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Proper name retrieval and structural integrity of cerebral cortex in midlife: A cross-sectional study

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ABSTRACT

There is currently little understanding on whether retrieval of proper names differs in midlife compared to young adulthood and if so, whether the age differences in this ability are associated with differences in structural integrity of the cerebral cortex. To answer these questions, we studied retrieval of proper names in 115 cognitively healthy middle-aged persons (49.7, ± 3.2), comparing their performance on a tip-of-the-tongue (TOT) task with that of 68 young persons (25.4, ± 3.5) from the Cam-Can data repository (http://www.mrc-cbu.cam.ac.uk/datasets/camcan/). Grey matter (GM) density and cortical thickness were used as indices of structural integrity of the cerebral cortex. The middle-aged (MA) group experienced more TOTs during proper names retrieval than young adults (YA), ($t = 3.789$, $p < .005$) and had considerably less GM density and cortical thickness across a range of brain areas bilaterally. Small clusters in left BA 45 and right BA 44 (cortical thickness) and in right BA 40 (volumetry) revealed group differences when accounting for TOTs. However, we observed no correlations between MA's TOT scores and GM volumes or cortical thickness of the brain regions typically reported as implicated in retrieval of proper names: left anterior temporal lobe, left insula, and left superior and middle temporal gyri.

1. Introduction

Research on the effects of aging on the brain and cognition in neurologically intact persons has traditionally focused on adults aged 60 years or more, despite the evidence suggesting that neurocognitive decline begins in the early 20s (Salthouse, 2010). Gradual changes in the brain that typically begin in early adulthood include reduction in the brain's overall size and weight, grey and white matter regional volume reduction and integrity deterioration, expansion of cerebral ventricles and sulci, cortical thinning, changes in functional connectivity, myelin integrity, concentration and receptor density of neurotransmitters, accumulation of neurofibrillary tangles, reduced synaptic density, and so forth (Giorgio et al., 2010; Lindenberger, 2014; Marstaller, Williams, Rich, Savage, & Burianova, 2015; Salat et al., 2004; Salthouse, 2009). Some cognitive functions appear to be more resilient to aging than others. For instance, vocabulary and general knowledge may continue to grow past the age of 60, whereas processing speed, memory, executive function and problem solving typically begin to deteriorate in early adulthood (Ackerman, 2008; Salthouse, 2010).

One domain particularly vulnerable to aging is knowledge of proper names. Knowledge of proper names serves an important cognitive function: it helps us to identify an entity despite its different manifestations or different contexts in which it appears, which in turn allows us to structure the world around us (Van Langendonck, 2007). More importantly, proper names allow us to achieve a unique reference even when our knowledge about the entity in question is limited (Burks, 1951). Cognitively healthy elderly persons have difficulties when retrieving proper names, with increased occurrences of tip-of-the-tongue states (Burke, MacKay, Worthley, & Wade, 1991; Cohen & Burke, 1993; Huijbers et al., 2016; James, 2006; Salthouse & Mandell, 2013; Shafto, Burke, Stamatakis, Tam, & Tyler, 2007; Shafto, Stamatakis, Tam, & Tyler, 2009). A tip-of-the-tongue (TOT) state is a metacognitive state in which a person is aware of his/her failure to retrieve the target word accompanied by a strong feeling that the sought for target is within reach. Difficulty in retrieving proper names was also found in persons with neurological conditions, such as Alzheimer's disease (Semenza, Nichelli, & Gamboz, 1996), Parkinson's disease and advanced multiple sclerosis (Semenza, 2009), after language-dominant temporal lobectomy (Tsukiura et al., 2002), and in aphasia due to brain injury

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(Miceli et al., 2000; Semenza & Zettin, 1988, 1989). In contrast to word retrieval deficits caused by brain damage, TOT experiences involve only a temporary inability to recall a specific word. However, even a temporary and only occasional inability to access knowledge of proper names, as in TOT states, is frustrating and indicates that there is something peculiar about proper names that makes them susceptible to forgetting.

Philosophical, linguistic, and neuropsychological theories agree that proper names have a special status in language. The long tradition of philosophical thinking on proper names involves debates regarding the question of how proper names name, i.e. whether they have meaning/sense or whether they are directly referential expressions (e.g. Frege, 1892/1949; Katz, 1977; Kripke, 1980; Mill, 1843; Russell, 1905; Searle, 1958, among others). As a linguistic category, proper names belong to language universals. Unlike verbs, which name events and states (De Almeida & Manouilidou, 2015), and unlike common nouns, which denote categories of objects, proper names refer to unique entities, such as persons, animals, places, buildings, brands, languages, and currencies. Thus, proper names lack the meaning in the sense in which common nouns have meanings. In some languages, they also differ in morpho-syntax and may follow different syntactic rules (Alego, 1973; Longobardi, 2005; Van Langendonck, 2007). Given the peculiar nature of proper names, it is not surprising that they figure differently than other semantic classes in memory (Bartlett, 1932). In general, proper names are more susceptible to forgetting than common nouns (Hanley, 2011; Salthouse & Mandell, 2013; Semenza, 2009; Semenza et al., 1996), even in case of name-occupation homophones (e.g., *Baker-baker*, *Potter-potter*), which cannot be explained by differences in phonological form or frequency of occurrence (Cohen & Burke, 1993).

