

Spatial Hearing Difficulties in Reaching Space in Bilateral Cochlear Implant Children Improve With Head Movements

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Objectives: The aim of this study was to assess three-dimensional (3D) spatial hearing abilities in reaching space of children and adolescents fitted with bilateral cochlear implants (BCI). The study also investigated the impact of spontaneous head movements on sound localization abilities.

Design: BCI children (N = 18, aged between 8 and 17) and age-matched normal-hearing (NH) controls (N = 18) took part in the study. Tests were performed using immersive virtual reality equipment that allowed control over visual information and initial eye position, as well as real-time 3D motion tracking of head and hand position with subcentimeter accuracy. The experiment exploited these technical features to achieve trial-by-trial exact positioning in head-centered coordinates of a single loudspeaker used for real, near-field sound delivery, which was reproducible across trials and participants. Using this novel approach, broadband sounds were delivered at different azimuths within the participants' arm length, in front and back space, at two different distances from their heads. Continuous head-monitoring allowed us to compare two listening conditions: "head immobile" (no head movements allowed) and "head moving" (spontaneous head movements allowed). Sound localization performance was assessed by computing the mean 3D error (i.e. the difference in space between the X-Y-Z position of the loudspeaker and the participant's final hand position used to indicate the localization of the sound's source), as well as the percentage of front-back and left-right confusions in azimuth, and the discriminability between two nearby distances. Several clinical factors (i.e. age at test, interimplant interval, and duration of binaural experience) were also correlated with the mean 3D error. Finally, the Speech Spatial and Qualities of Hearing Scale was administered to BCI participants and their parents.

Results: Although BCI participants distinguished well between left and right sound sources, near-field spatial hearing remained challenging, particularly under the "head immobile" condition. Without visual priors of the sound position, response accuracy was lower than that of their NH peers, as evidenced by the mean 3D error (BCI: 55 cm, NH: 24 cm, $p = 0.008$). The BCI group mainly pointed along the interaural

axis, corresponding to the position of their CI microphones. This led to important front-back confusions (44.6%). Distance discrimination also remained challenging for BCI users, mostly due to sound compression applied by their processor. Notably, BCI users benefitted from head movements under the "head moving" condition, with a significant decrease of the 3D error when pointing to front targets ($p < 0.001$). Interimplant interval was correlated with 3D error ($p < 0.001$), whereas no correlation with self-assessment of spatial hearing difficulties emerged ($p = 0.9$).

Conclusions: In reaching space, BCI children and adolescents are able to extract enough auditory cues to discriminate sound side. However, without any visual cues or spontaneous head movements during sound emission, their localization abilities are substantially impaired for front-back and distance discrimination. Exploring the environment with head movements was a valuable strategy for improving sound localization within individuals with different clinical backgrounds. These novel findings could prompt new perspectives to better understand sound localization maturation in BCI children, and more broadly in patients with hearing loss.

Key words: Children, Cochlear implant, Head movements, Sound localization, Spatial hearing, Virtual reality.

Abbreviations: 3D = three-dimensional; AGC = automatic gain control; BCI = bilateral cochlear implant; CI = cochlear implant; DRR = direct-to-reverberant energy ratio; HMD = head-mounted display; ILD = interaural-level differences; ITD = interaural time differences; NH = normal hearing; RMS = root-mean-square; SSQ = Speech, Spatial, and Qualities of Hearing Scale.

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INTRODUCTION

Spatial hearing is fundamental for our interactions with the physical and social environment: it allows detection of events beyond our visual field, efficient re-orienting of multisensory attention (Pavani et al. 2017) and auditory scene analysis (Kerber & Seeber 2012; Shinn-Cunningham et al. 2017). Spatial hearing is three-dimensional, as it allows the estimation of sound directionality (i.e., its position in azimuth and elevation), and distance. It relies on the correct interpretation of the auditory cues reaching the ears, notably the binaural cues supported by interaural-level differences (ILD) and interaural time differences (ITD); and spectral cues filtered by each pinna (e.g., Brungart 1999; Middlebrooks 2015). It is well established that accuracy of the auditory system is better in azimuth than distance (e.g. Middlebrooks & Green 1991).

The type of stimulus (notably its spectral characteristics) and the acoustic environment (reverberant or anechoic) are known factors that can influence sound localization (e.g., Brungart 1999; Brungart et al. 1999). However, the distance between the listener and the sounds also play an important role. The availability of

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auditory cues differs between the near-field (less than 1 m from the head) and the far-field (beyond 1 m). Sound directionality mainly relies on ITD in near and far spaces (Brungart 1999). Sound distance perception is specifically based on low-frequency ILDs (below 3 kHz) in the near-field, whereas other factors (e.g., room reverberation and spectral characteristics of the sound) are involved in the far-field (Middlebrooks & Green 1991; Brungart 1999). The closer the sound to the listener (less than 50 cm), the larger the low-frequency ILD is. That allows better accuracy in distance perception in the near-field compared to the far-field (Brungart & Rabinowitz 1999; Kolarik et al. 2016). Moreover, accuracy of distance perception is better for lateral than frontal sound sources (Brungart 1999; Kopčo & Shinn-Cunningham 2011).

Although spatial hearing critically relies on binaural and monaural cues (Middlebrooks 2015), interventions for auditory restoration may fail to fully preserve these auditory cues. For instance, it is well known that cochlear implant (CI) users mostly rely on ILD cues for sound localization, ITD cues are not fully available or are incorrectly processed by patients (Seeber et al. 2004, van Hoesel 2004). Likewise, while many technological advances have been made in recent years to promote speech understanding in noise, these same advances can have detrimental consequences on sound localization performance. One notable example is the automatic gain control (AGC) implemented in the CI processor which compresses the large intensity range of our auditory environment (i.e., from 0 to 120 dB HL) into a smaller intensity range (i.e., 10 to 20 dB HL) to comply with the more restricted electrical dynamics imposed by the CI (Dillon 2001). Hence, the AGC amplifies soft sounds, to make them better perceived by a listener, and it compresses loud sounds, to preserve the auditory system from discomfort and injury, aiming at a mean comfortable level (called the C-SPL) of 65 dB (Stöbich et al. 1999; Khing et al. 2013). This technology is valuable for speech understanding, but combines with other factors to increase distortions of ILDs, which are one of the few auditory cues available for CI users to localize sound sources (Archer-Boyd & Carlyon 2019).

These concerns are particularly relevant when one considers the developing auditory system of infants and children. The benefits of bilateral CIs (BCIs) in children with profound deafness have been documented in relation to several everyday life contexts (for review see Gordon et al. 2017), such as speech understanding in noisy environments (Misurelli & Litovsky 2012), opportunities for integration in mainstream schools (Gordon & Papsin 2009; Van Wieringen & Wouters 2015; Choi et al. 2020), and quality of life (Galvin & Mok 2016). To date, however, spatial hearing skills of BCI children and behavioral strategies to help promote these skills remain largely underinvestigated. The few studies that examined spatial hearing in this population reported substantial variability in children's abilities. Some documented performance at levels similar to normal-hearing (NH) listeners (Van Deun et al. 2010; Zheng et al. 2015; Killan et al. 2018), others reported chance level performance (Litovsky et al. 2004; Grieco-Calub & Litovsky 2010; Choi et al. 2017).

In addition to the limited number of pediatric studies, current approaches to spatial hearing limit our knowledge of localization capabilities in children. First, sound localization has only been examined in relation to responses in azimuth, without considering the two other dimensions of space (elevation and depth). Second, sampling of the auditory space has always been

constrained to the portion in front of the participant (Grieco-Calub & Litovsky 2010; Zheng et al. 2015; Choi et al. 2017), thereby neglecting back space. Sound perception in this region is fundamental because it is outside the visual field; hence, its monitoring relies crucially on the auditory modality alone. Third, all of the studies conducted so far examined BCI children in contexts in which the speaker array was visible throughout the experiment (see Table 1 for literature review). Any visual cue about the apparatus, even when seemingly uninformative, provides crucial priors to sound position (Da Silva 1985; Loomis et al. 1998). Visual priors are fully exploited during sound localization, as revealed by the study of visual dominance on spatial hearing in the context of audiovisual mismatch between perceptual cues (e.g., Kumpik et al. 2019). This implies that current data measured in laboratory may not fully reflect the actual performance of children in their daily life.

