The neurobiology of speech perception decline in aging

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Abstract

Speech perception difficulties are common amongst elderlies; yet the underlying neural mechanisms are still poorly understood. New empirical evidence suggesting that brain senescence may be an important contributor to these difficulties have challenged the traditional view that peripheral hearing loss was the main factor in the aetiology of these difficulties. Here we investigated the relationship between structural and functional brain senescence and speech perception skills in aging. Following audiometric evaluations, participants underwent MRI while performing a speech perception task at different intelligibility levels. As expected, with age speech perception declined, even after controlling for hearing sensitivity using an audiological measure (pure tone averages), and a bioacoustical measure (DPOAEs recordings). Our results reveal that the core speech network, centered on the supratemporal cortex and ventral motor areas bilaterally, decreased in spatial extent in older adults. Importantly, our results also show that speech skills in aging are affected by changes in cortical thickness and in brain functioning. Age-independent intelligibility effects were found in several motor and premotor areas, including the left ventral premotor cortex and the right SMA. Age-dependent intelligibility effects were also found, mainly in sensorimotor cortical areas, and in the left dorsal anterior insula. In this region, changes in BOLD signal had an effect on the relationship of age to speech perception skills suggesting a role for this region in maintaining speech perception in older ages perhaps by. These results provide important new insights into the neurobiology of speech perception in aging.

Keywords: speech processing, language, functional magnetic resonance imaging, brain senescence, insula, premotor cortex

Introduction

Understanding how the brain ages and the effects that brain aging have on the ability to communicate are major challenges in cognitive neurosciences. Indeed, communication difficulties are considered to be of greatest importance by elderlies (Jacobs-Condit 1984; Yorkston et al. 2010). Amongst the communication difficulties experienced by this population, a highly prevalent and disabling problem is a decline in the ability to comprehend speech in background noise, for example in the presence of multiple simultaneous talkers (Frisina and Frisina 1997; Plath 1991; Cooper and Gates 1991; Helfer and Wilber 1990; Strouse et al. 1998). Presbycusis, the aging of the auditory system, characterised notably by a loss of sensitivity to high frequency sounds, which affects approximately 20-40% of adults over 65 years (Gates and Mills 2005; Ries 1994) is known to reduce speech perception skills (Gates and Mills 2005; Ries 1994). However, empirical evidence demonstrates that speech perception decline can occur in the absence of presbycusis (Frisina and Frisina 1997; Humes et al. 2006; Helfer and Vargo 2009; Gordon-Salant and Fitzgibbons 2001; Helfer and Wilber 1990) and may be related instead to brain senescence (Wong et al. 2009; Sheppard et al. 2011; Wong et al. 2010; Hayes 1981). However, the specific neurobiological mechanisms underlying these difficulties remain unclear.

Interest in understanding the macro-structural and functional neurobiological causes of cognitive and behavioural aging is growing. A number of recent studies have examined the neurobiological underpinning of cognitive aging and begun to demonstrate that changes in the structure (e.g. Fjell and Walhovd 2010; Head et al. 2008; Walhovd et al. 2010; Westlye et al. 2011), functioning (e.g. Roski et al. 2013; Burianova et al. 2013; Campbell et al. 2012; Spaniol and Grady 2012) and connectivity (Campbell et al. 2012; Grady et al. 2010; Sambataro et al. 2010) of specific brain regions play a part in the cognitive/behavioural decline that is associated with normal aging. Few studies, however, have focused on languages and specifically on the perception of language. Nevertheless, using functional MRI, it has been shown that network efficiency in the supratemporal cortex during speech perception decreases as a function of age (Sheppard et al. 2011), suggesting a potential mechanism for the observed decreased in perception accuracy. Several different patterns of age-related differences in the blood-oxygen-level-dependent (BOLD) signal as a function of speech intelligibility have also been found in several areas including the anterior cingulate gyrus, middle frontal gyrus and supratemporal cortex during an auditory word-picture matching task (Wong et al. 2009; Wong et al. 2008). Despite their importance,

unimodal aging studies only provide a limited account on cognitive aging. A recent fMRI study found significant age-related structural decline in multiple brain areas involved in perceiving and producing speech, concomitant with regional changes in BOLD signal magnitude in multiple areas involved in processing and producing speech, including the ventral premotor cortex (PMv) and the supratemporal cortex (Tremblay et al. 2013). Multiple mediation analyses showed age-related regional BOLD signal changes during speech perception in the left PMv that were mediated by structural decline. However, BOLD signal changes in other regions (e.g. superior frontal gyrus) were independent from structural changes. These results reveal the complex and regionally heterogeneous relationship of brain structure and function. This complex relationship was also shown recently in a recent study of aging and language functions, which showed that gray matter density, which declines with age, is negatively associated with increased functional connectivity but overall decreased network efficiency (Meunier et al. 2014). In that study, increased functional connectivity was also negatively associated with performance (syntactic sensitivity). In a recent study on semantic processing semantic processing young and older adults were asked to judge whether two printed object names match on a particular feature (Peelle et al. 2013). Older adults who performed well on the task showed increased overall activity in bilateral premotor cortex and left lateral occipital cortex compared to young adults, and increased activity in these brain regions relative to poorer performing older adults who also showed gray matter atrophy in premotor cortex, further demonstrating a role for both macro-structural and macro-functional factors in aging of speech and language functions.

The goal of the present study was to further characterize the neural mechanisms that underlie speech perception decline in aging, focusing on structural and functional neural decline. An innovative analysis framework combining voxel-wise and region-of-interest serial mediation analyses was developed to address the question of the complex interplay between structural brain decline, functional changes and speech perception accuracy. Our results reveal that speech skills in aging are affected both by changes in brain structure (cortical thickness) and in brain functioning (change in BOLD MRI signal). One of the most intriguing finding of this study is the relative dissociation between functional and structural aging that we found which suggests that decline in speech perception is independently mediated by both structural and functional brain aging.

Methods

Participants

The study comprised a total of twenty-two subjects, which were divided into two groups. The young adult group was comprised of eleven healthy right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971) native speakers of Canadian French (mean age 25.7 ± 3.9 SD; range: 21-32 years; 7 females), with a mean (±SD) of 17.45 ± 2 years of education (range: 15-21). The older adult group was comprised of eleven healthy right-handed native speakers of Canadian French (mean age 68 ± 4.6; range: 61-74 years; 7 females), with a mean of 17.6 ± 2 years of education. Participants in both groups had normal or corrected-to-normal vision and no self-reported history of speech, voice, language, psychological, neurological or neurodegenerative disorder. Participants were screened for depression using the Geriatric Depression Scale (Yesavage et al. 1982) and their cognitive functioning was evaluated using the Montreal Cognitive Assessment scale (MOCA) (Nasreddine et al. 2003). Participants' characteristics are reported in Table 1. The study was approved by the Institutional Ethical Committee of the "Institut Universitaire en Santé Mentale de Québec".

Audiological assessment

Audiometric evaluations consisted of three parts: (1) pure tone audiometry, (2) speech recognition threshold, and (3) distortion product otoacoustic emissions recording (DPOAEs). (1) Pure tone audiometry was performed using a clinical audiometer (AC40, Interacoustic) for each ear separately, for the following frequencies: .25, .5, 1, 2, 3, 4, 6, 8, 12 and 16 kHz. For each participant, a standard pure tone average (PTA: average of threshold at .5, 1 and 2 kHz) was computed for the left and right ear. PTAs are classically used in clinical settings as a measure of hearing loss for speech because most speech sounds fall within this range (Stach 2010). (2) For speech recognition threshold (SRT) the percentage of monosyllabic words correctly identified at 40 dB over hearing threshold was evaluated using an AC40 audiometer. The percentage of correct answers was then calculated for each intensity level, beginning with 40 dB over hearing threshold with implementations of 5 dB. (3) DPOAEs provide an objective measure of cochlear outer hair cell function through the measurement of cochlear acoustic emissions. DPOAEs ($2f_1$-f_2, primary tone pressures P1 = 65 dB SPL and P2 = 55 dB SPL, pass signal-to-noise ratio = 6 dB) were elicited and recorded with a clinical otoacoustic emissions detector (Otoread 7.67, Interacoustic) with a miniature microphone inserted into the ear canal of the subject using a silicon eartip

insuring an optimal seal. DPOAEs were measured in two sessions for each ear separately: a low frequency session (f_2 frequency: 1.5, 2, 3, 4, 5 and 6 KHz; duration of 2 sec in average), followed by a high frequency session (f_2 frequency: 2, 4, 6, 8, 10 and 12 KHz).

Stimuli

The stimuli for the fMRI experiment were meaningless sequences of French syllables. A total of 81 sequences were created from combinations of 27 different simple French syllables (/pa/, /pe/, /py/, /ma/, /me/, /my/, /sa/, /se/, /sy/, /ʁa/, /ʁe/, /ʁu/, /ka/, /ke/, /ky/, /la/, /le/, /lu/, /ʒa/, /ʒe/, /ʒu/, /da/, /de/, /du/, /va/, /ve/, /vu/). None of the sequence was repeated. Each sequence was produced by a native male French speaker from Québec City in a sound-attenuated booth and recorded (sampling rate=44 kHz) using a unidirectional microphone (Rode, NT2-A) connected to a professional amplifier (Edirol, U-25EX). The sound files were saved directly to disk using Sound Studio 3.5.4 (Felt Tip Software), edited offline using Wave Pad Sound Editor 4.53 (NHC Software) to have a duration of 1200 ms, and normalized for root mean square (RMS) intensity. Intelligibility was manipulated by adding white noise to the sequences to reach a dB signal-noise ratio (SNR) of either 20 (mid) or -5 (low intelligibility) according to the following formula: dB SNR = $10\log_{10}(\text{Pressure}_{signal}/\text{Pressure}_{noise})$, following the procedure developed by Wong et al (Wong et al. 2008). 27 sequences contained no noise (high intelligibility), 27 had an SNR of 20 (mid intelligibility) and 27 sequences had a dB SNR of -5 (low intelligibility).

Procedures

During the fMRI session subjects listened to and repeated as quickly as possible meaningless sequences of three French syllables presented at three different intelligibility levels (high, mid, low). A resting condition (crosshair fixation) was also included as a baseline condition and interleaved with experimental trials; the order of the conditions and the number of rest trials were optimized using Optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq/). All stimuli were presented during the delay in acquisition (see MRI acquisition section below) using Presentation Software (Neurobehavioral System, CA, USA) through high quality MRI-compatible stereo electrostatic earplugs (Nordic Neurolab, Norway), which provide 30 dB of sound

attenuation. Subjects' verbal responses were recorded using a high quality MRI compatible optical omni-directional microphone (MO-2000, Sennheiser) with frequency response of 20 - 40 kHz and a maximal intensity of 134 dB SPL.

Acoustical and Behavioural data analysis

All acoustic analyses were performed using Praat software (Boersma and Weenink 2011). A semi-automatic procedure was first devised for segmenting participants' recorded utterances. For each participant, the procedure involved the automatic segmentation of each syllable based on an intensity and duration algorithm detection. Based on minimal duration and low intensity energy parameters, the algorithm automatically identified pauses between each syllable and set the syllable's boundaries on that basis. If necessary, these boundaries were hand-corrected, based on waveform and spectrogram analysis. A research assistant naive to the purpose of the study listened to the voice recordings, transcribed the responses and calculated the number of errors (mispronounced or missing syllables). A second research assistant validated the transcriptions. For each participant and each condition, the mean reaction time (RT) and duration were then computed. For each dependent measure (accuracy, RT and duration) an ANCOVA was performed with age group as the between-subject factor (young, older), Intelligibility (high, mid, low) as the within-subject factor (left, right) and PTA, DPOAEs and Sex as covariates. Whenever needed, post hoc comparisons were conducted. All such comparisons were non-directional.