Some findings indicate that there exists a dedicated area for retrieval of proper names (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Gorno-Tempini et al., 1998; Shafto et al., 2007), but there is currently no consensus on which area it is. One model promotes the notion of the critical role of the left anterior temporal lobe (ATL) in the retrieval of proper names (Abel et al., 2015; Damasio et al., 1996; Mehta et al., 2016; Tsukiura et al., 2002). Evidence supporting this model comes from a series of studies involving brain-damaged and neurologically intact subjects, using a range of methods, from positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electrocorticography to diffusion tensor imaging. Another model, which is based on PET evidence obtained from six healthy male subjects, argues for an amodal semantic network distributed across the left anterior and posterior extrasylvian temporal cortex (Gorno-Tempini et al., 1998). The model allows a degree of modularity within the network, with some areas being differentially involved in specific types of processing (e.g. faces, words, objects). For example, it was suggested that the anterior middle temporal gyrus (MTG) and superior temporal gyrus (STG) are the areas supporting retrieval of famous persons' names (Gorno-Tempini et al., 1998). A third model, based on f/MRI evidence, suggests that the left insula plays a critical role in retrieval of names and that increased TOT states during proper names retrieval indicate difficulties with phonological access to the mental lexicon (Shafto et al., 2007). The disparate research findings suggest that the fundamental question of neurobiological underpinnings of proper name retrieval has not been entirely resolved.

So far, most research on age-related decline in proper name retrieval has been focused on elderly persons, leaving largely unexplored the question of whether this cognitive ability is already affected in midlife. Given the evidence suggesting that increased age negatively affects proper name retrieval (Burke et al., 1991; James, 2006), in the present study we wanted to determine whether the ability to retrieve proper names would differ in midlife compared to young adulthood and if so, whether these differences would be related to differences in grey matter (GM) density and cortical thickness. We tested for age-differences in cortical thickness in addition to GM density because growing evidence indicates that cortical thinning is also an important index of atrophy in aging (Im et al., 2008; Lemaitre et al., 2010; Panizzon et al., 2009), with global cortical thinning becoming apparent by the third decade of life (Salat et al., 2004). Furthermore, considering previous findings indicating that left ATL, left MTG, STG and left insula support retrieval of proper names (Damasio et al., 1996; Gorno-Tempini et al., 1998; Shafto et al., 2007), we wanted to determine whether GM density and cortical thickness of these specific regions in middle-aged persons would be related to their ability to retrieve proper names. In general, greater GM density and thicker cortex have been associated with better cognitive performance, but associations between reduced density and normal cognition were also found. (For example, a negative correlation between GM density in the caudate nucleus and general intellectual ability in cognitively normal young people was reported by Frangou, Chitins, and Williams (2004).) Magnetic resonance imaging (MRI) allows *in vivo* studying of brain morphometrics, permitting insights into structural brain differences and possible associations between regional volumetric as well as cortical thickness properties and behavioral measures of proper names retrieval.

Thus, we studied retrieval of proper names in a sample of 115 cognitively healthy middle-aged persons (MA) (mean age 49.7, ± 3.2), comparing their performance on a tip-of-the-tongue (TOT) task with that of a group of 68 young adults (YA) (mean age 25.4, ± 3.5). In addition to comparing the two groups' performance on the TOT task, we explored group differences in overall GM density and cortical thickness obtained from MRI data, and tested for possible associations between volumes as well as cortical thickness of the regions that were previously identified as supporting proper names retrieval – left ATL, MTG, STG, and insula – and MA group's performance on the TOT task.

2. Materials and methods

2.1. Participants

Data used in the preparation of this work were obtained from the Cambridge Center for Ageing and Neuroscience (Cam-Can) data repository, available at http://www.mrc-cbu.cam.ac.uk/datasets/camcan/. The study followed the recommendations of the Helsinki Declaration on studies involving human subjects and was approved by the local ethics committee (see Shafto et al., 2014; Taylor et al., 2017 for details on the Cam-Can protocol). Cognitive and structural neuroimaging data were retrieved for 183 cognitively healthy subjects, including 115 middle-aged persons (age range 45–55 years, mean age 49.7, ± 3.2) and 68 young adults (age range 18–30 years, mean age 25.4, ± 3.5). There were no statistically significant differences in gender distribution between the groups (Pearson Chi-Square, $\chi^2 = 0.157$, $p = .692$). However, the original sample was reduced during image preprocessing (Section 2.3) due to removal of the images with an overall covariance below two standard deviations, which left a total of 168 subjects (MA = 102, mean age 49.7 ± 3.3; YA = 66, mean age 25.3 ± 3.5; t (1 6 6) = 46.066, $p < .005$). The sample reduction did not affect the gender distribution pattern (MA: 48 females, 54 males; YA: 29 females, 37 males; Pearson Chi-Square, $\chi^2 = 0.165$, $p = .684$, n.s.). The groups did not differ considerably in the total intracranial volume (t (1 6 6) = −0.054, $p = .95$, n.s.).

