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Structural brain differences between monolingual and multilingual patients with mild cognitive impairment and Alzheimer disease: Evidence for cognitive reserve

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ABSTRACT

Two independent lines of research provide evidence that speaking more than one language may 1) contribute to increased grey matter in healthy younger and older adults and 2) delay cognitive symptoms in mild cognitive impairment (MCI) or Alzheimer disease (AD). We examined cortical thickness and tissue density in monolingual and multilingual MCI and AD patients matched (within Diagnosis Groups) on demographic and cognitive variables. In medial temporal disease-related (DR) areas, we found higher tissue density in multilingual MCIs versus monolingual MCIs, but similar or lower tissue density in multilingual AD versus monolingual AD, a pattern consistent with cognitive reserve in AD. In areas related to language and cognitive control (LCC), both multilingual MCI and AD patients had thicker cortex than the monolinguals. Results were largely replicated in our native-born Canadian MCI participants, ruling out immigration as a potential confound. Finally, multilingual patients showed a correlation between cortical thickness in LCC regions and performance on episodic memory tasks. Given that multilinguals and monolinguals were matched on memory functioning, this suggests that increased gray matter in these regions may provide support to memory functioning. Our results suggest that being multilingual may contribute to increased gray matter in LCC areas and may also delay the cognitive effects of disease-related atrophy.

1. Introduction

Two independent lines of research provide evidence for bilingualism's potential impact on brain structure. Firstly, research with healthy younger and older adults indicates that speaking more than one language is associated with increase gray matter volume or thickness in language and cognitive control (LCC) areas (e.g., Klein et al., 2014). Secondly, research with patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) suggests that bilingualism may contribute to cognitive reserve, similar to other enriching lifestyle factors, as evidenced by differences in age of symptom onset (Alladi et al., 2013; Bialystok et al., 2014), and medial temporal lobe atrophy (Schweizer et al., 2012). Further, it has recently been proposed that the increased gray matter seen in older bilinguals may be one of a number of variables contributing to cognitive reserve seen in bilingual dementia patients (Gold, 2016).

However, the predictions made by these two independent lines of evidence have not been concurrently evaluated in the same participants. The current study seeks to examine the above proposal by comparing cortical thickness and tissue density in LCC brain areas and areas known to atrophy in MCI and AD (referred to here as disease-related [DR] areas), in a sample of monolingual and multilingual MCI and AD patients, matched (within Diagnosis Group) on cognitive functioning. We will next briefly review the findings from each of these lines of evidence. Although bilingualism is commonly defined as speaking more than one language (with most studies reporting

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participants who speak two languages), we use the term multilingualism when referring to our sample, as approximately half of our multilingual patients speak more than two languages.

1.1. Behavioral effects

Research over the last decade suggests that speaking more than one language may provide cognitive benefits, specifically in executive functions involving cognitive control (for a review see Dong and Li, 2015). Studies have shown that, compared to monolinguals, bilingual participants are less affected by irrelevant or competing stimuli (e.g., Bialystok and Martin, 2004; Bialystok et al., 2008), are better able to switch between two tasks (Garbin et al., 2010; Prior and Gollan, 2011) and are better able to inhibit pre-potent responses (Costa et al., 2009; Luk et al., 2011b). Further, this language-group difference tends to become more pronounced in old age, such that the disparity in performance between monolinguals and bilinguals is larger in older adults than in younger adults (Bialystok et al., 2004). Although the extent of a bilingual advantage in cognition has been the topic of much debate (e.g., Hilchey and Klein, 2011; Paap et al., 2015), its discussion is beyond the scope of this paper. Instead, we aim to contribute to the literature examining whether bilingualism relates to gray matter differences, and whether these structural brain differences may be linked to cognitive reserve.

1.2. Morphological effects

Studies that have demonstrated neuroplastic changes related to speaking more than one language have largely focused on healthy younger adults and, less commonly, on older adults. Researchers have found language group differences in grey matter in a number of brain areas related to executive functioning, language, and the control of language (here referred to as LCC), with increased brain matter for bilinguals compared to monolinguals. For younger adults these regions include the left inferior frontal gyrus (Klein et al., 2014), the left Heschl's gyrus (Ressel et al., 2012), the left putamen (Abutalebi et al., 2013), the right and left supramarginal gyri (Grogan et al., 2012), and the left and right cerebellum (Pliatsikas et al., 2014). For older adults, these brain areas include the left anterior inferior temporal gyrus (Abutalebi et al., 2014), the left and right inferior parietal lobe (Abutalebi et al., 2015a), and the left and right anterior cingulate cortex (Abutalebi et al., 2015b). The variability across studies in the brain areas implicated is hypothesized to be due to differences in analysis methods and sample selection (for comprehensive reviews see García-Pentón et al., 2015; Li et al., 2014). Other studies have failed to find language group differences in older participants using whole-brain VBM analyses (Gold et al., 2013a, 2013b) or in ROI analyses of the DR areas like the hippocampus, entorhinal cortex, or temporal pole (Olsen et al., 2015). Thus, there is accruing but variable evidence that, in healthy adults, being bilingual leads to greater tissue density and thicker cortex when compared to monolinguals.

1.3. MCI and AD

Because multilingualism can be viewed as a factor promoting neuroplasticity (Baum and Titone, 2014), the current investigation examines the impact of multilingualism on the brain structure of persons with Alzheimer's disease and those at risk for the disease (MCI).

Briefly, AD typically involves prominent episodic memory impairment, with deficits in at least one other cognitive domain, including executive functioning, visuospatial abilities, language functions, or personality/behaviour changes. These deficits must be of sufficient magnitude to lead to functional impairment. Cerebral atrophy begins in the entorhinal cortex, with evident cortical thinning found in the entorhinal cortex in the early phases of the illness (Román and Pascual, 2012) and progressing throughout the medial temporal lobes in the later stages (Lerch et al., 2005).

MCI is a clinical term used to describe an older adult in whom there is a concern (either by the self or significant other) about mild changes in cognitive function and who performs below expectations on age- and education-corrected objective tests. However, the person is not diagnosed with a dementia because these mild changes in cognition do not result in a functional impairment. MCI can be subdivided based on whether one single or multiple cognitive domains have been affected, and subdivided again based on whether or not the primary impairment is in memory. Therefore, there are four possible subtypes of MCI: (1) single domain amnestic MCI, (2) multiple domain amnestic MCI, (3) single domain non-amnestic MCI, and (4) multiple domain non-amnestic MCI. Research suggests that most MCI patients who go on to develop AD show an impairment in episodic memory (i.e., single or multiple domain amnestic MCI; Albert et al., 2011). Although significant neuronal loss is noted in the entorhinal cortex and hippocampus in MCI, many MCI patients do not show significant neuropathological changes (Mufson et al., 2012; Stephan et al., 2012). Notably, in comparison to MCI patients who remain stable over 7 years, MCI patients who convert to AD show greater cortical thinning at baseline in the superior and middle frontal gyri, superior, middle, and inferior temporal gyri, the fusiform gyrus, and parahippocampal regions (Julkunen et al., 2009).

