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1 **Brain plasticity and auditory spatial adaptation in patients with unilateral** 2 **hearing loss**

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41 The authors declare that they have no competing interest.

42

43

44

45 **Abstract:**

46 Unilateral hearing loss (UHL) alters binaural cues affecting speech comprehension and sound
47 localisation. While many patients with UHL perform poorly on binaural tasks, some are able to
48 adapt to monaural deficit. We aimed to identify patients with UHL who use compensatory
49 strategies and to explore the neural correlates of this adaptation using Mismatch Negativity
50 (MMN). We recruited 21 patients with UHL and we separated them into three groups using
51 cluster analysis based on measures of binaural processing. The resulting groups were referred
52 to as the better, moderate and poorer performers clusters (BPC, MPC and PPC). We measured
53 the MMN elicited by deviant sounds located 10°, 20° or 100° away from a standard sound. We
54 found that the BPC group had a significant MMN for all three deviant sounds, as in a group of
55 normal-hearing controls. In contrast, the PPC group and normal-hearing controls with an
56 earplug did not have a significant MMN for the 10° and 20° deviations. For the 100° deviation,
57 the scalp distribution was found to be maximal over central regions in the BPC group, while
58 the PPC group showed a more frontal distribution. Differences were also found for the N100
59 evoked by standard sounds, with the BPC group showing a contralateral pattern of activation,
60 as in the controls, and the PPC group showing more symmetrical hemispheric activation. These
61 results indicate that patients with UHL can develop adaptive strategies that are reflected by
62 sound processing differences at the cortical level.

63

64

65 **Introduction**

66 Binaural integration is an important function for sound localization and speech segregation.
67 Interaural time and intensity differences (ITD and ILD) are the main cues engaged in horizontal
68 localization (Grothe 2010), in addition to monaural spectral shape cues used predominantly for
69 vertical and front/back localization. Accordingly, unilateral Hearing Loss (UHL), leads to an

70 alteration of interaural balance, consequently altering spatial hearing in the horizontal plane.
71 This alteration is expressed by higher signal to noise ratios (SNR) to understand speech in noisy
72 environment and by a shift of the auditory space towards the better ear (Firszt et al., 2015;
73 Rothpletz et al., 2012; Vannson et al., 2015). Middlebrooks and colleagues investigated
74 auditory spatial adaptation after UHL (Makous & Middlebrooks, 1990) and found that patients
75 displayed variable spatial accuracy for sound localisation, ranging from near-normal to a total
76 shift of localisation towards the hearing side (Middlebrooks & Green, 1991). In contrast,
77 normal-hearing controls showed poor accurate sound localisation under monaural listening
78 conditions. Thus, UHL patients have highly variable speech reception thresholds (SRT). In a
79 study by (Vannson et al., 2017) the SRT score in a speech-in-noise test (French Matrix test)
80 were variable between subjects, some of them were considered as normal performers. This
81 inter-individual variability can be attributed to individual compensatory strategies, which may
82 differ between patients. The adaptive processes could involve a range of mechanisms, including
83 improved processing of monaural spectral shape cues and head-shadow effects (HSE),
84 (Batteau, 1967; Slattery & Middlebrooks, 1994; Van Wanrooij & Van Opstal, 2005) both of
85 which contain auditory spatial cues (Agterberg et al., 2011; Van Wanrooij & Van Opstal, 2004).
86 The acoustic compensatory mechanisms used by patients with UHL reflect a potential for
87 neuroplasticity (Alzaher et al., 2021). While there are evidences that human adult subjects can
88 adapt to monaural hearing (Keating et al 2016), the brain adaptation has been only reported in
89 animal models trough electrophysiological recording (Keating et al 2013, 2015). In humans,
90 functional imaging studies have shown cortical processing changes in UHL patients.
91 Specifically, while normal-hearing controls display higher activity in the hemisphere
92 contralateral to a monaural stimulus (Elberling et al., 1981; Pantev et al., 1986), UHL patients
93 show more symmetrical activation patterns (D. Bilecen et al., 2000; Ponton et al., 2001).
94 However, there are currently few studies that have investigated auditory cortical plasticity for

95 spatial hearing. In a previous study, we presented evidence that the functional integrity of the
96 auditory dorsal stream is affected by UHL, and that this contributes to the sound localisation
97 deficits (Vannson et al., 2020). However, further work is required to explore neural plasticity
98 in patients.

99 Studies on event related potentials (ERPs) have shown that the auditory mismatch negativity
100 (MMN) can be a useful marker of auditory dysfunction (Näätänen et al., 2015). To elicit a
101 MMN, repetitive sound stimuli, are presented, leading to a decline in the neural response due
102 to a passive store of repetitive information (Duncan et al., 2009). Whenever a rare change is
103 introduced to this repetitive sequence a new ERP response is automatically elicited (Näätänen
104 & Alho, 1997). The difference between these rare-stimulus ERPs and the repetitive-sound ERPs
105 yields the MMN waveform. It has been found that the MMN occurs in response to a variety of
106 stimulus disparities, including the sound spatial displacement (Deouell et al., 2006; Freigang et
107 al., 2014).

108 In this study, we analysed the MMN elicited by changes in sound location (spatial MMN) to
109 assess the functional reorganization and compensatory brain plasticity in patients with UHL.
110 We hypothesized that MMN can be a neural correlate that reflects spatial auditory behaviour,
111 and that MMN components would be associated with the inter-individual variability in spatial
112 hearing skills. The approach was considered to be well-suited for gaining insight into the neural
113 mechanisms inducing auditory plasticity in some patients with UHL.

114 **Materials and methods**

115 *Participants*

116 We recruited 20 normal-hearing subjects (NHS; 10 women), aged 20–35 years, and 21 patients
117 with UHL (12 women), aged 25–75 years. The participants underwent audiometric testing to
118 determine the pure tone average (PTA) thresholds for the following frequencies: 250, 500,
119 1000, 2000 and 4000 Hz. NHS with a PTA exceeding 15 dB were excluded from the study (n

120 = 0). All of the NHS had normal and symmetrical levels of hearing. The patients with UHL
 121 had normal hearing levels in the healthy ear, with an average PTA of 14.7 dB HL (standard
 122 deviation: 7.9), and moderate-to-profound hearing loss in the deaf ear, with an average PTA of
 123 82.27 dB HL (standard deviation: 29.1); the average PTA difference between the healthy and
 124 deaf ears was 67.5 dB (standard deviation: 32). Written informed consent was obtained from
 125 all of the participants before the experiment. The NHS were offered financial compensation
 126 following their participation in the study.

127 **Table 1. Patient characteristics**

128 *Abbreviations: PTA = 'pure tone average threshold', D. side= 'deafness side', DS = 'deaf*
 129 *side', HS = 'hearing side', RMS = 'average root mean square error for sound localisation'; M*
 130 *= 'male', F = 'female'; R = 'right ear', L = 'left ear', SSQ= 'Speech, Spatial and Qualities of*
 131 *Hearing Scale questionnaire', total D.= 'total deafness', Cong = 'congenital', Ch. = 'chronic'.*

| N | Age | Sex | D. side | PTA-DS | PTA-HS | RMS | D. onset | Etiology | SSQ |
|-----------------|-----|-----|---------|------------------|-----------------|------------------|----------|--------------|--------------|
| 1 | 65 | F | R | 36.5 | 12 | 8.2 | 2004 | Ch. Otitis | 3.9 |
| 2 | 49 | F | R | 38 | 14.5 | 31.2 | 2017 | Unknown | 2.6 |
| 3 | 71 | M | L | 41.5 | 21 | 6.08 | 2014 | Trauma | - |
| 4 | 63 | F | R | 46 | 17.5 | 15.2 | 2018 | Unknown | - |
| 5 | 69 | M | R | 65.5 | 14.5 | 21.1 | 2015 | Unknown | 5.3 |
| 6 | 37 | M | L | 67 | 28.5 | 17.8 | 2012 | Trauma | 1 |
| 7 | 25 | M | L | 68.8 | 11 | 28.05 | 2012 | Cholesteatom | 6.1 |
| 8 | 41 | F | R | 71 | 28 | 24.4 | 2018 | Unknown | - |
| 9 | 67 | M | L | 72 | 32.5 | 60.6 | 2008 | Unknown | 5.08 |
| 10 | 69 | M | R | 72.5 | 12.5 | 26.15 | 2019 | Menier | 9.75 |
| 11 | 40 | F | L | 72.5 | 9 | 27.2 | 2015 | Unknown | 3.66 |
| 12 | 81 | F | L | 79.5 | 28.5 | 30.9 | 2018 | Sudden | 6 |
| 13 | 25 | F | R | 86 | 3.5 | 28.05 | 2006 | Unknown | 5.75 |
| 14 | 67 | F | R | 93.8 | 16.3 | 40.3 | 2016 | Unknown | 3.1 |
| 15 | 57 | F | L | 100.5 | 8.5 | 21.5 | 2017 | Ch. Otitis | 4.6 |
| 16 | 68 | F | L | total D. | 20.5 | 32.2 | Cong | Sudden | 5.41 |
| 17 | 35 | M | R | total D. | 7 | 37.8 | 2010 | Unknown | 6.37 |
| 18 | 25 | M | R | total D. | 1.5 | 62.5 | 2010 | Trauma | 6.16 |
| 19 | 44 | M | R | total D. | 6 | 44.2 | Cong | Cong | 3 |
| 20 | 57 | F | L | total D. | 12 | 79.8 | Cong | Cong | 1.6 |
| 21 | 48 | F | L | total D. | 15.5 | 30.7 | Cong | Cong | 9.46 |
| Mean(SD) | | | | 82.2 (29) | 14.7 (8) | 32.1 (18) | | | 5 (2) |

132

133

134 *Sound localisation and speech-in-noise tasks*

135 For the sound localisation task, participants were seated in the centre of a semi-circular array
136 (1m radius) of 12 loudspeakers, which were positioned from 82.5° on the subject's right to -
137 82.5° on the subject's left, with 15° between each speaker. The participants held a tablet with a
138 picture of the surrounding speaker array on the screen. They were instructed to select the
139 speaker that corresponded to the location of the sound. The acoustic stimulus was white
140 Gaussian noise, band-pass filtered between 300 and 1200 Hz. We choose this stimulus as it
141 correspond to the one we used in the MMN protocol (see below) based on previous MMN
142 studies (Bennemann et al., 2013)(Freigang et al., 2014),. Before the sound localisation task,
143 participants underwent a training session where they were instructed to listen to the sound
144 coming from different loudspeakers at different times. The sound locations were
145 simultaneously shown on the tablet in order to familiarize the subjects with the sound space.
146 For the localisation test, the sound was presented through each of the 12 speakers in a random
147 order, with a total of two sound presentations for each speaker. The subjects were asked to
148 select the sound location on the tablet after each stimulus. The NHS performed the task under
149 two conditions: a binaural condition and a monaural condition. For the latter, an earplug was
150 used to produce an attenuation of 37 dB, and we added an earmuff that gives 37 dB attenuation;
151 this resulted in a total attenuation of 40 dB.

