located.

Visuospatial attentional control is a domain that has been reported to be improved by gaming experience (Wang et al., 2016; Bediou et al., 2018). In fact, a recent meta-analysis (Bediou et al., 2018), indicated robust effects of gaming experience on top-down attentional control tasks, including Flanker tasks. Greenwood and Parasuraman (2016) argue that in the initial stages of cognitive training the dorsal stream is recruited through a bottom-up process of distraction suppression, but as the need for distraction suppression is reduced with increasing skill, functional disconnection of the dorsal stream occurs. Thus, reduced load on dorsal stream function as a result of cognitive training may make attentional resources available for transfer to other tasks. Nagendra et al. (2017) reported improved performance of deaf individuals on a Stroop color-word task, as indexed by shorter response latency, after a video gaming intervention. In a Stroop color-word task, participants have to shield themselves from interference effects when the color and the word do not match (Scarpina and Tagini, 2017), in a manner analogous to the Flanker task. However, although the Stroop task is visual, interference effects are semantico-lexical rather than visuospatial.

Previous studies on hearing populations suggest that effects of gaming experience on visuospatial attention might be restricted to specific type of games. In particular, action video games (AVGs) have been suggested to be faciliative (Wang et al., 2016; Bediou et al., 2018). AVGs are described as fast paced, to rely on flexible use of visuospatial attention, and involve dealing with a multitude of objects on screen simultaneously. However, different criteria for labeling games are used in the literature, and what qualifies as an AVG and what does not, is not easily determined (see Bediou et al., 2018). Importantly, types of games other than AVGs have also been reported to improve cognition, and it has been suggested that specific changes in cognition are to be expected for specific type of games (i.e., near-transfer effects, Oei and Patterson, 2013). This notion is similar to the idea that differences in visuospatial attention between deaf and hearing individuals are specific and experience-based (Bavelier et al., 2006; Samar and Berger, 2017). Here, we wanted to investigate this association by comparing performance on a Flanker task of deaf individuals who report they play video or computer games, to those who report that they do not play such games.

In the present study, we predict the negative effect on response times of distracting stimuli in a Flanker task to be greater for deaf than hearing individuals (see e.g., Dye et al., 2007). However, as gaming experience has been shown to improve visuospatial attentional control (Bediou et al., 2018), and gamers are expected to show less interference from incongruent flankers than non-gamers, we predict that gamers will outperform non-gamers on the Flanker task.

MATERIALS AND METHODS

Participants

We included 16 early deaf (9 female) and 24 hearing (12 female) participants. All had normal or corrected-to-normal visual acuity and normal contrast sensitivity, as measured by Snellen chart (McGraw et al., 1995) and Pelli-Robson contrast sensitivity chart (Pelli and Robson, 1988), respectively. Due to recruitment constraints, deaf participants (*M* = 35.1, *SD* = 7.6, range 22–48) were on average almost 9 years older than the hearing participants (*M* = 26.5, *SD* = 7.5, range 19–40) and this difference was statistically significant, $t(22.2) = 3.44$, $p = 0.002$, $\varepsilon = 0.64$. However, there was no statistically significant difference between groups in non-verbal cognitive ability, $t(12.3) = 0.91$, $p = 0.38$, $\varepsilon = 0.25$, as measured on the Visual puzzles subset from WAIS-IV (Wechsler, 2008). All participants had completed at least high school (minimum of 12 years); six deaf and seven hearing participants had a university degree.

Deaf participants used Swedish Sign Language (Svenskt teckenspråk; STS) as their primary language. Nine were deaf from birth and the remaining seven were between 6 months and 3 years old when their deafness was confirmed. Five had deaf parents who signed with them from birth, and the rest started to learn sign language as soon as their deafness was discovered, and their parents started to use STS. For nine participants this was before the age of 3, and for one participant, this was in preschool years. One participant did not specify when they started using sign language.

Gaming Experience

To classify participants as a gamer or a non-gamer, participants answered a questionnaire (see **Supplementary Appendix A**; for similar procedures, see e.g. Rudner et al., 2015; Unsworth et al., 2015) on their gaming habits. Since the literature on gaming effects on visuospatial attention is limited to hearing populations, and we know little of whether reported effects generalize to deaf populations, assignment by self-report was applied instead of more extensive, and costly, longitudinal designs. Participants were asked how often (0 = Not at all, 1 = Less than once per week, 2 = One to three days per week, 3 = Four to six days per week, 4 = Every day, or 5 = Several times, every day) they had been playing computer and/or console games (including games on handheld consoles) during the last 6 months. We did not assess whether gaming intensity varied during this period, or if this period was a representative example of the individual's general gaming pattern. Based on self-reported gaming experience, participants were then categorized as a gamer or a non-gamer. All participants who reported having played any type of game on a computer or console or both during the last six months were defined as gamers (i.e., response categories 1–5). All participants who reported not playing computer or console games at all during the last 6 months were defined as non-gamers (i.e., response category 0). Among hearing participants, 12 (2 female) were categorized as gamers and 10 (8 female) as a non-gamers (two female participants did not report gaming experience), and among deaf participants, there were 8 gamers (3 female) and 8 non-gamers (6 female). Of the deaf gamers, 4 reported playing only console games and 1 played only computer games, the rest played both, and of the hearing gamers, 5 played console games only, 3 only computer games, and the rest played both computer and console games. We did not make sub-groups based on the type of games participants played (see **Supplementary Appendix B** for a list of the games participants reported playing). This was partly due to the small sample size, but also because the previous literature on gaming effects almost exclusively include hearing populations.

The Flanker Task

In the Flanker task (Eriksen and Eriksen, 1974), participants had to decide whether a target stimulus, which was an arrow presented at the center of a computer screen (e.g., Dye et al., 2007; Unsworth et al., 2015), pointed left or right, and respond by pressing the corresponding button on the keyboard. Specifically, if the target stimulus was an arrow pointing left, the participant was instructed to press the left Shift key (marked with an arrow pointing to the left drawn on a piece of self-adhesive paper) and if the target stimulus was an arrow pointing right, the participant was instructed to press the right Shift key (marked with an arrow pointing to the right drawn on a piece of self-adhesive paper). In each trial, the target stimulus was flanked by two arrows on each side. Congruent trials had flankers pointing in the same direction as the target (e.g.,←←←←←) and incongruent trials, in the opposite direction (e.g.,←←→←←). The participant was instructed to ignore the flanker arrows and respond to the direction of the target arrow. A trial began with a fixation point presented in the middle of the screen for 550 ms, which was immediately followed by a horizontal array, 8 cm wide, of five equally sized and equally spaced black arrows. The array remained on the screen for 2100 ms, after which the screen went blank for 800 ms before the start of the next trial. For an overview of the structure of the task, see **Figure 1**. The task was administered on a 12″ laptop computer using presentation software DMDX version 5.1.4.2 (Forster and Forster, 2003) and the distance between the participant's face and the screen was approximately 60 cm. Participants responded to 48 trials in total, with an equal number of congruent and incongruent trials. In half of the trials within each condition, the target pointed to the left, and in the other half to the right. The order of presentation was randomized for each participant. The dependent variable was average response time in ms on trials to which a correct response was given (both for congruent and incongruent trials).

Swedish Sign Language Sentence Repetition Test

To rule out inadequate sign language skills as an explanation for the results in the present study, deaf participants' STS skill was assessed on the Swedish Sign Language Sentence Repetition Test (STS-SRT, Schönström, 2014a,b). The STS-SRT is an adaptation of an American Sign Language sentence repetition test (ASL-SRT, Hauser et al., 2008) used to measure global sign language fluency of deaf adults. The STS-SRT is a reliable and valid test of STS skills in adults who have used STS since childhood (Schönström, 2014b). The test consisted of 31 trials with filmed STS sentences produced by a deaf native signing man. The sentences varied in length and in difficulty. The participant was instructed to watch the sentences and to reproduce them exactly as signed in the video clips, including the vocabulary and grammatical markers used. Before testing started, participants practiced on three sentences to make sure that they had understood the procedure. On each trial in the actual test, the participants saw a video clip presented on a laptop (12″ screen), and were given approximately 8 seconds to repeat the sentence before the next trial started. The front camera on the laptop was used to film responses. Responses were scored based on a guideline with instructions for each trial on a later occasion (Schönström, 2014b). For a response to be scored as correct, the participants had to reproduce the sentence exactly as it was performed. The dependent variable was number of correctly reproduced sentences (maximum = 31). Testing time was approximately 10 minutes.

Procedure

Participants were tested individually in a quiet room. Participants provided written informed consent before behavioral testing commenced. This study is part of a larger project and testing started with screening of visual acuity and visual contrast, before a cognitive test battery, including tests of episodic long-term memory, lip-reading ability, and phonological skill, in addition to the test of non-verbal cognitive ability (Visual puzzles, Wechsler, 2008), STS skill (STS-SRT, Schönström, 2014a) and the Flanker task reported here, was administered. Before the test battery was administered, participants performed one motor speed task and a physical matching task (Holmer et al., 2016) to become familiar with the set-up of the computerized testing. Testing took approximately 60 minutes in total. For deaf participants, an accredited STS interpreter was present during testing and provided verbatim translation of instructions. In a second part of the larger project, participants performed an fMRI experiment not reported here.

