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Grey matter volume in the right Angular Gyrus is associated with differential patterns of multisensory integration with ageing

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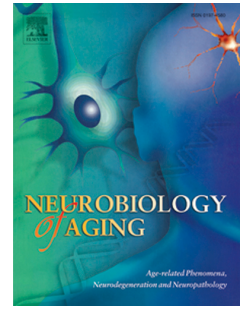
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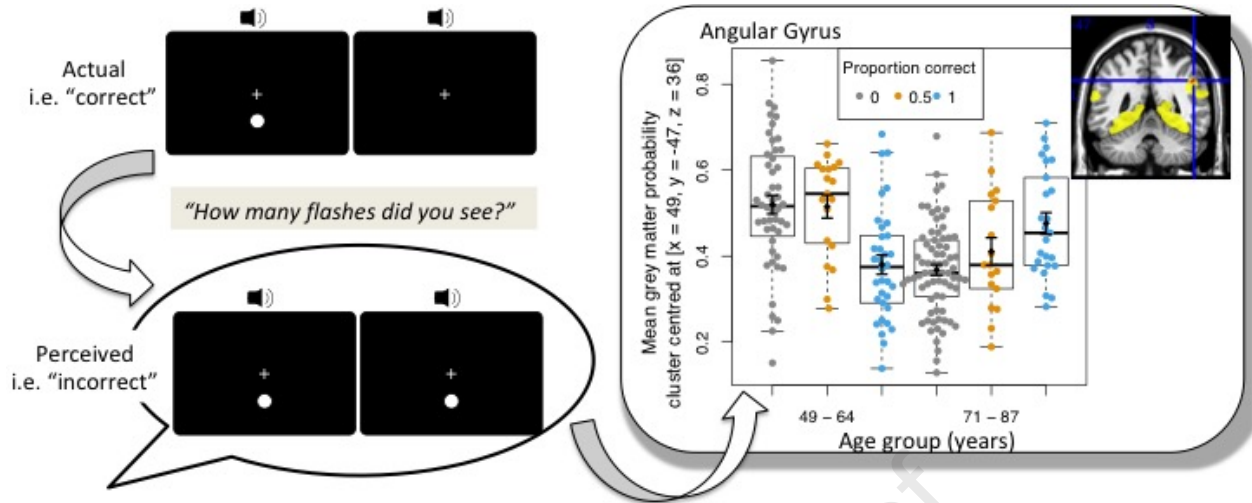
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12 **Data availability:** The datasets generated during and/or analysed during the  
13 current study are not publicly available due to data protection regulations but  
14 are accessible at TILDA on reasonable request.

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**Abstract**

24 Multisensory perception might provide an important marker of brain function in  
25 ageing. However, the cortical structures supporting multisensory perception in  
26 ageing are poorly understood. In this study, we compared regional grey  
27 matter volume in a group of middle-aged (n = 101; 49 – 64 years) and older (n  
28 = 116; 71 – 87 years) adults from The Irish Longitudinal Study on Ageing  
29 using Voxel Based Morphometry. Participants completed a measure of  
30 multisensory integration, the Sound-Induced Flash Illusion, and were grouped  
31 according to their illusion susceptibility. A significant interaction was observed  
32 in the right Angular Gyrus; in the middle-aged group, larger grey matter  
33 volume corresponded to stronger illusion perception whilst in older adults  
34 larger grey matter corresponded to less illusion susceptibility. This interaction  
35 remained significant even when controlling for a range of demographic,  
36 sensory, cognitive and health variables. These findings show that  
37 multisensory integration is associated with specific structural changes in the  
38 ageing brain and highlight the Angular Gyrus as a possible “cross-modal hub”  
39 associated with age-related change in multisensory perception.

40 **Keywords;** Multisensory, Sound-Induced Flash Illusion, Ageing, Audio-visual,  
41 Grey Matter Volume, Voxel Based Morphometry.

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**1. Introduction**

45 The ability to effectively combine information from across the senses,  
46 multisensory integration, is fundamental to several aspects of successful

47 ageing, including activities in daily living (de Dieuleveult et al., 2017), speech  
48 perception (Venezia et al., 2015) and balance maintenance (Bronstein, 2016;  
49 Merriman et al., 2015; Setti et al., 2011). Recently, multisensory integration  
50 has been emphasised as a candidate tool for probing healthy cognitive  
51 function across the lifespan (Denervaud et al., 2020; Murray et al., 2018;  
52 Wallace et al., 2020) as it appears closely linked with cognitive outcomes in  
53 ageing (Chan et al., 2015; Hernández et al., 2019). Despite this, very little is  
54 known regarding the correspondence between multisensory perception and  
55 brain structure in ageing. The aim of the current study was to identify if  
56 multisensory integration, assessed using the Sound-Induced Flash Illusion  
57 (SIFI; Shams et al., 2000), can inform differences in grey matter density in the  
58 ageing brain.

59 When information is received to more than one sense, our sensory systems  
60 use a number of cues, including spatial co-localisation and temporal  
61 synchrony between signals, to determine if inputs originate from the same  
62 source, and should therefore be integrated. For example, when following a  
63 conversation we would expect the lip movements and speech sounds of our  
64 companion to be closely linked in time and space, whereas irrelevant sounds  
65 may not be reliably matched. If signals do originate from the same source,  
66 integration may enhance perceptual judgements (e.g. speech  
67 comprehension). A traditional view was that sensory inputs are first  
68 represented in sensory specific cortices followed by convergence in  
69 multisensory areas including intraparietal sulcus, inferior parietal lobule and  
70 superior temporal sulcus (STS). However, most regions previously considered  
71 “sensory specific” are now known to respond to information from other

72 modalities (for reviews see Ghazanfar & Schroeder, 2006; Macaluso, 2006;  
73 Murray et al., 2016). Similarly unisensory inputs can activate multisensory  
74 association areas. Calvert et al. (2000) showed that when participants listened  
75 to/watched a story being read, unimodal visual and auditory stimuli both  
76 activated the STS but this activation was greater when auditory and visual  
77 stimuli were presented together and close in time. Similarly, audiovisual  
78 speech illusions such as the McGurk effect (McGurk & MacDonald, 1976),  
79 appear dependent on pre-stimulus STS activity (Keil et al., 2012), and both  
80 illusion perception and corresponding STS activation specifically occur when  
81 stimuli are synchronous (Jones & Callan, 2003). Functional evidence to date  
82 therefore shows that multisensory perception is associated with a widespread  
83 network of sensory specific and multisensory regions, and activation of these  
84 regions depends upon the synchronicity of multisensory inputs.

85 The Sound-Induced Flash Illusion (SIFI) provides a promising, and  
86 increasingly popular, avenue to investigate multisensory perception due to its  
87 high fidelity and ease of implementation (for reviews see Hirst, McGovern,  
88 Setti, et al., 2020; Keil, 2020). In this illusion, presenting one visual “flash” with  
89 two sequential auditory “beeps” results in the perception of two flashes, even  
90 though only one occurred. The illusion reflects optimal integration (Shams et  
91 al., 2005); that is, illusion perception is governed by the reliability of each  
92 sense (reliability weighting) and, in Bayesian terms, priors, reflecting the belief  
93 that a) multiple stimuli will occur in each sense and b) auditory and visual  
94 stimuli originate from a common cause (causal inference; Shams &  
95 Beierholm, 2010). In the brain, these neurocomputational processes occur in  
96 a spatiotemporal hierarchy, such that reliability weighting is thought to first

97 occur in parietal-temporal regions followed by frontal mechanisms guiding top-  
98 down causal inference (Cao et al., 2019). For example, recent fMRI work  
99 showed that activation in the lateral prefrontal cortex predominantly  
100 represented observers 'separate' vs. 'common' cause decisions (causal  
101 inference), whilst activation in the Frontal Eye Fields and intraparietal sulcus  
102 concurrently encoded visual and auditory spatial locations and subsequent  
103 motor responses, in addition to causal inference (Mihalik & Noppeney, 2020).  
104 Optimal integration facilitates effective action and perceptual decisions, taking  
105 into account current sensory function, viewing conditions and prior  
106 experience. For instance, when crossing the road on a foggy day we must  
107 reduce the weighting of visual information (owing to poor visibility) and  
108 consider the likelihood that the sound of a looming vehicle corresponds to the  
109 moving shape in the distance. Efficient sensory integration thus supports  
110 accurate and safe action in the multisensory world.