MR Image acquisition

The data were acquired on a whole-body Philips 3.0 Tesla Achieva TX at the Clinic IRM Québec-Mailloux in Québec City. Throughout the procedure, each participant's head was immobilized using a set of cushions and pads. Structural MR images were acquired with 3D T1-weighted MPRAGE sequence (TR = 8.2 ms, TE = 3.7 ms, FoV= 250 mm, flip angle = 8°, 256×256 matrix, 180 slices/volume, slice thickness = 1 mm, no gap). Single-shot EPI BOLD functional images were acquired using parallel imaging. Each functional EPI run began with six dummy scans to allow the magnetization to stabilize to a steady state. One hundred and eight functional images were acquired in a single run for this experiment in ~10 minutes (40 interleaved slices (3 mm

isotropic, no gap); SENSE = 2; TR = 6000 ms; acquisition time = 2140 ms, TE = 30 ms; FOV = 240 x 240 mm; 80 x 80 matrix; Flip angle: 90). With these parameters, the cerebellum was only partially covered for most participants. To reduce the noise during auditory stimuli presentation, to mitigate motion concerns, and to record verbal responses, a sparse sampling parallel acquisition technique (Gracco et al. 2005; Edmister et al. 1999; Eden et al. 1999; Hall et al. 1999) was used, which involves periods of 3800 ms of silence (MRI gradients turned off) interleaved with periods of data acquisition (2140 ms). The acquisition protocol is illustrated in Figure 1.

MR Image analysis

Pre-processing. All time series were spatially registered, motion-corrected, time-shifted, de-spiked and mean-normalized using AFNI (Cox 1996). All time points occurring during excessive motion, defined as >1 mm, were excluded from the analyses as part of the regression (Johnstone et al. 2006). Separate regressors for each intelligibility level (high, mid, low) were created for each participant; additional regressors were the mean, linear, and quadratic trend components, and the 6 motion parameters (x, y, z and roll, pitch and yaw). A linear least squares model was used to establish a fit to each time point of the hemodynamic response function for each condition. Event-related signals were deconvolved by linear interpolation, beginning at two seconds post stimulus onset and continuing at 6-sec intervals for 18 sec, using AFNI's tent function (i.e. a piecewise linear spline model). This resulted in regression weights (beta values) indexing percent signal change at each 6-sec interval. All analyses focused on the beta values for the first 6 sec post-stimulus onset time lag. The Freesurfer software package (Dale et al. 1999; Fischl et al. 1999; Fischl et al. 2004) was used to create surface representations of each participant's anatomy by inflating each hemisphere of the anatomical volumes to a surface representation and aligning it to a template of average curvature. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness (CT), calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale 2000). The maps were created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting sub-millimeter differences between groups. Procedures for the measurement of CT have

been validated against histological analysis (Rosas et al. 2002) and manual measurements (Kuperberg et al. 2003; Salat et al. 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al. 2006). SUMA was then used to import the surface representations into the AFNI 3D space and to project the functional data from the 3-dimensional volumes onto the 2-dimensional surfaces. The thickness maps were also exported to SUMA. Data were smoothed on the surface to achieve a target smoothing value of 6 mm using a Gaussian full width half maximum (FWHM) filter. Smoothing on the surface as opposed to smoothing on the volume ensures that white matter values are not included, and that functional data situated in anatomically distant locations on the cortical surface are not averaged across sulci (Argall et al. 2006; Desai et al. 2005).

Whole-brain thickness analysis. This analysis identified all cortical nodes that exhibited an age effect on CT using two-tailed t-tests for two independent samples (AFNI 3dttest++ program). Two covariates were included in the model: right ear PTA and right ear DP-OEAs. Since left and right ear PTA values were highly correlated ($r = .852$, $p \leq .0001$), and to avoid over-fitting the data, only the right ear PTA was entered in the model. For the DPOAEs, again left and right ear values were highly correlated ($r = .7$, $p = .0003$). The variable that was entered in the model was the DP amplitude at 5 kHz for the right ear, which maximally differed between groups. All hearing covariates (PTA and DPOAEs) were mean-centered across groups. The Monte Carlo simulation procedure implemented in Freesurfer, which takes into account the level of smoothing in the data, was used to identify significant clusters of age vulnerable vertices, with an individual vertex threshold of $p < .05$, corrected for multiple comparisons to achieve a family-wise error (FWE) rate of $p < 0.05$ (clusters ≥ 461 vertices).

Whole-brain BOLD analysis. To examine the core network for speech repetition across intelligibility levels, an intersection map was first computed for each subject (High $\cap$ Mid, $\cap$ Low intelligibility levels) (Nichols et al. 2005), which reveals regions involved in perceiving and producing sequences of syllables. All significantly active vertices ($p = .05$) for each of the three conditions were included in the subject final map. Separate group maps were generated for the young adults, the older adults and for all 22 subjects. The reliability

of the core speech perception network was investigated by computing a map representing the number of subject showing significant activity for each voxel. This was done separately for the young and older adults as well as for the entire group. In addition, for each subject the total number of active voxels for each hemisphere was calculated and entered into a repeated-measure ANCOVA with age as the between-subject factor, Hemisphere as the within-subject factor (left, right) and PTA, DPOAEs and Sex as covariates. To ensure that the statistical threshold that we used to threshold the individual conjunction maps did not have an undue influence on the output of this analysis we repeated it at four different significance levels (.1, .05, .01 and .005).

Next, an ANCOVA (AFNI 3dMVM program) with repeated measurements on Intelligibility level was computed across the whole brain. Age group (young, older) was used as the between subject factor, and the covariates were the right ear PTA and right ear DP-OAEs. This analysis identified all cortical nodes exhibiting a main effect of age (young, older), a main effect of Intelligibility (high, mid, low), and an age by Intelligibility interaction in the BOLD signal. The Monte Carlo simulation procedure implemented in Freesurfer was used to identify significant clusters of activated vertices, with an individual vertex threshold of $p < .05$, corrected for multiple comparisons to achieve a family-wise error (FWE) rate of $p < 0.01$ (clusters $\geq$ 237 vertices). Finally, to examine potential overlap between structural and functional brain aging, we computed the intersection map (Nichols et al. 2005) of (1) age effects on thickness, (2) age effects on BOLD, and (3) Age by Intelligibility interaction on BOLD.

ROI-based mediation analyses. Three separate analyses of regions of interests (ROI) were conducted based on the results of the whole-brain thickness and BOLD analyses (for the main Intelligibility effect and Intelligibility by Group interaction). For all ROIs identified through either one of these analyses, the CT value of each subject as well as the percent BOLD signal change for each intelligibility condition (high, mid, low) was extracted and entered into a serial mediation analysis to examine whether age-related changes in performance were mediated by regional thickness and BOLD signal. The mediation analyses were conducted using the PROCESS macro (model #6) for SPSS (http://www.afhayes.com/) (Preacher and Hayes 2004; Preacher and Hayes 2008b; Hayes 2013). Mediation analyses allow researchers to examine the mechanisms by which one variable affect another (Baron and Kenny 1986; Shrout and Bolger 2002; Preacher and Hayes 2008a, 2004;

MacKinnon et al. 2007). These analyses thus provide a powerful analytical framework for testing predictions about mechanisms to explain age effects. Serial multiple mediation analyses estimate the path coefficients in a multiple mediator model and generate bootstrap confidence intervals for total and specific indirect effects of X on Y through multiple mediator variables (M) that are assumed to causally influence another (in the statistical sense). The model that was used is illustrated in Supplementary Figure 1. In this serial mediation model, the dependent (y) variable was the errors in the low intelligibility condition (since it displayed the greatest age effects, even after controlling for hearing sensitivity differences), while the independent (x) variable was the categorical variable age group (young, older). Three covariates (right ear PTA, right ear DPOAEs (5 kHz), and sex) were included in both the mediator (M) and the dependent variable (Y) models. CT was used as the first mediator (M_1). Weighted combinations of the BOLD signal were used as second mediators. Three different BOLD signal combinations were computed to account for the variety of BOLD signal patterns found across ROIs rather than assuming a unique pattern. The first model was linear, which tested for a linear change in BOLD signal as a function of intelligibility levels. The second model (non-linear 1) was a quadratic model, in which the middle condition was assumed to be significantly different from the other two levels. The third model (non-linear 2) tested for the situation in which BOLD signal for the high and mid intelligibility levels differed for the low intelligibility level. This analysis allowed us to test several hypotheses: (1) higher CT is associated with better performance, (2) lower CT modulates BOLD signal which in turns modulates behaviour, (3) BOLD signal modulates performance.

For each ROI, a linear regression was used to test for a direct effect of age on thickness and BOLD (the *a* paths in the model). A linear regression was also conducted to test for an effect of thickness on BOLD signal (the *d* paths). Next, a series of multiple regressions was conducted, each including one of the mediators to examine (1) whether there was a direct effect of age on performance after removing the effect of thickness and BOLD (the *c'* path), and (2) whether there was an indirect effect of age on performance signal through thickness (*ab* paths), through BOLD (*ab* paths), or through thickness and BOLD (the *adb* paths). A bootstrapping approach was used to test for the significance of the indirect effects (Shrout and Bolger 2002) ($P < 0.05$, using bias-corrected bootstrapping with 10,000 samples). Bootstrapping involves the repeated extraction of samples, with replacement, from a dataset and the estimation of the indirect effect in each resampled data set.

Results

Hearing assessment

The complete results of the pure tone audiometry, including high frequencies audiometry, are plotted in Figure 2A. As shown in Figure 2B, examination of hearing sensitivity across groups, as measured by PTA (pure tone thresholds averaged across 500, 1000 and 2000 Hz), revealed significant between-group differences in both the right ($t_{(20)}$ = -4.23, $p \leq .001$, *bilateral*) and the left ear ($t_{(20)}$ = -5.05, $p \leq .001$, *bilateral*), with the older group exhibiting higher thresholds than the young. As shown in Figure 2C, speech reception thresholds were also significantly higher in older adults ($t_{(20)}$ = -3.66, p = .002, *bilateral*). Figure 3 summarizes the results for the analysis of the DPOAEs. The largest group difference was found at 5 kHz (right ear: $t_{(20)}$ = 4.18, $p \leq .001$, *bilateral*; left ear: $t_{(20)}$ = 7.55, $p \leq .001$, *bilateral*). The left and right PTA were highly correlated (r = .85), and so too were the left and right DPOAEs (r = .73).

Therefore, in all subsequent data analyses (including behavioural and fMRI data), hearing measures were used as covariates in analyses of covariance (ANCOVAs) to control for peripheral hearing sensitivity differences across groups. We chose to use two complementary measures to control for age-related hearing differences: an audiological measure (the PTA), and a bioacoustical measure (DPOAEs recordings) at 5KHz. PTA was used as a covariate because it is a clinically meaningful measure of hearing loss for speech. Indeed, most speech sounds fall within this range. PTA differed significantly across groups. However, a limit of PTA is that it is a self-reported measure. Therefore, we also included a measure of oto-acoustic emissions (DPOAEs), which are purely physiological response the measure the functioning of the cochlear micro-mechanics, and do not require an active answer from the subject. Using these two complementary hearing measures as covariates in all of our analyses allowed us to control, at least to some extent, for between-group hearing differences. Since the SRT correlated with PTA measures (right ear: r = .62; left ear: r = .52) we did not include it in our models. We used ANCOVAs because they provide a means of adjusting for sample differences on the covariate and provide an unbiased estimate of the population difference in means on the dependent variable. Though we cannot claim of having controlled for all possible hearing differences between our groups, we controlled for peripheral hearing sensitivity as measured by PTA and DPOAEs.

Behavioural data

As shown in Figure 4, the main age-related difference at the behavioural level was a decrease in accuracy for older compared to younger adults. A repeated-measure ANCOVA conducted on the number of syllables incorrectly produced with repeated measurements on intelligibility (high, mid, low) and with PTA, DPOAEs and Sex as covariates revealed a main effect of Intelligibility ($F_{(2,34)} = 18.83$, $p \leq .001$), an age by Intelligibility interaction ($F_{(2,34)} = 4.54$, $p = .018$) and no main effect of age ($F_{(1,17)} = 2.14$, $p = .160$). The effect of age on accuracy was maximal in the low intelligibility condition, with the young adults mispronouncing (mean±SD) 46.25±8.63% of the syllables, and older adults 68.47±11.8% of the syllables ($t_{(20)} = -5.03$, $p \leq .001$, *bilateral*). Hence, the effect of age was still present in the behavioural data, even after controlling for significant effect of PTA ($F_{(2,34)} = 10.03$, $p \leq .001$), but not DPOAE ($F_{(2,34)} = .91$, $p = .41$).

For response duration, a repeated measure ANCOVA with repeated measurements on intelligibility, and with PTA and Sex as covariates, revealed no main effect of intelligibility ($F_{(2,36)} = .35$, $p = .700$), no main effect of age ($F_{(1,18)} = .025$, $p = .975$), and no interaction ($F_{(2,36)} = .09$, $p = .771$). For RT, a repeated measure ANCOVA with repeated measurements on intelligibility and with PTA and Sex as covariates revealed no main effect of intelligibility ($F_{(2,36)} = .77$, $p = .471$), no main effect of age ($F_{(1,18)} = 1.18$, $p = .292$), and no interaction ($F_{(2,36)} = 1.18$, $p = .322$). Taken together, these findings demonstrate that compared to younger adults, older adults are less accurate but not slower in repeating speech sounds.