1.4. Cognitive reserve

Much of the research comparing monolingual and bilingual dementia patients is rooted in the cognitive reserve perspective. The cognitive reserve hypothesis was originally proposed to explain non-systematic differences in the association between the degree of brain damage and functional outcome (Stern, 2002). The theory posits that participation in cognitively stimulating life experiences contributes to cognitive reserve (Sattler et al., 2012; Verghese et al., 2006; Wilson and Bennett, 2003; Wilson et al., 2013), which affords an individual more flexible and/or efficient cognitive processing. This in turn allows an individual with some kind of brain insult to function at a level higher than would be predicted based on his/her level of neuropathology. In general, past studies exploring bilingualism and cognitive reserve tend to compare variables such as age of symptom onset and/or age of clinical diagnosis between monolinguals and bilinguals; structural brain measures have typically not been included. Although the findings are mixed, there is some evidence to support a delay in the symptoms or diagnosis of dementia for bilinguals as compared to monolinguals (for a review see, Guzmán-Vélez and Tranel, 2015). Recent research has also found a delay in symptom onset and diagnosis for bilingual patients with MCI compared to matched monolinguals (Bialystok et al., 2014; Ossher et al., 2013). Only one study to date has matched monolingual and bilingual AD patients on cognitive performance and then measured differences in neuropathology. Schweizer et al. (2012) found that bilinguals showed greater atrophy in DR brain areas (i.e., showed less brain matter) than monolinguals when measuring the radial width of the temporal horn and temporal horn ratio from CT scans, despite being matched on age, education, and cognitive performance.

In summary, these two families of findings may appear contradictory insofar as research with healthy younger and older adults suggest that bilinguals have *thicker* cortex/higher tissue density compared to monolinguals, while the cognitive reserve research hypothesizes that cognitively compromised bilinguals would have *less* brain matter than their monolingual peers. The critical difference between these literatures is the brain regions of interest. In the healthy adult literature, bilingualism is conceptualized as an enriching exercise that contributes to neuroplasticity. As such these studies have directly measured brain areas thought to be affected by bilingualism (i.e., LCC areas). In comparison, within the cognitive reserve literature, bilingualism is viewed as a contributor to cognitive reserve, which is indirectly measured by quantifying the discrepancy between disease progression (or brain

Table 1
Group means, standard errors, F-values, and *p*-values for demographic and neuropsychological variables.

	MCI						AD					
	Mono (n = 34)		Multi (n = 34)				Mono (n = 13)		Multi (n = 13)			
	M	SE	M	SE	F	*p*	M	SE	M	SE	F	*p*
Age at scan	73.6	0.9	73.7	1.0	0.01	*0.95*	78.5	1.5	78.0	1.5	0.06	*0.81*
MMSE at scan	26.7	0.4	27.6	0.3	2.16	*0.15*	22.5	0.9	22.5	1.0	0.00	*1.00*
Scan to assessment (days)	−18.5	12.3	10.7	25.4	0.36	*0.55*	160.1	104.7	90.3	83.1	0.77	*0.38*
Education (years)	12.5	0.7	12.3	0.7	0.05	*0.83*	12.7	1.0	12.1	1.1	0.17	*0.68*
Age at symptom onset[a]	68	1.1	67.8	1.3	0.02	*0.90*	74.3	1.5	72.6	1.6	0.44	*0.51*
Age at diagnosis[a]	71.5	0.9	72.2	1.0	0.28	*0.60*	77.1	1.6	76.7	1.3	0.04	*0.84*
	N	%	N	%			N	%	N	%		
Women	17	50	15	41			8	62	3	23		
Immigrant	7	21	20	59			2	15	7	54		
Bilingual	–	–	18	53			–	–	9	69		
Short delay verbal recall (%)	52.1	2.7	48.5	2.6	1.0	*0.32*	33.8	3.4	32.5	3.0	0.1	*0.82*
Long delay verbal recall (%)	25.5	3.1	22.7	3.5	0.5	*0.49*	6.0	1.7	5.3	2.3	< 0.1	*0.92*
Immediate recall visual reproduction	56.1	3.1	54.1	2.9	0.2	*0.64*	30.0	4.5	30.9	6.9	< 0.1	*0.91*
Delayed recall visual reproduction	21.8	3.4	22.9	3.3	0.1	*0.80*	5.1	2.5	8.1	3.5	0.1	*0.71*
Stroop Color Words (s)	38.7	2.2	36.3	2.0	0.2	*0.63*	65.0	13.7	64.3	7.5	< 0.1	*0.94*
Stroop Interference (s)	2.3	0.2	2.1	0.1	0.4	*0.51*	3.2	0.9	2.5	0.3	1.5	*0.23*
Spatial span total (/)	11.6	0.5	10.1	0.4	4.7	*0.03*	8.8	0.7	9.2	1.3	0.1	*0.72*
Block design (/68)	27.0	1.8	25.8	1.3	0.3	*0.61*	18.8	1.8	20.7	3.1	0.3	*0.60*
Trail A (s)	52.0	3.4	48.0	2.9	3.3	*0.57*	83.2	11.7	86.3	14.0	0.1	*0.78*
Orientation (%)	93.5	1.8	94.7	1.5	2.0	*0.66*	81.2	3.5	78.9	3.3	3.2	*0.57*
Clock (/10)	8.3	0.3	7.8	0.3	1.7	*0.20*	6.77	0.48	6.3	0.6	0.5	*0.50*

[a] Age of symptom onset information was assessed via family interviews in which an estimate of the year and month of onset of memory complaints was determined by the question, "Can you give the month and year when you first noticed memory problems (in the patient)?".

atrophy) and cognitive functioning. As such, the brain regions implicated are those medial temporal structures affected by MCI and AD (i.e., DR areas).

We further propose that the increased gray matter previously found in LCC areas may represent, or be related to, the neural mechanism supporting bilingualism's contribution to cognitive reserve. In other words, a bilingual's ability to maintain memory functioning in the face of disease-relevant neuropathology could be *dependent* on increased grey matter in brain areas related to bilingualism. In a review of bilingualism's contribution to cognitive reserve, Gold (2016) makes a similar proposal, that bilinguals may experience a delay in dementia symptoms because they are able to compensate by relying more on enhanced executive control abilities. If this were the case, one might expect a correlation between grey matter in LCC brain areas and DR cognitive performance (i.e., episodic memory). As such, enriching lifestyle factors like bilingualism could contribute to both functional reorganization and structural changes in the brain. We will address this question in the current study.

