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Gray matter volume in the right angular gyrus is associated with differential patterns of multisensory integration with aging

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A B S T R A C T

Multisensory perception might provide an important marker of brain function in aging. However, the cortical structures supporting multisensory perception in aging are poorly understood. In this study, we compared regional gray matter volume in a group of middle-aged (n = 101; 49–64 years) and older (n = 116; 71–87 years) adults from The Irish Longitudinal Study on Aging using voxel-based morphometry. Participants completed a measure of multisensory integration, the sound-induced flash illusion, and were grouped as per their illusion susceptibility. A significant interaction was observed in the right angular gyrus; in the middle-aged group, larger gray matter volume corresponded to stronger illusion perception while in older adults larger gray matter corresponded to less illusion susceptibility. This interaction remained significant even when controlling for a range of demographic, sensory, cognitive, and health variables. These findings show that multisensory integration is associated with specific structural differences in the aging brain and highlight the angular gyrus as a possible “cross-modal hub” associated with age-related change in multisensory perception.

1. Introduction

The ability to effectively combine information from across the senses, multisensory integration, is fundamental to several aspects of successful aging, including activities in daily living (de Dieuleveult et al., 2017), speech perception (Venezia et al., 2015), and balance maintenance (Bronstein, 2016; Merriman et al., 2015; Setti et al., 2011). Recently, multisensory integration has been emphasized as a candidate tool for probing healthy cognitive function across the lifespan (Denervaud et al., 2020; Murray et al., 2018; Wallace et al., 2020) as it appears closely linked with cognitive outcomes in aging (Chan et al., 2015; Hernández et al., 2019). Despite this, very little is known regarding the correspondence between multisensory perception and brain structure in aging. The aim of the present study was to identify if multisensory integration, assessed using the sound-induced flash illusion (SIFI; Shams et al., 2000), can inform differences in gray matter density in the aging brain.

When information is sent to more than one sense, our sensory systems use a number of cues, including spatial colocalization and temporal synchrony between signals, to determine if inputs originate from the same source and should therefore be integrated. For example, when following a conversation, we would expect the lip movements and speech sounds of our companion to be closely linked in time and space, whereas irrelevant sounds may not be reliably matched. If signals do originate from the same source, integration may enhance perceptual judgements (e.g., speech comprehension). A traditional view was that sensory inputs are first

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represented in sensory-specific cortices followed by convergence in multisensory areas including intraparietal sulcus, inferior parietal lobule, and superior temporal sulcus (STS). However, most regions previously considered "sensory specific" are now known to respond to information from other modalities (for reviews see Ghazanfar and Schroeder, 2006; Macaluso, 2006; Murray et al., 2016). Similarly unisensory inputs can activate multisensory association areas. Calvert et al. (2000) showed that when participants listened to/watched a story being read, unimodal visual and auditory stimuli both activated the STS, but this activation was greater when auditory and visual stimuli were presented together and close in time. Similarly, audiovisual speech illusions such as the McGurk effect (McGurk and MacDonald, 1976), appear dependent on prestimulus STS activity (Keil et al., 2012), and both illusion perception and corresponding STS activation specifically occur when stimuli are synchronous (Jones and Callan, 2003). Functional evidence to date therefore shows that multisensory perception is associated with a widespread network of sensory specific and multisensory regions, and activation of these regions depends on the synchronicity of multisensory inputs.

The SIFI provides a promising, and increasingly popular, avenue to investigate multisensory perception due to its high fidelity and ease of implementation (for reviews see (Hirst et al., 2020a; Keil, 2020)). In this illusion, presenting one visual "flash" with 2 sequential auditory "beeps" results in the perception of 2 flashes, even though only one occurred. The illusion reflects optimal integration (Shams et al., 2005); that is, illusion perception is governed by the reliability of each sense (reliability weighting) and, in Bayesian terms, priors, reflecting the belief that a) multiple stimuli will occur in each sense and b) auditory and visual stimuli originate from a common cause (causal inference; Shams and Beierholm, 2010). In the brain, these neurocomputational processes occur in a spatiotemporal hierarchy, such that reliability weighting is thought to first occur in parietal-temporal regions followed by frontal mechanisms guiding top-down causal inference (Cao et al., 2019). For example, recent functional magnetic resonance imaging (fMRI) work showed that activation in the lateral prefrontal cortex predominantly represented observers "separate" versus "common" cause decisions (causal inference), while activation in the frontal eye fields and intraparietal sulcus concurrently encoded visual and auditory spatial locations and subsequent motor responses, in addition to causal inference (Mihalik and Noppeney, 2020). Optimal integration facilitates effective action and perceptual decisions, taking into account current sensory function, viewing conditions, and prior experience. For instance, when crossing the road on a foggy day, we must reduce the weighting of visual information (owing to poor visibility) and consider the likelihood that the sound of a looming vehicle corresponds to the moving shape in the distance. Efficient sensory integration thus supports accurate and safe action in the multisensory world.