152 Speech-in-noise segregation (SpiN) was evaluated by determining speech reception thresholds
153 (SRT) using the French Matrix test (Jansen et al., 2012). This test consists of 50 different pre-
154 selected words that fall into five categories: 10 names, 10 verbs, 10 numerals, 10 objects and
155 10 colours. Random combinations of one word from each category produce 5-word sentences,
156 such as “Charlotte attrape douze ballons verts” (translation: Charlotte catches 12 green balls),
157 which are read out by a female French speaker. In our study, the sentences were presented in

158 variable levels of competing noise under three different conditions: (1) a diotic condition, where
159 the speech and noise were presented through a single loudspeaker located in the centre of the
160 array, (2) a dichotic condition, where the speech and noise were presented separately through
161 two different loudspeakers positioned at 60° and -60° , with the noise presented through the
162 speaker closest to the better ear, (3) a reversed dichotic condition, identical to the dichotic
163 condition, but with the speech presented through the speaker closest to the better ear. The
164 participants were asked to repeat the words that they heard. If the answer was correct, the level
165 of the noise was increased by 5 dB; if the answer was wrong, the level was reduced by 5dB.
166 The volume of the speech remained constant throughout the test and was set at 60 dB.

167 *EEG recordings*

168 Participants were seated in an armchair in a sound attenuated room, which had sound-absorbing
169 foam to reduce echoes. EEG recordings were obtained while a series of sounds were presented
170 through four loudspeakers. These were arranged in a semi-circular array around the
171 participants, at a distance of 90 cm and level with the participants' ears. An oddball paradigm
172 was used, designed to evoke a MMN, with the standard sound presented through a loudspeaker
173 located at 50° , and three deviant sounds, that differed only in terms of the spatial location,
174 presented through speakers positioned at 60° (10° difference), 70° (20° difference) and -50°
175 (100° difference; see figure 1). A total of 2000 sounds were randomly presented through the
176 four loudspeakers, with a probability of 85% for the standard position (with a minimum of 6
177 repetitions before the deviant), and 5% for each of the three deviant positions.

178

179 *Properties of acoustic stimulation*

180 The choice of stimulation type (frequency, intensity and duration) in MMN experiment is very
181 crucial because MMN characteristics (amplitudes and latency) depend on the magnitude of

182 difference between the physical sound properties of standard and deviant (Näätänen & Alho,
183 1997). Therefore, it was important to control all the physical properties to make sure of eliciting
184 a MMN strictly related to spatial deviation. The sound duration was set at 100 ms including a
185 10 ms fade in and 10 ms fade out (Duncan et al., 2009). The ISI slightly varied between 490
186 and 500 ms to prevent stimulus onset prediction (Bennemann et al., 2013). For frequency, it
187 was important to avoid a major intervention of intensity cues, that are more likely to elicit a
188 MMN response related to intensity differences (Paavilainen et al., 1989), we used a low
189 frequency band noise band-pass filtered between 300 and 1200 Hz (Bennemann et al., 2013;
190 Freigang et al., 2014). For similar concerns, we decided to avoid an intensity roving to minimize
191 deviances that are not strictly related to auditory spatial attributes (Cai et al., 2015; Deouell et
192 al., 1998, 2006, 2007; Näätänen & Alho, 1997; Paavilainen et al., 1989). Therefore the level of
193 stimulation was calibrated at sound level of 65 dB at the subjects head. During the EEG
194 recordings, the participants watched a silent, subtitled movie on a tablet screen placed at a
195 distance of 30 cm directly in front of them. They were instructed to ignore the sounds and to
196 read the subtitles of the silent movie.

197 The 20 NHS were randomly divided into two subgroups, with 10 subjects in each group. For
198 both of these groups, EEG recordings were obtained twice: once for a binaural condition and
199 again for a monaural condition, where hearing was attenuated on one side using an earplug and
200 earmuff. For the first subgroup, the hearing attenuation was on the side contralateral to the
201 standard sound (contralat condition); for the second subgroup, the attenuation was ipsilateral to
202 the standard sound (ipsi-condition). For the patients with UHL, EEG recordings were also
203 obtained twice in a random order across patients: once with the deaf ear contralateral to the
204 standard sound (contralat-condition), and again with the deaf ear ipsilateral to the standard
205 sound (ipsi-condition). The patients' better-hearing ear is mainly stimulated in the contralat-
206 condition, which enables lateralisation patterns of cerebral activation to be evaluated; in the

207 ipsilateral condition, spatial discrimination can be determined for the auditory hemifield that is
208 most impacted by the hearing loss. Although the stimulation was not strictly monaural, due to
209 varying degrees of residual hearing in the deaf ear, we reasoned that the stimulation at 50°
210 would only be perceived by the better-hearing ear in the contralat-condition. This reasoning is
211 based on: (1) the intensity of the standard sound (65 dB at the sound source, 42 dB at the
212 subjects' ipsilateral ear), (2) the attenuation of the bandpass noise due to the head-shadow effect
213 (head-shadow attenuation ~ 4 dB) and (3) the degree of hearing loss in the deaf ear (PTA
214 ranging from 36.5 dB HL to total deafness). Therefore, the residual hearing in the deaf ear
215 would not have affected the responses recorded at the cortical level in the contralat-condition,
216 because the sound levels did not exceed the auditory thresholds for that ear, with the exception
217 of one patient (who would have perceived a sound of 1.5 dB at the deaf ear).

218 The EEG recordings were obtained using an Active 2 system with 64 Ag/AgCl electrodes
219 placed according to the international 10-20 system. The CMS/DRL electrodes were designated
220 as the ground electrodes. Additional electrodes were placed at the right and left mastoids. The
221 impedance of the scalp electrodes was kept below 10 k Ω , and the default sampling rate was
222 used (2048 Hz).

223 *Data analysis*

224 *Analysis of the behavioural data*

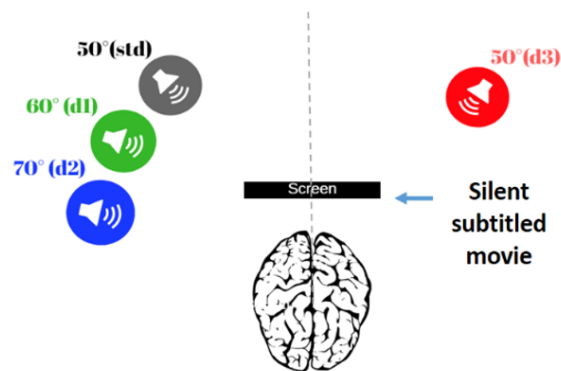
225 For the sound localisation task, the Root Mean Square (RMS) error was determined for each
226 spatial position. The average RMS error for all 12 locations was also determined for each
227 participant. To determine whether there was an effect of group on the average RMS error, we
228 used a linear mixed-effects model (lme4) in R followed by post-hoc multiple comparisons using
229 the glht function in R. The average RMS was calculated for the six speaker locations ipsilateral
230 to the better ear (non-deaf/unplugged) and for the six locations ipsilateral to the poorer ear

231 (deaf/plugged); these values were fitted in a separate linear mixed-effects model (lme4) to
232 determine whether there was an effect of side on the localisation performance (followed by
233 post-hoc comparisons). The level of significance was set at $p < 0.05$.

234 For the SpiN results, analyses were also run using a linear mixed-effects model (lme4 in R),
235 with group and condition as the main factors. Multiple post-hoc comparisons were then run
236 between the groups and conditions using the glht function in R.

237

238 *Analysis of the EEG recordings*



239

240 **Figure 1. EEG auditory stimulation setup.** The standard sounds were presented through a
241 loudspeaker located at 50° (grey), and the deviant sounds (oddballs) were presented through
242 loudspeakers located at 60° (green), 70° (blue), and -50° (red). The participants were asked to
243 ignore the sounds and to focus on a silent, subtitled movie during the recording session.

244

245 The EEG data were analysed offline using EEGLAB (version 14.1.1.b) and ERPLAB (version
246 8.10), an open-source toolbox (Delorme & Makeig, 2004; Lopez-Calderon & Luck, 2014) that
247 runs in Matlab (version 8.1.0.604 R2013a). The data were downsampled to 500 Hz and band-
248 pass filtered at 1–20 Hz (1813-point Kaiser windowed-sinc FIR filter, Kaiser beta = 5.65, firfilt
249 plugin version 1.5.3.) (Bennemann et al., 2013). Epochs were created for each sound stimulus,
250 600 ms in duration, including a 100 ms pre-stimulus baseline. Epochs with an amplitude
251 exceeding 100 μv were rejected. The epochs for each loudspeaker position were averaged for

252 each individual to generate ERP waveforms for the standard and three deviants. Difference
253 waveforms were obtained for each subject by subtracting the ERP for the standard from the
254 ERP for each of the deviants. The individual ERPs were averaged to generate grand averages
255 for the standard and three deviants. The difference waveforms were also averaged to generate
256 grand averages for the 10°, 20° and 100° deviations.

257 To determine the statistical significance of the MMN, we used a paired permutation test based
258 on randomization (David et al., 2020). This was run using the negative peaks for the individual
259 difference waveforms in a ± 10 ms window corresponding to the latency peak of the grand
260 average (GA) MMN at Fz electrode (Duncan et al., 2009). The analysis was run for each of the
261 three deviant sound locations.

262 To determine whether the MMN amplitudes and latencies differed between the groups and
263 deviant sound locations, we used a linear mixed-effects model (lme4). For this, the peak MMN
264 amplitude and latency were determined for each individual at the Fz electrode, and these were
265 fitted in the model with two factors: group (NHS-binaural, NHS-monaural, BPC and PPC; see
266 below for definition) and sound deviation (10°, 20° and 100°). Post-hoc tests were run using
267 the glht function for multiple comparisons.

268 Analyses were run to identify the electrode regions that had the largest MMN. As the MMN is
269 known to be most prominent at the fronto-central electrodes, we restricted the analyses to the
270 frontal and central scalp areas. We conducted a cluster comparison between the frontal (AF3,
271 AFz and AF4) and central (C1, Cz and C2) electrodes, and a linear mixed-effects model (lme4)
272 was used to analyse the peak MMN amplitude at each electrode as a function of the cluster
273 (frontal vs central), both between and within the subject groups. Permutation tests were run to
274 determine the significance of the MMN waveforms using Matlab version 2020b, and repeated
275 measures tests (lme4) and post-hoc tests (glht) were run to compare the MMN responses using
276 R library version 3.6.3 in R-Studio version 1.1.423.

277 ***K-means cluster analysis***

278 K-means cluster analysis is an exploratory data analysis technique that aims to maximise intra-
279 group homogeneity. Based on different measures, the k-means algorithm computes the
280 Euclidean distance with respect to the centroid of the variables fitted in the algorithm in order
281 to group those that are similar into a common cluster. As the 21 UHL patients in our study
282 differed greatly in terms of their demographic and clinical characteristics (age, duration of
283 deafness, PTA) and binaural listening skills, we conducted K-means cluster analysis to identify
284 subgroups with similar binaural performance. Prior to the analysis, the optimal number of
285 clusters was determined using the elbow method for the Within-cluster Sum of Squares (WSS)
286 (D. Sharma, 2019).

287 The cluster analysis was run using the behavioural results obtained for the sound localisation
288 and speech-in noise tasks, which both involved binaural processing. Five different measures
289 were included in the analysis: (1) the RMS errors for the sound localisation task; (2,3,4) the
290 three SRTs for the different speech-in-noise test conditions (described above); and (5) the
291 Speech, Spatial and Qualities of Hearing Scale scores (SSQ; an auto-evaluation of speech and
292 spatial auditory processing, run for each patient with UHL) (Vannson et al., 2015). The k-means
293 cluster analysis was conducted using R library version 3.6.3 in R-studio version 1.1.423.