1.5. Immigration

Concerning one final issue, the immigration status of research participants has a potentially important mediating or moderating effect on bilingualism's relationship with cognitive functioning (Bak and Alladi, 2014; Chertkow et al., 2010; Perani and Abutalebi, 2015; Schweizer et al., 2013). Being bilingual is often, although not always, associated with being an immigrant and, depending on one's geographical location, it can be difficult to find sizable research samples of either immigrant monolinguals or non-immigrant bilinguals. As such, many studies have either collapsed native-born and immigrant bilinguals together or have compared mostly immigrant bilinguals to mostly native-born monolinguals. Immigration is related to a number of health and cognitive outcomes (e.g., Fuller-Thomson et al., 2013) and may be associated with other cognitive reserve variables like occupation and leisure activity (Mondini et al., 2014). Thus, this is a crucial variable that we consider.

1.6. Summary

Taken together, there is a growing body of research from healthy adults, MCI patients, and AD patients that examines the effects of bilingualism on brain structure. The current research aims to bridge the gaps between these group-specific findings in several important ways:

1) Evidence exists that bilingualism results in thicker cortex in LCC brain areas. The current study will extend this research by examining whether the differences seen in healthy younger and older adults will be present in multilingual MCI and AD patients.
2) Only one study has examined neuroanatomical differences between monolingual and bilingual AD patients (Schweizer et al., 2012) and no work has been done in MCI patients. We aim to extend these findings by matching multilingual and monolingual MCI and AD patients on measures of DR cognitive performance (episodic memory) and examining structural DR brain differences among these four sub-groups. In our study, the DR brain areas examined were areas within the hippocampus, parahippocampal gyrus, and the rhinal sulcus.
3) We will examine whether LCC brain regions help to support or contribute to the hypothesized cognitive reserve in multilinguals. To examine this question, we will test whether there is a relationship between the LCC brain areas and measures of episodic memory.
4) Given the potential confound of immigration on the effects of bilingualism, we will replicate our analyses in a sub-group of non-immigrant monolingual and multilingual MCI patients, permitting us to determine whether the effect of immigration has a significant influence on the whole-group findings.

2. Materials and methods

2.1. Participants

Subjects were recruited through use of a database maintained by the Memory Clinic of the Jewish General Hospital in Montréal, Canada, a tertiary care referral clinic. Patients consented to the use of their MRI data for research purposes, in accordance with the requirements of the Research Ethics Board of the Jewish General Hospital. The current sample was restricted to individuals who had MRI scans conducted no earlier than the beginning November 2002, as significant upgrades were made to the scanner earlier that year. Table 1 provides information for demographic and neuropsychological variables for each group.

2.1.1. Diagnosis groups

Patients in the current study were diagnosed with MCI or AD. MCI subjects included in this study were clinically classified as “amnestic” or “amnestic plus” MCI, since memory was the major complaint, memory impairment was the main objective finding, and other cognitive domains were largely preserved on clinical evaluation. MCI diagnosis was carried out by trained neurologists or geriatricians using standardized criteria (as reviewed in Gauthier et al., 2006; and adapted from Petersen et al., 2001). AD was diagnosed by a neurologist or geriatrician in consultation with other Memory Clinic physicians, nurses, and neuropsychologists, using National Institute of Neurological and Communicative Disorders and Stroke- the Alzheimer’s disease and Related Disorders Association criteria (McKhann et al., 1984).

We excluded patients who identified as left-handed and those where there was evidence to believe that their cognitive function reverted to “normal” at some point following their initial MCI diagnosis. For a number of patients, an initial scan at the time of diagnosis was conducted prior to 2002 (and therefore on a different MRI machine); as such, the second scan was used for 24 MCI and 5 AD patients, and the third scan for 2 MCI patients. The finalized database analysed here consists of 94 patients, 68 with MCI and 26 with AD.

2.1.2. Language groups

Our sample had 34 monolingual MCI patients, 34 multilingual MCI patients, 13 monolingual AD patients, and 13 multilingual AD patients. Multilingualism was defined according to the criterion set out by Bialystok and colleagues (Bialystok et al., 2007) for bilingualism, namely that the majority of the participant’s life was spent regularly using at least two languages, and was based upon chart information derived from a neuropsychological interview. Details regarding age of acquisition and proficiency was not reliably available in all patients. Monolingual participants spoke only one language, and multilingual participants were defined as speaking two or more languages. Monolingual patients were either English or French speakers. Within the multilingual group, just over half were bilingual, with the majority being English/French or French/English bilinguals. Similarly, for those who spoke three or more languages, all but one spoke English, French, and one of a variety of other languages (e.g., Yiddish, Hebrew, Greek, Arabic, etc.).

Immigration was determined by the place of birth for each participant; however, age at of immigration to Canada was unknown. Numbers in the non-immigrant AD group were too small to achieve statistical power; therefore, data from only non-immigrant MCI patients were analysed (27 monolinguals and 14 multilinguals).

2.1.3. Matching variables

We matched each language group (monolingual or multilingual) within each Diagnosis Group (MCI or AD) on a number of measures of clinical severity and cognitive functioning: years of education, age at time of scan, time from neuropsychological assessment to scan, Mini Mental Status Examination (MMSE) score, and two tests of episodic memory (all $p > 0.15$). Episodic memory tests included: percentage of words recalled (short delay and long delay verbal recall score) from either the California Verbal Learning Test - Second edition (CVLT-II; Delis et al., 2000) or the Rey Auditory Verbal Learning Test (RAVLT; Spreen and Strauss, 1998), and raw immediate and delayed recall score from the Wechsler Memory Scale - III Visual Reproduction subtest (WMS III; Wechsler, 1997b). Note that over the course of time, the clinical assessment protocol changed such that some participants were assessed with the RAVLT (maximum possible total score = 15) and later participants were tested with the CVLT-II (maximum possible total score = 16). Thus, in order to combine data across participants, verbal recall performance is expressed as a percentage of the total possible score.

2.2. Cognitive functioning

Additional data from the neuropsychological assessments were analysed to examine whether the language groups differ from each other in other cognitive domains. Scores were derived from standardized neuropsychological tests administered during a clinical assessment session. The six measures included: The Victoria Stroop Task (Spreen and Strauss, 1998), the Spatial Span subtest from the WMS III; Block Design from the Wechsler Adult Intelligence Scale third edition (WAIS III; Wechsler, 1997a); Trails A (Reitan, 1958), orientation, and clock design (Rouleau et al., 1992).

