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**Behavioral training promotes multiple adaptive processes following acute hearing loss.**

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23 **Abstract**

24 The brain possesses a remarkable capacity to compensate for changes in inputs resulting from a  
25 range of sensory impairments. Developmental studies of sound localization have shown that  
26 adaptation to asymmetric hearing loss can be achieved either by reinterpreting altered spatial  
27 cues or by relying more on those cues that remain intact. Adaptation to monaural deprivation in  
28 adulthood is also possible, but appears to lack such flexibility. Here we show, however, that  
29 appropriate behavioral training enables monaurally-deprived adult humans to exploit both of  
30 these adaptive processes. Moreover, cortical recordings in ferrets reared with asymmetric hearing  
31 loss suggest that these forms of plasticity have distinct neural substrates. An ability to adapt to  
32 asymmetric hearing loss using multiple adaptive processes is therefore shared by different  
33 species and may persist throughout the lifespan. This highlights the fundamental flexibility of  
34 neural systems, and may also point toward novel therapeutic strategies for treating sensory  
35 disorders.

36

37 **Introduction**

38 A major challenge faced by the brain is how to maintain stable and accurate representations of  
39 the world despite changes in sensory input. This is important because the statistical structure of  
40 sensory experience varies across different environments (Mlynarski and Jost, 2014; Qian et al.,  
41 2012; Seydell et al., 2010), but also because long-term changes in sensory input result from a  
42 range of sensory impairments (Feldman and Brecht, 2005; Keating and King, 2015; Sengpiel,  
43 2014). Adaptation to altered inputs has been demonstrated in different sensory systems,  
44 particularly during development, and serves to shape neural circuits to the specific inputs

45 experienced by the individual (Margolis et al., 2014; Mendonca, 2014; Schreiner and Polley,  
46 2014; Sur et al., 2013). However, many ecologically important aspects of neural processing  
47 require the integration of multiple sensory cues, either within or across different sensory  
48 modalities (Seilheimer et al., 2014; Seydell et al., 2010). A specific change in sensory input may  
49 therefore have a considerable impact on some cues whilst leaving others intact. In such cases,  
50 adaptation can be achieved in two distinct ways, as demonstrated by recent studies of sound  
51 localization following monaural deprivation during infancy (Keating et al., 2013; Keating et al.,  
52 2015).

53         Monaural deprivation alters the binaural spatial cues that normally determine the  
54 perceived location of a sound in the horizontal plane (Figure 1A) (Kumpik et al., 2010; Lupo et  
55 al., 2010). Adaptation can therefore be achieved by learning the altered relationships between  
56 particular cue values and spatial locations (Gold and Knudsen, 2000; Keating et al., 2015;  
57 Knudsen et al., 1984), a process referred to as cue remapping. However, at least in mammals,  
58 monaural spectral cues are also available to judge sound source location in both the horizontal  
59 and vertical planes (Carlile et al., 2005). These spectral cues arise from the acoustic properties of  
60 the head and external ears, which filter sounds in a direction-dependent way (Figure 1B).  
61 Monaural deprivation has no effect on the spectral cues available to the non-deprived ear. This  
62 means it is possible to adapt by learning to rely more on these unchanged spectral cues, whilst  
63 learning to ignore the altered binaural cues (Kacelnik et al., 2006; Keating et al., 2013; Kumpik  
64 et al., 2010), a form of adaptation referred to as cue reweighting.

65         Developmental studies of sound localization plasticity following monaural deprivation  
66 have found evidence for both cue remapping (Gold and Knudsen, 2000; Keating et al., 2015;  
67 Knudsen et al., 1984) and cue reweighting (Keating et al., 2013), but it is not known whether

68 these adaptive processes can occur simultaneously. Indeed, until recently, it was thought that  
69 monaural deprivation might induce different adaptive processes in different species (Keating and  
70 King, 2013; Shamma, 2015). However, whilst we now know that ferrets use both cue remapping  
71 and reweighting to adapt to monaural deprivation experienced during development (Keating et  
72 al., 2013; Keating et al., 2015), it is not known whether the same neural populations are involved  
73 in each case.

74         It is also not known whether the ability to use both adaptive processes is restricted to  
75 specific species or developmental epochs. Although the mature auditory system can adapt to  
76 monaural deprivation using cue reweighting (Kumpik et al., 2010), conflicting evidence for cue  
77 remapping has been obtained in adult humans fitted with an earplug in one ear for several days  
78 (Florentine, 1976; McPartland et al., 1997). To the extent that adaptive changes in binaural cue  
79 sensitivity are possible in adulthood, as suggested by other sensory manipulations (Trapeau and  
80 Schonwiesner, 2015), these may occur at the expense of cue reweighting. It is therefore unclear  
81 whether the same adult individuals can adapt to a unilateral hearing loss using multiple adaptive  
82 processes. Although numerous studies have shown that spatial hearing is more plastic early in  
83 life (Keating and King, 2013; Knudsen et al., 1984; Popescu and Polley, 2010), behavioral  
84 training can facilitate accommodation to altered cues in adulthood (Carlile, 2014; Carlile et al.,  
85 2014; Kacelnik et al., 2006; Shinn-Cunningham et al., 1998). Here, we show that adult humans  
86 are equally capable of using both adaptive processes, provided they are given appropriate  
87 training. Moreover, our results suggest that cue remapping and reweighting are  
88 neurophysiologically distinct, which we confirmed by recording from auditory cortical neurons  
89 in ferrets reared with an intermittent hearing loss in one ear.

90

## 91 **Results**

92 Adult humans were trained to localize sounds from 12 loudspeakers in the horizontal plane  
93 (Figure 1-figure supplement 1A) whilst wearing an earplug in one ear (~5600 trials split into 7  
94 sessions completed in < 3 weeks). In order to directly measure the efficacy of training, earplugs  
95 were worn only during training sessions. This contrasts with previous work in which adult  
96 humans received minimal training, but were required to wear earplugs for extended periods of  
97 everyday life (Florentine, 1976; Kumpik et al., 2010; McPartland et al., 1997). On ~50% of  
98 trials, subjects were required to localize flat-spectrum broadband noise (0.5-20 kHz), which  
99 provide all of the available auditory spatial cues (Blauert, 1997). With these cue-rich stimuli,  
100 trials were repeated following incorrect responses (“correction trials”) and subjects were given  
101 performance feedback. Across training sessions, sound localization performance (% correct)  
102 gradually improved (Figure 1C-F; slope values > 0; bootstrap test,  $P < 0.01$ ; Cohen’s  $d = 1.43$ ),  
103 indicating that relatively short periods of training are sufficient to drive adaptation.