294

295 **Results**

296 ***Overall performance on the sound localisation and speech-in-noise tests***

297 Before dividing the patients with UHL into clusters, we analysed the overall group differences
298 on the sound localisation and speech-in-noise tests. A linear mixed-effects model was run
299 (lme4) with Group as main factor and Subjects as random effect, followed by post-hoc
300 comparisons between groups using glht function in R. It was found that the patients with UHL

301 had higher RMS localisation errors compared with the NHS in the binaural condition ($M =$
302 $32.1 \pm SD=17.8$ versus 15.6 ± 4.8 ; $p < 0.001$). However, when the NHS wore an earplug
303 (monaural condition), the RMS localisation errors significantly increased (39 ± 10.4 ; $p < 0.001$).
304 Although the level of hearing loss in the patients with UHL was far greater than the attenuation
305 produced by the earplug (mean PTA in UHL group = 82.2 ± 29.1 dB HL, versus 40 dB
306 attenuation from the earplug), there was no significant difference between the patients and the
307 NHS in the monaural condition ($p = 0.18$).

308 For the SpiN tests, it was found that the SRTs increased in the NHS after the introduction of an
309 earplug in both the dichotic (-14.5 ± 1.7 vs -2.5 ± 4.6 ; $p < 0.001$) and reversed dichotic conditions
310 (-15 ± 1.6 vs -12.3 ± 3.1 ; $p < 0.01$). The patients with UHL had higher SRTs compared with the
311 NHS (no earplug) for all three conditions ($p < 0.001$). However, when the NHS wore an earplug,
312 the SRTs did not differ significantly compared with the patients for the reversed dichotic
313 condition, where the speech was ipsilateral to the healthy/non plugged ear (-12.3 ± 3.1 vs -
314 10.3 ± 3.7 ; $p = 0.07$).

315 *Cluster analysis*

316 The K-means cluster analysis identified three clusters of patients with UHL: six better
317 performers (Better Performers Cluster; BPC), nine moderate performers (Moderate Performers
318 Cluster; MPC) and six poorer performers (Poor Performers Cluster; PPC). These three clusters
319 were divided according to several dimensions, which correspond to the principal components
320 that influence the distribution of the data points, as determined using centroids. In our analysis,
321 dimensions 1 and 2 contributed the most to the division (dimension 1: 39.9%, dimension 2:
322 24.5%), as shown in figure 2, while dimensions 3, 4 and 5 were less involved (22.1%, 10.6%
323 and 3%, respectively). To identify the behavioural test that most influenced the division into
324 clusters, we analysed the correlations between dimensions 1 and 2 and each of the behavioural
325 tests included in the cluster analysis. We found that the SpiN SRTs most influenced the cluster

326 division, as there was a strong correlation between dimension 1 and the SRTs, especially for
327 the diotic and dichotic conditions (table 2).

328 To determine whether demographic factors differed between the clusters, we ran correlation
329 analyses between dimensions 1 and 2 and certain clinical and demographic characteristics
330 (PTA, duration of deafness and age). It was found that dimension 2 correlated with the PTA (p
331 < 0.005), but the other correlations were not significant. To examine this further, we analysed
332 the difference in PTA levels between the three clusters using a linear mixed-effects model
333 (lme4) followed by post-hoc comparisons (glht function). The PTA was found to be
334 significantly lower in the BPC group (50.8 ± 16.3 dB HL) compared with the MPC group
335 (97 ± 24.1 dB HL; $p < 0.005$) and PPC group (91.6 ± 22.8 dB HL; $p < 0.05$); the difference
336 between the MPC and PPC groups was not significant ($p = 0.88$).

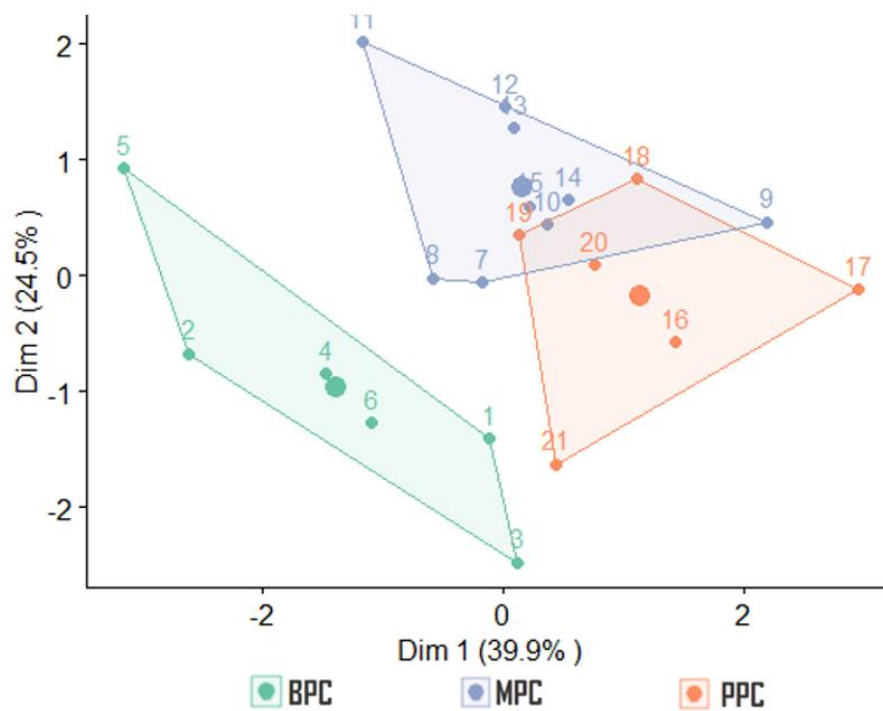
337 We ran further analyses to examine differences in the auditory test scores between the three
338 clusters. For this, we used a linear mixed-effects model followed by post-hoc comparisons
339 (lme4 and the glht function in R Studio). It was found that the BPC group had the lowest RMS
340 errors (18.7 ± 10.4) and the lowest SRT in the diotic (-3 ± 3.7) and dichotic (-1.2 ± 1.8) conditions
341 compared with the MPC group (RMS: 30.4 ± 7.4 ($p=0.2$); diotic SRT: -1.9 ± 1.5 ($p=0.6$); dichotic
342 SRT: 4.2 ± 1.6 ($p<0.001$)) and the PPC group (RMS: 48.7 ± 23 ($p<0.001$); diotic SRT: 1.65 ± 2.3
343 ($p<0.05$); dichotic SRT: 5.22 ± 2.3 ($p<0.001$)). For the reversed dichotic condition, there were
344 no significant differences between the three clusters. Thus, the correlation analysis presented
345 in table 2 shows high contribution of SRT in dichotic condition in the separation of the clusters.
346 In these conditions, the head shadow effect (HSE) is strongly involved, therefore we suggest
347 that BPC is the group that benefits the most from HSE compared to MPC and PPC.

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353 **Figure 2. Division of 21 patients with UHL into three clusters: Better Performers Cluster**
354 **(BPC), Moderate Performers Cluster (MPC) and Poor Performers Cluster (PPC). The large**
355 **dots in the middle of each cluster represent the centroids. Dimension 1 had the largest**
356 **influence on the division (39.9%).**

357

358 **Table 2. Correlation between the cluster analysis dimensions and the behavioural test**
359 **scores and demographic characteristics.**

360 *The analyses were restricted to the first two dimensions, as they contributed the most to the*
361 *division into clusters (see Figure 2; dimensions 1 + 2 = 64.4%).*

362

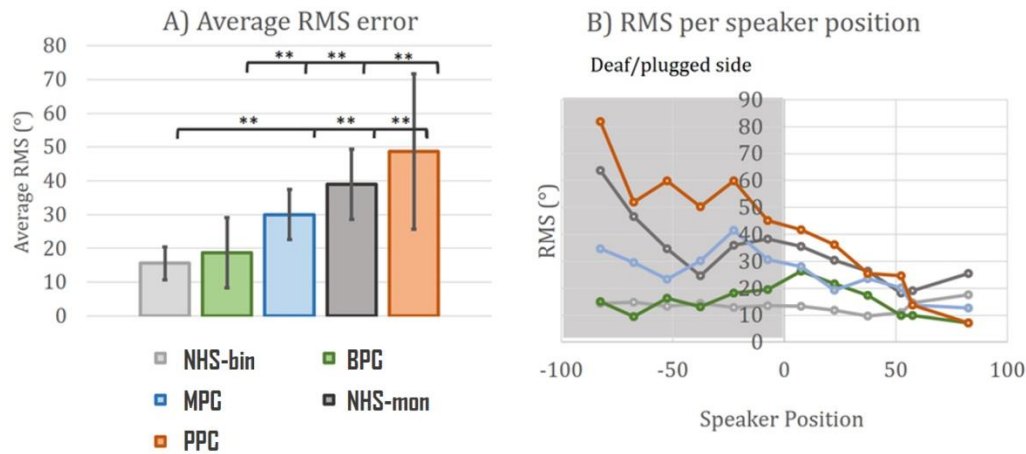
| Behavioral factor.Dimension | Corr | p-value | Demographic factor.Dimension | Corr | p-value |
|-----------------------------|-------|------------|------------------------------|-------|---------|
| RMS.Dim1 | 0.32 | 0.14 | PTA.Dim1 | 0.28 | 0.21 |
| RMS.Dim2 | 0.4 | 0.06 | PTA.Dim2 | 0.63 | 0.002* |
| SSQ.Dim1 | 0.3 | 0.18 | Age.Dim1 | 0.4 | 0.06 |
| SSQ.Dim2 | 0.6 | 0.002* | Age.Dim2 | -0.31 | 0.16 |
| Diotic.Dim1 | 0.84 | 1.671e-06* | Deafness duration.Dim1 | -0.07 | 0.75 |
| Diotic.Dim2 | -0.39 | 0.07 | Deafness duration.Dim2 | -0.41 | 0.059 |
| Dichotic.Dim1 | 0.81 | 7.512e-06* | | | |
| Dichotic.Dim2 | 0.44 | 0.04* | | | |
| Rev-Dich.Dim1 | 0.65 | 0.001* | | | |
| Rec-Dich.Dim2 | -0.55 | 0.009* | | | |

363

364

365 *Performance on the sound localisation test for the patient clusters*

366 We compared the sound localisation RMS for the three patient clusters (BPC, MPC and PPC)
 367 as well as the NHS group under binaural or monaural listening conditions (NHS-bin, NHS-
 368 mon). The linear mixed-effects model showed a main effect of group ($p < 0.001$). Post hoc
 369 comparisons showed that there was no significant difference between the NHS-bin (15.6 ± 4.8)
 370 and the BPC (18.8 ± 10.4) groups; however, with the earplug, the localisation errors significantly
 371 increased in the NHS (38.7 ± 10.4 ; $p < 0.001$), and the RMS errors were significantly higher
 372 compared with the BPC ($p < 0.001$) proving a strong adaptation to deafness, first in the BPC
 373 group despite the moderate hearing loss of 51 dB, second in MPC who had similar localisation
 374 errors as NHS after immediate ear plug. Of all the groups, the PPC had the highest localisation
 375 errors (48.7 ± 23). This was significantly higher than the NHS-bin ($p < 0.001$), BPC ($p < 0.001$)
 376 and MPC ($p < 0.01$) groups, but not the NH-mon group ($p=0.11$; figure 3A).



377

378

379 **Figure 3. A) RMS sound localisation errors for each group** (means and standard deviations).
380 **B) Mean localisation errors for each group** for the different loudspeaker positions. ** $p <$
381 0.01 . Abbreviations: NHS-bin= 'normal hearing subjects in binaural condition', NHS-mon= '
382 normal hearing subjects in monaural condition', BPC= 'better performers cluster', MPC=
383 'moderate performers cluster', PPC= 'poor performers cluster'.