Statistical Analysis

First, descriptive statistics and frequencies for control and background variables were calculated, and the distribution of response times from the Flanker task were visually inspected. Due

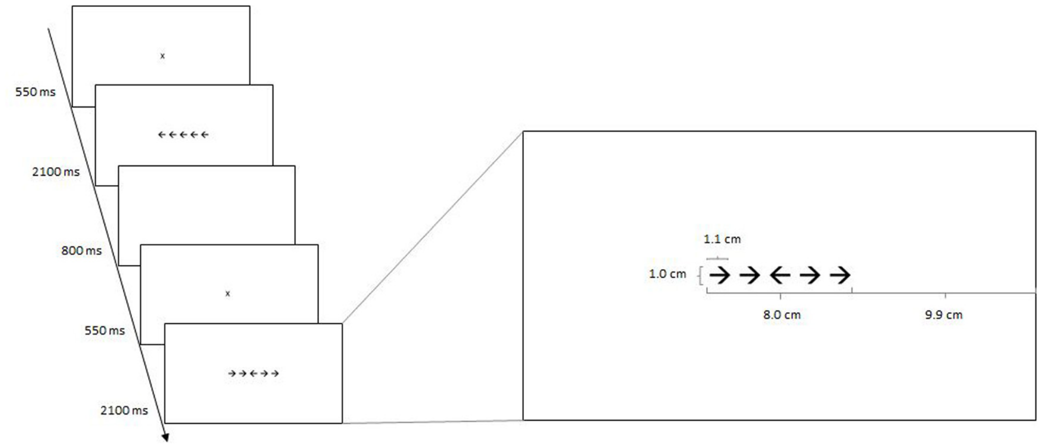

FIGURE 1 | On the left hand side, an overview of the structure of the Flanker task, with examples of one congruent trial (five arrows pointing in the same direction) and one incongruent trial (four flanking arrows pointing to the right, and the middle arrow pointing to the left). To the right, a depiction of how the arrows were displayed on the screen.

to the small sample size with associated potential threats of non-normality and low power, robust statistical methods were applied (Erceg-Hurn and Mirosevich, 2008; Wilcox, 2017). Statistical analysis was performed in RStudio version 1.2.5042 (RStudio Team, 2020), running R version 4.0.0 (R Core Team, 2020). Group comparisons on control and background variables: age, non-verbal cognitive ability, STS skill (only deaf participants), and gaming habits for gamers, were performed using yuen t-tests with the *yuen* function from package WRS2 (Mair and Wilcox, 2020). As an estimate of effect size the explanatory measure of effect size ε is reported, with values of 0.1, 0.3, and 0.5 corresponding to small, medium, and large effects (Mair and Wilcox, 2020). After that, Wilcox (2017) *bbwtrim* function was used to perform a robust mixed ANOVA with one within-group factor: Congruency (congruent, incongruent), and two between-group factors: Group (deaf, hearing) and Gaming (gamer, non-gamer), on response time (in ms) from the Flanker task. Effect size estimates ε for main effects of the ANOVA were calculated with the *yuen* function for between group effects and the *yuend* function for the within group effect, both from package WRS2 (Mair and Wilcox, 2020). Main effects were followed up by comparing means between levels of the factor, and simple main effects were followed up by comparing percentile bootstrapped confidence intervals, estimated using the *onesampb* function from WRS2 (Mair and Wilcox, 2020). To investigate associations between age and non-verbal cognitive ability and performance on the Flanker task, robust correlations were calculated with the *pbcor* function from WRS2 (Mair and Wilcox, 2020). The default value of a trim proportion of 0.2 was applied in all robust analyses. Due to a technical issue, the result was missing for one deaf non-gamer on the Flanker task. One hearing gamer and one hearing non-gamer performed on chance level on the Flanker task, indicating that they did not follow instructions. The mean performance of the sub-group that the participant belonged to was used for these three participants in analyses to maximize statistical power.

RESULTS

Characteristics of Deaf and Hearing Gamers and Non-gamers

Descriptive statistics on background variables for deaf and hearing gamers and non-gamers are reported in **Table 1**. Deaf participants demonstrated proficiency in STS skills, as assessed on the STS-SRT (mean performance was on par with mean performance from a previously tested group, $M = 17.7$ och SD = 4.9, Schönström, 2014a,b). No statistically significant differences on any background variables were seen between deaf gamers and non-gamers: age, $t(6.6) = 0.00$, $p = 1.00$, $\varepsilon = 0.00$, non-verbal cognitive ability, $t(8.7) = 2.08$, $p = 0.07$, $\varepsilon = 0.61$, and STS skill, $t(10) = 0.67$, $p = 0.52$, $\varepsilon = 0.31$. Similarly, hearing gamers and non-gamers did not differ on background variables: age, $t(8.7) = 0.00$, $p = 1.00$, $\varepsilon = 0.07$, and visual puzzles, $t(11.6) = 0.26$, $p = 0.80$, $\varepsilon = 0.13$. Thus, there were no underlying differences on background variables between gamers and non-gamers in either of the two groups.

To compare gaming habits of deaf and hearing gamers, ratings on how often they played computer respectively console games were compared. Groups reported similar gaming habits; for computer games, deaf gamers ($M = 0.63$, $SD = 0.74$) compared to hearing gamers ($M = 1.08$, $SD = 1.24$), $t(11.3) = 0.79$, $p = 0.45$, $\varepsilon = 0.27$, and for console games, deaf gamers ($M = 1.50$, $SD = 1.00$) compared to hearing gamers ($M = 0.92$, $SD = 0.67$), $t(10.4) = 1.43$, $p = 0.18$, $\varepsilon = 0.13$.

Flanker Task

As expected, deaf gamers ($M = 98\%$, $SD = 5.8$) and non-gamers ($M = 98\%$, $SD = 4.2$), as well as hearing gamers ($M = 99\%$, $SD = 1.4$, after exclusion of the participant who performed at chance level) and non-gamers ($M = 99\%$, $SD = 2.3$, after exclusion of the participant who performed at chance level) performed close to ceiling on accuracy on the Flanker task. Thus, response times for almost all trials were included in the analysis (see **Table 2** for descriptive statistics). The mixed robust ANOVA for response times in Flanker showed a main effect of congruency, $Q = 74.1$, $p < 0.001$, $\varepsilon = 0.32$, gaming, $Q = 5.40$, $p = 0.02$, $\varepsilon = 0.41$, and of Group, $Q = 5.09$, $p = 0.02$, $\varepsilon = 0.41$. Response time was faster for congruent ($M = 539$ ms, $SD = 110$) than incongruent ($M = 597$, $SD = 114$) trials, and gamers ($M = 541$ ms, $SD = 112$) responded faster than non-gamers ($M = 598$ ms, $SD = 102$), and hearing ($M = 557$ ms, $SD = 108$) responded faster than deaf ($M = 594$ ms, $SD = 108$). There was a statistically significant interaction between group and gaming, $Q = 8.89$, $p = 0.003$ (see **Figure 2**). Investigation of the confidence intervals for the group by gamer interaction, indicated that deaf gamers, 95% CI [475 ms, 562 ms], responded faster than deaf non-gamers, 95% CI [626 ms, 739 ms], and on par with hearing gamers, 95%

TABLE 1 | Descriptive statistics on background variables for deaf and hearing gamers and non-gamers.

Variable	Deaf				Hearing			
	Gamer ($n = 8$)		Non-gamer ($n = 8$)		Gamer ($n = 12$)		Non-gamer ($n = 10$)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	34.9	4.79	35.4	10.0	25.9	7.04	26.3	7.70
VP	12.8	4.06	9.63	2.39	12.5	2.88	12.5	1.96
STS-SRT	16.8	3.96	18.6	4.21				

VP = Visual puzzles, standardized score; STS-SRT = Swedish Sign Language-Sentence Reception Test, raw score.

TABLE 2 | Response times (mean, median, and standard deviation) for deaf and hearing gamers and non-gamers on congruent and incongruent trials in the Flanker task.

Trial type	**Deaf**						**Hearing**					
	Gamer (n = 8)			**Non-gamer (n = 8)**			**Gamer (n = 12)**			**Non-gamer (n = 10)**		
	M	***Mdn***	***SD***	***M***	***Mdn***	***SD***	***M***	***Mdn***	***SD***	***M***	***Mdn***	***SD***
Congruent	485	496	67	644	633	33	528	496	144	511	498	64
Incongruent	553	536	61	720	711	46	583	554	132	551	538	61

CI [468 ms, 631 ms]. Hearing non-gamers, [486 ms, 573 ms], responded faster than deaf non-gamers, but no difference was observed in comparison to hearing gamers. Thus, the main effect of gaming experience was explained by a group-specific effect for deaf participants that eliminated any difference in processing efficiency across groups.

Besides the interaction between Group and Gaming, interactions were not statistically significant (all *p*s > 0.05). Thus, our predictions that deaf individuals are more distracted and that gamers are less distracted by incongruent flanking stimuli were not supported. Non-verbal cognitive ability, $r_{pb} = -0.21$, $p = 0.19$, and age, $r_{pb} = 0.23$, $p = 0.16$, were not associated with response time on the Flanker task, and it is thus unlikely that these variables strongly influenced the pattern of results.

DISCUSSION

In the present study, we investigated the effect of naturally occurring gaming experience on visuospatial attentional control in early deaf signers. We predicted longer response times on the Flanker task for deaf compared to hearing participants and that this difference would be most apparent for incongruent trials. We also predicted that gamers would show less interference from flankers than non-gamers and outperform them on the Flanker task, especially for incongruent trials.

Our predictions were partially supported by the results. While both deaf and hearing groups had longer response times on incongruent than congruent trials, the deaf group did not show longer response times than the hearing group specifically on incongruent trials. Instead, the deaf group responded slower on both congruent and incongruent trials. Across groups, deaf non-gamers responded slower than hearing non-gamers, while there was no significant difference in performance between deaf gamers and hearing participants. Further, an effect of gaming was only observed in the deaf group, and we did not find evidence of a specific effect of gaming on incongruent trials.

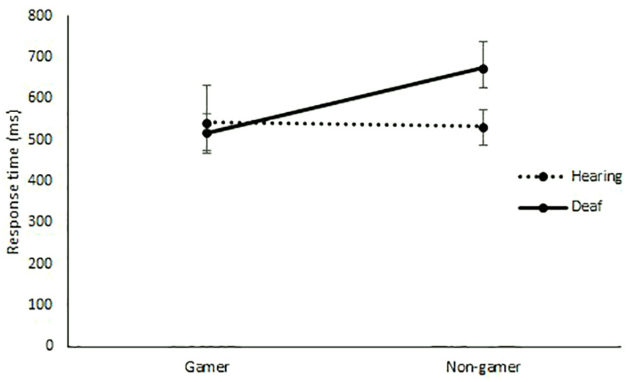

FIGURE 2 | Response time (in ms, *y*-axis) for gamers and non-gamers (*x*-axis) for deaf and hearing participants. Error bars represents 95% confidence intervals.