104 To determine the relative contributions of cue remapping and reweighting to these  
105 changes in localization accuracy, we measured the extent of adaptation for two additional  
106 stimulus types that restrict the availability of specific cues. For these cue-restricted stimuli,  
107 which were randomly interleaved with cue-rich stimuli, correction trials were not used and no  
108 feedback was given. The first of these additional stimulus types comprised broadband noise with  
109 a random spectral profile that varied across trials (Figure 1-figure supplement 1B). These stimuli  
110 disrupt spectral localization cues because it is unclear whether specific spectral features are  
111 produced by the filtering effects of the head and ears or are instead properties of the sound itself  
112 (Figure 1B) (Keating et al., 2013). Consequently, if subjects adapt to asymmetric hearing loss by  
113 giving greater weight to the spectral cues provided by the non-deprived ear, we would expect to

114 see less improvement in sound localization performance for random-spectrum sounds than for  
115 flat-spectrum sounds. This is precisely what we found (Figure 1E, F; random-spectrum slope  
116 values < flat-spectrum slope values; bootstrap test,  $P < 0.01$ ; Cohen's  $d = 1.18$ ; see also Figure 1-  
117 figure supplement 2), indicating that adaptation involves learning to rely more on spectral cues.

118         However, if adaptation were solely dependent on this type of cue reweighting, we would  
119 expect no improvement in sound localization for narrowband sounds, such as pure tones. This is  
120 because spectral cues require a comparison of sound energy at different frequencies, which is not  
121 possible for these sounds (Figure 1B) (Carlile et al., 2005). Improved localization of pure tones  
122 would therefore indicate adaptive processing of binaural cues. Because interaural time  
123 differences (ITDs) and interaural level differences (ILDs) are respectively the primary cues for  
124 localizing low- (< 1.5 kHz) and high-frequency ( $\geq 1.5$  kHz) tones (Blauert, 1997), we tested each  
125 of these stimuli separately. To detect changes in binaural sensitivity, and facilitate comparison  
126 with previous work (Keating et al., 2015; Kumpik et al., 2010), stimulus and response locations  
127 in the front and rear hemifields were collapsed. This produces a measure of performance that is  
128 insensitive to front-back errors, which reflect failures in spectral, rather than binaural,  
129 processing. We observed improvements in subjects' ability to localize both low- and high-  
130 frequency pure tones over time, demonstrated by a decline in error magnitude (Figure 2E,F;  $\Delta$   
131 error < 0; bootstrap test,  $P < 0.01$ ). The initial bias toward the side of the open ear was also  
132 reduced (Figure 2G,H;  $\Delta$  bias < 0; bootstrap test,  $P < 0.01$ ; low-frequency, Cohen's  $d = 0.7$ ;  
133 high-frequency, Cohen's  $d = 0.96$ ). Adaptation therefore involves a shift in the mapping of  
134 altered binaural cues onto spatial location. Together, these results show that subjects adapted to  
135 monaural deprivation using a combination of both cue remapping and cue reweighting.

136 We next considered the relationship between these two adaptive processes. Although cue  
137 remapping and cue reweighting share a similar time-course (significant correlation between the  
138 amount of remapping and reweighting across sessions; Figure 3A,  $r = 0.81$ ,  $P = 0.028$ ), the  
139 overall amount of cue remapping exhibited by each subject was independent of the amount of  
140 cue reweighting (Figure 3B,  $r = 0.03$ ,  $P = 0.90$ ). This inter-subject variability was not attributable  
141 to differences in the effectiveness of earplugs used (Figure 3-figure supplement 1). Instead, we  
142 found that these two adaptive processes are affected by the frequency composition of the  
143 stimulus in different ways (Figure 3C, interaction between sound frequency and adaptation type,  
144  $P = 0.005$ , permutation test). As expected, cue reweighting was greater for frequencies where  
145 spectral cues are most prominent in humans ( $\geq 4$  kHz, Figure 3C,  $P < 0.05$ , post-hoc test; Figure  
146 3-figure supplement 2) (Blauert, 1997; Hofman and Van Opstal, 2002), whereas equal amounts  
147 of cue remapping were observed for tones above and below 4 kHz (Figure 3C,  $P > 0.05$ , post-hoc  
148 test).

149 This indicates that these adaptive processes are relatively independent of one another and  
150 suggests that they may depend on distinct neural substrates. This motivated us to revisit  
151 neurophysiological measures of cue reweighting and remapping in ferrets reared with an  
152 intermittent hearing loss in one ear (Figure 3D) (Keating et al., 2013; Keating et al., 2015). In  
153 common with our human behavioral data, we found no correlation between the degree of cue  
154 reweighting and remapping in cortical neurons recorded from ferrets raised with one ear plugged  
155 (Figure 3E,  $r = 0.08$ ,  $P = 0.073$ ). The type of plasticity observed also depended on the frequency  
156 preference of the neurons (Figure 3F, interaction between best frequency and adaptation process,  
157  $P = 0.012$ , permutation test). Greater cue reweighting was found in neurons tuned to frequencies  
158 where spectral cues are most prominent in ferrets ( $> 8$  kHz, Figure 3F,  $P < 0.05$ , post-hoc test;

159 frequency tuning bandwidth at 10 dB above threshold ( $\mu \pm SD$ ) =  $0.97 \pm 0.51$  octaves) (Carlile  
160 and King, 1994; Keating et al., 2013), whereas equal amounts of cue remapping occurred in  
161 neurons tuned to low and high frequencies (Figure 3F,  $P > 0.05$ , post-hoc test). Thus, different  
162 neurons can exhibit cue remapping and reweighting in a relatively independent manner.

163

## 164 **Discussion**

165 We have shown that adult humans can adapt to asymmetric hearing loss by both learning to rely  
166 more on the unchanged spectral localization cues available and by remapping the altered binaural  
167 cues onto appropriate spatial locations. Recent work has shown that both adaptive processes  
168 occur in response to monaural deprivation during development (Keating et al., 2013; Keating et  
169 al., 2015). Our results suggest that this flexibility is likely to be a general feature of neural  
170 processing that also occurs in adulthood. Moreover, we show that these two forms of adaptation  
171 emerge together and that remapping of binaural spatial cues occurs at low as well as high  
172 frequencies, indicating plasticity in the processing of both ITDs and ILDs.

173         Although adaptive changes in sound localization have previously been observed when  
174 human subjects wear an earplug for prolonged periods of everyday life (Kumpik et al., 2010), we  
175 found here that much shorter periods of training are sufficient to induce adaptation to an episodic  
176 hearing loss. Our results also demonstrate that subjects adapt using a combination of cue  
177 remapping and cue reweighting. In contrast, previous work has shown that cue remapping did  
178 not occur when subjects wore an earplug most of the time for several days, and were therefore  
179 able to interact with their natural environments under these hearing conditions, but received  
180 relatively little training (Kumpik et al., 2010). This suggests that the nature of adaptation may



181 depend on the behavioral or environmental context in which it occurs. Consequently, it should be  
182 possible to devise training protocols that would help subjects to adapt to altered auditory inputs  
183 in ways that do not ordinarily occur, or occur more slowly, during the course of everyday life.

184         When both adaptive processes occur together, observed either behaviourally in adult  
185 humans or neurophysiologically in monaurally-deprived ferrets, there was no obvious  
186 relationship between the amount of cue remapping and reweighting. This is at least in part  
187 because the spatial cues involved differ in their frequency dependence. Whereas equal amounts  
188 of binaural cue remapping occurred at different frequencies, spanning the range where both ITDs  
189 and ILDs are available, reweighting of spectral cues was restricted to those frequencies where  
190 these cues are most prominent. This suggests that the neural substrates for cue remapping and  
191 reweighting are at least partially distinct, with separate populations of cortical neurons displaying  
192 different types of spatial plasticity depending on their frequency preferences and sensitivity to  
193 different spatial cues.

