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A neural signature of regularity in sound is reduced in older adults

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26

27   Abstract

28 Sensitivity to repetitions in sound amplitude and frequency is crucial for sound perception. As with other

29 aspects of sound processing, sensitivity to such patterns may change with age, and may help explain

30 some age-related changes in hearing such as segregating speech from background sound. We recorded

31 magnetoencephalography to characterize differences in the processing of sound patterns between

32 younger and older adults. We presented tone sequences that either contained a pattern (made of a

33 repeated set of tones) or did not contain a pattern. We show that auditory cortex in older, compared to

34 younger, adults is hyperresponsive to sound onsets, but that sustained neural activity in auditory cortex,

35 indexing the processing of a sound pattern, is reduced. Hence, the sensitivity of neural populations in

36 auditory cortex fundamentally differs between younger and older individuals, overresponding to sound

37 onsets, while underresponding to patterns in sounds. This may help to explain some age-related changes

38 in hearing such as increased sensitivity to distracting sounds and difficulties tracking speech in the

39 presence of other sound.

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Introduction

Many adults aged 50 or older experience challenges understanding speech in the presence of background sound (Pichora-Fuller, 2003; Pichora-Fuller et al., 2016), but the underlying neural sources contributing to such deficits are not fully understood. Speech contains rich, regular patterns, such as quasi-regular amplitude fluctuations at 4–5 Hz (Rosen, 1992; Varnet et al., 2017), and perceptual sensitivity to sound pattern and speech-in-noise perception correlate with each other (Holmes and Griffiths, 2019), suggesting shared mechanisms (Holmes et al., 2021). The perceptual processes through which sensitivity to such patterns may contribute to speech perception likely include the segregation of unique, concurrent sound streams (Schröger, 2005, 2007; Snyder and Alain, 2007; Winkler et al., 2009; Bendixen, 2014) and the recognition and prediction of relevant sound features (Jones and Boltz, 1989; Nobre et al., 2007; Henry and Herrmann, 2014; Nobre and van Ede, 2018). The current study is concerned with the degree to which patterns are represented in the brains of older individuals and whether neural sensitivity to patterns differs between younger and older adults.

The detection of a regular pattern in a sound is associated with an increase in a sustained, low-frequency, DC power offset in cortical electroencephalography (EEG) and magnetoencephalography (MEG) recordings (Barascud et al., 2016; Southwell et al., 2017; Herrmann and Johnsrude, 2018b). Sustained neural activity manifests as soon as a pattern, such as repetition of a set of tones, is present (Southwell et al., 2017; Herrmann and Johnsrude, 2018b; Southwell and Chait, 2018; Herrmann et al., 2021). It also manifests for spectrally coherent chord fluctuations (Teki et al., 2016), complex sounds made of isochronous tone sequences (Sohoglu and Chait, 2016), and repeated amplitude or frequency modulations (Gutschalk et al., 2002; Ross et al., 2002; Herrmann and Johnsrude, 2018b; Herrmann et al., 2019). Sustained activity increases with the degree of regularity of a pattern, for example, with increasingly coherent frequency modulation in sounds (Teki et al., 2016; Herrmann and Johnsrude, 2018b). The magnitude of sustained activity is thought to reflect prediction-related processes (Heilbron and Chait, 2018).

Accumulating evidence suggests that aging and age-related hearing loss are associated with a loss of inhibition throughout the auditory pathway following peripheral decline (Caspary et al., 2008; Rabang et al., 2012; Ouellet and de Villers-Sidani, 2014). This may render neurons in the aged auditory system hyperresponsive to sound (Hughes et al., 2010; Alain et al., 2012; Bidelman et al., 2014; Overton

79   and Recanzone, 2016; Presacco et al., 2016b, a; Herrmann et al., 2018) and shorten the time it takes for

80   neurons to regain responsiveness following adaptation to sound (de Villers-Sidani et al., 2010; Mishra et

81   al., 2014; Herrmann et al., 2016; Herrmann et al., 2019). Changes in inhibition, responsivity, and

82   adaptation associated with aging and hearing loss likely affect all aspects of hearing (Herrmann and

83   Butler, 2021), including sensitivity to sound patterns.

84   Some initial evidence suggests that sustained neural activity may be reduced in older compared

85   to younger people. Many years ago, Pfefferbaum and colleagues (1979) demonstrated that sustained

86   activity elicited by a short sine tone is reduced for older compared to younger adults. More recent work

87   indicates that younger individuals exhibit pattern-related sustained activity in response to amplitude-

88   modulated sounds, whereas older adults do not appear to, although the difference between these

89   groups was not significant (Herrmann et al., 2019). Another study yielded data suggestive of reduced

90   sustained activity in older compared to younger people in response to repeated tone sequences (Al Jaja

91   et al., 2020), but stimulus parameters differed between age groups in this paper. A controlled

92   experiment with sufficient power is thus required to elucidate whether sustained neural activity to

93   regular sound patterns differs between younger and older people.

94   Previous work investigating sustained neural activity in older adults has utilized low-density

95   electroencephalography (EEG; fewer than 20 electrodes; Pfefferbaum et al., 1979; Herrmann et al.,

96   2019; Al Jaja et al., 2020). This type of EEG is not very well suited for the localization of neural sources

97   generating scalp-recorded signals. Magnetoencephalography typically allows for better source

98   reconstruction than EEG, because magnetic fields are less distorted by the skull and scalp than the EEG-

99   recorded electric potentials (Hämäläinen et al., 1993; Hämäläinen and Hari, 2002). Previous MEG source

100   localizations in younger adults suggest that the auditory cortex underlies sustained neural activity (Hari

101   et al., 1980; Pantev et al., 1994; Pantev et al., 1996; Gutschalk et al., 2002; Ross et al., 2002; Okamoto

102   et al., 2011; Barascud et al., 2016; Teki et al., 2016) and that additional brain regions in parietal cortex,

103   frontal cortex, and hippocampus may also contribute (Tiitinen et al., 2012; Barascud et al., 2016; Teki et

104   al., 2016). Whether the neural sources of pattern-related sustained activity differ between younger and

105   older adults is unknown.