In the SIFI, when one flash is presented with 2 beeps, participants are more likely to perceive 2 flashes if audition is considered more reliable, if discontinuous stimuli are expected in the visual modality (e.g., Wang et al., 2019) or if auditory and visual stimuli are thought to arise from a common cause, for example, because they occur close in time. In healthy younger adults, presenting the second beep with increasing temporal separation from the flash-beep pair (stimulus-onset asynchrony, SOA) decreases illusion susceptibility (Shams et al., 2002) allowing measurement of the time window within which sensory integration occurs. The SIFI therefore gauges the sensitivity of the multisensory brain to temporal synchrony, and reduced SIFI susceptibility at longer SOAs may reflect efficient multisensory perception in younger adults.

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

The only study, to our knowledge, that has examined the structural correlates (in young adults) of SIFI susceptibility (de Haas et al., 2012) found that the gray matter volume of the primary visual cortex was negatively associated with susceptibility to the SIFI. Although, prior to the current study, the structural correlates of SIFI in older adults had yet to be investigated, evidence from other imaging modalities has suggested that older adults might make greater use of processes linking priors in perception. Chan et al. (2017) found that older adults manifested increased prestimulus beta-band activity during the SIFI and interpret this as reflecting greater use of perceptual priors. An increased use of priors in aging could reflect increased reliance on "rules of thumb" to guide perception, stronger priors built from a longer life experience, or both of these processes. It is currently unknown whether observed differences in neural dynamics correspond to structural differences in the aging brain because an investigation of the structural associates of SIFI perception, or multisensory perception in general, in older adults had yet to be conducted.

The aim of the present study was to identify if different patterns of SIFI susceptibility in aging are associated with underlying differences in gray matter volume. To address this, we focused on data acquired from a large cohort of older adults who took part in an MRI study within The Irish Longitudinal Study on Aging (TILDA). TILDA is the only nationally representative study on aging to date to incorporate a measure of multisensory function into its health care assessment and therefore provides a unique opportunity to gain insights into the role of multisensory perception in aging. In the current analysis, we focused on two groups: middle-aged (49–64 years) and older (71-87 years) adults within this study ($n = 217$) to provide the first exploration of the structural correlates of SIFI susceptibility in the aging brain.

2. Methods

2.1. Participants

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

The MRI sampling procedure was the same as that previously described (Boyle et al., 2020; Carey et al., 2019). In total, 578 participants attended for scanning; 18 did not provide data (due to claustrophobia/anxiety [n = 14] or MRI contraindication [n = 4]); 61 scans were excluded due to data quality and processing errors (motion artifacts [n = 33], gray matter/white matter lesions [n = 18], image shearing of the cerebellum [n = 2], or technical error [n = 8]). Participants reporting a medical history of Parkinson's disease, transient ischemic attack, or stroke were not included in the analysis (n = 15). After these exclusions, the total number of participant scans available for analysis was 484.

Participants' scans were excluded if the participant did not complete the SIFI test during the health assessment (n = 37) or if they were missing variables used as covariates in sensitivity analyses, including measures used to create cognitive factors (Montreal Cognitive Assessment, MoCA [n = 2], prospective memory [n = 1], Mini-Mental State Examination, MMSE [n = 1], Color Trails Task, CTT [n = 4], Choice Response Time, CRT [n = 10], Sustained Attention to Response Time, SART [n = 6](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)), physical and health measures (Body Mass Index, BMI [n =1], Timed Up and Go [n = 1], Center of Epidemiological Studies on Depression score [n = 3]), and sensory measures (visual acuity [n = 1], self-reported vision [n = 1], and hearing aid use [n = 1]). Participants with a MoCA score below 23, suggesting mild cognitive impairment (Carson et al., 2018), were also excluded (n = 45). For a clear comparison of aging effects from middle to older age while also modeling interactions with multisensory perception, we focused our analysis on the older (aged 71–87 years) and middle-aged (aged 49–64 years) members of our sample (identified using tertile cutoffs within our population; see Supplementary Figure S1). This sampling procedure was adopted from a previous study of the TILDA MRI cohort (Carey et al., 2019). Moreover, other studies have shown that age-related gray matter decreases in networks associated with sensory processing (e.g., the lateral occipital cortex) are most prominent in >75 year olds (Hafkemeijer et al., 2014). A final number of 217 participants were therefore included in our analysis (Table 1).