194         It is not known, however, whether remapping and reweighting occur at different stages of  
195 the processing hierarchy. Although experience-dependent plasticity in the processing of binaural  
196 cues has been observed at multiple levels of the auditory pathway (Keating et al., 2015; Popescu  
197 and Polley, 2010; Seidl and Grothe, 2005), the changes induced by unilateral hearing loss during  
198 development are more extensive in the cortex than in the midbrain (Popescu and Polley, 2010).  
199 Much less is known about the neural processing of spectral localization cues and how this might  
200 be affected by experience (Carlile et al., 2005; Keating et al., 2013). However, reweighting of  
201 these cues is likely to reflect a change in the way they are integrated with other cues, which is  
202 thought to occur in the inferior colliculus (Chase and Young, 2005). This is consistent with the  
203 finding that adaptive changes in sound localization behavior in monaurally deprived adult ferrets

204 rely on descending projections from the cortex to the inferior colliculus (Bajo et al., 2010). It is  
205 likely therefore that adaptive plasticity emerges via dynamic interactions between different  
206 stages of processing (Keating and King, 2015).

207         Although we found evidence for both cue reweighting and cue remapping in our human  
208 behavioral and ferret neurophysiological data, the nature of the episodic hearing loss in each case  
209 was very different. Whereas ferrets had one ear occluded for ~80% of the time over the course of  
210 several months of development (Keating et al., 2013; Keating et al., 2015), adult human subjects  
211 wore an earplug for only ~7 hours in total (1 hour every 1-3 days). It is not known whether  
212 comparable physiological changes to those observed in the ferrets are responsible for the rapid  
213 shifts in localization strategy in adult human listeners following these brief periods of acute  
214 hearing loss. Nevertheless, the close similarity in the results obtained in each species has  
215 important implications for the generality of our findings.

216         Our results emphasize the flexibility of neural systems when changes in sensory input  
217 affect ethologically important aspects of sensory processing, such as sound localization. They  
218 also reveal individual differences in the adaptive strategy adopted (Figure 3B). Further work is  
219 needed to understand the causes of these differences and to determine whether knowing how  
220 different individuals adapt to hearing loss could help tailor rehabilitation strategies. Our results  
221 also highlight the importance of training in promoting multiple adaptive processes, and this is  
222 likely to be relevant to other aspects of sensory processing (Feldman and Brecht, 2005; Keating  
223 and King, 2015; Sengpiel, 2014), particularly in situations where changes in sensory input affect  
224 some cues but not others.

225

## 226 **Materials and methods**

227 All procedures conformed to ethical standards approved by the Central University Research  
228 Ethics Committee (CUREC) at the University of Oxford. All work involving animals was  
229 performed under licenses granted by the UK Home Office under the Animals (Scientific  
230 Procedures) Act of 1986. 11 audiologically normal human subjects (2 male, 9 female; aged 18-  
231 30) took part in the behavioral study and provided informed written consent. Sample size was  
232 determined on the basis of previous work, in which effect sizes of 2 – 4.6 were observed in  
233 human subjects who adapted to an earplug in one ear (Kumpik et al., 2010). To achieve a desired  
234 power of 0.8 with an alpha level of 0.001, 6-10 subjects were therefore required. All subjects  
235 provided written informed consent and were paid for their participation. Neurophysiological data  
236 were obtained from 13 ferrets (6 male, 7 female), seven of which were reared with an  
237 intermittent unilateral hearing loss, the details of which have been described previously (Keating  
238 et al., 2013). Briefly, earplugs were first introduced to the left ear of ferrets between postnatal  
239 day 25 and 29, shortly after the age of hearing onset in these animals. From then on, an earplug  
240 was worn ~80% of the time within any 15-day period, with normal hearing experienced  
241 otherwise. To achieve this, earplugs were monitored routinely and replaced or removed as  
242 necessary. All remaining ferrets were reared under normal hearing conditions. Expected effect  
243 sizes were less clear for neurophysiological changes so sample sizes were chosen based on  
244 previous studies in our lab (Dahmen et al., 2010).

245 For both human and animal subjects, hearing loss was induced by inserting an earplug  
246 into one ear (EAR Classic), which attenuated (low-pass filter, attenuation of 20-40 dB in  
247 humans, and 15-45 dB in ferrets) and delayed (150  $\mu$ s in humans and 110  $\mu$ s in ferrets)  
248 acoustical input (Keating et al., 2013; Kumpik et al., 2010). For 10 of the 11 human subjects

249 tested, we measured hearing thresholds at 1-8 kHz in octave steps and assessed the impact on  
250 those thresholds of wearing an earplug in the trained ear (Figure 3-figure supplement 1). This  
251 yielded very similar results to those reported previously in humans (Kumpik et al., 2010).

252

253 Human behaviour

254 *Apparatus*

255 All human behavioural testing was performed in a double-walled sound attenuating chamber.  
256 Stimuli were presented to subjects using a circular array (1 m radius) of 12 loudspeakers (Audax  
257 TW025M0) placed at approximately head height, with loudspeakers positioned at 30° intervals  
258 (Figure 1-figure supplement 1A). This testing apparatus was similar to that used previously for  
259 both humans (Kumpik et al., 2010) and ferrets (Keating et al., 2015). Subjects sat at the mid-  
260 point of the loudspeaker array, with their head positioned on a chin-rest, and indicated the  
261 perceived location of each sound by using a mouse to click on a custom Matlab (Mathworks)  
262 GUI that represented the locations of different loudspeakers. All stimuli were generated in  
263 Matlab, sent to a real-time processor (RP2; Tucker Davis Technologies), then amplified and  
264 routed to a particular loudspeaker using a power multiplexer (PM2R; Tucker Davis  
265 Technologies).

266 *Stimuli*

267 Stimuli consisted of either pure tones (varying in frequency from 1-8 kHz in one-octave steps) or  
268 broadband noise. All stimuli were 100 ms in duration (including 10 ms cosine ramps), generated  
269 with a sampling rate of 97.6 kHz, and presented at 49-77 dB SPL in increments of 7 dB.

270 Different intensities and stimulus types were randomly interleaved across trials. Broadband noise  
271 stimuli (0.5-20 kHz) either had a flat spectral profile (flat-spectrum) or a spectral profile that  
272 varied randomly across trials (random-spectrum). Spectral randomization was produced by  
273 adding a vector to the logarithmic representation of the source spectrum (Figure 1-figure  
274 supplement 1B). This vector was created by low-pass filtering the spectra of Gaussian noise  
275 stimuli so that all energy was removed at frequencies  $> 3$  cycles/octave (Keating et al., 2013).  
276 This removed abrupt spectral transitions to which humans are relatively insensitive (i.e. the  
277 width of any remaining peaks and notches exceeded  $1/6^{\text{th}}$  of an octave) (Hofman and Van Opstal,  
278 2002). The RMS of this vector was then normalized to 10 dB.