2.3. MRI acquisition and pre-processing

High-resolution (1-mm isotropic) T1-weighted sagittal images were acquired on a Siemens SonataVision 1.5 T scanner (TR = 22, TE = 9.2) at the Montreal Neurological Institute (MNI), Brain Imaging Center. Structural images were submitted to the Civet pipeline (version 1.1.11; http://wiki.bic.mni.mcgill.ca/index.php/Civet) developed at the MNI for fully automated structural image analysis (Ad-Dab'bagh et al., 2006), whose steps are detailed elsewhere (Karama et al., 2009). All pipeline products (surfaces and volumes) were manually validated by the second author (J.N.), prior to morphometrical analysis consisting of both cortical thickness analysis (CTA) and voxel-based morphometry (VBM). Thickness values, generated by the pipeline, while measured in native space (mm), had their coordinates transformed into a standardized space (MNI ICBM), thus providing a common space for group-level analyses, and comparison with the literature. Prior to the analyses, thickness values were subjected to a 20-mm surface blur in order to increase the signal-to-noise ratio. For the VBM analyses, grey matter volumes derived from the Civet tissue classification stage were convolved with an 8-mm full-width at half-maximum (FWHM) 3D Gaussian blurring kernel, prior to being entered into the regression analyses. The focus of the VBM analysis was primarily on gray matter changes within medial structures, such as the hippocampus, since examination of cortical-level changes, while also seen within the VBM results, are best performed with the more sensitive CTA. As such, the VBM analysis should be seen as both extending and complementing the CTA.

2.4. Definition and sampling of a priori brain regions

Two families of hypothesis-driven, and anatomically-constrained, regions of interest (ROIs) were selected based on: 1) areas implicated in language and cognitive control (LCC regions) and 2) areas known to atrophy in MCI and AD (DR regions). Within each ROI, the specific vertex or voxel analysed was chosen based on either the specific coordinates given in relevant publications or, when not available, the general functional or anatomical brain region reported in the literature (e.g., BA45, or left inferior frontal gyrus), and was then refined by the results of our exploratory regression analyses. This process allowed us to account for individual variability in the location of functional substrates, subtle differences in coordinate systems, and differences that could have been introduced by image pre-processing and template registration. As such, we were able to analyze the vertex or voxel with the strongest effect in our data, while remaining within a given ROI as guided by our *a priori* hypotheses and the literature. For example, Abutalebi et al. (2014) found decreased grey matter volume (using VBM) in the left anterior temporal lobe at xyz = [−45, −4, −36] (MNI-space) in healthy older adults, whereas we sampled the left anterior temporal lobe at xyz = [−51, −10, −40], as this location,

Table 2
LCC ROI world coordinates and Brodmann area numbers for both the current study and from supporting research.

	Current study				Prior research			
Anatomical location	Hemisphere		Coordinates	BA	Hemisphere	Coordinates	BA	References
1) Inferior frontal gyrus								
(a)	L_iFG	L	−49, 27, 20	45	L	−25, 25, 20	47	(Klein et al., 2014)
(b)	R_iFG	R	55, 30, 0	45	R	30, 20, −9	13	(Klein et al., 2014)
2) Anterior temporal gyrus								
(a)	L_aTG	L	−51, −10, −40	20	L	−45, −4, −36	21/20	(Abutalebi et al., 2014)
(b)	R_aTG	R	55, 5, −31	21	R	–	–	(Abutalebi et al., 2014)
3) Medial superior frontal gyrus (ACC)								
(a)	L_mSFG	L	−6, 31, 41	8	L	–	–	(Abutalebi et al., 2015b)
					R	5, 38, −8	24	(Abutalebi et al., 2015b)
4) Inferior parietal lobule								
(a)	L_iPL	L	−39, −69, 47	39	L	−45, −59, 48	40/39	(Mechelli et al., 2004)
					R	56, −53, 42	40/39	(Mechelli et al., 2004)
					L	−48, −59, 47	40/39	(Abutalebi et al., 2015a)
					R	56, −53, 42	40/39	(Abutalebi et al., 2015a)
5) Supramarginal gyrus								
(a)	L_SMG	L	−59, −26, 35	40	L	−50, −50, 46	40/39	(Grogan et al., 2012)
(b)	R_SMG	R	62, −37, 40	40	R	44, −54, 52	40/39	(Grogan et al., 2012)
6) Cerebellum								
		L	−39, −59, −29		L	−22, −92, −30		(Pliatsikas et al., 2014)
		R	41, −55, −31		R	26, −86, −46		(Pliatsikas et al., 2014)
		R	7, −49, −49		R	18, −44, −20		(Pliatsikas et al., 2014)
7) Ventromedial prefrontal cortex								
(a)	R_vmPFC	R	3, 44, −15	11/32	L	–	–	(Abutalebi et al., 2014)
					R	–	–	(Abutalebi et al., 2014)
8) Putamen								
					L	–	–	(Abutalebi et al., 2013)
9) Heschl's gyrus								
					L	−52, −13, 5	22/41	(Ressel et al., 2012)
					R	–	–	(Ressel et al., 2012)

Notes: Abbreviations: BA = Brodmann's area; L = left; R = right; aTG = anterior temporal gyrus; Cer = cerebellum; cerTon = cerebellar tonsil; iFG = inferior frontal gyrus; iPL = inferior parietal lobule; mSFG = medial superiorfrontal gyrus; SMG = supramarginal gyrus; vmPFC = ventromedial prefrontalcortex; – = information not provided in study. When not included in study, BA determined using Mango version 3.17 (http://rii.uthscsa.edu/mango/) and mni2tal (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html).

while still in close spatial proximity to that of Abutalebi et al., showed the largest effect in our exploratory regression analysis in our patient samples. ROIs that did not contain significant vertices/voxels in the global regression analysis were not further analysed. As our choice of ROIs for the LCC regions was motivated by a relatively small pool of empirical findings in younger and or bilingual participants, we provide our sampling coordinates in Table 2 to facilitate comparison with that literature.

2.5. Statistical analyses

Demographic and neuropsychological variables were assessed with ANOVAs and planned comparisons were conducted to examine the effects of language group within each Diagnosis Group. With regard to the imaging data, statistical analyses were carried out in a similar manner for both the cortical thickness and VBM data, with the dependent variable (DV) being native-space, vertex-level cortical thickness (measured in millimeters, CTA), or voxel-level, grey matter tissue density (VBM). For the exploratory analyses, two regression equations were run over all vertices and voxels: one to examine the effects of Language and Diagnosis Group, and another to test for a significant interaction between these two variables. In both cases, age (at time of scan), Language Group (monolingual or multilingual), and Diagnosis Group (MCI or AD) were covariates in the regression analyses. These statistical analyses were performed using specialized software packages (Lerch, 2010, 2011), running under the R statistical analysis software (www.R-project.org; R Core Team, 2013). Results of these exploratory regressions were used to identify a set of xyz coordinates, closely matching the *a priori* defined ROIs motivated by the literature. These coordinates were subsequently used to sample thickness and tissue density values for use in further analyses.

Identification of additional regions (i.e., those not included in the list of *a priori* ROIs), was subsequently carried out by inspection of significant focal effects identified in the exploratory regressions, following application of a false-discovery rate (FDR) threshold of $q = 0.05$, thus correcting for multiple comparisons across all vertices/voxels over which the regressions were run. Significant effects of spatial extent were also investigated via a cluster analysis (see Section 3.2), using a cluster defining threshold of $p = 0.001$, as suggested by Eklund et al. (2016).