2.2. Behavioral data: tip-of-the-tongue task

In the tip-of-the-tongue task, participants were presented with 50 pictures of faces that represented famous people (actors, musicians, politicians, etc.). The task was to name a person upon seeing a picture. The pictures were presented in a pseudorandom order. Before each trial, a fixation cross was presented for 1000 ms, which was followed by a picture that remained on the screen for 500 ms. The task allowed three categories of responses: "know" response, i.e. retrieval of the name, "don't know" response if they did not know who the person on the picture was, and a TOT response, meaning they knew who the

person was but could not retrieve the name (see Shafto et al., 2014 for more details on the task). In the present study, we focus on the number of TOT states in each group, hypothesizing that it will be higher in the MA than in the YA group. For completeness, we report the groups' "know" and "don't know" responses. Note that in the scoring phase, the "know" responses were subdivided into "know-correct" and "know-incorrect" responses, which allows further insights into participants' metacognition regarding proper names.

2.3. MRI data acquisition and preprocessing

MRI data was collected at a single site (MRC-CBSU) using a 3T Siemens TIM Trio scanner with a 32-channel head coil, as described in Shafto et al. (2014) and Taylor et al. (2017). Briefly, high resolution structural T1-weighted images were obtained using a Magnetization Prepared RApid Gradient Echo (MPRAGE) sequence, with the following parameters: Repetition Time (TR) = 2250 ms, Echo Time (TE) = 2.99 ms, flip angle = 9 degrees, field of view (FOV) = 256 × 240 × 192 mm, voxel size 1 × 1 × 1 mm, GRAPPA acceleration factor = 2, acquisition time = 4 min and 32 s.

Imaging data was processed using Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging), including VBM8 (http://dbm.neuro.uni-jena.de/vbm/) and SPM Masking (Ridgway et al., 2009) toolboxes, implemented in MATLAB R2007a (MathWorks, Natick, MA). Structural T1-weighted images were first realigned so that the origin of each T1 scan was set to the AC/PC line. The realigned structural T1-weighted images were then segmented into six tissue classes (grey matter, white matter, cerebrospinal fluid partitions, skull, soft tissue outside the brain, and air/other stuff outside the head) by using New Segment in SPM8. Non-linear deformations for warping all grey matter (GM) and white matter (WM) images were obtained in DARTEL (Ashburner, 2007). The DARTEL-imported versions of GM and WM maps were used in the next step to generate flow fields and a series of average templates to which the data were iteratively aligned. The final template, which was registered to MNI (Montreal Neurological Institute) space by an affine transformation, and the flow fields obtained in the previous step were applied to the native GM maps. The spatially normalized GM maps were smoothed using an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel, with the smoothed and spatially normalized images preserving amount so that areas that expanded during warping were correspondingly reduced in intensity. After checking the data quality and sample homogeneity, to improve the homogeneity we removed the maps with an overall covariance below two standard deviations, which left a total of 168 subjects (Section 2.1).

For the statistical model in SPM, we created an explicit mask instead of applying a default criterion that all subjects should have voxel intensity above a certain pre-specified threshold. The mask was created using the SPM Masking Toolbox, following an operator-independent strategy that allows an optimal threshold to be found when creating a binarized average image (Ridgway et al., 2009).

Estimates of cortical thickness (CT) were obtained from cortical surface reconstructions, which were computed from T1 images using FreeSurfer (v. 6.0, http://surfer.nmr.mgh.harvard.edu/), following the protocol described elsewhere (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999). Briefly, the preprocessing steps followed the recommendations available on the FreeSurfer website (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview) and included: skull-stripping, registration, intensity normalization, Talairach transformation, tissue segmentation, and surface parcellation. The resulting surface maps were visually inspected for any inaccuracies before finally calculating cortical thickness, i.e. the distance from the GM-WM to GM-CSF (cerebrospinal fluid) boundaries at each vertex. Thus obtained cortical thickness maps were smoothed using a Gaussian kernel with a full-width half-maximum of 10 mm and submitted to statistical analyses.

2.4. Definition of regions of interest

Regions of interest (ROIs) included left ATL, MTG, STG and insula. The volumetric ROIs were defined using WFU PickAtlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Burdette, & Kraft, 2003) incorporated in SPM 8. They were coregistered to a T1-weigthed normalized image and resampled to 1.5 × 1.5 × 1.5 mm voxels to match the voxel size of the preprocessed GM maps. Individual GM volumes of the ROIs were extracted from the warped, smoothed GM images by summing up modulated GM voxel values within the respective ROI. Since the proportion of GM depends on the brain size (Lüders, Steinmety, & Jänecke, 2002), the obtained GM volumetric ROI values were normalized by estimated total intracranial volume (TIV) to correct for different brain sizes in statistical analysis. TIV was calculated as the sum of total volumes of the GM, WM, and CSF partitions.