Imaging data

Whole-brain thickness analyses

First, we identified voxels that showed an age-related difference in surface-based CT controlling for hearing sensitivity (PTA, DPOAEs). As shown in Figure 5, this analysis revealed several spatially focused cortical areas distributed across the two hemispheres, including the right medial prefrontal cortices and right supramarginal gyrus (SMG), and left ventral primary motor area, and premotor areas. A list of all age vulnerable regions is presented in Table 2.

Whole-brain BOLD analyses

For the analysis of the BOLD signal, we first examined the core network for listening to and repeating syllable sequences, within and across age groups. The results of these analyses are shown in Figure 6. As can be seen in Figure 6A, this core speech network was bilateral and centered around the primary auditory area in the transverse temporal gyrus and sulcus and on the primary motor area in the ventral central sulcus. At an individual significance level of $p = .05$, the ANCOVA conducted on the number of active voxels, with factors Hemisphere and Age, and using sex, PTA and DPOAEs as covariates, revealed that this network was significantly more widespread for young than older adults ($F_{(1,16)} = 7.11$, $p = .017$). There were no effect of Hemisphere ($F_{(1,16)} = .30$, $p = .592$) and no interaction between Age and Hemisphere ($F_{(1,16)} = .18$, p = .678). As mentioned in the method section, this analysis was repeated at three other individual significance levels ($p = .10$, .05, .01 and .005). The findings were identical across all four analyses. Given the robustness of this finding, a mediation analysis was conducted on the number of speech repetition errors in the low intelligibility condition (controlling for hearing sensitivity and sex) with activation spread as the mediator variable. This analysis revealed that spatial extent in the left hemisphere had a negative inverse effect on repetition error rate. Results show that age was negatively associated with the number of activated voxels ($a_2 = -8032.9$), while spatial extent was positively associated with the number of errors ($b_1 = .0017$), leading to a significant negative indirect effect of age on error rate through spatial extent in the left hemisphere ($a_2b_1 = -13.49$, SE: 10.22, CI = -32.18 to -3.27), suggesting an age-related increase in processing efficiency. There was no evidence that age influenced error rate independent of its effect on BOLD ($c' = 17.32$, SE: 9.5, $p = .089$), indicative of a *complete mediation*. In the right hemisphere, no direct or indirect effect of spatial extent was found.

Next we examined regions that were sensitive to Intelligibility, as well as those who showed an interaction between Age and Intelligibility interaction using a voxel wise ANCOVA controlling for hearing sensitivity (PTA, DPOAEs). As shown in Figure 7, regions sensitive to intelligibility were largely left lateralized and circumscribed to the ventral premotor and ventral primary motor areas of the frontal lobe. Figure 8 shows the regions whose sensitivity to intelligibility varied as a function of age (*i.e.* Age by Intelligibility interaction).

This included the left dorsal anterior superior insula, the right SMA, the right dorsal primary motor area (M1d), and right dorsal somatosensory cortex in the posterior dorsal part of the postcentral gyrus and sulcus. Activation were also found more caudally in the parietal lobe, including in the posterior intraparietal sulcus and superior parietal gyrus. A list of all regions identified through these analyses is presented in Table 3. A list of all regions showing a main effect of age is included in the Supplementary Materials.

Functional vs. structural effects of aging

To visualize the interplay between regions exhibiting age-sensitivity in BOLD signal and/or in CT, three statistical maps were overlaid: (1) the map of the main effect of age on CT, (2) the map of the main effect of age on BOLD, and (3) the map of age by intelligibility interaction on BOLD (Figure 9). This analysis revealed no joint age-sensitive area indicative of a partial dissociation between structural and functional aging.

Functional ROI analyses

The functional ROI analysis consisted in examining, using a powerful mediation framework, whether the regions identified through either the whole-brain analyses (CT analysis and BOLD), which are reported in Tables 2 and 3, were related to the behavioural patterns that we identified. Therefore, for each of these regions, the BOLD signal in each condition and the CT were extracted for each participant. Each of these regions was then submitted to a series of serial mediation analyses. Three types of indirect effects (mediations) on speech errors were examined: (1) indirect effects of age on accuracy through CT (type 1), (2) indirect effects of age on accuracy through BOLD (type 2), and (3) indirect effects of age on accuracy through CT and BOLD (serial mediation: type 3). For all indirect effect, the unstandardized regression coefficients are reported along with bias-corrected bootstrap confidence intervals (CI), which are used to tests whether the indirect effects are different from zero (non-directional significance tests). All CIs are based on 10,000 bootstrap samples. These results are summarized in Tables 2 and 3.

First we examined the regions identified through the whole-brain CT analysis. A negative (inverse) indirect effect of CT on the relationship of age to speech errors (*i.e.* increased accuracy) was found in only one region identified through the whole-brain analysis of CT: the right posterior insula (*pIns*; see table 2 and Figure

5). In this region, an increase in age was associated with a decrease in thickness (a_1 = -.40). Thickness, in turns, was positively associated with the number of speech errors (b_3 = 19.58), leading to a significant negative indirect effect of age on speech errors through CT (a_1b_1 = -7.9, SE: 5.2, CI = -18.1 to -1.99). There was however evidence that age influenced speech errors independent of its effect on CT (c' = 26.44, SE: 8.04, p = .009), meaning that with age, performance decreased, and indicative of a *partial mediation* of CT. Though we found no region that mediated the relationship of age to performance through BOLD, four regions showed a direct positive effect of BOLD on speech errors (i.e. an increase in number of errors), which was independent of both thickness and age: the left dorsal M1/PM (*M1d/PMd)* (b_1 = 19.03, SE: 9.04, CI = 3.17 to 34.8), the right anterior medial prefrontal cortex (*amPFC*) (b_1 = 27.28, SE: 9.24, CI = 11.07 to 43.49), the right paracentral gyru and sulcus (PARA) (b_1 = 19.45, SE: 7.16, CI = 6.88 to 32.01), and the right pre-SMA (b_1 = 30.88, SE: 15.14, CI = 4.33 to 57.44). In all these regions, increased BOLD led to increased speech errors. The right PARA also exhibited a direct positive effect of CT on speech errors independent of age (b_3 = 19.32, SE: 8.81, CI = 3.86 to 34.78).

Next we examined the regions identified through the whole-brain Age by Intelligibility interaction in BOLD signal. In the left superior sulcus of the dorsal anterior insula (daIns – see Figure 8), age was negatively associated with non-linearly weighted BOLD (a_2 = -.49), while BOLD was negatively associated speech errors (b_1 = -23.27), leading to a significant positive indirect effect of age on speech error rate through BOLD signal in this region (a_2b_1 = 11.63, SE: 9.38, CI = 1.81 to 31.27), suggesting a decrease in neural processing efficiency. There was no evidence that age influenced speech errors independent of its effect on BOLD (c' = 8.32, SE: 8.06, p = .31), indicative of a *complete mediation*. In addition to this mediation effect, a direct effect of BOLD on speech errors was also found in two regions, which was independent of age: the left dorsal rostral postcentral gyrus (*PostCGd* – see Figure 8) (b_1 = 41.59, SE: 18.88, CI = 8.49 to 74.69), and the left occipital-temporal sulcus (*OTSL* – see Figure 8) (b_4 = -11.18, SE: 3.42, CI = -17.18 to -5.18), where the direct effect of thickness on speech errors was also significant (b_3 = 20.34, SE: 9.04, CI = 4.48 to 36.22).

Finally, we examined the regions identified through the whole-brain intelligibility BOLD analysis. Only a direct effect of CT on speech errors was found in the left dorsal precentral gyrus (PMd, see Figure 7) (b_3 = 18.83, SE: 8.8, CI = 3.4 to 34.26).

As above-mentioned, no serial mediation effects were found in our dataset. Still, the direct effect of CT on BOLD (independent of speech errors and age) was examined to reveal potential brain structure-function relationships. Three regions were identified through the analyses of the interaction of age and intelligibility (the left dorsal rostral postcentral gyrus (PostCd), the right ventral anterior insula (vaIns) and right dorsal PM (PMd)), and one through the analysis of the main effect of intelligibility on BOLD signal (the left PMv). This effect was positive in right PostCd (d_1 = .79, SE: .32 CI = .15 to 1.43) and in the right PMd (d_2 = .85, SE: .35, CI = .22 to 1.4). This effect was negative in the right vaIns (d_3 = -.53, SE: .22, CI = -.91 to -.14) and in the right PMv, this effect was negative (d_2 = -.41, SE: .17, CI = -.71 to -.11).

Discussion

This study is the first multimodal aging study focusing on the ability to perceive speech in relation to both structural and functional brain changes, using a complex and innovative mediation analysis framework combining voxel-wise and ROI approaches. Our main objective was to characterize the effect of functional and structural neural decline on the ability to repeat sequences of meaningless auditory syllables presented at various intelligibility levels. The use of meaningless syllables is key to study perceptual skills while avoiding linguistic (e.g. lexical or semantic) top-down effects that facilitate perception and can potentially mask speech perception difficulties. Nonsenses syllables are sensitive to hearing impairments and useful in quantifying its effects (Stach 2010). Our results indicate an age-related decline in the ability to repeat meaningless sequences of syllables in noise. Importantly this effect was still present after controlling for hearing differences across groups in terms of PTA and DPOAEs at 5KHz, suggesting that aging of the central nervous system contributes to speech perception decline in normal aging, consistent with previous findings (Frisina and Frisina 1997). Importantly, we show that the combination of structural and functional measures to study brain aging at the macro-anatomical level is critical to understand changes in speech perception, as these two phenomena appears to be – at least partially – dissociated. From a methodological point of view, the analysis framework that we report here, which was first used to characterize functional brain patterns during a speech task in young and older individuals (Tremblay et al. 2013), was confirmed as a successful approach to link structural, functional and behavioural processes to better understand cognitive aging.

Direct and indirect influence of CT on speech accuracy

Several localized cortical regions were identified including the right supramarginal gyrus (SMG), posterior right insula, left ventral anterior insula, right anterior medial prefrontal cortex, left ventral precentral gyrus and sulcus, in which CT, a measure of the depth of the cortical mantle (Fischl and Dale 2000; Fischl et al. 1999), whose validity has been demonstrated (Kabani et al. 2001) was thinner in older compared to younger adults, consistent with the notion that CT decline is one of the most reliable biomarkers of structural brain aging (De Leon et al. 1997; van Velsen et al. 2013) also consistent with the notion that structural aging, though widespread, is regionally heterogeneous with some regions showing more acute vulnerability than other regions (van Velsen et al. 2013; Fjell et al. 2009; Thambisetty et al. 2010; Chee et al. 2009). Our findings are consistent with a recent study that employed a similar surface-based procedure to study normal aging in a large group of 86 individuals, in which age-related thinning of CT was found in precentral and medial prefrontal cortices, insula, SMA and SMG (Chen et al. 2011). Medial prefrontal thinning was also reported in other large-scale studies (Fjell et al. 2009; Chee et al. 2009). While the general phenomenon of age-related cortical thinning is well known, few studies have described the effect of cortical thinning (or more generally structural brain aging) on speech and language (Peelle et al. 2011; Wong et al. 2010). Moreover, in most studies, measures of peripheral hearing were not included as controls in the analyses because teasing apart hearing from non-hearing aging effects was not the primary objectives of these studies.

We found limited evidence of an age-related impact of CT on speech performance. Our finding of such effect is limited to the right posterior insula that had a partial indirect effect on the relationship of age to speech perception independent of peripheral hearing sensitivity. This effect was positive, meaning that the indirect effect of age on performance through thickness was an increase in performance. Holding thickness constant however, the direct effect of age on performance was negative. Though the left insula has been more consistently associated with speech (Dronkers 1996; Ogar et al. 2006; Riecker et al. 2000; Ackermann and Riecker 2004), the right insula is also active during syllable perception and production (Tremblay and Small 2011d; Bohland and Guenther 2006; Ghosh et al. 2008), word production (Peeva et al. 2010) as well as sentence listening and

repetition (Tremblay and Small 2011a), suggesting that it forms a core part of the speech production/perception network.

