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## Sound localization in patients with bilateral vestibulopathy

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# 1 Sound localization in patients with bilateral vestibulopathy

## 2 ABSTRACT

### 3 Purpose:

4 The goal of this study was to evaluate if bilaterally (partially) absent vestibular function during  
5 static sound localization testing, would have a negative impact on sound localization skills.  
6 Therefore, this study compared horizontal static sound localization skills of normal-hearing  
7 patients with bilateral vestibulopathy (BV) and healthy controls.

### 9 Methods:

10 Thirteen normal-hearing patients with BV and thirteen age-matched healthy controls were  
11 included. Sound localization skills were tested using seven loudspeakers in a frontal semicircle,  
12 ranging from  $-90^\circ$  to  $+90^\circ$ . Sound location accuracy was analyzed using the root-mean-square  
13 error (RMSE) and the mean absolute error (MAE). To evaluate the severity of the BV  
14 symptoms, the following questionnaires were used: Dizziness Handicap Inventory (DHI),  
15 Oscillopsia severity questionnaire (OSQ), 12-item Spatial, Speech, and Qualities Questionnaire  
16 (SSQ12), and Health Utilities Index Mark 3 (HUI3).

### 18 Results:

19 The RMSE and MAE were significantly larger (worse) in the BV group than in the healthy  
20 control group, with respective median RMSE of  $4.6^\circ$  and  $0^\circ$ , and a median MAE of  $0.7^\circ$  and  
21  $0^\circ$ . The subjective reporting of speech perception, spatial hearing, and quality of life only  
22 demonstrated a moderate correlation between DHI (positive correlation) and HUI total score  
23 (negative correlation), and localization scores.

### 25 Conclusion:

26 Static sound localization skills of patients with BV were only mildly worse compared to healthy  
27 controls. However, this difference was very small and therefore most likely due to impaired  
28 cognitive function. The vestibular system does not seem to have a modulating role in sound  
29 localization during static conditions, and its impact is negligible in contrast to the impact of  
30 hearing impairment. Furthermore, the subjective reporting of speech perception, spatial  
31 hearing, and quality of life was not strongly correlated with localization scores.

### 33 Keywords

34 Bilateral Vestibulopathy, Sound Localization, Auditory Perception, Vestibular Function  
35 Tests, Hearing Loss

## 36 INTRODUCTION

37 The auditory (cochlea) and vestibular (endolymphatic duct, semicircular canals, utricle,  
38 saccule) components of the inner ear share a common embryologic origin, which is the otocyst  
39 or otic vesicle [1]. Due to the location in the inner ear, it was originally assumed that the  
40 semicircular canals were involved in sound localization. In 1824, Pierre Flourens made the first  
41 step in unraveling their true function, by surgically sectioning semicircular canals in pigeons  
42 [2]. After the procedure, all pigeons showed abnormal head movements and the inability to fly,  
43 but their hearing appeared to be spared. This discovery opened up further studies of the  
44 semicircular canals as functionally distinct from the cochlea. Nowadays, it is clear that the  
45 vestibular organs provide our central nervous system with information regarding the motion of  
46 the head as well as its orientation in the Earth's gravitational field, which is required for  
47 maintaining our balance and gaze stabilization. Recent findings have expanded the influence of  
48 the vestibular system to other functions such as spatial cognition, circadian rhythm, and several  
49 autonomic functions [3-5].

50 Bilateral partial or complete loss of vestibular function is a rare disease, known as bilateral  
51 vestibulopathy (BV) [6]. The bilateral impairment of vestibulo-ocular (VOR) and vestibulo-  
52 spinal reflexes in patients with BV mainly result in gait unsteadiness, postural imbalance, and  
53 blurred vision during head movements (i.e. oscillopsia). Due to the close anatomic relationship  
54 between inner ear vestibular and hearing structures, a large proportion of patients with BV are  
55 affected by sensorineural hearing loss [4]. Strong evidence exists that patients with BV suffer  
56 from impaired spatial cognition [3-5].

57 Unlike the retina, the cochlea is organized tonotopically, with position in the cochlea  
58 representing frequency instead of spatial location. The localization of sounds in the horizontal  
59 plane in humans, who have fixed external ears in contrast to most other mammals, is mainly  
60 based on interaural differences in time of arrival (ITD) and sound level (ILD), both of which  
61 require the use of binaural hearing. ITD and ILD cues are respectively used for localizing low-  
62 frequency and high-frequency sounds [7]. Secondary, monaural spectral cues (direction-  
63 dependent spectral filtering by the head and pinnae) are also used, allowing patients with  
64 unilateral deafness to perform horizontal sound localization to a lesser extent [8].

65 Although vision is the most important source of information, spatial representation is not  
66 limited by this. Auditory cues also play an important role as they cover a much wider field  
67 compared to the frontal field of visual cues. Unexpected sounds provoke reflexive fast head  
68 movements toward the sound source, allowing the stimulus to be visually encoded at a high  
69 resolution. A good sound localization ability is crucial for personal safety and facilitates speech  
70 understanding in noisy circumstances. Among blind humans, auditory space perception is all  
71 the more important and after several months of training, many of them are even capable of  
72 using echolocation through tongue clicks, similar to bats [9].

73 Due to their fixed external ears, humans are at a disadvantage compared to some animal species,  
74 as they are unable to use the vestibulo-auricular reflex, which consists of rapid compensatory  
75 pinnae movements in the opposite direction of head movements to optimize dynamic auditory  
76 space perception [10]. Nevertheless, humans perceive the auditory world to be stable despite  
77 constant body and head movements, due to the integration of vestibular, neck proprioceptive,  
78 and efference copy signals (i.e. the prediction of sensory consequences of one's own actions)  
79 regarding the motion of the head as well as its orientation in the Earth's gravitational field [11].

80 This process is known as multisensory integration and depends on different forms of sensory  
81 stimuli presented simultaneously, that are integrated depending on the reliability and  
82 importance of each stimulus [12]. The interaction between visual and auditory cues is well  
83 investigated, in contrast to the interaction between auditory and vestibular cues which is often  
84 neglected.