2.2. Sound-induced flash illusion assessment

Participants completed a task based on the SIFI task (see Hernández et al., 2019; Hirst et al., 2019 for further details) as part of the TILDA health care assessment. Each participant was seated approximately 60 cm in front of a laptop computer and instructed to fixate on a cross at the center of the screen. In the first block of trials, participants judged the number of flashes presented. Flashes (1.5° visual angle; approximately 5° below fixation; 16 ms duration) and beeps were presented in one of 5 possible stimulus combinations (2 beeps +2 flashes [2B2F]; 1 beep +1 flash [1B1F]; 0 beeps +2 flashes [0B2F]; 0 beeps +1 flash [0B1F]; 2 beeps +1 flash [2B1F]). On 2B2F trials, a synchronous flash and beep pair was followed by a second flash-beep pair presented at one of three SOAs: 70, 150, or 230 ms. On critical “illusory” trials (2B1F), one of the beeps was synchronous with the flash and the second occurred either before (-230, -150, or -70 ms) or after (70, 150, or 230 ms) the flash, referred to as “Pre” and “Post” conditions, respectively. In this block, there were therefore 12 trial types, each presented twice in a random order. In a second block of trials, participants judged the number of beeps, presented via the laptop speakers. In this block, 2 beeps (3500 Hz; approximately 80 dB; 10 ms duration; 1 ms ramp) were presented with no flashes (2B0F) at one of three SOAs: 70, 150, or 230 ms. These 3 possible trial types were each presented twice, in a random order. A practice block was presented before each block containing one trial from each condition (excluding 2B1F “Pre” conditions and 0B1F and 2B2F at 150 and 230 ms). Vocal responses were recorded by the nurse, who sat near the participant, using the number keys on a laptop. The SIFI took approximately 6 minutes for each participant.

2.3. Image acquisition and processing

The MRI data was obtained with a mean (SD) of 62 (40) days after the health assessment. The neuroimaging scans were acquired at the National Center for Advanced Medical Imaging, St. James's Hospital, Dublin, Ireland, via a 3T Philip's Achieva system with a 32-channel head coil. The protocol included a variety of scans per participant, including a T1-weighted MR image acquired using a 3D Magnetization–Prepared Rapid Gradient Echo (MP-RAGE) sequence, with the following parameters: FOV (mm): 240 x 240 x 162; 0.8 × 0.8 × 0.9 mm^3 resolution; SENSE factor: 2; TR: 6.7 ms; TE: 3.1 ms; and flip angle: 8°.

Images were preprocessed using the statistical parametric mapping (SPM12) toolbox (Wellcome Department of Cognitive

Table 1
Sample characteristics of age groups (stratified by accuracy on the 230 ms SOA (post) condition to allow comparisons of interacting groups)

Accuracy	Older			Middle aged			All
	1	0.5	0	1	0.5	0	
	N = 25	N = 18	N = 73	N = 34	N = 19	N = 48	N = 217
Age							
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]
Sex n (%)							
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)
Education n (%)							
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)
MoCa							
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]

See Section 3.2.1 for calculation details of visual acuity and self-reported sensory functions.
MoCa, Montreal Cognitive Assessment.

Neurology, Institute of Neurology, London, UK) in MATLAB R2017b (MathWorks, Sherborn, MA, USA). The preprocessing pipeline was identical to that previously described (Boyle et al., 2020). The code used to auto-reorient and preprocess the data is available at https://github.com/rorytboyle/brainPAD. All images were nonlinearly registered to a custom DARTEL template generated from the group mean of all eligible preprocessed scans (i.e., before our study-specific behavioral exclusion criteria), affine registered to Montreal Neurological Institute (MNI) space (1 mm^3) and resampled with modulation to preserve the total amount of signal from each voxel. Images were smoothed with a 4 mm full-width at half maximum Gaussian kernel and visually inspected for accurate segmentation.