Direct age-independent effects of CT on performance were also found in the right paracentral area, left medial occipital-temporal sulcus (OTS) and left PMd. In all these regions, larger CT was associated with increased error rate (decreased accuracy). Several other studies have documented such inverse effect. For instance, a reliable inverse relationship between thickness and free recall was found in the left medial paracentral/cingulate sulcus in a sample of older healthy adults scanned in four different scanners (Dickerson et al. 2008). A positive relation between anxiety and depression scores and CT has been found in the right ventral medial prefrontal cortex (Ducharme et al. 2013). Relatedly, a study on the CT and neuronal density performed on the brain of Einstein revealed thinner cortex with increased density in Einstein's brain compared to normal controls (Anderson and Harvey 1996). Such inverse relationships could indicate cortical pruning associated with more efficient processing. In sum, our results are among the firsts to demonstrate age-dependent and age-independent effects of CT on speech perception.

Direct and indirect influence of BOLD signal on speech accuracy

Our analysis of the core speech perception network, which covered most of the supratemporal cortex bilaterally as well as ventral primary motor and premotor areas, reveals a global decrease in BOLD signal in aging. Lower BOLD signal in aging can be interpreted in at least two distinct ways: reduced neural functioning or increase in processing efficiency. Here, we showed, using mediation analyses, that this global decrease in spatial extent had a beneficial indirect effect on the relationship of age to performance. Prior work has shown that expertise is associated with regional decrease in brain activation in young adults during object recognition (Wiesmann and Ishai 2011) and auditory perception (Petrini et al. 2011; Berkowitz and Ansari 2010), suggesting that increased processing efficiency can be accompanied with lower BOLD signal. We speculate that the decrease in spatial extent of the overall speech network reflects increased neural efficiency across the whole speech network. This of course does not mean that regional decline in BOLD signal in specific areas cannot be related to a decline in speech perception. It simply means that greater overall decline in BOLD signal across intelligibility levels was not associated with an increased error rate.

Indeed, at the regional level, we did find negative effects of BOLD signal decline. Such effect was found in the anterior superior circular sulcus of the left insula (corresponding to the dorsal anterior insula (daIns) identified in a previous study (Nelson et al. 2010)). The indirect effect of the left daIns on the relationship of age to speech errors was detrimental. This region is typically reported in studies of speech production (Riecker et al. 2000; Ghosh et al. 2008; Ackermann and Riecker 2004; Bohland and Guenther 2006; Peeva et al. 2010; Kemeny et al. 2005), speech perception (Tremblay and Small 2011b, d) and oro-facial movements (Grabski et al. 2012; Martin et al. 2004; Corfield et al. 1999), suggesting that it is part of the core speech network. A role for this region in speech production was emphasized by Dronkers et al (Dronkers 1996; Ogar et al. 2006) who showed, using voxel-based morphometry, that lesion to this region is related to speech apraxia, a disorder of speech planning. It could be argued that because our task required the articulation of syllables, which necessitate the recruitment of motor areas, the role of the insula is in supporting articulation. However, given that the effect of age on accuracy increased commensurate to a decline in stimuli intelligibility, while articulation complexity was kept constant across intelligibility levels, we suggest that it contributed to either perceptual or attentional, but not motor, processes. An fMRI study that investigated syllable discrimination at various intelligibility levels (Binder et al. 2004) showed that the BOLD signal in the bilateral anterior insula was positively correlated with RT while BOLD signal in the supratemporal cortex was positively correlated with syllable discrimination accuracy, suggesting that the anterior is involved in decision making while the supratemporal region is involved in sound identification. In the present study, the BOLD signal in the left daIns increased as a function of decreased intelligibility for the young adults, consistent with this idea, while in the older adults, not only was the signal lower but it no longer showed an intelligibility effect. Though all participants were screened for cognitive functioning using the MOCA (Nasreddine et al. 2003), which argues against a cognitive deficit as a factor influencing accuracy, we did not perform a test of selective or sustained auditory attention. As discussed in Nelson et al (Nelson et al. 2010), the anterior insula is among the most commonly reported activation site across fMRI studies. Based on resting state functional and task-related fMRI studies, these authors suggest that the anterior insula contributes to general executive processes involved in goal-oriented tasks. The present results are consistent with this idea, with the need for monitoring/attention increasing as intelligibility decreases. Interestingly, the age by intelligibility interactions in the BOLD signal also revealed several parietal regions in

the right hemisphere including the posterior intraparietal sulcus, the dorsal postcentral gyrus and sulcus and the superior parietal gyrus, some of which are known for their involvement in the so-called dorsal attention network (DAN) (Corbetta et al. 2008). DAN is typically found for visual tasks, while the auditory attentional network seems to be located more ventrally in the inferior parietal lobe (Braga et al. 2013; Seydell-Greenwald et al. 2013). None of these dorsal parietal regions, however, showed a relationship to performance, perhaps reflecting compensatory mechanisms to supplement a ventral attention network in older ages. Additional studies are needed to better understand the role of attention and attention-related brain regions in the aetiology of speech perception difficulties in normal aging. The link between speech perception and auditory attention (sustained, selective) has only been scarcely investigated, and yet attention may play an important part in the aetiology of communicative difficulties in aging.

Intelligibility-related BOLD signal modulation

Intelligibility-modulated BOLD signal was found in premotor/sensorimotor, mainly in the left hemisphere, including in the ventral premotor area (PMv), ventral primary motor area (M1v) and dorsal somatosensory cortex. This finding is consistent with the results of a PET study of passive sentence listening in which premotor and prefrontal areas, but not auditory areas, were modulated by intelligibility levels (Scott et al. 2004). Another PET study comparing sentence listening in quiet and noise also yielded no modulation of auditory areas (Salvi et al. 2002). The finding of activation in premotor areas in processing syllables is consistent with the notion that it is involved in both speech production (Peeva et al. 2010; Tremblay and Small 2011d, c) and perception (Wilson et al. 2004; Tremblay and Small 2011d; Skipper et al. 2005; Tremblay et al. 2012; Callan et al. 2010; Callan et al. 2006; Pulvermüller et al. 2006). According to the DIVA (Directions Into Velocities of Articulators) model of speech production, speech sound maps are represented in the ventral premotor cortex (Guenther et al. 2006; Guenther 1994, 1995). It is therefore possible that degraded speech signal leads to a decline in the level of activation in corresponding speech sound maps in this region. Consistent with this idea, recent transcranial magnetic stimulation studies (TMS) have shown that stimulation of the left PMv has little or no effect on people's ability to perceive or categorize intelligible speech sounds (Sato et al. 2009). In contrast, TMS to PMv has a stronger impact on speech perception when intelligibility is reduced (Meister et al.

2007), demonstrating that this region is sensitive to the quality of the auditory speech signal. More recently, it was demonstrated that TMS to this region can influence speech sound categorization (Grabski et al. 2013). Relatedly, correct identification of phonemes in noise has also been associated with increased activation in PMv relative to trials in which the phonemes were incorrectly identified (Callan et al. 2010). Taken together, these results support a role for left PMv in speech processing, which increases commensurate to speech sound intelligibility, providing some support to theories of speech perception that postulate a role for motor/phonological information in speech perception (Galantucci et al. 2006; Schwartz et al. 2010). Interestingly, activation in the SMA increased as intelligibility decreased, perhaps reflecting a more difficult selection of the appropriate motor programs due to the increased ambiguity, consistent with a role for this area in selecting motor programs for speech (Tremblay and Gracco 2006; Tremblay et al. 2008; Tremblay and Gracco 2009; Tremblay and Small 2011c) as well as non-speech motor behaviours (Lau et al. 2004; Lau et al. 2006; Deiber et al. 1996; Van Oostende et al. 1997).

Relationship between brain structure and brain function in aging

One of the most intriguing finding of this study is the relative dissociation between functional and structural aging. Though unexpected, this dissociation between age-related differences in BOLD signal and age-related differences in brain structure is consistent with a recent study that investigated age-related changes in resting state CBF and CT in healthy adults, in which little overlap was found (Chen et al. 2011). Nyberg et al. also found little overlap in functional and structural aging in a circumscribed region of the right frontal cortex during a semantic categorization task (Nyberg et al. 2010); others have found age-related changes in task-related BOLD that were independent from changes in gray matter volume (Roski et al. 2013). Likewise, there is limited overlap between brain regions showing abnormal reductions in cerebral blood flow (CBF) in neurological diseases such as Huntington's disease and brain regions showing structural atrophy (Chen et al. 2012). The finding that BOLD signal and CT independently predict performance in older individuals suggests that they may be associated with distinct risk factors for age-related communication difficulties, which stresses the importance of assessing them both to uncover the normal and pathological neurobiological aging mechanisms.

Though we did not find causal (in the statistical sense) relationship between thickness, BOLD and behaviour, we did find significant age-independent interactions between brain structure and BOLD signal in several cortical areas (left PMv, left dorsal postcentral gyrus, right dorsal anterior insula, and right PMd). In half of these regions (left dorsal postcentral gyrus, right PMd), cortical thinning led to increased BOLD signal, and negative in the other half (right insula, left PMv). The finding of localized effects of regional CT on BOLD signal suggests that that the dissociation found between structural and functional brain aging may only be partial. Further studies are needed to continue investigate the complex interplay of brain anatomy, brain physiology and behaviour.

Conclusion

We demonstrated important age-related structural and functional neural differences associated with speech perception after controlling for peripheral hearing loss. The use of an innovative mediation framework combining voxel-wise and ROI analyses allowed us to examine direct and indirect relationships between brain structure, brain function and speech-related neural mechanisms, and revealed that these relationships can be either beneficial or detrimental to behavioural outcome. Understanding age-related vulnerabilities of the neural speech system is critical to developing new intervention strategies to maintain communication throughout aging, which could contribute to redefining old age for millions of people worldwide.

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References

Ackermann H, Riecker A (2004) The contribution of the insula to motor aspects of speech production: a review and a hypothesis. Brain and language 89 (2):320-328. doi:10.1016/S0093-934X(03)00347-X

S0093934X0300347X [pii]

Anderson B, Harvey T (1996) Alterations in cortical thickness and neuronal density in the frontal cortex of Albert Einstein. Neuroscience letters 210 (3):161-164

Argall BD, Saad ZS, Beauchamp MS (2006) Simplified intersubject averaging on the cortical surface using SUMA. Human Brain Mapping 27 (1):14-27

Baron RM, Kenny DA (1986) The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. Journal of personality and social psychology 51 (6):1173-1182

Berkowitz AL, Ansari D (2010) Expertise-related deactivation of the right temporoparietal junction during musical improvisation. Neuroimage 49 (1):712-719. doi:10.1016/j.neuroimage.2009.08.042

Binder JR, Liebenthal E, Possing ET, Medler DA, Ward BD (2004) Neural correlates of sensory and decision processes in auditory object identification. Nat Neurosci 7 (3):295-301. doi:10.1038/nn1198

Boersma P, Weenink D (2011) Praat: doing phonetics by computer. 5.2.10 edn.,

Bohland JW, Guenther FH (2006) An fMRI investigation of syllable sequence production. Neuroimage 32 (2):821-841. doi:S1053-8119(06)00447-2 [pii]

10.1016/j.neuroimage.2006.04.173

Braga RM, Wilson LR, Sharp DJ, Wise RJ, Leech R (2013) Separable networks for top-down attention to auditory non-spatial and visuospatial modalities. Neuroimage 74:77-86. doi:10.1016/j.neuroimage.2013.02.023

Burianova H, Lee Y, Grady CL, Moscovitch M (2013) Age-related dedifferentiation and compensatory changes in the functional network underlying face processing. Neurobiology of aging 34 (12):2759-2767. doi:10.1016/j.neurobiolaging.2013.06.016

Callan D, Callan A, Gamez M, Sato MA, Kawato M (2010) Premotor cortex mediates perceptual performance. Neuroimage 51 (2):844-858. doi:S1053-8119(10)00195-3 [pii]

10.1016/j.neuroimage.2010.02.027

Callan DE, Tsytsarev V, Hanakawa T, Callan AM, Katsuhara M, Fukuyama H, Turner R (2006) Song and speech: brain regions involved with perception and covert production. Neuroimage 31 (3):1327-1342. doi:S1053-8119(06)00055-3 [pii]

10.1016/j.neuroimage.2006.01.036

Campbell KL, Grady CL, Ng C, Hasher L (2012) Age differences in the frontoparietal cognitive control network: implications for distractibility. Neuropsychologia 50 (9):2212-2223. doi:10.1016/j.neuropsychologia.2012.05.025