In addition to all these methodological aspects, two key features may limit our broader understanding of the auditory spatial skills of BCI children. First, previous studies with BCI children typically prevented head movements while listening to the sounds (see Table 1). Although most investigators did not use a chin rest, children were always instructed to face forward during sound delivery and refrain from moving their head. In some studies, the experimenter remained next to the child during the sound localization task to validate this constraint (Van Deun et al. 2010; Choi et al. 2017). Yet, it has long been acknowledged that head movements play a key role in sound localization (Wallach 1940). Humans use head movements to focus on the speaker in complex hearing situations (Wightman & Kistler 1999). In addition, head rotations and head translations (Wallach 1940; Perrett & Noble 1997) lead to changes in binaural cues which prove useful for resolving front-back confusion in people with NH (Brimijoin et al. 2010) and even more so in people with hearing impairment (Brimijoin et al. 2012). The impact of spontaneous head movements on auditory spatial performance has been highlighted in CI adults (Mueller et al. 2014; Pastore et al. 2018; Fischer et al. 2020), but it remains entirely overlooked in pediatric populations. This implies that current data measured in laboratory may be a limited approximation of the actual sound localization ability of children in their daily life, where head movements during sounds occur spontaneously.

The second key feature that remained overlooked is the study of near-by regions of auditory space. In the present study, we examined spatial hearing abilities in the near-field, referred to hereafter as “reaching space.” As a matter of fact, while many studies have been conducted in the far-field in the last decades, the reaching space has been largely overlooked in children. This portion of space is particularly relevant for social interactions, where fast motor responses are needed in case of an approaching auditory object (e.g., a bee), when reaching toward a sound source (e.g., a musical toy) or when orienting towards a nearby talker (Kolarik et al. 2016). Finally, a recent study (Valzolgher et al. 2020a) has shown that the possibility to interact with near-field sounds by reaching to the sound sources directly can promote head movements during listening in case of simulated hearing impairment (monaural ear-plugging) and result in faster adaptation altered auditory cues.

In the present study, we examined (1) spatial hearing abilities in the near-field in BCI and NH children, considering front and back space, and different sound distances and (2) the impact of spontaneous versus restrained head movements during sound

TABLE 1. Literature review on sound localization in bilateral cochlear implant children

		Killan et al. (2018)	Choi et al. (2017)	Zheng et al. (2015)	Grieco-Calub and Litovsky (2010)	Van Deun et al. (2010)	Litovsky et al. (2004)
Population	Number of BCI children	10	13	19	21	30	3
	Age at test (yrs)	5–18	7–18	4–9	5–14	4–15	8–12
	Binaural experience (mo)	12	>12	13–51	3–28	12–44	3
Experience	Simultaneous/sequential CI	All simultaneous	Unknown	3 simultaneous, 16 sequential	All sequential	All sequential	All sequential
	Loudspeaker positions in azimuth	5 positions (–60° to 60°)	13 positions (–90° to 90°)	15 positions (–70° to 70°)	15 positions (–70° to 70°)	9 positions (–60° to 60°)	15 positions (–70° to 70°)
	Type of sound stimulus	Short sentence (3 words)	Bisyllabic word (“ja-yeon”)	Bisyllabic word (25 different)	Bisyllabic word (“baseball”)	1-sec bell-ring	Pink noise
	Head movements free	Yes	No	No	No	No	No
	Speaker visible	Yes	Yes	Yes	Yes	Yes	Yes
	Feedback	No	No	Yes	Yes	Yes	Yes
	Mean RMS error (degrees)	16.2 (range 11–22.6)	39.4 (range 30.6–50.5)	28.5 (range 13.8–47.6)	(range 19–56)	(range 13–63)	55 (range unknown)

BCI, bilateral cochlear implant; CI, cochlear implantation; RMS error, root mean square error.

emission on performance. To these aims and in the attempt to overcome existing limitation in the testing conditions, we developed a novel approach to near-field sound localization testing (European patent n°WO2017203028A1), based on virtual reality and real-time motion tracking that implements emission of real sounds. This allows for the study of spatial hearing with (1) very limited constraints on sound source locations and responses; (2) control of all available visual cues; (3) recorded pointing responses in 3D space; and (4) continuous recording of head movements. Within this virtual reality approach, the latter feature ensures reproducibility of sound source positioning across trials and participants, and it enables active listening strategies during and after sound delivery.

Performance of BCI users was compared to that of age-matched NH controls. Based on previous studies on sound localization and the known consequences of early auditory deprivation on the development of binaural processing (Litovsky 2015), we predicted that BCI children would perform worse than NH peers. Specifically, we expected errors to emerge both in azimuth and distance since CI processing limits ILD extraction which is one of the key auditory cues for sound localization in this population. Finally, we aimed to investigate the impact of head movements on sound localization performance by comparing a condition where the head was immobile during sound emission and another one where head movements were allowed. Based on previous results on hearing impaired adults (Mueller et al. 2014; Pastore et al. 2018), we predicted that BCI children would benefit from this active listening condition, especially when resolving front–back confusion.

MATERIALS AND METHODS

This clinical prospective study was approved by the Ethical Committee (Ile de France II, N° 18.09.19.37537 RIPH2), and recorded in clinicaltrials.gov (NCT03738592).

Participants

Eighteen children and adolescents aged between 8.3 and 16.7 years (mean age \pm SD: 12.1 \pm 2.7 years) fitted with two

CIs were recruited from a referral center for pediatric cochlear implantation. Inclusion criteria included age at testing over 8 years old, a minimum of 2 years of binaural experience to avoid large setting variations of their device, no areflexia and no attention disorders. Binaural experience ranged from 24 to 169 months (mean 67.3 \pm 32.4 months). BCI users were all bilateral CI daily users and had excellent monosyllabic word recognition performance (mean with left CI: 96.8 \pm 3.3%, and with right CI: 95.6 \pm 4.6%). Additional information about demographics and device settings (i.e., implants, sound processors, programming parameters, and sound coding strategies) are summarized in Table 2. Importantly, children wore their own CI processors (i.e., all were new generation processors including AGC, and two microphones, one at the front, and one at the rear). To test children with the settings, they were most familiar with in their daily life no parameters adjustments were made before testing. All but two children used the omnidirectional mode with their CIs. As we only used one sound source without back noise, this resulted in all BCI children being stimulated in the omnidirectional mode.

Eighteen age-matched NH controls were also recruited through advertisement to take part in the study (mean age \pm SD: 12.3 \pm 2.5 years; range 8.7–17 years). None of them had any history of hearing loss, middle ear problems, oculomotor or neurological disorders.

Apparatus and Stimuli

All tests were performed in a reverberant room (6 m \times 3 m, reverberation time RT_{60} : 0.36 s) which belongs to the Neuro-immersion research facility using a new virtual reality and motion tracking system (Fig. 1A). This is comprised of a head-mounted display (HMD) (HTC VIVE System, resolution: 1080 \times 1200 px, Field of View: 110°, Refresh rate: 90 Hz) and two tracked VIVE devices (one placed above a loudspeaker, the other on the pointer held by the participant). Tracking accuracy of the HTC VIVE System is adequate for behavioral research purposes (Verdelet et al. 2019). Specifically, the HTC VIVE has subcentimeter accuracy (9.0 mm when trackers are static; 9.4 mm when trackers are dynamic). Eye-tracking technology

TABLE 2. Demographics of bilateral cochlear implant children and device information