Cortical thickness ROIs were defined based on the Desikan-Killiany atlas (Desikan et al., 2006) and, like the volumetric data, also included left ATL, MTG, STG and insula. Average thickness values of the ROIs were calculated automatically as part of the FreeSurfer analysis pipeline. These ROI values were not normalized by TIV, because cortical thickness has been shown to be independent from head size (Barnes et al., 2010; Panizzon et al., 2009). The average cortical thickness values extracted from these regions were entered in SPSS 22 (Statistical Package for Social Science) (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY, USA, IBM Corp. Released 2013) for further analysis.

2.5. Statistical analyses

The preprocessed GM volumetric maps of the two groups were entered in a full-factorial ANOVA in SPM8 with the age groups (MA, YA) as a between-subject factor, TOT scores as a covariate of interest, and TIV and gender as covariates of no interest. Gender was included as a nuisance variable because of the evidence suggesting gender differences in GM volumes of regions such as insula as well as in overall proportion of GM in the brain (e.g., Barnes et al., 2010; Raz et al., 1997; Ruigrok et al., 2014). The results were assessed at a statistical threshold of 0.05, corrected for multiple comparisons by using familywise error (FWE) rate, at a cluster size of $k \geq 20$ contiguous voxels. Since VBM data is known to be nonstationary, leading to false positive results in smooth regions even when the true signal is absent and, conversely, preventing detection of true positive clusters in rough regions (Ashburner & Friston, 2000; Hayasaka, Phan, Liberzon, Worsley, & Nichols, 2004; Worsley, Andermann, Koulis, MacDonald, & Evans, 1999), the resulting T-maps were corrected for nonstationary smoothness following the protocol described by Kurth, Gaser, and Luders (2015).

Statistical analysis of cortical thickness maps was performed using a GLM model in FreeSurfer, with the contrasts set to test the same hypothesis as the model for the volumetric data described above and the significance threshold at $p < .05$, but applying a false discovery rate (FDR) instead to correct for multiple comparisons.

Further analyses were performed in SPSS. The values extracted from the ROIs were compared between the groups using analysis of covariance (ANCOVA), with each ROI's value as dependent variable, the age group as a fixed factor, and gender as a covariate of no interest. Pearson's correlation test was used to establish possible associations between the values of each ROI and TOT scores in the MA group. An alpha level of 0.05 was set for all statistical tests, except for the correlation test, for which the significance threshold was set at 0.01 after correcting for multiple comparisons using a Bonferroni correction. All tests were two-tailed.

3. Results

3.1. Behavioral results

The two groups differed considerably in the retrieval of proper

names, with the MA group experiencing more TOT states (mean 12.6, ± 6.6) than the YA group (mean 9 ± 5.3), t (166) = 3.789, $p < .005$. The MA group also produced more "know-incorrect" responses (mean 5.1 ± 3.4) than the YA group (mean 2.9 ± 2.4), t (166) = −4.578, $p < .005$. However, the YA group produced significantly more "don't know" responses (mean 22.1 ± 11.3) than the MA group (mean 10.5 ± 8.6), t (166) = 7.353, $p < .005$. They also produced considerably less "know-correct" responses (mean 15.2 ± 9.4) than the MA group (20.2 ± 9.8), t (166) = −3.250, $p = .001$. The groups' means for each type of response are displayed in a supplementary graph (S-Fig. 1).

3.2. Neuroimaging whole-brain-based findings

Consistent with previous findings on age-associated reduction in grey matter volume and cortical thinning, we found differences in both metrics of structural integrity in a range of areas, with the MA group having less density and thinner cortex relative to the YA group. More specifically, clusters with less GM density in MA were found in the right supramarginal gyrus, angular gyrus, superior temporal and occipital gyri bilaterally, in the prefrontal region, cingulate gyrus and the cerebellum (Fig. 1).

Furthermore, clusters with significantly less thickness in MA were found in the insula bilaterally, left fusiform gyrus, superior parietal, superior frontal and middle temporal areas, and in the right precentral, postcentral, and posterior cingulate areas (Fig. 2).

Considering TOT scores, an effect of age was found in left BAs 8 and 9, and in right BAs 40 and 7 in GM density data. However, after correcting for multiple comparisons at the cluster level (Kurth et al., 2015), only the clusters in the right hemisphere survived (Fig. 3).

Additionally, the cortical thickness data revealed two small clusters indicating an interaction between age and TOTs: in the left pars triangularis (peak voxel corresponding to Talairach coordinates X = −47, Y = 34.6, Z = −7.5), and in the right pars opercularis (peak voxel corresponding to Talairach coordinates X = 51.9, Y = 7.1, Z = 3.5) (Fig. 4).