111 In the SIFI, when one flash is presented with two beeps, participants are more  
112 likely to perceive two flashes if audition is considered more reliable, if  
113 discontinuous stimuli are expected in the visual modality (e.g. Wang et al.,  
114 2019) or if auditory and visual stimuli are thought to arise from a common  
115 cause, for example, because they occur close in time. In healthy younger  
116 adults, presenting the second beep with increasing temporal separation from  
117 the flash-beep pair (Stimulus Onset Asynchrony, SOA) decreases illusion  
118 susceptibility (Shams et al., 2002) allowing measurement of the time window  
119 within which sensory integration occurs. The SIFI therefore gauges the  
120 sensitivity of the multisensory brain to temporal synchrony, and reduced SIFI

121 susceptibility at longer SOAs may reflect efficient multisensory perception in  
122 younger adults.

123 SIFI susceptibility can be considered in terms of magnitude, regardless of  
124 SOA, or susceptibility across SOAs. The magnitude of SIFI susceptibility is  
125 high for short SOAs even in younger adults, however in older adults this  
126 magnitude is sustained over longer SOAs (e.g. McGovern et al., 2014), in line  
127 with age-related widening of the temporal binding window. There remains little  
128 consensus on whether differences in sustained susceptibility at longer SOAs  
129 indicates efficient or inefficient perception. One possibility is that sustained  
130 susceptibility is adaptive, enabling older adults to capitalize on information  
131 from several senses despite declines in unisensory precision and accuracy  
132 (e.g. Hirst, Setti, et al., 2019). Conversely, sustained SIFI susceptibility at long  
133 SOAs has been associated with several pathological outcomes, including  
134 poorer cognitive scores (Hernández et al., 2019), cognitive impairment (Chan  
135 et al., 2015) and fall risk (Merriman et al., 2015; Setti et al., 2011). The exact  
136 mechanism linking broader integration in the SIFI with these negative  
137 outcomes remains unknown. Understanding what these age-related changes  
138 in perception can tell us about the underlying structure, and function, of the  
139 brain is therefore of prominent interest.

140 The only study, to our knowledge, that has examined the structural correlates  
141 (in young adults) of SIFI susceptibility (de Haas et al., 2012) found that the  
142 grey matter volume of the primary visual cortex was negatively associated  
143 with susceptibility to the SIFI. Although the structural correlates of SIFI in  
144 older adults have yet to be investigated, evidence suggests that older adults  
145 might make greater use of processes linking priors in perception. Chan et al.,

146 (2017) found that older adults manifested increased pre-stimulus beta-band  
147 activity during the SIFI, and interpret this as reflecting greater use of  
148 perceptual priors. An increased use of priors in ageing could reflect increased  
149 reliance on “rules of thumb” to guide perception, stronger priors built from a  
150 longer life experience, or both of these processes. It is currently unknown  
151 whether observed differences in neural dynamics correspond to structural  
152 differences in the ageing brain, since an investigation of the structural  
153 associates of SIFI perception, or multisensory perception in general, in older  
154 adults has yet to be conducted.

155 The aim of the present study was to identify if different patterns of SIFI  
156 susceptibility in ageing are associated with underlying differences in grey  
157 matter volume. To address this, we focused on data acquired from a large  
158 cohort of older adults who took part in an MRI study within The Irish  
159 Longitudinal Study on Ageing (TILDA). TILDA is the only nationally  
160 representative study on ageing to date to incorporate a measure of  
161 multisensory function into its healthcare assessment and therefore provides a  
162 unique opportunity to gain insights into the role of multisensory perception in  
163 ageing. In the current analysis, we focused on two groups: middle-aged (49 –  
164 65 years) and older (>75 years) adults within this study (n = 217) to provide  
165 the first exploration of the structural correlates of SIFI susceptibility in the  
166 ageing brain.

## 167 **2. Methods**

### 168 **2.1 Participants**

169 Participants were drawn from wave 3 of TILDA, a population representative  
170 sample of individuals aged over 50 from across the Republic of Ireland (for  
171 details of the sampling design see Whelan and Savva, 2013). Participants  
172 completed a Computer Assisted Personal Interview (CAPI), which was carried  
173 out by a trained interviewer, as well as a comprehensive clinic-based health  
174 assessment in which the SIFI was administered. The study was approved by  
175 the Faculty of Health Sciences Ethics Committee, Trinity College Dublin,  
176 Ireland, and protocols conformed with the Declaration of Helsinki. All  
177 participants provided written, informed consent when they first participated in  
178 the study and again at testing in wave 3 (the data from which are focus of this  
179 study). Additional ethics approval was received for the MRI sub-study from the  
180 St James's Hospital/Adelaide and Meath Hospital, inc. National Children's  
181 Hospital, Tallaght Research Ethic Committee, Dublin, Ireland. Those  
182 attending for MRI also completed an additional MRI-specific consent form.

183 The MRI sampling procedure was the same as that previously described  
184 (Boyle et al., 2020; Carey et al., 2019). In total, 578 participants attended for  
185 scanning; 18 did not provide data (due to claustrophobia/nerves [n=14], or  
186 MRI contraindication [n=4]); 61 scans were excluded due to data quality and  
187 processing errors (motion artifacts [n = 33], grey matter/white matter lesions  
188 [n = 18], image shearing of the cerebellum [n = 2], or technical error [n = 8]).  
189 Participants reporting a medical history of Parkinson's Disease, Transient  
190 Ischaemic Attack or Stroke were not included in the analysis (n = 15).

191 Following these exclusions the total number of participant scans available for  
192 analysis was 484.

193 Participants' scans were excluded if the participant did not complete the SIFI

194 test during the health assessment (n = 37) or if they were missing variables  
195 used as covariates in sensitivity analyses, including measures used to create  
196 cognitive factors (Montreal Cognitive Assessment, MoCA [n = 2], prospective  
197 memory [n = 1], Mini Mental State Examination [n = 1], Colour Trails Task,  
198 CTT [n = 4], Choice Response Time [n = 10], Sustained Attention to  
199 Response Time, SART [n = 6]<sup>1</sup>), physical and health measures (Body Mass  
200 Index, BMI [n = 1], Timed Up and Go, TUG [n = 1], Centre of Epidemiological  
201 Studies on Depression, CESD, score [n = 3]) and sensory measures (visual  
202 acuity [n = 1], self-reported vision [n = 1], hearing aid use [n = 1]). Participants  
203 with a MoCA score below 23, suggesting mild cognitive impairment (Carson et  
204 al., 2018), were also excluded (n = 45). For a clear comparison of ageing  
205 effects from middle- to older-age whilst also modelling interactions with  
206 multisensory perception, we focused our analysis on the older (aged 71–87  
207 years) and middle-aged (aged 49 – 64 years) members of our sample  
208 (identified using tertile cut offs within our population; see Supplementary  
209 Figure S1). This sampling procedure was adopted from a previous study of  
210 the TILDA MRI cohort (Carey et al., 2019). Moreover, other studies have  
211 shown that age-related grey matter decreases in networks associated with  
212 sensory processing (e.g. the lateral occipital cortex) are most prominent in  
213 >75 year olds (Hafkemeijer et al., 2014). A final number of 217 participants  
214 were therefore included in our analysis (Table 1).