	First cochlear implant					Second cochlear implant					Duration of binaural experience (mo)				
	BCI group	Sex	Age at testing (mo)	Etiology	Onset of profound deafness	Age at CI1 (mo)	Internal Part, Processor, Ear side	Strategy	Microphone	Age at CI2 (mo)		Internal Part, Processor, Ear side	Strategy	Microphone	Interimplant interval (mo)
	B01	M	136	Genetic	Prelingual	28	Digisonic SP EVO, SAPHYR SP, L	Crystalis XDP	Omnidirectional	91	Digisonic SP EVO, SAPHYR SP, R	Crystalis XDP	Omnidirectional	63	44
	B02	F	133	Genetic (connexin 26)	Perlingual	40	Nucleus CI512, CP950, R	ACE	Omnidirectional	68	Freedom CI24RE, CP950, L	ACE	Omnidirectional	28	64
	B03	F	146	Genetic (connexin 26)	Prelingual	13	Freedom CI24RE, CP1000, R	ACE	Omnidirectional	74	Freedom CI24RE, CP1000, L	ACE	Omnidirectional	61	72
	B04	M	178	Meningitis	Prelingual	8	Nucleus CI24R, CP950, L	ACE	Omnidirectional	9	Nucleus CI24R, CP950, R	ACE	Omnidirectional	1	169
	B05	F	139	Unknown	Perlingual	90	Nucleus CI422, CP910, R	ACE	Directional	107	Nucleus CI422, CP910, L	ACE	Directional	17	32
	B06	F	158	Unknown	Prelingual	34	HiRes90K, Naida, L	HiRes Optima-S	Omnidirectional	108	HiRes90K Advantage, Naida, R	HiRes Optima-S	Omnidirectional	74	49
	B07	M	162	Meningitis	Postlingual	52	Digisonic SP, SAPHYR SP, L	MPIS XDP	Omnidirectional	52	Digisonic SP, SAPHYR SP, R	MPIS XDP	Omnidirectional	0	110
	B08	M	110	Unknown	PRELINGUAL	25	Freedom CI24RE, CP1000, R	ACE	Directional	45	Freedom CI24RE, CP1000, L	ACE	Directional	20	64
	B09	M	207	Unknown	Prelingual	38	Nucleus CI24R, CP910, R	ACE	Omnidirectional	140	Freedom CI24RE, CP810, L	ACE	Omnidirectional	102	67
	B10	F	104	Cytomegalovirus	Prelingual	19	Freedom CI24RE, CP1000, L	ACE	Omnidirectional	31	Freedom CI24RE, CP1000, R	ACE	Omnidirectional	12	73
	B11	F	154	Unknown	Prelingual	48	Nucleus CI512, CP950, L	ACE	Omnidirectional	91	Freedom CI24RE, CP950, R	ACE	Omnidirectional	43	62
	B12	M	122	Unknown	Prelingual	15	Nucleus CI512, CP1000, R	ACE	Omnidirectional	48	Freedom CI24RE, CP1000, L	ACE	Omnidirectional	33	74
	B13	M	106	Unknown	Prelingual	75	HiRes90K Advantage, Naida, L	HiRes Optima-S	Omnidirectional	81	HiRes90K Advantage, Naida, R	HiRes Optima-S	Omnidirectional	6	24
	B14	F	162	Unknown	Perlingual	65	Digisonic SP EVO, SAPHYR SP, L	Crystalis XDP	Omnidirectional	106	Digisonic SP EVO, SAPHYR SP, R	Crystalis XDP	Omnidirectional	41	55
	B15	M	200	Genetic (connexin 26)	Prelingual	28	Nucleus CI24R, CP910, R	ACE	Omnidirectional	127	Freedom CI24RE, CP1000, L	ACE	Omnidirectional	99	72
	B16	M	117	Unknown	Perlingual	55	Concerto FlexSoft, OPUS 2, L	FS4-p	Omnidirectional	84	Synchony Standard, SONNET, R	FS4-p	Omnidirectional	29	32
	B17	F	174	Genetic	Prelingual	17	Freedom CI24RE, CP1000, R	ACE	Omnidirectional	101	Freedom CI24RE, CP1000, L	ACE	Omnidirectional	84	73
	B18	M	100	Genetic (connexin 26)	Prelingual	12	Freedom CI24RE, CP1000, R	ACE	Omnidirectional	23	Freedom CI24RE, CP1000, L	ACE	Omnidirectional	11	75

BCI, bilateral cochlear implant; CI1, first cochlear implantation; CI2, second cochlear implantation; L, left; R, right.

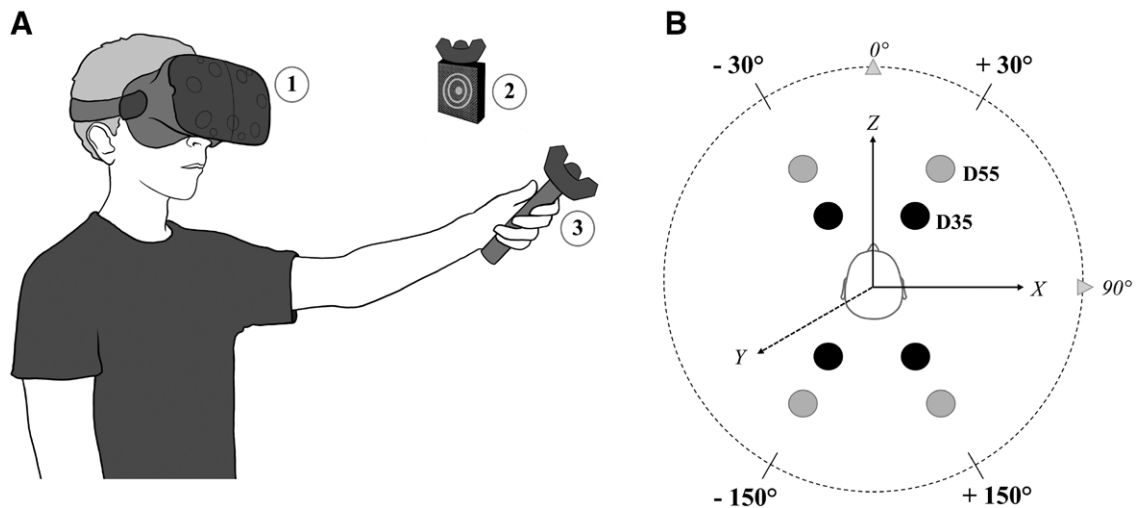


Fig. 1. Experimental setup. A, Apparatus based on the virtual reality system, comprising (1) a head-mounted display (HTC VIVE), (2) a VIVE tracker mounted on a loudspeaker, and (3) another tracker mounted on a hand-held pointer. Head and trackers positions were recorded in real time by two cameras, and defined in a head-centered system. B, Sound localization setup. Black and gray circles indicate two target distances in reaching space, at 35 cm (D35) and 55 cm (D55). Three axes were defined according to the reference frame (i.e., participant head-centered): X, azimuth; Y, elevation; and Z, distance.

(SensoriMotoric Instruments, Berlin, Germany; www.smivision.com; 60 Hz frequency and 0.5 degrees spatial precision) was added to the HMD to allow monitoring of initial eye position throughout testing. The whole setup was controlled using a custom program made with Unity (2017.4.10f1) which enabled: (1) control of the HMD visual display; (2) accurate positioning of the loudspeaker at the beginning of each trial; (3) control over sound delivery; and (4) recording of the exact position of all tracked elements (loudspeaker, participant's head with the HMD, participant's hand, and cyclopean gaze position) in three-dimensional space (azimuth, elevation, and distance). The position of all tracked elements (i.e., the HMD and VIVE trackers) was expressed in a head-centered reference frame. The head-centered position was calculated by collecting the 3D position of both ears (using the VIVE controller), and averaging these positions to obtain the origin of the head-centered system.

Only one loudspeaker (mini speaker model JBL GO Portable from HARMAN International Industries, Northridge, CA; 68.3 × 82.7 × 30.8 mm, Output Power 3.0 W; frequency response: 180 Hz–20 kHz) was used to sample the auditory space around the head. With the tracker fixed on it, the loudspeaker position was tracked and controlled in real time. For each trial, the experimenter held the loudspeaker in his hand and moved it to the desired position (predetermined and defined in head-centered coordinates). The loudspeaker coordinates were indicated by two main cues delivered to the experimenter: (1) visual cues (on a computer screen for azimuth and distance position) and (2) an echo radar signal (for elevation, given by an in-ear headphone nonaudible to the participant). Hence, this enabled the choice of whatever position in space without any physical constraints on loudspeaker placement.

Motor responses were obtained using a hand-held pointer (i.e., a wand with a tracker fixed on it). Participants were informed that they had to place the pointer in the exact position of the perceived sound. This allowed us to record children's responses in 3D, considering azimuth, elevation and distance perception.

