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ORIGINAL ARTICLE

Structural brain aging and speech production: a surface-based brain morphometry study

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Abstract While there has been a growing number of studies examining the neurofunctional correlates of speech production over the past decade, the neurostructural correlates of this immensely important human behaviour remain less well understood, despite the fact that previous studies have established links between brain structure and behaviour, including speech and language. In the present study, we thus examined, for the first time, the relationship between surface-based cortical thickness (CT) and three different behavioural indexes of sublexical speech production: response duration, reaction times and articulatory accuracy, in healthy young and older adults during the production of simple and complex meaningless sequences of syllables (e.g., /pa–pa-pa/ vs. /pa-ta-ka/). The results show that each behavioural speech measure was sensitive to the complexity of the sequences, as indicated by slower reaction times, longer response durations and decreased articulatory accuracy in both groups for the complex sequences. Older adults produced longer speech responses, particularly during the production of complex sequence. Unique age-independent and age-dependent relationships between brain structure and each of these behavioural measures were found in several cortical and subcortical regions known for their involvement in speech production, including the bilateral anterior insula, the left primary motor area, the rostral supramarginal gyrus, the right inferior frontal sulcus, the bilateral putamen and caudate, and in some region less typically associated with speech production, such as the posterior cingulate cortex.

Keywords Speech production · Cortical thickness · Anterior insula · Aging · Subcortical volume

Introduction

One of the most distinctive features of speech production is its serial ordering, that is, the organization of speech movements into precise, smooth and coordinated temporal sequences of lips, tongue, and jaw movements to produce fluent speech (Lashley 1951). Speech motor sequencing is the planning of the order of each movement within a sequence. In mature speakers, speech sequences can be produced at the rate of up to six to nine syllables per second, making speech production faster than any other discrete human motor behaviour (Kent 2000). Evidence is accumulating suggesting that, with age, the ability to produce sequential speech movements undergoes important changes, including a decrease in rate (Fozo and Watson 1998; Wohlert and Smith 1998; Duchin and Mysak 1987; Searl et al. 2002), and an increase in the duration of individual speech movements (Morris and Brown 1987; Ryan and Burk 1974; Smith et al. 1987; Dromey et al. 2014). Moreover, an age-related increase in articulatory errors for the repetition of complex multisyllabic nonwords compared to simpler ones has been reported (Sadagopan and

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Smith 2013). Consistent with this finding, recent results from our group show an age-related decline in articulatory accuracy, with older adults committing more errors during the production of complex sequences of speech sounds compared to younger adults (Bilodeau-Mercure et al. 2015). Together, these results suggest that speech motor sequencing mechanisms are affected by the normal aging processes. However, the neurobiological mechanisms that underlie speech motor sequencing, and their decline, are still largely unknown.

Motor sequencing mechanisms have been studied in different response modalities, including hand and finger movements. Functional brain imaging studies (fMRI) have shown that, for these modalities, motor sequencing is implemented within a neural network involving cortical premotor areas [i.e., the supplementary motor area (SMA), the lateral premotor cortex (PM)], the cerebellum and the basal ganglia (BG) (Gerloff et al. 1997; Bengtsson et al. 2005; Macar et al. 2002). Other studies have show shown that the anterior insula (AI) is involved in motor timing/sequencing during finger tapping tasks (Lewis and Miall 2002; Bengtsson et al. 2004). For speech production, brain-imaging studies focusing on motor sequencing are still scarce. Nevertheless, a few fMRI studies have identified brain regions that contribute to motor planning in general (which includes sequencing), including the SMA, the AI, the inferior frontal gyrus (IFG) and the cerebellum (Brendel et al. 2010; Riecker et al. 2005). Comparing the production of overt mono- and multisyllabic words, Shuster and Lemieux (2005) identified brain areas that are sensitive to the number of syllables (multi > monosyllabic), which included activation in the left inferior parietal lobule (IPL), the left IFG and the left PM. Because words containing more than one syllable require within-word sequencing, these results do suggest a role for these regions in speech motor sequencing. Bohland and Guenther 2006 compared the production of simple repetitive sequences of syllables (ta–ta-ta) to the production of more complex alternating sequences (ka-ru-ti) using fMRI. Results revealed a distributed network of regions that are sensitive to syllable sequence complexity, including the bilateral dorsal AI, the ventral premotor cortex (PMv), the BG, the inferior frontal sulcus (IFS), the SMA, the pre-SMA, and the bilateral cerebellum. Using a repetition suppression fMRI paradigm and an innovative analysis strategy to isolate brain regions that are sensitive to different levels of speech representations (phoneme, syllable, syllable sequence) during the production of nonwords, Peeva and colleagues (2010) showed a pattern of response consistent with sensitivity to supra-syllabic sequencing (i.e., the sequencing of syllables) in the right superior lateral cerebellum. However, in one of the experimental condition ("reordered"), participants were asked to repeat nonwords whose syllables were re-ordered from one trial to the next (e.g., /zeklo, kloze/), a task that tapped onto sequencing mechanisms. Activation in this task was found in several areas including the bilateral AI, the BG, the SMA, and the bilateral cerebellum. Taken together, these studies have identified a number of regions potentially involved in speech motor sequencing, including the AI, the PM, the BG, the IFS, the SMA, the pre-SMA, and the cerebellum. It is possible that differences across studies are related to the fact that sequencing mechanisms occurring within word boundaries (Shuster and Lemieux 2005) are different from those involved in the production of meaningless sequences of syllables (Bohland and Guenther 2006), which could be more taxing given that it requires the formation of sequences of units that do not frequently co-occur. This hypothesis is consistent with the Gradient order DIVA model (GODIVA) (Bohland et al. 2010), which builds on one of the most elaborate neurobiological models of speech production, the DIVA model (Guenther et al. 2006; Guenther 1995; Guenther et al. 1998). GODIVA postulates that sequencing for speech occurs both within and across the syllable boundary, involving the pre-SMA for coding abstract syllable frames, the left IFS for coding specific phonemes in specific syllable positions in a sequence, and, at the subcortical level, the caudate and thalamus (via the internal part of the globus pallidus) to link and modulate the connections between these regions. Hence, there is theoretical and empirical evidence for the existence of neural sequencing mechanisms involved in speech production.

The general objectives of the present study were (1) to broaden current understanding of the neurobiology of motor sequencing during speech production, and (2) to explore age-related changes that occur within this system. Instead of investigating BOLD/behaviour relationships, here we adopted a neurostructural imaging approach to address this important question. Structural imaging, including cortical thickness (CT), a measure of the depth of the cortical mantle (Fischl and Dale 2000; Fischl et al. 1999a), is a powerful tool to investigate the neural underpinning of human cognition and behaviour, including speech and language processing (e.g., Golestani et al. 2002, 2007; Wong et al. 2008; Sebastián-Gallés et al. 2012; Mechelli et al. 2004; Roehrich-Gascon et al. 2015; Grogan et al. 2009), memory (e.g., Engvig et al. 2010; Dickerson et al. 2008; Burggren et al. 2011; Van Petten et al. 2004) and motor behaviour (e.g., Wei et al. 2011; Anderson et al. 2002; Kennedy and Raz 2005). For example, performance of healthy adults on a phonetically irregular word reading task has been found to correlate with CT in several brain regions that are implicated in the production of language, including the anterior and posterior segments of the superior temporal gyrus (STG) (Blackmon et al. 2010). Similarly, Grogan et al. (2009) investigated the relationship between performance

on semantic and phonemic fluency tasks in healthy adults and found a positive correlation between gray matter density in left inferior temporal cortex in semantic relative to phonemic fluency, and in the pre-SMA, a region that has been involved in speech motor preparation, for phonemic compared to semantic fluency. These and other studies demonstrate that the study of regional brain structure in regions involved in spoken language production can provide information about speech and language skills.

In addition to being associated with behavioural language performance, structural imaging, in particular imaging of CT, is a powerful biomarker of both normal and pathological aging (e.g., De Leon et al. 1997; van Velsen et al. 2013; Storsve et al. 2014). In humans, CT development is primarily driven by the genesis of neurons (Rakic 1988), which occurs primarily during prenatal and perinatal life. With age, CT declines in a spatially heterogeneous manner, with different brain regions showing different aging trajectories (Fjell and Walhovd 2010; Fjell et al. 2009a, b; Salat et al. 2004). Increases and decreases in CT that occur in adulthood would be related to alterations at the levels of synapses, dendrites, and dendritic spines. For example, age-related losses in the number of dendrites in pyramidal cells in the human primary motor cortex (Nakamura et al. 1985), in the superior temporal cortex (Jacobs and Scheibel 1993) and the prefrontal cortex (de Brabander et al. 1998; Scheibel et al. 1975) have been reported. Importantly, a few studies have documented a relationship between age, regional brain structure and language processing and production tasks including accuracy and reaction times in picture naming (Obler et al. 2010), speech perception in noise (Wong et al. 2010) and phonological retrieval (Shafto et al. 2007). Moreover, in a previous study from our group, we found that the relationship between age and articulatory accuracy during a syllable sequence repetition task was mediated by CT in the right insula (Bilodeau-Mercure et al. 2014).

Because CT is sensitive to several kinds of spoken language production measures (e.g., fluency scores, irregular word reading score, speed of phonetic learning, syllable repetition accuracy in noise, number of correctly named words, reaction time), and since it has been shown to decline in regions involved in speech processing and production, in the present study we examined whether the structure of regions that have been associated with speech motor planning, including the SMA, AI, inferior frontal cortex and cerebellum, is related to different speech production indexes (reaction time, articulatory accuracy and response duration) in young and older adults using a sequential sublexical production task. Based on the sublexical speech production literature, we expected to find different kinds of relationships between CT and speech measures, including age-dependent and age-independent relationships between overall speech measures and CT in regions involved in sublexical speech production (e.g., AI, M1, PMv, SMA, IFG/IFS, cerebellum and striatum). We also expected to find relationships between sequencing complexity, speech measures and CT in regions involved in sequential behaviour (e.g., AI, SMA, IFG/IFS, cerebellum). Specifically, in these regions, we expected CT to correlate negatively with complexity-related speech production difficulty. Based on the previous results from our group, we expected response accuracy to be the speech measure most affected by aging (Bilodeau-Mercure et al. Revisions submitted; Bilodeau-Mercure et al. 2014). Our results reveal that response duration, not accuracy, was the speech measure most affected by aging. Moreover, we found a distributed network of regions showing significant relationships between CT and each of our behavioural measures, including the bilateral AI, left primary motor area (M1), right IFS, and bilateral striatum, providing new and important insights into the neural architecture of the systems supporting speech production in adulthood.

Materials and methods

Participants

The study comprised a total of thirty healthy native adult speakers of Canadian French, which were divided into two groups (young, older). The young adult group was comprised of fifteen healthy right-handed adults as assessed by the Edinburgh Handedness Inventory (Oldfield 1971) (mean age 26.8 ± 4.82 SD; range 20–34 years; 9 females), with a mean (±SD) of 17.33 ± 1.9 years of education (range 15–21). The older adult group was comprised of fifteen healthy right-handed adults (mean age 68 ± 3.9; range 61–74 years; 10 females), with a mean of 18.3 ± 5.3 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 (#280-2011).