85 Vestibular cues from both the otoliths and semicircular canals may influence the perceived  
86 location of a fixed sound source. During rotational acceleration of the body, the perception of  
87 the auditory target will shift to the opposite direction of the self-rotation and will come back to  
88 the midline when a constant velocity is reached [13]. The reverse is true during deceleration.  
89 This phenomenon is called the “audiogyral illusion”. In addition, rapid head turns can cause a  
90 compression of the auditory spatial perception, in analogy with visual saccades causing visual-  
91 spatial compression [14]. Such compression of the auditory scene was also observed during  
92 linear acceleration of the body, with a distortion of the sound image in the direction of  
93 movement during forward self-motion [15]. This phenomenon is called “audiographic illusion”.  
94 Other studies have used a slow rotational room, demonstrating a shift of the sound image in the  
95 direction of the resultant linear gravito-inertial force [13, 16]. Furthermore, auditory perception  
96 is also influenced by changes in body position relative to gravity (body tilt) [17]. By creating  
97 different dynamic listening conditions, the above studies have demonstrated that localization  
98 accuracy is affected by vestibular stimulation. The question remains whether the vestibular  
99 system plays a role during static listening conditions since this has never been properly  
100 investigated. During these static conditions, vestibular cues are absent, except for the constant  
101 gravity vector which is sensed by the saccule. However, the vestibular system may have a  
102 modulating role in sound localization during static conditions. Therefore, patients with BV are  
103 a very interesting research group. Visual-spatial cognition is compromised in patients with BV,  
104 and the same may be true for auditory space perception.  
105 To conclude this introduction, we hypothesized that the presence of a bilateral normal vestibular  
106 function during localization testing is also required to optimally localize a static sound source  
107 during static listening conditions. The goal of this study was to evaluate if bilaterally (partially)  
108 absent vestibular function during the localization test itself, will affect static sound localization  
109 skills. Therefore, this study compared horizontal sound localization skills of normal-hearing  
110 patients with BV and healthy controls, using a fixed sound source and during static listening  
111 conditions (primary outcome). Furthermore, this study investigated whether static sound  
112 localization skills of patients with BV were correlated with the subjective reporting of speech  
113 perception, spatial hearing, and quality of life (secondary outcome).

## 114 MATERIAL AND METHODS

### 115 Study design

116 A cross-sectional matched sample study was conducted at our ENT department, from  
117 September 2017 to March 2020.

118

### 119 Inclusion and exclusion criteria

120 All patients with BV were diagnosed at our department. All patients underwent vestibular,  
121 otological, neurological, MRI brain, and genetic examination. Patients with BV with clinical  
122 signs indicating cognitive or cerebellar impairment and other neurological diseases were  
123 excluded. The inclusion criteria were as follows:

- 124 • bilaterally reduced vestibular response in accordance with the BV Bárány Society  
125 guidelines [6], documented by:
  - 126 ○ caloric response: sum of bithermal maximum peak slow phase velocity on each  
127 side  $< 6^\circ/\text{s}$ , and/or
  - 128 ○ rotatory chair test: horizontal angular vestibulo-ocular reflex gain  $< 0.1$  upon  
129 sinusoidal stimulation, and/or
  - 130 ○ video-head impulse test (vHIT): bilaterally pathological horizontal angular  
131 vestibulo-ocular reflex gain  $< 0.6$ .
- 132 • unaided bilateral pure tone average (PTA) of 0.5, 1 and 2kHz  $\leq 25$  dB
- 133 • at least 18 years old

134 Furthermore, age-matched healthy subjects with normal hearing were included to establish  
135 normative data for the localization set-up. The following inclusion criteria were used: bilateral  
136 PTA<sub>0.5, 1 and 2kHz</sub>  $\leq 25$  dB, and no history of otovestibular disorders which was questioned  
137 verbally. Older age is associated with worse sound localization skills, whereas gender has no  
138 impact [18]. Therefore, only age matching was applied at a range of  $\pm 5$  years.

## 139 Measurement

### 140 Sound localization

141 CCITT (Comité Consultatif International Téléphonique et Télégraphique) noise bursts of 1-  
142 second duration were presented and were roved by  $\pm 5$  dB (sound levels between 65 and 75 dB  
143 SPL). Sounds were digitally generated in MATLAB (The Mathworks 7.4). The sounds were  
144 delivered via broadband Fostex 6301 loudspeakers.

145 The protocol used in this experiment was reported previously by Mertens et al. [19]. Sound  
146 localization skills were investigated in an unaided condition in a sound-treated room. Seven  
147 loudspeakers located in a frontal semicircle in a horizontal plane at subject's head level were  
148 used (Figure 1). Each of the seven loudspeakers was assigned a number, which was visible to  
149 the participants (Figure 1). Speakers were 0.8 m from the listener's head and stimulus  
150 coordinates ranged from  $-90^\circ$  to  $+90^\circ$  in azimuth at intervals of  $30^\circ$ . Azimuth for loudspeaker  
151  $k$  was represented by  $\varphi_k$ . In each trial, six stimuli were offered from each speaker in a random  
152 sequence, which makes a total of 42 stimuli. Sound localization referred to sound source  
153 identification.

154 This test was performed in both the patient group and in the healthy controls. No practice  
155 sessions were allowed, and the first attempt was recorded. To avoid bias from the head shadow  
156 effect, participants were not allowed to move their heads during stimulus presentations; this  
157 was enforced by the examiner. Subjects did not receive feedback about their performance  
158 during testing. For each of the 42 stimulus presentations, the participant had to indicate the  
159 perceived location of the sound source by saying the corresponding number of the loudspeaker.  
160 The judged azimuth in response to a loudspeaker  $k$  was recorded ( $\psi_k$ ) and plotted on a confusion  
161 matrix. The X-axis represents the target loudspeaker  $\varphi_k$  and de Y-axis represents judged  
162 azimuth  $\psi_k$ .

163 Overall sound localization accuracy was analyzed using the root-mean-square error (RMSE)  
164 (equitation 1). Since RMSE distorts the localization accuracy by giving more weight to larger  
165 errors, the mean absolute error (MAE) was used as well (equitation 2). RMSE is calculated as  
166 the root-mean-square of the magnitudes of the differences between the azimuth angle of the  
167 sound presenting speaker ( $\varphi_k$ ) and the azimuth angle of the judged speaker ( $\psi_k$ ) across all 42  
168 stimulus presentations. MAE is the absolute error in degrees, divided by the total amount of  
169 stimulus presentations (i.e. 42 stimuli).

$$170 \quad (1) \text{ RMSE} = \sqrt{\frac{1}{NM} \sum_{k=1}^N (\psi_k - \varphi_k)^2}$$

$$171 \quad (2) \text{ MAE} = \frac{1}{NM} \sum_{k=1}^N |\psi_k - \varphi_k|$$

172  $M$  is the number of stimuli per loudspeaker (= 42);  $N$  is the number of speakers (= 7).