3. Results

3.1. Cognitive functioning

See Table 1 for means and standard errors of neuropsychological variables, and F- and *p*-values from planned comparisons of language groups within each Diagnosis Group. There was a main effect of Diagnosis Group (all $p < .001$) for all neuropsychological variables, with MCI patients outperforming AD patients. No main effect of Language Group was found for any other neuropsychological variables, (all $p > 0.207$).

3.2. Imaging – exploratory analyses

Application of the additive regression equation over all vertices yielded significant findings for both the Age and Diagnosis effects. The effect of Age (not shown, as they are not central to this investigation) was broadly, and bilaterally distributed over association cortex, including regions within anterior temporal, parietal, and prefrontal areas, medial SFG and entorhinal cortex, reflected the expected pattern of increased thinning associated with age. This spatial pattern was

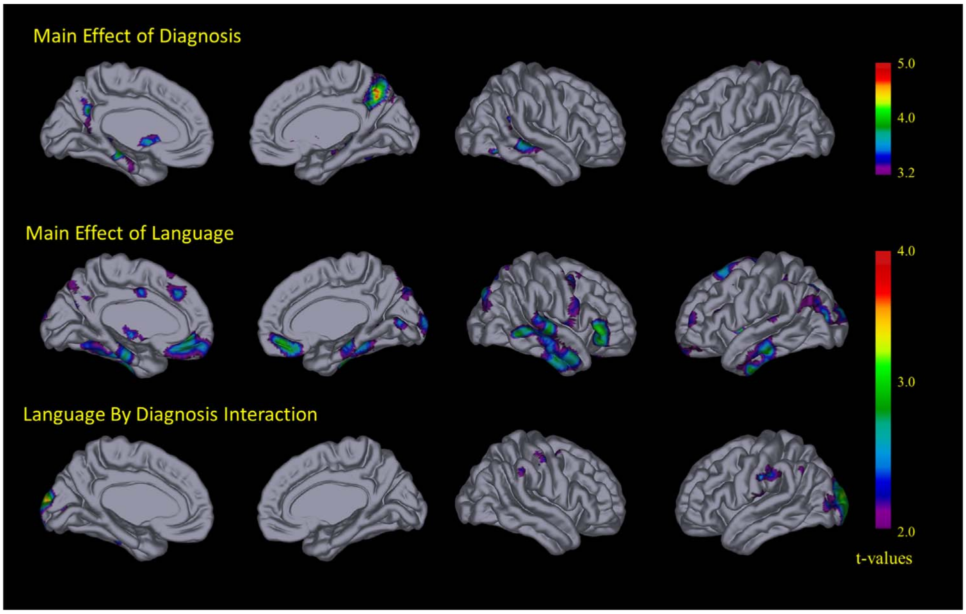

Fig. 1. (Top row) T-statistics resulting from the regression of cortical thickness onto the Diagnosis condition (MCI versus AD) superimposed onto an averaged, elderly cortical surface. T-statistics, ranging between 3.2 and 5.0, represent significant vertices following and FDR correction for multiple comparison at q = 0.05. Hotter colors indicate areas of significant cortical thinning in the AD participants. (Middle row) T-statistics resulting from the regression of cortical thickness onto the Language condition (monolingual versus multilingual) superimposed onto an averaged, normal elderly cortical surface. T-statistics are thresholded at t = 1.96, reflecting a p-value of p = 0.05 (uncorrected for multiple comparisons). Hotter colors reflect areas in which multilinguals demonstrate thicker cortex than monolinguals. (Bottom row) T-statistics indicating a significant interaction between the Language and Diagnosis variables, superimposed onto an averaged, normal elderly cortical surface. T-statistics are thresholded at t = 1.96, reflecting a p-value of p = 0.05 (uncorrected for multiple comparisons). Hotter colors reflect areas in which cortex was found to be thicker for multilinguals under the MCI condition relate to the AD condition.

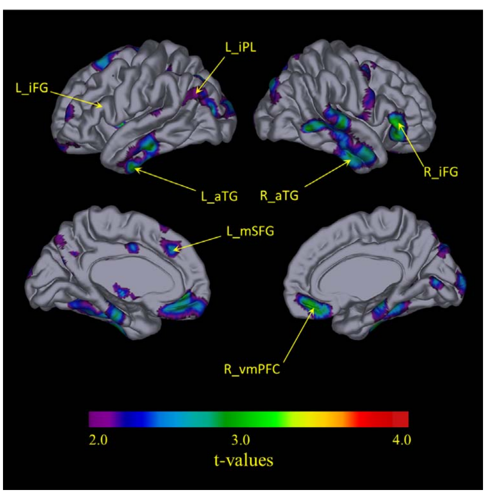

Fig. 2. T-statistics resulting from the regression of cortical thickness onto the Language condition (monolingual versus multilingual) superimposed onto an averaged, normal elderly cortical surface. See Table 1 for details regarding the highlighted peaks.

similarly reflected in the cluster analysis results. The effect of Diagnosis, as seen in both the vertex-level regressions and the cluster analysis (see top row, Fig. 1) was primarily limited to the right precuneus, and posterior MTG, and the left parahippocampal gyrus. Neither the additive model's Language effect, nor the interactive model's Language by Diagnosis interaction was found to yield any significant vertices, following FDR correction for multiple comparisons. Fig. 1 (middle row) and Fig. 2 shows the uncorrected t-values for the Language main effect, whereas Fig. 1 (bottom row) shows the uncorrected t-values for the interaction effects. These results are used for sampling point selection.

3.3. Imaging – group comparison analyses

These results, highlighting structural differences between Language and Diagnostic groups, were computed on values extracted from sampling-points from within *a priori*-defined LCC and DR regions, and refined by the exploratory analyses. See Tables 3a and 3b for t- and *p*-values from the regression analyses, separated by ROI family.[1] In order to control for Type I error, a family-wise error rate was set for each of the two families of regions, dividing the nominal alpha value (0.05) by the number of brain regions tested. Thus, for the LCC family of analyses involving 12 cortical regions, alpha was 0.05/12 = 0.004, and for the DR family of analyses involving alpha was 0.05/6 = 0.008. Below, we present the results separated by ROI family (LCC, DR), first reporting any main effects of Language Group, followed by Language Group by Diagnosis Group interactions when reliable.

3.3.1. LCC regions

3.3.1.1. Language group effects. As can be seen in Fig. 3a and b and in Table 3a, there was a main effect of language group in all of the LCC brain areas (all $p < 0.026$, uncorrected for multiple comparisons), indicating greater cortical thickness for multilinguals compared to monolinguals. After controlling for Family-wise Type I error, this language group difference remain significant for the right inferior frontal gyrus, right ventromedial prefrontal cortex, right cerebellum, and right cerebellar tonsil. None of the regions showed a reliable effect of Diagnosis Group (all p's > 0.066). The putamen and Heschl's gyrus did not exceed a threshold of $t > 2.00$ in the exploratory regression analyses, and therefore were not further processed.