3.3. Regions-of-interest-based findings

After adjusting for gender and using a Sidak correction for multiple comparisons, pairwise comparisons of the estimated marginal means of the extracted volumetric ROI values revealed **a** statistically significant group difference only in one ROI: left superior temporal gyrus, F (1,164) = 5.793, $p = .017$, $\eta_p^2 = 0.03$). The same model revealed statistically significant group differences in cortical thickness in all four ROIs: left superior temporal gyrus, F (1,164) = 37.663, $p < .005$, $\eta_p^2 = 0.187$; left middle temporal gyrus, F (1,164) = 22.997, $p < .005$, $\eta_p^2 = 0.123$; left temporal pole, F (1,164) = 3.869, $p = .05$, $\eta_p^2 = 0.023$; and left insula, F (1,164) = 26.088, $p < .005$, $\eta_p^2 = 0.137$.

However, there were no statistically significant associations between either the volumetric ROI values or cortical thickness ROI values and TOT scores in the MA group.

4. Discussion

The present data suggests that cognitively healthy middle-aged people experience significantly more TOT states when retrieving proper names than young adults. They also retrieve more incorrect names, believing that they have retrieved the correct ones. Young people appear to have more awareness when they do not know names, and in this particular study they were less familiar with the famous people on pictures.

The age-related differences in the present sample suggesting less GM density and cortical thickness in the MA group across a range of areas are consistent with previous findings on the effects of aging on structural integrity of the cerebral cortex (Raz et al., 1997; Raz et al., 2005; Salat et al., 2004; Salthouse, 2009, 2010). When accounting for TOTs and regressing out gender and TIV using GM volumetric data obtained in VBM analyses, we found an effect of age in a small cluster in the right inferior parietal lobe (BAs 40, 7), while the cortical thickness data revealed a small cluster in the left pars triangularis (BA 45) and in the right pars opercularis (BA 44). However, the present data does not suggest significant correlations between the MA group's TOT scores and neither the volumes nor cortical thickness of the left ATL, STG, MTG, and insula.

Looking at other sources of evidence on the neural basis of proper naming, we find that studies on aphasia with a selective deficit for proper names due to brain damage do not support the notion of unique neural substrate for proper names. Instead, they reveal a heterogeneous lesion distribution, implicating the left thalamus, left parieto-occipital lobe, left internal capsule, left fronto-temporal and the left temporal lobe (Fery et al., 1995; Luccelli & De Renzi, 1992; Miceli et al., 2000; Moreaud, Pellat, Charnallet, Carbonnel, & Brennen, 1995; Semenza & Zettin, 1989). As an example, the left temporal pole was spared, while inferolateral and inferomedial temporal regions were damaged in patient APA, who suffered from selective anomia for the names of famous people, without the comparable disorders for other proper names or common nouns (Miceli et al., 2000). Although name retrieval deficits due to brain damage involve intricacies not present in TOT states during name retrieval in healthy people, the heterogeneity of areas associated with proper naming deficit cannot be neglected when addressing the neural basis of proper naming.

Furthermore, the complexity of TOT experiences implies that these

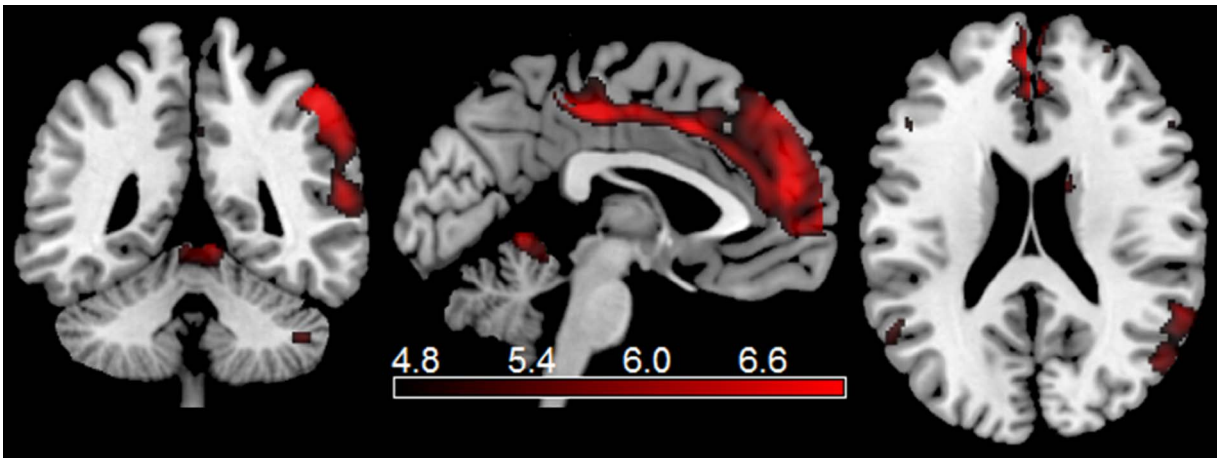

Fig. 1. Group differences in GM density, showing areas with significantly more ($p < .05$ FWE) density in the YA group.