384

385 We also examined whether the side of the sound stimulation (deaf/plugged vs non-
386 deaf/unplugged) affected the RMS localisation errors. For this, we averaged the RMS errors for
387 the six loudspeakers on the side of the better/unplugged ear and for the six loudspeakers on the
388 side of the plugged/deaf ear. We found that there was a significant difference between the two
389 sides, with more localisation errors on the deaf/plugged side in the NHS-mon (40.6 ± 13.3 ; $p <$
390 0.001) and the PPC (58.18 ± 12.9 ; $p < 0.001$), but not the BPC (15.2 ± 3.6 ; $p > 0.05$) compared to
391 healthy/non plugged side (NHS-mon= 25.8 ± 6.6 ; PPC= 24.8 ± 13 ; BPC= 15.3 ± 7.6).

392 Altogether, our results are in agreement with previous data showing that UHL patient; but also
393 NHS through training (see Florentine 1976, MacPartland et al 1997, Keating 2016) can develop
394 adaptive strategies for spatial hearing based on head shadow effect and monaural spectral cues.
395 Based on the cluster analysis, our data emphasize that the individual patients may use different
396 adaptive strategies which are independent of the hearing severity

397 **EEG results for the patient clusters**

398

399 In this study, there were two monaural stimulation conditions during the EEG recordings: (1)
400 with the standard sounds presented ipsilateral to the deaf /plugged ear, and (2) with the standard
401 sounds presented contralateral to the deaf/plugged ear. In this section, we focus on the first of
402 these, the ipsilateral condition, because this has a greater effect on the ability to detect spatial
403 deviation from the standard sound position. The EEG results for the second condition, the
404 contralateral condition, are provided in the supplementary material.

405 ERPs were obtained for the standard and deviant sounds and averaged for the different groups.
406 The ERPs were characterized by a negative deflection peaking between 90 and 150 ms after
407 the sound onset, which is known as the N100. Previous work has shown that the amplitude of
408 the N100 varies according to the novelty of the stimulation. In the case of a repetitive stimulus
409 (the standard), a memory trace is formed leading to a decrease in the amplitude of the N100.
410 We were able to observe this habituation to the repetitive standard sounds in the NHS-bin and
411 BPC groups. However, the PPC group had a higher N100 amplitude for the standard sounds,
412 thus suggesting that each sound stimulus was processed as novel and unexpected, despite the
413 repetition. For the NH-mon group, the N100 amplitude was small; this may relate to the binaural
414 stimulation prior to the monaural condition, which may have led to a residual memory trace
415 causing habituation (figure 4).

416 We observed a MMN in the ERP difference waveforms (deviant - standard), characterized by
417 a negative deflection peaking between 150 and 250 ms. The amplitude and latency of the MMN
418 varied according to the magnitude of the spatial deviation from the standard position. The
419 amplitude difference between the groups and conditions was taken to reflect the spatial
420 sensitivity of auditory processing, with higher MMN amplitudes reflecting greater sensitivity
421 to spatial change. We therefore expected to find differences in the MMN responses for the
422 different patient clusters, in line with their performance on the sound localisation task.

423 We tested the statistical significance of the MMN for the three deviant sounds in each group
424 (NHS and the three UHL clusters). This was carried out using a permutation test based on
425 randomization for the waveforms at the Fz electrode. Note that the MMN amplitude is
426 determined after the N100 latency window to prevent the results from being affected by
427 differences in the N100 for the standard and deviant sounds. It was found that a MMN was
428 present for all three deviant sound locations in the NHS-bin and BPC groups ($p < 0.05$). In the
429 MPC group, a MMN was present for the 20° and 100° deviations; in the NH-mon and PPC
430 groups, it was only present for the 100° deviation ($p < 0.05$). The MMN amplitudes were
431 compared between the different groups, but data were only included if a MMN had been found
432 to be present. The MMN amplitudes and latencies for each group are shown in table 3.

433 *Table 3. MMN amplitudes and latencies at the Fz electrode for each spatial deviation (10°,*
434 *20° and 100°) for the five groups (NH-bin: n = 20, NH-mon: n = 10, BPC: n = 6, MPC: n = 9,*
435 *PPC: n = 6). Data are only shown if a significant MMN had been identified at the Fz electrode*
436 *(using a permutation test based on randomisation for the individual MMN peaks in a window*
437 *±10 ms around the grand average peak). Abbreviations: NHS-bin= ‘normal hearing subjects*
438 *in binaural condition’, NHS-mon= ‘normal hearing subjects in monaural condition’, BPC=*
439 *‘better performers cluster’, MPC= ‘moderate performers cluster’, PPC= ‘poor performers*
440 *cluster’, ns= ‘not significant’, AOD= ‘angle of deviation’, $p > 0.05$.*

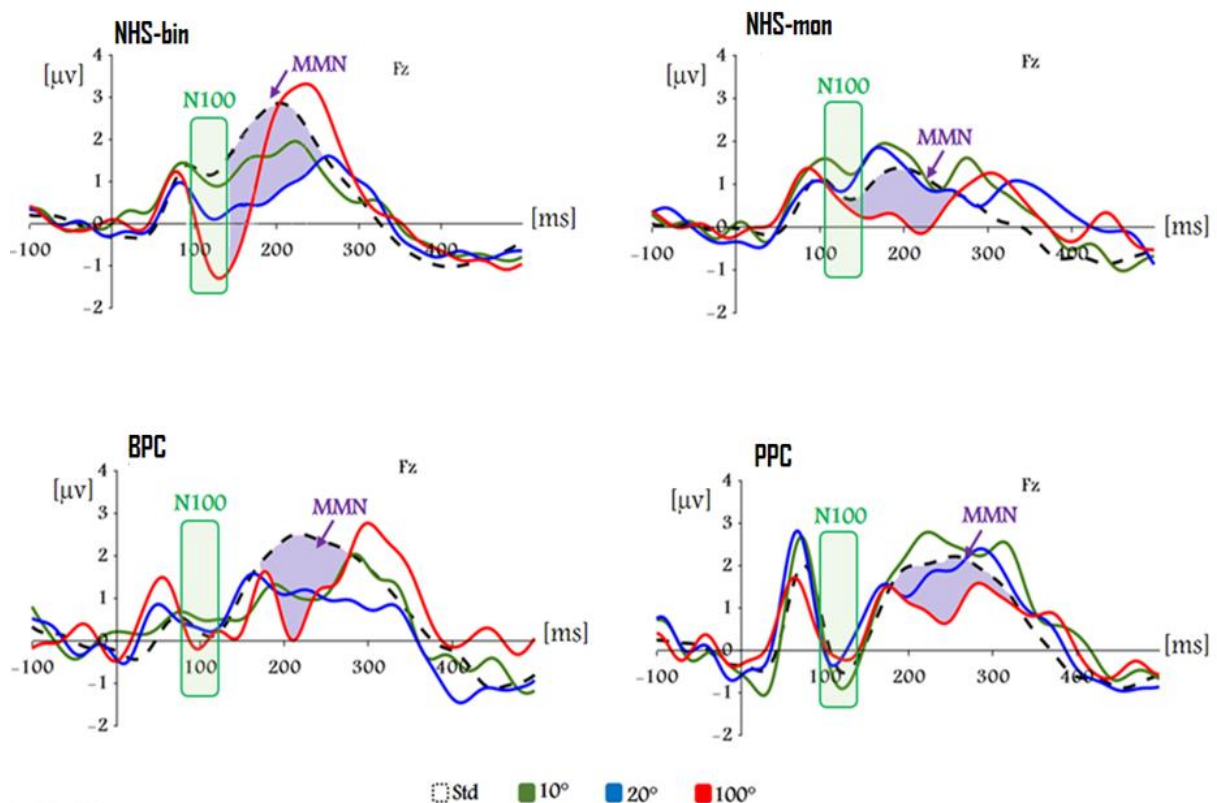
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| Group | AOD | Peak MMN latency (Grand average) | Peak indiv. MMN amp. (10 ms around latency peak) |
|--------|------|-------------------------------------|---|
| NH bin | 10° | 194 ms | -2 μ V \pm 1.2 |
| | 20° | 192 ms | -2.8 μ V \pm 0.9 |
| | 100° | 140 ms | -3.7 μ V \pm 1.9 |
| NH mon | 10° | <i>ns</i> | <i>ns</i> |
| | 20° | <i>ns</i> | <i>ns</i> |
| | 100° | 214 ms | -1.3 μ V \pm 1.4 |
| BPC | 10° | 246 ms | -1.5 μ V \pm 1 |
| | 20° | 222 ms | -1.7 μ V \pm 1.1 |
| | 100° | 216 ms | -3 μ V \pm 1.8 |
| MPC | 10° | <i>ns</i> | <i>ns</i> |
| | 20° | 194 ms | -0.5 μ V \pm 0.8 |
| | 100° | 200 ms | -1.1 μ V \pm 1.2 |
| PPC | 10° | <i>ns</i> | <i>ns</i> |
| | 20° | <i>ns</i> | <i>ns</i> |
| | 100° | 244 ms | -1.8 μ V \pm 0.6 |

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Figure 4. Group ERPs for standard and deviant. Grand average ERPs for the standard and deviant sounds at the Fz electrode. The separate plots are for the four groups: NHS-bin ($n = 20$), NHS-mon ($n = 10$), BPC ($n = 6$) and PPC ($n = 6$). The boxes shaded in green highlight the negative deflection of the sensory N100. The areas shaded in purple represent the MMN, which is the difference between the standard and deviant waveforms, in this case for the 100°

452 deviation [6]. Results for the MPC group are shown in the supplementary material.
453 Abbreviations: NHS-bin= ‘ normal hearing subjects in binaural condition’, NHS-mon= ‘
454 normal hearing subjects in monaural condition’, BPC= ‘better performers cluster’, PPC=
455 ‘poor performers cluster’.