Chee MW, Chen KH, Zheng H, Chan KP, Isaac V, Sim SK, Chuah LY, Schuchinsky M, Fischl B, Ng TP (2009) Cognitive function and brain structure correlations in healthy elderly East Asians. Neuroimage 46 (1):257-269. doi:10.1016/j.neuroimage.2009.01.036

Chen JJ, Rosas HD, Salat DH (2011) Age-associated reductions in cerebral blood flow are independent from regional atrophy. Neuroimage 55 (2):468-478. doi:10.1016/j.neuroimage.2010.12.032

Chen JJ, Salat DH, Rosas HD (2012) Complex relationships between cerebral blood flow and brain atrophy in early Huntington's disease. Neuroimage 59 (2):1043-1051. doi:10.1016/j.neuroimage.2011.08.112

Cooper JC, Jr., Gates GA (1991) Hearing in the elderly--the Framingham cohort, 1983-1985: Part II. Prevalence of central auditory processing disorders. Ear and hearing 12 (5):304-311

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58 (3):306-324. doi:10.1016/j.neuron.2008.04.017

Corfield DR, Murphy K, Josephs O, Fink GR, Frackowiak RS, Guz A, Adams L, Turner R (1999) Cortical and subcortical control of tongue movement in humans: a functional neuroimaging study using fMRI. J Appl Physiol 86 (5):1468-1477

Cox RW (1996) AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. Computers and Biomedical Research 29 (3):162-173

Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based Analysis: I. Segmentation and surface reconstruction. NeuroImage 9 (2):179-194

De Leon MJ, George AE, Golomb J, Tarshish C, Convit A, Kluger A, De Santi S, McRae T, Ferris SH, Reisberg B, Ince C, Rusinek H, Bobinski M, Quinn B, Miller DC, Wisniewski HM (1997) Frequency of

hippocampal formation atrophy in normal aging and Alzheimer's disease. Neurobiology of aging 18 (1):1-11

Deiber MP, Ibanez V, Sadato N, Hallett M (1996) Cerebral structures participating in motor preparation in humans: a positron emission tomography study. Journal of neurophysiology 75 (1):233-247

Desai R, Liebenthal E, Possing ET, Waldron E, Binder JR (2005) Volumetric vs. surface-based alignment for localization of auditory cortex activation. NeuroImage 26 (4):1019-1029

Dickerson BC, Fenstermacher E, Salat DH, Wolk DA, Maguire RP, Desikan R, Pacheco J, Quinn BT, Van der Kouwe A, Greve DN, Blacker D, Albert MS, Killiany RJ, Fischl B (2008) Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage 39 (1):10-18. doi:10.1016/j.neuroimage.2007.08.042

Dronkers NF (1996) A new brain region for coordinating speech articulation. Nature 384 (6605):159-161. doi:10.1038/384159a0

Ducharme S, Albaugh MD, Hudziak JJ, Botteron KN, Nguyen TV, Truong C, Evans AC, Karama S (2013) Anxious/Depressed Symptoms are Linked to Right Ventromedial Prefrontal Cortical Thickness Maturation in Healthy Children and Young Adults. Cereb Cortex. doi:10.1093/cercor/bht151

Eden GF, Joseph JE, Brown HE, Brown CP, Zeffiro TA (1999) Utilizing hemodynamic delay and dispersion to detect fMRI signal change without auditory interference: the behavior interleaved gradients technique. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 41 (1):13-20

Edmister WB, Talavage TM, Ledden PJ, Weisskoff RM (1999) Improved auditory cortex imaging using clustered volume acquisitions. Hum Brain Mapp 7 (2):89-97

Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proceedings of the National Academy of Sciences of the United States of America 97 (20):11050-11055. doi:10.1073/pnas.200033797

Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis: II: Inflation, flattening, and a surface-based coordinate system. NeuroImage 9 (2):195-207

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004) Automatically parcellating the human cerebral cortex. Cerebral Cortex 14 (1):11-22. doi:10.1093/cercor/bhg087

Fjell AM, Walhovd KB (2010) Structural brain changes in aging: courses, causes and cognitive consequences. Reviews in the neurosciences 21 (3):187-221

Fjell AM, Westlye LT, Amlien I, Espeseth T, Reinvang I, Raz N, Agartz I, Salat DH, Greve DN, Fischl B, Dale AM, Walhovd KB (2009) High consistency of regional cortical thinning in aging across multiple samples. Cereb Cortex 19 (9):2001-2012. doi:10.1093/cercor/bhn232

Frisina DR, Frisina RD (1997) Speech recognition in noise and presbycusis: relations to possible neural mechanisms. Hearing research 106 (1-2):95-104

Galantucci B, Fowler CA, Turvey MT (2006) The motor theory of speech perception reviewed. Psychon Bull Rev 13 (3):361-377

Gates GA, Mills JH (2005) Presbycusis. Lancet 366 (9491):1111-1120. doi:10.1016/S0140-6736(05)67423-5

Ghosh SS, Tourville JA, Guenther FH (2008) A neuroimaging study of premotor lateralization and cerebellar involvement in the production of phonemes and syllables. Journal of speech, language, and hearing research : JSLHR 51 (5):1183-1202. doi:10.1044/1092-4388(2008/07-0119)

Gordon-Salant S, Fitzgibbons PJ (2001) Sources of age-related recognition difficulty for time-compressed speech. Journal of speech, language, and hearing research : JSLHR 44 (4):709-719

Grabski K, Lamalle L, Vilain C, Schwartz JL, Vallee N, Tropres I, Baciu M, Le Bas JF, Sato M (2012) Functional MRI assessment of orofacial articulators: neural correlates of lip, jaw, larynx, and tongue movements. Hum Brain Mapp 33 (10):2306-2321. doi:10.1002/hbm.21363

Grabski K, Tremblay P, Gracco VL, Girin L, Sato M (2013) A mediating role of the auditory dorsal pathway in selective adaptation to speech: a state-dependent transcranial magnetic stimulation study. Brain research 1515:55-65. doi:10.1016/j.brainres.2013.03.024

Gracco VL, Tremblay P, Pike B (2005) Imaging speech production using fMRI. Neuroimage 26 (1):294-301. doi:S1053-8119(05)00072-8 [pii]

10.1016/j.neuroimage.2005.01.033

Grady CL, Protzner AB, Kovacevic N, Strother SC, Afshin-Pour B, Wojtowicz M, Anderson JA, Churchill N, McIntosh AR (2010) A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. Cereb Cortex 20 (6):1432-1447. doi:10.1093/cercor/bhp207

Guenther FH (1994) A neural network model of speech acquisition and motor equivalent speech production. Biological cybernetics 72 (1):43-53

Guenther FH (1995) Speech sound acquisition, coarticulation, and rate effects in a neural network model of speech production. Psychological review 102 (3):594-621

Guenther FH, Ghosh SS, Tourville JA (2006) Neural modeling and imaging of the cortical interactions underlying syllable production. Brain and language 96 (3):280-301. doi:S0093-934X(05)00115-X [pii] 10.1016/j.bandl.2005.06.001

Hall DA, Haggard MP, Akeroyd MA, Palmer AR, Summerfield AQ, Elliott MR, Gurney EM, Bowtell RW (1999) "Sparse" temporal sampling in auditory fMRI. Hum Brain Mapp 7 (3):213-223

Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, Busa E, Pacheco J, Albert M, Killiany R, Maguire P, Rosas D, Makris N, Dale A, Dickerson B, Fischl B (2006) Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 32 (1):180-194. doi:10.1016/j.neuroimage.2006.02.051

Hayes AF (2013) Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. Methodology in the Social Sciences. The Guilford Press

Hayes D (1981) Central auditory problems and the aging process. In: Beasley DS, Davis GA (eds) Aging, communication processes and disorders. Grune & Stratton, New York, pp 257-266

Head D, Rodrigue KM, Kennedy KM, Raz N (2008) Neuroanatomical and cognitive mediators of age-related differences in episodic memory. Neuropsychology 22 (4):491-507. doi:10.1037/0894-4105.22.4.491

Helfer KS, Vargo M (2009) Speech recognition and temporal processing in middle-aged women. Journal of the American Academy of Audiology 20 (4):264-271

Helfer KS, Wilber LA (1990) Hearing loss, aging, and speech perception in reverberation and noise. Journal of speech and hearing research 33 (1):149-155

Humes LE, Lee JH, Coughlin MP (2006) Auditory measures of selective and divided attention in young and older adults using single-talker competition. The Journal of the Acoustical Society of America 120 (5 Pt 1):2926-2937

Jacobs-Condit LE (1984) Gerontology and Communication Disorders. American Speech-Language-Hearing Association, Rockville

Johnstone T, Ores Walsh KS, Greischar LL, Alexander AL, Fox AS, Davidson RJ, Oakes TR (2006) Motion correction and the use of motion covariates in multiple-subject fMRI analysis. Human Brain Mapping 27:779-788

Kabani N, Le Goualher G, MacDonald D, Evans AC (2001) Measurement of cortical thickness using an automated 3-D algorithm: a validation study. Neuroimage 13 (2):375-380. doi:10.1006/nimg.2000.0652

Kemeny S, Ye FQ, Birn R, Braun AR (2005) Comparison of continuous overt speech fMRI using BOLD and arterial spin labeling. Hum Brain Mapp 24 (3):173-183. doi:10.1002/hbm.20078

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B (2003) Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60 (9):878-888

Lau H, Rogers RD, Passingham RE (2006) Dissociating response selection and conflict in the medial frontal surface. Neuroimage 29 (2):446-451. doi:10.1016/j.neuroimage.2005.07.050

Lau HC, Rogers RD, Haggard P, Passingham RE (2004) Attention to intention. Science 303 (5661):1208-1210. doi:10.1126/science.1090973

MacKinnon DP, Fairchild AJ, Fritz MS (2007) Mediation analysis. Annual review of psychology 58:593-614. doi:10.1146/annurev.psych.58.110405.085542

Martin RE, MacIntosh BJ, Smith RC, Barr AM, Stevens TK, Gati JS, Menon RS (2004) Cerebral areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study. Journal of neurophysiology 92 (4):2428-2443. doi:10.1152/jn.01144.2003

Meister IG, Wilson SM, Deblieck C, Wu AD, Iacoboni M (2007) The essential role of premotor cortex in speech perception. Current Biology 17:1692-1696

Meunier D, Stamatakis EA, Tyler LK (2014) Age-related functional reorganization, structural changes, and preserved cognition. Neurobiology of aging 35 (1):42-54. doi:10.1016/j.neurobiolaging.2013.07.003

Nasreddine ZS, Chertkow H, Phillips N, Bergman H, Whitehead V (2003) Sensitivity and Specificity of The Montreal Cognitive Assessment (MoCA) for Detection of Mild Cognitive Deficits. Can J Neurol Sci 30 (30)

Nelson SM, Dosenbach NU, Cohen AL, Wheeler ME, Schlaggar BL, Petersen SE (2010) Role of the anterior insula in task-level control and focal attention. Brain structure & function 214 (5-6):669-680. doi:10.1007/s00429-010-0260-2

Nichols T, Brett M, Andersson J, Wager T, Poline JB (2005) Valid conjunction inference with the minimum statistic. Neuroimage 25 (3):653-660. doi:S1053-8119(04)00750-5 [pii]

10.1016/j.neuroimage.2004.12.005

Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, Lind J, Pudas S, Persson J, Nilsson LG (2010) Longitudinal evidence for diminished frontal cortex function in aging. Proceedings of the National Academy of Sciences of the United States of America 107 (52):22682-22686. doi:10.1073/pnas.1012651108

Ogar J, Willock S, Baldo J, Wilkins D, Ludy C, Dronkers N (2006) Clinical and anatomical correlates of apraxia of speech. Brain and language 97 (3):343-350. doi:10.1016/j.bandl.2006.01.008

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1):97-113

Peelle JE, Chandrasekaran K, Powers J, Smith EE, Grossman M (2013) Age-related vulnerability in the neural systems supporting semantic processing. Frontiers in aging neuroscience 5:46. doi:10.3389/fnagi.2013.00046

Peelle JE, Troiani V, Grossman M, Wingfield A (2011) Hearing loss in older adults affects neural systems supporting speech comprehension. The Journal of neuroscience : the official journal of the Society for Neuroscience 31 (35):12638-12643. doi:10.1523/JNEUROSCI.2559-11.2011