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<sup>1</sup> The 6 participants excluded due to SART were because of missing data (n = 2), missing over 50% of the possible go trials (n = 3) or pressing on over 80% of the “don’t go” trials (n = 1)

	Older			Middle-Aged			All
Accuracy	1	0.5	0	1	0.5	0	
	N=25	N=18	N=73	N=34	N=19	N=48	N=217
<b>Age</b>							
M (SD)	75.8 (4.39)	74.9 (3.33)	75.5 (4.07)	58.6 (4.16)	58.3 (2.58)	58.5 (3.84)	67.6 (9.35)
Median [Min, Max]	75.0 [71.0, 87.0]	75.0 [71.0, 81.0]	74.0 [71.0, 87.0]	59.5 [49.0, 64.0]	58.0 [53.0, 63.0]	58.0 [51.0, 64.0]	71.0 [49.0, 87.0]
<b>Sex n (%)</b>							
Male	14 (56.0)	10 (55.6)	31 (42.5)	20 (58.8)	9 (47.4)	21 (43.8)	105 (48.4)
Female	11 (44.0)	8 (44.4)	42 (57.5)	14 (41.2)	10 (52.6)	27 (56.2)	112 (51.6)
<b>Education n (%)</b>							
Primary	5 (20.0)	1 (5.6)	15 (20.5)	4 (11.8)	0 (0)	8 (16.7)	33 (15.2)
Secondary	8 (32.0)	8 (44.4)	26 (35.6)	10 (29.4)	6 (31.6)	21 (43.8)	79 (36.4)
Third	12 (48.0)	9 (50.0)	32 (43.8)	20 (58.8)	13 (68.4)	19 (39.6)	105 (48.4)
<b>MoCa</b>							
Mean (SD)	26.2 (1.94)	25.8 (1.86)	26.0 (1.97)	27.6 (1.92)	26.9 (1.82)	26.8 (1.97)	26.5 (2.01)
Median [Min, Max]	26.0 [23.0, 29.0]	26.0 [23.0, 29.0]	26.0 [23.0, 30.0]	28.0 [23.0, 30.0]	27.0 [23.0, 30.0]	27.0 [23.0, 30.0]	27.0 [23.0, 30.0]

**Table 1.** Sample characteristics of age groups (stratified by accuracy on the 230ms SOA (post) condition to allow comparisons of interacting groups). See section 3.2.1 for calculation details of visual acuity and self-reported sensory functions. MoCa = Montreal Cognitive Assessment.

## 216 2.2 Sound-Induced Flash Illusion Assessment

217 Participants completed a task based on the SIFI (see Hernández et al., 2019;  
218 Hirst, Setti, Kenny, & Newell, 2019 for further details) as part of the TILDA  
219 healthcare assessment. Each participant was seated approximately 60 cm in  
220 front of a laptop computer and instructed to fixate on a cross at the centre of  
221 the screen. In the first block of trials, participants judged the number of flashes  
222 presented. Flashes (1.5° visual angle; approximately 5° below fixation; 16 ms  
223 duration) and beeps were presented in one of 5 possible stimulus  
224 combinations (2 Beeps + 2 Flashes [2B2F]; 1 Beep + 1 Flash [1B1F]; 0 Beeps  
225 + 2 Flashes [0B2F]; 0 Beeps + 1 Flash [0B1F]; 2 Beeps + 1 Flash [2B1F]). On

226 2B2F trials, a synchronous flash and beep pair was followed by a second  
227 flash-beep pair presented at one of three SOAs; 70, 150 or 230 ms. On critical  
228 “illusory” trials (2B1F) one of the beeps was synchronous with the flash and  
229 the second occurred either before (-230, -150, or -70 ms) or after (70, 150, or  
230 230 ms) the flash, referred to as “Pre” and “Post” conditions respectively. In  
231 this block, there were therefore 12 trial types, each presented twice in a  
232 random order. In a second block of trials, participants judged the number of  
233 beeps, presented via the laptop speakers. In this block 2 beeps (3500 Hz;  
234 approximately 80 dB; 10 ms duration; 1 ms ramp) were presented with no  
235 flashes (2B0F) at one of three SOAs; 70, 150 or 230 ms. These three possible  
236 trial types were each presented twice, in a random order. A practice block was  
237 presented before each block containing one trial from each condition  
238 (excluding 2B1F “Pre” conditions, 0B1F and 2B2F at 150 and 230 ms). Vocal  
239 responses were recorded by the nurse, who sat near the participant, using the  
240 number keys on a laptop. The SIFI took approximately 6 minutes for each  
241 participant.

### 242 **2.3 Image acquisition and processing**

243 The MRI data was obtained with a mean (SD) of 62 (40) days after the health  
244 assessment. The neuroimaging scans were acquired at the National Centre  
245 for Advanced Medical Imaging (CAMI), St. James’ Hospital, Dublin, Ireland,  
246 via a 3T Philip’s Achieva system with a 32-channel head coil. The protocol  
247 included a variety of scans per participant, including a T1-weighted MR image  
248 acquired using a 3D Magnetisation Prepared Rapid Gradient Echo (MP-  
249 RAGE) sequence, with the following parameters: FOV (mm): 240 x 240 x 162;  
250 0.8 × 0.8 × 0.9 mm<sup>3</sup> resolution; SENSE factor: 2; TR: 6.7 ms; TE: 3.1 ms; flip

251 angle: 8°.

252 Images were preprocessed using the Statistical Parametric Mapping (SPM12)  
253 toolbox (Wellcome Department of Cognitive Neurology, Institute of Neurology,  
254 London, UK) in MATLAB R2017b (Mathworks, Sherborn, MA, USA). The  
255 preprocessing pipeline was identical to that previously described (Boyle et al.,  
256 2020). The code used to auto-reorient and preprocess the data is available at  
257 <https://github.com/rorytboyle/brainPAD>. All images were non-linearly  
258 registered to a custom DARTEL template generated from the group mean of  
259 all eligible preprocessed scans (i.e. prior to our study-specific behavioural  
260 exclusion criteria), affine registered to MNI space (1 mm<sup>3</sup>) and resampled with  
261 modulation to preserve the total amount of signal from each voxel. Images  
262 were smoothed with a 4 mm full-width at half maximum Gaussian kernel and  
263 visually inspected for accurate segmentation.

## 264 **2.4 Statistical analysis**

265 Analyses were conducted using SPM12 in MATLAB (2020a). Voxel-wise  
266 statistical comparisons were performed on the whole brain. We then assessed  
267 whether peak effects fell within a mask, defined using AAL regions highlighted  
268 from a review of neuroimaging studies using the SIFI (Hirst, McGovern, et al.,  
269 2020). These regions were extracted, merged and smoothed with a 4mm  
270 kernel in SPM. The image file for this mask, and all resulting contrast images,  
271 can be found at  
272 [https://osf.io/n2mdp/?view\\_only=5dff377db9854e839e18862ceb96a4e4](https://osf.io/n2mdp/?view_only=5dff377db9854e839e18862ceb96a4e4).

273 For each analysis participants were grouped based on their accuracy in the  
274 critical, illusory (2B1F), condition of the SIFI test. Importantly, because two

275 trials were presented per condition participants could score one of three  
276 discrete values, 0, 0.5 or 1 proportion correct, although proportion is  
277 traditionally considered continuous, we had three distinct classes of  
278 individuals available for our analysis. Four analyses were therefore conducted  
279 with grouping based on accuracy in either the “Pre” (-230 and -150 ms SOA)  
280 or “Post” conditions (150 and 230 ms SOA). Short SOA conditions (70 ms)  
281 were not included because previous studies, including those with the TILDA  
282 cohort, showed that older adults were less susceptible to the illusion at this  
283 SOA, likely due to reduced temporal acuity in ageing (Hirst, McGovern, et al.,  
284 2020). Indeed, participants in this study had the lowest accuracy for judging  
285 two, unimodal, flashes and two, unimodal, beeps, at 70 ms relative to other  
286 SOAs (see supplementary table S4). Our base model for each analysis was a  
287 full factorial design with 2 factors, Accuracy group (0, 0.5, 1) and Age group  
288 (middle aged and older aged), whilst controlling for sex (Supplemental Figure  
289 S2). Due to unequal sample sizes, we assumed unequal variance across  
290 groups in our design. An absolute threshold mask of 0.2 was implemented  
291 and images were proportionally scaled using total intracranial volume. All  $p$   
292 values are reported corrected for Family-Wise Error (FWE) based on the  
293 whole brain. Due to known statistical concerns regarding cluster-wise  
294 inference (Eklund et al., 2016), we focused on peak-level significance for our  
295 conclusions.