173

### 174 Vestibular testing

175 Only the patients underwent vestibular testing to confirm the diagnosis of BV. All vestibular  
176 testing was performed by experienced examiners. Bilateral bithermal caloric irrigations were  
177 performed with water at  $30^\circ\text{C}$  and  $44^\circ\text{C}$  for 30 seconds. The examination was performed in a  
178 dark room with the patient in supine position with a head-incline of  $30^\circ$ . Nystagmus was  
179 recorded using electronystagmography. The parameter used for both ears was the maximum  
180 slow-phase velocity at the time of maximum response. Rotatory chair tests were performed in  
181 a dark room using sinusoidal rotation at 0.05 Hz with a peak velocity of  $60^\circ/\text{s}$ , using  
182 electronystagmography. The determined parameter was VOR gain. More detailed methodology  
183 and normative data have previously been described [20]. The vHIT was performed using the

184 commercially available ICE impulse vHIT goggles (Natus ®, formerly known as Otometrics).  
185 These vHIT goggles have three incorporated gyroscopes to determine the angular head velocity  
186 and an infrared camera that records the velocity of the right eye. VOR gain was defined as the  
187 ratio of the area under the eye velocity curve to the head velocity curve from the impulse onset  
188 until the head velocity returned to zero again [21]. The horizontal, anterior, and posterior  
189 semicircular canals were examined, however, only VOR gain of the horizontal canals was  
190 included in this study. Horizontal impulses were performed with head velocities >200°/s. Mean  
191 VOR gain of ten impulses was used as final outcome parameter.  
192 In addition, saccular function was evaluated by cVEMP testing. Details on the procedure have  
193 been published previously [22]. In short, a patient's saccular function was quantified by the  
194 response of the ipsilateral sternocleidomastoid muscle to air-conducted 500 Hz tone bursts  
195 presented monaurally through insert phones. The test was performed with an auditory evoked  
196 potential system equipped with electromyographic software (Neuro-Audio, Difra, Belgium),  
197 with self-adhesive electrodes (Blue Sensor, Ambu, Denmark). The generated wave response  
198 included a typically biphasic shape, with two distinctive peaks (p13, n23). While decreasing  
199 the sound intensity of the tone bursts, the simulation threshold was evaluated. When such a  
200 p13n23 wave response was seen at 95 dB HL or lower, the cVEMP response was considered  
201 present, whereas the cVEMP response was considered absent when no p13n23 wave response  
202 was seen above 95 dB HL. Due to a technical error with the cVEMP device, no results could  
203 be obtained in four subjects with BV, 1 to 4 (Table 2).

204

#### 205 Pure-tone Audiometry

206 Unaided pure-tone air-conduction thresholds (0.125 – 8 kHz) were determined using an  
207 Interacoustics AC40 Clinical audiometer in a sound-treated room. PTA<sub>0.5, 1 and 2kHz</sub> (in dB HL)  
208 of both ears were calculated. Both the patients with BV and the healthy controls underwent  
209 hearing testing.

210

#### 211 **Patient-reported outcome measures**

212 To evaluate the impact of BV on health-related quality of life, all patients with BV were sent  
213 the following questionnaires before the study visits. At the start of each test visit, all  
214 questionnaires were reviewed with the examiner and possible ambiguities were clarified.

215

#### 216 Dizziness Handicap Inventory (DHI)

217 The DHI is a validated questionnaire to evaluate the effect of dizziness and loss of balance on  
218 quality of life [23]. This questionnaire consists of 25 items distributed over three subscales:  
219 emotional, functional, and physical aspects of daily life. For each item, patients had to choose  
220 between three answers: no (zero points), sometimes (two points), and yes (four points). The  
221 total score ranges from zero (no difficulty) to one hundred (highest difficulty), with higher DHI  
222 scores indicating a greater self-perceived handicap. Scores ranging from 16 to 24 points are  
223 considered a mild handicap, 36 to 52 points a moderate handicap, and > 54 points a severe  
224 handicap.

225

#### 226 Oscillopsia severity questionnaire (OSQ)

227 This questionnaire evaluates the frequency of oscillopsia during everyday situations [24].  
228 Patients had to rate nine situations, on a scale of zero (never oscillopsia in this situation) to five  
229 (always oscillopsia in this situation), with higher oscillopsia scores indicating a greater impact  
230 of oscillopsia on quality of life. In healthy US participants, scores range from 8.8 to 15.3 for  
231 ages 19 – 75 [25].

232



233 Short Version of the Spatial, Speech, and Qualities Questionnaire (SSQ12)

234 This twelve-item version of the SSQ was utilized to evaluate the self-perceived disability in  
235 daily life activities [26]. Patients had to rate twelve items, on a scale of zero (absolutely not) to  
236 ten (absolutely). The higher the SSQ scores, the greater the ability. The 6<sup>th</sup> (SSQ12/6), 7<sup>th</sup>  
237 (SSQ12/7), and 8<sup>th</sup> (SSQ12/8) questions of this questionnaire are specifically related to spatial  
238 hearing and will therefore be evaluated separately, in addition to the total SSQ12 score (Table  
239 1). Normal values of the normal hearing US population include 8.8 for ages 18 – 22 and 7.7 for  
240 ages 64 – 80 [27].

241

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SSQ12/6	You are outside. A dog barks loudly. Can you tell immediately where it is, without having to look?
SSQ12/7	Can you tell how far away a bus or a truck is, from the sound?
SSQ12/8	Can you tell from the sound whether a bus or truck is coming towards you or going away?

---

242 **Table 1.** The full 6th, 7th, and 8th questions of the SSQ12 questionnaire [26].

243

244 Health Utilities Index Mark 3 (HUI3)

245 This is a validated questionnaire to evaluate the health-related quality of life [28]. Eight specific  
246 domains are assessed: vision, hearing, speech, ambulation, agility, cognition, and pain, each on  
247 a scale with five or six response options. A total score ranging from one (perfect health) to zero  
248 (death) was obtained, with lower scores for poorer self-reported quality of life. The HUI3 is  
249 often used for economic cost-utility analysis. The HUI3-scores of the general US population  
250 are highly dependent on age, with reported mean scores of 0.854 for ages 18 – 44, 0.779 for  
251 ages 45 – 64, and 0.694 for ages over 65 [29].