3.3.1.2. Interaction effects. Fig. 3c shows the mean cortical thickness values for which there was a significant (uncorrected) Language Group by Diagnosis Group interaction at vertices sampled within bilateral supramarginal gyrus (p = 0.014 and p = 0.027, respectively). However, this finding, does not remain significant at $p = 0.05$ after controlling for multiple comparisons.

3.3.2. Disease-related regions

3.3.2.1. Language group effects. As seen in Fig. 4a, greater gray matter tissue density was found within the multilingual group compared to the monolingual group (collapsed across Diagnosis Groups) in both left and right hippocampi (all *ps* < 0.009). Both regions remain significant after correcting for multiple comparisons. These regions also showed a

[1] Additionally, see Table B.1 (in Supplementary Materials) for the precise sampling coordinates in MNI-152 coordinates space, as well as the mean cortical thickness (and standard error) and tissue density for monolingual and multilingual MCI and AD patients.

Table 3a
Language and cognitive control (LCC) regions: Language and diagnosis group main effects and interactions.

	Language effect		Patient effect		Interaction	
	t	*p*	t	*p*	t	*p*
Left inferior frontal gyrus[CT]	2.27	*0.026*	− 0.57	*0.571*		
Right inferior frontal gyrus[CT]	3.26	*0.002*	0.35	*0.729*		
Left medial superior frontal gyrus[CT]	2.67	*0.009*	0.45	*0.651*		
Right ventromedial prefrontal cortex[CT]	3.28	*0.001*	− 1.11	*0.270*		
Left anterior temporal gyrus[CT]	2.98	*0.004*	− 1.74	*0.086*		
Right anterior temporal gyrus [CT]	2.72	*0.008*	− 1.57	*0.120*		
Left inferior parietal lobule [CT]	2.98	*0.004*	− 1.19	*0.239*		
Left cerebellum[VBM]	2.95	*0.004*	− 1.49	*0.140*		
Right cerebellum[VBM]	3.15	*0.002*	− 1.8	*0.075*		
Right cerebellar tonsil[VBM]	4.61	*0.001*	1.64	*0.105*		
Left supramarginal gyrus [CT]	2.70	*0.010*	1.86	*0.066*	− 2.51	*0.014*
Right supramarginal gyrus [CT]	2.69	*0.103*	1.13	*0.263*	− 2.24	*0.027*

CT = Cortical thickness.

Table 3b
Disease-related (DR) brain regions: Language and diagnosis group main effects and interactions.

	Language effect		Patient effect		Interaction	
	t	*p*	t	*p*	t	*p*
Left hippocampus[VBM]	2.70	*0.008*	− 2.65	*0.009*		
Right hippocampus[VBM]	2.69	*0.008*	− 3.44	*0.001*		
Left rhinal sulcus[VBM]	2.21	*0.029*	1.80	*0.075*	− 2.45	*0.016*
Right rhinal sulcus[VBM]	1.12	*0.265*	1.07	*0.289*	− 2.07	*0.041*
Right posterior parahippocampal gyrus[VBM]	1.72	*0.089*	1.30	*0.195*	− 3.13	*0.002*
Left posterior parahippocampal gyrus[VBM]	1.62	*0.110*	1.46	*0.148*	− 2.7	*0.008*

VBM = Voxel-based morphometry.

significant effect of Diagnosis Group, with higher tissue density for MCI than AD patients (all ps from < 0.01).

3.3.2.2. Interaction effects. As seen in Fig. 4b, the left and right parahippocampal gyri and the left and right rhinal sulci show a similar pattern, with the overall trend towards increased tissue density in the multilingual MCIs compared to the monolinguals and the reverse pattern (i.e., lower tissue density in the multilinguals compared to monolinguals) in the AD patients. This was supported by a reliable Language Group by Diagnosis Group interaction for voxels within the left and right parahippocampal gyri ($p = 0.008$ and $p = 0.002$ respectively; maintained following Type I correction), and left and right rhinal sulci ($p = 0.016$ and $p = 0.041$; which did not survive correction for Family-wise Type I error). Planned comparisons indicated that multilingual MCI patients had higher tissue density than monolingual MCI patients in voxels within the right parahippocampal gyrus, while the opposite pattern was found in the AD patients (i.e., lower tissue density for multilinguals compared to monolinguals) in the left and right parahippocampal gyri.

3.3.2.3. MCI conversion. Recall that within a group of MCI patients, some will likely progress to AD, whereas others will not. To explore whether these potential subgroups differed in the pattern of findings, we divided our monolingual and multilingual MCI groups by whether or not the patient has since been diagnosed with AD. The average follow-up period was 8.5 years, with 12 of the non-converted MCI patients having been followed for less than 5 years. A Language Group by Conversion Group ANOVA indicated that amongst the MCI patients who as yet had not converted to AD, multilingual MCIs showed a pattern of thicker cortex and higher tissue density in vertices/voxels within the LCC and DR areas compared to monolingual MCIs. In contrast, there were no Language Group difference among those MCIs who later converted to AD.[2] See Table 4 for group means, standard errors, F-values, and *p*-values for monolingual and multilingual MCI converters and non-converters.

3.3.3. Correlational results

Bivariate correlations were used to examine the relationship between memory variables and cortical thickness of vertices within LCC areas. By necessity, these correlations were conducted within each group separately, as we expected the pattern of results to differ. Table 5 shows the resulting Pearson's *r* and *p* values. For the monolingual MCI patients, there were no correlations between episodic memory recall scores (short delay verbal, long delay verbal, immediate visual, delayed visual) and LCC cortical thickness. In contrast, a number of significant correlations were found for the multilingual MCI patients between the long delay verbal recall score and brain regions, including the left inferior frontal gyrus, left pre-supplementary motor area, left anterior temporal gyrus, and left supramarginal gyrus, and between the delayed visual recall score and the left anterior temporal gyrus and right cerebellum. For the AD patients, we only examined the short delay verbal and immediate visual recall scores, as many patients scored at floor on the long delay measures. For the monolingual AD patients, there was

[2] Note that period over which participants were followed did not differ reliably between non-converter monolinguals and multilinguals. However, we caution that these post-hoc analyses should be replicated.