Although there was a statistically significant main effect of group on performance on the Flanker task, this effect was explained by longer latencies for deaf non-gamers compared to the other participants. Deaf gamers performed similar to hearing participants. With enhanced visuospatial perception in deaf compared to hearing participants under some circumstances (Loke and Song, 1991; Chen et al., 2006; Dye et al., 2009), worse performance on tasks demanding control of visuospatial attention might seem contradictory. However, these seemingly contradictory findings might be explained by differences in ventral versus dorsal stream processing, and their relative contribution to the behavioral task (Samar and Berger, 2017). Proksch and Bavelier (2002) proposed that congenital deafness alters visuospatial attention in such a way that more attentional resources are used for processing stimuli outside central vision (also, see Bavelier et al., 2006). In a visuospatial perception task designed to invoke dorsal stream functions, this will lead to better ability to, e.g., detect stimuli in the periphery (e.g., Dye et al., 2009), but in a task that relies more on ventral stream processing, and suppression of dorsal stream elements, performance might be impaired (e.g., Dye et al., 2007). Like Lauro et al. (2014), here we used a static task that could be argued to rely on ventral stream processing, and in line with what Lauro et al. (2014) reported, we saw worse performance in deaf compared to hearing individuals. Thus, our results lend further behavioral support to the notion of potentially altered ventral stream processing in deaf populations (Weisberg et al., 2012; Samar and Berger, 2017). On the other hand, we did not find evidence that deaf participants are more distracted by incongruent flanking stimuli than hearing participants. In line with previous data (e.g., Dye et al., 2007), we reasoned that the effect of incongruency would become stronger as a consequence of the redistribution of visuospatial attention. It is likely that the small sample in combination with the complexity of the design might have been at play here. To maximize power and minimize bias due to potential non-normality in the data, robust methods were used in analysis. Although this was likely to be the best analytic approach for the purposes of the present study, the results are still constrained by the available data. In addition to the limited amount of individuals, the Flanker task only included 24 congruent and 24 incongruent trials. This number of trials is similar to what others have used (i.e., 30 for each type in Unsworth et al., 2015), but more trials are likely to produce more stable estimates when averaging within individual, with reduced noise in the analysis as a result (Brysbaert, 2019). These factors: small sample, complex design, and small number of trials, are likely to have reduced the probability of detecting a group by congruency interaction. Thus, we cannot rule out the possibility that deaf individuals are more distracted by incongruent flanking stimuli in a Flanker task than hearing individuals.

Based on the present study we suggest that deaf individuals with recent gaming experience reveal a level of visuospatial attentional control similar to that revealed by hearing individuals in a task that presumably draws upon ventral stream processing. To our knowledge, only one previous study has investigated effects of gaming on cognition in a deaf population (on a Stroop color-word task, Nagendra et al., 2017), and that study also reported a positive effect. Our findings extend the results of Nagendra et al.'s (2017) study, by showing an effect of gaming in another executive domain. Importantly, the effect of gaming in the present study was not simply driven by sign language proficiency, since sign language skills did not differ between deaf gamers and non-gamers. Greenwood and Parasuraman (2016) argue that cognitive training leads to functional disconnection of the dorsal stream, releasing attentional resources for transfer to other tasks. Because a specific effect of gaming is found only for deaf individuals with potentially enhanced dorsal stream skills, one interpretation is that this group has more resources to transfer as a result of the cognitive training inherent in gaming. A potential group-specific effect of gaming experience in deaf individuals needs to be followed up in future work. In particular, combining behavioral and brain imaging measures will help us illuminate potential alterations in dorsal and/or ventral stream processing. Related to this, an effect should also be compared between congenitally deaf individuals and individuals with acquired deafness.

Previous studies in hearing individuals have reported effects of gaming on the kind of attentional control demanded by a Flanker task (Bediou et al., 2018). However, here we did not see any effect of gaming in the hearing group, and there was no significant interaction between gaming and congruency. Although it might be the case, as some argue, that gaming experience does not lead to any meaningful effects on cognitive functions in hearing individuals (Kristjánsson, 2013; Powers et al., 2013), the present study had some limitations that might explain why our results were not in line with our prediction. As already mentioned, statistical power was restricted due to the small sample size, another issue might be that our definition of a gamer was not as strict as definitions applied in previous studies in the literature (e.g., Bediou et al., 2018). Further, self-reported gaming habits during the last six months determined group assignment. In hearing individuals, there is evidence to suggest that gaming effects vary as a function of gaming genre (however, see a discussion on issues in defining genres in Bediou et al., 2018). In particular, action video games (AVGs) seem to have the most robust effects (Wang et al., 2016; Bediou et al., 2018). Gamers in the present study played a wide variety of games (see **Supplementary Appendix B**), ranging from simple puzzle games (not typically categorized as AVGs, e.g., Tetris) to first-person shooters (commonly categorized as AVGs, e.g., Counter-strike), and there was also variability in what type of platform they preferred for playing games (i.e., some played games on stationary consoles, others on a computer, and yet others on both these types of platforms). Self-report measures are convenient, but they do not always reflect actual behavior, and this is true also in the case of gaming experience (Kahn et al., 2014). Besides the potentially low correspondence to actual behavior, the temporal resolution of the self-report measure included here was coarse. It is possible that effects of video games on visuospatial attention are transient (similar to effects of gaming on attitudes, e.g., Sestir and Barthalow, 2010), which might have then influenced our results. As two examples, we do not know whether participants in one group had more recent gaming experience than the participants in the other group, or if participants had played for only a limited period during the time for which they reported their habits. Our approach was, however, intentional and motivated by a number of factors. Most importantly, we did not find any previous study on the effect of gaming experience on visuospatial attention in deaf individuals, but plenty of evidence to suggest that visuospatial processing differs between deaf and hearing individuals (Bavelier et al., 2006). Thus, we had little reason to assume that findings from hearing populations would be exactly the same for deaf individuals. However, since we did find an effect in deaf individuals, and saw that groups reported similar gaming habits, this could mean that effects of gaming experience on visuospatial attentional control are observed with a lower dose of exposure in this population. One explanation for this could be that the mechanisms are somewhat different across groups, and more malleable to visuospatial experience for deaf individuals. It is reasonable to assume that effects arising from gaming experience are constrained by baseline levels across tasks, and with different baselines in visuospatial attention across deaf and hearing populations, the pattern across groups is influenced by task selection. Oei and Patterson (2013) suggest that game characteristics constrain transfer, and here we propose that the characteristics of the gamer will produce similar constraints. It is thus important to further investigate the role of different types of gaming experiences in visuospatial perception, and visuospatial attention in particular, in deaf individuals. Experimental designs are a way forward, with active manipulation of gaming experience, although that might become more and more challenging with gaming turning into a mainstream leisure activity in society. As an alternative, using fine-grained correlational approach, for example, by following participants over a longer period of time and using active measures of gaming experience, such as ecological momentary assessment (Kirchner and Shiffman, 2008), might be useful in future studies. Also, the longevity of gaming effects on cognition is something that needs to be addressed in such work.

CONCLUSION

Visuospatial attention is altered by early deafness. The results of the present study show better visuospatial attentional control in deaf signers who play video games than those who do not. Gaming experience may help harness the changes in visuospatial attention displayed by deaf individuals for better attentional control. Thus, gaming might be a useful intervention for shielding deaf children from potential visuospatial distractions.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethical Review Board, Linköping, Sweden (dnr 2016/344-31). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EH, MR, and JA designed the study. JA collected data. KS scored performance on the STS-SRT. EH performed the data analysis. All authors were involved in the interpretation of results as well as preparing and finalizing the manuscript, after a draft version was prepared by EH.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.534741/full#supplementary-material

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An EZ-Diffusion Model Analysis of Attentional Ability in Patients With Retinal Pigmentosa

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Retinitis pigmentosa (RP) is characterized by visual acuity decrease and visual field loss. However, the impact of visual field loss on the cognitive performance of RP patients remains unknown. In the present study, in order to understand whether and how RP affects spatial processing and attentional function, one spatial processing task and three attentional tasks were conducted on RP patients and healthy controls. In addition, an EZ-diffusion model was performed for further data analysis with four parameters, mean decision time, non-decision time, drift rate, and boundary separation. It was found that in the spatial processing task, compared with the control group, the RP group exhibited a slower response speed in large and medium visual eccentricities, and slower drift rate for the large stimulus, which is strongly verified by the significant linear correlation between the visual field eccentricity with both reaction time ($p = 0.047$) and non-decision time ($p = 0.043$) in RP patients. In the attentional orienting task and the attentional switching task, RP exerted a reduction of speed and an increase of non-decision time on every condition, with a decrease of drift rate in the orienting task and boundary separation in the switching task. In addition, the switching cost for large stimulus was observed in the control group but not in the RP group. The stop-signal task demonstrated similar inhibition function between the two groups. These findings implied that RP exerted the impairment of spatial cognition correlated with the visual field eccentricity, mainly in the peripheral visual field. Moreover, specific to the peripheral visual field, RP patients had deficits in the attentional orienting and flexibility but not in the attentional inhibition.

Keywords: retinal pigmentosa, EZ-diffusion model, attentional orientation, attentional flexibility, attentional inhibition

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INTRODUCTION

Retinitis pigmentosa (RP) is a group of hereditary retinal diseases characterized functionally by the degeneration of rod and cone photoreceptors (Hamel, 2006). Progressive peripheral visual field loss, also known as visual field constriction or tunnel vision, is one of the most significant clinical manifestations (Gordon and Johns, 1984).

Visual dysfunction has a negative impact in the information processing (Turatto et al., 1999). Specifically, RP leads to a deficit in visual information perception and motor perception.

For example, RP patients experience the compression of spatial information and perceptual magnification in their visual fields (Wittich et al., 2011), a phenomenon known as perceptual filling-out (Temme et al., 1985). Besides, RP patients exhibit an increase in the minimum motion threshold and a decrease in the maximum motion threshold in motion coherence (Alexander et al., 1998). It is also suggested that RP patients with severe vision loss failed to perceive changes in various dot contrasts and sizes, implying that information processing is closely related to the remnant vision (Alexander et al., 1999).

Although accumulating evidence suggests a general impairment in visual information processing in RP patients (Herse, 2005; Wittich et al., 2011), to date, no precise quantitative account exists of their special cognitive performance induced by visual field loss, especially the attentional ability which is fundamental for cognitive processing in the peripheral and central visual fields. One way to quantify the cognitive function is by conducting an observational experiment to obtain such information as reaction time (RT) and accuracy on a specific experiment. Actually, people tend to slow down response speed for a higher accuracy (Ratcliff et al., 2016; Wagenmakers et al., 2017). In order to propose concrete mechanisms that drive observed behavior and explore the underlying processes that determine performance on an experiment, the effect of such speed-accuracy trade-off should be taken into consideration during the process of data analysis. As successful cognitive process models, the drift diffusion model (Ratcliff, 1978; Ratcliff et al., 2016) and its simplified version EZ-diffusion model (Moustafa et al., 2015) have been widely applied to compensate for the insensitivity of the original data of accuracy and RT, and the insufficient consideration of the speed-accuracy trade-off.