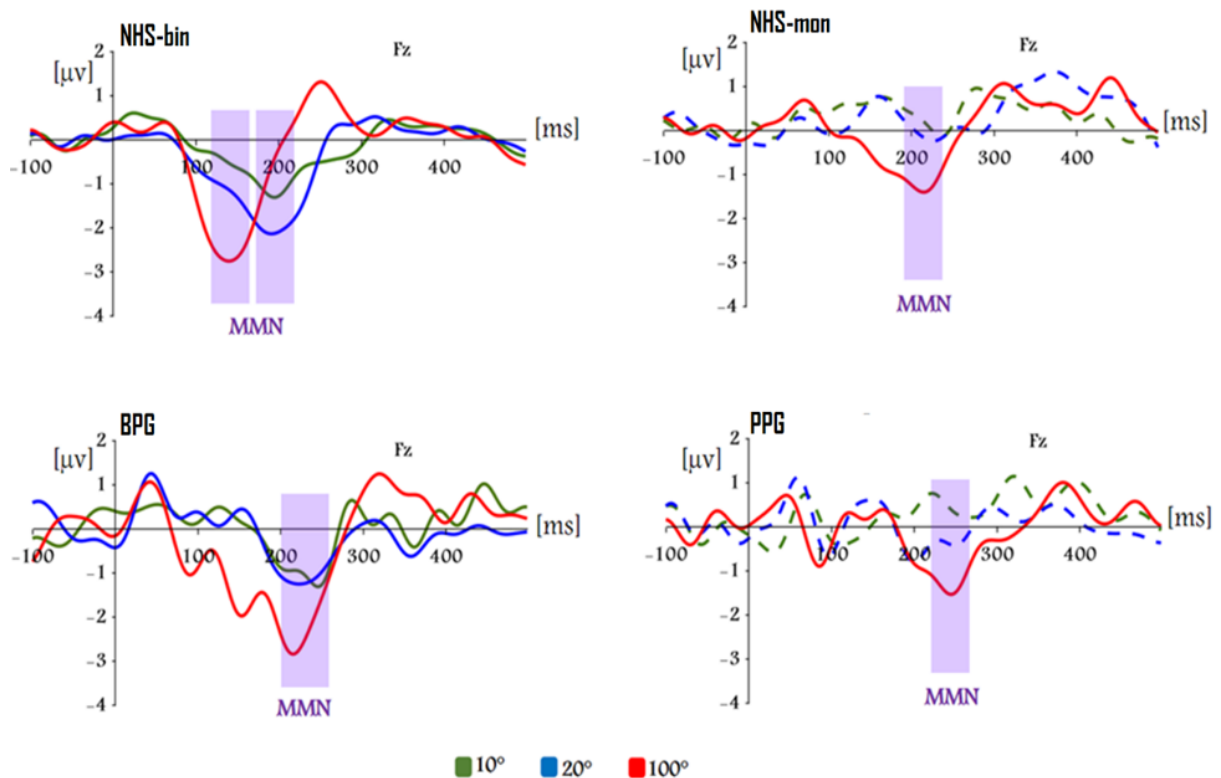
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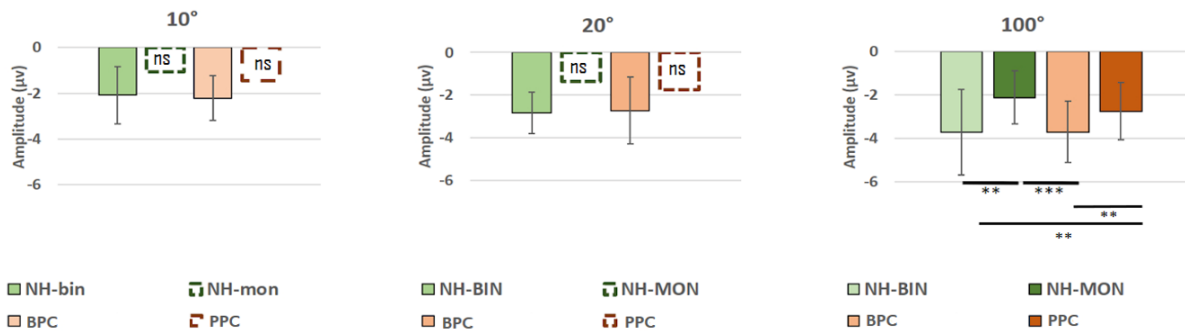
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462 **Figure 5.** Difference waveforms for the 3 deviations. Difference waveforms (deviant ERP –
463 standard ERP) at the Fz electrode for each of the three deviant sounds (10°, 20° and 100°
464 deviation). The separate plots are for the four groups: NHS-bin (n = 20), NHS-mon (n = 10),
465 BPC (n = 6), and PPC (n = 6). The dashed lines show the difference waveforms that did not
466 have significant negativity in the permutation test. Abbreviations: NHS-bin= ‘ normal hearing
467 subjects in binaural condition’, NHS-mon= ‘ normal hearing subjects in monaural condition’,
468 BPC= ‘better performers cluster’, MPC= ‘moderate performers cluster’, PPC= ‘poor
469 performers cluster’.

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473
 474 **Figure 6. Comparison of mean individual MMN peaks at 3 deviation positions.** Mean MMN
 475 amplitude peaks at the Fz electrode for the 10°, 20° and 100° deviations. The means and
 476 standard deviations are shown for each of the four groups: NH-bin ($n = 20$), NH-mon ($n = 10$),
 477 BPC ($n = 6$), and PPC ($n = 6$). If the MMN amplitudes were not significant, according to a
 478 permutation test, the means are shown using dashed lines. The asterisks show statistically
 479 significant differences based on multiple comparisons with the *glht* function in R.
 480 Abbreviations: NHS-bin= 'normal hearing subjects in binaural condition', NHS-mon= '
 481 normal hearing subjects in monaural condition', BPC= 'better performers cluster', PPC=
 482 'poor performers cluster', ns= 'not significant'; ** $p < 0.01$; *** $p < 0.001$.

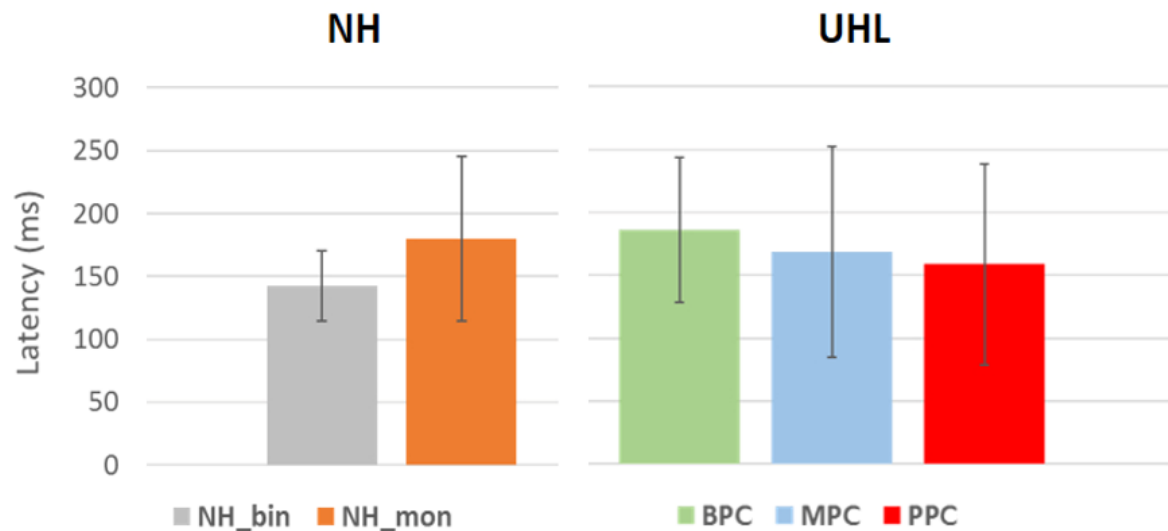
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484 A linear mixed-effects model was run to analyse the individual MMN peak amplitudes. This
 485 showed a progressive increase in the MMN with increasing deviation from the standard sound
 486 location for the group with normal binaural hearing (Table 4). Analyses were also run for the
 487 MMN latency, using the *glht* function in R for multiple comparisons to study latency variation
 488 according to the angle. This revealed a decreased MMN latency for the 100° deviation
 489 (138 ± 24.9 ms) compared with the 10° deviation (199.4 ± 62.2 ms; $p < 0.05$) in the group with
 490 normal binaural hearing ($n = 20$); there was also a tendency for a decreased latency for the 100°
 491 deviation compared with the 20° deviation in these subjects (190.4 ± 58.4 ms; $p = 0.06$).

492 A significant MMN was present for the 100° deviation in all of the groups. The amplitude of
 493 this MMN was higher in the NHS-bin and BPC ($-3.6 \mu\text{v} \pm 1.4$) groups compared with the NHS-
 494 mon ($-2.1 \mu\text{v} \pm 1.2$) and PPC ($-2.7 \mu\text{v} \pm 1.3$) groups ($p < 0.05$); the NHS-bin and BPC groups
 495 did not differ significantly.

496 We ran a further analysis to determine whether the MMN latencies differed between the five
 497 groups (NHS-bin, NHS-mon, BPC, MPC and PPC). For this, the NHS-bin group was restricted
 498 to the 10 participants who later underwent ipsilateral monaural stimulation (ipsi-condition), as

499 we were testing for a group effect. The analysis was run using the latency of the individual
500 MMN amplitude peaks in a linear mixed-effects model (lme4). It was found that there was no
501 significant main effect of group ($p = 0.12$; figure 7).



502

503 **Figure 7. Peak latency for 100° of deviation.** MMN latency at the Fz electrode for the 100°
504 sound deviation. The latencies were determined for each participant at the peak MMN
505 amplitude. The means and standard deviations (error bars) are shown for each group (NHS-
506 bin, $n = 10$; NHS-mon, $n = 10$; BPC, $n = 6$; MPC, $n = 9$; PPC, $n = 6$). There was no significant
507 difference between the five groups ($p > 0.05$). Abbreviations: NHS-bin= 'normal hearing
508 subjects in binaural condition', NHS-mon= 'normal hearing subjects in monaural condition',
509 BPC= 'better performers cluster', MPC= 'moderate performers cluster', PPC= 'poor
510 performers cluster', ns= 'not significant'; ** $p < 0.01$; *** $p < 0.001$.

511 **Topographic distribution of the MMN**

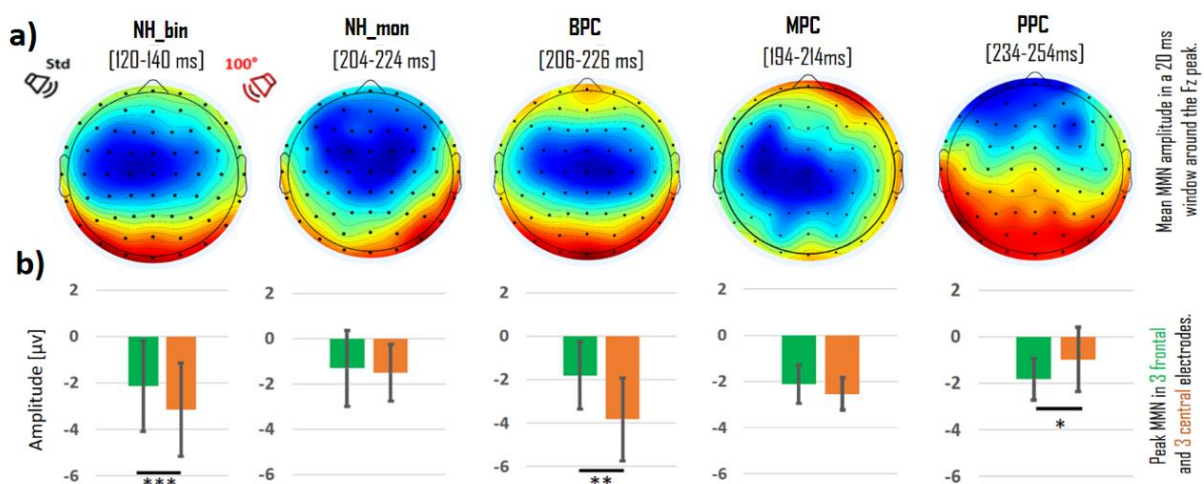
512 We analysed whether variation in the scalp distribution of the MMN relates to deafness or the
513 adaptation to deafness. Previous work has shown that the MMN is maximal at the frontal and
514 central electrodes (Fz and Cz) (Näätänen et al., 2017; Zhang et al., 2011). Higher activation at
515 the central electrodes has been related to attentional switching due to the automatic detection
516 of deviants (Opitz, Rinne, Mecklinger, Yves Von Cramon, et al., 2002), while lower activation
517 has been related to a limited ability to discriminate or integrate surrounding sounds. Higher
518 activation at the frontal compared to the central areas has been related to the cognitive demands
519 involved in ignoring auditory stimuli and concentrating on a set task (Campbell & Sharma,

520 2013). For our analyses, we therefore focused on three frontal electrodes (AF3, AFz and AF4)
521 and three central electrodes (C1, Cz and C2). We restricted our analysis to the 100° sound
522 deviation because the MMN was significant for all five groups and the large deviation would
523 have led to more marked attentional switching.

524 We ran a linear mixed-effects model with cluster and range of interest (frontal vs central) as
525 factors, and subjects as random effect, followed by a post-hoc comparisons (glht function in R).
526 The scalp distribution of the MMN is shown in figure 8 for the NHS-bin, NHS-mon, BPC, MPC
527 and PPC groups. The patterns of activation were observed to be similar for the NHS-bin and
528 BPC groups, characterized by higher central electrode activation and lower frontal electrode
529 involvement.