Peeva MG, Guenther FH, Tourville JA, Nieto-Castanon A, Anton JL, Nazarian B, Alario FX (2010) Distinct representations of phonemes, syllables, and supra-syllabic sequences in the speech production network. Neuroimage 50 (2):626-638. doi:S1053-8119(09)01354-8 [pii]

10.1016/j.neuroimage.2009.12.065

Petrini K, Pollick FE, Dahl S, McAleer P, McKay LS, Rocchesso D, Waadeland CH, Love S, Avanzini F, Puce A (2011) Action expertise reduces brain activity for audiovisual matching actions: an fMRI study with expert drummers. Neuroimage 56 (3):1480-1492. doi:10.1016/j.neuroimage.2011.03.009

Plath P (1991) Speech recognition in the elderly. Acta Otolaryngology 476 (Suppl.):127-130

Preacher KJ, Hayes AF (2004) SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behavior research methods, instruments, & computers : a journal of the Psychonomic Society, Inc 36 (4):717-731

Preacher KJ, Hayes AF (2008a) Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 40 (3):879-891

Preacher KJ, Hayes AF (2008b) Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behavior Research Methods 40:879-891

Pulvermüller F, Huss M, Kherif F, Moscoso del Prado Martin F, Hauk O, Shtyrov Y (2006) Motor cortex maps articulatory features of speech sounds. Proceedings of the National Academy of Sciences 103 (20):7865-7870

Riecker A, Ackermann H, Wildgruber D, Dogil G, Grodd W (2000) Opposite hemispheric lateralization effects during speaking and singing at motor cortex, insula and cerebellum. Neuroreport 11:1997-2000

Ries PW (1994) Prevalence and characteristics of persons with hearing trouble: United States, 1990-91. Vital and health statistics Series 10, Data from the National Health Survey (188):1-75

Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B (2002) Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58 (5):695-701

Roski C, Caspers S, Lux S, Hoffstaedter F, Bergs R, Amunts K, Eickhoff SB (2013) Activation shift in elderly subjects across functional systems: an fMRI study. Brain structure & function. doi:10.1007/s00429-013-0530-x

Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B (2004) Thinning of the cerebral cortex in aging. Cereb Cortex 14 (7):721-730

Salvi RJ, Lockwood AH, Frisina RD, Coad ML, Wack DS, Frisina DR (2002) PET imaging of the normal human auditory system: responses to speech in quiet and in background noise. Hearing research 170 (1-2):96-106

Sambataro F, Murty VP, Callicott JH, Tan HY, Das S, Weinberger DR, Mattay VS (2010) Age-related alterations in default mode network: impact on working memory performance. Neurobiology of aging 31 (5):839-852. doi:10.1016/j.neurobiolaging.2008.05.022

Sato M, Tremblay P, Gracco VL (2009) A mediating role of the premotor cortex in phoneme segmentation. Brain and language 111 (1):1-7. doi:S0093-934X(09)00041-8 [pii]

10.1016/j.bandl.2009.03.002

Schwartz J, Basirat A, Ménard L, Sato M (2010) The Perception-for-Action-Control Theory (PACT): A perceptuo-motor theory of speech perception Journal of Neurolinguistics

Scott SK, Rosen S, Wickham L, Wise RJ (2004) A positron emission tomography study of the neural basis of informational and energetic masking effects in speech perception. The Journal of the Acoustical Society of America 115 (2):813-821

Seydell-Greenwald A, Greenberg AS, Rauschecker JP (2013) Are you listening? Brain activation associated with sustained nonspatial auditory attention in the presence and absence of stimulation. Hum Brain Mapp. doi:10.1002/hbm.22323

Sheppard JP, Wang JP, Wong PC (2011) Large-scale cortical functional organization and speech perception across the lifespan. PloS one 6 (1):e16510. doi:10.1371/journal.pone.0016510

Shrout PE, Bolger N (2002) Mediation in experimental and nonexperimental studies: new procedures and recommendations. Psychological methods 7 (4):422-445

Skipper JI, Nusbaum HC, Small SL (2005) Listening to talking faces: motor cortical activation during speech perception. Neuroimage 25 (1):76-89. doi:S1053-8119(04)00673-1 [pii]
10.1016/j.neuroimage.2004.11.006

Spaniol J, Grady C (2012) Aging and the neural correlates of source memory: over-recruitment and functional reorganization. Neurobiology of aging 33 (2):425 e423-418. doi:10.1016/j.neurobiolaging.2010.10.005

Stach BA (2010) Clinical Audiology: An Introduction. Delmar, Clifton Park, NY, USA

Strouse A, Ashmead DH, Ohde RN, Grantham DW (1998) Temporal processing in the aging auditory system. The Journal of the Acoustical Society of America 104 (4):2385-2399

Thambisetty M, Wan J, Carass A, An Y, Prince JL, Resnick SM (2010) Longitudinal changes in cortical thickness associated with normal aging. Neuroimage 52 (4):1215-1223. doi:10.1016/j.neuroimage.2010.04.258

Tremblay P, Baroni M, Hasson U (2012) Processing of speech and non-speech sounds in the supratemporal plane: Auditory input preference does not predict sensitivity to statistical structure. Neuroimage 66C:318-332. doi:10.1016/j.neuroimage.2012.10.055

Tremblay P, Dick AS, Small SL (2013) Functional and structural aging of the speech sensorimotor neural system: functional magnetic resonance imaging evidence. Neurobiology of aging. doi:10.1016/j.neurobiolaging.2013.02.004

Tremblay P, Gracco VL (2006) Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence. Neuroimage 33 (3):947-957. doi:10.1016/j.neuroimage.2006.07.041

Tremblay P, Gracco VL (2009) Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS). Brain research 1268:112-124. doi:10.1016/j.brainres.2009.02.076

Tremblay P, Shiller DM, Gracco VL (2008) On the time-course and frequency selectivity of the EEG for different modes of response selection: evidence from speech production and keyboard pressing. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 119 (1):88-99

Tremblay P, Small SL (2011a) From language comprehension to action understanding and back again. Cereb Cortex 21 (5):1166-1177. doi:10.1093/cercor/bhq189

Tremblay P, Small SL (2011b) From language comprehension to action understanding and back again. Cerebral Cortex 21 (5):1166-1177. doi:10.1093/cercor/bhq189

Tremblay P, Small SL (2011c) Motor response selection in overt sentence production: a functional MRI study. Frontiers in psychology 2:253. doi:10.3389/fpsyg.2011.00253

Tremblay P, Small SL (2011d) On the context-dependent nature of the contribution of the ventral premotor cortex to speech perception. Neuroimage 57 (4):1561-1571. doi:10.1016/j.neuroimage.2011.05.067

Van Oostende S, Van Hecke P, Sunaert S, Nuttin B, Marchal G (1997) FMRI studies of the supplementary motor area and the premotor cortex. Neuroimage 6 (3):181-190. doi:10.1006/nimg.1997.0287

van Velsen EF, Vernooij MW, Vrooman HA, van der Lugt A, Breteler MM, Hofman A, Niessen WJ, Ikram MA (2013) Brain cortical thickness in the general elderly population: The Rotterdam Scan Study. Neuroscience letters 550:189-194. doi:10.1016/j.neulet.2013.06.063

Walhovd KB, Fjell AM, Dale AM, McEvoy LK, Brewer J, Karow DS, Salmon DP, Fennema-Notestine C (2010) Multi-modal imaging predicts memory performance in normal aging and cognitive decline. Neurobiology of aging 31 (7):1107-1121. doi:10.1016/j.neurobiolaging.2008.08.013

Westlye LT, Grydeland H, Walhovd KB, Fjell AM (2011) Associations between regional cortical thickness and attentional networks as measured by the attention network test. Cereb Cortex 21 (2):345-356. doi:10.1093/cercor/bhq101

Wiesmann M, Ishai A (2011) Expertise reduces neural cost but does not modulate repetition suppression. Cognitive neuroscience 2 (1):57-65. doi:10.1080/17588928.2010.525628

Wilson S, Saygin A, Sereno M, Iacoboni M (2004) Listening to speech activates motor areas involved in speech production. Nat Neurosci 7 (7):701-702

Wong PC, Ettlinger M, Sheppard JP, Gunasekera GM, Dhar S (2010) Neuroanatomical characteristics and speech perception in noise in older adults. Ear and hearing 31 (4):471-479. doi:10.1097/AUD.0b013e3181d709c2

Wong PC, Jin JX, Gunasekera GM, Abel R, Lee ER, Dhar S (2009) Aging and cortical mechanisms of speech perception in noise. Neuropsychologia 47 (3):693-703. doi:S0028-3932(08)00462-4 [pii] 10.1016/j.neuropsychologia.2008.11.032

Wong PC, Uppunda AK, Parrish TB, Dhar S (2008) Cortical mechanisms of speech perception in noise. Journal of speech, language, and hearing research : JSLHR 51 (4):1026-1041. doi:51/4/1026 [pii] 10.1044/1092-4388(2008/075)

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1982) Development and validation of a geriatric depression screening scale: a preliminary report. Journal of psychiatric research 17 (1):37-49

Yorkston KM, Bourgeois MS, Baylor CR (2010) Communication and aging. Physical medicine and rehabilitation clinics of North America 21 (2):309-319. doi:10.1016/j.pmr.2009.12.011

Figures

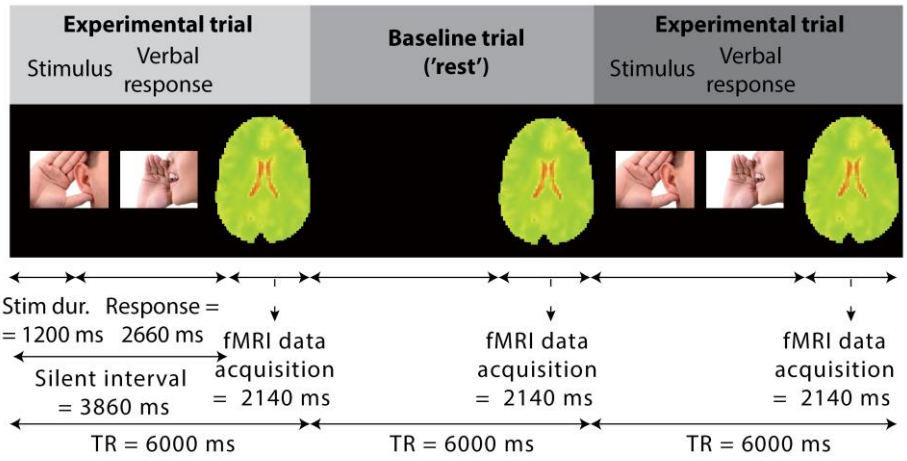


Figure 1. Illustration of the sparse-sampling MRI data acquisition protocol that was used in the present study, and experimental paradigm.

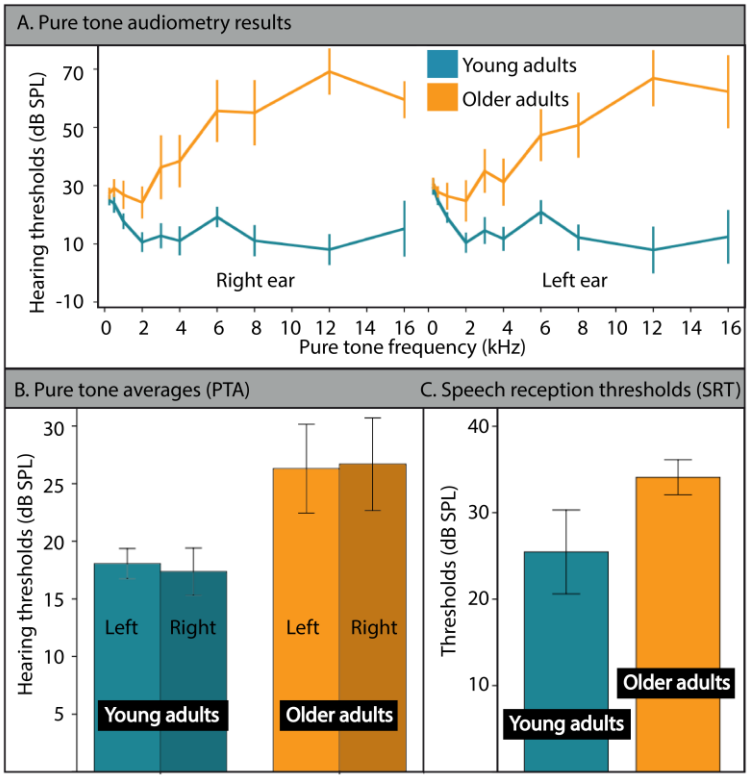


Figure 2. A. Pure tone audiometry results for the young and older adults. B. Pure tone averages (in dB) for the young (blue bars) and older adults (orange bars) provided separately for the left and right ear. C. Speech reception thresholds (in dB) for the young (blue bars) and older adults (orange bars).