The sound stimulus was 3 seconds of white noise, modulated in amplitude at 2.5 Hz frequency (modulation depth at 80%), and delivered at 70 dB SPL when measured one meter from the participant's head (corresponding to 76.6 dB SPL at 35 cm, and 73 dB SPL at 55 cm). The background noise measured at the beginning of the experiment was 33.7 dB SPL.

Unbeknownst to the participant, 8 predetermined sound positions within reaching space were used so that they could reach each sound source without leaving their chair. The loudspeaker could be located at +30°, +150°, -30°, and -150° in azimuth (see Fig. 1B positive values indicating right space and negative values left space) with respect to the participant's straight ahead. Two distances were evaluated in the near-field (reaching space) for each azimuthal position: D35, at 35 cm (13 3/4") from the participant's head, and D55 at 55 cm (21 5/8"). Elevation remained constant throughout the study at ear level but children were unaware of this.

Procedure

Before the experimental session, we collected self-report data from BCI participants on their perceived spatial hearing abilities in daily life. We administered an adapted version of the Speech, Spatial, and Qualities of Hearing Scale (SSQ) to BCI children (SSQ-Child, Galvin & Noble 2013) and their parents (SSQ-Parents, Galvin & Noble 2013). Each SSQ questionnaire was divided into three subscales: (1) speech perception; (2) spatial hearing; and (3) other qualities of hearing. Questionnaire data were collected face to face with children and over the phone with parents, three times 1 week apart. Hence, an observation period of 1 week was allowed for parents to fill out each subscale after paying attention to their child's behavior in the less common situations of daily life.

Before testing, all participants were introduced to the apparatus and the sound localization task by watching a short video. The video informed them that they would be sitting on a rotating chair which allowed them to easily access all sound sources around them, and they would localize a sound source delivered in the near-field within their reachable space. At the end of each

trial (sound emission), the experimenter rapidly removed the loudspeaker to avoid any collision during the pointing phase. For this reason, children were instructed to wait until the sound ended before pointing.

Upon entering the experimental room, the children saw the environment and objects present in the physical space, but received no prior information about the loudspeaker positions used in the study. They were invited to wear the HMD and they underwent a 5-minute training session to ensure that the instructions in the video had been fully understood. This training included different elevations (high and low), distances (near the head and arm outstretched), and azimuthal positions (left/right, and front/back). Participants were encouraged to point either with the left or right hand in order to comfortably reach the sound's perceived position. Participants clearly saw that there were no visual clues in the HMD to help them guess the exact location of sound targets. If no discomfort was reported, the experimental session then began.

Two experimenters were present in the testing room: the first one placed the loudspeaker in the position indicated by the computer and the second one provided information or explanations to the children during the test if necessary. The noises produced by the first experimenter while placing the loudspeaker were not informative (for details, see Supplemental Digital Content 1, <http://links.lww.com/EANDH/A846>, which shows a control experiment).

Each testing session included two listening conditions: head immobile (HI) and head moving (HM) during sound delivery. Under the “head immobile” (HI) condition, participants were instructed to keep their head fixed during sound emission and were only allowed head movements during the response phase. Under the “HM” condition, participants were encouraged, but not forced, to move their head both during sound emission and during the response phase. Overall, the experiment lasted 20 minutes and consisted of 96 trials: 12 repetitions for each sound position, equally distributed among the two listening conditions. An ABBA counterbalancing scheme was used to control for the effects of listening condition order (HM-HI-HI-HM or HI-HM-HM-HI), each block comprising 24 trials. For each group (BCI and NH), half of the participants followed the first order, whereas the other followed the second one.

To ensure reproducibility of trials, several controls were used, specifically for head alignment since no chin rest was used. Hence, at the beginning of each trial, three concomitant conditions had to be validated to trigger sound emission: (1) the head and (2) eyes were aligned with the participant's midsagittal plane, (3) the loudspeaker fell within the predetermined 3D location (see video and comments in Supplemental Digital Content 2, <http://links.lww.com/EANDH/A847> and Supplemental Digital Content 3, <http://links.lww.com/EANDH/A846>, which show the two listening conditions).

To summarize, in this experiment we explored the ability of children to discriminate different sound positions in azimuth and in distance and their answers were evaluated by manual pointing in 3D.

Data Analysis

Kinematic analyses on head and hand movements were performed with a custom-written MATLAB program. This allowed us to reject trials where participants anticipated hand movements during sound emission or performed head movements

during the HI condition. As these analyses were performed after the experiment, rejected trials were not replaced.

Statistical analyses and data visualization were performed using the R-studio environment (www.rstudio.com). First, we separately analyzed sound performance in the azimuthal plane and in distance. For azimuth, the percentage of front-back and left-right confusions was assessed as a function of listening condition for each participant. We also calculated the mean absolute error in degrees for each participant as a function of the real sound position (i.e., error between the sound source and the hand pointing response). For distance, we assessed discriminability between two nearby distances, D35 and D55 within each group.

As we recorded a motor response in 3D, we then computed a variable called the 3D error, corresponding to the difference in space between the X-Y-Z position of the loudspeaker and the participant's final hand position used to indicate the localization of the sound's source. This was adapted from the system introduced by Rakerd and Hartmann (1986) (see also Grantham et al. 2008). The 3D error was calculated for each participant, collapsing across all sound positions, according to the formula:

3D error = $\sqrt{\bar{C}^2 + \bar{s}^2}$, where \bar{C} is the mean of the vector norm between the sound source and the hand pointing position, and \bar{s} is the standard deviation. The 3D error mean and standard deviation were computed irrespective of sound position. The main advantage of the 3D error is that it combines response errors across the three spatial dimensions, and also takes into account each participant's response variability.

Finally, to evaluate the improvement in sound localization by head motion in the HM condition we calculated an index of Listening Improvement “*I*” for each participant with the following formula: $I = (\text{HI 3D error} - \text{HM 3D error}) / \text{HI 3D error}$. The HI 3D error corresponded to the 3D error under the HI condition, and the HM 3D error to the 3D error under the HM condition. The index “*I*” was normalized for each participant which allowed us to have an objective measure of each participant's improvement independently of their baseline performance under the HI condition. We also correlated “*I*” with the percentage of trials where at least one movement was performed during sound emission under the HM condition.

RESULTS

Overall, 2.6 % of trials were rejected in the NH group and 5.2% in the BCI group. Trials were rejected either for head movements during sound emission under the HI condition (2.8% of trials for NH children and 4% for BCI children) or for anticipated hand movement responses in either of the listening conditions (2.4% of trials for NH children and 6.4% for BCI children). This indicates that all participants easily complied with the instructions and easily adapted to our novel methodology for spatial hearing measurement.

Condition HI: HI During Sound Emission

First, we compared sound localization performance between groups with the H during sound emission. Figure 2 shows mean responses for NH and BCI children. Figure 2A shows sound discrimination as a function of side (i.e., left or right space) and distance (i.e., 35 or 55 cm). Almost all trials BCI children were as good as NH children in discriminating sounds from left and right space, confusing stimulus side in only 7.9% of cases