Stimuli and procedures

The stimuli were 120 meaningless sequences of six French syllables with either a consonant–vowel (CV) structure or a consonant–consonant–vowel (CCV) structure. The choice

Table 1 Participants' characteristics

	Young adults ($N = 15$)				Older adults ($N = 15$)			
	Mean	Std. error	Min	Max	Mean	Std. error	Min	Max
Age	26.80	1.25	20.00	34.00	68.07	1.03	61.00	74.00
Education (in number of years)	17.33	0.49	15.00	21.00	18.13	1.37	11.00	33.00
Handedness	19.40	0.21	18.00	20.00	19.87	0.09	19.00	20.00
MOCA (/30)	29.73	0.66	27.00	38.00	27.73	0.36	26.00	30.00
Yesavage depression scale	2.47	0.53	0.00	6.00	0.93	0.40	0.00	5.00

of using syllables as opposed to words or sentences is key to study maximal speech production performance, which was our objective, while avoiding linguistic top–down effects (e.g., lexical access and semantic processing). Moreover, maximal performance tests are frequently used in screening and in the assessment of motor speech disorders (Kent et al. 1987). They are useful in evaluating the flexibility of a talker, and the range of their articulatory capabilities. Visual syllables were chosen to reduce the need for working memory during the task (the visual syllables remained on the screen for the entire trial) and avoid the potential confounding effect of hearing acuity, in particular in the older participants.

Half of the sequences were simple, consisting of one syllable repeated six times (e.g., /pa–pa-pa–pa-pa–pa/), while the other half was complex consisting of three alternating syllables (e.g., /pa-ta-ka-pa-ta-ka/). All stimuli were presented using Presentation Software (Neurobehavioral System, CA, USA). Participants were asked to read the sequence on the screen and to repeat it aloud. One sequence was presented per trial. Participants' verbal responses were recorded using a high quality MRI compatible optical omni-directional microphone (MO-2000, Sennheiser). The task was divided into two runs of approximately 10 min each. Within each run, the order of the conditions and the number and duration of rest trials were randomized using OPTseq 2 (http://surfer.nmr.mgh.harvard.edu/optseq/). This task was performed in the MRI environment while collecting functional MRI (fMRI) data which are reported elsewhere (Tremblay et al. 2015).

Acoustical and behavioural data analysis

All acoustic analyses were performed using Praat software (Boersma and Weenink 2011). A semi-automatic procedure was used for segmenting participants' responses. For each participant, the procedure involved the automatic segmentation of each sequence based on an intensity and duration algorithm detection. Based on minimal duration and low intensity energy parameters, the algorithm automatically established the sequence's boundaries. Whenever necessary, these boundaries were manually adjusted, based on waveform and spectrogram analysis, by a collaborator that was blind to the experimental condition, expected response, and group assignment to minimize the possible experimenter-induced bias. This was necessary because of the reduced SNR in the MRI environment.

For each participant and each condition, the mean reaction time (RT) and duration were computed. For the analyses of errors, a research assistant naive to the purpose of the study listened to the voice recordings, transcribed the responses and calculated the articulatory accuracy, that is, number of errors, including both errors of omission and commission. A second research assistant validated the transcriptions. Whenever a disagreement occurred between the research assistants, a third research assistant, also naive to the purpose of the study, was asked to transcribe the response. A response was included in the analysis only if there was agreement between at least two assistants. No trials were excluded because of a disagreement between the research assistants. The percentage of incorrect responses was calculated. The resulting data were entered in a 2×2 ANOVA with Group as the between-subject factor, and complexity as the within-subject factor. A separate ANOVA was conducted for each of the behavioural measure (RT, articulatory accuracy and response duration).

To further examine speech performance, we classified the type of errors that were committed as well as the position of the errors in the sequences (i.e., first vs. second half of the sequences). Nine different error types were identified, which are detailed in Table 2. For the purpose of statistical analyses, however, because some subtypes of errors were extremely rare, errors were grouped into three broad categories: sound exchange, sound insertion and sound deletion. Chi square tests were used to determine whether the distribution of within-sequence errors (first vs. second half of the sequence) varied as a function of age, again separately for the simple and complex sequences. Another set of tests was conducted to determine whether the distribution of the different types of errors varied as a function of age, separately for the simple and complex sequences.

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

Table 2 List of the different types of errors

Type of error	Segment(s) affected	Examples
Sound exchange	Vowel (V)	/gɛ/ → /ge/
	Consonant (C)	/de/ → /te/
	Consonant–vowel (CV)	/vrɛ/ → /flɛ/
	Syllable (S)	/kle/ → /trɛ/
Sound insertion	Vowel (V)	/blo/ → /bolo/
	Consonant (C)	/bo/ → /bro/
	Consonant–consonant (CC)[a]	/vlɛ/ → /blvlɛ/
	Syllable (S)	New syllable inserted in sequence
Sound deletion	Consonant (C)	/krou/ → /kou/

[a] The segments do not need to be adjacent

City. Throughout the procedure, the 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 also acquired using parallel imaging but will not be reported in this manuscript. The structural MRI data were always acquired at the beginning of the MRI session, and lasted for about 6 min, thereby reducing the likelihood of being contaminated by motion artefacts.

T1 image analysis

Pre-processing

The T1 images were first visually inspected to detect potential motion-related artefacts (blurring, ghosts, shades). The Freesurfer software package (Fischl et al. 1999a, 2004), which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/) was used for cortical reconstruction and volumetric segmentation. First, non-brain tissue was removed using a hybrid watershed/surface deformation procedure (Segonne et al. 2004). An automated Talairach transformation was then applied, followed by intensity normalization (Sled et al. 1998), tessellation of the gray matter/white matter boundary, automated topology correction (Fischl et al. 2001; Segonne et al. 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al. 1999; Dale and Sereno 1993; Fischl and Dale 2000). Once the cortical models were completed, surface inflation was performed (Fischl et al. 1999a), and registration to a spherical atlas which utilizes individual cortical folding patterns to match cortical geometry across subjects (Fischl et al. 1999b), was done to conduct whole-brain surface group analyses of CT.

Global brain senescence

Two global age-related measured of brain morphometry were computed for each hemisphere: (1) the total cortical gray matter volume (cc), and (2) the mean surface-based cortical thickness (mm). For each measure, we performed two univariate analyses of variance (ANOVA) with hemisphere as a within-subject factor, age group as the fixed factor, and response duration, articulatory accuracy and reaction times (RT) as continuous quantitative covariates. In the first analysis, average response duration, articulatory accuracy and RT were included as covariates. Next, for each covariate (duration, RT, articulatory accuracy), we computed a complexity score (performance in complex sequence − performance in simple sequence) and used these complexity scores as covariates in the analysis to examine their relation to whole-brain CT and volume.

Detailed analysis of cortical thickness

Whole-brain cortical thickness (CT) measures were obtained from FreeSurfer routines calculating the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface, using both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness (Fischl and Dale 2000). The CT maps were created using spatial intensity gradients across tissue classes and are, therefore, not simply reliant on absolute signal intensity. The individual CT data were smoothed using a 10-mm full-width-at-half-maximum Gaussian filter. 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). The maps produced are not restricted to the voxel

resolution of the original data and thus are capable of detecting sub-millimeter differences between groups.

The individual CT maps were exported to SUMA (Saad and Reynolds 2012), where group-level analyses were conducted on the surface. For the whole-brain CT measures, we identified, using independent sample t tests (AFNI 3dttest ++ program), the nodes in which CT was statistically associated with age, as well as with response duration, RT and articulatory accuracy. For this analysis, Age group was the between-subject factor, and response duration, RT and articulatory accuracy were entered in the statistical model as continuous quantitative covariates. To examine the relationship between CT, sequence complexity and speech measures, a second analysis was conducted. For this analysis, complexity-dependent difficulty scores were computed for each of the speech measure (response duration, RT and articulatory accuracy) by comparing performance level during the complex and the simple sequences and used as covariates. A value of zero, thus, indicates no effect of complexity on performance. For response duration and RT, positive values indicate that participants' RT were slower for the complex compared to the simple sequence production (complexity effect). For accuracy, negative values indicate that participants' response were less accurate for the complex compared to the simple sequence production (complexity effect). For both analyses, 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. For both analyses, an individual vertex threshold of $p < 0.05$, corrected for multiple comparisons to achieve a family-wise error (FWE) rate of $p < 0.01$ (clusters $\geq$ 631 vertices) was used.

Post-hoc regression analyses to illustrate main effects and decompose interactions

To illustrate the direction of the main effects identified through the whole-brain group analyses, and to decompose the interactions, we extracted, for each participant, the average thickness of all the clusters identified through the whole-brain group analyses using a mask of the group result (AFNI 3dROIstats program). For each cluster, the average thickness was calculated across all nodes for each participant. These data were then fitted using the linear curve estimation function in SPSS Statistics (IBM, Version 22). These analyses are not independent from the ANCOVA analyses, in the same way that post hoc analyses are not independent from the main effects. Thus, they are not meant to provide additional and independent information but rather clarify the ANCOVA results and visualize the interactions.

Subcortical structures

To examine the relationship between behaviour and brain morphometry at the sub-cortical level, we used the automated procedure for volumetric analyses implemented in Freesurfer. This procedure relies on the segmentation of subcortical structure, which is based on voxel intensity, spatial comparisons with a probabilistic training atlas as well as comparisons to neighboring voxel labels (Fischl et al. 2002). The subcortical structures of interest were the subregions of the BG (caudate, putamen, pallidum), and the thalamus and cerebellum, which are involved in motor planning. For each of these bilateral subcortical structures (i.e., caudate, putamen, pallidum, thalamus, and cerebellum), a volume measurement was obtained from the native anatomical data. For the cerebellum, the parcellation is coarse and only distinguishes the gray matter in the left and right hemispheres. For each subcortical volume, we examined whether there was a relationship between speech performance and volume using a multiple regression model in which age and volume were included as predictors and the dependent variable was the behavioural measure. This was done separately for each behavioural measure (response duration, RT and articulatory accuracy).

Results

Behavioural results

First, we examined whether the behavioural variables were correlated using Spearman's rho correlations. Response duration did not correlate with accuracy ($\rho = 0.25$, $p = 0.21$) or RT ($\rho = 0.22$, $p = 0.28$) and RT did not correlate with accuracy ($\rho = -0.082$, $p = 0.68$). Next, we examined each of the behavioural measures separately.