279         These random-spectrum stimuli allowed us to determine which spectral features are  
280 behaviorally important (see Figure 3-figure supplement 2), whilst making very few assumptions  
281 about the nature of these features in advance. Their unpredictable nature also prevented subjects  
282 from learning which spectral features were properties of the sound source. If subjects had learned  
283 that particular spectral features were invalid cues to sound location (i.e. they were not caused by  
284 the filtering effects of the head and ears and were instead properties of the sound source), they  
285 might have learned to ignore these features when judging sound location. This would have  
286 prevented us from measuring cue reweighting because our ability to do so requires subjects to  
287 misattribute spectral properties of the stimulus to the filtering effects of the head and ears.

## 288 *Training*

289 Subjects were initially familiarized with the task under normal hearing conditions, receiving  
290 feedback for all stimuli. Once an asymptotic level of performance was reached, they were trained  
291 to localize sounds whilst wearing an earplug in either the left (8 subjects) or right (3 subjects)

292 ear. Subjects completed 7 training sessions over ~3 weeks, with no more than 2 days between  
293 each session. Each session comprised ~800 trials and lasted ~45 minutes, with short breaks  
294 provided every ~15 minutes. Whilst undergoing training with an earplug in place, feedback was  
295 only provided for flat-spectrum broadband noise stimuli.

296 On trials where feedback was provided, correct responses were followed by a brief period  
297 during which the GUI background flashed green, with the GUI background flashing red for  
298 incorrect responses. The overall % correct score achieved for all feedback trials was also  
299 displayed by the GUI. Where feedback was given, incorrect responses were followed by  
300 “correction trials” on which the same stimulus was presented. Successive errors made on  
301 correction trials were followed by “easy trials”, on which the stimulus was repeated continuously  
302 until subjects made a response. Recent work has shown that head-movements may enhance  
303 adaptation to changes in auditory spatial cues (Carlile et al., 2014). On easy trials, subjects were  
304 therefore allowed to move their heads freely until a response was made. Subjects were also not  
305 allowed to respond during the first 3 s of easy trials (i.e. any responses made during this period  
306 were ignored), which was visually indicated to subjects by the GUI background turning blue. In  
307 previous work, ferrets received broadly similar feedback when performing a sound localization  
308 task (i.e. incorrect trials were followed by correction trials and easy trials, with the latter  
309 allowing for the possibility of head-movements) (Keating et al., 2013; Keating et al., 2015).  
310 However, instead of a GUI, ferrets received a small water reward for physically approaching the  
311 correct speaker location whilst the absence of water reward indicated an incorrect response.

312

313 *Analyses*

314 Sound localization performance for pure tones was calculated by first collapsing stimulus and  
315 response locations in the front and rear hemifields. This was done to provide a measure of  
316 performance that is unaffected by front-back errors, which primarily reflect a failure in spectral,  
317 rather than binaural, processing. To facilitate comparison with previous work (Keating et al.,  
318 2015), the average error magnitude (mean unsigned error) was then used to quantify the  
319 precision of these sound localization responses. The mean signed error was also calculated to  
320 provide a measure of sound localization bias (Kumpik et al., 2010). Although we measured cue  
321 remapping at a number of frequencies above 1.5 kHz (2, 4 and 8 kHz), we found comparable  
322 training-induced changes in both bias (Kruskal-Wallis test,  $P = 0.18$ ) and error magnitude  
323 (Kruskal-Wallis test,  $P = 0.58$ ). These data were therefore pooled to facilitate comparison  
324 between cue remapping for tones above and below 1.5 kHz, which should respectively reflect  
325 changes in ILD and ITD processing (Blauert, 1997).

326 To assess the extent of cue reweighting at different frequencies, we used a method based  
327 on reverse correlation, which reveals the frequencies where spectral cues become more  
328 behaviorally important with training (Figure 3-figure supplement 2) (Keating et al., 2013). Note  
329 that the scale of the reverse correlation map (RCM) does not necessarily resemble that of the  
330 HRTF because the RCM is affected by the amount of spectral randomization present in stimuli  
331 (greater randomization typically produces larger RCM features) as well as the dependence on  
332 individual spectral features for localizing sounds in particular directions (i.e. if responses to a  
333 particular location can be induced by multiple spectral features or cues, then any given feature  
334 will not always be present when responses are made to that location; averaging over these data  
335 therefore reduces the scale of features detected by reverse correlation).

336 This analysis showed that training increased the behavioral importance of spectral cues at  
337 frequencies  $\geq 4$  kHz, but not below (Figure 3-figure supplement 2). In other words, we found  
338 greater reweighting of spectral cues at higher frequencies. This is consistent with human head-  
339 related transfer functions, which show that spectral cues are most prominent at frequencies  $\geq 4$   
340 kHz (Blauert, 1997; Hofman and Van Opstal, 2002). For frequencies above and below 4 kHz, we  
341 therefore calculated the average change in spectral feature strength separately, which provided a  
342 low- and high-frequency measure of cue reweighting. To facilitate comparison between different  
343 adaptive measures, we also separately calculated the average amount of cue remapping for tones  
344 above and below 4 kHz. Measures for different adaptive processes, which are expressed in  
345 different units, were then standardized by converting them to z scores.

346

## 347 Neurophysiology

348 All neurophysiological procedures have been previously described in detail (Keating et al., 2013;  
349 Keating et al., 2015). Bilateral extracellular recordings were made under medetomidine/ketamine  
350 anaesthesia from primary auditory cortex units ( $n = 505$ ) in response to virtual acoustic space  
351 stimuli generated from acoustical measurements in each animal. These stimuli recreated the  
352 acoustical conditions associated with either normal hearing or an earplug in the left ear and were  
353 used to manipulate individual spatial cues independently of one another.

354 Cue weights were determined by calculating the mutual information between neuronal  
355 responses and individual spatial cues. A weighting index was then used to calculate the weight  
356 given by each neuron to spectral cues provided by the right ear (i.e. contralateral to the  
357 developmentally-occluded ear) relative to all other available cues. The mapping between



358 binaural spatial cues and neurophysiological responses was measured by determining the best  
359 ILD for each unit, which represented the ILD corresponding to the peak of the binaural  
360 interaction function (see Keating et al., 2015 for more details). Best ILDs and weighting index  
361 values were converted to z scores using the corresponding means and standard deviations of data  
362 obtained from controls. Data were normalized separately for different hemispheres and  
363 frequency bands. Measures of cue reweighting and remapping for each unit therefore  
364 respectively reflected changes in weighting index values and best ILDs relative to those observed  
365 in controls.

366         Frequency tuning was calculated using 50-ms tones (0.5 – 32 kHz in 0.25 octave steps,  
367 varying between 30 – 80 dB SPL in increments of 10 dB). Characteristic frequency (CF) and  
368 bandwidth were calculated in a manner similar to that described previously (Bartlett et al., 2011;  
369 Bizley et al., 2005). Briefly, firing rates were averaged across stimulus repetitions (n = 30) of  
370 each combination of frequency and level. This matrix was then smoothed with a boxcar function  
371 0.75 octaves wide, following which a threshold was applied that was equal to the spontaneous  
372 rate plus 20% of the maximum firing rate. CF was defined as the frequency that elicited the  
373 greatest response at threshold. Bandwidth was measured at 10 dB above threshold by first  
374 calculating the area underneath the tuning curve. We then identified a rectangle that had the same  
375 area but constrained its height to be equal to the maximum firing rate. The width of this rectangle  
376 then provided a measure of bandwidth that approximates the width at half-maximum for a  
377 Gaussian tuning curve (Bartlett et al., 2011).