252

253 **Statistical analysis**

254 Sample size estimations were calculated using G-Power software version 3.1.9.6 [30], using an  
255 alpha value of 0.05 and a beta value of 0.20 (power of 80%). Regarding RMSE, the primary  
256 outcome parameter, the one-tailed Mann-Whitney U test was selected. Based on the first results,  
257 the following input parameters were used: standard deviation (SD) healthy controls = 2, SD  
258 patients with BV = 6, mean effect healthy controls = 1, mean effect patients with BV = 6. This  
259 calculation yielded 24 individuals divided between both groups. Regarding the secondary  
260 outcome, the correlation bivariate normal model, two-tailed, was selected. Using a Spearman's  
261 rho correlation coefficient of 0.7 (strong positive correlation), a total sample size of at least 13  
262 was required. Smaller correlation coefficients required a sample size larger than 13.

263 Data were collected in OpenClinica LLC (Waltham, MA, USA), an online database for  
264 electronic data registration and data management developed for clinical research, and SPSS  
265 Statistics Version 26.0 (IBM Corp. Armonk, NY) was used for the statistical analyses. Data  
266 concerning demographics, hearing status, and localization accuracy were summarized for both  
267 the patients with BV as the healthy controls, using descriptive statistics. Given the small sample  
268 size and non-normal distribution, quantitative data were presented as median and range  
269 (minimum and maximum). For the same reason, a non-parametric test (Mann-Whitney U test)  
270 was used to compare both groups for statistically significant differences (primary outcome).  
271 Within the BV group, localization accuracy was correlated with demographics (age, gender),  
272 hearing data (mean PTA<sub>0.5, 1 and 2kHz</sub> left and right, difference PTA<sub>0.5, 1 and 2kHz</sub> left and right),  
273 vestibular tests (caloric test, rotatory chair, vHIT, cVEMP) and questionnaires (SSQ12 and

274 subquestions 6-8, HUI, DHI, OSQ), using Spearman's rho correlation coefficient ( $\rho$ ) (secondary  
275 outcome). P-values below 0.05 were considered statistically significant.

## 276 RESULTS

### 277 Participants

278 Considering the in- and exclusion criteria, thirteen normal hearing patients with BV were  
279 included. A summary of the demographics, hearing results, presumed cause of BV, and  
280 vestibular test data of the included patients with BV can be found in Table 2.

281 Thirteen age-matched healthy subjects with normal hearing were included to establish  
282 normative data for the localization set-up. Age matching was applied at a range of  $\pm 5$  years.  
283 An overview of the healthy subjects' demographics and hearing data is presented in Online  
284 Resource 1.

285 The age and hearing status were nearly the same in both patients with BV and healthy controls,  
286 with respectively a mean age of 57.2 and 57.9 years and a mean  $PTA_{0.5, 1 \text{ and } 2\text{kHz}}$  of 11.3 and  
287 14.5 dB HL. Gender was not equally distributed, with a male:female ratio of 10:3 among the  
288 patients with BV and 5:8 among healthy controls.

289 As illustrated in Table 2 and Online Resource 1, nearly all patients and healthy controls had  
290 relatively symmetric hearing at all frequencies. The mean interaural  $PTA_{0.5, 1 \text{ and } 2\text{kHz}}$  differences  
291 in patients with BV and healthy subjects were respectively 2.85 dB and 3.23 dB.  
292

### 293 Localization

294 Five patients (38%) with BV made no errors, compared to twelve (92%) of the healthy controls.  
295 The RMSE and MAE were larger (i.e. worse) in the BV group than in the healthy controls ( $p$ -  
296 value = 0.014) (Figure 2). The median RMSE of patients with BV and healthy controls were  
297 respectively  $4.6^\circ$  (range 0 -  $18.5^\circ$ ) and  $0^\circ$  (range 0 -  $6.5^\circ$ ). The median MAE of patients with  
298 BV and healthy controls were respectively  $0.7^\circ$  (range 0 -  $5.0^\circ$ ) and  $0^\circ$  (range 0 -  $1.4^\circ$ ). The  
299 MAE and RMSE scores were not correlated with age, mean  $PTA_{0.5, 1 \text{ and } 2\text{kHz}}$  of both ears,  $PTA_{0.5,$   
300  $1 \text{ and } 2\text{kHz}}$  difference between both ears, or gender. Furthermore, MAE and RMSE scores were  
301 not correlated with vestibular tests including mean vHIT gain of both ears, presence of a  
302 cVEMP response (unilateral absent response = 0.5, bilateral absent response = 0, or bilateral  
303 present response = 1), rotatory chair test gain or mean maximum slow-phase velocity at the  
304 time of maximum response of both ears. An overview of the individual confusion matrixes and  
305 localization scores of the patients with BV is shown in Figure 3.

Subject	Age at test moment (years)	Gender (F = female, M = male)	Presumed cause of BV	PTA <sub>0.5, 1</sub> and 2kHz right ear (dB HL)	PTA <sub>0.5, 1</sub> and 2kHz left ear (dB HL)	vHIT right (gain)	vHIT left (gain)	Caloric irrigation right: sum of bithermal max SPV (°/s)	Caloric irrigation left: sum of bithermal max SPV (°/s)	Rotatory chair test (gain)	cVEMP right (present or absent)	cVEMP left (present or absent)
1	55	M	Idiopathic	13	7	0.31	0.78	3	0	0.02	#	#
2	74	F	Idiopathic	25	22	1.01	0.74	3	4	0.1	#	#
3	65	M	Idiopathic	13	15	0.56	0.45	5	4	0.1	#	#
4	57	M	Idiopathic	7	13	0.44	0.45	0	0	0.09	#	#
5	60	M	Bilateral vestibular neuritis	7	10	0.2	0.25	0	0	0.11	present	present
6	29	M	Idiopathic	5	0	#	#	0	0	0.22	present	present
7	39	F	Idiopathic	3	0	0.82	0.88	0	0	0.04	absent	absent
8	72	M	Idiopathic	22	22	0.4	0.27	3	0	0.05	absent	absent
9	56	M	Idiopathic	10	13	0.09	0.41	0	0	0.02	absent	absent
10	49	M	Idiopathic	2	2	0.42	0.92	7	0	0.07	present	absent
11	72	M	Idiopathic	18	17	#	#	2	4	#	present	absent
12	68	F	Head trauma	25	20	0.73	0.63	0	3	#	absent	absent
13	47	M	Idiopathic	2	2	0.82	0.79	1	3	#	present	absent

306  
307  
308

**Table 2.** Overview of the demographics, hearing results, presumed cause of BV, and vestibular test data of the included patients with BV. #, missing data.