530 The NHS-mon group showed a different pattern, with equal activation at the frontal and central
531 regions (-1.3 ± 1.6 vs -1.5 ± 1.2 ; $p = 0.52$). The PPC group presented a reversed pattern of
532 activation compared with the NHS-bin and BPC groups, characterized by weak activation at
533 the central electrodes and higher activation at the pre-frontal areas (-1.8 ± 0.8 vs -0.9 ± 1.3 ; $p <$
534 0.05).

535



536

537 **Figure 8. Scalp distribution of the MMN evoked by a 100° deviation in sound location.** The
538 plots are based on the mean MMN amplitude in a 40 ms time window centred on the MMN
539 peak. The bar charts show the mean amplitudes of the individual MMN peaks at the three
540 frontal (AF3, AFz, AF4) and three central electrodes (C1, Cz, C2). Abbreviations: NHS-bin = ‘

541 *normal hearing subjects in binaural condition*, NHS-mon= '*normal hearing subjects in*
542 *monaural condition*', BPC= '*better performers cluster*', MPC= '*Moderate performers cluster*',
543 *PPC= 'poor performers cluster'*; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

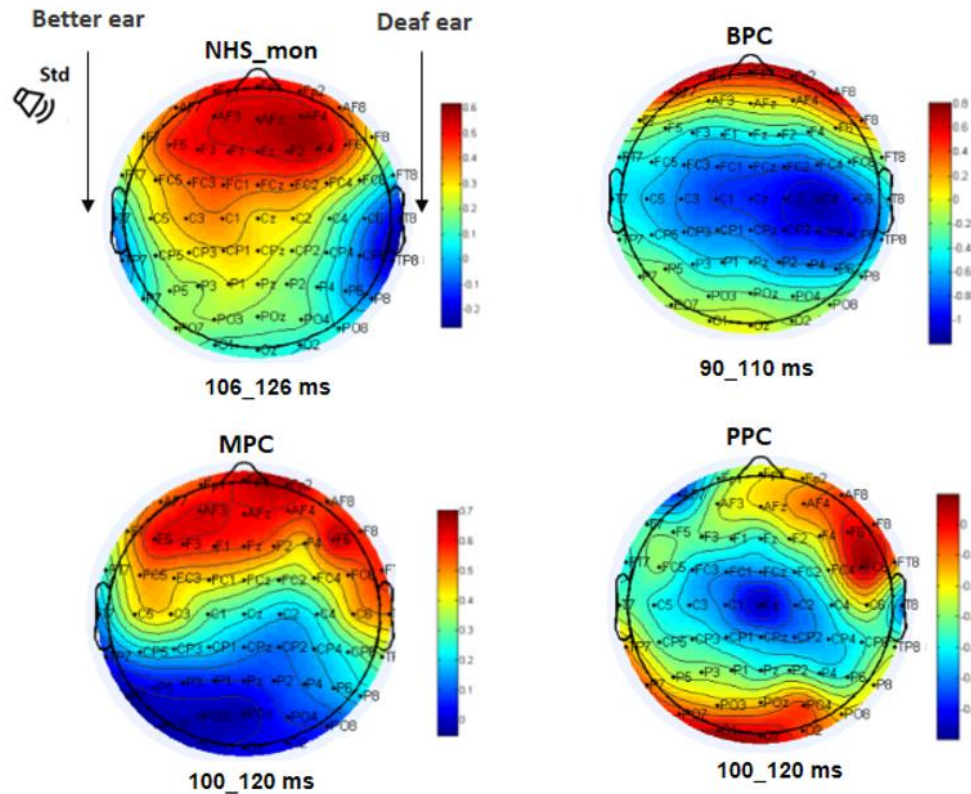
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545 Thus, the central electrode activations were higher in the NHS-bin (-3.1 ± 1.9) and BPC ($-$
546 3.8 ± 1.9) groups compared with the NH-mon (-1.5 ± 1.2 ; $p < 0.01$) and PPC (-0.9 ± 1.3 ; $p < 0.01$)
547 groups.

548 For the MPC we observed a pattern between that seen for the BPC group (greater activity over
549 the central regions) and the PPC group (greater activity over the frontal regions). There was no
550 significant difference between the MMN amplitudes at the frontal and central regions in the
551 MPC group, unlike the PPC and BPC groups, a pattern that was also seen in the NHS with an
552 earplug.

553 ***Interhemispheric asymmetry of the N100***

554 To further explore differences in the cortical activation patterns for the different UHL clusters,
555 we analysed responses to the standard sound in the contralateral condition (when the
556 unplugged/better ear was located on the same side as the standard sound, which was positioned
557 at 50°). For this, we focused on the distribution of the N100 across the scalp and its
558 lateralisation.



559

560 *Figure 9. Scalp distribution of the N100 response. The results are shown for a 20 ms time*
561 *window centred on the N100 peak, as determined at the Fz electrode. This peak is positive for*
562 *the NHS-mon and MPC groups (see supplementary material Figure 13).*

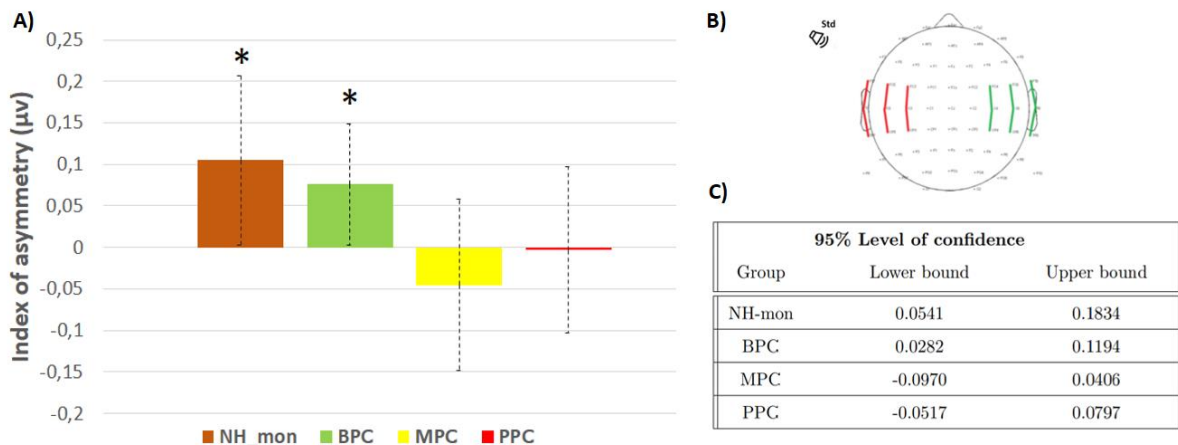
563 Figure 9 shows the scalp distribution of the N100 in a 20 ms time window centred on the N100
564 peak at the Fz electrode. It can be seen that the BPC and NHS-mon groups showed higher
565 contralateral activation as a response to the standard sound, but this was not apparent for the
566 MPC and PPC groups.

567 To analyse these hemispheric asymmetry patterns, we calculated an Asymmetry Index (AI).
568 For this, nine pairs of electrodes were identified over the N100 generators, referred to as the
569 Region Of Interest (ROI), as shown in figure 10b. Asymmetry indices were calculated for each
570 of these electrode pairs, using the individual N100 peak values, with the following formula:

571
$$AI = (\text{contralat response} - \text{ipsi response} / \text{contralat response} + \text{ipsi response})$$

572 When the index is positive, this indicates that there is an asymmetrical pattern of contralateral
573 cortical activation. The overall AI was calculated by averaging the AIs for all nine pairs of
574 electrodes in the ROI.

575 We found that the overall AI values were positive for the NHS-mon and BPC groups, whereas
576 they were negative or close to zero for the MPC and PPC groups (figure 10a). A bootstrap
577 analysis revealed that the AI values were significantly positive (different from zero) for the
578 NH-mon and BPC groups, but not for the MPC and PPC groups. These results indicate that
579 auditory stimuli predominantly activate the contralateral hemisphere in the NH-mon and BPC
580 groups. This is expected based on the functional lateralisation of the auditory system. In
581 contrast, the MPC and PPC groups had a more symmetrical activation pattern, which is
582 characteristic of the central reorganization observed in patients with unilateral deafness.
583



584

585 **Figure 10. Comparison of asymmetry indexes between groups.** a) Asymmetry index values for
586 the NH-mon, BPC, MPC and PPC groups. These were calculated based on the N100 peak
587 values at nine electrode pairs located over the N100 generators. The means and standard
588 deviations are shown. B) Region of Interest (ROI) for the asymmetry index. C) Confidence
589 intervals for the individual asymmetry indices, determined using bootstrap analysis.
590 Abbreviations: NHS-bin= 'normal hearing subjects in binaural condition', NHS-mon=
591 'normal hearing subjects in monaural condition', BPC= 'better performers cluster',
592 MPC= 'moderate performers', 'PPC= 'poor performers cluster'; ** $p < 0.01$; *** $p < 0.001$.

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597 **Discussion**

598 Studies on deafness have classically focused on how the degree of hearing loss affects auditory
599 processing. Many studies have explored how profound deafness affects the auditory processing
600 pathway and its effects on speech comprehension, spatial discrimination and sound localisation.
601 However, relatively few studies have considered the neural processes that follow partial hearing
602 loss. Here, we investigated the neural reorganisation in moderate-to-severe UHL and how this
603 relates to different levels of auditory performance. We adopted a new approach to identify
604 subgroups of patients with similar binaural auditory skills, which involved clustering analysis
605 revealing a subset of patients with near-normal auditory spatial abilities and a near-normal
606 MMN, in spite of their significant hearing loss (PTA = 51 dB HL; BPC). These patients display
607 the classic contralateral pattern of auditory processing in response to sounds at the better-
608 hearing ear. At the other end of the spectrum, we identified a subgroup of patients with marked
609 auditory spatial deficits (PPC; PTA = 91 dB HL), a lack of the usual contralateral pattern of
610 auditory activation while the MMN exhibited an accentuated frontal distribution, which may
611 relate to cognitive deficits induced by the deafness.

612 *Spatial hearing and unilateral hearing loss*

613 The patients in our study had unilateral hearing loss ranging from moderate (PTA ~40dB HL)
614 to profound (>90dB HL, including total deafness), and they varied greatly in terms of their
615 spatial hearing deficit. Although hearing loss level (PTA) was not fitted in the clustering model,
616 level of hearing loss was found to correlate with the spatial deficit as reported (Firszt et al.,
617 2013; Heinrich et al., 2015; Humes et al., 1980; Nelson et al., 2019; Vannson et al., 2017).
618 However, some patients with severe hearing loss (PTA > 70dB HL) were found to have normal
619 levels of performance on sound localisation (RMS) or speech-in-noise (SRT) tasks (e.g.,
620 patients 8, 9 and 15; table 1), while others with total unilateral deafness had higher performance
621 levels than monaural controls. These results are in line with our previous study (Vannson et al.,
622 2017), where we identified two subgroups of patients who differed in terms of their SpiN

623 performance with no significant difference in their PTA, suggesting that PTA cannot be the
624 only criterion to explore auditory adaptation.

625 In the present study, a cluster analysis was run using the performance levels on tasks involving
626 binaural processing. This meant that the separation of patients into subgroups did not depend
627 on the degree of hearing loss in a strictly linear fashion. Indeed, the patients in the MPC and
628 PPC groups had similar levels of hearing loss (severe-to-profound; mean levels: 97 and 92 dB
629 HL, respectively), although the patients in the BPC group had a lower mean PTA (moderate-
630 to-severe; mean level: 51 dB HL). Despite the similar hearing levels, the MPC and PPC patients
631 differed in terms of their performance on the SpiN and sound localisation tasks; the BPC
632 patients were found to perform as well as NHS.