378

379 Statistical analyses

380 Confidence intervals at the 95% level were estimated empirically for different measures using  
381 10,000 bootstrapped samples, each of which was obtained by re-sampling with replacement from  
382 the original data. These samples were then used to construct bootstrapped distributions of the  
383 desired measure, from which confidence intervals were derived. A bootstrap procedure was also  
384 used to assess the significance of group differences. First, the difference between two groups was  
385 measured using an appropriate statistic (e.g. difference in means, t-statistic, or rank-sum  
386 statistic). The data from different groups were then pooled and re-sampled with replacement to  
387 produce two new samples, and the difference between these samples was measured using the  
388 same statistic as before. This procedure was subsequently repeated 10,000 times, which provided  
389 an empirical estimate of the distribution that would be expected for the statistic of interest under  
390 the null hypothesis. This bootstrapped distribution was then used to derive a *P* value for the  
391 difference observed in the original sample. In all cases, two-sided tests of significance were used,  
392 with Bonferroni correction used to correct for multiple comparisons. Cohen's *d* was also  
393 calculated to provide a measure of the effect size for different types of adaptation in adult  
394 humans.

395         The significance of factor interactions was also assessed using permutation tests (Manly,  
396 2007). This involved randomly permuting observations across different factors and calculating  
397 an *F* statistic for each factor and interaction (i.e. the proportion of variance explained relative to  
398 the proportion of unexplained variance). This procedure was repeated many times in order to  
399 assess the percentage of repetitions that produce *F* values greater than those obtained for the non-  
400 permuted data. This percentage then provided an estimate of the *P* values associated with each  
401 effect under the null hypothesis. Precise details of the permutation procedure used have been  
402 described elsewhere (Manly, 2007). Additional comparisons between conditions were made

403 using appropriate post-hoc tests corrected for multiple comparisons. Although bootstrap and  
404 permutation tests were used because they make fewer distributional assumptions about the data,  
405 conventional parametric and non-parametric statistical tests were also performed and produced  
406 very similar results (not reported).

407

#### 408 **Author contributions**

409 This study was conceived and designed by P.K. and A.J.K. The behavioral experiments were  
410 performed by P.K., O.R.P. and O.B. The electrophysiological recordings were carried out by  
411 P.K. and J.C.D. Data analysis was performed by P.K. and O.R.P. The paper was written by P.K.,  
412 O.R.P. and A.J.K.

413

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416 (WT076508AIA) to A.J.K.

417

418

419 **Figure 1.** Effect of training on localization of broadband noise stimuli in the horizontal plane by monaurally  
420 deprived human listeners. **(A)** When one of these sounds is presented on one side of the head, it will be louder and  
421 arrive earlier at the ipsilateral ear (blue), producing interaural time and level differences, which are respectively the  
422 primary cues to sound location at low and high frequencies. **(B)** Because of acoustic filtering by the head and ears,  
423 the spectrum of a sound at the tympanic membrane (post-filtering, color) differs from that of the original sound (pre-  
424 filtering, black) and varies with location (amplitude in dB is plotted as a function of frequency; color indicates  
425 different locations). These spectral cues make it possible to localize sounds using a single ear, but only for sounds  
426 that have relatively flat spectra (solid lines) and are sufficiently broadband (shape of spectra in narrow frequency  
427 bands varies little with location – see shaded gray region). When spectral features are artificially added to the pre-  
428 filtered sound source (dotted lines), these added features can be misattributed to the filtering effects of the head and

429 ears. This produces sound localization errors (e.g. dotted green spectrum is more easily confused with solid  
430 turquoise spectrum because of additional peak at high frequencies). The extent of these errors allows us to infer  
431 subjects' reliance on spectral cues. **(C, D)** Joint distribution of stimulus and response obtained from the first (C) and  
432 last (D) training session for an individual subject with an earplug in the right ear. Grayscale indicates the number of  
433 trials corresponding to each stimulus-response combination. Data are shown for trials on which flat-spectrum stimuli  
434 were used (i.e. all spatial cues were available). **(E)** Sound localization performance (% correct) as a function of  
435 training session for the same subject. Scores for each session (dots) were fitted using linear regression (lines) to  
436 calculate slope values, which quantified the rate of adaptation. Relative to flat-spectrum stimuli (blue), much less  
437 adaptation occurred with random-spectrum stimuli (pink), which limit the usefulness of spectral cues to sound  
438 location (Figure 1-figure supplement 1). **(F)** Adaptation rate is shown for flat- and random-spectrum stimuli for each  
439 subject (gray lines;  $n = 11$ ). Positive values indicate improvements in localization performance with training. Mean  
440 adaptation rates across subjects ( $\pm$  bootstrapped 95% confidence intervals) are shown in blue and pink. Similar  
441 results are observed if front-back errors are excluded and changes in error magnitude are calculated (Figure 1-figure  
442 supplement 2). Dotted black lines indicate adaptation rates observed previously in humans (Kumpik et al., 2010;  
443 total adaptation reported divided by number of sessions,  $n = 8$ ).

444

445 **Figure 2.** Effect of training on localization of pure tone stimuli in the horizontal plane by monaurally deprived  
446 human listeners. **(A-D)** Joint distributions of stimulus and response obtained from the first (A,C) and last (B,D)  
447 training sessions for low- (A,B) and high-frequency (C,D) tones. Data are shown for an individual subject wearing  
448 an earplug in the left ear, with grayscale indicating the number of trials corresponding to each stimulus-response  
449 combination. Because pure tones can be accurately localized only by using binaural spatial cues, which are  
450 susceptible to front-back errors, data from the front and rear hemifields have been collapsed. **(E)** Mean error  
451 magnitude plotted as a function of training session for the same subject shown in A-D. Data are plotted separately  
452 for low- (1 kHz, dark blue) and high-frequency (8 kHz, light blue) tones. Scores for each session (dots) were fitted  
453 using linear regression (lines) to calculate slope values, which quantified the change in error magnitude ( $\Delta$  error)  
454 with training. Improved performance was associated with a reduction in error magnitude, producing negative values  
455 for  $\Delta$  error. **(F)**  $\Delta$  error for low- and high-frequency tones plotted for each subject (gray lines;  $n = 11$ ). Mean values  
456 for  $\Delta$  error across subjects ( $\pm$  bootstrapped 95% confidence intervals) are shown in blue. Although there are  
457 pronounced individual differences for the adaptation observed at the two tone frequencies, almost all values are  $< 0$ ,  
458 indicating that error magnitude declined over the training sessions. Dotted red line shows  $\Delta$  error values that would  
459 have been observed if subjects had adapted as well as ferrets reared with a unilateral earplug (Keating et al. 2015;  
460 total  $\Delta$  error reported for ferrets was divided by the number of training sessions used in the present study,  $n = 7$ ;  
461 normalization used in previous work has been removed to facilitate comparison). **(G)** Bias in sound localization  
462 responses plotted as a function of training session for the subject in E. Positive values indicate that responses were  
463 biased toward the side of the open ear. Data are plotted separately for low- (1 kHz, dark blue) and high-frequency (8  
464 kHz, light blue) tones. Scores for each session (dots) were fitted using linear regression (lines) to calculate slope  
465 values, which quantified the change in response bias ( $\Delta$  bias) with training. Negative values of  $\Delta$  bias indicate a shift  
466 in response bias toward the side of the plugged ear. **(H)**  $\Delta$  bias for low- and high-frequency tones plotted for each  
467 subject (gray lines;  $n = 11$ ). Mean values for  $\Delta$  bias across subjects ( $\pm$  bootstrapped 95% confidence intervals) are  
468 shown in blue.