2.4. Statistical analysis

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

For each analysis, participants were grouped based on their accuracy in the critical, illusory (2B1F), condition of the SIFI test. Importantly, because 2 trials were presented per condition, participants could score one of three discrete values, 0, 0.5, or 1 proportion correct, although proportion is traditionally considered continuous, we had 3 distinct classes of individuals available for our analysis. Four analyses were therefore conducted with grouping based on accuracy in either the “Pre” (-230 and -150 ms SOA) or “Post” conditions (150 and 230 ms SOA). Short SOA conditions (70 ms) were not included because previous studies, including those with the TILDA cohort, showed that older adults were less susceptible to the illusion at this SOA, likely due to reduced temporal acuity in aging (Hirst et al., 2019, 2020b). Indeed, participants in this study had the lowest accuracy for judging 2, unimodal, flashes and 2, unimodal, beeps, at 70 ms relative to other SOAs (see Supplementary Table S4). Our base model for each analysis was a full factorial design with 2 factors, accuracy group (0, 0.5, and 1) and age group (middle aged and older aged), while controlling for sex (Supplemental Figure S2). Because of unequal sample sizes, we assumed unequal variance across groups in our design. An absolute threshold mask of 0.2 was implemented, and images were proportionally scaled using total intracranial volume. All *p* values are reported corrected for family-wise error (FWE) based on the whole brain. Because of known statistical concerns regarding cluster-wise inference (Eklund et al., 2016), we focused on peak-level significance for our conclusions.

3. Results

Because participants were grouped based on behavioral performance in illusory conditions, we focus our results section on differences in gray matter volume between these groups. However, it is notable that these groups performed very similarly in non-illusory control conditions (see Supplementary Table S4).

3.1. Nonadjusted models

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

There was a significant accuracy by age group interaction for gray matter volume in the right angular gyrus (AG) ($p_{FWE} = 0.003$, $F = 20.2$, $Z = 5.62$, cluster equivK = 37, AG; x = 49, y = -47, z = 36). This effect occurred only when participants were grouped based on accuracy at 230 ms (post). As shown in Fig. 1, increased gray matter in the right AG was associated with greater illusion susceptibility in middle-aged adults (i.e. proportion correct of 0), whereas in older adults, increased gray matter in the right AG was associated with reduced illusion susceptibility (i.e. proportion correct of 1). The main effect of accuracy grouping failed to reach significance across models, and there were no significant peak-level interactions between age group and accuracy for any of the additional conditions.

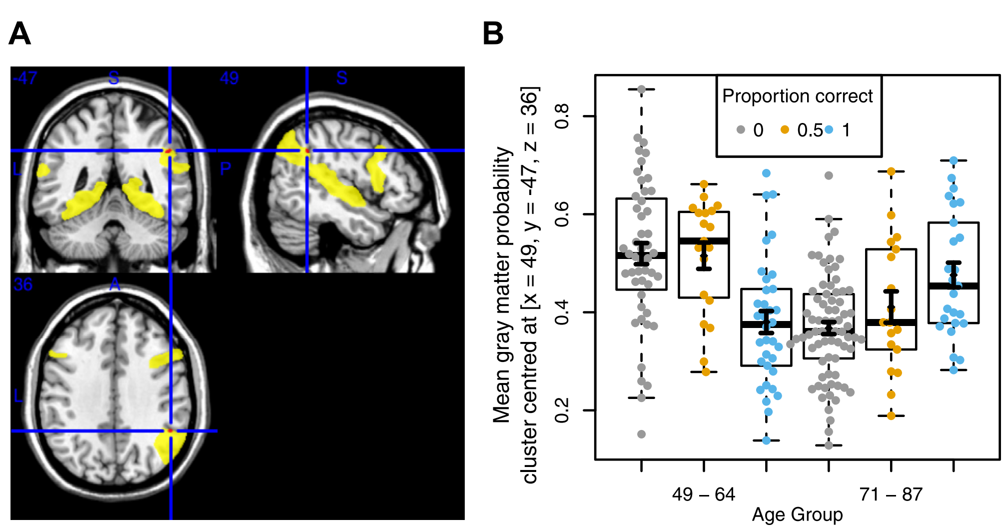

Fig. 1. A) Significant age group by accuracy (in 230 ms “Post” condition) interaction in the right AG (red) overlaid on the ROI mask (yellow) (B) Mean gray matter probability for extracted cluster in each group. Boxplots illustrate interquartile range and median. Black diamonds with error bars indicate group means and standard errors. (For interpretation of the references to color in this figure legend, the reader is referred to the online version of this article.)

3.2. Adjusted sensitivity analyses

The data available from TILDA allowed us to control for a range of potentially confounding variables. We therefore conducted 3 further sensitivity models to consider sensory differences, cognitive function, and physical and mental health.