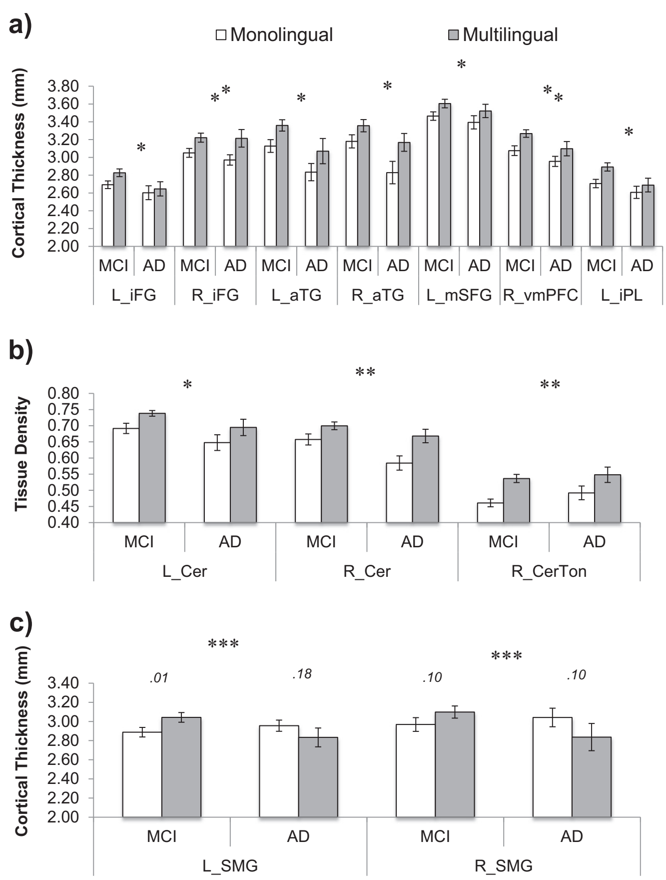

Fig. 3. (a) Cortical thickness (mm) of monolingual and multilingual MCI and AD patients in LCC ROIs. (b) Tissue density of monolingual and multilingual MCI and AD patients in LCC ROIs. (c) Interaction effects between Language and Diagnosis Groups on cortical thickness within LCC ROIs. Italicized numbers are *p*-values from planned comparisons. Error bars = +/- 1 standard error. * = main effect of Language group significant at 0.05, ** = main effect of Language group significant at 0.004 (0.05/12); *** = Interaction effect significant at 0.05; **** = Interaction effect significant at 0.004 (0.05/12). Abbreviations: aTG = anterior temporal gyrus; Cer = cerebellum; cerTon = cerebellar tonsil; iFG = inferior frontal gyrus; iPL = inferior parietal lobule; L = Left; mSFG = medial superior frontal gyrus; R = Right; SMG = supramarginal gyrus; vmPFC = ventromedial prefrontal cortex.

only one significant correlation (immediate visual recall score and the left inferior parietal lobule). In contrast, there were several reliable correlations in the multilingual AD patients, namely between the short delay verbal recall score and the left inferior frontal gyrus, right inferior frontal gyrus, and left supramarginal gyrus. Fig. 5 shows illustrates the scatterplots for the reliable correlations between verbal memory performance and the left inferior frontal gyrus for the multilingual MCI and AD participants (upper right and lower right panels, respectively) compared to the non-reliable correlations for the monolingual MCI and AD participants (upper left and lower left panels, respectively).

3.3.4. *Immigration group analyses*

To examine the potential influence of immigration on the current data, we repeated our regression analyses on a sub-sample of non-immigrant patients. Importantly, the two language groups did not differ on demographic variables, MMSE, age, years of education (all $p > 0.09$) nor in the same set of neuropsychological variables as the larger sample ($p > 0.155$). Vertices and voxels of interest were based on those used in the entire sample, but adjusted to the location of the largest t-statistic within the general functional region within these subgroups. Table 6 shows the demographic information, coordinates, mean cortical thickness/grey matter density, and t and *p* values. With regards to DR brain areas, multilinguals had higher tissue density values in voxels within

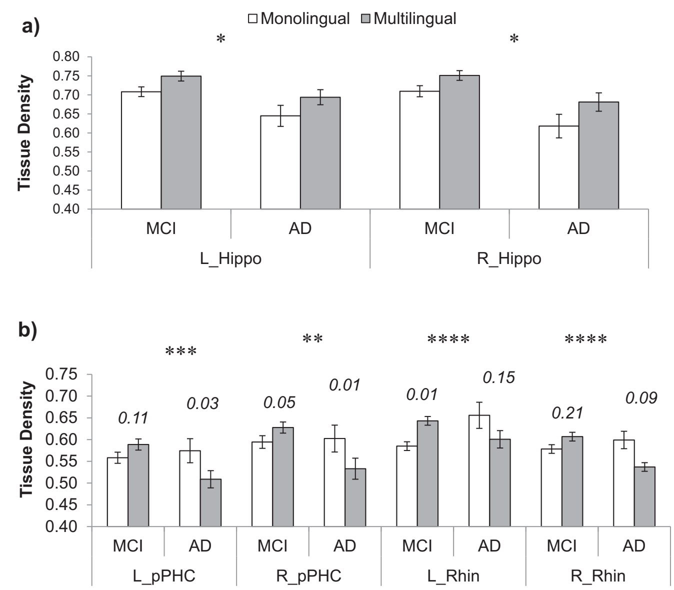

Fig. 4. Tissue density of disease-related brain regions analysed in monolingual and multilingual MCI and AD patients. (a) Tissue density of the hippocampus, which shows a significant Language Group effect. (b) Tissue density of posterior parahippocampal cortex and rhinal cortex, which show a significant interaction between Language Group and Diagnosis Group. Italicized numbers are *p*-values from planned comparisons. Error bars = +/- 1 standard error. * = main effect of Language group significant at 0.05; ** = main effect of Language group significant at 0.008 (0.05/6); *** = Interaction effect significant at 0.05; **** = Interaction effect significant at 0.008 (0.05/6). Abbreviations: Hippo = hippocampus; L = Left; pPHC = posterior parahippocampal cortex; Rhin = rhinal; R = Right.

the left and right entorhinal and perirhinal cortices; however, these were subtle and did not survive correction for multiple comparisons. No differences were found in the voxels of interest within the left or right hippocampi. With regards to LCC areas, these results largely confirmed those found with the whole sample, showing thicker cortex in the multilingual group than in the monolingual group, which includes vertices within the left and right inferior frontal gyri, left and right anterior temporal gyri, left inferior parietal lobule, and the right cerebellar tonsil. Results were more reliable in the right hemisphere than the left. Only the right anterior temporal gyrus, left inferior parietal lobule, and the right cerebellar tonsil survived correction for multiple comparisons. No differences were seen in the anterior cingulate cortex, putamen, or the medial frontal cortex.

4. Discussion

The aim of the present study was to investigate whether a history of speaking more than one language contributes to structural brain differences in MCI and AD patients. Specifically, cortical thickness and grey matter density were measured in monolingual and multilingual groups of MCI and AD patients, who were (within each Diagnosis Group) matched on episodic memory functioning, MMSE, age (at time of scan), and education. We found 1) multilingual MCI and AD patients showed increased brain matter in the form of thicker cortex and higher grey matter density compared to matched monolinguals in LCC brain areas, 2) evidence for the contribution of bilingualism to cognitive reserve in AD patients, but not MCI patients, 3) both AD and MCI multilinguals show positive correlations between episodic memory scores and certain brain regions outside of the medial temporal region, suggesting that multilinguals may have access to a compensatory network that offsets medial temporal lobe changes and helps maintain some degree of memory functioning, and finally, 4) we largely replicated the LCC area results within a group of non-immigrant MCI patients, indicating that the results were not likely due to any potential influence of

Table 4
Group means, standard errors, F-values, and *p*-values for monolingual and multilingual MCI converters and non-converters.