For response duration, the Bonferroni-corrected repeated measure ANCOVA revealed a main effect of age group ($F_{(1,25)} = 8.45$, $p = 0.007$). The overall response duration was $\sim$17 % longer in older adults compared to younger adults, with a mean response duration of 1.76 ± 0.3 s in young adults and 2.07 ± 0.24 s in older adults. Post-hoc comparison revealed that this difference was significant $t_{(26)} = -2.91$, $p = 0.013$). A significant main effect of complexity was also found ($F_{(1,26)} = 113.42$, $p \leq 0.0001$), whereby the complex sequences (mean 1.99 ± 0.52 s) were associated with longer duration compared to the simple sequences (mean 1.72 ± 0.43 s). This difference was significant ($t_{(26)} = 8.6$, $p \leq 0.0001$). In addition to the main effects, there was also as an age by complexity interaction ($F_{(1,25)} = 11.702$, $p = 0.002$). This interaction revealed that older adults responses were $\sim$13 % longer for the simple sequences

(with a mean response duration of 1.67 ± 0.31 s in young adults and 1.89 ± 0.31 s in older adults ($t_{(26)} = -2.19$, $p = 0.037$), and ~21 % longer for the complex sequences (with a mean response duration of 1.86 ± 0.2 s in young adults and 2.25 ± 0.3 s in older adults ($t_{(26)} = -3.03$, $p = 0.005$). To understand the age effect on speech response duration, the speech recordings were inspected, which revealed that older adults seemingly broke down the sequences into two parts, that is, they produced the first three syllables first, took a short break, and produced the last three syllables, despite the fact that all participants were specifically instructed to produce the sequence of six sounds in one chunk. To test this hypothesis, a research assistant naive to the purpose of the study segmented the pause between first and second halves of the sequences for all trials in the first run; the duration was then automatically extracted using Praat. A *t* test for independent samples with age as the between-subject factor revealed that the duration of the pause was, on average, 81 ms longer for the older than it was for the younger adults ($t_{(22)} = -3.14$, $p = 0.005$). The mean pause duration for the young adults was 74 ± 0.021 ms while it was 156 ± 0.09 ms for the older adults. The behavioural results are presented in Fig. 1.

For RT (in seconds), the ANOVA revealed a main effect of complexity ($F_{(1,25)} = 120.073$, $p \leq 0.0001$), with a mean RT for the simple sequences of 900 ± 124 ms and 1013 ± 132 ms for the complex sequences, representing an increase of ~13 % in RT. There was no main effect of age ($F_{(1,25)} = 2.91$, $p = 0.100$) and no age by complexity interaction ($F_{(1,25)} = 1.663$, $p = 0.209$).

For articulatory accuracy, the ANOVA revealed a main effect of complexity ($F_{(1,25)} = 60.46$, $p \leq 0.0001$), with a mean of 96.73 ± 2.93 % correct for the simple sequences and 80.7 ± 11.67 % for the complex sequences, representing a decline of ~16 % in accuracy. There was no main effect of age ($F_{(1,25)} = 1.51$, $p = 229$) and no age by complexity interaction ($F_{(1,25)} = 0.065$, $p = 0.801$). To determine whether the type and position of errors, as opposed to the number of errors, differed across groups, we examined, for each sequence type (i.e., simple, complex) the distribution of within-sequences errors (i.e., first half and second half) as a function of age. A Chi square test of independence revealed no relationship between age and the position of the errors (simple sequence: $\chi^2_{(1,N=120)} = 0.02$, $p = 0.89$, complex sequence: $\chi^2_{(1,N=493)} = 0.09$, $p = 0.75$). Finally, we examined whether the distribution of each type of errors (i.e., exchange, insertion, deletion) varied as a function of age. A Chi square test of independence revealed no relationship between age and type of errors (simple sequence: $\chi^2_{(2,N=120)} = 4.90$, $p = 0.09$, complex sequence: $\chi^2_{(2,N=493)} = 2.8$, $p = 0.25$). These results can be found in supplementary material S1.

Imaging results

Global brain senescence

In the left hemisphere, the mean cortical gray matter volume was 233.49 cc (±18.97 cc) for the young adults and 213.44 cc (±13.52 cc) for the older adults. In the right hemisphere, the mean cortical gray matter volume was 236.12 cc (±18.72 cc) for the young adults and 215.94 cc (±14.91 cc) for the older adults. The ANCOVA result revealed a main effect of age ($F_{(1,2)} = 6.29$, $p < 0.02$), no effect of hemisphere, no age by hemisphere interaction and no effect of any of the behavioural covariates (RT, duration, articulatory accuracy).

The average CT, in the left hemisphere, was 2.42 mm (±0.11 mm) for the young adults and 2.27 mm (±0.058 mm) for the older adults. In the right hemisphere, it was 2.44 mm (±0.11 mm) for the young adults and 2.29 mm (±0.06 mm) for the older adults. The ANCOVA results revealed a main effect of age group ($F_{(1,2)} = 10.04$, $p < 0.004$), no effect of hemisphere, no age group by hemisphere interaction and no effect of any of the behavioural covariates (RT, duration, articulatory accuracy).

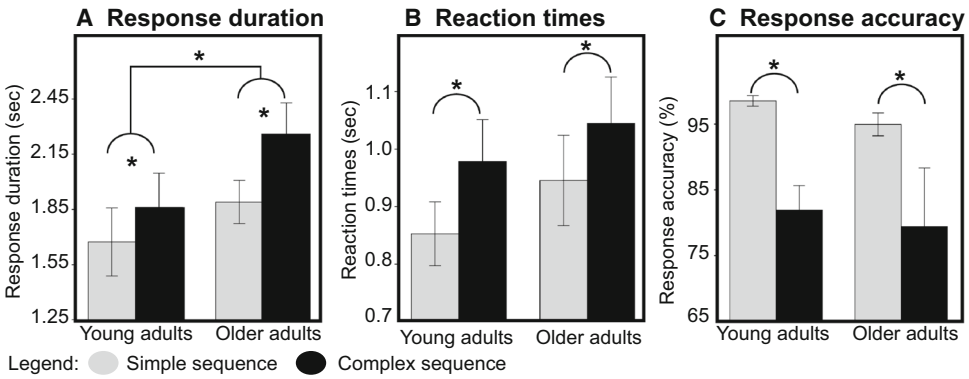

Fig. 1 Behavioural results. **a** Response duration, **b** Reaction times and **c** Response accuracy displayed as a function of response complexity and age. *Asterisks* indicate significant differences

Whole-brain cortical surface thickness analysis

First, we examined the voxel-wise relationship between CT and age groups across the entire cortical mantle. As can be seen in Fig. 2 (blue), significant thinning of the cortical mantle was widespread, including the bilateral supratemporal cortex, the entire supramarginal gyrus (SMG), several parts of the insula, the medial prefrontal and lateral premotor cortices. A detailed description of all the regions in which a significant age difference was found is provided in Table 3; thickness maps for the young and older adults are provided as supplementary material S2.

Next, we examined the relationship between CT and the three different speech measures across the entire cortical mantle. For response duration, as can be seen in Fig. 3a, we found a significant inverse relationship between CT and response duration in several cortical areas, covering an extended surface of 2785 mm^2, which included the bilateral dorsal AI (dAI), meaning that thicker cortex was associated with shorter speech response durations. In a few cortical areas, shown in Fig. 3b, which included the right dAI and the left superior temporal gyrus and sulcus (STG/S), the direction of the relationship between CT and duration varied as a function of age. For the dAI, the expected inverse relationship, that is, shorter responses associated with thicker cortex, was observed in young adults whereas a positive relationship was observed for the older adults (i.e., longer responses associated with thicker cortex). For the left STG/S, a different pattern was found, with a positive relationship between CT and duration for the older adults and no relationship for the young adults. As shown in Fig. 4a, the analysis also revealed a significant inverse relationship between CT and difficulty scores (duration difference for the complex–simple sequence conditions) in several cortical areas, meaning that greater CT was associated with reduced complexity-related speech difficulty. This was found in the bilateral dAI, left M1, left superior temporal sulcus (STS) and right ventral posterior insula (vPI). In a few regions, illustrated in Fig. 4b, including the left dAI, we found that the relationship between difficulty scores and CT varied as a function of age. In the left dAI, for example, we found a strong inverse linear relationship between CT and difficulty scores in young adults (meaning that greater CT in dAI was associated with reduced complexity-related difficulty), but no relationship between CT and complexity scores in the older adults. The duration effects are detailed in Table 4. Table 7 shows that regions in which a relationship between CT and duration was found covered a total surface of 8773 mm^2.

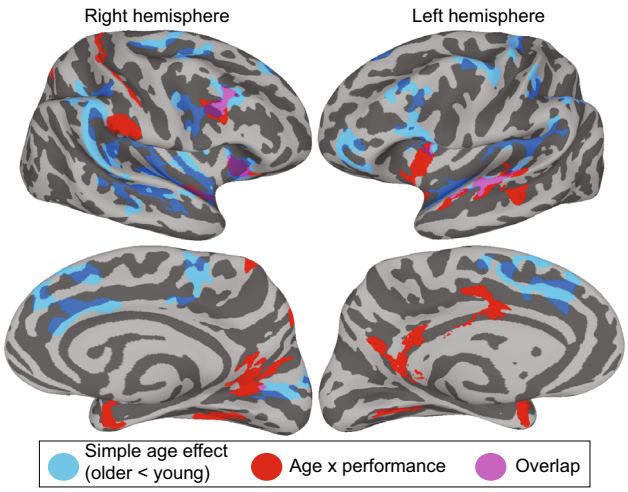

Fig. 2 Regions showing a significant age difference in CT (young > older, in *blue*), a significant relationship between age, performance and CT (shown in *red*), and the intersection of these two maps, that is, brain regions showing a main effect of age as well as a relationship between age and one of the behavioural measures (shown in *purple*). Results are shown on the group average smoothed white matter folded surface in which *dark gray regions* represent sulci while *pale gray areas* represent gyri

The relationship between CT and RT was, overall, more spatially circumscribed, covering a total surface of only 2500 mm^2. A simple relationship between CT and overall RT was found in only two areas: the left posterior cingulate gyrus and sulcus (pCing), and the left dorsal central sulcus/postcentral gyrus. In both regions, this relationship was, perhaps unexpectedly, positive, that is, thicker cortex was associated with longer RT. An example of this pattern is illustrated in Fig. 5a (pCing). The analysis also revealed that in three cortical regions, the relationship between CT and RT varied as a function of age (right postcentral gyrus, left posterior cingulate, right IFS). In all regions, no significant relationship was found in older adults; while in young adults, a significant linear relationship was found between RT and CT, which was either inverse (postcentral gyrus) or positive (pCing, IFS). An example of this response pattern is shown in Fig. 5b (IFS). In one region, the right STG, we found a relationship between RT difficulty scores and CT. This relationship was positive, meaning that greater CT was associated with increased complexity-related difficulty. Finally, the analysis also revealed that the relationship between CT and RT difficulty scores varied as a function of age group in the right ventral AI (vAI), left rostral supramarginal gyrus (rostral SMG) and left posterior ventral cingulate gyrus. In these regions, there was a positive relationship between complexity and CT in young adults, meaning that greater CT was associated with increased complexity-related difficulty, and a tendency for an inverse relationship in older adults. RT effects are detailed in Tables 5 and 7.