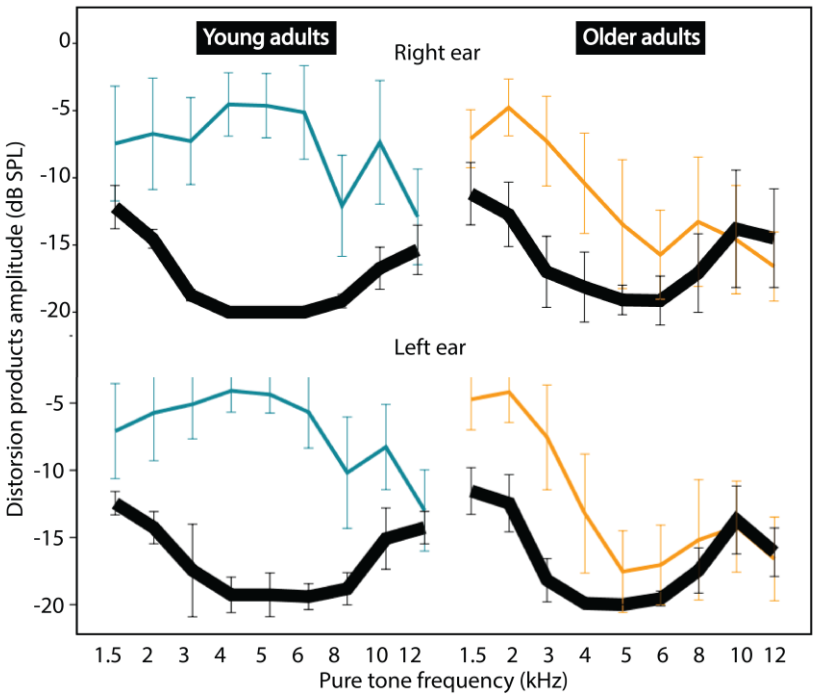


Figure 3. Distortion product oto-acoustic emissions (DPOAEs) for the young (blue line) and older adults (orange line), for the right ear (top row) and left ear (bottom row). Error bars represent the standard error of the mean.

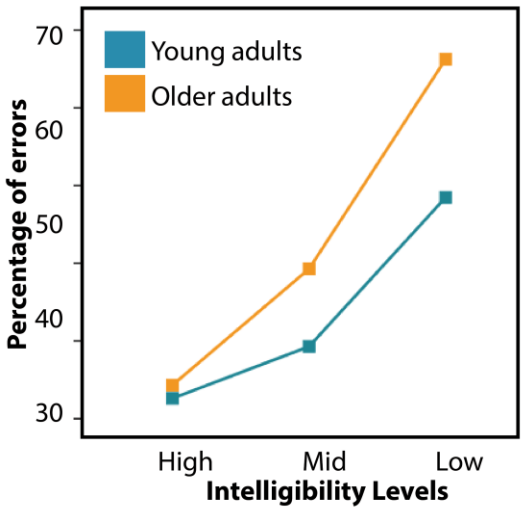


Figure 4. Line graphs illustrating the percentage of mispronounced syllables for each group at each intelligibility level (High, Mid, Low).

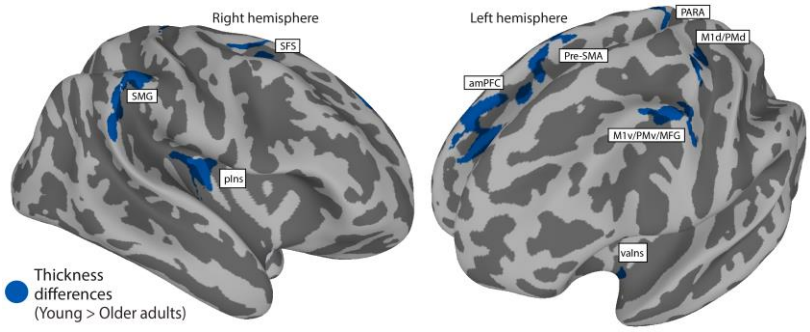


Figure 5. Group differences in cortical thickness corrected for multiple comparisons. Regions in blue were thinner in older compared to young adults. Thickness differences are shown on the group average smoothed white matter folded surface in which dark gray regions represent sulci while pale gray areas represent gyri.

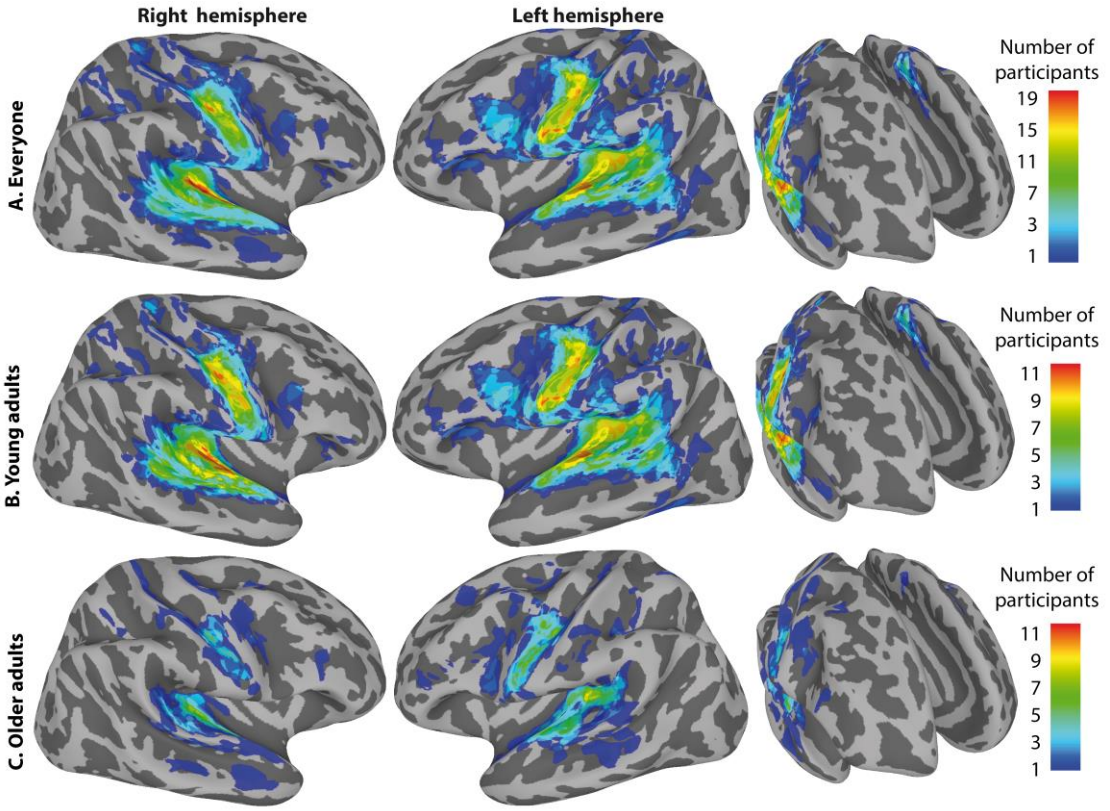


Figure 6. Colour-coded results of the conjunction analysis (core speech network). The colour scale represents the number of subject in which each node was significantly active at each intelligibility level (high, mid, and low). Regions in red are those in which the conjunction was present in the largest number of subjects. In A, all subjects are included in the conjunction. In B, only the young adults are included, and in C, only the older adults. As can be seen in the figure, the spatial extent of the network decreases with age. Activation is shown on the group average smoothed white matter folded surfaces. From left to right: the right lateral hemisphere, left lateral hemisphere and left medial wall.

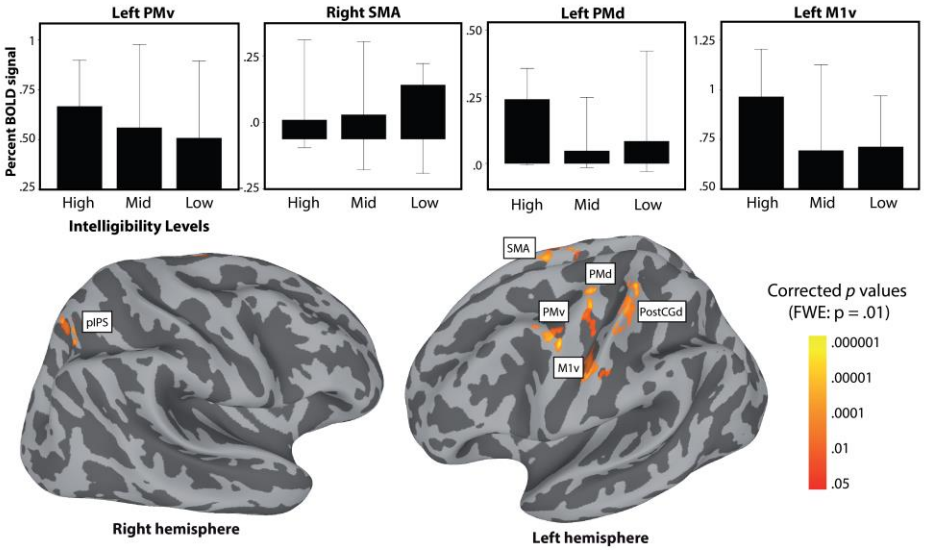
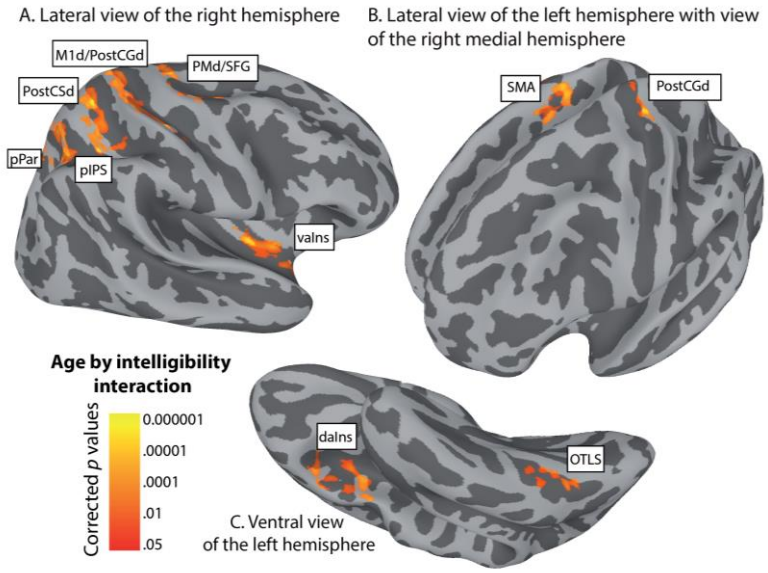


Figure 7. Regions significantly modulated by intelligibility at the group-level, corrected for multiple comparisons. Activation is shown on the group average smoothed white matter folded right and left lateral surfaces. The plots at the top of the figure illustrate patterns of brain activity (expressed as the median percentage of signal change) across intelligibility levels in four different areas identified through this analysis.



The error bars represent the confidence interval.

Figure 8. Regions exhibiting a significant Age by intelligibility interaction at the group-level, corrected for multiple comparisons. The figure includes a view of right and left lateral hemispheres and left ventral hemisphere at the bottom. Activation is shown on the group average smoothed white matter folded right and left lateral surfaces. A view of the left ventral brain is included at the bottom of the figures.

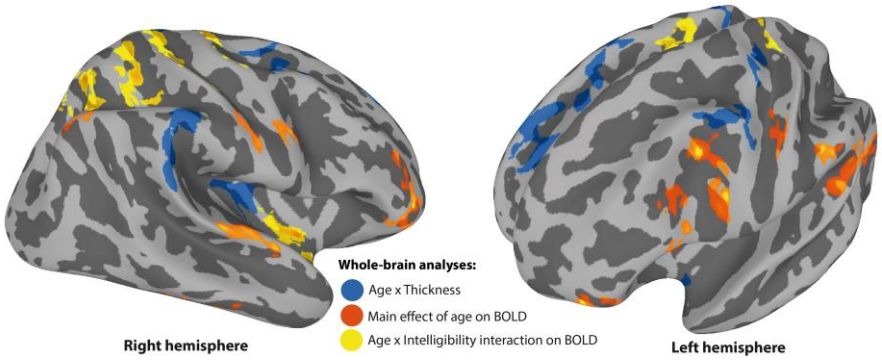


Figure 9. Overlay of all of the age effects found in the study. In blue are regions showing a significant main effect of age on cortical thickness. In yellow are regions showing a significant age by intelligibility interaction. In orange are voxels showing a significant main effect of age. Regions exhibiting a significant Age by intelligibility interaction at the group-level, corrected for multiple comparisons. Activation is shown on the group average smoothed white matter folded right and left lateral surfaces. The figure includes a view of right and left lateral hemispheres, as well as a view of the right medial wall. The overlay of all age-sensitive voxels reveals no overlap between thickness and BOLD aging effects.