In this study, four experiments were established to investigate the cognitive impairment in the central and peripheral visual fields of RP patients. Experiment 1 aimed to evaluate the spatial processing in the periphery and central visual fields with various field sizes. Due to RP-related progressive loss in the peripheral visual field, the following experiments focused specifically on the peripheral visual field. Accordingly, the ability of basic attentional orienting was examined in Experiment 2, and the attentional inhibition and attentional flexibility were tested in Experiments 3 and 4, respectively. In the last part of our study, we analyzed the data with the EZ-diffusion model and tried to explore the duration of spatial and attentional processes including the decision and non-decision time in the central and peripheral visual fields.

MATERIALS AND METHODS

Patients and Clinical Examinations

We have no prior beliefs or pilot data to estimate the minimum required sample size to observe a significant difference between groups. We recruited 19 RP patients and 13 healthy subjects for Experiment 1 because this number reflects the average sample size in similar RP studies (Alexander et al., 1998, 1999; Wittich et al., 2011). Based on the results of Experiment 1, we conducted a power analysis by using an alpha of 0.05, one-tailed, power of 0.8, and the effect size from Experiment 1. The effect size was computed to reflect a between-subject design. We found a minimum required sample size to be 7 for RP patients and 5 for healthy subjects. Thus, same number of participants were enrolled for each experiment.

In this study, RP patients (RP group) were recruited from the Second Hospital of Beijing Armed Police Corps office. Healthy subjects chosen from the patients' family and matched by age and gender serve as the control group. For each subject, the following examinations were taken, including E decimal charts, visual field evaluations, slit-lamp biomicroscopy, and fundus inspection. The research protocol was approved by the Ethics Committee of the Capital Medical University, China. The complete details of the entire study design and procedures involved were in accordance with the Declaration of Helsinki. Written informed consent was obtained prior to participation.

RP patients were included only if they fulfilled the following criteria: (1) were $\geq$ 18 years of age; (2) with night blindness; (3) with peripheral visual loss; (4) with typical abnormal fundus appearance, including change in retinal pigmented epithelium; (5) without movement disorders;, and (6) without achromatopsia. Healthy subjects should have either normal or corrected normal vision acuity ($\geq$ 1.0), clear ocular media, and normal-appearing fundi. For both groups, exclusion criteria included a history of major physiological and psychological diseases.

Materials, Apparatus, and Procedures

In this study, each participant completed four experiments in a random order in a soundproof, light-isolated chamber with a constant temperature of 25°C (SD = 1°C) (**Figure 1**). The participant was seated in front of a 17-in. computer screen (Lenovo ColorSync), positioned approximately 57 cm distant from his eyes. Stimulus presentation was controlled with E-Prime (Psychology Software Tools Inc., Pittsburgh, United States). For each experiment, training trial identical to the formal one was initially conducted 20 times.

Experiment 1 (The spatial processing task): The stimulus picture consisted of one black circle and one black target number. There were three sizes of circle with a visual angle of 3.5°, 5°, and 7°, respectively, horizontally from the center fixation. The target number (between 1 and 9) was oriented clockwise in 0°, 90°, 180°, or 270° either inside or outside the circle, with 0° defined as the upright of the circle. The font size of the number was either 22-px, 31-px, or 44-px, congruent with the size of the circle. There was a total of 132 trials with stimulus of each size appearing randomly and equally. The formal trial began with the appearance of a central fixation cross "+" for 500 ms, followed by a stimulus for 3,000 ms. Each participant was instructed to press the left (or right) key of the mouse at the appearance of target number inside (or outside) the circle. Once the button was pressed, the stimulus would disappear followed by a 500 ms blank interval, and the next trial began (**Figure 1B**).

Experiment 2 (The attentional orienting task): The target was one of four black geometrical figures (rectangle, diamond, circle, and triangle), presented with 7° in eccentricity horizontally from the center fixation. There were a total of 146 trials with figure

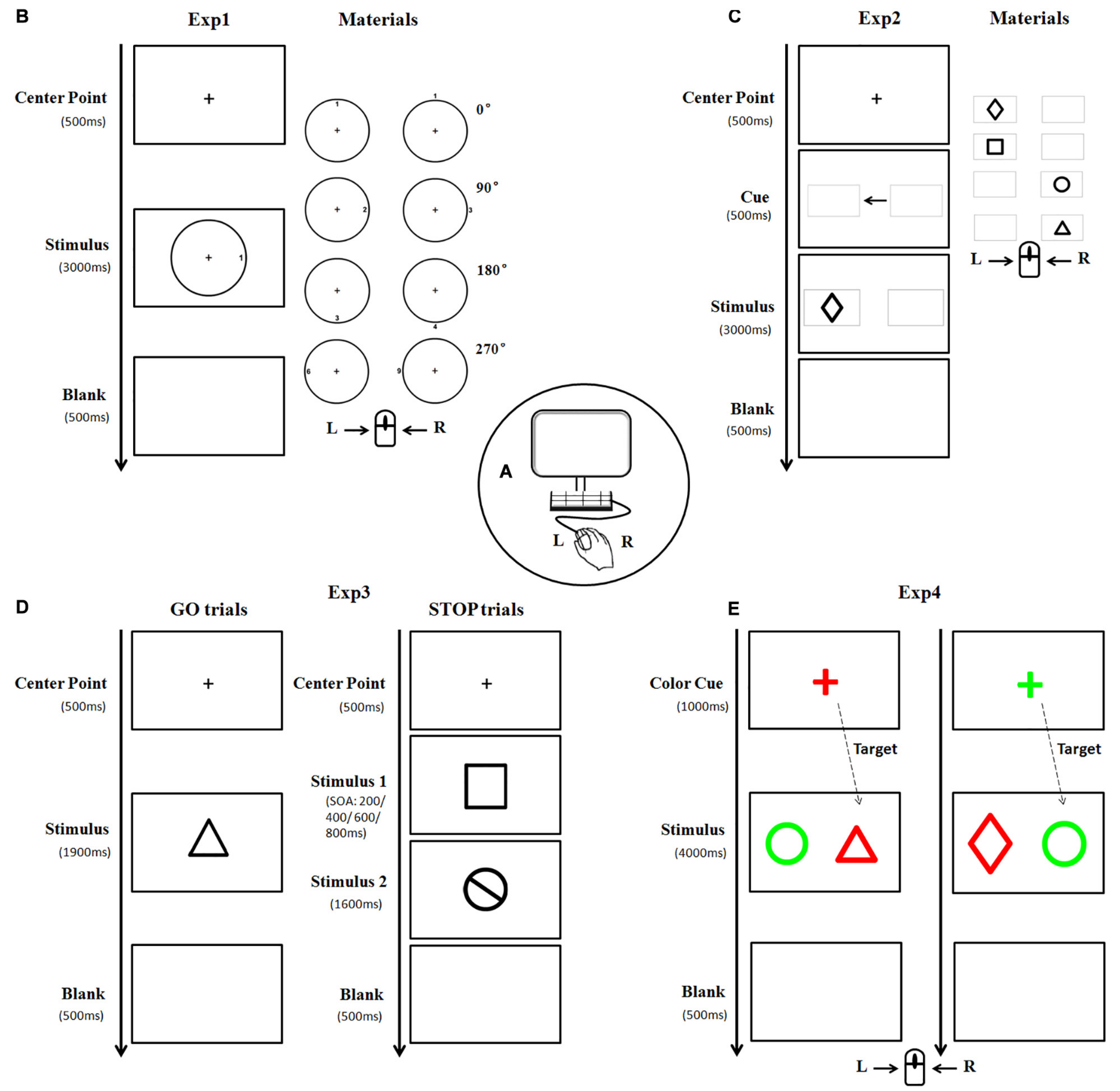

FIGURE 1 | A diagram illustrating the experimental materials and procedures. Subjects were seated in front of a computer screen **(A)** to perform four experiments in a random order. In Experiment 1, the stimulus picture consisted of one circle and one target number. The target number was oriented clockwise in 0, 90, 180, or 270° either inside or outside the circle, respectively **(B)**. Each subject was asked to press the left/right key of the mouse according to the outer/inner location of the targets. Stimulus in Experiment 2 was presented as one of four black geometrical figures **(C)**. Each subject pressed the key according to the left/right location of the target. Experiment 3 consisted of GO and STOP trials. The materials in the GO trial were similar to that in Experiment 2, whereas, the stimulus in the STOP trial is a black-stop symbol **(D)**. Subjects were instructed to press the left key of the mouse in the absence of STOP stimulus, otherwise, withhold the action. As for Experiment 4, the stimulus was a pair of different geometric figures (as described in Experiment 2) placed horizontally, with one highlighted in *red* and the other in *green* **(E)**. The figure with the same color as the cue was regarded as the target. Subjects were asked to press the left/right key of the mouse if the target is (or is not) a triangle figure (Exp, experiment).

form and location appeared randomly and equally. The formal trial began with the appearance of a central fixation cross "+" for 500 ms, followed by two identical gray horizontal boxes (width = 7.4°, *SD* = 0°; height = 4.7°, *SD* = 0°) presented for 500 ms with a black central arrow in between. Afterward, a target appeared inside either the ipsilateral (96, 65.8%) or contralateral (50, 34.2%) box for 3,000 ms (**Figure 1C**). Each participant was instructed to quickly press the left (or right) key of the mouse according to the location (left or right) of the box where the target figure appeared.

Experiment 3 (The stop-signal task): This experiment consisted of GO and STOP trials. Similar to Experiment 2, the stimulus in GO trial (53.8%) was one of four black geometrical figures, whereas, the stimulus in STOP trial (46.2%) was a black-stop symbol. These stimuli appeared in either large size or small size (width = 14°/10°, *SD* = 0°; height = 14.13°/11.1°, **SD** = 2.40°/1.33°, presented at 7 and 5° in eccentricity horizontally from the center fixation, respectively). After the appearance of a central fixation cross "+" for 500 ms, a GO stimulus would appear for 1,900 ms, sometimes followed by a STOP stimulus with stimulus onset asynchronies (SOAs) of either 200, 400, 600, or 800 ms. Each participant was instructed to press the left key of mouse in the absence of STOP stimulus, otherwise, withhold his action (**Figure 1D**). There were a total of 208 trials in this experiment, including 112 GO trials and 96 STOP trials (24 STOP trials for each SOA).