469

470 **Figure 3.** Relationship between different adaptive processes. **(A)** Time-course of behavioral adaptation for adult  
471 humans, measured by the amount of cue reweighting (pink) and remapping (blue). Data are normalized (z scores) to  
472 facilitate comparison between different adaptation measures. All data have been averaged across subjects. **(B)**  
473 Comparison between the amount of behavioral cue reweighting and remapping for individual human subjects (black  
474 dots;  $n = 11$ ). Variation in the degree of adaptation across subjects was not attributable to differences in earplug  
475 effectiveness (Figure 3-figure supplement 1). **(C)** Amount of cue remapping (blue) and cue reweighting (pink)  
476 observed at frequencies above (lighter shades) and below (darker shades) 4 kHz. Greater reweighting of spectral  
477 cues (more positive values) is observed  $> 4$  kHz, which is where spectral cues are most prominent in humans.  
478 Frequency-specific measures of cue reweighting were determined using reverse correlation (see Methods, Figure 3-  
479 figure supplement 2). **(D)** Bilateral extracellular recordings were performed in the primary auditory cortex of ferrets  
480 reared with an earplug in one ear. These data were then compared with controls to obtain measures of cue

481 reweighting and cue remapping (see Methods). **(E)** Cue reweighting versus cue remapping, with each dot  
482 representing either a single neuron or small multi-unit cluster ( $n = 505$ ). **(F)** Amount of cue remapping (blue) and  
483 cue reweighting (pink) observed for neurons tuned to frequencies above (lighter shades) or below (darker shades) 8  
484 kHz. Greater reweighting of spectral cues (more positive values) is observed  $> 8$  kHz, which is where spectral cues  
485 are most prominent in ferrets. Relative to humans, spectral cues in ferrets are shifted toward higher frequencies  
486 because of differences in head and external ear morphology.

487

488 **Figure 1-figure supplement 1.** Experimental setup and stimuli. **(A)** Schematic illustrating the circular loudspeaker  
489 array used for sound localization training. Subjects sat at the centre of this array, facing in the direction indicated by  
490 the arrow. **(B)** Spectral profile for a random-spectrum stimulus (black). Spectra were filtered to eliminate abrupt  
491 spectral transitions to which the auditory system is insensitive (see Methods). The overall amount of spectral  
492 randomization was also fixed on each trial ( $SD = 10$  dB). Although the spectrum varied considerably across trials  
493 (many different examples are shown in gray), the mean spectrum was relatively flat (red). **(C)** Our randomization  
494 procedure allowed us to set the amount of randomization and overall level of each stimulus, but these parameters  
495 could still vary within individual frequency bands. We can measure this for a single stimulus by dividing its  
496 spectrum (gray) into one-octave bands and calculating the mean  $\pm$  SD amplitude values for each band (black). This  
497 indicates that the level (mean) and amount of randomization (SD) of each frequency band fluctuates on each trial.  
498 **(D,E)** To determine whether these differences have an impact on sound localization, we compared the random-  
499 spectrum stimuli presented on correct (pink) and incorrect (blue) trials. Relative to mislocalized stimuli, we found  
500 that the amount of spectral randomization was smaller for correctly localized stimuli, but only at higher frequencies  
501 (D, indicated by asterisk; significant interaction between frequency and correctness of response,  $P < 0.001$ ,  
502 ANOVA;  $P < 0.05$ , post hoc test). In other words, the spectra of correctly-localized sounds tended to be relatively  
503 flat at high frequencies. No differences in sound level were observed between stimuli on correct and incorrect trials  
504 (E). Data show mean  $\pm$  SEM. **(F)** To understand the implications of this for sound localization, we subdivided trials  
505 into groups (deciles) based on the amount of spectral randomization at high frequencies (1<sup>st</sup> decile represents 10% of  
506 trials with the smallest amount of spectral randomization) and quantified sound localization accuracy (% correct) for  
507 each group. This indicates that some of our random-spectrum stimuli were more difficult to localize than others,  
508 with performance declining as spectral randomization increased at high frequencies. It also supports the view that  
509 increasing amounts of spectral randomization progressively degrade the usefulness of spectral cues, which are most  
510 prominent at high frequencies.

511

512 **Figure 1-figure supplement 2.** Effect of training on localization by human listeners of broadband stimuli using  
513 same analysis method as for narrowband stimuli in Figure 2. **(A-D)** Joint distributions of stimulus and response  
514 obtained from the first (A,C) and last (B,D) training sessions for flat- (A,B) and random-spectrum (C,D) stimuli.  
515 Data are shown for an individual subject wearing an earplug in the left ear, with grayscale indicating the number of  
516 trials corresponding to each stimulus-response combination. Stimulus- and response-locations in the front and rear  
517 hemifields have been collapsed to provide a measure of sound localization that is insensitive to front-back errors.  
518 **(E)** Mean error magnitude plotted as a function of training session for the same subject shown in A-D. Data are  
519 plotted separately for flat- (turquoise) and random-spectrum (red) stimuli. Scores for each session (dots) were fitted  
520 using linear regression (lines) to calculate slope values, which quantified the change in error magnitude ( $\Delta$  error)  
521 with training. Improved performance was associated with a reduction in error magnitude, producing negative values  
522 for  $\Delta$  error. **(F)**  $\Delta$  error for flat- and random-spectrum stimuli plotted for each subject (gray lines;  $n = 11$ ). Mean  
523 values for  $\Delta$  error across subjects ( $\pm$  bootstrapped 95% confidence intervals) are shown in color. Adaptation occurs  
524 for both flat- and random-spectrum stimuli ( $\Delta$  error values are significantly  $< 0$ ;  $P < 0.01$ , bootstrap test), but the  
525 extent of adaptation is greater for flat-spectrum stimuli ( $P < 0.01$ , bootstrap test on the within-subject differences in  
526  $\Delta$  error). **(G)** Bias in sound localization responses plotted as a function of training session for the subject in E.  
527 Positive values indicate that responses were biased toward the side of the open ear. Data are plotted separately for  
528 flat- (turquoise) and random-spectrum (red) stimuli. Scores for each session (dots) were fitted using linear regression  
529 (lines) to calculate slope values, which quantified the change in response bias ( $\Delta$  bias) with training. Negative values  
530 of  $\Delta$  bias indicate an adaptive shift in response bias toward the side of the plugged ear. **(H)**  $\Delta$  bias for flat- and  
531 random-spectrum stimuli plotted for each subject (gray lines;  $n = 11$ ). Mean values for  $\Delta$  bias across subjects ( $\pm$

532 bootstrapped 95% confidence intervals) are shown in color. No changes in bias were observed for either stimulus  
533 type ( $\Delta$  bias values do not deviate significantly from 0;  $P > 0.05$ , bootstrap test).