106   In the current study we recorded MEG from younger and older adults while they listened to

107   sound sequences. Sequences were made by taking pure tones at different frequencies and either

108   repeating the same small set of these in the same order, so that a regular pattern is heard, or by

109   presenting them pseudo-randomly so that no pattern is present. We investigate whether sustained

110   neural activity to a regular sound pattern differs between younger and older individuals. We also

111   examine whether auditory cortex is generally more responsive to sound in older, compared to younger

112   adults, as has been previously reported (Bidelman et al., 2014; Herrmann et al., 2018).

Methods and Materials

114   *Participants*

115   Twenty-six younger (mean: 26.7 years; range: 21–33 years; 13 males and 13 females) and twenty-five

116   older adults (mean: 63.9 years; range: 53–73 years; 11 males and 14 females) participated in the current

117   study. Participants reported no neurological disease or hearing impairment, gave written informed

118   consent, and were paid for their participation. None of the participants wore a hearing aid or reported

119   having been prescribed a hearing aid. We focused on a typical sample of older individuals, allowing for

120   the possibility of some degree of hearing impairment. The study was conducted in two sessions on

121   separate days (range: 1-43 days apart; median: 7 days apart; no age-group difference: t_{49} = 0.99, p =

122   0.327). The study was conducted in accordance with the Declaration of Helsinki, the Canadian Tri-Council

123   Policy Statement on Ethical Conduct for Research Involving Humans (TCPS2-2014), and was approved

124   by the local Nonmedical Research Ethics Board of the University of Western Ontario (protocol ID:

125   106570).

126   *Hearing assessment and hearing thresholds*

127   Pure-tone audiometric data were acquired for each participant (Figure 1). The pure-tone average

128   hearing threshold (i.e., the mean across the 0.25, 0.5, 1, 2, and 4 kHz frequencies) was larger for older

129   compared to younger adults (t_{49} = 7.79, p = $4{\times}10^{-10}$, r_e = 0.744; Figure 1, right). This indicates a mild-to-

130   moderate hearing impairment in many of the older adults and is consistent with the high-frequency

131   sloping loss characteristic of age-related hearing impairment (Moore, 2007; Plack, 2014) as well as with

132   previous electrophysiological studies that investigated differences in sound processing between younger

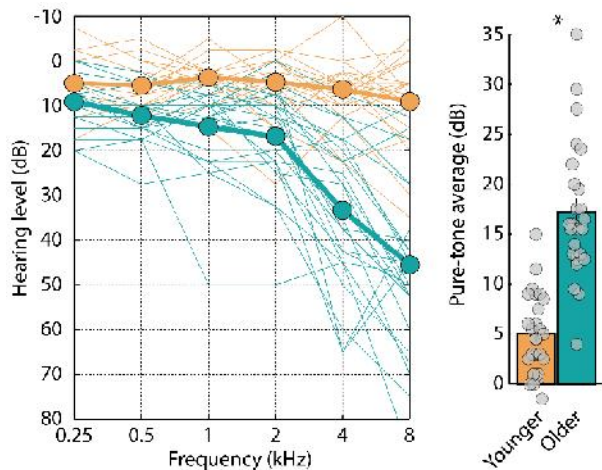133   and older adults (Presacco et al., 2016b; Herrmann et al., 2018).

Figure 1: Audiograms and pure-tone average hearing threshold. Left: Audiograms for each participant. Thin lines reflect individual participant data. Thick lines reflect the mean across participants. Right: Pure-tone average hearing threshold (mean across 0.25, 0.5, 1, 2, and 4 kHz). Gray dots reflect the threshold for individuals.

134   For each participant, we measured the hearing threshold (i.e., sensation level [SL]) using a

135   method-of-limits procedure (Herrmann and Johnsrude, 2018a; Herrmann et al., 2019) as a reference

136   threshold in MATLAB software for sound presentation. Participants listened to a 12-s pure tone with a

137   frequency of 1323 Hz that changed continuously in intensity at a rate of 5 dB/s (either decreased [i.e.,

138   starting at suprathreshold levels] or increased [i.e., starting at subthreshold levels]). Participants pressed

139   a button when they could no longer hear the tone (intensity decrease) or when they started to hear the

140   tone (intensity increase); the sound stopped after button press. The sound intensity at the time of the

141   button press was noted for 6 decreasing sounds and 6 increasing sounds (decreasing and increasing

142   sounds alternated), and these were averaged to determine the individual hearing threshold. The mean

143   hearing threshold was elevated for older compared to younger adults (t_{49} = 5.208, p = 3.7×10^{-6}, r_e =

144   0.597), which was expected given the audiograms (Figure 1).

145   All acoustic stimuli described below were presented at 55 dB above each individual's hearing

146   threshold – that is, at 55 dB sensation level – in order to control for audibility across age groups. Because

147   hearing thresholds were on average elevated for older compared to younger adults, sounds during the

148   MEG recordings were on average more intense in sound-pressure level (SPL) in older compared to

149   younger individuals. Higher sound levels can lead to larger brain responses to sound onsets (Picton et

150   al., 1974; Picton et al., 1978; Pfefferbaum et al., 1979; Polich et al., 1988; Schadow et al., 2007; Herrmann

151   et al., 2018) as well as for sustained activity (Picton et al., 1978; Pfefferbaum et al., 1979). Because we

152   hypothesized that regularity-related sustained activity would be smaller for older compared to younger

153   adults, playing sounds at a higher level for older adults only works against this hypothesis. Presenting

154   sounds at sensation level was thus favorable in the current study. However, a higher sound level for

155   older compared to younger adults could bias statistical analyses for investigations of age-related

156   hyperresponsivity to sound, for which we expect larger responses in older compared to younger adults.

157   Hence, for these analyses, we also used a subgroup of 14 participants of each age group for which the

158   hearing threshold – and thus the sound level of the acoustic presentation – did not differ (t_{26} = 0.956, p

159   = 0.348, r_e = 0.184; younger mean [±sd]: -94.16 dB ±1.39, older mean [±sd]: -93.36 dB ±2.65[1]) to confirm

160   our results.