Experiment 4 (The attentional switching task): Stimuli in this experiment were a pair of horizontally placed geometric figures (as described in Experiment 2), highlighted in red (RGB: 255, 0, 0) and green (RGB: 0, 255, 0), respectively. There was a total of 186 trials with large stimulus (width = 5°, SD = 0°; height = 5.57°, SD = 1.32°) and small stimulus (width = 3.5°, SD = 0°; height = 3.88°, SD = 0.85°), which were presented at 10 and 7° in eccentricity horizontally from the center fixation, respectively, and appeared randomly and equally. A colorful central fixation cross "+" (font size of 64-px) was first displayed in either red (RGB: 255, 0, 0) or green (RGB: 0, 255, 0) randomly as a cue for 1,000 ms, followed by the appearance of a stimulus for 3,000 ms. The figure with the same color of the cue was regarded as the target. Each participant was instructed to press the left (or right) key of the mouse if the target was (or was not) a triangle figure (**Figure 1E**).

The EZ-Diffusion Model

Drift diffusion model and its simplified version EZ-diffusion model have been widely applied in various cognitive tasks, including the direction discrimination task (Metin et al., 2013), reward and punishment learning task (Moustafa et al., 2015), response signal and Go/No-Go tasks, value-based decision making, as well as conflict tasks for ADHD (Metin et al., 2013), schizophrenia (Moustafa et al., 2015), and healthy groups (Ratcliff et al., 2016). In EZ-diffusion model, the observed RT can be separated into mean decision time (MDT) and non-decision time (Ter). Ter can be further divided into information encoding time (the period before information accumulation to a response) and motor time (the period after information accumulation) (Wagenmakers et al., 2017). Information accumulation begins at a certain level, proceeds over time with drift rate [information processing speed (v)], and halts once either the upper or the lower boundary is reached, during which the distance is called boundary separation (A).

Data Analysis and Statistical Analysis

Accuracy (ACC) was defined as the number of correct response (in percentage) in relation to the original response number, and RT as the time period between the stimulus onset and the participant's response. Only trials with RT in the range of 200 and 3,000 ms were included for further data analysis (98.62% of all correct trials). However, trials with appropriate RT, but the incorrect response would be excluded from the analysis of RT. In addition, several EZ-diffusion model parameters were calculated according to the formula described elsewhere, including v, A, *MDT*, and *Ter* (Wagenmakers et al., 2017).

Prior to statistical analyses, we compared the expected data with the observed data by coefficients analysis using R software to find whether this model fits our data quite well or the statistical analysis was valid enough. The following results indicated R^2 = 0.125 and 0.222 for accuracy and RT in Experiment 1, R^2 = 0.105 and 0.242 in Experiment 2, and R^2 = 0.147 and 0.149 in Experiment 4, respectively, which verified that the EZ model provides a good fit to our data and can confidently investigate the differences in performance between RP patients and controls.

Statistical analyses were performed by using SigmaStat 3.5 (SAS Institute Inc., Cary, NC). Group differences in demographics, clinical data, and experimental data were analyzed using independent samples t-tests (for quantitative data), Fisher's exact test (for categorical data), and two-way ANOVA (for quantitative data) where appropriate. Holm-Sidak test was conducted as *post hoc* test to analyze differences between and within subjects. The correlation between the RT, EZ-diffusion model parameters, and the visual field eccentricity was processed using Pearson correlation in Experiment 1. All tests were two sided, and statistical significance was defined as $p < 0.05$ for multiple comparisons.

RESULTS

Demographics

Table 1 presents the demographic and clinical characteristics of the study population. There was no significant difference between the two groups in terms of sex ratio, age, educational attainment, Edinburgh hand scale, and Mini-Mental State Examination (MMSE), respectively. However, in either right or left eye, a significant lower corrected visual acuity was found in the RP group (right eye: 95% CI, 0.27–0.42; $p < 0.001$; left eye: 95% CI, 0.13–0.25; $p < 0.001$), when compared with the control group (right eye: 95% CI, 0.99–1.08; left eye: 95% CI, 0.98–1.04). In this study, RP patients had disease duration of 95% CI, 5.31–9.63 years, among which 9 patients had a family history (**Table 1**).

Effect of RP on Spatial Processing

Experiment 1 was designed to evaluate the spatial processing in the peripheral and central visual fields with various field sizes. **Figure 2** showed the results of ACC, RT, and EZ-diffusion model parameters in two groups. A distinct longer RT was observed in the RP group in comparison with the control group for large (eccentricity 7°) (RP: 95% CI, 970.51–1,416.02 ms; control: 95% CI, 626.03–909.45 ms; p = 0.001) and medium stimuli (eccentricity 5°) (RP: 95% CI, 881.97–1,236.94 ms; control: 95% CI, 881.97–1,236.94 ms; p = 0.008), respectively. While there was no significant change of RT for the small stimulus (eccentricity 3.5°) between two groups (RP: 95% CI, 811.45–1,123.46 ms; control, 95% CI, 619.30–899.95 ms), statistically significant

TABLE 1 | Demographics and clinical data in RP and control groups.

	RP group (95% CI)	Control group (95% CI)	*T*-value	*P*-value (*t*-test)
95% CI				
Subject number	19	13		
Male/Female	12/7	9/4		1.000[#]
Age (years old)	34 (29.15–38.94)	28.28 (26.02–30.47)	1.905	0.066
Education levels (years)	12.63 (10.48–14.78)	15.23 (14.33–16.13)	−2.599	0.053
Edinburgh hand scale	87.91 (82.25–93.55)	87.89 (79.47–96.31)	0.003	0.998
MMSE	27.94 (27.45–28.44)	28.00 (27.01–28.98)	−0.098	0.923
VA (log MAR)				
RE (mean ± SD)	0.34 (0.27–0.42)	1.04 (0.99–1.08)	19.275	< 0.001
LE (mean ± SD)	0.19 (0.13–0.25)	1.02 (0.98–1.04)	15.762	< 0.001
Family history (*n*, %)	9 (47%)			
Disease duration (years)	7.47 (5.31–9.63)			

RP, retinal pigmentosa; MMSE, Mini-Mental State Examination; VA, visual acuity; MAR, minimum angle of resolution; RE, right eye; LE, left eye.
[#]Fisher's exact test.

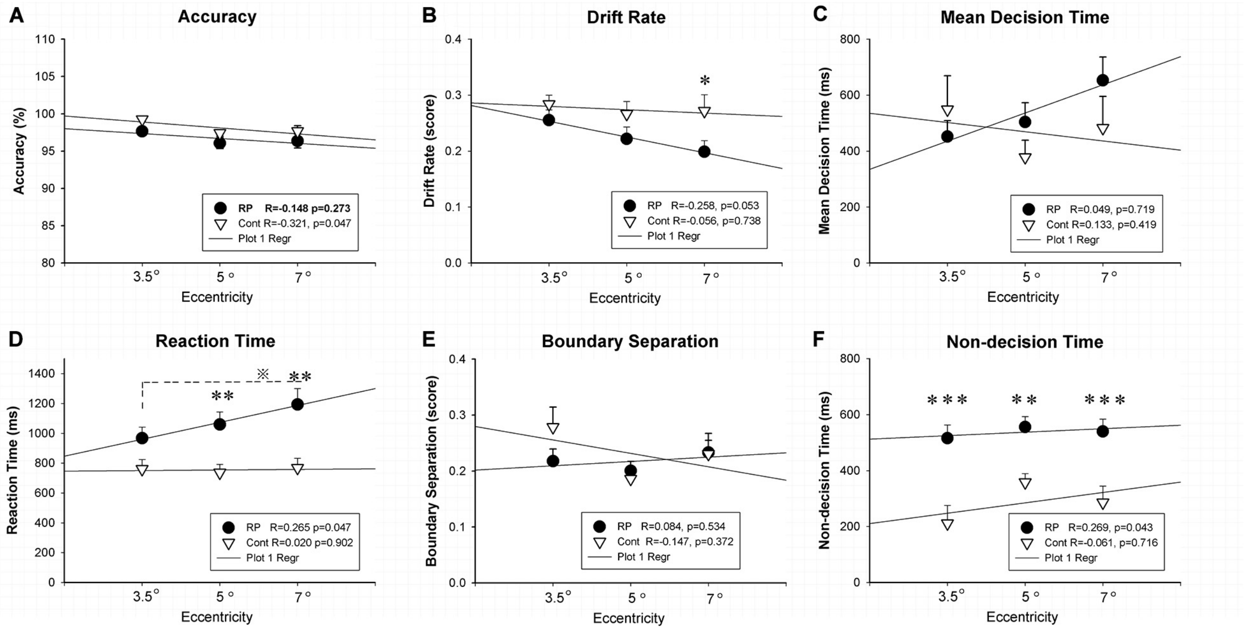

FIGURE 2 | The results for the spatial processing task (Experiment 1). Results of accuracy **(A)**, RT **(D)**, and EZ-diffusion model parameters, as well as their correlations with visual field eccentricity were presented in two groups. The RP group responded much slower to large (eccentricity 7°) and medium stimuli (eccentricity 5°) when compared with the control group. In addition, the RP group presented significantly smaller *v* for the large stimulus **(B)** and longer *Ter* at each eccentricity than the control group **(F)**, respectively. There were no significant differences between the two groups in mean decision time **(C)** and boundary separation **(E)** at each eccentricity, respectively. In addition, a significant correlation of visual field eccentricity was observed with RT **(D)** and Ter **(F)** in the RP group, respectively. (RP, retinal pigmentosa; Cont, control). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, RP group vs. control group; ※$p < 0.05$, eccentricity 7° vs. eccentricity 5°.

difference between large and small stimuli was observed in the RP group ($p = 0.039$), suggesting an impaired spatial processing in RP patients in the peripheral visual field.