### 296 **3. Results**

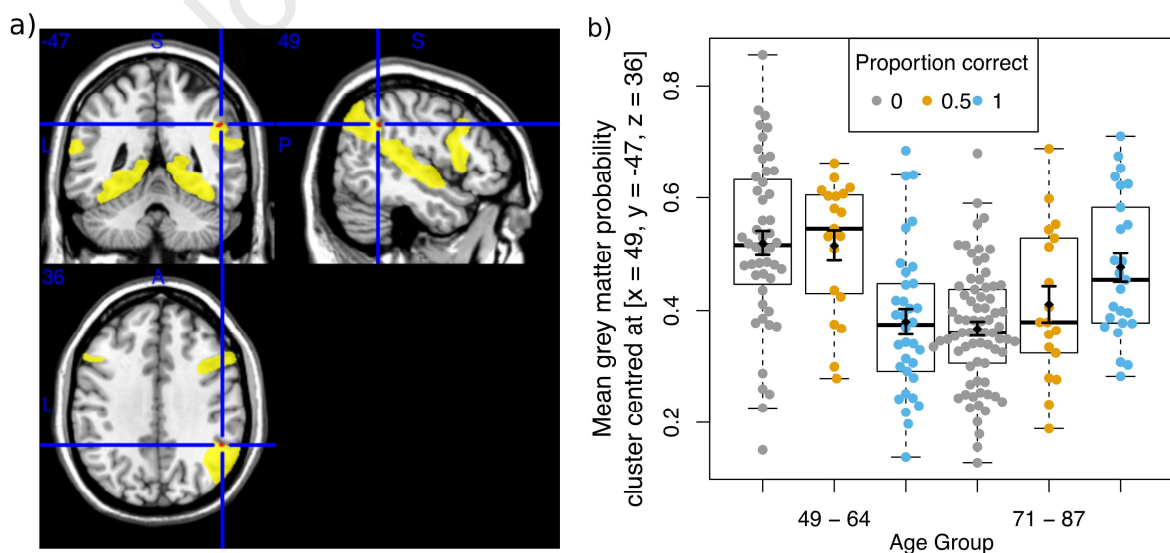
297 Because participants were grouped based on behavioural performance in  
298 illusory conditions, we focus our results section on differences in grey matter  
299 volume between these groups. However, it is notable that these groups

300 performed very similarly in non-illusory control conditions (see supplementary  
301 table S4).

### 302 3.1 Non-adjusted models

303 As expected widespread differences in grey matter volume were observed  
304 between middle-aged and older adult groups. Age-related decreases were  
305 most prominent in the right hippocampus, left amygdala and frontal cortex  
306 (complete statistical results can be found at  
307 [https://osf.io/n2mdp/?view\\_only=5dff377db9854e839e18862ceb96a4e4](https://osf.io/n2mdp/?view_only=5dff377db9854e839e18862ceb96a4e4)).

308 There was a significant Accuracy by Age group interaction for grey matter  
309 volume in the right Angular Gyrus ( $p_{FWE} = .003$ ,  $F = 20.2$ ,  $Z = 5.62$ , cluster  
310 equivK = 37, AG;  $x = 49$ ,  $y = -47$ ,  $z = 36$ ). This effect occurred only when  
311 participants were grouped based on accuracy at 230 ms (Post). As shown in  
312 Figure 1, increased grey matter in the right AG was associated with greater  
313 illusion susceptibility in middle-aged adults, whereas in older adults, increased



**Figure 1.** a) Significant Age group by Accuracy (in 230 ms “Post” condition) interaction in the right AG (red) overlaid on the ROI mask (yellow) b) Mean grey matter probability for extracted cluster in each group. Boxplots illustrate inter-quartile range and median. Black diamonds with error bars indicate group means and standard errors.

314 grey matter in the right AG was associated with reduced illusion susceptibility.

315 The main effect of accuracy grouping failed to reach significance across

316 models and there were no significant peak-level interactions between Age

317 group and Accuracy for any of the additional conditions.

### 318 **3.2 Adjusted sensitivity analyses**

319 The data available from TILDA allowed us to control for a range of potentially

320 confounding variables. We therefore conducted three further sensitivity

321 models to consider sensory differences, cognitive function and physical and

322 mental health.

#### 323 **3.2.1 Sensory function**

324 To control for individual differences in sensory function, the following factors

325 were incorporated into our model; self-reported vision and self-reported

326 hearing (1 = Excellent to 5 = Poor), visual acuity (100 – 50 \* LogMAR visual

327 acuity in the best eye), auditory and visual temporal discrimination (accuracy

328 for judging 2 auditory stimuli or 2 visual stimuli with 70 ms SOA respectively)

329 and hearing aid use (yes/no). All non-binary factors were mean-centred. The

330 significant Age group by Accuracy interaction held when including sensory

331 measures in the model. That is, a significant peak was observed in the right

332 AG ( $x = 49$ ,  $y = -47$ ,  $z = 36$ ;  $p_{\text{FWE}} = .004$ ,  $F = 20.15$ ,  $Z = 5.61$ , cluster equivK =

333 31). As in our base model, there were widespread effects of ageing and no

334 main effect of accuracy.

#### 335 **3.2.2 Cognitive function**

336 Our second sensitivity analysis controlled for differences in education (1 =

337 Primary, 2 = Secondary, 3 = Tertiary/Higher) and cognitive function. TILDA

338 collected data using a large battery of cognitive assessments, therefore, to  
339 limit multicollinearity an exploratory factor analysis was conducted on 27  
340 cognitive measures (Hirst et al., In Prep<sup>a</sup>), the derived factors were;  
341 “Executive Function” reflecting mainly performance on the CTT (Maj et al.,  
342 1993), “Memory” reflecting mainly immediate and delayed recall of word lists  
343 and “Processing Speed” reflecting performance on a Choice Response Time  
344 task (see Supplementary Figure S2). All factors were included in the model as  
345 mean-centred covariates. The Age group by Accuracy interaction in the right  
346 AG held when considering measures of cognitive function in the model ( $p_{\text{FWE}}$   
347 = .008,  $F = 19.2$ ,  $Z = 5.47$ , cluster equivK = 28) and there remained  
348 widespread ageing effects and no main effect of accuracy in this model.

### 349 **3.3.3 Physical and mental health**

350 Our final sensitivity model controlled for differences in depression (CESD) and  
351 physical health measures including; BMI, TUG time, self-reported physical  
352 activity level (see Supplementary Table 3), mean (seated) arterial blood  
353 pressure (calculated as (systolic + (2 \* diastolic))/3), use of cardiovascular  
354 medication (antihypertensives, yes/no), history of one or more cardiovascular  
355 disease or event (angina, heart attack, heart failure, heart murmur, arterial  
356 fibrillation, see Supplementary Table 2), self-reported high cholesterol  
357 (yes/no), diabetes (yes/no), smoking history (1 = never smoked, 2 = past  
358 smoker, 3 = current smoker). All non-binary covariates were mean-centred.  
359 The Age group by Accuracy interaction in the right AG held when considering  
360 health measures in the model ( $p_{\text{FWE}} = .005$ ,  $F = 19.79$ ,  $Z = 5.55$ , cluster  
361 equivK = 40), there remained widespread age effects and no main effect of  
362 accuracy.

363

#### 4. Discussion

364 In this study we sought to identify structural grey matter differences  
365 associated with multisensory integration in ageing. We compared a group of  
366 middle-aged and older adults who had completed the Sound-Induced Flash  
367 Illusion (SIFI) and an MRI study as part of The Irish Longitudinal Study on  
368 Ageing (TILDA). A significant interaction was observed in the right Angular  
369 Gyrus (AG) such that increased grey matter volume in middle-aged adults  
370 was associated with increased susceptibility to the SIFI illusion, whilst  
371 increased grey matter volume in older adults was associated with decreased  
372 susceptibility to the illusion. To our knowledge, this is the first study to  
373 investigate grey matter differences associated with multisensory, in particular  
374 audiovisual, integration in ageing (but see O'Callaghan et al., (2018) for an  
375 investigation of sensorimotor training on grey matter volume in older adults).