161   *Acoustic stimulation and procedure*

162   Acoustic stimuli were 4-s long sequences that each consisted of 96 pure-tone pips arranged in twelve

163   sets of eight tones each (see also Barascud et al., 2016; Herrmann and Johnsrude, 2018b; Southwell and

164   Chait, 2018; Herrmann et al., 2021). Each set had a duration of 0.333 s. Pips were 0.0417 s in duration

165   with attack and decay times of 0.007 s, and no gap between tones, or sets. The frequency of each tone

166   was one of 150 possible values between 700 and 2500 Hz (logarithmically spaced).

167   Acoustic stimuli were presented in two conditions, 'Pattern-Absent' and 'Pattern-Present', which

168   occurred with equal probability (50%). In the 'Pattern-Absent' condition, tones with different

169   frequencies were presented in pseudo-random order without a pattern, whereas in the 'Pattern-

170   Present' condition, tones transitioned from random to a regular pattern 1 s (3 sets) after sound onset.

171   For the 'Pattern-Absent' condition, 8 new frequency values were randomly selected for each of the 12

172   sets (Figure 2, top). In the 'Pattern-Present' condition, 8 new frequency values were randomly selected

173   for each of the first 3 sets (0–1 s; similar to 'Pattern-Absent'), and then 8 new random frequency values

174   were selected and repeated in the same order for the remaining 9 sets, thereby creating a regular

175   pattern (Figure 2, bottom). These conditions are similar to the sounds used in previous studies that

176   investigated sustained neural activity (Barascud et al., 2016; Southwell et al., 2017; Herrmann and

177   Johnsrude, 2018b).

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[1] The dB values are derived from MATLAB. More negative values reflect softer sound intensities. These dB values can be interpreted relative to each other, whereas the absolute magnitude is related to hardware and software conditions, such as sound card, transducers, and MATLAB internal settings.
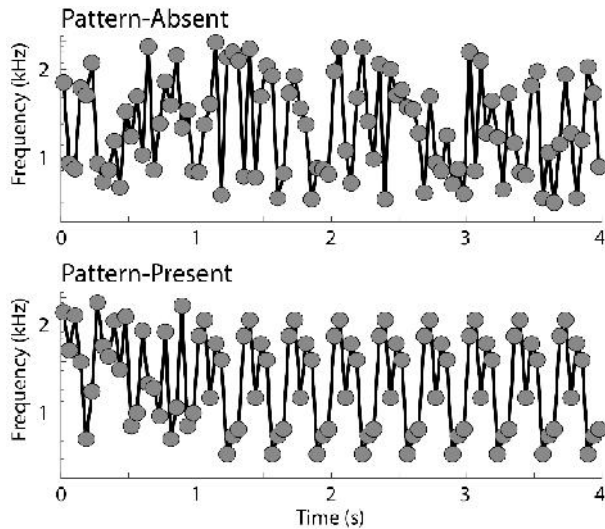
Figure 2: Schematic of acoustic stimulation for 'Pattern-Absent' and 'Pattern-Present' conditions. Sound frequency is displayed on the y-axis and dots reflect the sound frequency of individual tones of the tone sequence.

178   In each of the two recording sessions, participants were presented with one 12-min block of
179   stimulation as part of recording sessions for an additional project not presented here. The data from the
180   experimental blocks reported here were recorded in the beginning of the recording sessions.
181   Participants listened passively to sixty 4-s sound sequences of each condition per session, while watching
182   a muted movie of their choice, with subtitles, that was projected into the electromagnetically shielded
183   room via a mirror system. Trials of the Pattern-Absent and the Pattern-Present conditions were
184   presented pseudo-randomly throughout the block, such that each condition could occur maximally
185   three times in direct succession. Across both sessions, participants listened to 120 trials per condition.
186   Trials were separated by a 2-s inter-stimulus interval.

187   *Magnetoencephalographic recordings and initial preprocessing*
188   Magnetoencephalographic data were recorded using a 306-channel Neuromag Vectorview MEG
189   (MEGIN Oy, Helsinki, Finland; sampling rate: 1000 Hz, online filter: DC–330 Hz) at the Max Planck
190   Institute for Human Cognitive and Brain Sciences in Leipzig, Germany. Data were recorded in an
191   electromagnetically shielded room (AK3b, Vacuumschmelze, Hanau, Germany). The signal space
192   separation (SSS) method (maxfilter© version 2.2.15; default parameter setting L_{in} = 8; L_{out} = 3) was used
193   to suppress external interference, interpolate bad channels, and transform each person's individual data
194   to the sensor space of the first block of the first session to ensure the data are in a common space (Taulu
195   et al., 2004; Taulu et al., 2005).

196 *Combination of magnetometer and gradiometer channels*

197 The Vectorview MEG device records magnetic fields using 102 magnetometers and 204 gradiometers in

198 102 locations distributed around the head. In order to account for all data that were recorded, we

199 combined signals from magnetometer and gradiometer channels (Herrmann et al., 2018).

200 Magnetometers and gradiometer differ in their configuration, such that magnetometers measure

201 magnetic fields in Tesla (T), while gradiometers (a coupled pair of magnetometers) measure differences

202 in the same magnetic fields over a distance of 0.0168 m in Tesla per meter (T/m). The combination of

203 channel types requires accounting for their different units. We transformed all channels into

204 magnetometer channels, because such a model only requires a linear interpolation that results in the

205 same unit for all channels. To this end, we applied the following transformation matrix to each of the

206 102 sensor triplets (i.e., one triplet comprises two gradiometer channels and one magnetometer

207 channel):

208 $$X_{S_i} = S \times X$$

209 where X consists of a 3 × n matrix (with n being the number of data samples over time). The three

210 rows of X refer to the two gradiometers and one magnetometer (i.e., one triplet). S refers to a 5 × 3

211 scaling matrix with the following elements:

212 $$S = \begin{matrix} -0.0084 & 0 & 1 \\ 0.0084 & 0 & 1 \\ 0 & -0.0084 & 1 \\ 0 & 0.0084 & 1 \\ 0 & 0 & 1 \end{matrix}$$

213 The value 0.0084 reflects half of the distance between the two gradiometer loops measured in

214 meters, and the transformation constitutes a linear approximation of the magnetic field at each of the

215 triplets. The transformation replaces the sensor triplet by a sensor quintet of magnetometers. The

216 columns of S refer to the triplet of two gradiometers and one magnetometer and the rows of S refer to

217 the resulting five magnetometers. This procedure resulted in signals from 510 magnetometer channels

218 centered on and around 102 locations around a participant's head (Herrmann et al., 2018).