For the analysis on the EZ-diffusion model, a significantly smaller *v* was revealed in the RP group only in a large field (95% CI, 0.16–0.24; $p = 0.020$) when compared with the control group (95% CI, 0.21–0.33). This result indicated a slower processing speed in RP patients in the peripheral visual field. Moreover, the deficit in information coding was also observed in RP patients, which was proved by the *Ter* significantly longer than their healthy counterparts in either large (RP: 95% CI, 448.26–632.26 ms; control, 95% CI, 156.74–414.31 ms; $p < 0.001$), medium (RP: 95% CI, 477.77–633.90 ms; control, 95% CI, 289.94–426.16 ms; $p = 0.005$), or small visual field (RP: 95% CI, 416.87–614.63 ms; control, 95% CI, 71.22–351.43 ms; $p < 0.001$). Taken together, RP patients presented a far more serious defect phenomenon on the spatial processing in their peripheral visual field, which may relate to the peripheral visual field loss in these patients (**Figure 2**). Additionally, by Pearson correlation analysis, significant correlation of visual field eccentricity was observed with RT ($R = 0.265$, $p = 0.047$) and Ter ($R = 0.269$, $p = 0.0430$) in RP patients, respectively. Whereas no significant correlation of visual field eccentricity was found with other EZ-diffusion model parameters in RP patients, as well as RT and all EZ-diffusion model parameters in the control group (**Figure 2**).

Effect of RP on the Attentional Orienting

Experiment 2 was conducted to investigate the attentional orienting by judging the location of stimulus in the peripheral visual field. The results of ACC, RT, and several EZ-diffusion model parameters are presented in **Figure 3**. The effect of attentional orienting can be reflected by comparing the high proportion of valid stimuli (ratio > 70%) with the low proportion of invalid stimuli (ratio < 30%). However, in this study, no significant effect was found in RT data of 96 valid stimuli (ipsilateral, 65.8%) in comparison with 50 invalid stimuli (contralateral, 34.2%), probably because the valid/invalid ratio was not particularly high. Therefore, all the data (both the valid and invalid stimuli) were finally integrated to analyze the difference between the RP and the control groups. Compared with their healthy counterparts (95% CI, 356.56–450.97 ms), RP patients exhibited a much longer RT (95% CI, 477.12–636.83 ms; $p = 0.004$). Under the EZ-diffusion model analysis, there was no statistical significance of group between difference in neither *A* nor *MDT*. However, the RP group exhibited a distinct smaller v (95% CI, 0.33–0.40; $p = 0.006$) and longer Ter (95% CI, 219.39–301.24 ms; $p = 0.003$) than the control group (v: 95% CI, 0.46–0.52; Ter: 95% CI, 112.11–213.25 ms), indicating that RP could lead to a deficit in the information processing speed and encoding speed (**Figure 3**).

Effect of RP on the Attentional Inhibition

Experiment 3 was conducted to assess the patient's attentional inhibition by observing the ability of control in the peripheral visual field. **Figure 4** illustrated the results of RT and ACC in two groups. In the GO and STOP trials, the statistically significant difference could not be evaluated between two groups in either ACC or RT. Results in GO trial indicated that RP patients had general performing ability, similar to their healthy counterparts. In addition, regardless of grouping and stimulus size, a significantly lower ACC was found with 800 ms SOA, compared with that with 200, 400, and 600 ms SOA, respectively. Results of ACC in the STOP trials suggested a similar outcome when treated with SOA in the two groups, indicating that the RP group presented similar symptom of the attentional inhibition when compared with the control group (**Figure 4**).

Effect of RP on the Attentional Flexibility

As for Experiment 4, the attentional flexibility under sustained and switching conditions in the peripheral visual field was evaluated. Results of ACC, RT, and the EZ-diffusion model parameters in the two groups are presented in **Figures 5**, **6**, respectively. The attentional flexibility is mainly reflected by the difference between the switching and the sustained conditions, which is the so-called switching cost. The greater the switching cost means the stronger the flexibility. Interestingly,

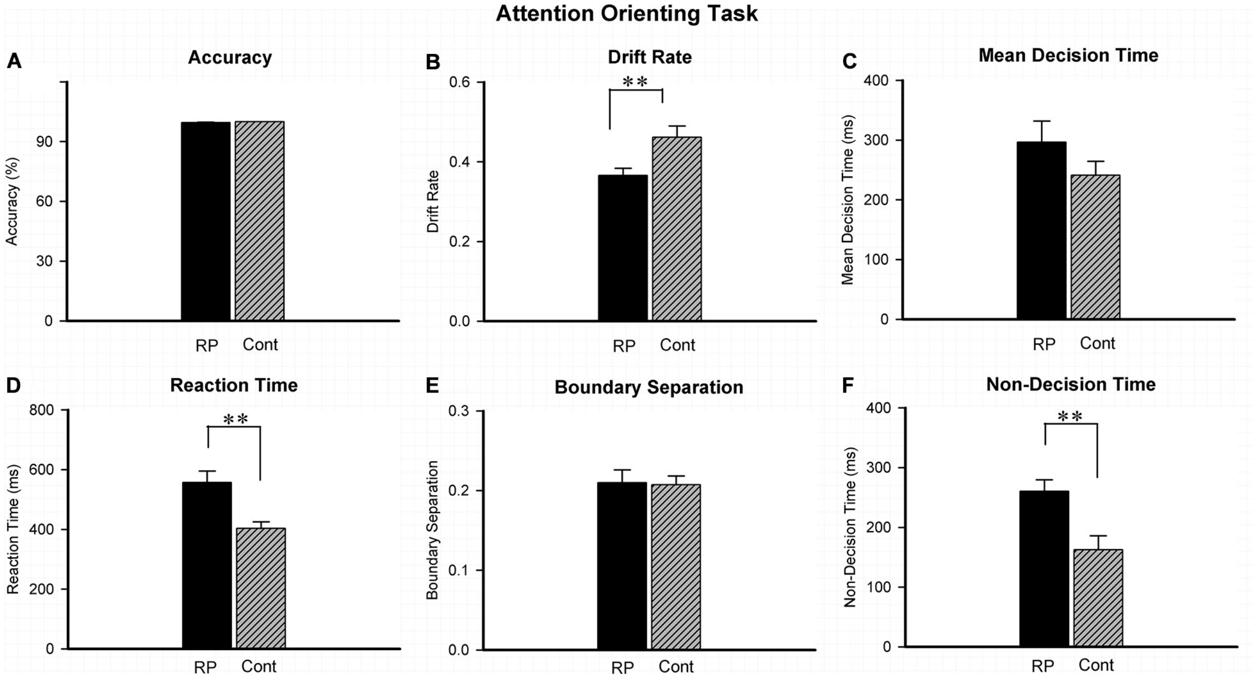

FIGURE 3 | The results for the attentional orienting task (Experiment 2). Results of accuracy **(A)**, RT **(D)**, and EZ-diffusion model parameters were presented in two groups. Compared with the control group, the RP group responded much slower in attentional orientation. In addition, the RP group presented significantly smaller *v* **(B)** and longer Ter than the control group **(F)**, respectively. There were no significant differences between the two groups in mean decision time **(C)** and boundary separation **(E)**, respectively. (RP, retinal pigmentosa; Cont, control). $^{**}p < 0.01$, RP group vs. control group.

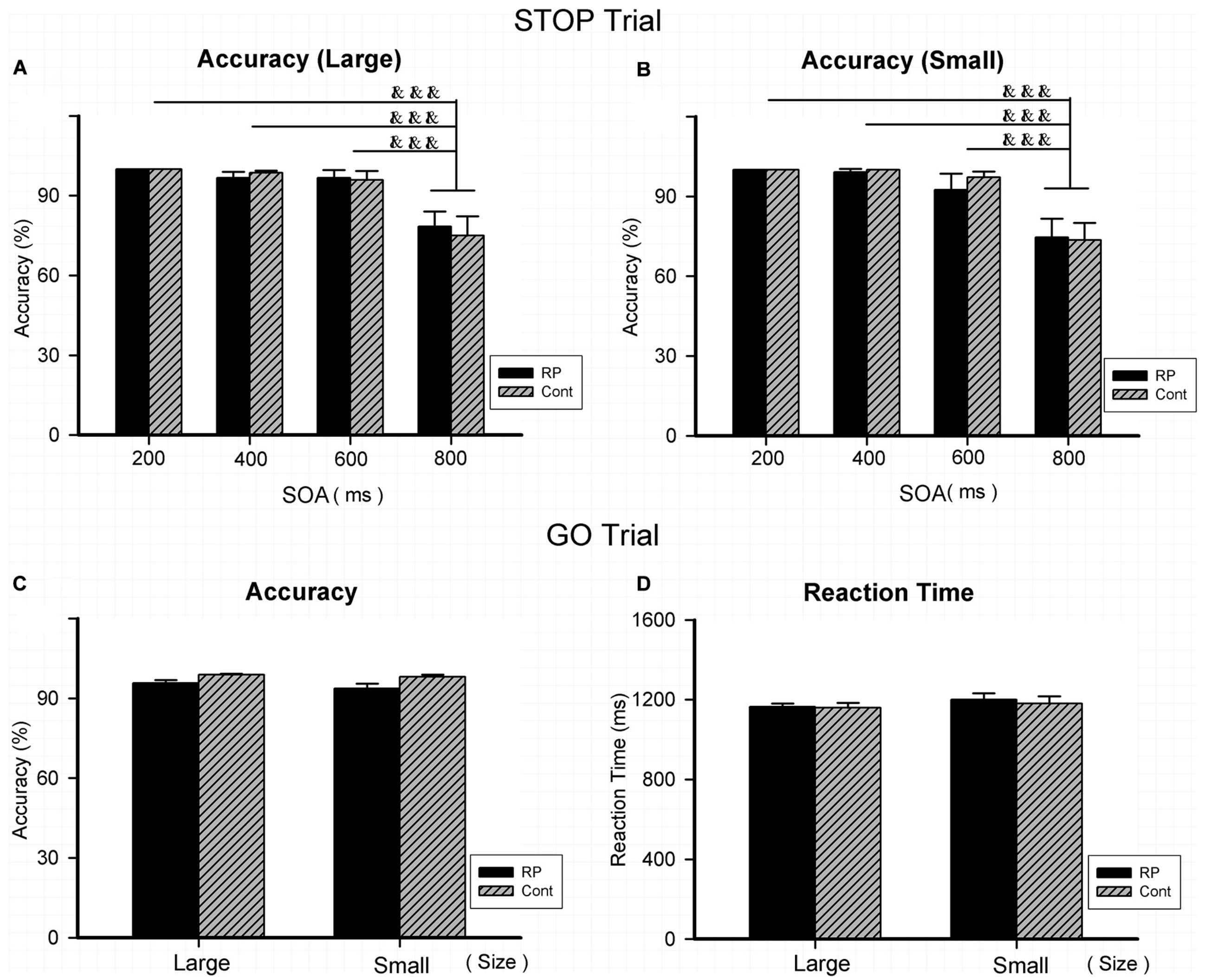

FIGURE 4 | The results for the stop-signal task (Experiment 3). Results of accuracy and RT were presented for the STOP and GO trials in two groups. As for the STOP trials, there was no significant difference between the two groups in accuracy for either large **(A)** or small stimulus **(B)**. In addition, regardless of group and stimulus size, significantly lower ACC was found with 800 ms SOA, compared with that with 200, 400, and 600 ms SOA, respectively. As for the GO trials, statistically significant difference did not exist between the two groups for large and small stimuli in either accuracy **(C)** or RT **(D)**, respectively. (RP, retinal pigmentosa; Cont, control; SOAs, stimulus onset asynchronies). $^{\&\&\&}p < 0.001$, compared with that with 800 ms.