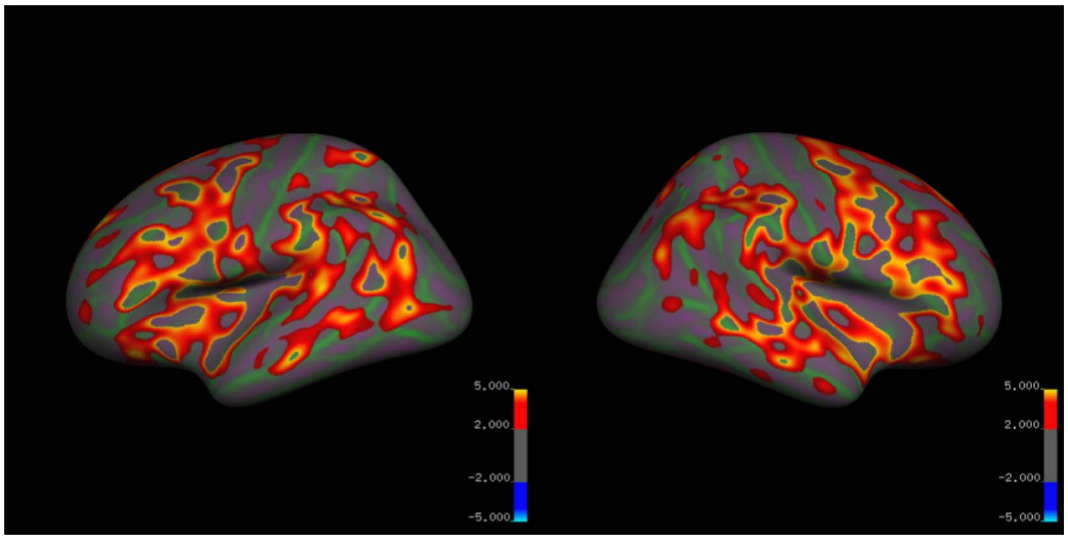

Fig. 2. Areas with clusters showing statistically significant ($p < .05$ FDR) group differences in cortical thickness, with YA having more thickness than MA.

states are likely supported by a range of brain areas, which may be preferentially implicated in different aspects of TOT states. TOT states cannot be reduced to failed attempts to access the mental lexicon, because they also contain a person's awareness of their inability to retrieve a word (e.g. name) as well as the impression that the target word is within reach. In addition to accessing and searching the long term memory (semantic memory, including "individual semantics" [Semenza, 2009]), these states require sufficient attention resources to support selection and inhibition processes, working memory to sustain retrieved representations and support comparisons of the retrieved word with the picture used as a cue to the target name, generation of additional cues that may prompt retrieval, metacognitive monitoring and engaging strategies that may facilitate retrieval (Koriat & Nussinson, 2014; Schwartz & Metcalfe, 2014). Indeed, previous findings on the critical role of the left temporopolar area emphasize the semantic aspect of name retrieval (Abel et al., 2015; Damasio et al., 1996; Tsukiura et al., 2002), whereas the findings indicating the role of insula in TOTs relate to its phonological aspect (Shafto et al., 2007, 2009). Other brain areas are expected to contribute to other aspects of TOTs, such as anterior cingulate cortex participating in metacognitive monitoring (Huijbers et al., 2016). The implication of left BA 45, right BA 44 and right BA 40 in TOT states in the present data might indicate generation of additional cues to prompt retrieval, such as attempting to recall a famous person's name based on information on their occupation.

Previous studies on verbal fluency indicate a functional segregation of Broca's area (left BAs 44 and 45), with BA 45 supporting category fluency and BA 44 supporting letter fluency (Katzev, Tuescher, Hennig, Weiller, & Kaller, 2013; Okada et al., 2013; Paulesu et al., 1997). These findings have been interpreted as indicating that BA 45 may contribute to the retrieval of words through their meaning, and BA 44 via an articulatory code (Amunts et al., 2004; Paulesu et al., 1997). Our cortical thickness data are compatible with this view, suggesting that substantial cortical thickness age-differences in left BA 45 and right BA 44 are related to more TOTs in the MA group. This interpretation is based on the assumption that the contribution of right hemisphere regions to language function increases with increased age (Obler et al., 2010).

The role of right BA 40 in the present findings is less clear. The left supramarginal gyrus has been implicated in a range of language-related functions, including syntax. While the syntactic theory of proper names developed by Longobardi (2005) nicely explains deficits in proper name retrieval at the sentence level (see Semenza, 2009 for a review), it is not clear how to extend its applicability to contexts not involving sentences, without resorting to, for instance, propositional inner speech. On the other hand, the role of SMG in executive processes during proper name retrieval would better explain its association with TOTs. For instance, SMG was found to support resolving ambiguity in the mapping between sensory inputs and motor outputs in word processing (Oberhuber et al., 2016).