219 *Preprocessing of magnetoencephalographic data*

220 Data were high-pass filtered (0.7 Hz; 2391 points, Hann window), low-pass filtered (20.3 Hz, 119 points,

221 Kaiser window), down-sampled to 250 Hz, and divided into 6-s long epochs time-locked to sound onset

222   (from 1 s before to 5 s after sound onset). Independent components analysis (runica method, Makeig et

223   al., 1996; logistic infomax algorithm, Bell and Sejnowski, 1995; Fieldtrip implementation, v20130727,

224   Oostenveld et al., 2011) was used to identify and remove activity related to blinks, horizontal eye

225   movements, muscle activity, and noisy channels. Identification of components related to these non-

226   brain activities was done manually through visual inspection of component time courses, topographies,

227   and frequency spectra by BH. Epochs in which a signal change larger than 8 Picotesla (pT) occurred in

228   any channel were excluded. The remaining data were used to investigate age differences in evoked

229   responses to the onset of the sounds.

230   In order to investigate the sustained neural activity, the same pipeline was computed a second

231   time, with the exception that high-pass filtering was omitted. Omission of the high-pass filter is necessary

232   to investigate sustained activity, because the response is a very low-frequency signal reflecting a DC shift

233   (Barascud et al., 2016; Southwell et al., 2017; Herrmann and Johnsrude, 2018b). Activity related to

234   blinks, horizontal eye movements, muscle activity, and noisy channels was removed using the identified

235   components from the high-pass filtered data. Epochs in which a signal change larger than 8 pT occurred

236   in any channel were excluded.

237   *Analysis of responses to sound onset*

238   High-pass filtered data were used to investigate whether neural responses to the onset of the sounds

239   differed between age groups. This analysis aimed to test whether the auditory cortex of older adults is

240   hyperresponsive to sound, consistent with reduced inhibition (Caspary et al., 2008; Hughes et al., 2010;

241   Juarez-Salinas et al., 2010). Data from the Pattern-Absent and Pattern-Present conditions were averaged

242   because both conditions were identical for the first second of the sound. Epochs ranging from -0.15 s to

243   0.5 s time-locked to sound onset were extracted. Absolute values were calculated for signals of each

244   channel (because magnetic fields have opposite polarities in directions perpendicular to the tangential

245   orientation aspect of the underlying neural source). The mean signal from the pre-stimulus period (-0.15

246   to 0 s) was subtracted from the signal at each time point, separately for each channel (baseline

247   correction). Responses were averaged across channels, resulting in one response time course per

248   participant.

249   For the statistical analysis, differences in response amplitude between age groups were assessed

250   for each time point using independent samples t-tests. False discovery rate was used to account for

251 multiple comparisons (Benjamini and Hochberg, 1995; Genovese et al., 2002). We confirmed the results

252 with two independent samples t-tests that contrasted the amplitudes of the M50 (0.03–0.06 s) and

253 M100 (0.09–0.13 s) between age groups, which have previously been shown to differ between younger

254 and older adults (Sörös et al., 2009; Alain et al., 2012; Herrmann et al., 2018).

255 *Analysis of pattern-related sustained activity*

256 Non-high-pass filtered data were used to investigate whether sustained neural activity associated with

257 a pattern in sounds differs between age groups. The 6-s epochs (-1 to 5 s, time-locked to sound onset)

258 were used. Absolute values were calculated for signals of each channel and the mean signal from the

259 pre-stimulus period (-1 to 0 s) was subtracted from the signal at each time point, separately for each

260 channel (baseline correction). Responses were averaged across channels, resulting in one response time

261 course per condition and per participant.

262 Statistical analysis focused on responses during the last half of each stimulus: the 2–4 s time

263 window. By 2 s, the repeating set of tones would have been presented 3 times (2 full repetitions) in the

264 Pattern-Present condition (Barascud et al., 2016; Teki et al., 2016; Herrmann and Johnsrude, 2018b). An

265 ANOVA with the within-subjects factor Condition (Pattern-Absent, Pattern-Present) and the between-

266 subjects factor Age Group (younger, older) was calculated.

267 *Source localization of magnetoencephalographic data*

268 Anatomically constrained source localization was used to localize the sources underlying the neural

269 activity in sensor space. Individual T1-weighted MR images (3T Magnetom Trio, Siemens AG, Germany)

270 were available for each participant. The MR images were used to construct inner skull surfaces (volume

271 conductor) and mid-gray matter cortical surfaces (source model; using Freesurfer and MNE software;

272 https://surfer.nmr.mgh.harvard.edu/;   http://www.martinos.org/mne/).   The   MR   and   the   MEG

273 coordinate systems were co-registered using MNE software, which included an automated and iterative

274 procedure that fitted the >300 digitized head surface points (Polhemus FASTRAK 3D digitizer) to the MR

275 reconstructed head surface (Besl and McKay, 1992). The inner skull was extracted from the MR images

276 using MNE software and used to calculated lead fields using the boundary element model as

277 implemented in Fieldtrip software (Nolte, 2003). Inverse solutions were calculated using the sLORETA

278 method (Pascual-Marqui, 2002). Neural activity was spatially smoothed across the surface using an

279   approximation to a 6-mm FWHM Gaussian kernel (Han et al., 2006). Individual cortical representations

280   were transformed to a common coordinate system (fsaverage standard brain; Fischl et al., 1999b).

281   Workbench software (v1.4.2; https://www.humanconnectome.org/) was used for visualization of source

282   localizations morphed to the pial cortical surface of the fsaverage standard brain (Fischl et al., 1999a).

283   Source localizations were calculated for onset responses and for sustained neural activity. In order to

284   visualize and analyze pattern-related auditory cortex activity, we averaged source-localization

285   amplitudes across regions of the superior temporal plane (A1, A4, PBelt, MBelt, and LBelt) using the

286   brain parcelations of the Human Connectome Project (Glasser et al., 2016).

287   *Effect sizes*

288   Effect sizes are provided as partial η^2 for ANOVAs and as r_e ($r_{equivalent}$) for t-tests (Rosenthal and Rubin,

289   2003). r_e is equivalent to the square root of partial η^2 for ANOVAs.