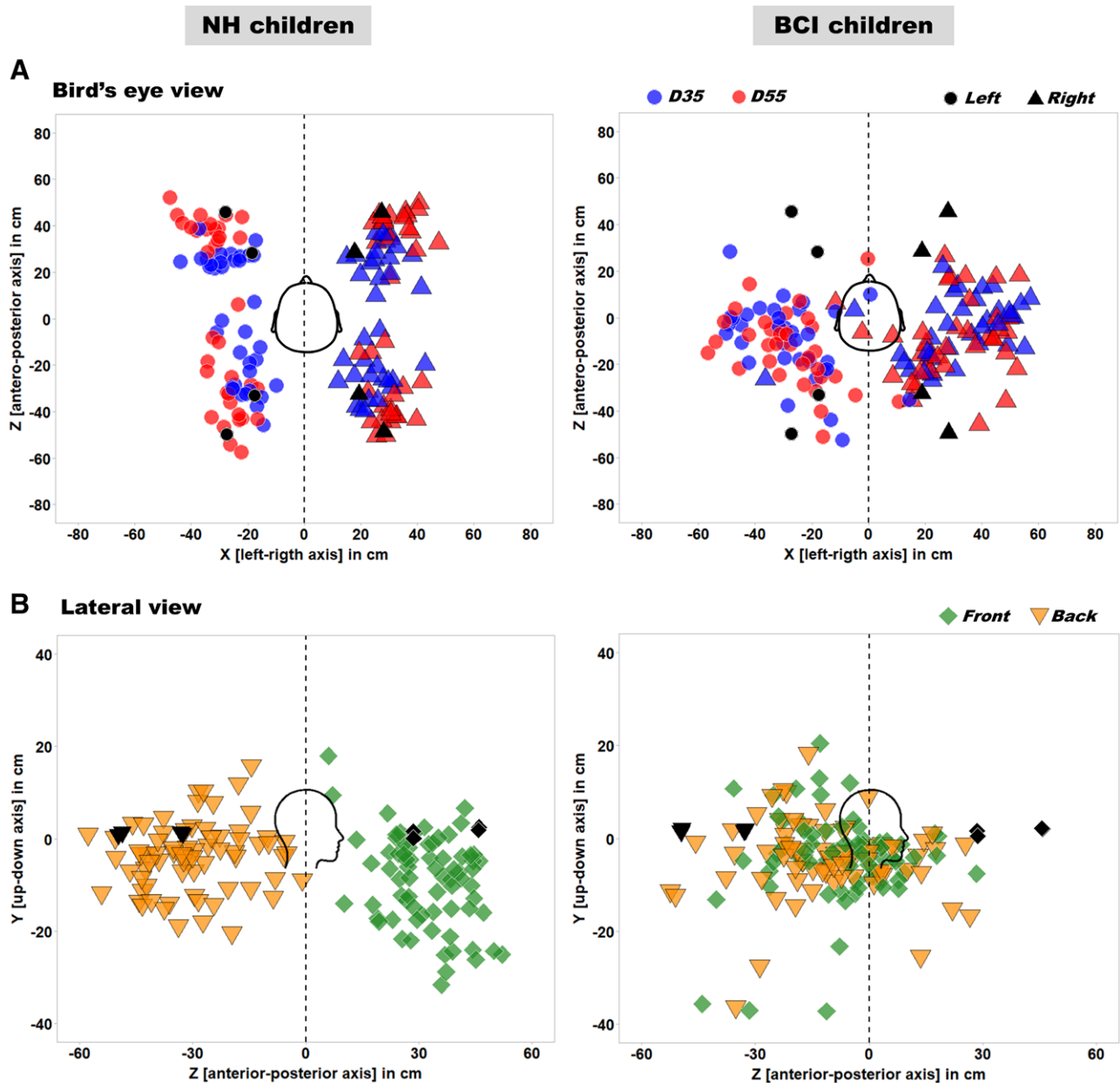


Fig. 2. Three-dimensional sound localization performance of normal-hearing (NH) and bilateral cochlear implant (BCI) children under the head immobile condition. Black symbols represent the sound sources and colored dots correspond to the mean response of each participant per target. A, Bird's eye view showing hand responses as a function of stimulation side (circles for left sounds and triangles for right sounds) and distances (blue and red for 35 and 55 cm sound sources, respectively). B, Lateral view showing hand responses as a function of front stimulation (green diamonds) and back stimulation (yellow triangles).

(compared to 0.5% for NH peers). This figure also shows that their hand pointing was more lateralized, without a clear distinction between the four stimulation quadrants as was the case for the NH children. The separation of the blue (35 cm) and red (55 cm) points for NH but not for BCI children demonstrates that sound discrimination in distance is possible for NH children both in front and behind, whereas it seems to be more difficult for BCI children.

Figure 2B shows front-back discrimination. This figure shows that NH children easily segregated front sources from back sound sources but that this ability was degraded in BCI children, who mainly pointed towards the interaural axis next to their CIs. This led to substantial front-back confusions, 44.6%

(range 31.7–62.5), whereas NH children confused front and back space in only 2.1% of cases (range 0–16.7; Chi-squared test, $p < 0.001$). Front-back localization accuracy in BCI children was close to chance performance.

To characterize sound localization performance as a function of group and sound position we first focused on separate space dimensions. The mean absolute error in azimuth was overall higher for BCI compared to NH participants (BCI: $58.8^\circ \pm 8.4^\circ$; NH: $16.2^\circ \pm 6.5^\circ$; main effect of group: $F(1, 34) = 298.6$, $p < 0.001$). Figure 3 shows sound localization as a function of sound distance in each group. Sounds located at 55 cm from the center of the head were perceived on average at 47.5 ± 13.2 cm by the BCI group and at 50.9 ± 7.1 cm by the NH group. The

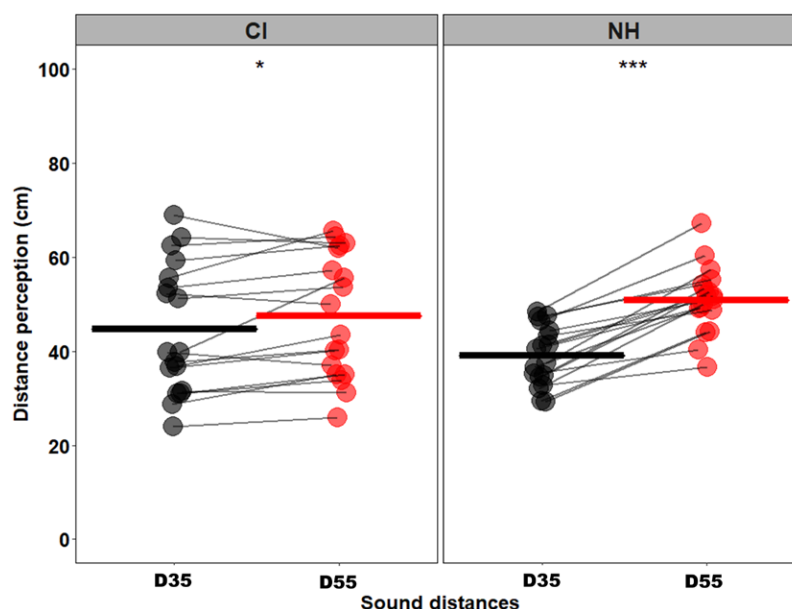


Fig. 3. Sound distance perception in normal-hearing (NH) and bilateral cochlear implant (BCI) children under the head immobile condition. Thick lines represent the mean response distances for each group for D35 (black lines: i.e., sound sources at 35 cm), and D55 (red lines: i.e., sound sources at 55 cm). Thin black lines join black and red dots for each participant. Asterisks indicate significant differences (paired t-test, $*p < 0.05$; $***p < 0.001$).

closest sounds (located at 35 cm) were perceived on average at 44.6 ± 13.9 cm by the BCI group and at 39 ± 6.3 cm by the NH group. Notably, both groups were able to perceive a difference between D35 and D55 stimulations (on paired t-test: BCI: $t(17) = -2.417$, $p = 0.027$; NH: $t(17) = -9.471$, $p < 0.001$), but this was clearer in NH children.

We next examined the 3D error which took into account all three spatial dimensions. Table 3 summarizes the 3D error as a function of group (NH or BCI), listening condition (HI or

HM), front-back position, and stimulation side (left or right). Individual data show substantial variability across participants, mainly in the BCI group (see Tables in Supplemental Digital Contents 4 and 5, <http://links.lww.com/EANDH/A846>). Under the HI condition, the 3D error was higher in BCI (mean \pm SD: 55 ± 13.3 cm) compared to NH participants (24.2 ± 5.6 cm). An ANOVA with group and the front-back position as variables, revealed a significant two-way interaction ($F(1, 34) = 8.04$, $p = 0.008$) caused by larger 3D errors for front than back targets in the BCI group ($p = 0.0002$, Bonferroni corrected) but not in the NH group ($p = 0.868$, Bonferroni corrected). This reflects the large number of front-to-back confusions in the BCI group reported above. A similar analysis with group and stimulation side as variables revealed only the main effect of group ($F(1, 34) = 0.86$, $p = 0.359$) caused by larger errors overall for BCI compared to NH participants.