The relationship between CT and articulatory accuracy was also relatively circumscribed, covering a total surface of 3175 mm^2 (compared to 8773 mm^2 for duration). First,

Table 3 Age differences in cortical thickness (young > older)

Region	Hemi	*x*	*y*	*z*	Nodes	Area	*t*	*p*
Superior sulcus of the posterior insula, extending into the planum temporale and superior temporal gyrus	Left	−62	−10	−3	4241	1587.5	−5.407	0.0000131
Anterior cingulate gyrus and sulcus, extending into the medial superior frontal gyrus (pre-supplementary motor area and medial prefrontal cortex)	Left	−8	41	29	1635	746.82	−4.977	0.0000396
Anterior insula, superior circular sulcus, and posterior inferior frontal gyrus	Left	−34	16	11	2478	736.86	−4.715	0.0000780
Dorsal postcentral gyrus and sulcus	Left	−37	−18	67	1261	474.5	−4.425	0.0001654
Inferior parietal lobule, including both angular and supramarginal gyri	Left	−45	−46	47	1769	393.08	−4.73	0.0000750
Orbital gyrus	Left	−44	40	−16	804	321.89	−4.282	0.0002395
Ventral precentral gyrus and sulcus	Left	−51	−9	49	1144	296.51	−4.747	0.0000718
Postcentral gyrus and sulcus	Left	−41	−30	42	889	292.37	−3.882	0.0006704
Anterior insula, posterior insula, supramarginal gyrus, supratemporal cortex including the planum temporale, transverse temporal gyrus and sulcus	Right	38	−1	2	7436	2700.72	−7.493	0.0000001
Superior temporal sulcus and middle temporal gyrus	Right	50	−19	−5	1856	736.55	−4.324	0.0002148
Anterior cingulate gyrus and sulcus	Right	8	42	5	1420	622.92	−5.337	0.0000156
Middle frontal gyrus	Right	48	26	32	1713	620.99	−5.194	0.0000226
Cuneus, extending into the calcarine sulcus	Right	9	−87	27	958	539.97	−5.185	0.0000231
Anterior dorsal insula (adIns)	Right	40	33	−7	1122	411.1	−3.65	0.0012099
Postcentral sulcus, intraparietal sulcus and inferior parietal lobule (including both supramarginal and angular gyri)	Right	40	−30	38	1741	406.65	−5.553	0.0000090
Lateral and medial superior frontal sulcus and gyrus	Right	15	50	36	676	322.97	−3.787	0.0008544
Medial superior frontal gyrus (SMA-proper)	Right	7	−17	62	1125	298.79	−3.814	0.0007976
Superior frontal sulcus and dorsal precentral sulcus	Right	23	−5	60	764	235.15	−4.853	0.0000545
Middle frontal gyrus	Right	34	11	55	1077	214.93	−4.229	0.0002746

no relationship between CT and overall articulatory accuracy was found. There were, however, age-dependent relationships between CT and articulatory accuracy in the left vAI, at the junction of the planum polare and temporal pole (PP/TP), as well as in the right parieto-occipital sulcus and cuneus (POS/CN), and in the para-hippocampal gyrus. As shown in Fig. 6a, in the left vAI, this relationship was negative in young adults, meaning that thicker cortex was associated with less accurate responses. In older adults, there was no relationship between CT and accuracy. In the right POS/CN, in young adults, this relationship was positive, meaning that thicker cortex was associated with more accurate responses. In older adults, there was no relationship between CT and articulatory accuracy. In the PP/TP, there was no relationship between CT and articulatory accuracy in young adults, while there was a positive relationship in the older adults, meaning that thicker cortex was associated with more accurate responses. The analysis also revealed a relationship between CT and articulatory accuracy difficulty scores (Fig. 6b) in the left dAI [extending into the ventrolateral prefrontal cortex (VLPFC), specifically the ventral part of the inferior frontal gyrus], the right POS/CN, right occipital pole and right superior frontal gyrus and sulcus (SFG/SFS). In all of these regions with the exception of the SFG, this relationship was positive, meaning that thicker cortex was associated with smaller complexity effects. Finally, the analysis revealed that the relationship between CT and complexity-related difficulty varied as a function of age in the right dorsal central sulcus (M1/S1), the right rostral SMG and the right POS/CN (Fig. 6c). In two of these regions, the rostral SMG and the POS/CN, there was a positive linear relationship between complexity scores and CT in young adults, meaning that thicker cortex was associated with smaller complexity effects, but no relationship in the older adults. In M1/S1, there was a significant negative relationship between accuracy complexity scores and CT in young adults, meaning that thicker cortex was associated with larger complexity effects, but no relationship in the older adults. Accuracy effects are detailed in Tables 6 and 7.

Specificity of the brain/behaviour relations reported

To examine the specificity of the relationships between CT, age and speech performance, we computed an intersection map of all regions that showed an interaction between age

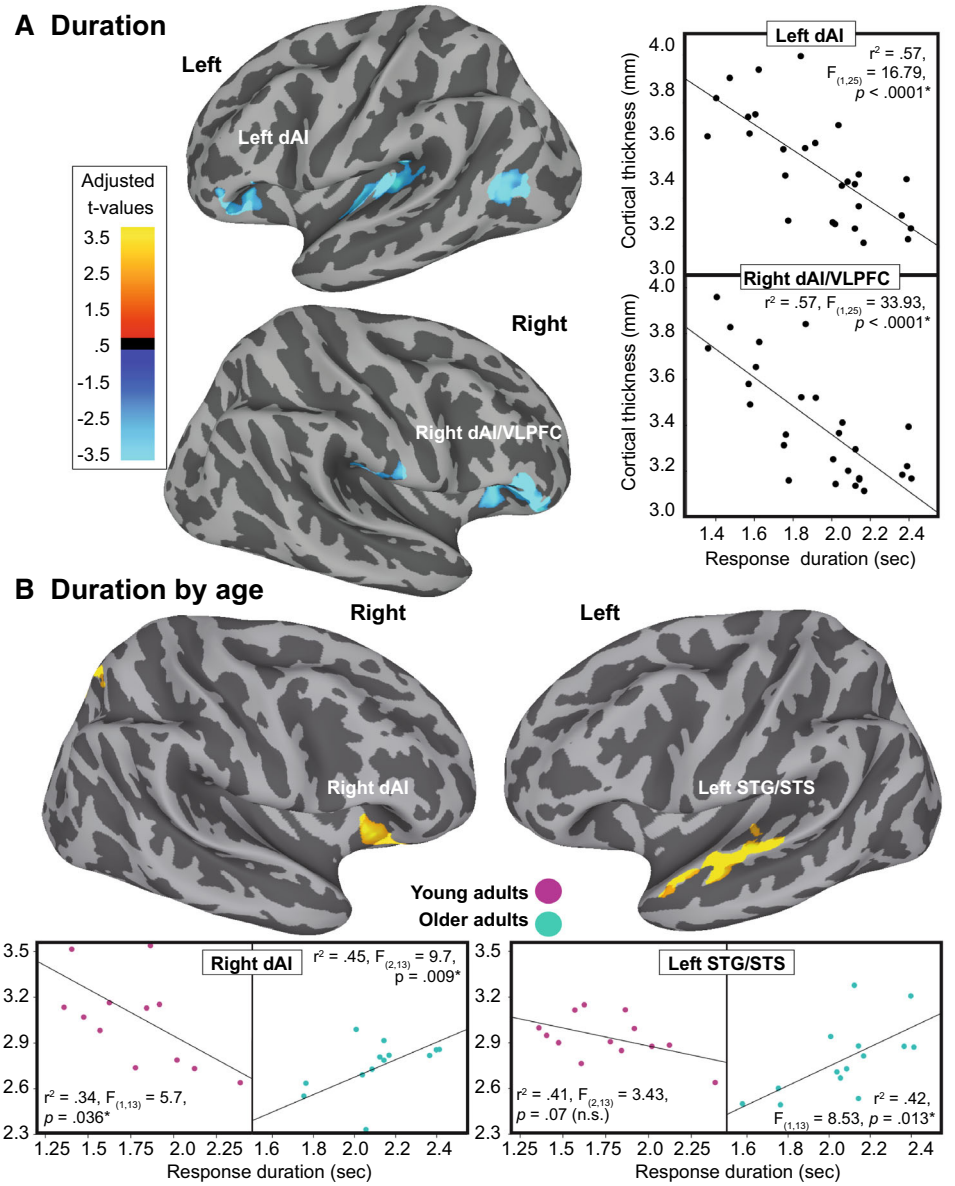

Fig. 3 **a** Cortical regions exhibiting an interaction between CT and response duration. Results are shown on the group average smoothed white matter folded surface. The *scatter plots* on the *right* end side of the figure illustrate this relationship in two cortical regions (left and right dAI). **b** Cortical regions exhibiting an interaction between CT, duration and age. The *scatter plots* at the *bottom* of the figure illustrate this relationship in two cortical regions (right dAI and left STG/STS; *pink dots* young adults; *green dots* older adults)

and any of the behavioural measures (i.e., either an Age by Duration interaction, and Age by Articulatory Accuracy interaction; an Age by Response duration interaction; an Age by Complexity by Duration interaction, an Age by Complexity by Articulatory Accuracy interaction, or an Age by Complexity by Response duration interaction). As can be seen in Fig. 2, while a relationship between age and CT was found in a broadly distributed network of regions (shown in blue in the figure), representing a total surface area of 11,960 mm^2, the thinning effects that were associated with our speech performance measures (shown in red in the figure), were much more constrained, representing a total surface area of 6092 mm^2, and they rarely overlapped with the areas showing a global decline in CT, with the exception of the left AI, right IFS, and right STG. This is consistent with our finding, reported in "Global brain senescence", that whole brain structural measures (CT, volume) did not correlate with any of our behavioural measures, demonstrating the specificity of the relationship between CT and our behavioural measures of speech production.

Subcortical analyses

In the putamen, we found an inverse linear relationship between overall response duration (left putamen: $F_{(1,25)} = 9.39$, $p = 0.005$; right putamen: $F_{(1,25)} = 6.69$, $p = 0.016$), meaning that greater volume was associated with reduced duration. In the left putamen, there was also an inverse linear relationship between volume and duration