290   *Data availability*

291   This study was not pre-registered. MEG data in BIDS format (Pernet et al., 2019) are available at

292   https://figshare.com/projects/A_Neural_Signature_of_Regularity_in_Sound_is_Reduced_in_Older_Ad

293   ults/121803.

294   Results

295   *Responses to sound onset are enhanced in older compared to younger adults*

296   Figure 3A displays the neural response time courses elicited by the onset of the sounds. Responses were

297   larger in older compared to younger adults in the M50 and M100 time windows (black line in Figure 3A,

298   FDR-thresholded). Figure 3B/C shows the mean amplitudes and topographical distributions for the M50

299   and M100 time windows. Larger neural responses for older compared to younger adults were also

300   observed for the subgroups of 14 participants per age group for which hearing thresholds – and thus

301   sound-presentation levels – did not differ (M50: t_{26} = 4.812, p = 5.5×10^{-5}, r_e = 0.686; M100: t_{26} = 4.257,

302   p = 2.3×10^{-4}, r_e = 0.641; all participants: M50: t_{49} = 6.295, p = 8.2×10^{-8}, r_e = 0.669; M100: t_{49} = 4.015, p =

303   2×10^{-4}, r_e = 0.497). Finally, regressions calculated to predict M50 or M100 responses from age group,

304   while including sensation-level threshold and audiometric pure-tone average as co-variates, also

305 revealed an effect of age group (M50: t_{47} = 3.199, p = 0.002; M100: t_{47} = 2.571, p = 0.013). These results

306 demonstrate that even when sound level does not differ between younger and older adults, older adults

307 exhibit hyperresponsiveness to sound. There was no age difference for the M200 (0.16–0.22 s: t_{49} =

308 1.088, p = 0.282). Source localizations show activity in superior temporal cortex, including auditory

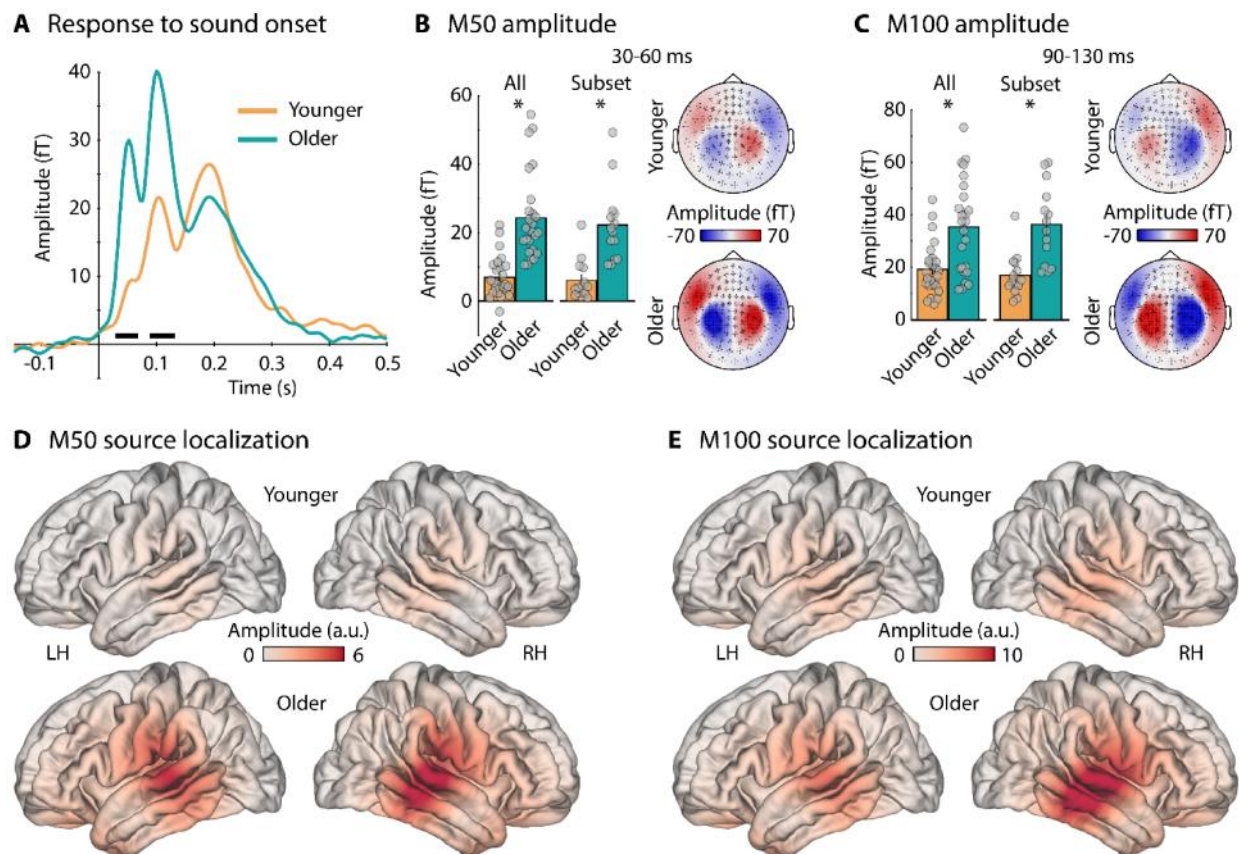309 cortex, underlying M50 and M100 responses in both age groups (Figure 3D/E).