534

535 **Figure 3-figure supplement 1.** Variation across subjects in the degree of adaptation to acute asymmetric hearing  
536 loss is not related to differences in earplug effectiveness. **(A)** Effect of earplug on mean hearing threshold ( $\Delta$   
537 threshold  $\pm$  SD) is plotted as a function of frequency. Positive values indicate thresholds were higher when an  
538 earplug was worn. Data from Kumpik et al. (2010) are replotted (red) alongside those from the present study (black).  
539 For visualization purposes, symmetric displacements along the x-axis have been introduced to each dataset. **(B)** A  
540 significant correlation ( $P < 0.05$ ) was observed between  $\Delta$  threshold and the initial drop in sound localization  
541 performance when an earplug was worn during the first training session ( $\Delta$  performance; change in % correct  
542 relative to normal hearing conditions averaged across all stimulus types). In other words, initial sound localization  
543 deficits were more extensive when the earplug produced greater attenuation. Each dot represents an individual  
544 subject. **(C,D)** No obvious relationship was observed between  $\Delta$  threshold and the degree of remapping (C) or  
545 reweighting (D) observed in individual subjects (dots).

546

547 **Figure 3-figure supplement 2.** Determining the behavioral importance of spectral features at different frequencies  
548 using reverse correlation. **(A)** Although the mean spectrum of random-spectrum stimuli was close to zero when  
549 averaged across all trials (black), distinct spectral features emerged when averaging was restricted to trials on which  
550 subjects responded to a particular location (gray/color). This provides insight into which spectral features influence  
551 sound localization behavior. To reduce the noise in this estimate, a threshold was applied (mean  $\pm$ 1.5 SD, dashed  
552 lines) and this process was repeated for each response location to construct a reverse correlation map. **(B)** Reverse  
553 correlation map showing the mean stimulus spectrum associated with each response location. Color is proportional  
554 to spectral amplitude, as illustrated in A. In order to quantify the behavioral importance of spectral features in  
555 different frequency bands, we calculated the ‘feature strength’ by averaging the unsigned magnitude of these  
556 spectral features across locations. **(C)** Cue reweighting plotted as a function of frequency. Cue reweighting was  
557 estimated by calculating training-induced changes in feature strength (i.e. feature strength values obtained in the first  
558 session were subtracted from those obtained in subsequent sessions; these differences in feature strength were then  
559 averaged). Positive cue reweighting values indicate an increase in feature strength, which reflects increased  
560 behavioral importance of spectral cues. Dotted line shows the upper 95% confidence interval for cue reweighting  
561 values that would be expected under the null hypothesis that cue reweighting did not occur. Values above this line  
562 (red symbols) indicate cue reweighting values that are significantly greater than chance.