376 A practical consideration highlighted by the current study is that the described  
377 effects occurred only for SIFI susceptibility in the SOA of 230 ms "Post"  
378 condition. In general, the participants in the TILDA cohort were more  
379 susceptible to the illusion when the first beep *preceded* the flash-beep pair  
380 (Hirst et al., 2020). This contrasts with reported effects in young adults, in  
381 which integration appears stronger when the beep follows the flash (e.g.  
382 Dixon & Spitz, 1980; Stevenson et al., 2012) and may suggest a shift in the  
383 symmetry of the temporal binding window with age. Since only three studies  
384 using the SIFI (including TILDA) have included SOAs where the beep  
385 precedes the flash-beep pair (Hirst, McGovern, et al., 2020), understanding  
386 differences in pre- and post-flash effects requires further investigation.

387 One study to date has investigated grey matter differences associated with  
388 SIFI perception, and this study focused on young adults. De Haas et al.  
389 (2012) found that grey matter in primary visual cortex negatively predicted  
390 SIFI perception. A limitation of the SIFI paradigm in TILDA is that, to minimise  
391 testing time within the healthcare assessment, the number of trials is limited to  
392 two per condition. This meant that our SIFI data were not well suited to the  
393 correlational approach implemented by De Haas et al. (2012). Instead we  
394 treated proportion correct as a discrete grouping factor. This exploratory  
395 analysis highlights a region of interest to researchers investigating  
396 multisensory perception in ageing, the AG. However future work, containing a  
397 larger number of trials would enable more in depth modelling of multisensory  
398 perception in the ageing brain (including approaches such as signal detection  
399 theory e.g. McGovern et al., 2014).

#### 400 **4.1 The Angular Gyrus (AG) in multisensory perception**

401 The AG has been described as a “cross-modal hub” and “convergence zone”  
402 (for review see Seghier, 2013). Situated between occipital, temporal and  
403 parietal poles, it plays a central role in the coordination of several systems  
404 associated with perception, action and cognition. Given the proposed role of  
405 the AG in sensory integration it has unsurprisingly been linked with SIFI  
406 perception in younger adults and effects reported so far with SIFI have been  
407 right lateralised. Transcranial Magnetic Stimulation (TMS) applied specifically  
408 to the right AG reduces SIFI susceptibility (Hamilton et al., 2013; Kamke et al.,  
409 2012). In an fMRI investigation Watkins, Shams, Tanaka, Haynes and Rees  
410 (2006) found stronger activation of V1, the right Superior Temporal Sulcus  
411 (rSTS) and the right Superior Colliculus for trials inducing the illusion versus

412 no illusion. Together, these studies show that the right AG is a region that is  
413 critical to SIFI perception and support a lateralisation of processing.

414 Despite strong evidence for a role of AG in SIFI perception, the nature of the  
415 role it plays requires consideration. This region has sparse connectivity with  
416 primary sensory cortices (Binder et al., 2009) and is located superior to the  
417 temporo-parietal region recruited in reliability weighted fusion (Cao et al.,  
418 2019). Thus, the AG does not necessarily play a role in early sensory fusion.  
419 It is possible that the AG supports higher order cognitive processing  
420 associated with SIFI perception. The AG has rich direct projections with  
421 regions associated with memory and attention, including the hippocampus via  
422 the inferior longitudinal fascicle, the superior frontal gyrus via the  
423 occipitofrontal fascicle, and medial and inferior frontal gyri via the second and  
424 third branch of the superior longitudinal fascicle respectively (Seghier, 2013).  
425 In line with this, several studies have shown that SIFI is related to cognitive  
426 ability including memory and general cognitive function (Hernández et al.,  
427 2019; Michail & Keil, 2018). The link between SIFI perception and cognitive  
428 performance may therefore lie in the AG. In the current study we controlled for  
429 a large number of covariates but individual differences in cognition did not  
430 mediate the observed effects, indeed, the location and size of the cluster  
431 remained highly similar across analyses. These findings highlight the AG as a  
432 candidate region of interest to understand how the SIFI is associated with  
433 cognition.

434 The AG has been associated with numerical cognition, which would also  
435 underlie SIFI performance, because it involves numerical judgements  
436 (Dehaene et al., 2003; Hamilton et al., 2013). For example, in a previous

437 study using the line bisection task, priming participants with lower numbers  
438 typically biases participants' responses towards the left, and TMS to the right  
439 AG disrupts this effect (Cattaneo et al., 2009). One of the numerical functions  
440 of the AG therefore appears to be the spatial representation of numbers. The  
441 control measures included in our sensitivity analysis can account for this to  
442 some degree. Our factor "Executive function" was highly representative of  
443 CTT performance, which involves visuospatial scanning of numbers. Similarly,  
444 in our controls of sensory function, we included accuracy for judging two  
445 flashes and two beeps when presented unimodally at 70 ms SOA. We  
446 therefore also controlled for unisensory numerical judgements. However, we  
447 cannot rule out that other facets of numerical cognition, that we were not able  
448 to control for, contribute towards the observed associations.

#### 449 **4.2 The differential effect of grey matter volume in AG with ageing**

450 The main finding of this study was that grey matter in the AG corresponded to  
451 differing patterns of illusion susceptibility in older and middle-aged adults; in  
452 older adults those susceptible to the SIFI had less grey matter than those who  
453 were not susceptible; in middle-aged adults those susceptible had more grey  
454 matter than those not susceptible. We speculate that this pattern reflects a  
455 shift in the interactions of the AG with other brain regions from middle to late  
456 adulthood.

457 Ageing has been reported to be associated with a functional reorganisation of  
458 the brain and older adults have been proposed to engage different brain  
459 regions to perform the same tasks as younger adults (i.e. compensation,  
460 Cabeza et al., 2018). An example involving the AG is observed in memory

461 retrieval, in which older adults recruit more posterior regions (such as the AG  
462 and occipital gyri) compared with middle-aged adults (Bréchet et al., 2018). If  
463 the functional use of the AG shifts with age, we cannot assume that grey  
464 matter in the AG should have the same relationship with behaviour across  
465 age groups. However, as evidence regarding neural reorganisation in ageing  
466 remains inconclusive (Morcom & Henson, 2018; Morcom & Johnson, 2015),  
467 this interpretation is speculative.

468 Older adults may process multisensory perceptual decisions differently to  
469 younger adults. With reference to Bayesian Causal inference (Cao et al.,  
470 2019; Körding et al., 2007; Rohe et al., 2018; Shams & Beierholm, 2010),  
471 older adults might make greater use of perceptual priors when making  
472 temporal judgements compared with younger adults. Chan et al. (2017)  
473 reported increased pre-stimulus beta activity, associated with linking priors  
474 and predictions, in older adults whilst performing the SIFI task. Similarly, in  
475 speech perception, where bimodal auditory and visual inputs might improve  
476 speech comprehension (i.e. multisensory enhancement), older adults show  
477 greater multisensory enhancement relative to younger adults only when words  
478 are embedded in unpredictable semantic content (Maguinness et al., 2011),  
479 suggesting that older adults rely on predictions informed by context and priors  
480 to make perceptual judgements.

481 The AG might act as a “convergence zone” between bottom-up and top-down  
482 information (see Figure 3 in Seghier, 2013). In multisensory perception, the  
483 degree of top-down influence may alter the relative contributions of sensory  
484 information (the likelihood, in Bayesian terms) and prior expectations  
485 (including the causal prior) to the final estimate. Whilst the current analysis

486 cannot speak to the relative inputs to the AG, our findings suggest the AG has  
487 a contrasting impact on perception in middle-aged and older adults, perhaps  
488 suggesting this region interacts differently with other areas within this network.  
489 Future work can address this hypothesis through computational modelling (to  
490 alter the relative weights of priors and reliability in perceptual judgements) and  
491 connectivity analyses. The current findings highlight the AG as a candidate  
492 seed region for future connectivity models of how perception and cognition  
493 are bridged in the ageing brain.