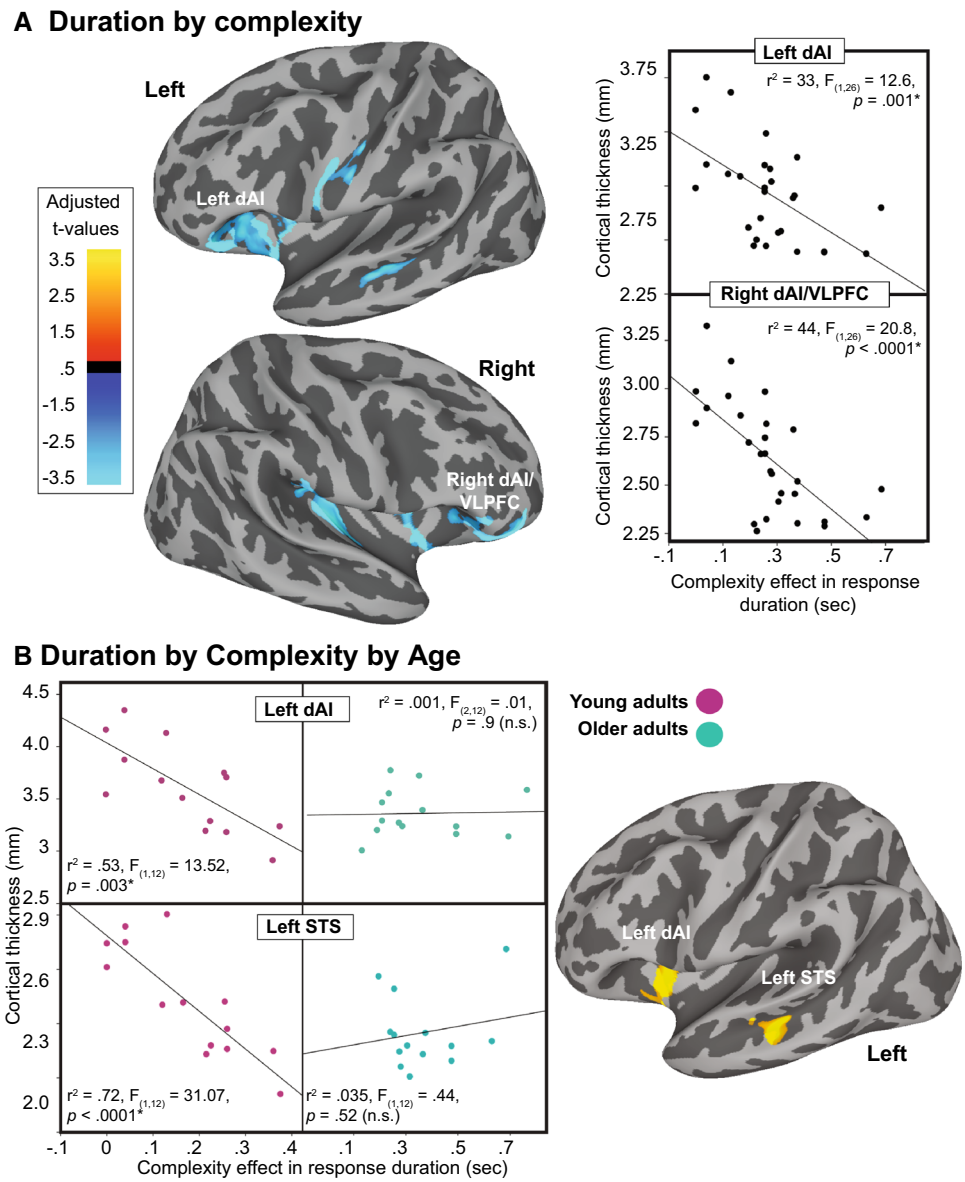

Fig. 4 **a** Cortical regions (shown on the group average smoothed white matter folded surface) exhibiting a relationship between CT, and complexity effects in response duration. Note that positive values (*right* side) on the *x*-axis indicate that complex sequences were more difficult (longer) than the simple ones. The *scatter plots* on the *right* end side of the figure illustrate this relationship in two cortical regions (left and right dAI). **b** Cortical regions exhibiting a relationship between CT, complexity effects in response duration and age. The *scatter plots* on the *left* end side of the figure illustrate this relationship in two cortical regions (left dAI and left STS; *pink dots* young adults; *green dots* older adults)

complexity scores ($F_{(1,24)} = 7.58$, $p = 0.011$), meaning that greater volume was associated with reduced complexity-related difficulty. No relationship between the right putamen volume and behavioural measures of speech production was found.

In the bilateral caudate, an inverse relationship between volume and overall response duration was found (left caudate: $F_{(1,23)} = 11.64$, $p = 0.002$; right caudate: $F_{(1,22)} = 14.33$, $p = 0.001$), meaning that greater volume was associated with reduced response duration. In both regions, there was also an inverse linear relationship between volume and duration complexity scores (left caudate: $F_{(1,22)} = 4.9$, $p = 0.036$; right caudate: $F_{(1,22)} = 4.67$, $p = 0.041$), meaning that greater volume was associated with reduced complexity-related difficulty. The analysis also revealed a more complex relationship between volume, duration complexity scores and age (left caudate: $F_{(1,22)} = 8.07$, $p = 0.01$; right caudate: $F_{(1,22)} = 6.28$, $p = 0.02$). To decompose this complex interaction, we plotted caudate volume against complexity effects separately for young and older adults. As can be seen in Supplementary Figure S3, this analysis revealed that the significant relationship between volume and complexity-related duration effects was driven by the older adults, in which greater volume was associated with reduced complexity-related difficulty. There was no relationship between volume was associated and complexity-related difficulty in younger adults.

There was no relationship between the thalamus, pallidus, and cerebellum hemispheres and any of the

Table 4 Relationship between CT and response duration

Analysis	Region	Hemi	*x*	*y*	*z*	Nodes	Area	*t*	*p*
Duration	Posterior supratemporal cortex, including planum temporale, transverse temporal gyrus and sulcus, and posterior insula	Left	−40	−33	6	2197	745.35	−4.053	0.000432
	Anterior dorsal insula	Left	−30	34	0	747	324.57	−3.297	0.002927
	Calcarine sulcus, cuneus	Left	−13	−75	12	706	322.5	−4.804	0.000062
	Anterior part of the superior occipital sulcus	Left	−44	−69	9	830	212.83	−4.564	0.000115
	Anterior dorsal insula	Left	−34	19	11	765	177.13	−3.314	0.002806
	Anterior insula, extending into the inferior frontal gyrus (pars orbitalis and triangularis)	Right	51	39	−9	2142	648.19	−5.556	0.000009
	Rostral supramarginal gyrus	Right	49	−18	16	1136	354.55	−3.59	0.001408
Duration × age	Superior temporal gyrus	Left	−61	−21	3	1383	490.69	4.919	0.000046
	Lingual gyrus	Left	−13	−71	−6	930	368.48	4.189	0.000305
	Fusiform gyrus, collateral sulcus	Right	30	−62	−5	805	431.89	5.844	0.000004
	Anterior dorsal insula	Right	30	24	−5	759	289.93	3.767	0.000899
	Precuneus, superior parietal gyrus	Right	9	−68	57	799	173.85	3.724	0.001003
Complexity effect in duration	Anterior insula	Left	−29	13	−15	2688	1014.32	−3.561	0.001515
	Ventral central sulcus and precentral gyrus	Left	−41	−13	32	742	268.54	−3.61	0.001339
	Superior temporal sulcus	Left	−48	−23	−10	680	188.74	−3.833	0.000760
	Posterior part of the lateral sulcus, extending into the posterior ventral insula	Right	41	−22	5	1411	482.16	−4.119	0.000365
	Orbital gyrus, inferior frontal gyrus pars orbitalis, anterior dorsal insula	Right	43	53	−9	1377	480.57	−4.664	0.000089
	Ventromedial superior frontal gyrus and sulcus and anterior cingulate	Right	5	28	−18	796	339.75	−3.867	0.000697
	Mid dorsal insula	Right	34	10	5	806	281.24	−4.079	0.000404
	Rostral supramarginal gyrus	Right	48	−23	19	810	232.58	−3.968	0.000538
Age by complexity effect in duration	Anterior dorsal insula	Left	−35	13	−5	660	260.82	4.371	0.000190
	Superior temporal sulcus	Left	−52	−32	−9	635	200.59	4.677	0.000086
	Calcarine sulcus and cuneus	Right	21	−68	10	678	263.34	5.181	0.000023
	Parahippocampal gyrus	Right	23	−4	−35	1063	221.23	−4.582	0.000110

behavioural measures. The lack of finding in the cerebellum could be due to the rather coarse parcellation used (left vs. right gray matter).

Discussion

In this study, we explored, for the first time, the relationship between regional cortical thickness and three behavioural speech measures (RT, response duration and articulatory accuracy) in healthy young and older adults during speech production. Specifically, we examined the production of simple and complex meaningless sequences of visually presented syllables that varied in sequencing complexity while minimizing cognitive demands. Our results demonstrate that the sequence complexity manipulation resulted in slower, longer and less accurate speech, in all participants. With age, we found a heightened detrimental effect of sequence complexity on speech performance, which was reflected in longer speech response durations but not reduced accuracy. Relationships between brain structure and speech measures were found in a number of regions, including the bilateral AI, M1, the right IFS, left STG/STS, bilateral striatum (putamen and caudate). Interestingly, each measure exhibited a unique pattern of correlations with CT, which was expected given the lack of correlations between the speech measures, and is also consistent with previous studies that have explored the relationship between brain structure and two or more behavioural measures of language or cognition (e.g., Obler et al. 2010; Manoach et al. 2000; Wilde et al. 2011; Neta et al. 2014). In several regions, we found that the relationship between CT and speech measures was different in the young and older adults, also consistent with a previous study (Lovden et al. 2013). Importantly, our analysis of the specificity of the relationship between speech measures, age and CT clearly demonstrates that only a small fraction (7.5 %, representing 900 mm^2) of the regions in which CT

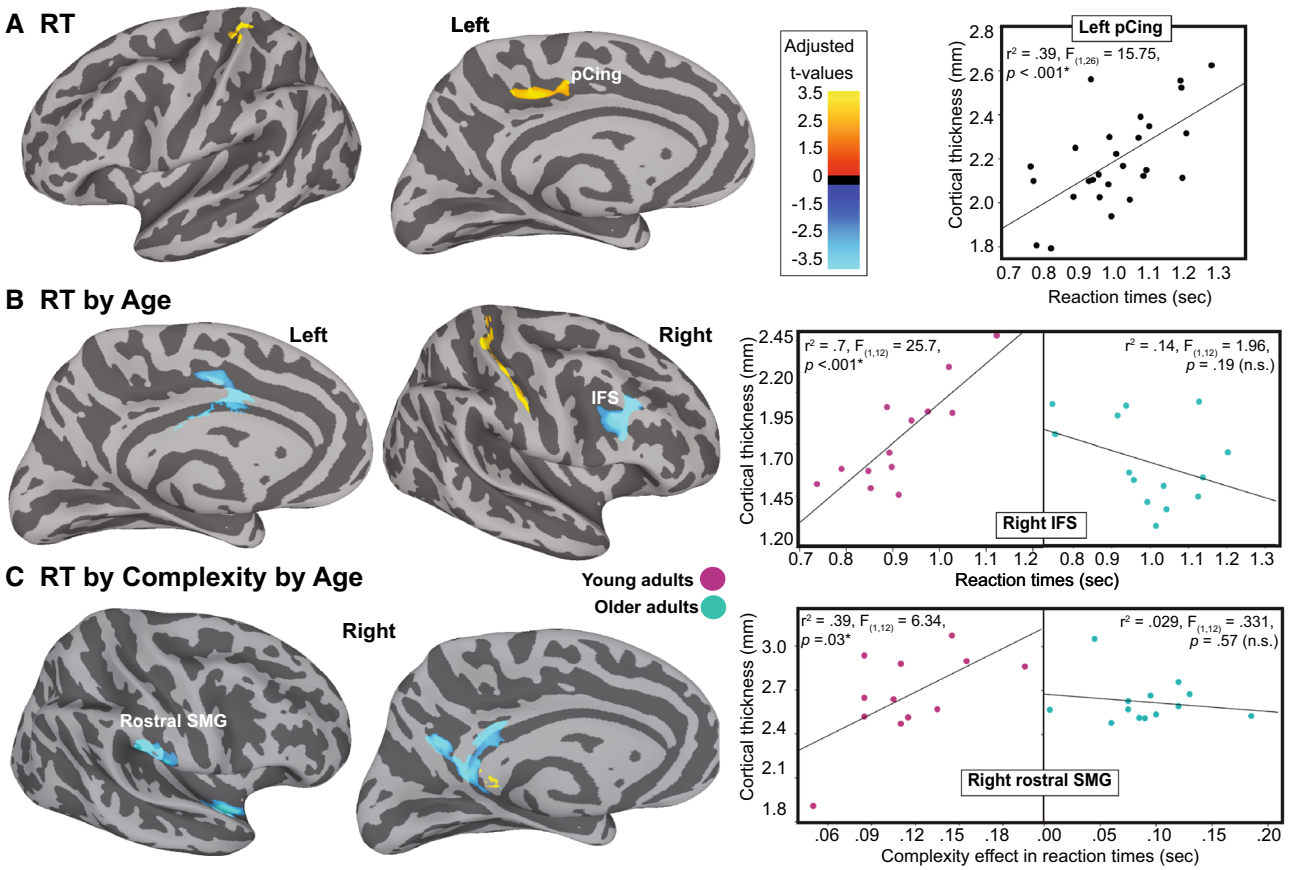

Fig. 5 RT effects. **a** Cortical regions (shown on the group average smoothed white matter folded surface) exhibiting a relationship between CT and RT. The *scatter plot* on the *right* end side of the figure illustrates this relationship in the left pCing. **b** Cortical regions exhibiting a relationship between CT, RT and age. The *scatter plots* illustrate this relationship in the right IFS (*pink dots* young adults; *green dots* older adults). **c** Cortical regions exhibiting a relationship between CT, complexity effects in RT and age. The *scatter plots* illustrate this relationship in the right rostral SMG (*pink dots* young adults; *green dots* older adults)