3.2.1. Sensory function

To control for individual differences in sensory function, the following factors were incorporated into our model: self-reported vision and self-reported hearing (1 = excellent to 5 = poor), visual acuity (100−50 * LogMAR visual acuity in the best eye), auditory and visual temporal discrimination (accuracy for judging 2 auditory stimuli or 2 visual stimuli with 70 ms SOA, respectively), and hearing aid use (yes/no). All nonbinary factors were mean-centred. The significant age group by accuracy interaction held when including sensory measures in the model. That is, a significant peak was observed in the right AG (x = 49, y = -47, z = 36; $p_{FWE} = 0.004$, $F = 20.15$, $Z = 5.61$, cluster equivK = 31). As in our base model, there were widespread effects of aging and no main effect of accuracy.

3.2.2. Cognitive function

Our second sensitivity analysis controlled for differences in education (1 = primary, 2 = secondary, 3 = tertiary/higher) and cognitive function. TILDA collected data using a large battery of cognitive assessments, therefore, to limit multicollinearity, an exploratory factor analysis was conducted on 27 cognitive measures (analysis not reported here; see Supplementary Material for plots). We term the derived factors "Executive Function" reflecting mainly performance on the CTT (Maj et al., 1993), "Memory" reflecting mainly immediate and delayed recall of word lists, and "Processing Speed" reflecting performance on a CRT task (see Supplementary Figure S2). All factors were included in the model as mean-centred covariates. The age group by accuracy interaction in the right AG held when considering measures of cognitive function in the model ($p_{FWE} = 0.008$, $F = 19.2$, $Z = 5.47$, cluster equivK = 28) and there remained widespread aging effects and no main effect of accuracy in this model.

3.2.3. Physical and mental health

Our final sensitivity model controlled for differences in depression (CESD score) and physical health measures including, BMI, Timed Up and Go time, self-reported physical activity level (see Supplementary Table 3), mean (seated) arterial blood pressure (calculated as (systolic + (2 * diastolic))/3), use of cardiovascular medication (antihypertensives, yes/no), history of one or more cardiovascular disease or event (angina, heart attack, heart failure, heart murmur, and arterial fibrillation, see Supplementary Table 2), self-reported high cholesterol (yes/no), diabetes (yes/no), and smoking history (1 = never smoked, 2 = past smoker, 3 = current smoker). All nonbinary covariates were mean-centred. The age group by accuracy interaction in the right AG held when considering health measures in the model ($p_{FWE} = 0.005$, $F = 19.79$, $Z = 5.55$, cluster equivK = 40), there remained widespread age effects and no main effect of accuracy.

4. Discussion

In this study, we sought to identify structural gray matter differences associated with multisensory integration in aging. We compared a group of middle-aged and older adults who had completed the SIFI and an MRI study as part of TILDA. A significant interaction was observed in the right AG such that increased gray matter volume in middle-aged adults was associated with increased susceptibility to the SIFI illusion, while increased gray matter volume in older adults was associated with decreased susceptibility to the illusion. To our knowledge, this is the first study to investigate gray matter differences associated with multisensory, in particular audiovisual, integration in aging (but see O'Callaghan et al. (2018) for an investigation of sensorimotor training on gray matter volume in older adults).

A practical consideration highlighted by the present study is that the described effects occurred only for SIFI susceptibility in the SOA of 230 ms "Post" condition. In general, the participants in the TILDA cohort were more susceptible to the illusion when the first beep *preceded* the flash-beep pair (Hirst et al., 2020b). This contrasts with reported effects in young adults, in which integration appears stronger when the beep follows the flash (e.g., Dixon and Spitz, 1980; Stevenson et al., 2012) and may suggest a shift in the symmetry of the temporal binding window with age. Because only 3 studies using the SIFI (including TILDA) have included SOAs where the beep precedes the flash-beep pair (Hirst et al., 2020a), understanding differences in preflash and postflash effects requires further investigation.

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

4.1. The angular gyrus (AG) in multisensory perception

The AG has been described as a "cross-modal hub" and "convergence zone" (for review see Seghier, 2013). Situated between occipital, temporal, and parietal poles, it plays a central role in the coordination of several systems associated with perception, action, and cognition. Given the proposed role of the AG in sensory integration, it has unsurprisingly been linked with SIFI perception in younger adults and effects reported so far with SIFI have been right lateralized. Transcranial magnetic stimulation applied specifically to the right AG reduces SIFI susceptibility (Hamilton et al., 2013; Kamke et al., 2012). In a fMRI investigation, Watkins et al. (2006) found stronger activation of V1, the right superior temporal sulcus and the right superior colliculus for trials inducing the illusion versus no illusion. Together, these studies show that the right AG is a region that is critical to SIFI perception and support a lateralization of processing.