309 **Patient-reported outcome measures**

310 Except for 2 patients with BV who did not complete the OSQ, there were no missing data. The  
311 mean scores of the DHI, OSQ and HUI3 were respectively 28.2 (SD = 7.2), 20.9 (SD = 2.5)  
312 and 0.82 (SD = 0.06). The mean scores of SSQ12, SSQ12/6, SSQ12/7 and SSQ12/8 were  
313 respectively 7.5 (SD = 0.7), 8.3 (SD = 0.6), 8.3 (SD = 0.5) and 8.7 (SD = 0.5). An overview is  
314 presented in Table 3. There was a moderately positive correlation between the DHI and the  
315 RMSE/MAE scores ( $\rho = 0.690$  for RMSE with  $P < 0.01$  and  $\rho = 0.660$  for MAE with  $P < 0.05$ )  
316 and a moderate negative correlation between the HUI total score and the MAE score ( $\rho = -0.621$   
317 with  $P < 0.05$ ). There were no other statistically significant correlations between MAE/RMSE  
318 scores and other questionnaires.

Subject	DHI	OSQ	HUI3 total score	SSQ12 total score	SSQ12/6	SSQ12/7	SSQ12/8
1	52	23	0.46	9.1	9.0	8.0	10.0
2	56	#	1,00	7.6	10.0	9.0	10.0
3	14	9	0.97	9.3	10.0	10.0	10.0
4	42	11	0.91	4.4	10.0	10.0	10.0
5	14	17	0.92	7.2	7.5	7.5	7.5
6	28	22	0.54	7.3	10.0	9.0	9.0
7	16	21	0.97	9.1	5.0	8.0	8.0
8	48	#	0.63	5.3	10.0	8.0	10.0
9	28	27	0.72	6.8	7.0	7.0	8.0
10	16	27	0.97	9.8	10.0	10.0	10.0
11	6	11	0.97	10.0	10.0	10.0	10.0
12	86	36	0.65	3.0	5.0	5.0	5.0
13	8	26	0.97	6.6	8.0	7.0	8.0

319 **Table 3.** Overview of questionnaires data of patients with BV. #, missing data.

## 320 DISCUSSION

321 The goal of this study was to evaluate if bilaterally (partially) absent vestibular function during  
322 the localization test itself, would affect sound localization skills. Therefore, the primary  
323 objective was to compare horizontal sound localization skills of normal-hearing patients with  
324 BV and healthy controls, using a fixed sound source and during static listening conditions. Our  
325 study showed that normal-hearing patients with BV had worse static sound localization skills  
326 compared to healthy controls. However, the statistically significant difference between both  
327 groups was very small, especially compared to patients with unilateral deafness (mean MAE =  
328  $60^\circ$ , mean RMSE =  $80^\circ$ ), indicating that ITD and ILD cues are much more important than  
329 vestibular cues during static sound localization (Figure 4) [31].

330 Experiencing vertigo can effectively shift the sound localization image, as was demonstrated  
331 by Lewald et al. [32] using cold water irrigation during static listening conditions to stimulate  
332 one of the vestibular systems. Once BV is diagnosed, vertigo is an uncommon symptom, and  
333 as a result, the patients with BV in our study did not experience vertigo during sound  
334 localization testing. Patients with BV show a wide variety of often subtle symptoms, the most  
335 important ones being gait unsteadiness, postural imbalance, and oscillopsia. However, there  
336 was no obvious correlation between the subjective reporting of speech perception, spatial  
337 hearing, and quality of life on the one hand and the sound localization scores on the other hand.  
338 Therefore, the reduced sound localization scores in patients with BV could not be explained by  
339 induced sound image shifts as a consequence of asymmetric impairment of the vestibular  
340 organs.

341 Most patients with BV diagnosed at our department had some form of hearing loss. Hearing  
342 loss has been demonstrated to be an important independent risk factor for dementia and could  
343 therefore affect spatial hearing [33]. Furthermore, binaural hearing is essential to localize  
344 sounds in the horizontal plane. Therefore, patients with BV with hearing loss were excluded.  
345 Mild asymmetric hearing levels might also degrade spatial hearing, with a shift of the sound  
346 localization image to the better hearing ear. Just noticeable differences of ITD and ILD have  
347 been well investigated for different kinds of localization stimuli, sound frequencies, and  
348 localization angles. Previous studies showed that in optimal conditions, the threshold for ITD  
349 was 10 to 20  $\mu\text{sec}$  and the threshold for ILD was 0.5 to 1 dB [7]. In our study, all included  
350 patients and healthy controls had more or less symmetric hearing at all frequencies. The mean  
351 interaural PTA<sub>0.5, 1 and 2kHz</sub> difference in patients with BV was 2.85 dB, which was less compared  
352 to the healthy subjects (3.23 dB), and no correlation could be found between mean interaural  
353 PTA<sub>0.5, 1 and 2kHz</sub> difference and localization scores. Following a persistent mild asymmetric  
354 hearing loss, adaptation may be achieved either by learning a new relationship between the  
355 altered binaural cues and sound source location or by relying to a greater extent on monaural  
356 spectral cues [34, 35]. It is therefore unlikely that hearing status in our patient group had an  
357 adverse impact on their localization accuracy.

358 Several studies suggested a link between vestibular function and cognition [3-5]. Spatial  
359 cognition and navigation seemed to be significantly impaired in patients with BV [5, 36-39].  
360 Moreover, recent studies showed evidence of a general cognitive decline [40, 41]. A systematic  
361 review by Dobbels et al. [4] pointed out that none of the studies investigating cognition in  
362 patients with BV corrected for hearing loss, meaning that the cognitive decline in patients with  
363 BV might be partially or completely caused by comorbid hearing loss. Therefore, Dobbels et  
364 al. [3] evaluated the cognition in patients with BV while correcting for hearing impairment,  
365 using a cognitive test battery specifically adapted to visually support oral instructions: the  
366 Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired  
367 Individuals (RBANS-H) [42]. The RBANS-H allowed evaluation of five different subscales of  
368 cognition, namely immediate memory/learning, visuospatial ability, language, attention, and

369 delayed memory, which are summed to provide a total score. After correcting for hearing  
370 impairment, patients with BV scored significantly worse on the "attention" subscale. Attention  
371 deficit and cognitive impairment in patients with BV might have had a negative impact on the  
372 localization scores.