494 A final observation is that differing hypotheses have been presented regarding  
495 the role of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA)  
496 and multisensory perception in younger versus older adults. GABA  
497 concentrations are thought to decrease with age resulting in altered inhibitory  
498 control (Pauwels et al., 2018) which might, in turn, limit the inhibition of  
499 irrelevant cross-sensory information (Mozolic et al., 2011; although see  
500 Guerreiro et al., 2010, 2013; Hirst, Kicks, et al., 2019; Van Gerven &  
501 Guerreiro, 2016). In younger adults however, a positive association between  
502 GABA in the STS and integration has been observed (Balz et al., 2016). The  
503 role of GABA on multisensory (including SIFI) perception in older adults  
504 remains to be tested, and future work may be needed to examine if similar  
505 relationships between GABA concentrated in superior temporal regions has  
506 similar associations with multisensory perception in older adult groups.

507

### Conclusions

508 To our knowledge, the current study is the first to assess structural grey  
509 matter differences associated with multisensory integration in ageing, using

510 the SIFI. We show specific interactions in the AG, a region known to be  
511 associated with the coordination of several senses and cognitive processes.  
512 Middle-aged and older adults showed differing associations between grey  
513 matter in the AG and illusion perception. We interpret these effects as  
514 indicating a shift in the functional role of the AG with age, possibly relating to  
515 the balance of top-down and bottom-up inputs. Future research comparing the  
516 structural and functional connectivity of the AG in the ageing brain is needed  
517 to test this hypothesis. These findings show that multisensory integration,  
518 assessed using the SIFI, can be linked to specific structural changes in the  
519 ageing brain.

## 520 References

- 521 Balz, J., Keil, J., Roa Romero, Y., Mекle, R., Schubert, F., Aydin, S.,  
522 Ittermann, B., Gallinat, J., & Senkowski, D. (2016). GABA concentration  
523 in superior temporal sulcus predicts gamma power and perception in the  
524 sound-induced flash illusion. *NeuroImage*, *125*, 724–730.  
525 <https://doi.org/10.1016/j.neuroimage.2015.10.087>
- 526 Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is  
527 the semantic system? A critical review and meta-analysis of 120  
528 functional neuroimaging studies. *Cerebral Cortex*, *19*(12), 2767–2796.  
529 <https://doi.org/10.1093/cercor/bhp055>
- 530 Boyle, R., Jollans, L., Rueda-Delgado, L. M., Rizzo, R., Yener, G. G.,  
531 McMorrow, J. P., Knight, S. P., Carey, D., Robertson, I. H., Emek-Savaş,  
532 D. D., Stern, Y., Kenny, R. A., & Whelan, R. (2020). Brain-predicted age  
533 difference score is related to specific cognitive functions: a multi-site  
534 replication analysis. *Brain Imaging and Behavior*.

- 535 <https://doi.org/10.1007/s11682-020-00260-3>
- 536 Bréchet, L., Grivaz, P., Gauthier, B., & Blanke, O. (2018). Common  
537 Recruitment of Angular Gyrus in Episodic Autobiographical Memory and  
538 Bodily Self-Consciousness. *Frontiers in Behavioral Neuroscience*, *12*, 1–  
539 10. <https://doi.org/10.3389/fnbeh.2018.00270>
- 540 Bronstein, A. M. (2016). Multisensory integration in balance control. In  
541 *Handbook of Clinical Neurology* (Vol. 137, pp. 57–66).  
542 <https://doi.org/10.1016/B978-0-444-63437-5.00004-2>
- 543 Cabeza, R., Albert, M., Craik, F., Duarte, A., Grady, C., Nyberg, L., Park, D.,  
544 Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018).  
545 Cognitive neuroscience of healthy aging: Maintenance, reserve, and  
546 compensation. *Nature Reviews Neuroscience*, *19*(11), 701–710.  
547 <https://doi.org/10.1038/s41583-018-0068-2>. Cognitive
- 548 Calvert, G. A., Campbell, R., & Brammer, M. J. (2000). Evidence from  
549 functional magnetic resonance imaging of crossmodal binding in the  
550 human heteromodal cortex. *Current Biology*, *10*(11), 649–657.  
551 [https://doi.org/10.1016/S0960-9822\(00\)00513-3](https://doi.org/10.1016/S0960-9822(00)00513-3)
- 552 Cao, Y., Summerfield, C., Park, H., Giordano, B. L., & Kayser, C. (2019).  
553 Causal Inference in the Multisensory Brain. *Neuron*, *102*(5), 1076-  
554 1087.e8. <https://doi.org/10.1016/j.neuron.2019.03.043>
- 555 Carey, D., Nolan, H., Kenny, R. A., & Meaney, J. (2019). Cortical covariance  
556 networks in ageing: Cross-sectional data from the Irish Longitudinal  
557 Study on Ageing (TILDA). *Neuropsychologia*, *122*, 51–61.  
558 <https://doi.org/10.1016/j.neuropsychologia.2018.11.013>
- 559 Carson, N., Leach, L., & Murphy, K. J. (2018). A re-examination of Montreal

- 560 Cognitive Assessment (MoCA) cutoff scores. *International Journal of*  
561 *Geriatric Psychiatry*, 33(2), 379–388. <https://doi.org/10.1002/gps.4756>
- 562 Cattaneo, Z., Silvanto, J., Pascual-Leone, A., & Battelli, L. (2009). The role of  
563 the angular gyrus in the modulation of visuospatial attention by the  
564 mental number line. *NeuroImage*, 44(2), 563–568.  
565 <https://doi.org/10.1016/j.neuroimage.2008.09.003>
- 566 Chan, J. S., Kaiser, J., Brandl, M., Matura, S., Prvulovic, D., Hogan, M., &  
567 Naumer, M. (2015). Expanded temporal binding windows in people with  
568 mild cognitive impairment. *Current Alzheimer Research*, 12(1), 61–68.  
569 <https://doi.org/10.2174/1567205012666141218124744>
- 570 de Dieuleveult, A. L., Siemonsma, P. C., van Erp, J. B. F., & Brouwer, A.-M.  
571 (2017). Effects of aging in multisensory integration: A systematic review.  
572 *Frontiers in Aging Neuroscience*, 9(80), 1–14.  
573 <https://doi.org/10.3389/fnagi.2017.00080>
- 574 de Haas, B., Kanai, R., Jalkanen, L., & Rees, G. (2012). Grey matter volume  
575 in early human visual cortex predicts proneness to the sound-induced  
576 flash illusion. *Proceedings of the Royal Society B: Biological Sciences*,  
577 279(1749), 4955–4961. <https://doi.org/10.1098/rspb.2012.2132>
- 578 Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits  
579 for number processing. *Cognitive Neuropsychology*, 20(3–6), 487–506.  
580 <https://doi.org/10.1080/02643290244000239>
- 581 Denervaud, S., Genatz, E., Matusz, P. J., & Murray, M. M. (2020).  
582 Multisensory gains in simple detection predict global cognition in  
583 schoolchildren. *Scientific Reports*, 1–30. [https://doi.org/10.1038/s41598-](https://doi.org/10.1038/s41598-020-58329-4)  
584 [020-58329-4](https://doi.org/10.1038/s41598-020-58329-4)

- 585 Dixon, N. F., & Spitz, L. (1980). The detection of auditory visual desynchrony.  
586 *Perception*, 9(6), 719–721. <https://doi.org/10.1068/p090719>
- 587 Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI  
588 inferences for spatial extent have inflated false-positive rates.  
589 *Proceedings of the National Academy of Sciences of the United States of*  
590 *America*, 113(28), 7900–7905. <https://doi.org/10.1073/pnas.1602413113>
- 591 Ghazanfar, A. A., & Schroeder, C. E. (2006). Is neocortex essentially  
592 multisensory? *Trends in Cognitive Sciences*, 10(6), 278–285.  
593 <https://doi.org/10.1016/j.tics.2006.04.008>
- 594 Guerreiro, M. J. S., Murphy, D. R., & Van Gerven, P. W. M. (2010). The role  
595 of sensory modality in age-related distraction: a critical review and a  
596 renewed view. *Psychological Bulletin*, 136(6), 975–1022.  
597 <https://doi.org/10.1037/a0020731>
- 598 Guerreiro, M. J. S., Murphy, D. R., & Van Gerven, P. W. M. (2013). Making  
599 sense of age-related distractibility: The critical role of sensory modality.  
600 *Acta Psychologica*, 142(2), 184–194.  
601 <https://doi.org/10.1016/j.actpsy.2012.11.007>
- 602 Hafkemeijer, A., Altmann-Schneider, I., de Craen, A. J. M., Slagboom, P. E.,  
603 van der Grond, J., & Rombouts, S. A. R. B. (2014). Associations between  
604 age and gray matter volume in anatomical brain networks in middle-aged  
605 to older adults. *Aging Cell*, 13(6), 1068–1074.  
606 <https://doi.org/10.1111/accel.12271>
- 607 Hamilton, R. H., Wiener, M., Drebing, D. E., & Branch Coslett, H. (2013).  
608 Gone in a flash: Manipulation of audiovisual temporal integration using  
609 transcranial magnetic stimulation. *Frontiers in Psychology*, 4, 1–7.