Figure 3: Neural responses to the onset of sounds. A: Time courses of neural activity (root-mean square amplitude, averaged across all channels). The black line indicates a significant difference between age groups (FDR-thresholded). B: Mean activity and topographies for the M50 time window (30–60 ms) for all participants and the subset of 14 participants for which sound level did not differ between younger and older adults. C: Mean activity and topographies for the M50 time window (90–130 ms) for all participants and the subset of 14 participants. D: Source localization for the M50 time window. E: Source localization for the M100 time window. *p ≤ 0.05

310 *Pattern-related sustained activity is reduced in older compared to younger adults*

311 Figure 4A and B show response time courses and topographical distributions for the Pattern-Absent and

312 the Pattern-Present condition for both age groups. The ANOVA for the 2-4 s time window revealed a

313 Condition × Age Group interaction ($F_{1,49}$ = 9.839, p = 0.003, n_p^2 = 0.167; also significant for the subset of

314 participants for which sound level did not differ: $F_{1,26}$ = 6.792, p = 0.015, n_p^2 = 0.207): While both age

315 groups show larger sustained activity for the Pattern-Present compared to the Pattern-Absent condition

316 (younger: $F_{1,25}$ = 49.692, p ≤ 1×10^{-6}, n_p^2 = 0.665; older: $F_{1,24}$ = 6.287, p = 0.019, n_p^2 = 0.208), this difference

317 was larger in younger compared to older adults (Figure 4C). There was no difference between age groups

318 for the Pattern-Absent condition ($F_{1,49}$ = 0.528, p = 0.471, n_p^2 = 0.011). The main effect of Condition ($F_{1,49}$

319 = 45.185, p ≤ 1×10^{-6}, n_p^2 = 0.48) and the main effect of Age Group ($F_{1,49}$ = 6.994, p = 0.011, n_p^2 = 0.125)

320 were also significant.

321   In order to explore the relation between the response to sound onset and the regularity-related

322 sustained activity effects in older adults, we calculated the difference between the Pattern-Present and

323 the Pattern-Absent conditions and correlated the response difference with the M50 and M100

324 responses to sound onset. Correlations were not significant (M50: r = -0.075, p = 0.722, df = 23; M100:

325 r = -0.011, p = 0.957, df = 23). However, the relation between hyperactivity in response to sound and

326 hearing loss is non-linear (Qiu et al., 2000; Salvi et al., 2017; Herrmann and Butler, 2021), and we may

327 thus not expect a linear correlation between hyperactivity and changes in regularity-related sustained
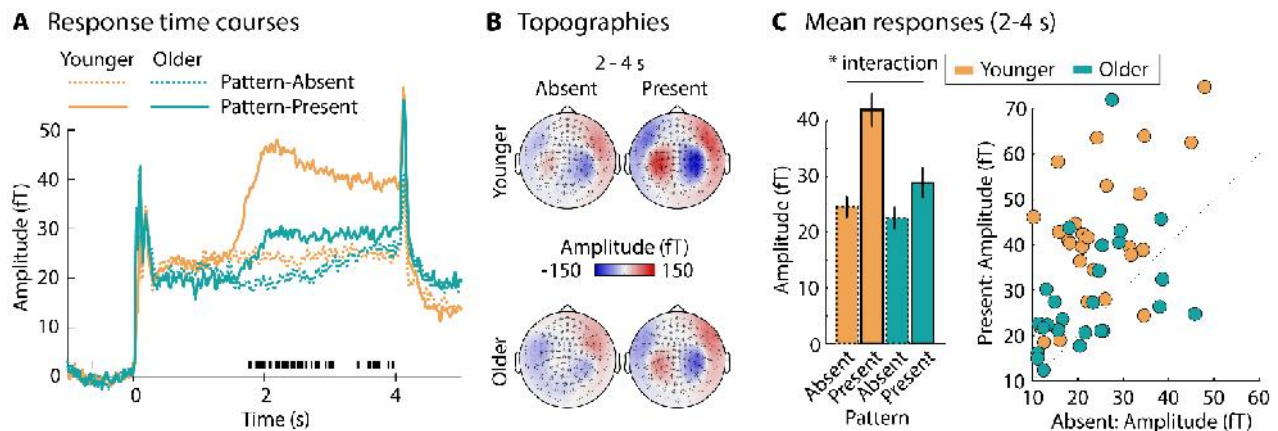
328 activity in older adults.

Figure 4: Pattern-related sustained activity. A: Response time courses (root-mean square amplitude, averaged across all channels). The black markings below the time courses indicate the time points at which the Condition × Age Group interaction was significant (FDR-thresholded). B: Topographical distributions for each condition and age group for the 2-4 s time window. C: Mean responses in the 2-4 s time window. Bar graphs reflect the mean across participants. Error bars are the standard error of the mean. Data points for each participant are shown on the right. Data points above the diagonal (dashed line) reflect a larger response for the Pattern-Present compared to the Pattern-Absent condition.

329

330   Source localizations revealed that the strongest activity associated with pattern-related

331   sustained activity was present in superior temporal cortex and auditory cortex (Figure 5A). Indeed, we

332   observed the same interaction for auditory cortex activity ($F_{1,49}$ = 10.68, p = 0.002, n_p^2 = 0.179; Figure

333   5B/C; for the subset of participants: $F_{1,26}$ = 7.299, p = 0.012, n_p^2 = 0.219) that we observed in sensor

334   space (Figure 4C), such that the increase in sustained activity for the Pattern-Present compared to the

335   Pattern-Absent condition was significant for both age groups (younger: $F_{1,25}$ = 50.652, p ≤ 1×10⁻⁶, n_p^2 =

336   0.670; older: $F_{1,24}$ = 23.833, p = 5.6×10⁻⁵, n_p^2 = 0.498), with a larger difference in younger compared to

337   older adults. In contrast to the sensor space data of sustained activity, sustained activity in auditory

338   cortex elicited by the Pattern-Absent condition was also larger for younger compared to older adults

339   ($F_{1,49}$ = 4.704, p = 0.035, n_p^2 = 0.088; Figure 5B/C), consistent with observations of reduced sustained

340   activity to a sine tone in older compared to younger adults (Pfefferbaum et al., 1979). Main effects of