That naming with proper names cannot be confined to a single region and requires a larger network of areas instead (Miceli et al., 2000; Semenza, 2006; Semenza, 2011) is also supported by findings on the role of white matter tracts in this cognitive function. Susceptibility of the prefrontal white matter to aging may lead to disconnections within

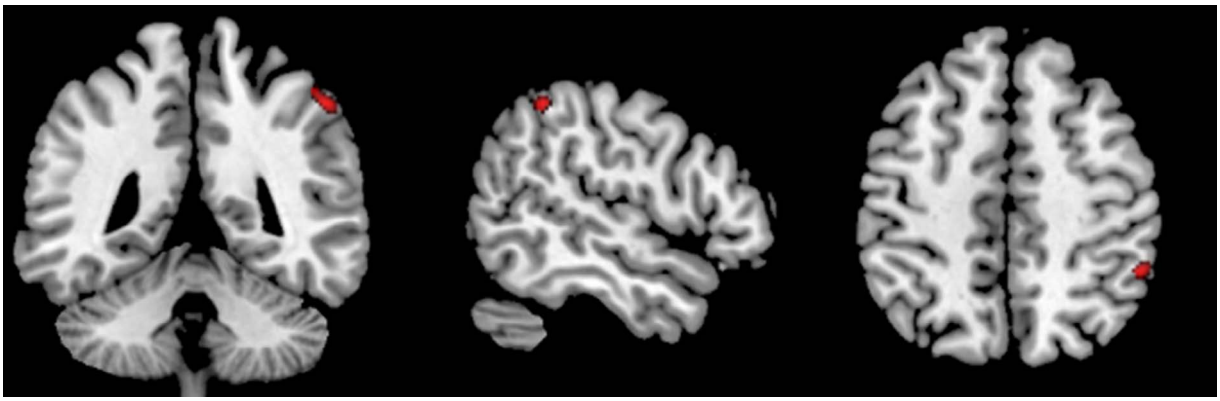

Fig. 3. Clusters showing significant ($p < .05$ FWE) effect for age accounting for TOT and regressing out TIV and gender.

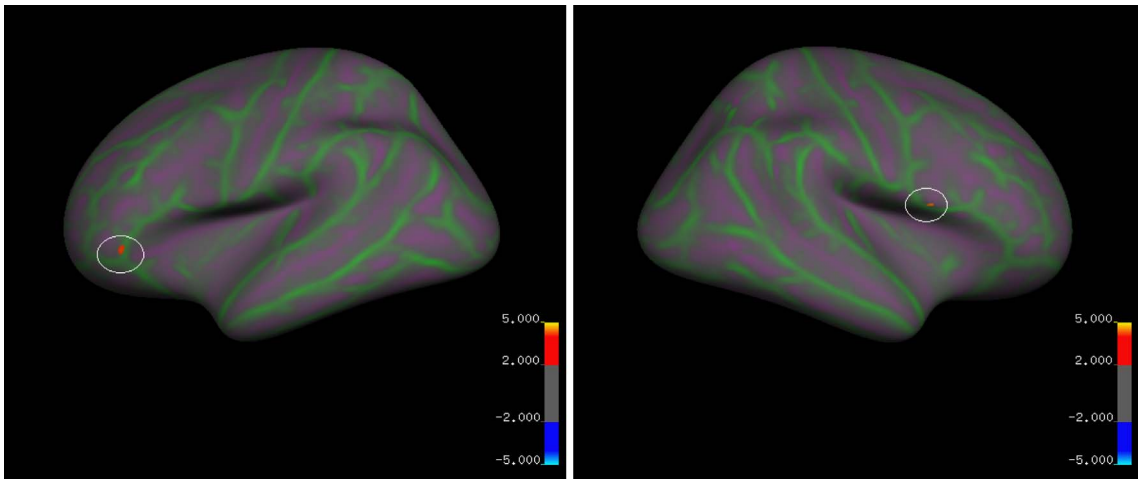

Fig. 4. Results of cortical thickness analyses showing small, significant ($p < .05$ FDR) clusters (circled) for the effect of age accounting for TOT and regressing out gender: left pars triangularis (BA 45) (left panel), and right pars opercularis (BA44) (right panel).