373 This study showed that patients with BV had mildly worse sound localization skills as was  
374 hypothesized. However, this difference was very small and therefore most unlikely due to  
375 bilaterally absent vestibular function, but rather as a consequence of the attention deficit and  
376 cognitive impairment. The duration of the existing BV would have been an interesting  
377 parameter to include, since BV patients with a longer disease duration might hypothetically  
378 have had a greater impact on their cognitive functions with consequently worse sound  
379 localization skills. However, patients were unable to provide an exact date of BV onset and  
380 therefore we decided to omit this parameter.

381 This study investigated auditory space perception in the horizontal plane during static listening  
382 conditions, using a static sound source. During these conditions, the only active vestibular  
383 vector was the gravity vector, which is sensed by the saccule. The cVEMP assesses the saccular  
384 function and its afferent pathways. No correlation could be found between cVEMP response  
385 and localization scores. However, correlations between vestibular test results and localization  
386 scores mean little since patients with BV have little to no residual vestibular function. These  
387 correlations would have been interesting if we had included the vestibular test results of the  
388 healthy subjects.

389 This is the second study to investigate sound localization skills of patients with BV. Recently,  
390 Dobbels et al. [43] performed the same sound localization test on 69 patients with BV under  
391 best-aided conditions (with hearing aids and/or cochlear implants) as they hypothesized a  
392 correlation between sound localization skills and frequency of falling. They had to reject this  
393 hypothesis as there was no significant difference between the RMSE of the fallers (mean RMSE  
394  $41.5^\circ \pm 29.8^\circ$ ) versus the non-fallers (mean RMSE  $39.4^\circ \pm 33.5^\circ$ ). These localization scores  
395 were much worse compared to the scores in our study, since not only normal hearing patients  
396 with BV were included in the present study. Despite the best-aided conditions, hearing aids  
397 and/or cochlear implants were not able to provide normal binaural hearing. The impact of ITD  
398 and ILD cues on localization scores was therefore much greater than the impact of BV.

399 Interestingly, the relationship between vestibular function and sound localization goes both  
400 ways. Not only visual cues but also auditory cues can be used as spatial landmarks to improve  
401 postural stability [44, 45]. Furthermore, hearing aids in elderly patients seem to improve the  
402 stability during Romberg test and decrease the risk of falling [46].

403 The subjective reporting of speech perception, spatial hearing, and quality of life was measured  
404 with several questionnaires (SSQ12, DHI, OSQ, HUI3), of which only a moderate correlation  
405 could be demonstrated between DHI (positive correlation) and HUI total score (negative  
406 correlation), and localization scores (secondary objective). The DHI scores indicate that the  
407 handicap was perceived as severe by 2 patients with BV (15%) and as moderate by 3 (23%).  
408 Mean HUI3, DHI, and OSQ scores in our study are better, compared to the mean scores of  
409 patients with BV in other studies [4, 47, 48]. The better mean HUI3 score in our study can be  
410 explained by the fact that patients with BV in our study did not have comorbid hearing loss,  
411 whereas most patients with BV included in the other studies showed moderate to severe hearing  
412 loss which has a negative impact on quality of life. Hearing loss may also have a negative  
413 impact on postural stability as mentioned earlier and may therefore cause worse mean DHI  
414 scores. Furthermore, by only including normal hearing patients with BV, several common  
415 causes with hearing impairment that are associated with worse DHI scores due to recurrent  
416 vertigo attacks (such as some genetic etiologies and Meniere's disease) are excluded. No further  
417 conclusions can be drawn due to the small sample size.



418 Despite the small impairment of the static sound localization scores in patients with BV, there  
419 is an obvious self-perceived impact on sound localization during everyday life. Five (38%) of  
420 the patients with BV showed impaired SSQ12/6, SSQ12/7, and SSQ12/8 scores, which are the  
421 SSQ12 subscores specifically related to spatial hearing. However, these subscores represent  
422 mainly localization ability during dynamic listening conditions, in which an adequate vestibular  
423 function is probably more important. In healthy subjects, localization accuracy was affected by  
424 creating dynamic listening conditions [13-17]. In future research, it would be interesting to  
425 investigate similar localizations tests with dynamic listening conditions in patients with BV. In  
426 analogy with an impaired visual acuity during dynamic situations due to the impaired VOR in  
427 patients with BV, we hypothesize that sound localization accuracy of patients with BV will be  
428 worse compared to healthy subjects due to a larger shift of the sound localization image during  
429 head rotations. Finally, in 6 (46%) of the patients with BV, a significant impact on the total  
430 SSQ12 score could be demonstrated. This is partly due to the worse SSQ12/6, SSQ12/7, and  
431 SSQ12/8 scores. In addition, some patients with BV probably showed reduced speech  
432 comprehension due to limited presbycusis.

433 The small sample size was one of the biggest limitations of this study. BV is a rare condition  
434 with often subtle symptoms, leaving many patients undiagnosed. Patients with obvious  
435 symptoms such as severe hearing loss might seek medical attention faster. Therefore, most of  
436 the patients with BV diagnosed at our center showed some form of hearing loss. Secondly, this  
437 study only investigated horizontal sound source localization, using a fixed sound source and  
438 during static listening conditions, which is an egocentric task. However, this covered only a  
439 small part of auditory space perception. It would be interesting to expand this investigation to  
440 vertical and distance sound localization and allocentric tasks. The reality is a lot more complex  
441 with dynamic sound sources, which is difficult to create as shifts of sound sources are  
442 accompanied by the creation of unintentional sounds. Furthermore, it would be interesting to  
443 perform localizations tests with dynamic listening conditions in patients with BV, as mentioned  
444 earlier.