the switching cost for large stimulus existing in the control group (sustained condition: 95% CI, 630.67–809.28 ms; switching condition: 95% CI, 763.65–1,044.71 ms; $p = 0.044$) was not observed in the RP group (sustained condition: 95% CI, 777.31–1005.89 ms; switching condition: 95% CI, 825.91–1,073.61 ms; $p = 0.435$) (**Figure 5**).

Significantly, RP patients presented a worse performance in RT when compared with their healthy counterparts for small stimulus under sustained (RP: 95% CI, 877.48–1,083.95 ms; control: 95% CI, 684.01–958.81 ms; $p = 0.004$) and switching condition (RP: 95% CI, 928.56–1,090.02 ms; control: 95% CI, 764.21–956.27 ms; $p = 0.026$), as well as for large stimulus under sustained condition (RP: 95% CI, 777.31–1,005.89 ms; control: 95% CI, 630.67–809.28 ms; $p = 0.041$). These findings suggested that RP led to the impairment in reaction speed under both conditions, with a more severe symptom under sustained condition.

By the EZ-diffusion model analysis, under sustained and switching conditions, significantly smaller *A* and longer Ter were observed in the RP group than the control group for both large and small stimuli, respectively (**Figure 6**). Besides, the RP group showed slower *v* for small stimulus under sustained condition (RP: 95% CI, 0.18–0.27; control: 95% CI, 0.26–0.39; $p = 0.011$). Notably, the switching cost for large stimulus existing in the control group in Ter (under sustained condition: 95% CI, 135.46–234.09 ms; under switching condition: 95% CI, 162.03–496.78 ms; $p = 0.036$) was not found in the RP group, which may be due to the considerably longer Ter in the RP group for large stimulus under sustained condition (RP: 95% CI, 408.15–548.95 ms; control: 95% CI, 135.46–234.09 ms; $p < 0.001$). Our

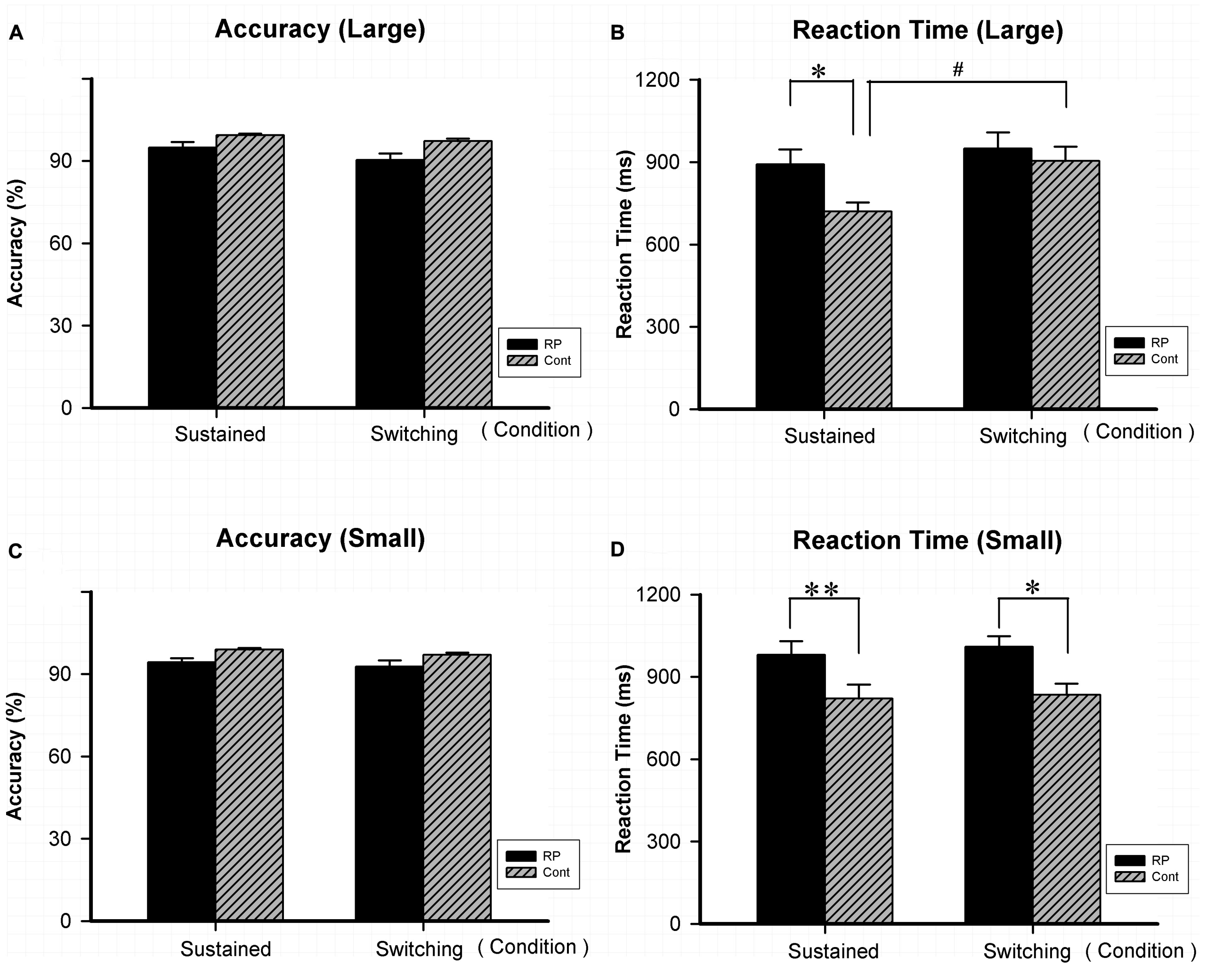

FIGURE 5 | The results for the attentional switching task (Experiment 4). Results of accuracy and RT for large and small stimuli under sustained and switching conditions are presented. As for accuracy, there was no significant difference between the two groups under either sustained or switching condition for either large **(A)** or small stimulus **(C)**. As for RT, significantly worse performance was found in the RP group for small stimulus **(D)** under sustained and switching condition, as well as for large stimulus **(B)** under sustained condition. The switching cost (longer RT was found under switching condition than under sustained condition) for large stimulus existed in the control group, but *not* in the RP group. (RP, retinal pigmentosa; Cont, control). $^{*}p < 0.05$, $^{**}p < 0.01$, RP group vs. control group; $^{\#}p < 0.05$, switching condition vs. sustained condition.

findings in Ter explained the disappearance of switching cost in RT, since the RP group has longer encoding time than the control group under sustained condition (**Figure 6**).

DISCUSSION

The spatial processing and attentional ability of RP patients in both the central and peripheral visual fields has never been examined before, and we firstly reported the findings as mentioned in the "Result" section. Our findings demonstrated that RP patients exhibited impairment in spatial processing correlated with the visual field eccentricity and mainly in the peripheral visual field. Moreover, specific to the peripheral visual field, RP patients exhibited deficits in attentional orienting and flexibility, whereas no deficits were found in attentional inhibition.

Previously, the stimuli were presented at a visual angle of about 1, 3, or 5° horizontally from the central fixation point, and the deficits of spatial processing was only observed at the largest angle in RP patients (Wittich et al., 2011). Similar results were found in this work, in which the eccentricity range was expanded to 3.5, 5, and 7° from boundary to the center, respectively, and considerable impairment mainly existed at two bigger angles. EZ-diffusion model analysis further indicated that such slow performance in RP patients relates to the long non-decision time for each size stimulus and slow drift rate v for large stimulus. The similar phenomenon, also observed in myopic patients, was thought to be associated with the narrowed visual perception field at large eccentricity (Turatto et al., 1999). This

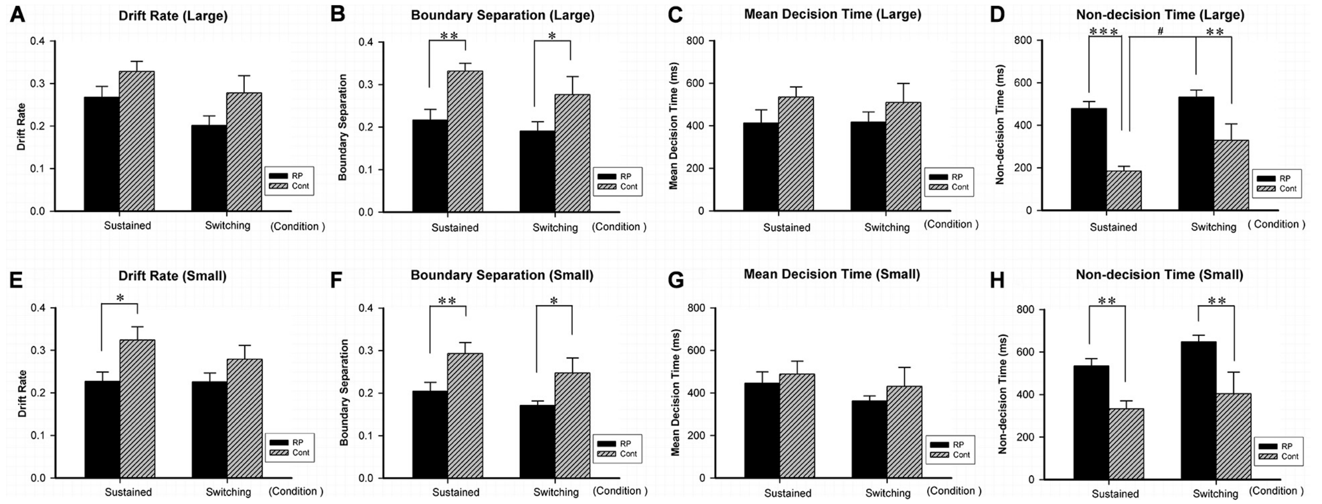

FIGURE 6 | The results for the attentional switching task (Experiment 4). Results of EZ-diffusion model parameters for large **(A–D)** and small **(E–H)** stimuli under sustained and switching conditions are presented. Under sustained and switching conditions, significantly smaller *A* **(B,F)** and longer Ter **(D,H)** were observed in the RP group than the control group for both large and small stimuli, respectively. Besides, the RP group showed shorter Ter **(E)** for small stimulus under sustained condition. The switching cost (longer Ter was found under switching condition than under sustained condition) for large stimulus existed in the control group, but *not* in the RP group. (RP, retinal pigmentosa; Cont, control). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, RP group vs. control group; $^{\#}p < 0.05$, switching condition vs. sustained condition.