the networks supporting speed of processing, episodic memory, and executive functions (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2010). Since slowing in processing speed is key feature of cognitive aging, it seems plausible that this general slow-down in processing may occasionally affect proper name retrieval in healthy people, preventing timely binding of multiple processes or representations and leading to TOT states. Looking specifically at the anatomical connectivity supporting language, we find that changes in white matter microstructure integrity of the uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF) have been associated with retrieval of names of unique and non-unique entities respectively (Mehta et al., 2016). Both fasciculi support the ventral stream for language, where UF connects the anterior temporal lobe and orbito-frontal cortex, and ILF connects the occipital lobe with the temporal pole (Kljajevic, 2014). Furthermore, an awake surgery study involving 18 patients who underwent removal of a left hemisphere glioma (either frontal or temporal glioma) reported that the patients with the UF resection were significantly impaired in naming famous faces and objects in comparison with patients without removal of the UF when assessed three months after the surgery (Papagno et al., 2011). The present finding on the involvement of BAs 44, 45 and 40 opens the question of whether the dorsal connectivity within the language network too might play a role in TOT states during proper naming, in particular segment III of the superior longitudinal fasciculus, which links Broca's area with inferior parietal lobe, including BA 40.

Several limitations of the present study should be acknowledged. First, the cross-sectional design precludes making inferences on changes caused by aging. One could object that the pattern of age-related differences observed in the present sample does not have to coincide with the pattern of changes that would have been obtained in a longitudinal study. For different reasons, both cross-sectional and longitudinal approaches to cognitive aging are insufficiently equipped to handle the full complexity of relations within "age-brain-cognition triangle" (Raz & Lindenberger, 2011; Salthouse, 2011). (For instance, an issue in longitudinal studies is practice effects.) Note, however, that the observed pattern of more TOT states, and less GM density and cortical thickness in the MA group relative to YA is consistent with previous findings on neuro-cognitive changes due to Aging (Section 1).

Second, we did not account for some variables that might be relevant for the observed neuro-cognitive differences. For instance, education has a critical role in cognitive reserve, alongside other factors such as socio-economic status (Sperling, Mormino, & Johnson, 2014) or bilingualism (Gold, Johnson, & Powell, 2013), and variation in cognitive reserve has been related to differential vulnerability of cognitive functioning. Vascular risk factors such as hypertension or genetic factors, such as apolipoprotein E 4/4 (ApoE ε4), which have deleterious effect on the aging brain (Raz et al., 2005), may have further contributed to the heterogeneity of the present study sample. Indeed, large individual variation within age groups that appears to increase with increased age has been often considered the main source of doubt whether age itself could be a sufficient explanatory variable of observed changes (Martin et al., 2014; Salthouse, 2010).

Third, the structural integrity differences indicating less density and thickness in the MA group raise the possibility of neuropathology in this group. Previous studies have shown that atrophy is typical of the aging brains, even when they remain free from dementia (Jack et al., 2014; Lindenberger, 2014). Atrophy reflects neuronal injury or neurodegeneration, i.e. a progressive shrinkage and loss of neurons that impairs neuronal function (Jack et al., 2012, 2016). Since we do not have *in vivo* evidence indicating absence of Alzheimer's pathology in the present sample, we cannot rule out the possibility that some of our MA subjects harboured Alzheimer's pathology, although middle-age as defined in the present study (45–55 years of age) does not represent a high-risk factor for age-related neurodegenerative diseases such as Alzheimer's disease (AD) (Jack et al., 2014). Regardless, even in cognitively intact persons with positive AD-biomarkers, such as increased cortical amyloid load (Dubois et al., 2007, 2010, 2014; Jack et al., 2010; Sperling et al., 2011), atrophic changes are less pronounced than for example regional hypometabolism (Kljajevic, Grothe, Ewers, & Teipel, 2014), and increased amyloid load – not atrophy – was found to be associated with word retrieval deficits in such subjects (Papp et al., 2015). The mechanisms underlying cognitive decline in a typically aging brain (Bülow & Söderqvist, 2014; Harrison, Weintraub, Mesulam, & Rogalski, 2012; Rowe & Kahn, 1987) differ from those leading to AD (Fjell et al., 2010; Morrison & Hof, 1997) and the present study rests on the assumption that it involved a typical rather than a pathological sample.

Finally, the ROIs in our study were selected based on previous neuroimaging findings and defined by using WFU PickAtlas (volumetric) and Desikan-Killiany atlas (cortical thickness) (Section 2.4). Still, anatomical boundaries of a specific ROI do not necessarily confine a function and aging processes affecting GM density and cortical thickness do not necessarily follow anatomical boundaries of a region. Without using the exact same clusters that were described in these previous studies and relying on an atlas instead, the definition of ROIs is bound to a degree of approximation.

In conclusion, our data suggests that the ability to retrieve names is worse in middle-aged cognitively healthy subjects than in cognitively healthy young people. Consistent with previous findings, we found less GM density and cortical thickness in middle-aged relative to young subjects in a range of areas. However, we found no evidence suggesting significant correlations between the higher TOT scores in the MA group

and GM volumes or cortical thickness in the left ATL, STG, MTG, and insula, which have been found to support retrieval of proper names. Instead, we observed associations between left BA 45, right BA 44, right BA 40, and TOT states, which implicate a wider network of areas in TOTs during proper naming.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandc.2017.11.003.

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