TABLE 3. Sound localization performance in NH and BCI children

	3D error (cm)	
	BCI	NH
	Mean (SD)	Mean (SD)
HI		
Front		
Left	59.8 (15.2)	23.2 (7.4)
Right	60 (14.5)	24.5 (8.5)
Back		
Left	46.8 (17.2)	24 (7.1)
Right	50.1 (19.3)	22.8 (8.3)
Overall	55 (13.3)	24.2 (5.6)
HM		
Front		
Left	48.2 (17.2)	23.8 (6.2)
Right	46.7 (14.7)	25.6 (7.6)
Back		
Left	44.4 (18.5)	23 (7.1)
Right	42.2 (16.2)	21.3 (6.8)
Overall	46.4 (13.1)	23.7 (5.6)

Performance errors are expressed in 3D (3D error), which represents the absolute and variable errors for the three spatial dimensions in each group. The mean errors were segregated with respect to listening condition, HI and HM, front and backspace, and stimulation side (left and right). These values were then combined to create an overall error for each listening condition.

BCI, bilateral cochlear implant; HI, head immobile; HM, head moving; NH, normal hearing.

Condition HM: Head Movements During Sound Emission

Under the HM condition, children were free and encouraged to move their head during sound emission. We evaluated the impact of head movements on localization performance in the same way as for the HI condition. Figure 4A and C shows mean responses for BCI children as a function of side, distance, and front-back sound sources. Even when head movements were allowed sound discrimination remained difficult, D35 was perceived on average at 45.4 ± 13.9 cm, and D55 at 48.7 ± 14.1 cm, but discrimination of front-back sources improved. This is illustrated in Figure 4D, which shows a significant decrease in front-back confusions, from 44.6% to 25.1%, under HI and HM conditions (McNemar test, $p < 0.001$). The individual data show that performance improved in 12 out of 18 children (67%) and remained stable for the other six. Notably, there was a significant increase in left-right confusions from 8.3% to 15.2% (McNemar test, $p < 0.001$; see Fig. 4B), mainly in six children (33%) for

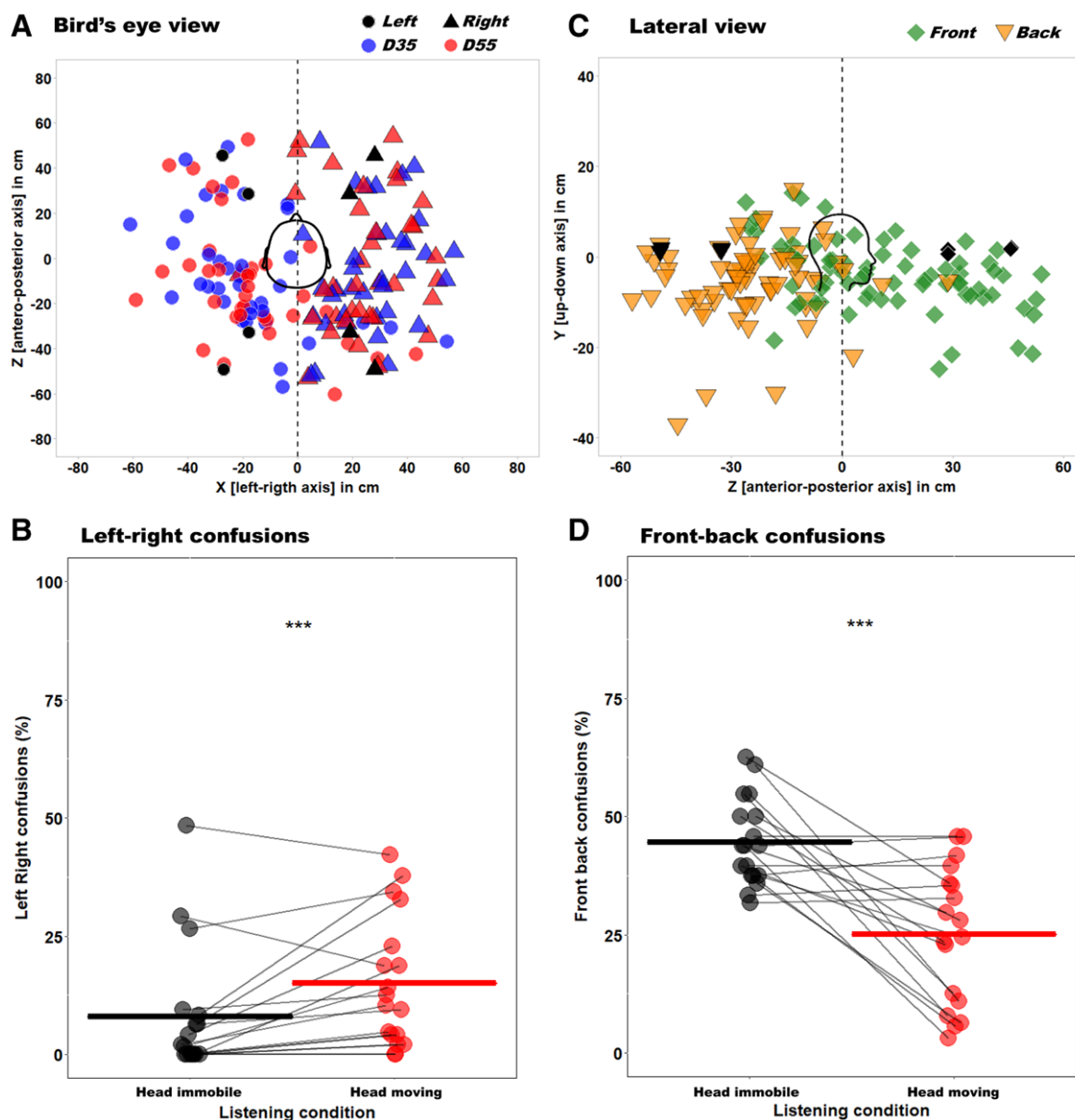


Fig. 4. Three-dimensional sound localization performance of children fitted with bilateral cochlear implant during the head moving condition. A, Bird's eye view showing hand responses as a function of stimulation side (circles for left sounds and triangles for right sounds) and distances (blue and red for 35 and 55 cm sound sources, respectively). Black symbols represent the sound sources and colored dots correspond to the mean response of each participant per target. B, Left-right confusions as a function of listening condition. Thick black lines represent the mean percentage of confusions when head movements were forbidden, and the thick red line when head movements were free during sound emission. Thin black lines join black and red dots for each BCI participant. C, Lateral view showing hand responses for front-back stimulations. D, Front-back confusions as a function of listening condition. Asterisks indicate significant differences (McNemar test, *** $p < 0.001$). BCI, bilateral cochlear implant; NH, normal hearing.

back sound sources (Fig. 4A). Visualization of pointing data for NH participants are available in Supplemental Digital Content 6, <http://links.lww.com/EANDH/A846>; no significant changes occurred in this group.