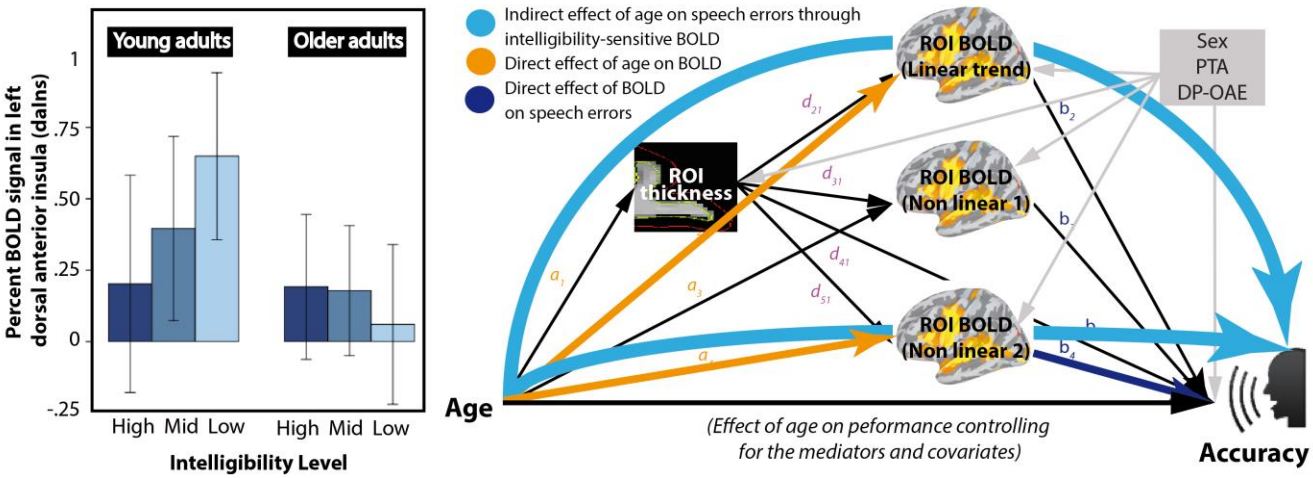


Figure 10. Analysis of the left dorsal anterior insula (*daIns*). On the left is a plot representing activity in this region expressed as a percentage of change as a function of intelligibility level and age. On the right is the result of the serial mediation analysis for the left anterior insula. Bold lines indicate significant effects.

Tables

Table 1. Participants characteristics by age group

	Young adults (N = 11)				Older adults (N = 11)			
	Minimum	Maximum	Mean	Std. Deviation	Minimum	Maximum	Mean	Std. Deviation
Age	21.00	32.00	25.73	3.88	61.00	74.00	68.00	4.56
Education	15.00	21.00	17.45	2.02	11.00	33.00	17.55	5.73
Handedness	18.00	20.00	19.27	.90	19.00	20.00	19.82	.40
MOCA	27.00	30.00	29.18	1.08	26.00	29.00	27.18	1.08
Depression scale	.00	6.00	2.27	2.24	.00	5.00	1.00	1.79

Table 2. FWE-corrected age effects in cortical thickness at the whole brain level. Coordinates are in Talairach space and represent the peak surface node for each of the cluster (FWE: $p = .05$, minimum cluster size: 461 contiguous surface nodes, each significant at $p < .05$). Cluster size is calculated in number of surface nodes, and area is in mm2.

Region	Hemi	x	y	z	t	Exact *p*	Size (nodes)	Area (mm)	Results of the mediation analyses
Para-hippocampal gyrus, extending into the lingual gyrus	Left	-18	-34	-10	-3.81	0.00140012	1276	561.1	No mediation effect
Dorsal central sulcus and precentral gyrus (M1d/PMd)	Left	-28	-23	61	-2.62	0.0179224	592	247.75	Direct positive effect of BOLD on speech errors
Ventral precentral gyrus and sulcus (M1v/PMv), extending into the middle frontal gyrus (MFG)	Left	-39	4	50	-2.35	0.0311099	875	221.59	No mediation effect
Long and short gyri of the ventral anterior insula (vaIns)	Left	-34	4	-19	-2.68	0.015495	856	147.93	No mediation effect
Anterior medial prefrontal cortex including superior frontal gyrus, medial frontal gyrus and anterior cingulate gyrus (amPFC)	Right	16	52	33	-2.49	0.023422	936	445.21	Direct positive effect of BOLD on speech errors
Supramarginal gyrus (SMG)	Right	61	-24	42	-3.75	0.00159492	977	294.73	No mediation effect
Medial frontal gyrus (pre-SMA)	Right	9	22	50	-3.11	0.00650454	738	290.19	Direct positive effect of BOLD on speech errors
Inferior circular sulcus of the posterior insula (pIns)	Right	37	-18	-1	-2.79	0.012567	657	240.47	Indirect effect of cortical thickness on the relationship of age to speech errors
Paracentral gyrus and sulcus (PARA)	Right	6	-39	71	-2.72	0.015175	573	132.62	Direct positive effect of BOLD on speech errors Direct positive effect of cortical thickness on speech errors
Superior frontal sulcus (SFS)	Right	30	11	54	-2.13	0.0480779	536	121.96	No mediation effect

Table 3. FWE-corrected whole brain BOLD results. A. Main effect of Age; B. Main effect of Intelligibility and C. Age x Intelligibility interaction. Coordinates are in Talairach space and represent the peak surface node for each of the cluster (FWE: $p = .01$, minimum cluster size: 237 contiguous surface nodes, each significant at $p < 0.05$). Cluster size is calculated in number of surface nodes, and area is in mm2.

Effect	*Region*	Hemi	x	y	z	F	*p*	Size (nodes)	Area (mm)	Results of the mediation analyses
Intelligibility	*Dorsal rostral postcentral gyrus (most likely corresponding to Brodmann areas 3 and 1) (PostCd)*	Left	-34	-34	71	9.231	0.000580	734	225.5	No mediation effect
	Ventral central sulcus (M1)	Left	-48	-20	39	8.577	0.000899	474	212.32	No mediation effect
	Dorsal precentral gyrus (PMd)	Left	-33	-20	69	8.338	0.001058	389	157.51	Direct effect of cortical thickness on repetition errors
	Posterior cingulate gyrus	Left	-5	-40	28	9.059	0.000651	508	136.13	No mediation effect
	Ventral precentral gyrus and sulcus (PMv)	Left	-51	-6	49	8.591	0.000891	324	85.85	Direct effect of cortical thickness on BOLD
	Calcarine sulcus and cuneus	Right	8	-71	15	9.098	0.000634	255	137.65	No mediation effect
	Posterior cingulate gyrus	Right	6	-35	37	5.671	0.007228	261	90.08	No mediation effect
	Superior frontal gyrus extending medially into the SMA-proper	Right	15	-2	66	7.747	0.001592	285	82.22	No mediation effect
	Posterior intraparietal sulcus (pIPS) extending into the transverse occipital sulcus.	Right	23	-63	57	7.856	0.001475	268	50.53	No mediation effect
Age x Intelligibility	*Posterior cingulate gyrus*	Left	-5	-35	30	9.004	0.000675	698	197.58	No mediation effect
	Superior circular sulcus of the dorsal anterior insula (daIns)	Left	-32	21	12	7.874	0.001457	694	175.71	Positive indirect effect of age on speech error through BOLD
	Occipito-temporal lateral sulcus (OTLS)	Left	-41	-61	-9	8.354	0.001046	316	118.69	Direct effect of BOLD on speech errors Direct effect of thickness on speech errors
	Dorsal rostral postcentral gyrus/central sulcus (PostCGd)	Left	-25	-32	71	9.511	0.000483	312	117.74	Direct effect of BOLD on speech errors Direct effect of cortical thickness on BOLD

	Inferior frontal gyrus, pars triangularis (ventral)	Left	-41	33	-1	6.269	0.004613	330	112.04	No mediation effect
	Dorsal central sulcus and dorsal rostral postcentral gyrus (M1d/PostCd)	Right	46	-18	50	14.792	0.000020	2041	664.88	No mediation effect
	Dorsal postcentral sulcus (PostCSd)	Right	25	-45	63	11.495	0.000138	1158	290.63	No mediation effect
	Posterior intraparietal sulcus extending into the transverse occipital sulcus (pIPS)	Right	23	-62	57	10.871	0.000203	878	200.15	No mediation effect
	Long and short gyri of the ventral anterior insula (vaIns)	Right	38	4	-7	11.865	0.000110	437	172.77	Direct effect of cortical thickness on BOLD
	Medial frontal gyrus (SMA-proper)	Right	9	-19	69	6.659	0.003462	490	151.71	No mediation effect
	Dorsal precentral sulcus (PMd)	Right	33	-7	51	9.328	0.000544	332	105.66	Direct effect of cortical thickness on BOLD
	Posterior cingulate gyrus	Right	6	-35	36	7.715	0.001628	308	93.66	No mediation effect
	Dorsal precentral sulcus and superior frontal gyrus (PMd/SFG)	Right	19	-17	68	9.636	0.000445	284	76.24	No mediation effect
	Superior parietal gyrus extending into the precuneus (pPar)	Right	10	-76	49	6.668	0.003439	265	61.15	No mediation effect

Supplementary Table. FWE-corrected whole brain BOLD results. A. Main effect of Age. Coordinates are in Talairach space and represent the peak surface node for each of the cluster (FWE: $p = .01$, minimum cluster size: 237 contiguous surface nodes, each significant at $p < 0.05$). Cluster size is calculated in number of surface nodes, and area is in mm^2.

Effect	*Region*	Hemi	x	y	z	F	*p*	Size (number of nodes)	Area (mm)
Age	*Ventral precentral sulcus (PMv)*	Left	-37	7	38	21.406	0.000001	731	284.58
	Planum temporale	Left	-54	-49	33	18.286	0.000003	772	270.14
	Sulcus sub-parietal and posterior cingulate gyrus	Left	-8	-47	31	16.154	0.000010	645	210.15
	Ventral central sulcus (M1v)	Left	-51	-20	41	10.964	0.000191	285	150.86
	Medial frontal gyrus (pre-SMA)	Left	-7	17	54	14.376	0.000026	344	141.19
	Orbital gyrus	Left	-40	52	-11	22.869	0.0000004	326	140.64
	Temporal pole	Left	-28	13	-41	16.159	0.000010	385	131.59
	Anterior cingulate gyrus and sulcus	Left	-4	13	28	8.923	0.000712	336	122.01
	Inferior frontal gyrus, pars opercular	Left	-51	-15	19	12.772	0.000064	373	98.63
	Superior temporal sulcus	Left	-41	-77	24	14.425	0.000025	359	89.13
	Supramarginal gyrus (inferior)	Left	-54	-38	27	13.13	0.000052	297	79.5
	Inferior frontal sulcus	Left	-38	20	24	8.048	0.001291	237	78.87
	Supramarginal gyrus (superior)	Left	-58	-32	39	18.648	0.000003	315	75.69
	Orbital sulcus and gyrus	Right	43	48	-3	32.863	0.00000001	849	300.68
	Superior temporal gyrus	Right	67	-21	5	19.937	0.000001	760	200.04
	Fusiform gyrus, extending into the occipito-temporal sulcus and inferior temporal gyrus	Right	40	-31	-23	73.319	0.0000000000002	465	159.32
	Inferior circular sulcus of the insula	Right	46	7	-24	12.676	0.000068	296	146.64
	Ventral postcentral gyrus	Right	62	-5	31	11.823	0.000113	452	110.58
	Ventral precentral gyrus	Right	55	7	32	20.375	0.000001	304	95.68
	Angular gyrus	Right	49	-62	46	11.55	0.000133	292	67.02