563

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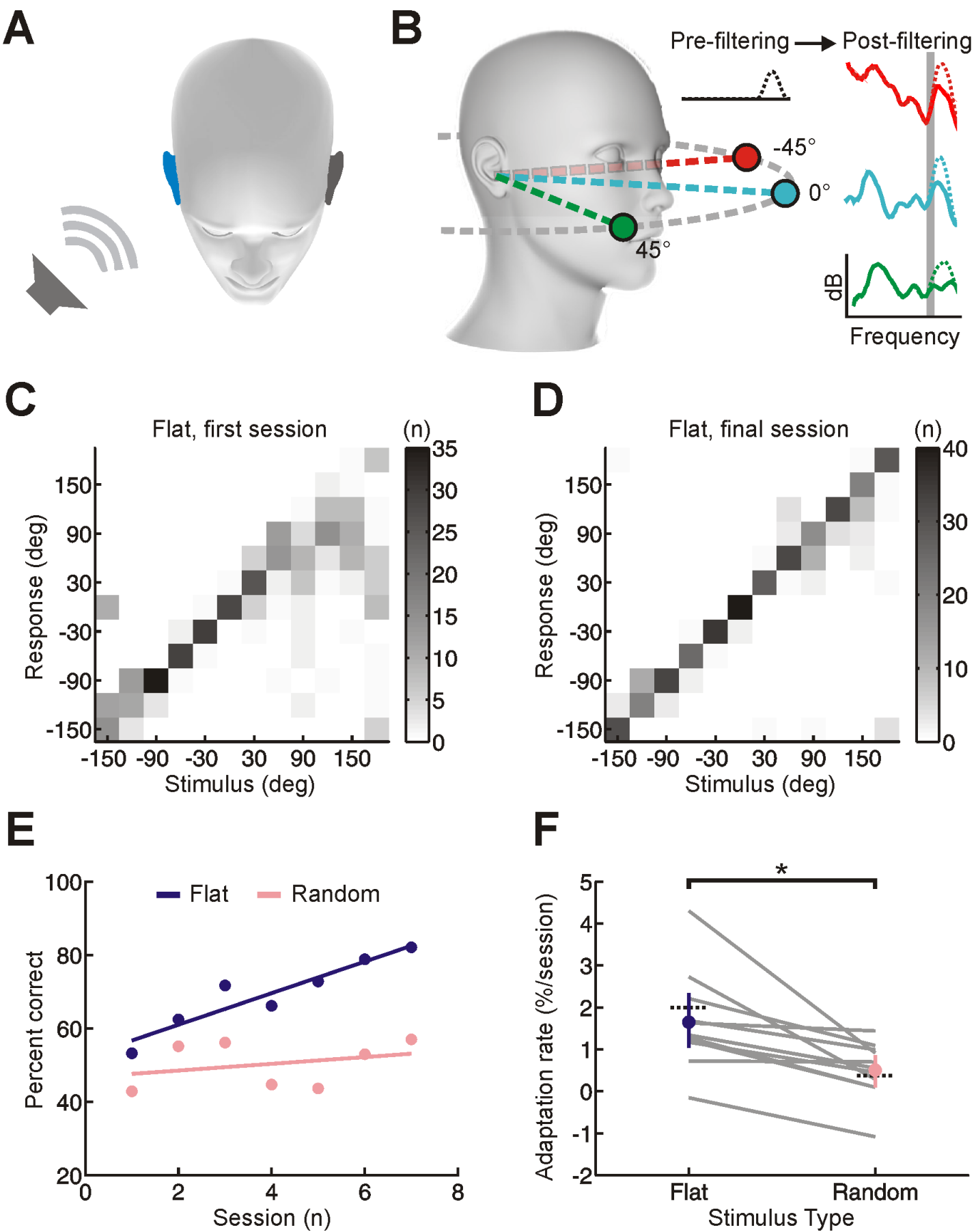
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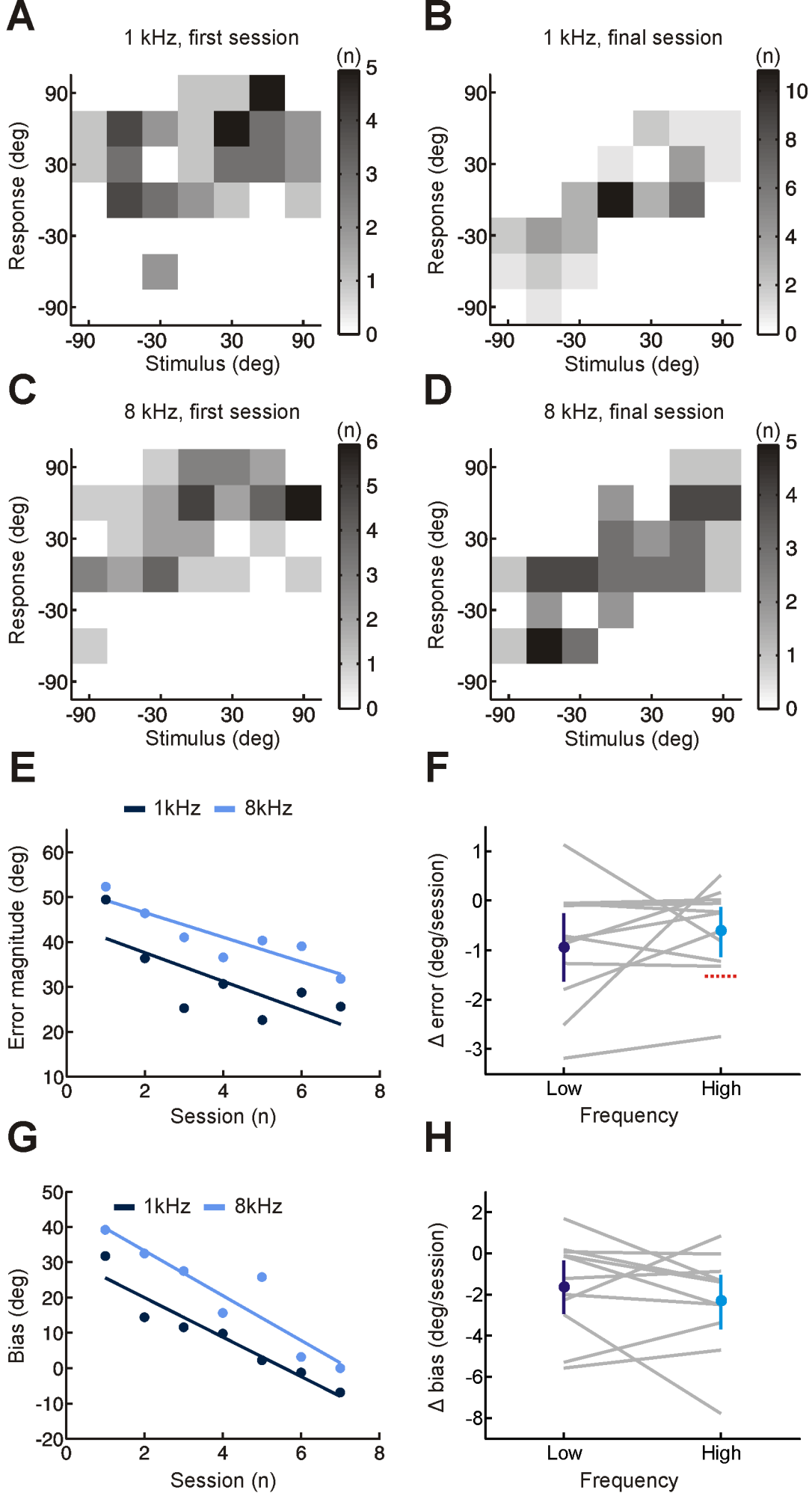
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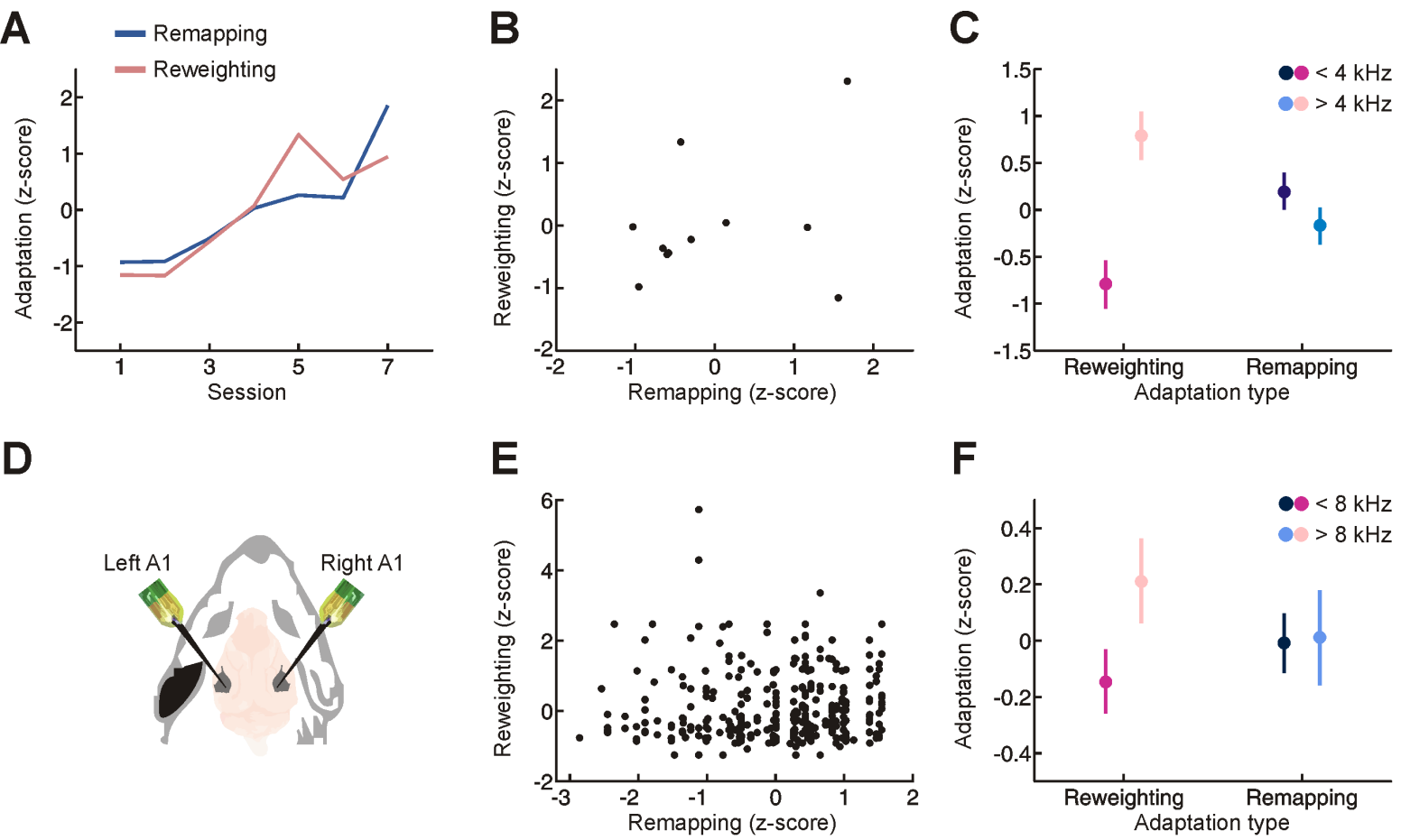




**Figure 1**



**Figure 2**



**Figure 3**