Figure 5A illustrates 3D error changes for each participant under HI and HM listening conditions. The 3D error significantly decreased in the BCI group by 8.6 cm (paired t-test, $t(17) = 3.41$, $p = 0.003$) compared to the NH group who only decreased by 0.5 cm (paired t-test, $t(17) = 0.84$, $p = 0.412$). A mixed ANOVA on the 3D error, with group, listening condition, and front-back position as variables revealed a significant three-way interaction ($F(1, 34) = 4.89$, $p = 0.034$). The significant improvement caused by active listening concerned specifically the BCI group

when pointing to front targets ($p < 0.001$, Bonferroni corrected) but not when pointing to back targets ($p = 0.15$, Bonferroni corrected). No significant improvement emerged for the NH group, either for front targets ($p = 0.98$, Bonferroni corrected) or back targets ($p = 0.95$, Bonferroni corrected). When participants were free to move their heads during sound delivery, we noticed that head behavior differed across trials and participants. Hence, we assessed if the percentage of trials with at least one head movement during sound emission correlated with a change in localization performance. This change was computed as a Listening Improvement index, considering individual performance under the HI condition (see Methods section for details). We found a strong positive correlation between the Listening Improvement

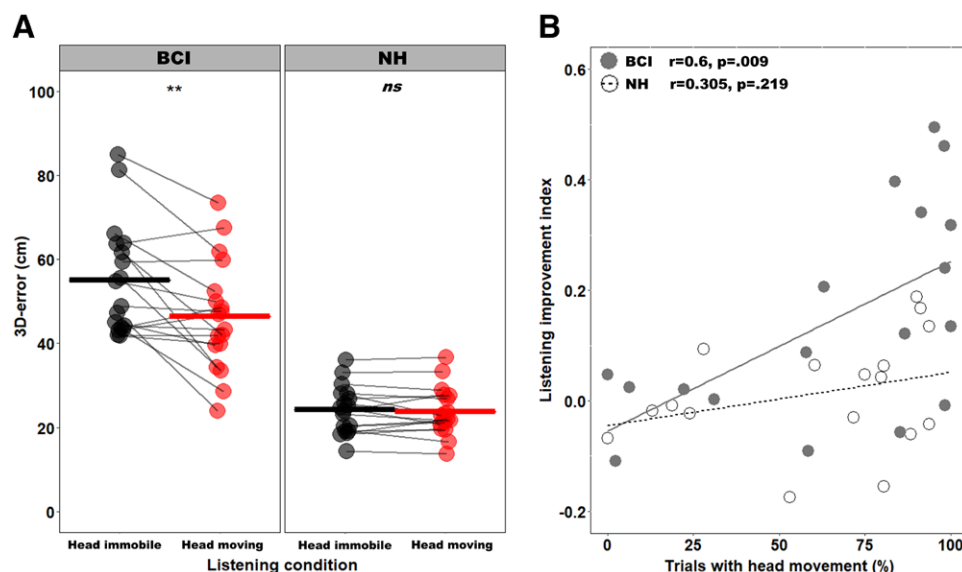


Fig. 5. Effect of head motion on spatial performance. A, Three-dimensional 3D error in both groups (BCI and NH) as a function of listening condition. Thick lines represent the mean 3D error within each group during HI listening (black) and HM listening (red) condition. Thin black lines join black and red dots for each participant. Asterisks indicate significant differences (paired t-test, $**p < 0.01$). B, Listening improvement index as a function of the percentage of trials with at least one head movement during sound emission. BCI, bilateral cochlear implant; NH, normal hearing.

index and the percentage of trials with head movements for the BCI group (Pearson correlation, $r = 0.6, p = 0.009$; see Fig. 5B), whereas no correlation emerged for the NH group (Pearson correlation, $r = 0.305, p = 0.219$). This suggests that exploring with the head had a positive effect on localization performance of BCI children. This effect was not found in the NH group, most likely because performance under the HI condition was already at ceiling for this group.

Clinical Predictors for Sound Localization Performance

We first explored the effect of clinical predictors on sound localization performance in the BCI group in the HI listening condition, for comparison with previous work that also adopted a similar listening condition (Killan et al. 2019). Specifically, we focused on age at test, interimplant interval, and duration of binaural experience (i.e., the time between the second CI and age at test). The 3D error was correlated with interimplant interval (Pearson correlation, $r = 0.721, p < 0.001$; see Fig. 6), but also with age at test (Pearson correlation, $r = 0.693, p = 0.001$). As these two clinical variables were also correlated with one another (Pearson correlation, $r = 0.659, p = 0.003$), we ran a partial correlation to test whether the relation between the 3D error and interimplant delay held up when controlling for the effect of age. The partial correlation remained significant ($p = 0.047$), reinforcing the conclusion that the greater the interimplant delay, the greater the 3D error is. We also ran a partial correlation between the 3D error and age at test, after controlling for interimplant delay. The partial correlation was not significant ($p = 0.096$). There was no correlation between the 3D error and the duration of binaural experience (Pearson correlation, $r = 0.041, p = 0.872$). Noticeably in the NH group, we found a significant negative correlation between age at test and 3D error (Pearson correlation, $r = -0.541, p = 0.02$). The older the NH children, the lower the 3D error is.

Finally, we examined if the results of the SSQ questionnaire correlated with the 3D error. No significant correlation between the mean score of subscale B (specific to spatial hearing) emerged, for children (Pearson correlation, $r = 0.04, p = 0.874$) or parents ($r = -0.12, p = 0.644$). Comparing self-assessment of all items by children to their parents, we found a positive correlation ($r = 0.53, p = 0.024$) with a mean score slightly higher for children (7.2 points; range 5.8–8.6) than parents (6.7 points; range 4.7–8.3).

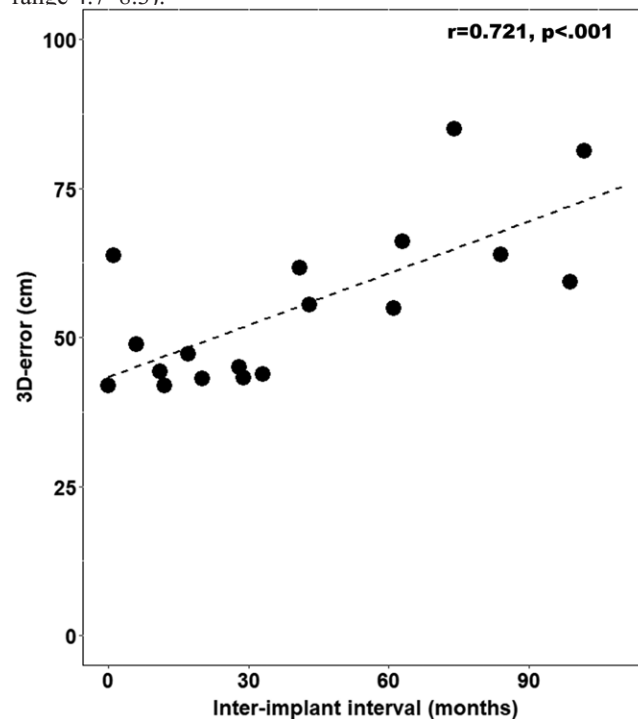


Fig. 6. Three-dimensional error (in centimeters) under the head immobile condition as a function of interimplant interval (in months).

DISCUSSION

The present study examined sound localization abilities of young BCI users (aged 8–17 years old) compared to NH peers in reaching space. This is a portion of space in which many social interactions occur in daily life, and in which we interact with sound sources through avoidance and reaching movements (e.g., Valzolgher et al., 2020a). To this aim we used a portable virtual reality and kinematic tracking system which allowed us to deliver real sounds within reaching distance from the listener, at reproducible head-centered coordinates. This same equipment also allowed us to pursue our additional aim, the investigation of the role of spontaneous head movements in spatial hearing abilities during sound emission.

Spatial Hearing Abilities for BCI Users

In our sound localization experiment, sound sources were presented laterally, in front and back space. Without free head exploration during sound presentation, BCI children performed at chance in front/back discrimination, pointing consistently along the interaural axis. This phenomenon has already been observed in adult CI users (Mueller et al. 2014; Pastore et al. 2018), and it could largely be attributed to the ambiguity introduced by the omnidirectional mode of the CI microphone settings which merges front and back sound sources (Fischer et al. 2020).

Until now, studies on sound localization in CI children only reported absolute azimuthal errors in front space, and these did not exceed 39.4° (Zheng et al. 2015; Choi et al. 2017; Killan et al. 2018). This is substantially lower than the azimuth error we observed here (i.e., mean absolute error of 59°). This difference could reflect the greater uncertainty about sound position that participants may have experienced in our study, since they were informed that sounds could be delivered anywhere around them within reaching distance. In addition, they gave their responses in 3D (i.e., by indicating a point in space with a hand-held pointer) and they did not receive any feedback after their answer. Most importantly, no visual cues were available to support sound localization, unlike previous reports which used a touch screen for response validation and all loudspeaker positions were visible (Grieco-Calub & Litovsky 2010; Zheng et al. 2015; Killan et al. 2018).