## 445 **CONCLUSION**

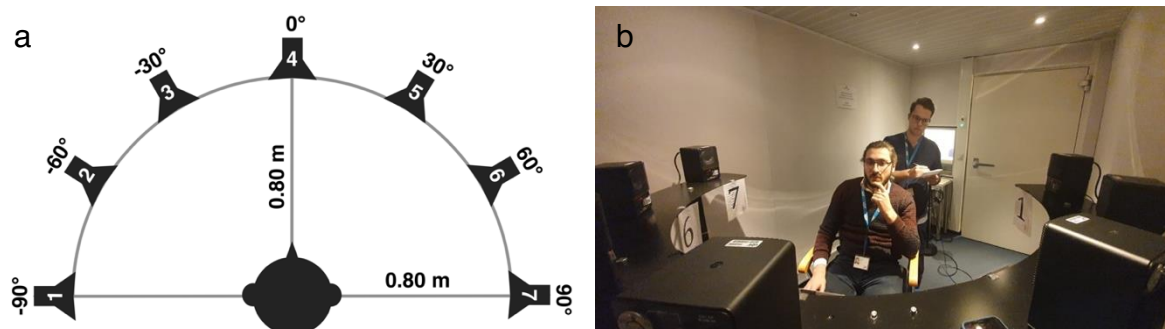
446 Most patients with BV had difficulties localizing sounds due to their hearing loss. Even those  
447 with preserved binaural hearing had worse horizontal sound localization skills, using a static  
448 sound source and during static listening conditions, compared to age-matched healthy controls.  
449 However, this difference was very small and therefore most likely due to impaired cognitive  
450 function. The vestibular system does not seem to have a modulating role in sound localization  
451 during static conditions, and its impact is negligible in contrast to the impact of hearing  
452 impairment. Furthermore, the subjective reporting of speech perception, spatial hearing, and  
453 quality of life was not strongly correlated with localization scores. Future studies should  
454 examine the auditory space perception of patients with BV during dynamic listening conditions,  
455 to evaluate if dynamic auditory acuity is diminished analogous to the reduced dynamic visual  
456 acuity in patients with BV.

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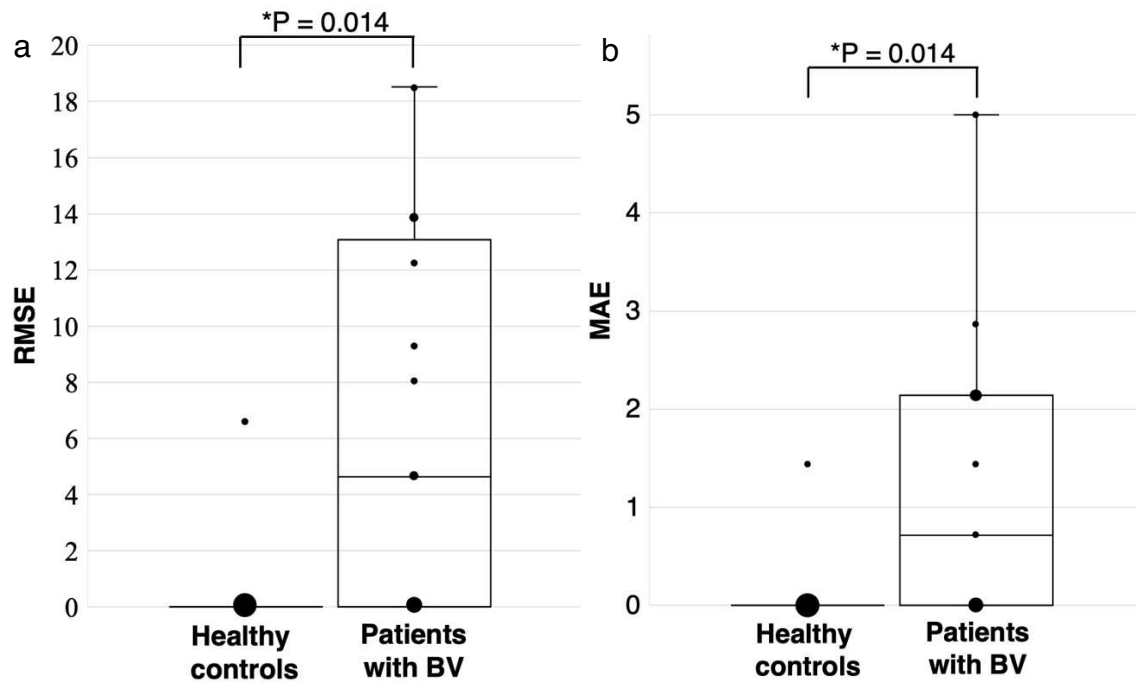
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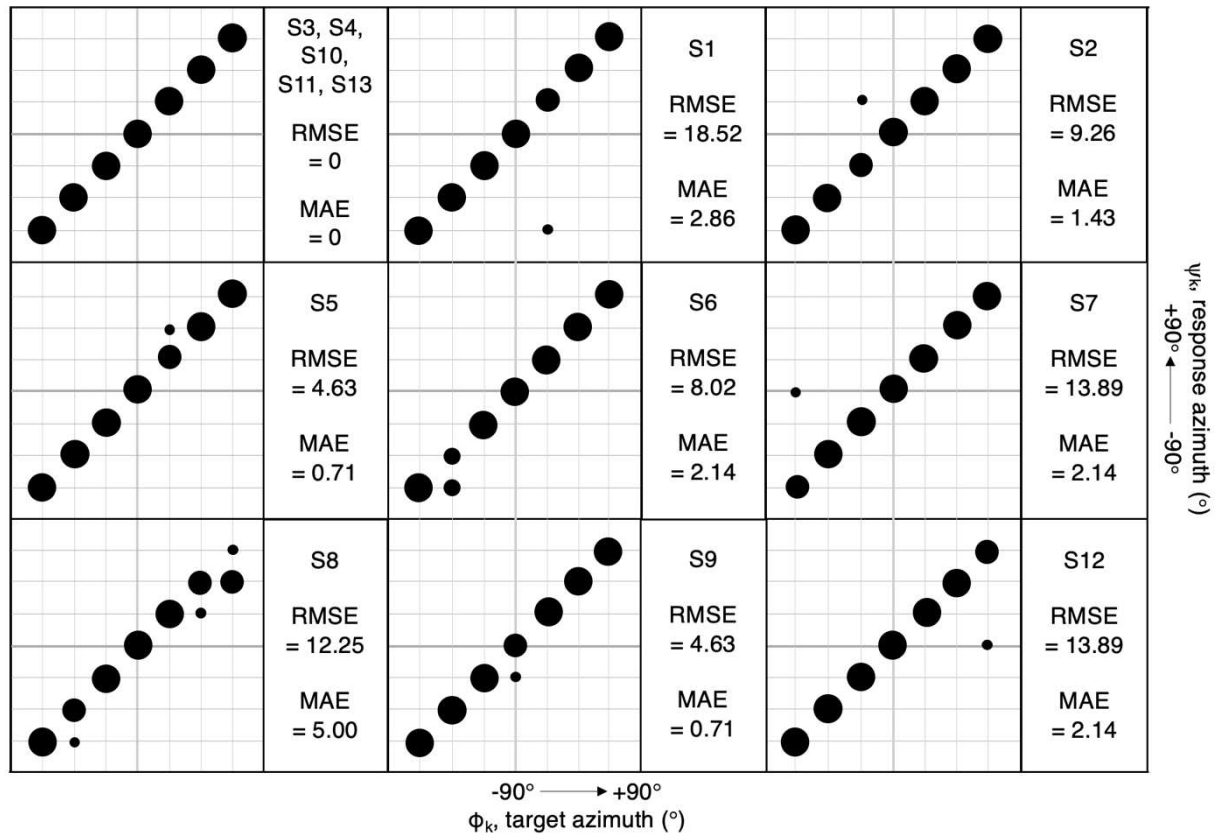
**Fig. 1** Localization set-up: 7 Broadband Fostex 6301 loudspeakers at intervals of 30°, located in a frontal horizontal semicircle at the subject's head level. (a) Schematic representation and (b) picture of set-up.