Table 5 Relationship between CT and RT

Analysis	Region	Hemi	*x*	*y*	*z*	Nodes	Area	*t*	*p*
RT	Posterior cingulate gyrus and sulcus	Left	−15	−24	44	763	205.35	3.684	0.001110
	Dorsal central sulcus and postcentral gyrus	Left	−27	−31	56	686	198.91	3.325	0.002731
Age × RT	Posterior cingulate sulcus and gyrus	Left	−4	−5	29	715	226.39	−4.204	0.000293
	Postcentral gyrus and central sulcus (S1/M1)	Right	37	−31	65	1118	382.25	4.786	0.000065
	Inferior frontal sulcus	Right	42	21	22	640	205.59	−4.299	0.000229
Complexity effect in RT	Superior temporal gyrus	Right	61	−6	−5	651	179.3	4.08	0.000403
Age by complexity effect in RT	Subparietal sulcus and precuneus, extending ventrally into the posterior cingulate gyrus	Left	−11	−57	34	1465	408.87	−4.151	0.000336
	Anterior ventral insula	Right	52	3	−12	824	438	−4.81	0.000061
	Rostral supramarginal gyrus	Right	61	−23	24	916	255.6	−7.042	0.0000002

declined with age also correlated with behavioural speech measures. Moreover, most of the regions that were identified have been reported in fMRI studies of syllable sequence production. In theses studies, clusters of activation are typically found in the bilateral insula, the bilateral M1, the bilateral IFG/IFS, the STG, the bilateral planum temporale, the putamen and caudate nuclei, the bilateral SMA, and the superior cerebellar cortex (e.g., Shuster 2009; Bohland and Guenther 2006; Peeva et al. 2010; Ghosh et al. 2008; Soros et al. 2006; Alario et al. 2006;

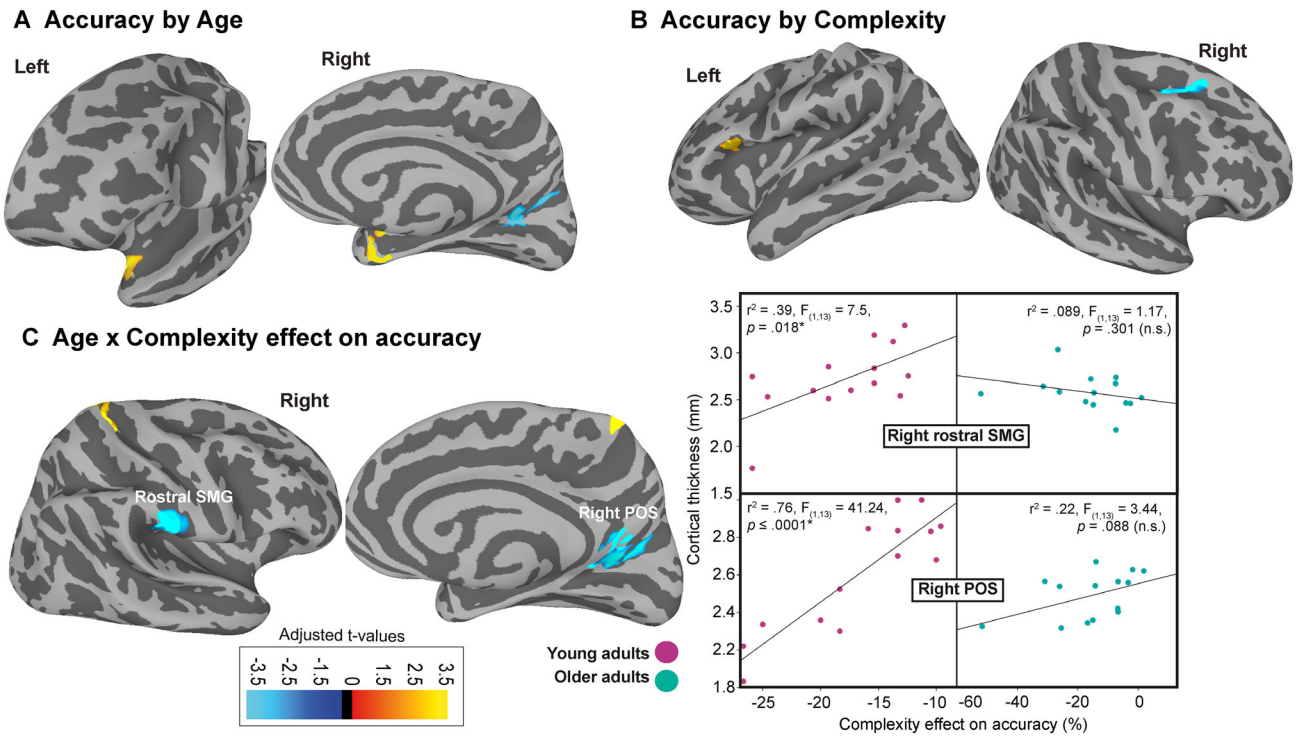

Fig. 6 Accuracy effects. **a** Cortical regions (shown on the group average smoothed white matter folded surface) exhibiting an interaction between CT, accuracy and age. **b** Cortical regions exhibiting an interaction between CT, and complexity effects in accuracy. **c** Cortical regions exhibiting an interaction between CT, complexity effects in accuracy and age. The *scatter plots* on the *right* end side of the figure illustrate this relationship in the right rostral SMG and POS (*pink dots* young adults; *green dots* older adults). Note that the more negative the values on the *x*-axis, the greater the effect of complexity (decreased accuracy)

Table 6 Relationship between CT and response accuracy

Analysis	Region	Hemi	*x*	*y*	*z*	Nodes	Area	*t*	*p*
Age × accuracy	Planum polare extending into the temporal pole and anterior insula	Left	−37	1	−47	1545	374.49	4.712	0.000079
	Parieto-occipital sulcus and cuneus	Right	20	−69	29	1145	460.18	−4.657	0.000091
	Temporal pole, extending into the parahippocampus gyrus	Right	31	−1	−20	967	216.59	4.208	0.000290
Complexity effect in accuracy	Anterior dorsal insula	Left	−43	25	8	650	147.07	3.193	0.003780
	Parieto-occipital sulcus and cuneus	Right	5	−65	28	1288	443.7	3.914	0.000618
	Occipital pole	Right	8	−94	0	632	261.64	3.618	0.001312
	Superior frontal sulcus and gyrus	Right	31	6	54	740	148.8	−3.658	0.001186
Age × complexity effect in accuracy	Parieto-occipital sulcus and cuneus	Right	17	−54	21	1581	662.51	−4.98	0.000039
	Postcentral gyrus and central sulcus (S1/M1)	Right	16	−35	72	1031	249.56	3.852	0.000724
	Rostral supramarginal gyrus	Right	61	−21	27	799	210.8	−4.727	0.000076

Lotze et al. 2000; Bilodeau-Mercure et al. 2014; Brendel et al. 2010; Riecker et al. 2008; Brendel et al. 2011; Riecker et al. 2002). In the present study, the structure of several of these regions correlated with the different indexes of speech production including AI, IFS, M1, STG, the putamen and caudate nuclei. The lack of cerebellar findings should be interpreted with caution because of the very coarse parcellation that was used. It is possible that a more sophisticated parcellation would have produced different results.

Regions less typically implicated with speech production were also identified including the posterior cingulate gyrus and the superior frontal sulcus. These findings are discussed in the following paragraphs.

Table 7 Number of voxels showing significant brain/behaviour correlation

	Total	Left hemi	Right hemi	% of grand total	% of grand total for LH	% of grand total for RH
Duration	2785.12	1782.38	1002.74	19.3	28.2	12.3
Duration × age	1754.84	859.17	895.67	12.1	13.6	11.0
Complexity effect in duration	3287.9	1471.6	1816.3	22.8	23.3	22.3
Age by complexity effect in duration	945.98	461.41	484.57	6.5	7.3	6.0
Total duration	8773.84	4574.56	4199.28	60.7	72.4	51.6
RT	404.26	404.26	0	2.8	6.4	0.0
RT × age	814.23	226.39	587.84	5.6	3.6	7.2
Complexity effect in RT	179.3	179.3	0	1.2	2.8	0.0
Age by complexity effect in RT	1102.47	408.87	693.6	7.6	6.5	8.5
Total RT	2500.26	1218.82	1281.44	17.3	19.3	15.8
Accuracy	0	0	0	0.0	0.0	0.0
Accuracy × age	1051.26	374.49	676.77	7.3	5.9	8.3
Complexity effect in accuracy	1001.21	147.07	854.14	6.9	2.3	10.5
Age by complexity effect in accuracy	1122.87	1	1122.87	7.8	0.0	13.8
Total accuracy	3175.34	522.56	2653.78	22.0	8.3	32.6
Total	14449.44	6315.94	8134.5	100.0	100.0	100.0

Neurostructural correlates of response duration

Speech response durations were significantly longer in older compared to younger adults, being on average ~300 ms longer for older adults, which represents a 17 % age-related increase in duration. This increase appears to be related to different chunking strategies, with older adults pausing (briefly) half way through the sequences. Changes in response duration of that magnitude have been reported in the literature on aging and motor control (Doose and Feyereisen 2001; Diggles Buckles 1993), and are usually assumed to reflect a combination of peripheral and central factors (Seidler et al. 2010). Indeed, it has been shown that older adults exhibit decreased oral tactile sensitivity (Wohlert and Smith 1998; Calhoun et al. 1992; Wohlert 1996), decreased lip strength (Wohlert and Smith 1998), and decreased maximal tongue strength (Neel and Palmer 2012). However, one study has shown that tongue maximal strength is a poor predictor of articulation rate (Neel and Palmer 2012), suggesting limited contribution of these physiological factors. The present finding of significant correlations between response duration, age and regional CT suggests that changes at the level of the central nervous system play a part in the etiology of speech-related behavioural changes, though the cross-sectional nature of the present study does not allow us to determine whether these changes are causal in nature.