could lead to the ignorance of patients on the peripheral visual stimulus and to allocate few attentional resources to the periphery field, causing a defective attentional orienting and processing (Turatto et al., 1999). In view of an even more severe visual field dysfunction than myopia patients, it is not surprisingly to find that RP patients, with progressive peripheral field loss, exhibited impairment of spatial processing in the peripheral field.

Our finding of significant correlation of visual field eccentricity with RT and Ter in RP patients provides additional evidence that the impairment of spatial processing speed was mainly caused by visual field loss. Nevertheless, many other factors should also be considered, including luminance contrast, spatial contrast, duration and receptor sampling density of stimuli, contrast sensitivity, glare sensitivity of human eye (Szlyk et al., 1995; Herse, 2005). It was suggested that RP patients may exhibit an elevation in threshold to vernier, letter, and grating visual acuity (Sandberg and Berson, 1983; Alexander et al., 1986, 1991, 1992a,b), a reduction in grating contrast sensitivity (Temme et al., 1985; Turano, 1991; Turano and Wang, 1992; Alexander et al., 1998), as well as a delay in flash detection and a loss of flicker sensitivity (Marmor, 1981; Alexander et al., 1995; Akeo et al., 2002). Notably, compared with their healthy counterparts, such influencing factors may have more severe impact on RP patients, and a slightly functional loss would be considerably amplified. For example, with the decrement of luminance, the environmental adaptability decreases and the contrast sensitivity threshold increases in RP patients, leading to their difficulty in walking, driving, reading the street signs, and crossing obstacles at night (Herse, 2005). In parallel, the slight changes of stimulation in pattern contrast (Michelson) or in temporal frequency sensitivity will cause more errors in the symmetry discrimination for RP patients, and the error number presents a functional change related to the visual field eccentricity (Szlyk et al., 1995). Due to the importance of the human eye characteristics, further investigations are warranted to understand the relationship among the spatial processing, visual field loss, and contrast sensitivity in RP patients.

As reported, an RP patient is prone to being tripped by obstacles during walking, implying an attentional deficit or orientation difficulty (Herse, 2005). Our findings from Experiment 2 suggested that there was a deficit in attentional orienting in the peripheral field (7° from the central fixation point). By the EZ-diffusion model analysis, the decrease of response speed in orienting was proved to be attributable to declined drift rate and increased non-decision time. It is widely recognized that attentional orienting is associated with the frontoparietal network, including the dorsal and ventral attentional network (Vincent et al., 2008; Farrant and Uddin, 2015). The attentional information processing through this network was reportedly delivered *via* primary visual area (V1), where the earliest neural activity of cognition was detected (Li, 1999; Chen et al., 2016). As demonstrated in myopic and strabismus amblyopia patients (Mori et al., 2002; Thiel and Sireteanu, 2009; Baranton et al., 2014), those with V1 lesion may be at risk of damaging the attentional network and therefore causing the orienting difficulty. In this regard, the decreased activities in V1, previously reported in RP patients (Ferreira et al., 2017) may at least partly interpret their attentional orienting deficit revealed in the present study.

Attentional switching refers to a process of reorganizing attentional set with the change of goal and task and therefore reflects the attentional flexibility. People usually keep the present attentional set active with sustained attention, and then activate a new one while leaving the previous one with switching attention (Mayr and Keele, 2000). Consequently, they tend to respond substantially slower and with higher error rate under switching condition than sustained condition (Monsell, 2003). Such discrepancy in RT between two kinds of trials is known as the attentional switching cost (Meiran and Chorev, 2005). It is worthwhile to notice that attentional switching cost only existed in large stimulus trial in the control group but not in either large or small stimulus trial in the RP group. The disappearance of the switching cost in RP patients should be ascribed to the lengthening of RT and information encoding time under sustained condition. RP patients presented a reduction of boundary separation and non-decision time under both sustained and switching conditions, especially under sustained condition. Such findings, taken together with the decrease in drift rate in the sustained trial with small size, implied that RP patients have difficulty in maintaining visual stability. An increase of eye movement was previously reported in RP patients during walking (Yoshida et al., 2014). Visual instability may relate to the narrowed visual field, since healthy subjects constricted to narrowed visual field presented increased pause frequency, prolongation of reading time, and increased eye movements during reading (Turano et al., 1993). The visual instability in RP patients could be explained by the insufficient sampling, the impaired spatial and temporal contrast sensitivity, the decreased threshold for motor perception, or the combination of the above (Wittich et al., 2011).

Several brain areas have already been reported in the process of sustained attention, such as prefrontal (Wilkins et al., 1987), parietal (Thakral and Slotnick, 2009), V1 area, and anterior cingulate cortex (Kerns et al., 2004; Silver and Ress, 2007). Among these areas, the first three were reported to be damaged in RP patients (Yoshida et al., 2014; Ferreira et al., 2017) which may result in the instability of sustained attention. Also, it is reported that activities of an attentional network including frontal and parietal areas were related to the drift rate in diffusion model (Karalunas et al., 2012), which is likely associated with the sustained attentional deficit in RP patients revealed in our study. Hence, further investigations are warranted to understand the underlying neural mechanisms behind our findings.

As recognized, an effective information processing relies on three inseparable and interactive aspects, that is, attentional orienting, switching, and inhibition. Deficit in either aspect will lead to a damaged processing; for example, an individual with hyperactivity may fail to control himself from the interference of novel information and was found with deficit in attentional inhibition by the stop-signal task (Rasmussen et al., 2015; Grane et al., 2016). In this work, RP patients exhibited a deficit in the attentional orienting and flexibility but not in attentional inhibition. Although the stop-signal task applied in this study was structured with 53.8% GO trials and 46.2% STOP trials, it was shown that the accuracy increases with the difficulty of inhibition (SOA), and its accuracy curve is similar to that of the typical stop-signal task with a high proportion of GO trials (∼75%) (data not shown), indicating the validity of our experimental design. As such, the presented normal inhibition function in RP patients may, in turn, provide additional evidence that the impairment in spatial processing should be attributable to the deficit in attentional orienting and flexibility revealed in this study.

Additional information about recognition processing is obtained from the EZ-diffusion model analysis. Generally, an increase in RT could be interpreted by a slow motor response (Ter), increased boundary separation (A), and/or decreased drift rate (v) (Ratcliff et al., 2016). Notably, the result of Experiment 4 gave the evidence for the impulsive information processing style (i.e., significantly lower in boundary estimates). Therefore, it is quite likely that the slow performance of RP patients was associated with either the reduction in drift rate, or the increase in non-decision time, or both. Since the drift rate represents the rate of information accumulation and reflects the efficiency of information processing (Karalunas et al., 2012), its reduction found in Experiments 1, 2, and 4 indicates a general impairment in the information processing in RP patients, leading to reduced reaction speed. Similar to patients with visual field loss including glaucoma and unilateral anterior ischemic optic neuropathy, RP patients exhibited longer RT than their healthy counterparts in certain experiments (Nowomiejska et al., 2010). Additionally, RP exerts an increase in the non-decision time in these three experiments. Considering that all responses were key responses in these experiments, non-decision time mainly reflects the duration of information encoding. The information encoding may link to the visual acuity in some way. It is speculated that impaired visual acuity or restricted visual field may credit to reduced fixation stability for amblyopic and RP patients (Chung et al., 2015; Zipori et al., 2018; Raveendran et al., 2019), suggesting that the poor information encoding could be caused by the visual instability in RP patients. Further study on RP patients with poor visual acuity demonstrated that eye-movement training may lead to an improvement in the recognition performance (Yoshida et al., 2014).

Interestingly, the RP-induced extension during the encoding processing in attentional orienting and switching could partly give the reason for the slow performance of RP patients presented in Experiments 1 and 4. Also, V1 area may be involved in the impairment during the information processing as observed from RP patients. This abnormal activation of V1 area due to the reduction in pigment optical density of cone photoreceptors was related to the information processing, including the spatial perception, and discrimination, attentional shifting (Chirimuuta et al., 2003; Fortenbaugh et al., 2008; Eichhorn et al., 2009). On the other hand, the deficit in boundary separation was only found in the attentional switching task, suggesting a possible impairment in the information processing caution in RP patients.

CONCLUSION

Or study found that RP exerted impairment in spatial processing mainly in the peripheral visual field, which may be attributable to the decrease of information processing speed and increase of information encoding time. Moreover, specific to the peripheral visual field, RP patients exhibited normal inhibition function but impaired attentional orienting and flexibility. The impairment of attentional orienting is mainly related to the decrease of processing speed and poor performance of information encoding. Meanwhile, the impaired attentional flexibility is quite likely related to the prolongation of information encoding time under sustained condition due to visual instability.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-LL, J-FL, and G-XN conceived the study, participated in the design, and wrote most of the manuscript. S-FZ, Y-YW, LZ, Y-LY, M-WG, and C-QL performed the experiments. Y-YW and Y-LY analyzed the data and helped in drafting the manuscript. All authors read and approved the final manuscript.

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