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

The AG has been associated with numerical cognition, which would also underlie SIFI performance because it involves numerical judgments (Dehaene et al., 2003; Hamilton et al., 2013). For example, in a previous study using the line bisection task, priming participants with lower numbers typically biases participants' responses toward the left and transcranial magnetic stimulation to the right AG disrupts this effect (Cattaneo et al., 2009). One of the numerical functions of the AG therefore appears to be the spatial representation of numbers. The control measures included in our sensitivity analysis can account for this to some degree. Our factor "Executive function" was highly representative of CTT performance, which involves visuospatial scanning of numbers. Similarly, in our controls of sensory function, we included accuracy for judging two flashes and two beeps when presented unimodally at 70 ms SOA. We therefore also controlled for unisensory numerical judgments. However, we cannot rule out that other facets of numerical cognition, that we were not able to control for, contribute toward the observed associations.

4.2. *The differential effect of gray matter volume in AG with aging*

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

Aging has been reported to be associated with a functional reorganization of the brain, and older adults have been proposed to engage different brain regions to perform the same tasks as younger adults (i.e., compensation, Cabeza et al., 2018). An example involving the AG is observed in memory retrieval, in which older adults recruit more posterior regions (such as the AG and occipital gyri) compared with middle-aged adults (Bréchet et al., 2018). If the functional use of the AG shifts with age, we cannot assume that gray matter in the AG should have the same relationship with behavior across age groups. However, as evidence regarding neural reorganization in aging remains inconclusive (Morcom and Henson, 2018; Morcom and Johnson, 2015) this interpretation is speculative.

Older adults may process multisensory perceptual decisions differently to younger adults. With reference to Bayesian causal inference (Cao et al., 2019; Körding et al., 2007; Rohe et al., 2019; Shams and Beierholm, 2010), older adults might make greater use of perceptual priors when making temporal judgments than younger adults. Chan et al. (2017) reported increased prestimulus beta activity, associated with linking priors and predictions, in older adults while performing the SIFI task. Similarly, in speech perception, where bimodal auditory and visual inputs might improve speech comprehension (i.e., multisensory enhancement), older adults show greater multisensory enhancement relative to younger adults only when words are embedded in unpredictable semantic content (Maguinness et al., 2011), suggesting that older adults rely on predictions informed by context and priors to make perceptual judgments.

The AG might act as a "convergence zone" between bottom-up and top-down information (see Figure 3 in Seghier, 2013). In multisensory perception, the degree of top-down influence may alter the relative contributions of sensory information (the likelihood, in Bayesian terms) and prior expectations (including the causal prior) to the final estimate. While the current analysis cannot speak to the relative inputs to the AG, our findings suggest the AG has a contrasting impact on perception in middle-aged and older adults, perhaps suggesting this region interacts differently with other areas within this network. Future work can address this hypothesis through computational modeling (to alter the relative weights of priors and reliability in perceptual judgments) and connectivity analyses. The current findings highlight the AG as a candidate seed region for future connectivity models of how perception and cognition are bridged in the aging brain.

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

5. Conclusions

To our knowledge, the present study is the first to assess structural gray matter differences associated with multisensory integration in aging, using the SIFI. We show specific interactions in the AG, a region known to be associated with the coordination of several senses and cognitive processes. Middle-aged and older adults showed differing associations between gray matter in the AG and illusion perception. We interpret these effects as indicating a shift in the functional role of the AG with age, possibly relating to the balance of top-down and bottom-up inputs. Future research comparing the structural and functional connectivity of the AG in the aging brain is needed to test this hypothesis. These findings show that multisensory integration, assessed using the SIFI, can be linked to specific structural changes in the aging brain.

Author contribution statement

The Irish Longitudinal Study on Aging (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 (based on the Sound-Induced Flash Illusion) was designed and integrated into TILDA by A.S and F.N.N. MRI preprocessing was conducted by R.B. under the supervision of R.W. The statistical analysis for the current article 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.

Disclosure statement

The authors have no known competing interests to declare.

Data availability

The data sets generated during and/or analyzed during the present study are not publicly available due to data protection regulations but are accessible at TILDA on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.12.004.

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