We also explored sound perception in depth by favoring accessibility of auditory cues to BCI children. We opted for a lateral arrangement of sounds, as this gives an advantage for distance judgements compared to medial sources (Kopčo & Shinn-Cunningham 2011). Moreover, in the near-field, distance perception mostly relies on low-frequency ILD (Brungart 1999; Seeber et al. 2004), which are partially restored binaural cues in BCI users. Despite these aspects, compared to NH children, BCI children had substantial difficulties in discriminating sound sources spaced 20 cm in depth. They perceived a mean difference of 3 cm between the two sources versus the 11 cm observed for NH children. Recent findings suggest that the AGC currently implemented in new generation CI processors are mostly unsynchronized and degrades ILDs by applying a broadband compression above loudness threshold (Dorman et al. 2014). Depending on the position of the sound source and its loudness, the compression can apply for the CI closest to the sound source, and not for the contralateral one (because the sound level becomes below the compression threshold with the

head shadow effect). Moreover, the AGC can increase the low-frequency components of the CI close to the sound source, thus leading to inverted ILDs (Dorman et al. 2014; Archer-Boyd & Carlyon 2019). These situations could lead to instances of maximal distortions of ILDs. In the present study, it is possible that BCI children were able to extract ILD cues to perceive small variations between close distances but these cues were occasionally too distorted to provide veridical information for each distance. Interestingly, we also noticed substantial variability in distance judgments in both groups, suggesting a differential maturation between children that continues at least until adolescence.

In sum, these findings highlight limitations of sound localization abilities of BCI children in azimuth and distance. However, it is likely that children are less negatively affected than expected, possibly because in their daily life they rely on multisensory perception. In recent reviews, several authors have noted that vision plays a key role in calibrating spatial hearing abilities (Tabry et al. 2013; Valzoghner et al. 2020b), especially during the first 10 years of development (King 2009). This is particularly important for azimuthal and distance perception of a stimulus (Zahorik 2001; Calcagno et al. 2012), and to a lesser extent for vertical judgments (Shelton & Searle 1980). To have a perception of the environment that is as accurate and consistent as possible, individuals with a hearing impairment tend to use vision to compensate for spatial hearing difficulties (King 2009). The children's reports support this assumption, since none of the sound localization difficulties demonstrated here emerged in the self-reported experiences of BCI users or their care-givers. Indeed, neither BCI children nor their parents reported major spatial hearing impairments in daily life on the SSQ questionnaire (Galvin & Noble 2013).

An Important Role of Head Movements for BCI Children

The pioneering works by Wallach in NH adults has shown that head movements, a natural orienting behavior (Kim et al. 2013), are helpful to disambiguate front and back sound sources, especially if they are close to the midline (Wallach 1940). Head motion creates important changes in binaural cues (ILD and ITD) by increasing information about level and time differences perceived by each ear. Until now, it was unclear if BCI children could extract relevant auditory information from head movements, or instead they might be disturbed by them. A study conducted by Mueller et al. (2014) in seven BCI adult users highlighted that head movements did not give them any benefits to sound localization accuracy when short speech sentences (less than 1 second) were delivered in a background noise of 60 dB SPL. However, a significant decrease of front-back confusions was observed for longer sentences (2 and 4.5 seconds) but without improvement of the absolute angular accuracy.

In the present study, BCI children significantly decreased their overall 3D error (from 55 to 46 cm) and their front-back confusions (from 44.6% to 25.1%) when they were allowed to perform spontaneous head movements during a 3-second sound emission. This suggests that despite their limited access to auditory cues, BCI children are able to extract and interpret binaural dynamic differences induced by head movements. These results are in line with a recent study in which a similar improvement of front-back confusions (from 41.9% to 6.7%) was demonstrated

in BCI adults (Pastore et al. 2018). Head behavior in BCI children was unrelated to their age at test. Instead, the higher the percentage of trials on which BCI children spontaneously moved their head during sound delivery, the greater their improvement in overall performance. For NH children, no benefit of head motion emerged, probably because they were already performing at ceiling with their head still in our experimental conditions. In further studies, it would be interesting to repeat the test in a more complex auditory environment (e.g., with competing background noise) to uncover the extent of head motion benefits in this pediatric population.

Individual Variability

The study of sound localization abilities in children is relatively recent, with less than two decades of research conducted in NH children of the age range we tested here (Litovsky et al. 2004). For this reason, several questions remain open, including the degree of maturation of the brain circuits involved in this specific task in NH children. In the present study, we found a negative correlation between the 3D error and chronological age at test in NH children. This suggests that the multiple sensory and cognitive components contributing to spatial hearing—from auditory processing to mapping sounds in spatial coordinates—undergo maturation processes that continue until adolescence, and may thus be more complex than expected based on the results of previous studies (Litovsky 2011; Kühnle et al. 2013; Freigang et al. 2015; Litovsky 2015).

For BCI children, clinical factors are also likely to contribute to explaining performance and interindividual variability. We found a correlation between interimplant interval and 3D error under the HI condition, which remained significant after controlling for chronological age at test. Since 2012, bilateral cochlear implantation is standard practice in France (Simon et al. 2019), thus only the youngest children in our cohort benefited from a sequential cochlear implantation with a short delay. This observation is in keeping with a recent study (Killan et al. 2019) which showed that a longer interimplant delay was a poor prognostic for spatial hearing abilities, mainly due to asymmetric brain processing after a 24-month interval (Gordon et al. 2008, 2013; Kral et al. 2019). This could explain why we expected (based on, e.g., Zheng et al. 2015; Killan et al. 2019) but did not observe a significant improvement in spatial hearing abilities with increased binaural experience. It is possible that this correlation is more sensitive in the first 2 years after cochlear implantation, when localization performance improves rapidly and parallels experience-induced plasticity (Kral & Tillein 2006; Gordon et al. 2011). In sum, variability of BCI performance is more complex than expected. Future studies might leverage longitudinal approaches to gain deeper insights into the roles of these and other individual differences.

Perspectives

Our new approach for measuring spatial hearing in the near-field has been validated in a virtual reality platform easy to access in clinical practice (HTC VIVE; Verdelet et al. 2019; Valzolgher et al. 2020a,b). These first results give new information about children's performance, both when they have typical hearing, and when they are deafness but fitted with BCI. However, to approximate even further the children's everyday environments, it would be useful to add complexity to our

sound localization task, with background noise or changes in sound elevation. This could provide further insights into the understanding of how BCI children extract dynamic monaural cues. In addition, it could help to clarify our preliminary results on the progressive and non-linear maturation of spatial hearing in each space dimension for NH children. We hypothesize that sound discrimination in distance could mature later than azimuthal judgement. Owing to the different auditory cues at play to render distance perception in the far compared to the near-field, it will be important to extend research to the far-field to evaluate whether and to what extent spatial hearing maturation in distance differs from the near-field. Finally, spontaneous head movements significantly improved sound localization performance in BCI children. While it is still unclear to what extent BCI children use this valuable strategy in their daily environment, it seems essential to pay more attention to this orienting behavior in future studies of clinical assessment or spatial hearing rehabilitation. For example, in line with speech therapy rehabilitation, it could be helpful to train the most severely impaired BCI users to localize various sounds in a controlled environment.

CONCLUSION

BCI children and adolescents display important spatial localization deficits compared to their NH peers. These deficits hamper sound localization in all spatial dimensions, but go undetected on self-report questionnaires. All BCI children had some localization skills (i.e., left/right discrimination) but in the context of other spatial hearing difficulties related to front-back confusions and distance perception, which likely resulted from the reduction in auditory cues resulting from the implant settings (e.g., omnidirectional mode) and sound adjustments. Notably, BCI children improved under conditions of free head exploration during sound emission. This suggests that head movements could represent a rehabilitation entry strategy to help BCI users when faced with complex auditory scenes in daily life.

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All the authors significantly contributed to this work. A.C., V.G., A.F., and F.P. designed the experiment, A.C. and V.G. performed experiments, A.C., V.G., and F.P. analyzed the data and wrote the paper. E.T. provided cochlear implant participants, while J.G. oversaw participants' inclusions and help in the ethical procedures required for the study. G.V. and R.S. implemented the experiments. All authors discussed the results, reviewed the manuscript and approved the final version of the revised manuscript.

V.G., R.S., A.F., and F.P. filed a patenting procedure for the system reported in this study, patent pending. The other authors have no conflicts of interest to disclose.

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