341   Condition ($F_{1,49}$ = 73.205, p ≤ 1×10⁻⁶, n_p^2 = 0.599) and Age Group ($F_{1,49}$ = 10.176, p = 0.002, n_p^2 = 0.172)
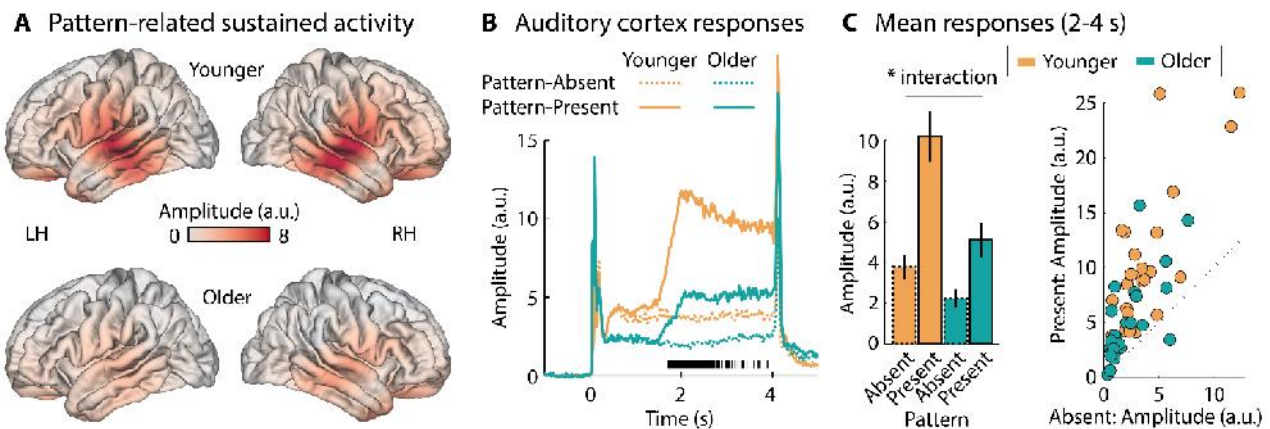
342   were also significant.

Figure 5: Source localization of pattern-evoked sustained activity. A: Source localization of pattern-related sustained activity (difference between Pattern-Present and Pattern-Absent conditions). B: Response time courses from auditory cortex. The black markings below the time courses indicate the time points at which the Condition × Age Group interaction was significant (FDR-thresholded). C: Mean auditory cortex responses in the 2-4 s time window. Bar graphs reflect the mean across participants. Error bars are the standard error of the mean. Data points for each participant are shown on the right. Data points above the diagonal (dashed line) reflect a larger response for the Pattern-Present compared to the Pattern-Absent condition.

343   Discussion

344   The current magnetoencephalography study investigated age-related differences in auditory cortical

345   responsivity to sound onsets and to the presence of a pattern in sounds. We showed that older adults

346   elicit larger responses in auditory cortex to sound onsets compared to younger adults. This response

347   enhancement indicates that auditory cortex of older adults is hyperresponsive to sound. Despite this

348   age-related hyperresponsiveness, sustained neural activity in auditory cortex to sound patterns was

349   diminished in older compared to younger people. Our results suggest that neural responses in auditory

350   cortex are fundamentally altered in older adults such that cortical activity overrepresents sound onsets,

351   whereas it underrepresents temporally coherent structure in sounds.

352   *Hyperresponsiveness of auditory cortex in older adults*

353   We demonstrated that neural responses in the M50 and M100 time window following sound onset are

354   enhanced in older compared to younger adults (Figure 3A-C). We localized the M50 and M100 responses

355   to auditory cortex (Figure 3D/E; consistent with previous work Pantev et al., 1988; Maess et al., 2007;

356   Okamoto and Kakigi, 2014; Herrmann et al., 2018), suggesting that auditory cortex in older adults is

357   hyperresponsive. This is in line with a growing literature showing that neural responses to sound onsets

358   are enhanced in older compared to younger adults (Ross and Tremblay, 2009; Sörös et al., 2009; Lister

359   et al., 2011; Alain et al., 2012; Bidelman et al., 2014; Herrmann et al., 2016; Herrmann and Johnsrude,

360   2018a). Similar observations have been made for aged monkeys (Juarez-Salinas et al., 2010; Recanzone,

361   2018) and aged rodents (Hughes et al., 2010), as well as for non-human mammals whose auditory

362   periphery was damaged through high-intensity sound exposure (Popelár et al., 1987; Syka et al., 1994;

363   Schormans et al., 2019) or ototoxic drugs (Qiu et al., 2000; for detailed reviews see Auerbach et al., 2014;

364   Zhao et al., 2016; Salvi et al., 2017; Herrmann and Butler, 2021).

365   Hyperresponsiveness to sound is thought to result from hyperexcitable neural circuits due to a

366   loss of inhibition in the auditory system following peripheral decline (Caspary et al., 2008; Takesian et

367   al., 2012). The functional role of the loss of inhibition and hyperexcitability is still debated (Zhao et al.,

368   2016; Asokan et al., 2018; Herrmann and Butler, 2021), but likely includes homeostatic processes to

369   regulate excitation (Caspary et al., 2008; Zhao et al., 2016) and a state of increased plasticity that enables

370   cortical reorganization (Cisneros-Franco et al., 2018; Cisneros-Franco and de Villers-Sidani, 2019). A

371   balanced level of excitation and inhibition is crucial for neural function (Wehr and Zador, 2003; Silver,

372   2010; Isaacson and Scanziani, 2011), and the fact that we observed hyperresponsiveness to sound in

373   older compared to younger adults suggests that neural function of auditory cortex was altered in our

374   sample of older individuals. Hyperresponsivity to sharp attacks in sound may underlie increased

375   distractibility by irrelevant sounds in older compared to younger adults (Parmentier and Andrés, 2010)

376   and difficulties comprehending speech in the presence of an interfering, modulated background masker

377   (Millman et al., 2017; Goossens et al., 2018).

378   *Pattern-related activity is reduced in older compared to younger adults*

379   In order to investigate whether neural sensitivity to a pattern in sounds differs between younger and

380   older adults, we presented sounds that either contained a pattern (made of a sequence of a repeated

381   set of pure tones at different frequencies) or did not contain a pattern (made of a sequence of tones at

382   pseudo-randomly selected frequencies; Figure 2). For both younger and older adults, we observed that

383   sustained neural activity increased after the onset of a sound pattern relative to sounds without a

384   pattern. Previous work in younger adults has revealed similar increases in sustained activity for different

385   types of patterns, including tone sequences such as those we have utilized here (Gutschalk et al., 2002;

386   Ross et al., 2002; Keceli et al., 2012; Barascud et al., 2016; Sohoglu and Chait, 2016; Teki et al., 2016;

387   Southwell et al., 2017; Herrmann and Johnsrude, 2018b; Southwell and Chait, 2018; Herrmann et al.,

388   2019; Herrmann et al., 2021).