633 *Brain plasticity and adaptation in unilateral deafness*

634 We linked binaural performances to neural events evoked by changes in the sound location. In
635 hearing impaired patients, the ERPs evoked by different acoustic features are translated on the
636 behavioural level by similar levels of discrimination for those features (Cai et al., 2015; Ponton
637 & Don, 1995; A. Sharma et al., 1993). Similar links were also found in our study : the BPC
638 group had a mean RMS error of 15° and a MMN sensitive to 10° of deviation; in the PPC group
639 and monaural controls, the average RMS was around 50° and the MMN was correspondingly
640 absent for sound separations of 10° and 20°. In contrast, a MMN was present for all groups in
641 the case of a 100° deviation. All together, we demonstrate that MMN is an accurate neural
642 marker of spatial hearing skills.

643 Auditory processing is characterised by a contralateral ear dominance, i.e. representation of the
644 contralateral sound field in each hemisphere (Phillips & Gates, 1982). In UHL patients, this
645 cortical asymmetry is altered, with a dominance shift from contralateral to ipsilateral with
646 respect to the better-hearing ear(D. Bilecen et al., 2000; Deniz Bilecen et al., 1998). We

647 previously demonstrated (Vannson et al., 2020) that the ipsilateral shift relates to sound
648 localisation deficits, thus suggesting that the change disrupts representations of the sound field.
649 In the present study, the cluster analysis enabled the separation of patients into different groups
650 according to their binaural processing skills, irrespective of the degree of hearing loss. We
651 found that the cluster with near-normal spatial skills (BPC) presented a N100 that was larger
652 over contralateral cortex following stimulation of the better-hearing ear, as in controls. In
653 contrast, the groups with poor skills (MPC and PPC) did not show this lateralised pattern,
654 showing instead a bilateral response to monaural stimulation. These results support our previous
655 findings of an ipsilateral shift following UHL (Karoui et al., 2022; Vannson et al., 2020), and
656 are in line with our hypothesis that contralateral dominance is a functional prerequisite for
657 accurate spatial hearing and corresponds to representations of the contralateral sound field. In
658 further support of this, patients with UHL who received a cochlear implant for their deaf ear
659 have been found to have both restored auditory spatial skills (Bernstein et al., 2016; Grieco-
660 Calub & Litovsky, 2010; Vermeire & Van De Heyning, 2009; Zeitler et al., 2015) and restored
661 contralateral dominance (Debener et al., 2008; Legris Id et al., 2018; Sandmann et al., 2015).
662 The hearing controls with an earplug performed as poorly on the spatial tasks as the PPC, and
663 they did not have a significant MMN for the smaller spatial deviants. However, they were found
664 to have the normal contralateral pattern of N100 responses. Previous work has shown that UHL
665 patients with a cochlear nerve resection display a shift from contralateral to ipsilateral
666 dominance, but this can take several months (D. Bilecen et al., 2000; Burton et al., 2012). This
667 can therefore account for the normal contralateral pattern seen in the controls with an earplug,
668 as the monaural stimulation was of short duration.

669 It could be argued that the patients in the BPC group had undergone an ipsilateral shift in
670 auditory processing, but that this was reversed over time through adaptation and the use of
671 monaural spatial cues. However, this could not explain the lack of adaptation in the other patient

672 clusters, who had similar durations of deafness. Further studies are required to understand the
673 factors that may lead to or predict the auditory adaptation seen in certain patients.

674 ***Potential indication of cognitive deficits in unilateral deafness***

675 The patients in the PPC group had a marked spatial hearing deficit, which was reflected by the
676 absence of a MMN at 10° and 20° of deviations but present at 100° deviation. Thus, MMN was
677 largely generated in the frontal lobes in these patients (Deouell et al., 1998; MH et al., 1990).
678 Nonetheless, the NHS and BPC groups showed higher MMN signal in the central regions. We
679 hypothesize that this difference may relate to cognitive deficits in the PPC caused by a high
680 demand of executive resource implication to compensate for the hearing loss.

681 MMN alteration is known to be associated with cognitive decline and various neurological
682 disorders (e.g. Alzheimer's disease and schizophrenia), this alteration is usually reflected by
683 prolonged latencies, decreased amplitudes and/or a changed scalp topography. The MMN
684 alteration could be linked to an impairment in involuntary attention switching or to short-term
685 memory deficits which is necessary for the MMN to be elicited (Bennemann et al., 2013;
686 Näätänen et al., 2004). In our study, the stronger MMN signal at the frontal scalp locations in
687 the PPC group may relate to a deficit in short term memory processing as reported in adults and
688 children with hearing loss (Kral et al., 2016; Lin et al., 2013), leading to a lack of passive spatial
689 encoding in the oddball paradigm (Lin et al., 2013; M et al., 2012).

690 The increased MMN signal over the frontal regions seen in the PPC group, and to a lesser extent
691 in the MPC group, may reflect an extended brain network that compensates for the auditory
692 spatial deficit. The frontal regions have been implicated in listening effort in numerous
693 neuroimaging studies (Opitz et al., 2002; Sörqvist et al., 2016), and deficits in speech-in-noise
694 comprehension have been linked to stronger frontal activation in hearing-impaired patients
695 (Campbell & Sharma, 2013).

696 Cognitive deficit originated from a higher cognitive load and listening effort in UHL patients
697 (Opitz et al., 2002) leads to isolation and lack of communication when hearing deficit is
698 untreated. Auditory rehabilitation could have a beneficial role in delaying cognitive deficit
699 especially in the type of patients corresponding to the MPC group who are still preserving
700 executive functions reflected by pre attentive processing of spatial deviance. These patients
701 could potentially benefit from a sound amplification up to 45–60 dB HL, which could improve
702 their adaptation. Thus, audio-visual training has been shown to effectively improve spatial
703 hearing skills and adaptation strategies (Strelnikov et al., 2011; Valzolgher et al., 2022)

704 **Conclusion**

705 This study shows that a substantial proportion of patients with UHL perform at a near-normal
706 level on auditory spatial tasks, which can be attributed to adaptive strategies to compensate the
707 disruption to binaural cues. The severity of the hearing loss cannot fully account for either the
708 level of impairment on sound localisation tasks or the degree of recovery. We demonstrate that
709 the adaptation to UHL is reflected at the cortical level, as shown by differences in the auditory
710 spatial MMN that may relate to cognitive and memory deficits, including short term memory.
711 Although the mechanisms that underlie the inter-individual variability remain unclear, our
712 results imply that rehabilitation strategies would be effective either through conventional
713 hearing aids or through perceptual learning.

714

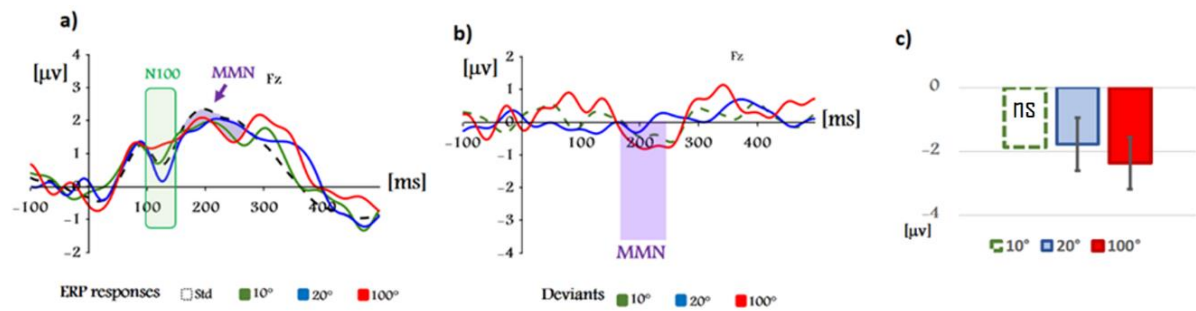
715

716 **Supplementary material**

717 *1- Results for the MPC group (behavioural and electrophysiological)*

718 The cluster analysis identified three subgroups of patients with UHL based on their performance
719 on the binaural tasks. The MPC group was found to have severe-to-profound hearing loss that
720 did not differ significantly from the PPC group (97 ± 24 dB HL vs 92 ± 23 dB HL, respectively).
721 However, the MPC group had intermediate levels of performance on the sound localisation
722 task, with significantly better scores than the PPC group (30.4 ± 7.4 vs 48.7 ± 23 ; $p < 0.005$) and
723 poorer scores than the BPC group (30.4 ± 7.4 vs 18 ± 10.4 ; $p < 0.005$); the MPC group's
724 performance was similar to the NHS with an earplug (attenuation = 39 dB; 30.4 ± 7.4 vs 39 ± 10.4 ;
725 $p = 0.26$). For the SpiN task, the MPC group had better thresholds than the PPC group (diotic
726 condition: -1.9 ± 1.5 vs 1.6 ± 2.3 ; $p < 0.05$) but poorer thresholds than the BPC group (-3 ± 3.7 ; p
727 < 0.05). These results show that performance on the different binaural tasks improves from the
728 PPC group up to the BPC group.

729 In line with the behavioural results, the MPC group showed an intermediate MMN response to
730 the spatial deviant sounds compared with the BPC and PPC groups. In the ipsilateral condition
731 (standard sound ipsilateral to the deaf ear), a MMN was evoked for all three deviant sound
732 locations in the BPC group (10° , 20° and 100° ; $p < 0.05$), for two sound locations in the MPC
733 group (20° and 100° ; $p < 0.05$) and for only one sound location in the PPC group (100° ; $p <$
734 0.05).



735

736 **Figure 11. ERP and MMN responses in MPC.** a) Event-related potentials for the standard
737 and deviant sounds in the MPC group ($n = 9$). Results are shown for the Fz electrode in the
738 ipsilateral condition (deaf side ipsilateral to the standard sound). B) Difference waveforms
739 (deviant – standard) for the three different deviant sounds. The dashed line for the 10° deviation
740 shows that the MMN was not significant according to a permutation test ($p < 0.05$). c) MMN
741 peaks at the Fz electrode (means and standard deviations for the individual values). The dashed
742 line shows that the MMN was not significant (ns).

743

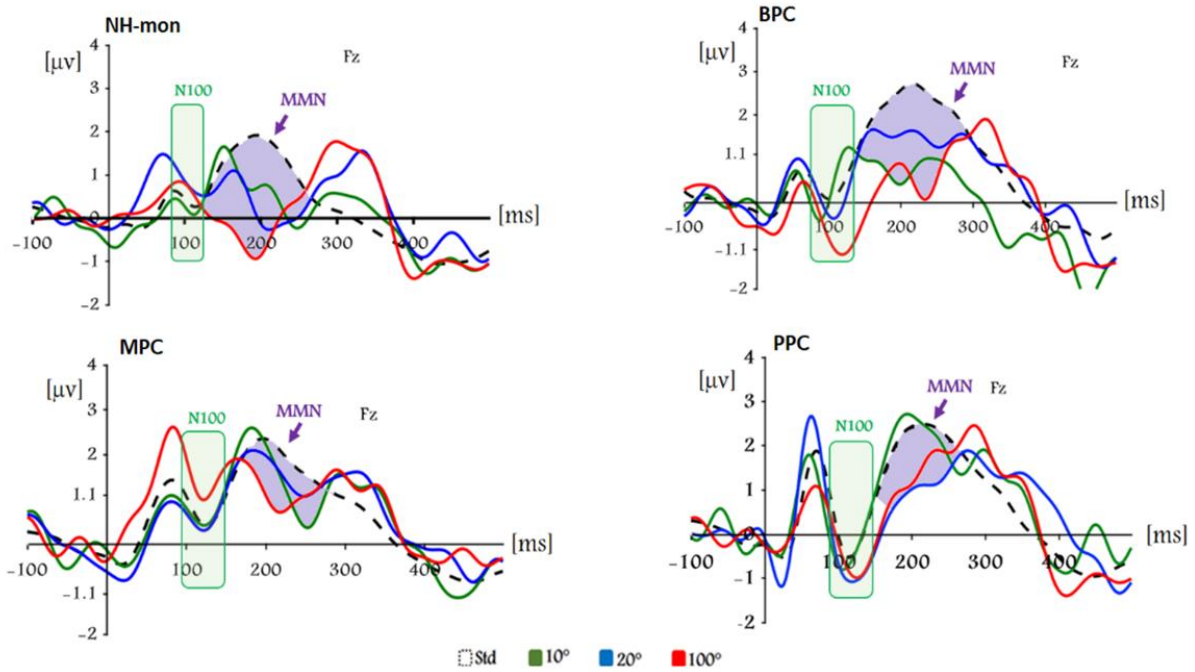
744 Altogether, the MPC group can be seen to have intermediate results for the behavioural (sound
745 localisation and SpiN) and cortical (MMN) measures, which lie between the BPC/NHS-bin and
746 PPC/NHS-mon groups. As the patients in the MPC group have severe hearing loss (97 dB HL),
747 they have presumably developed adaptive strategies that enable improved but non-optimal
748 spatial hearing.