- 610 <https://doi.org/10.3389/fpsyg.2013.00571>
- 611 Hernández, B., Setti, A., Kenny, R. A., & Newell, F. N. (2019). Individual  
612 differences in ageing, cognitive status, and sex on susceptibility to the  
613 sound-induced flash illusion: A large-scale study. *Psychology and Aging*,  
614 *34*(7), 978–990. <https://doi.org/10.1037/pag0000396>
- 615 Hirst, R. J., Kicks, E., Allen, H. A., & Cragg, L. (2019). Cross-modal  
616 interference-control is reduced in childhood but maintained in aging: A  
617 lifespan study of stimulus- and response-interference in cross-modal and  
618 unimodal Stroop tasks. *Journal of Experimental Psychology: Human  
619 Perception and Performance*, *45*(5), 553.
- 620 Hirst, R. J., McGovern, D. P., Setti, A., Shams, L., & Newell, F. N. (2020).  
621 What you see is what you hear: Twenty years of research using the  
622 Sound-Induced Flash Illusion. *Neuroscience & Biobehavioral Reviews*,  
623 *118*, 759–774. <https://doi.org/10.1016/j.neubiorev.2020.09.006>
- 624 Hirst, R. J., Setti, A., De Looze, C., Akuffo, K. O., Peto, T., Kenny, R. A., &  
625 Newell, F. N. (2020). The Effect of Eye Disease, Cataract Surgery and  
626 Hearing Aid use on Multisensory Integration in Ageing. *Cortex*.  
627 <https://doi.org/10.1016/j.cortex.2020.08.030>
- 628 Hirst, R. J., Setti, A., Kenny, R. A., & Newell, F. N. (In prep). *Multisensory  
629 integration is associated with Executive Function and Memory but not  
630 Processing Speed in ageing*.
- 631 Hirst, R. J., Setti, A., Kenny, R., & Newell, F. N. (2019). Age-related sensory  
632 decline mediates the Sound-Induced Flash Illusion: Evidence for  
633 reliability weighting models of multisensory perception. *Scientific Reports*,  
634 *9*(19347). <https://doi.org/10.1038/s41598-019-55901-5>

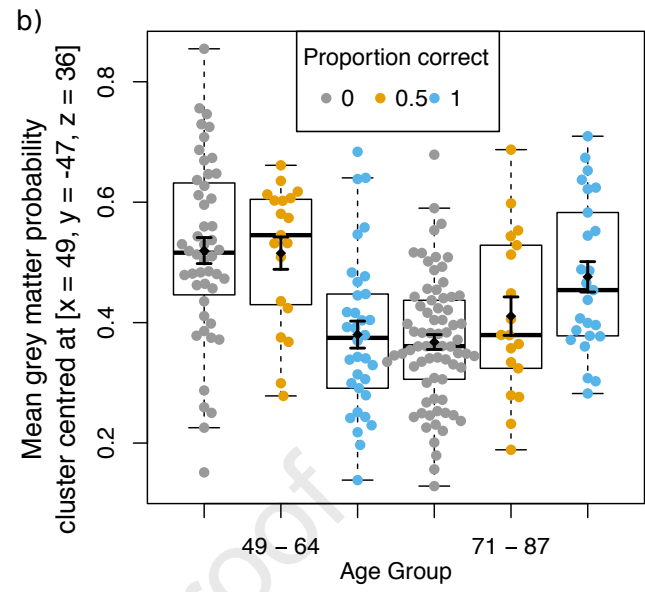
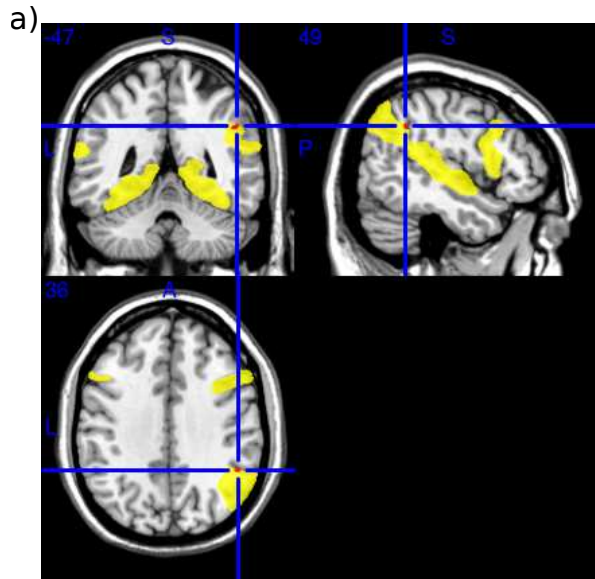
- 635 Jones, J. A., & Callan, D. E. (2003). Brain activity during audiovisual speech  
636 perception: An fMRI study of the McGurk effect. *NeuroReport*, *14*(8),  
637 1129–1133. <https://doi.org/10.1097/00001756-200306110-00006>
- 638 Kamke, M. R., Vieth, H. E., Cottrell, D., & Mattingley, J. B. (2012). Parietal  
639 disruption alters audiovisual binding in the sound-induced flash illusion.  
640 *NeuroImage*, *62*(3), 1334–1341.  
641 <https://doi.org/10.1016/j.neuroimage.2012.05.063>
- 642 Keil, J. (2020). Double Flash Illusions: Current Findings and Future Directions.  
643 *Frontiers in Neuroscience*, *14*. <https://doi.org/10.3389/fnins.2020.00298>
- 644 Keil, J., Müller, N., Ihssen, N., & Weisz, N. (2012). On the variability of the  
645 McGurk effect: Audiovisual integration depends on prestimulus brain  
646 states. *Cerebral Cortex*, *22*(1), 221–231.  
647 <https://doi.org/10.1093/cercor/bhr125>
- 648 Körding, K. P., Beierholm, U., Ma, W. J., Quartz, S., Tenenbaum, J. B., &  
649 Shams, L. (2007). Causal inference in multisensory perception. *PLoS*  
650 *ONE*, *2*(9). <https://doi.org/10.1371/journal.pone.0000943>
- 651 Macaluso, E. (2006). Multisensory processing in sensory-specific cortical  
652 areas. *Neuroscientist*, *12*(4), 327–338.  
653 <https://doi.org/10.1177/1073858406287908>
- 654 Maguinness, C., Setti, A., Burke, K. E., Kenny, R. A., & Newell, F. N. (2011).  
655 The effect of combined sensory and semantic components on audio-  
656 visual speech perception in older adults. *Frontiers in Aging Neuroscience*,  
657 *3*, 1–9. <https://doi.org/10.3389/fnagi.2011.00019>
- 658 Maj, M., D’Elia, L., Satz, P., Janssen, R., Zaudig, M., Uchiyama, C., Starace,  
659 F., Galderisi, S., & Chervinsky, A. (1993). Evaluation of two new