389   We showed that sustained neural activity to a pattern in sounds is reduced in older compared to

390   younger adults. Hence, although neural responses to the onset of sound was enhanced in older adults,

391   neural sensitivity to a pattern in sounds was reduced. Diminished sustained activity for older compared

392   to younger adults is consistent with previous indications of an age-related reduction in sustained activity

393   for short (<1 s) pure tones (Pfefferbaum et al., 1979), amplitude modulations (Herrmann et al., 2019),

394   and repeated patterns in tone sequences (Al Jaja et al., 2020). However, low statistical reliability and

395   differences in stimulus parameters between age groups did not allow drawing firm conclusions from the

396   latter two studies. Our results demonstrate clearly that pattern-related sustained activity indeed is

397   reduced in older adults.

398   Sensitivity to sound patterns is crucial for a variety of auditory functions, enabling a listener to

399   segregate concurrent sound streams (Schröger, 2005, 2007; Snyder and Alain, 2007; Winkler et al., 2009;

400   Bendixen, 2014) and recognize and predict relevant sounds (Jones and Boltz, 1989; Nobre et al., 2007;

401 Henry and Herrmann, 2014; Nobre and van Ede, 2018). By demonstrating a correlation between

402 perceptual sensitivity to sound patterns and speech comprehension abilities (Holmes and Griffiths,

403 2019) and common substrates in auditory cortex (Holmes et al., 2021), previous work further indicates

404 a functional relation or common underlying mechanism between the processing of regularities in sounds

405 and speech comprehension. A reduction in sustained activity may thus indicate that sound patterns are

406 processed less well in neural circuits in older compared to younger adults, which may, in part, explain

407 the challenges older adults experience comprehending speech in the presence of background sound.

408   Participants in the current study were presented with sound sequences while they watched a

409 muted, subtitled movie of their choice. Participants' attention was thus directed away from the sounds,

410 although the degree of attentional focus was not experimentally constrained in the current study.

411 Previous work indicates that regularity-related sustained activity can be increased if participants perform

412 a difficult sound-related task relative to a difficult visual task (Herrmann and Johnsrude, 2018b). Larger

413 regularity-related sustained activity in younger compared to older adults could thus be, in part, the result

414 of younger adults attending more to the sounds than older adults. However, younger and older adults

415 typically enjoy watching a movie in such experiments, where they are not required to perform a sound-

416 related task. Moreover, larger responses in older compared to younger adults to the sound onset may

417 indicate greater attentional capture by sounds for older adults (see also Parmentier and Andrés, 2010;

418 Weeks and Hasher, 2014), but regularity-related sustained activity was decreased for them. Differences

419 in the degree of attention to sounds between age groups are thus unlikely to explain the observed

420 differences in regularity-related sustained activity.

421   The current source localizations suggest that auditory cortex is the main source underlying

422 pattern-related sustained activity in both younger and older adults (Figure 5A). Previous work in younger

423 individuals also indicated that auditory cortex underlies sustained neural activity (Hari et al., 1980;

424 Pantev et al., 1994; Pantev et al., 1996; Gutschalk et al., 2002; Ross et al., 2002; Gutschalk et al., 2004;

425 Gutschalk et al., 2007; Okamoto et al., 2011; Keceli et al., 2012; Barascud et al., 2016; Teki et al., 2016),

426 but that brain regions in frontal cortex, parietal cortex, and hippocampus may additionally contribute

427 (Tiitinen et al., 2012; Barascud et al., 2016; Teki et al., 2016). However, in the latter work, statistical

428 difference maps were calculated and used to identify neural sources. Statistical difference maps may

429 also capture effects related to activity spread due to volume conduction and may thus not reflect activity

430   originating from these higher-level brain regions (e.g., auditory responses to sound onset were spread

431   to parietal cortex in Teki et al., 2016, suggesting that spread may also affect their sustained activity in

432   parietal cortex related to sound patterns).

433   We further showed that sustained activity in auditory cortex to sounds that did not contain a

434   pattern was also reduced in older compared to younger adults (Figure 5B/C). Sounds without a pattern

435   were made of a sequence of pure tones whose frequency changed randomly for each tone. Such tone

436   sequences are perceptually more structured than noise and the auditory system may treat them as a

437   pattern of low saliency. This is consistent with the observation of reduced sustained activity to short

438   pure tones in older compared to younger adults (Pfefferbaum et al., 1979). Our data thus indicate that

439   the sensitivity of the aged auditory cortex is reduced for sounds containing a pattern (here repetition of

440   a set of tones at different frequencies) as well as for sequences with random tone frequencies.

441   It is clear from previous work that temporally regular – and thus predictable – structure in sounds

442   that forms a pattern elicits sustained neural activity (Gutschalk et al., 2002; Barascud et al., 2016;

443   Herrmann and Johnsrude, 2018b). However, additional work suggests that the magnitude of pattern-

444   related sustained activity is related to the degree of novelty or predictability of a pattern, such that

445   sustained activity decreases when a pattern is frequently, compared to infrequently, heard (Gutschalk

446   et al., 2007; Herrmann et al., 2021). A reduction in sustained activity in older adults may thus result from

447   reduced processing of the pattern as well as from reduced novelty of the pattern, but further behavioral

448   research is needed to investigate the perceptual consequences of the altered cortical sensitivity

449   observed here.

450   Conclusions

451   In the current study, we recorded magnetoencephalography to characterize differences between

452   younger and older adults in the processing of a pattern in sounds. We presented continuous tone

453   sequences that either contained a pattern (made of a repeated set of tones at different frequencies) or

454   did not contain a pattern (random tone frequencies). We showed that auditory cortex in older adults is

455   hyperresponsive to sound onsets, but that sustained neural activity in auditory cortex, indexing the

456   processing of sound patterns, is reduced. Hence, neural populations in auditory cortex fundamentally

457   differ between younger and older individuals in their sensitivity to sound features, hyperresponding to

458 sound onsets, while underresponding to patterns in sounds. This may help to explain some age-related

459 changes in hearing such as increased sensitivity to distracting sounds and difficulties tracking speech in

460 the presence of other sound.

Author contributions

468 BH conceptualized and designed the study, recorded data, analyzed the data, interpreted the results,

469 and wrote the manuscript. BM analyzed the data, interpreted the results, and edited the manuscript. ISJ

470 conceptualized and designed the study, interpreted the results, and edited the manuscript.

Declaration of conflicts of interest

472 None.

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