Graphics program used: PowerPoint (Microsoft)



**Fig. 2** Localization parameters of both the patients with BV and the healthy controls. (a) represents the root-mean-square error (RMSE) and (b) the mean absolute error (MAE). Significant differences between both groups are indicated by an asterisk, including accompanied p-values.

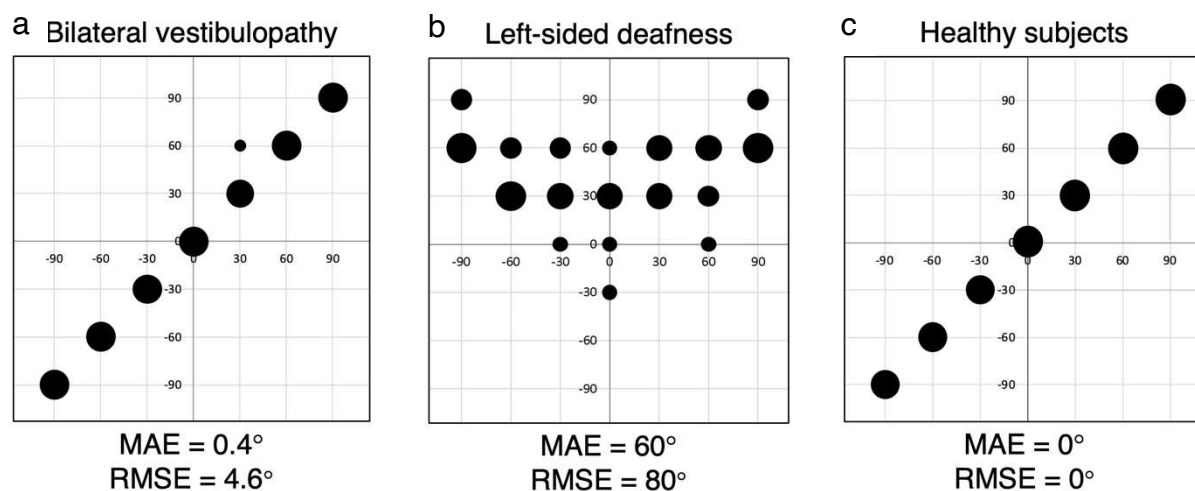
Graphics program used: IBM SPSS Statistics (version 27) and edited in PowerPoint (Microsoft)



**Fig. 3** An overview of the individual confusion matrixes and localization scores of all patients with BV. Seven loudspeakers located in a frontal semicircle in a horizontal plane at subject's head level were used, ranged from  $-90^\circ$  to  $+90^\circ$  in azimuth at intervals of  $30^\circ$ . In each trial, six stimuli were offered from each speaker in a random sequence, which makes a total of 42 stimuli. For each of the 42 stimulus presentations, the judged azimuth in response to a loudspeaker  $k$  was recorded ( $\psi_k$ ) and plotted on this confusion matrix. The X-axis represents the target loudspeaker  $\phi_k$  and the Y-axis represents judged azimuth  $\psi_k$ . Overlapping points are represented on the matrix by larger spheres, with a maximum size of 6 points and a minimum size of 1 point. Every point along the  $y = x$  line, represents a correct sound source identification. Root-mean-square error (RMSE) is calculated as the root-mean-square of the magnitudes of the differences between the azimuth angle of the sound presenting speaker ( $\phi_k$ ) and the azimuth angle of the judged speaker ( $\psi_k$ ) across all 42 stimulus presentations. Mean absolute error (MAE) is the absolute error in degrees, divided by the total amount of stimulus presentations (i.e. 42 stimuli). The numbering of the subjects (S) corresponds to Table 2.

Graphics program used: PowerPoint (Microsoft)





**Fig. 4** Examples of mean sound localization skills in (a) patients with BV, (b) patients with single-sided deafness and (c) healthy subjects with the respective confusion matrix. Seven loudspeakers located in a frontal semicircle in a horizontal plane at subject's head level were used, ranged from  $-90^\circ$  to  $+90^\circ$  in azimuth at intervals of  $30^\circ$ . In each trial, six stimuli were offered from each speaker in a random sequence, which makes a total of 42 stimuli. For each of the 42 stimulus presentations, the judged azimuth in response to a loudspeaker was recorded and plotted on this confusion matrix. The X-axis represents the target loudspeaker, and the Y-axis represents judged azimuth. Overlapping points are represented on the matrix by larger spheres, with a maximum size of 6 points and a minimum size of 1 point. Every point along the  $y = x$  line, represents a correct sound source identification. Root-mean-square error (RMSE) is calculated as the root-mean-square of the magnitudes of the differences between the azimuth angle of the sound presenting speaker and the azimuth angle of the judged speaker across all 42 stimulus presentations. Mean absolute error (MAE) is the absolute error in degrees, divided by the total amount of stimulus presentations (i.e. 42 stimuli).

Graphics program used: PowerPoint (Microsoft)



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