- 660 neuropsychological tests designed to minimize cultural bias in the  
661 assessment of HIV-1 seropositive persons: A WHO study. *Archives of*  
662 *Clinical Neuropsychology*, 8(2), 123–135.  
663 <https://doi.org/10.1093/arclin/8.2.123>
- 664 McGovern, D. P., Roudaia, E., Stapleton, J., McGinnity, T. M., & Newell, F. N.  
665 (2014). The sound-induced flash illusion reveals dissociable age-related  
666 effects in multisensory integration. *Frontiers in Aging Neuroscience*,  
667 6(250), 1–9. <https://doi.org/10.3389/fnagi.2014.00250>
- 668 McGurk, H., & MacDonald, J. (1976). Hearing lips and seeing voices. *Nature*,  
669 264, 746–748. <https://doi.org/10.1038/264746a0>
- 670 Merriman, N. A., Whyatt, C., Setti, A., Craig, C., & Newell, F. N. (2015).  
671 Successful balance training is associated with improved multisensory  
672 function in fall-prone older adults. *Computers in Human Behavior*, 45,  
673 192–203. <https://doi.org/10.1016/j.chb.2014.12.017>
- 674 Michail, G., & Keil, J. (2018). High cognitive load enhances the susceptibility  
675 to non-speech audiovisual illusions. *Scientific Reports*, 8, 1–11.  
676 <https://doi.org/10.1038/s41598-018-30007-6>
- 677 Mihalik, A., & Noppeney, U. (2020). Causal Inference in Audiovisual  
678 Perception. *The Journal of Neuroscience*, 40(34), 6600–6612.  
679 <https://doi.org/10.1523/JNEUROSCI.0051-20.2020>
- 680 Morcom, A. M., & Henson, R. N. A. (2018). Increased prefrontal activity with  
681 aging reflects nonspecific neural responses rather than compensation.  
682 *Journal of Neuroscience*, 38(33), 7303–7313.  
683 <https://doi.org/10.1523/JNEUROSCI.1701-17.2018>
- 684 Morcom, A. M., & Johnson, W. (2015). Neural Reorganization and

- 685 Compensation in Aging. *Journal of Cognitive Neuroscience*, 27(7), 1275–  
686 1285. [https://doi.org/10.1162/jocn\\_a\\_00783](https://doi.org/10.1162/jocn_a_00783)
- 687 Mozolic, J. L., Long, A. B., Morgan, A. R., Rawley-Payne, M., & Laurienti, P.  
688 J. (2011). A cognitive training intervention improves modality-specific  
689 attention in a randomized controlled trial of healthy older adults.  
690 *Neurobiology of Aging*, 32(4), 655–668.  
691 <https://doi.org/10.1016/j.neurobiolaging.2009.04.013>
- 692 Murray, M. M., Eardley, A., Edginton, T., Oyekan, R., Smyth, E., & Matusz, P.  
693 J. (2018). Sensory dominance and multisensory integration as screening  
694 tools in aging. *Scientific Reports*, 8(1), 8901.  
695 <https://doi.org/10.1038/s41598-018-27288-2>
- 696 Murray, M. M., Thelen, A., Thut, G., Romei, V., Martuzzi, R., & Matusz, P. J.  
697 (2016). The multisensory function of the human primary visual cortex.  
698 *Neuropsychologia*, 83, 161–169.  
699 <https://doi.org/10.1016/j.neuropsychologia.2015.08.011>
- 700 O’Callaghan, G., O’Dowd, A., Stapleton, J., Merriman, N. A., Roudaia, E., &  
701 Newell, F. N. (2018). Changes in regional brain grey-matter volume  
702 following successful completion of a sensori-motor intervention targeted  
703 at healthy and fall-prone older adults. *Multisensory Research*, 31(3–4),  
704 317–344. <https://doi.org/10.1163/22134808-00002604>
- 705 Pauwels, L., Maes, C., & Swinnen, S. P. (2018). Aging, inhibition and GABA.  
706 *Aging*, 10(12), 3645–3646. <https://doi.org/10.18632/aging.101696>
- 707 Rohe, T., Ehlis, A.-C., & Noppeney, U. (2018). The neural dynamics of causal  
708 inference in perception. In *bioRxiv*. <https://doi.org/10.1101/504845>
- 709 Seghier, M. L. (2013). The angular gyrus: Multiple functions and multiple

- 710 subdivisions. *Neuroscientist*, 19(1), 43–61.  
711 <https://doi.org/10.1177/1073858412440596>
- 712 Setti, A., Burke, K. E., Kenny, R. A., & Newell, F. N. (2011). Is inefficient  
713 multisensory processing associated with falls in older people?  
714 *Experimental Brain Research*, 209(3), 375–384.  
715 <https://doi.org/10.1007/s00221-011-2560-z>
- 716 Shams, L., & Beierholm, U. R. (2010). Causal inference in perception. *Trends*  
717 *in Cognitive Sciences*, 14(9), 425–432.  
718 <https://doi.org/10.1016/j.tics.2010.07.001>
- 719 Shams, L., Kamitani, Y., & Shimojo, S. (2000). What you see is what you  
720 hear. *Nature*, 408(6814), 788. <https://doi.org/10.1038/35048669>
- 721 Shams, L., Kamitani, Y., & Shimojo, S. (2002). Visual illusion induced by  
722 sound. *Cognitive Brain Research*, 14(1), 147–152.  
723 [https://doi.org/10.1016/S0926-6410\(02\)00069-1](https://doi.org/10.1016/S0926-6410(02)00069-1)
- 724 Shams, L., Ma, W. J., & Beierholm, U. (2005). Sound-induced flash illusion as  
725 an optimal percept. *NeuroReport*, 16(17), 1923–1927.  
726 <https://doi.org/10.1097/01.wnr.0000187634.68504.bb>
- 727 Stevenson, R. A., Zemtsov, R. K., & Wallace, M. T. (2012). Individual  
728 differences in the multisensory temporal binding window predict  
729 susceptibility to audiovisual illusions. *Journal of Experimental*  
730 *Psychology. Human Perception and Performance*, 38(6), 1517–1529.  
731 <https://doi.org/10.1037/a0027339>.Individual
- 732 Venezia, J. H., Matchin, W., & Hickok, G. (2015). Multisensory Integration and  
733 Audiovisual Speech Perception. In *Brain Mapping: An Encyclopedic*  
734 *Reference* (Vol. 2, Issue August 2018). Elsevier Inc.

- 735 <https://doi.org/10.1016/B978-0-12-397025-1.00047-6>
- 736 Wallace, M. T., Woynaroski, T. G., & Stevenson, R. A. (2020). Multisensory  
737 integration as a window into orderly and disrupted cognition and  
738 communication. *Annual Review of Psychology*, 71(1).  
739 <https://doi.org/10.1146/annurev-psych-010419-051112>
- 740 Wang, A., Sang, H., He, J., Sava-Segal, C., Tang, X., & Zhang, M. (2019).  
741 Effects of cognitive expectation on sound-induced flash illusion.  
742 *Perception*, 48(12), 1214–1234.  
743 <https://doi.org/10.1177/0301006619885796>
- 744 Watkins, S., Shams, L., Tanaka, S., Haynes, J. D., & Rees, G. (2006). Sound  
745 alters activity in human V1 in association with illusory visual perception.  
746 *NeuroImage*, 31(3), 1247–1256.  
747 <https://doi.org/10.1016/j.neuroimage.2006.01.016>  
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### Highlights

- We assessed grey matter (GM) volume and sensory integration in middle and older age
- In middle-age, right Angular Gyrus (AG) GM was larger in those who integrated more
- In older age GM in the right AG was smaller in those who integrated more
- The AG may be a key structure tied to altered multisensory processing in ageing
- Multisensory integration might provide a marker of neurological health in ageing

Journal Pre-proof

**Author contribution statement:** The Irish Longitudinal Study on Ageing (TILDA) is an interdisciplinary project co-ordinated by R.A.K. The MRI acquisition protocol was designed and set up by A.F., J.M. and J.F.M. The multisensory assessment protocol (the Sound-Induced Flash Illusion) was designed and integrated into TILDA by A.S and F.N.N. MRI pre-processing was conducted by R.B. under the supervision of R.W. The statistical analysis for the current paper was developed by R.J.H., R.W., A.S. and F.N.N. with the consultation of C.D.L. (Cognitive Neuroscience and Neuroimaging lead on TILDA), J.C., S.K. and W.W. The analysis was conducted by R.J.H. who also prepared the manuscript for publication for which all authors provided feedback and revisions. All authors approved the final version of the manuscript for submission.