Perhaps not surprisingly, we found a correlation between CT in the left ventral primary motor cortex (M1v), sequence complexity and response duration. As expected, this correlation was negative, meaning that, in general, participants with thicker cortex in the left M1v showed reduced complexity-related difficulty. M1v is active in all studies of syllable production (e.g., Shuster 2009; Bohland and Guenther 2006; Peeva et al. 2010; Ghosh et al. 2008; Soros et al. 2006; Alario et al. 2006; Lotze et al. 2000; Bilodeau-Mercure et al. 2014; Brendel et al. 2010; Riecker et al. 2008; Brendel et al. 2011; Riecker et al. 2002). M1v is generally believed to be involved primarily with the execution of orofacial movements including speech (Riecker et al. 2005) rather than in response planning. It is possible that articulation of complex sequences, which was slower than the simple sequences, is taxing for M1v, resulting in an association between complexity-related difficulty and CT in M1.

One of the most important findings of the current study is a relationship between CT in the bilateral dAI and speech response duration. This relationship was modulated by age (right dAI), sequence complexity (bilateral dAI) and age by sequence complexity (left dAI). In general, participants with thicker cortex in the bilateral dAI produced shorter speech responses, and, importantly, they showed reduced complexity-related difficulty, suggesting that increased speech sequencing proficiency is associated with the structure of the dAI. Because the complex sequences contained the same number of syllables and sounds than the simple ones, the complexity effect on response duration suggests a difference in chunking strategy, which could suggest a role for the AI in speech motor planning, and more specifically sequencing. A large number of fMRI studies have shown AI activation during speech production in healthy adults (Bohland and Guenther 2006;

Bookheimer et al. 2000; Haller et al. 2005; Riecker et al. 2002, 2008; Ackermann and Riecker 2004; Riecker et al. 2005; Peschke et al. 2009; Moser et al. 2009). Moreover, Dronkers et al. (Dronkers 1996; Ogar et al. 2006) have shown, using voxel-based morphometry, that lesions to this region are related to speech apraxia, a disorder of speech programming that affects sequencing. Other studies have also shown that AI is involved in motor timing/sequencing in other modalities such as finger tapping (Lewis and Miall 2002; Bengtsson et al. 2004), supporting the idea of a role for this region in programming sequential motor responses. Previous studies have reported that aging of AI is associated with a decline in speech and language skills, including speech perception in noise (Bilodeau-Mercure et al. 2014) and sentence comprehension (Peelle et al. 2010). Importantly, however, AI is also known to be among the most commonly reported activation sites across fMRI studies (Nelson et al. 2010). AI could, thus, contribute to human goal-oriented motor tasks including speech in a general manner, possibly in terms of attentional control or monitoring, rather than to speech production per se. For example, in a previous study from our group, we found increased activation in dAI as a function of speech intelligibility (Bilodeau-Mercure et al. 2014). Because articulatory and sequencing difficulty were kept constant, it is possible that the increase in activation in this region reflected increased attentional control, which is known to decline with age (Zhou et al. 2011; Carriere et al. 2010; Gamboz et al. 2010; Jennings et al. 2007). A role for AI as a cognitive/executive hub has been suggested (Menon and Uddin 2010; Chang et al. 2013), in which AI is involved in detecting salient events for additional processing (Seeley et al. 2007). According to this view, saliency, whether emotional, cognitive or homeostatic, would be detected by AI, which would then initiate attentional control (Menon and Uddin 2010). In the present study, however, we believe that memory, attention and monitoring were equivalent across sequencing complexity levels, because (1) the instructions remained on the screen throughout the trials (minimizing memory load), (2) the conditions were completely randomized and (3) the pace was fast, meaning that participants needed to be attentive throughout. Hence, it is possible that the relationship between AI's structure and speech production may reflect a role in motor sequencing. Consistent with this notion, a modulation in this region was recently reported by Shuster (2009) for the production of two-syllable non-words compared to the production of real words. Interestingly, in this study, the words and non-words were composed of equally complex and frequent first syllables as well as identical phonotactic probability. The authors suggested that, consistent with the notion of whole words motor plans (Bybee and Scheibman 1999; Bybee 2002), real words are easier to articulate because they are pre-chained (pre-sequenced), whereas non-words are not, thereby requiring more effortful sequencing. Additional studies are needed to clarify the specific role of the AI in speech production, particularly in terms of motor response sequencing.

Interestingly, in the left dAI, the relationship between CT and response duration was stronger for the young than the older adults. It is possible that the importance of the left dAI in speech production weakens with age, possibly because of age-related neural plasticity, that is, neural reorganisation that would occur within the speech system to compensate for neural atrophy. Reorganisation could also be functional, meaning that older adults could rely on different cognitive or motor strategies, which may serve to reduce the role of the dAI in speech production in late adulthood, thereby limiting the functional impact of its structural decline. These mechanisms could be triggered at a certain threshold to maintain behaviour despite regional structural atrophy. In the present study, the oldest participant was only 74 years. Additional studies with older individuals are needed to better characterize lifetime changes in the relationship between regional brain structure and speech behaviour in the AI and beyond.

In some of the analyses in which we identified a relationship between CT in dAI and response duration, though the locus was always in dAI, it extended into the VLPFC, specifically the ventral segment of the orbital and triangular part of the right IFG. This was the case for the relationship between CT and overall response duration, and between CT and response duration complexity scores. The VLPFC has been suggested to be involved in first order executive processes, such as selection, comparison and judgments of stimuli held in short-term memory (e.g., Petrides 2005). It is possible that this region participates in simple speech production tasks by providing domain-general attentional/executive support.

In addition to the AI/VLPFC findings, we also found that CT in a large portion of the left STG/STS was related to response duration and age. The left STG/STS was active in previous studies of speech sequence (Bohland and Guenther 2006) and nonword production (Peeva et al. 2010; Shuster 2009). Contemporary neurobiological models of spoken word production and speech motor control have suggested that the posterior STG contains auditory syllable target maps (Hickok 2012) or auditory target maps for common syllabic, sub-syllabic (phoneme) and supra-syllabic speech sounds (Golfinopoulos et al. 2010; Guenther 2006; Guenther et al. 2006). The finding of a relationship between this region's structure and speech response duration is, therefore, in line with the general idea of a role for the left STG/STS in sublexical speech production. Interestingly, we observed that the relationship between speech response duration and CT in this region

was positive in the older adults (longer response durations associated with thicker cortex) and not significant for the younger adults. The positive relationship between CT and response duration indicates that despite the loss of CT in older adults, older adults who had a thicker cortex within the STG/S performed worse (i.e., increase in response duration) than older adults with a thinner cortex. At first, this relationship might seem counter-intuitive given that increase in morphometric measures (grey matter density or volume) are typically associated with better performance on language tasks (Zhang et al. 2013; Grogan et al. 2009). However, a few studies have reported decrease in CT associated with better performance on language tasks (Porter et al. 2011; Roehrich-Gascon et al. 2015). A decrease in CT combined with better performance on language tasks in young adults has been attributed to cortical pruning, the refinement of dendritic branching and synaptic connections (Brenhouse and Andersen 2011). Through pruning mechanisms, cortical connections that are necessary and frequently used are retained whereas non-preferred cortical connections are lost (Porter et al. 2011). While the extent to which analogous cellular changes are responsible for a reduction in CT in adulthood is unclear, it is possible that despite the overall decrease in CT associated with aging, older adults who had more efficient brain maturation processes during childhood and adolescence (i.e.,. thinner CT as teenager and young adults) may benefit from more efficient sensorimotor interaction processes associated with auditory target maps resulting in shorter speech response duration. Another possible explanation is that the neurobiological aging mechanism by which the cortex in the STG/STS becomes thinner is non-detrimental, perhaps reflecting some form of experience-induced structural plasticity, but that the absence of this normal mechanism leads to a decline in performance. Finally, it is also possible that the inverse relationship between CT and response duration observed in the older adults is the result of a decrease in the gray–white matter contrast in aging (Salat et al. 2009; Magnaldi et al. 1993). However, because we have found the expected negative relationship in other parts of the cortex, this suggests that, if it holds, the hypothesis of decreased contrast only applies to specific brain regions. Further studies are required to gain a deeper insight into the neurobiological mechanisms underlying cognitive and behavioural changes in aging.

In a smaller, more anterior part of the left STG/STS, we also found a 3-way relationship between sequence complexity effect in response duration, age and CT. In this region, younger adults who struggled with sequence complexity had thinner cortex (i.e., the expected negative relationship), while older adults showed no relationship between complexity and CT. This supports the notion of a role for the left STG/STS in producing speech. Given that older adults showed an overall decline in performance compared to the younger adults, and a stronger effect of complexity, it is possible that the negative effect of age-related thinning of the STG/STS on performance levels over time, perhaps reflecting a decline in the accuracy of the stored auditory speech maps, such that at a certain point in late life, or passed a specific thickness threshold, further decline does not have a significant functional impact (plateau). The hypothesis of a nonlinear aging process is consistent with the notion that, while speech production skills do decline with age, people do tend to remain functional, suggesting a non-linear progression. It could also suggest an increased reliance on other mechanisms, or on different kinds of speech sound maps (i.e., tactile). Future studies comparing the neurobiological underpinning of speech production in middle-aged adults, in addition to young and older adults, will allow us to put this hypothesis to the test.

Another interesting finding of the present study is that the volume of the striatum was positively associated with speech response duration. In the left putamen a positive age- independent relationship was found, meaning that large putamen volumes were associated with better performance. In contrast, in the bilateral caudate, this relationship was present only in older adults. This could suggest a form of *brain reserve capacity* or BRC (Satz 1993; Stern 2003; Steffener and Stern 2012; Stern 2002), meaning that, up to a certain amount of structural decline, in early adulthood, the nervous system is capable of compensating for a loss in caudate volume, after which a behavioural decline begin to appear. It has been suggested that the caudate nucleus is involved in speech planning, and more specifically sequencing speech motor responses, receiving input from both the IFS and pre-SMA (Bohland et al. 2010). The caudate is also active during memory-driven manual sequencing tasks (Menon et al. 2000), and during a sequence learning (Bischoff-Grethe et al. 2004) suggesting of a role in higher order cognitive/executive aspects of movement preparation. While the volume of the putamen and caudate were both related to speech sequencing skills, it is likely that their involvement in speech production is distinct. Indeed, the putamen is often considered the main motor structure of the striatum, being connected to M1 and premotor cortex through frontal–basal–ganglionic–thalamic loops, while the caudate nucleus is connected to prefrontal structures but not M1 (Postuma and Dagher 2006; Alexander et al. 1986, 1990; Hoover and Strick 1999). Using fMRI, Ghosh et al. (2008) reported an increase in the activation level of several areas including the bilateral putamen for the production of disyllabic sequences compared to the production of monosyllables, which support the notion of a role for this region in response sequencing. Interestingly, it has been

shown that both the putamen and caudate are functionally connected to the insula (Postuma and Dagher 2006), which was also correlated with speech sequencing skills in the present study. It is possible that the putamen is involved in the temporal organisation of motor plans while the caudate and insula may contribute to planning the sequences at a supra-motor or executive level. Additional research is needed to test these predictions empirically.