749

750 **2- MMN in the contralateral condition**

751 Accurately locating sound sources is more difficult when sounds are presented ipsilateral to the
752 deaf/plugged ear. The MMN was analysed for this condition (ipsilateral condition) to study the
753 neural correlates of adaptive plasticity. However, the contralateral condition (standard sounds
754 presented contralateral to the deaf/plugged ear) is also of interest, as this can provide further

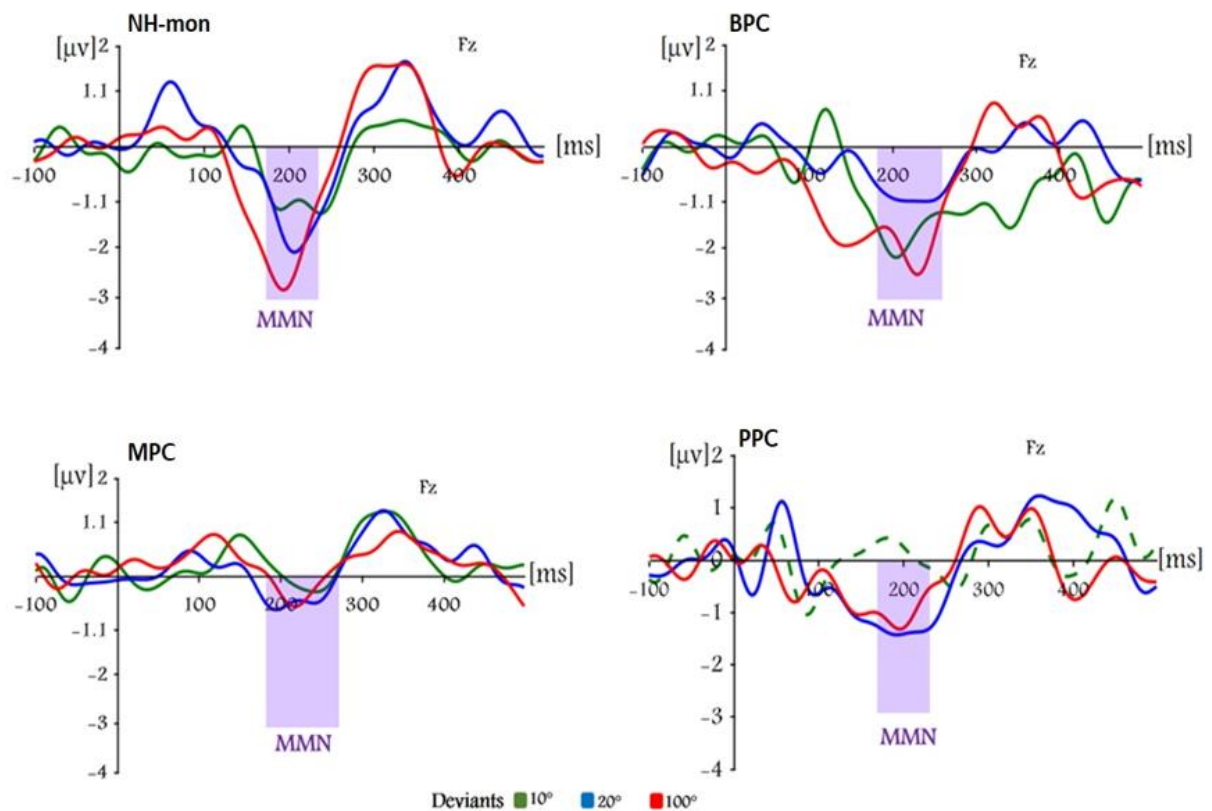
755 data concerning binaural integration and reveal differences between the ipsilateral and
756 contralateral conditions.
757



758

759 **Figure 13. Group ERPs for standard and deviants in contralateral condition.** Data are shown
760 for the Fz electrode in four groups: NH-mon ($n = 10$), BPC ($n = 6$), MPC ($n = 9$) and PPC (n
761 $= 6$). The boxes shaded in green highlight the negative deflection of the N100. The areas shaded
762 in purple represent the MMN, which is the difference between the standard and deviant
763 waveforms [6]. Note that the MMN amplitude is determined after the N100 latency window to
764 prevent the results from being affected by differences in the N100 for the standard and deviant
765 sounds.

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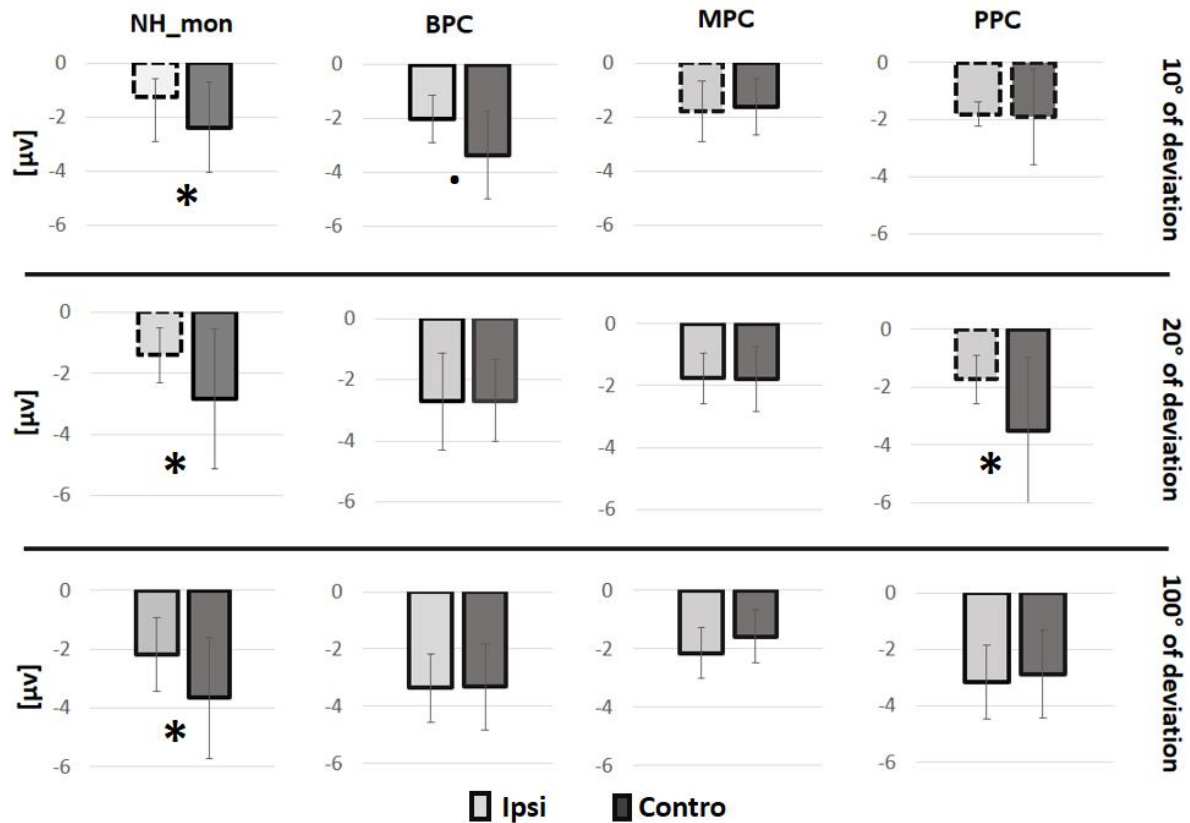
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Figure 14. Difference waveforms at the Fz electrode for the contralateral condition. The separate plots are for the four groups: NHS-mon (n = 10), BPC (n = 6), MPC (n = 9) and PPC (n = 6). A permutation test based on randomisation was run using the individual MMN peaks (identified in a ± 10 ms window around the grand average peak). This revealed a significant MMN for the three deviant positions for all groups except the PPC group, which did not have a significant MMN for the 10° deviation (green dashed line).



775
776 *Figure 15. Average individual MMN peak amplitudes at the Fz electrode for the three deviant*
777 *sounds. Results are shown for the four groups (NHS-mon, BPC, MPC and PPC) for the*
778 *ipsilateral (ipsi) and contralateral (contralat) conditions. Dashed lines represent a non-*
779 *significant MMN according to a permutation test based on randomization. Significant*
780 *differences between the contralateral and ipsilateral conditions are shown by an asterisk (* p*
781 *<0.05).*

782
783
784 For the ipsilateral condition, the permutation tests (see materials and methods) showed that
785 there was no significant MMN for the 10° and 20° deviations in the NHS-mon and PPC groups;
786 there was also no significant MMN for the 10° deviation in the MPC group. In contrast, for the
787 contralateral condition, a significant MMN was found to be present for all deviant positions in
788 all of the groups, with the sole exception of the 10° deviation in the PPC group. This result
789 implies that the PPC group still had difficulty detecting small (10°) spatial deviance when the
790 sound was presented ipsilateral to the better-hearing ear. This is not the case for the MPC group.
791 We compared the MMN amplitudes obtained for the three deviant sounds (10°, 20° and 100°),
792 the two conditions (ipsilateral and contralateral), and the different groups (NHS-mon, BPC,

793 MPC and PPC). For this, a linear mixed-effects model (lme4) was run followed by multiple
794 comparisons (glht function in R). As predicted, the side of the stimulation (deaf ear/earplug
795 ipsilateral or contralateral to the standard sound) had a large effect for the NHS-mon group,
796 with different MMN amplitudes for all three deviation positions (10°: ns vs -2.3 ± 1.6 , 20°: ns
797 vs -2.8 ± 2.2 ; 100°: -2.1 ± 1.2 vs -3.6 ± 2 , for the ipsilateral and contralateral conditions,
798 respectively). The PPC group also showed an amplitude difference between the ipsilateral and
799 contralateral conditions for the 20° deviance (ns vs -3.5 ± 2.5). However, the side of the
800 stimulation did not have a significant effect in the BPC group ($p > 0.05$). In addition, the MMN
801 amplitude for the 100° deviation did not differ significantly between the two stimulation sides
802 for any of the three patient groups ($p > 0.05$). This finding could be attributed to head-shadow
803 effects, which would enable the patients to detect spatial deviations that cross the midline,
804 irrespective of the stimulation side or level of hearing loss.

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809

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