Neurostructural correlates of reaction times

Reaction time were significantly affected by sequence complexity (being on average ~100 ms longer for the complex than the simple sequences), representing a ~13 % increase, most likely reflecting a longer response preparation time needed to plan the temporal organisation of the different sounds forming the sequences. In general, the relationship between CT and RT was independent of sequence complexity, in contrast to the relationship between CT and response duration, which was more heavily modulated by sequence complexity.

A relationship between RT and CT was found only in two regions of the left hemisphere, namely the dorsal postcentral gyrus and the pCing. The pCing has been implicated in the default mode network, a network of brain regions active when an individual is not focused on the outside world but 'resting' (Shulman et al. 1997; Raichle et al. 2001; Mazoyer et al. 2001). Interestingly, since the correlation showed that increased thickness in this region was associated with longer RT, and given that this region supports inward-related processes, this may suggest that individuals with a general tendency to be oriented towards inner processes rather than external stimuli may have thicker cortex in this region, which may be associated with the capacity to react quickly to external stimuli.

A relationship between thickness, RT and age was found in the right IFS, suggesting a role for this region in speech production. Specifically, we found a positive relationship between CT and RT in young adults (i.e., increased CT was associated with longer RT), while there was no relationship in older adults. The positive relationship suggests that cortical thinning in the right IFS is associated with faster speech production in young adults. Previous studies have attributed decreased CT combined with better performance on language task to cortical pruning mechanisms (Porter et al. 2011; Roehrich-Gascon et al. 2015). As mentioned in "Neurostructural correlates of response duration", an age-related loss in structure/function relationship may indicate that a region becomes less critical with age for the production of speech, which may be accomplished through a smaller network. Alternatively, it is also possible that beyond a certain amount of structural decline, neural reorganisation occurs to compensate for normal age-related brain atrophy. In a previous fMRI study from our group, we found that the bilateral IFS was involved in repeating auditory-triggered sequences of syllables (Bilodeau-Mercure et al. 2014), though it was not modulated by the complexity of the sequences. In contrast, Bohland and Guenther (2006), also using fMRI, found that activation in the left IFS was greater for the production of complex vs. simple speech sequences. Averbeck and colleagues (2002, 2003), using single-cell recordings in the macaque right prefrontal cortex (an area homologous to the IFS in humans), showed activity in this region during a sequencing task consisting of drawing a series of segments to form a geometrical shape, suggesting a role for the right IFS in manual action sequencing. The IFS has also been implicated in non-motor sequencing task. For example, Huettel et al. (2002) found activation in the bilateral IFS during the processing of visually presented sequences geometrical shapes. Olesen and colleagues (2004) found activation in the right IFS in a working memory tasks requiring the processing of sequential information. In sum, the finding of a relationship between the structure of the right IFS and RT in a sequential speech tasks appears consistent with the literature suggesting a role for this region in sequential tasks, though the specific contribution of the right vs. left IFS in speech sequencing remains uncertain, whether it reflects a motor or non-motor (e.g., memory) sequencing process. Given that the stimuli in the present study were sequences of visually presented letters, it is possible that the correlation that we found between the right IFS and RT reflects the processing/storage of the visual stimuli in memory, which appears to be a right-lateralized function, rather than speech motor sequencing. Additional data is needed to clarify the role of both the left and right IFS in motor vs. non-motor sequencing during speech production.

Another interesting finding for the neurostructural basis of RT is that thickness in the right rostral SMG was positively associated with complexity effect in RT. The rostral part of the bilateral SMG is known for its involvement in the action observation/imitation network as it shares connections with inferior and middle frontal, premotor, primary motor and somatosensory areas (Caspers et al. 2010, 2011, 2012). In terms of language processing, Shalom and Poeppel (2008) have proposed that, in general, the inferior parietal lobule is involved in processing sublexical information, more specifically accessing subparts of stored items. Specifically, the more rostral part of the SMG would be involved with the processing of sounds and single phonemes, while the other components of the SMG would be involved with larger language units. Others have suggested that the rostral SMG is involved in sublexical storage during language processing (Deschamps et al. 2014). The hypothesis of a sublexical processing or storage function for the rostral SMG is supported by the present

finding of a relationship between thickness in this region and speech RT in a sublexical task that required both analyzing the visually presented syllables before producing them, and storing the sequence elements (syllables) during processing and production. Interestingly, this relationship was detrimental in the young adults, meaning that more thickness was associated with greater complexity effects in RT. The absence of such relationship in older adults suggests that perhaps the importance of the right rostral SMG, as well as the right IFS, weakens with age, possibility due to age-related neural plasticity. Longitudinal aging studies are needed to better characterize lifetime changes that occur over the lifespan within the structures that support speech functions and help clarify the relationship between regional brain structure and speech production speed.

Neurostructural correlates of articulatory accuracy

Articulatory accuracy was, like response duration and RT, modulated by sequence complexity, declining by ~16 % from the simple to the complex sequences for all participants. Articulatory accuracy was not, however, modulated by age, contrary to previous findings from our group (Bilodeau-Mercure et al. 2015; Bilodeau-Mercure et al. 2014). In these studies, however, articulatory complexity was higher (Bilodeau-Mercure et al. 2015), or speech was triggered auditorily, which may explain this difference.

There was no relationship between overall articulatory accuracy and CT in any cortical or subcortical region, and, in general, the unique relationship between CT and accuracy was much more spatially limited than that of response duration or even RT. The majority of the voxels exhibiting sensitivity to accuracy were located in the right hemisphere (2654 voxels in the right hemisphere, and only 522 in the left hemisphere), including the parieto-occipital sulcus and cuneus, the SFS, the dorsal precentral gyrus and sulcus, the dAI and the rostral SMG.

Interestingly, we found that thicker cortex in the region of the right POS/CN was associated with less complexity-related errors. While these two regions are not commonly associated with speech production, they are often engaged in tasks requiring the processing of visual information (Henson et al. 1999; Pessoa et al. 2002; Tan et al. 2000). Given that the stimuli in the current study where visual sequences of syllables, it is, therefore, possible that the positive relationship between CT in these regions and speech production reflects a more efficient mapping of orthographic information into syllable representations, which translated into decreased sequence complexity effects (for similar conclusions, refer to: Vingerhoets et al. 2003).

Another interesting finding is that of a 3-way relationship between thickness, age and complexity-related errors in the rostral part of the SMG (Caspers et al. 2006, 2008, 2013). Thicker cortex in this region was associated with less complexity-related errors in the younger adults (i.e., better performance), while, in the older adults, it was not related to performance. As discussed in "Neurostructural correlates of reaction times", it has been suggested that the rostral part of the bilateral SMG is involved with the processing/storage of sounds and single phonemes during language processing. In the present study, we found that thickness in this region was associated with complexity effects in both RT and accuracy in a visually triggered sublexical speech task in young adults, exhibiting a beneficial relationship with accuracy and a detrimental relationship with RT. This suggests a key role for this region in supporting speech production processes in relationship with sequence complexity, at least in young adulthood. Indeed, the relationship between the right rostral SMG and performance is only present for the young adults, suggesting that the importance of this region in supporting speech functions declines with age. This suggests a change in cognitive or language processing strategy during speech production, or a reorganisation within the neural system supporting speech production, whereby a simpler neural network might be sufficient to support speech function in older ages. It has been shown that, with age, neural networks degrade to a more locally organized topology, with a decrease in long-distance connectivity and an increase in local connectivity (e.g., Andrews-Hanna et al. 2007; Montembeault et al. 2012; Hafkemeijer et al. 2014; Damoiseaux et al. 2008; Song et al. 2014; Li et al. 2015; Wang et al. 2012). While the present findings cannot speak to the underlying cause of the apparent age-related decline in the relationship between speech production and the structure of the right rostral SMG, right IFS and left dAI, our findings suggest that a number of neurobiological aging mechanisms affect the ability to speak, and call for additional studies to uncover the underlying neurobiological principles.

The more is not always the merrier

In this study, ~60 % of all the cortical regions revealed by the whole-brain ANCOVA (25/43) showed a positive relationship between CT and behavioural performance, supporting the intuitive notion that increased thickness is associated with better performance. However, in ~40 % (18/43) of these regions, the relationship was in the opposite direction, with increased CT associated with decreased performance. Interestingly, other groups have reported significant negative correlations between CT and spoken language performance (e.g., Roehrich-Gascon et al. 2015; Porter et al. 2011; Bilodeau-Mercure et al. 2014), or between CT and cognitive tasks (Dickerson et al. 2008).

For example, Porter et al. (2011) reported a negative relationship between CT and verbal fluency in several regions including the bilateral superior and middle temporal gyrus, left IPL, and left IFG. At least two broad classes of neurobiological mechanisms can explain a regional decline in CT. The first is neural *degeneration* (neuronal loss, or a deterioration of synapses, dendrites, and spines), which has been observed in elderly adults in M1 (Nakamura et al. 1985), the superior temporal cortex (Jacobs and Scheibel 1993) and the prefrontal cortex (de Brabander et al. 1998; Scheibel et al. 1975; Huttenlocher 1979). Degeneration has either a deleterious effect on behaviour or no effect at all. This mechanism, thus, cannot explain the finding of thinner cortex associated with better performance. The second mechanism is *pruning*, which is a refinement of dendritic branching and synaptic connections (Brenhouse and Andersen 2011), resulting from the loss of non-preferred cortical connections in favor of retaining the connections that support necessary and frequently used skills (Porter et al. 2011). Pruning, which results in faster neuronal processing, occurs throughout adolescence and continues in early adulthood (Bramen et al. 2012; Giedd et al. 1999; Gogtay et al. 2004). It is, therefore, possible that the negative relationship between CT and performance in specific cortical regions results from a more efficient early brain maturation process. Additional longitudinal studies are necessary to clarify the influence of inter-individual differences in brain maturational processes on cognitive, language and motor skills in late adulthood, and to understand how early maturational process interact with later neural degeneration mechanisms.

Conclusion

In the present study, we used a neurostructural approach to study the neural basis of speech production in adulthood. Our results demonstrate that the speech of older adults is as accurate but slower than that of younger adults, particularly during the production of complex sequences of syllables. Our findings of a distributed network of regions, including large parts of the cortex as well as the striatum, whose thickness or volume was related to different measures of speech production (response duration, RT and accuracy) support models of speech production that document a distributed cortical–subcortical network of regions involved in producing language. Importantly, these findings also demonstrate that surface-based CT is a useful experimental tool that can be used to quantify inter-individual differences in brain structure in healthy participants and their relationship with specific aspects of behaviour (e.g., RT, articulatory accuracy and response duration) during the processing and production of syllable sequences. Though the present study contains a number of limitations (including a small non-probabilistic sample size, limited age-range coverage especially in the older group and the acquisition of only one structural image per participant, which limited our ability to detect movement artefacts), the present findings are an important step towards understanding the effects of neurobiological aging on the ability to communicate verbally, which is central to our ability to participate in society.

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