	Non-Converted						Converted					
	Mono (n = 23)		Multi (n = 28)				Mono (n = 11)		Multi (n = 6)			
	M	SE	M	SE	F	*p*	M	SE	M	SE	F	*p*
Left inferior frontal gyrus	2.67	0.06	2.83	0.05	4.62	*0.035*	2.73	0.06	2.82	0.13	0.50	*0.481*
Right inferior frontal gyrus	3.01	0.06	3.25	0.06	8.57	*0.005*	3.14	0.1	3.10	0.11	0.09	*0.772*
Left medial superior frontal gyrus	3.45	0.06	3.63	0.05	5.13	*0.027*	3.49	0.09	3.48	0.16	0.00	*0.951*
Right ventromedial prefrontal cortex	3.06	0.07	3.28	0.04	7.31	*0.009*	3.11	0.09	3.21	0.15	0.49	*0.486*
Left anterior temporal gyrus	3.07	0.09	3.40	0.06	8.84	*0.004*	3.25	0.12	3.18	0.22	0.12	*0.727*
Right anterior temporal gyrus	3.19	0.09	3.42	0.07	4.14	*0.046*	3.16	0.14	3.05	0.19	0.32	*0.575*
Left inferior parietal lobule	2.71	0.05	2.90	0.05	5.78	*0.019*	2.70	0.1	2.87	0.11	1.48	*0.228*
Left cerebellum	0.70	0.02	0.74	0.01	3.57	*0.063*	0.68	0.03	0.74	0.03	2.52	*0.117*
Right cerebellum	0.65	0.02	0.71	0.01	5.92	*0.018*	0.68	0.03	0.67	0.03	0.06	*0.811*
Right cerebellar tonsil	0.47	0.02	0.54	0.01	13.26	*0.001*	0.44	0.02	0.50	0.04	3.03	*0.086*
Left supramarginal gyrus	2.82	0.05	3.07	0.06	10.66	*0.002*	3.03	0.06	2.92	0.13	0.70	*0.406*
Right supramarginal gyrus	2.93	0.07	3.08	0.05	3.00	*0.088*	3.04	0.08	3.19	0.12	0.93	*0.481*
Left hippocampus	0.71	0.02	0.75	0.01	4.51	*0.038*	0.71	0.03	0.73	0.03	0.32	*0.572*
Right hippocampus	0.71	0.02	0.76	0.01	4.11	*0.047*	0.71	0.02	0.72	0.05	0.17	*0.680*
Left rhinal sulcus	0.58	0.02	0.65	0.02	5.49	*0.022*	0.59	0.02	0.62	0.03	0.47	*0.497*
Right rhinal sulcus	0.58	0.02	0.61	0.02	1.35	*0.249*	0.58	0.02	0.59	0.04	0.03	*0.867*
Left posterior parahippocampal gyrus	0.56	0.02	0.60	0.01	2.23	*0.141*	0.55	0.02	0.56	0.05	0.03	*0.876*
Right posterior parahippocampal gyrus	0.59	0.02	0.64	0.01	4.89	*0.031*	0.60	0.02	0.59	0.04	0.17	*0.685*

immigration. We will examine each of these results below.

4.1. LCC brain areas

One of the major findings of this study was the evidence for contribution of bilingualism to structural brain changes in LCC brain areas in persons with or at risk for AD. We found greater grey matter in multilinguals (both MCI and AD) as compared to monolinguals in left and right inferior frontal gyri, left medial superior frontal gyrus, right ventromedial prefrontal cortex, left and right anterior temporal gyri, left parietal lobule, left and right cerebellum, and right cerebellar tonsil.

Previous research has found neuroanatomical differences between monolingual and bilingual adults without neurological disease and has posited that the differences in brain structure seen between the

Table 5
Correlation results between brain regions associated with bilingualism and episodic memory scores.

	MCI							
	Delayed verbal recall				Delayed visual recall			
	Mono		Multi		Mono		Multi	
	r	*p*	r	*p*	r	*p*	r	*p*
Left inferior frontal gyrus	0.03	*0.86*	0.39	*0.02*	0.07	*0.68*	0.18	*0.32*
Right inferior frontal gyrus	0.00	*0.99*	0.24	*0.18*	− 0.02	*0.92*	0.19	*0.30*
Left medial superior frontal gyrus	0.21	*0.23*	0.42	*0.02*	− 0.10	*0.59*	0.27	*0.12*
Right ventromedial prefrontal cortex	0.18	*0.32*	0.25	*0.15*	0.00	*1.00*	0.25	*0.17*
Left anterior temporal gyrus	0.08	*0.65*	0.37	*0.03*	0.12	*0.50*	0.40	*0.02*
Right anterior temporal gyrus	0.24	*0.18*	0.19	*0.28*	0.18	*0.31*	0.29	*0.11*
Left inferior parietal lobule	0.14	*0.44*	0.20	*0.25*	0.16	*0.35*	0.27	*0.13*
Left supramarginal gyrus	− 0.03	*0.87*	0.36	*0.04*	− 0.03	*0.89*	0.20	*0.27*
Right supramarginal gyrus	0.04	*0.83*	0.18	*0.31*	0.05	*0.79*	0.30	*0.10*
Left cerebellum	0.11	*0.54*	− 0.01	*0.96*	0.23	*0.20*	− 0.05	*0.79*
Right cerebellum	− 0.10	*0.58*	0.00	*0.99*	− 0.10	*0.58*	0.37	*0.04*
Right cerebellar tonsil	0.17	*0.35*	− 0.05	*0.78*	0.12	*0.51*	0.17	0.35
	AD							
	Immediate Verbal Recal				Immediate Visual Recall			
	Mono		Multi		Mono		Multi	
	r	*p*	r	*p*	r	*p*	r	*p*
Left inferior frontal gyrus	0.08	*0.79*	0.65	*0.02*	− 0.23	*0.56*	0.09	*0.81*
Right inferior frontal gyrus	0.14	*0.64*	0.56	*0.05*	− 0.01	*0.98*	0.31	*0.39*
Left medial superior frontal gyrus	0.24	*0.44*	0.41	*0.17*	0.02	*0.96*	0.20	*0.59*
Right ventromedial prefrontal cortex	0.04	*0.91*	0.16	*0.61*	− 0.01	*0.98*	0.29	*0.41*
Left anterior temporal gyrus	− 0.16	*0.59*	0.55	*0.05*	0.16	*0.69*	0.04	*0.91*
Right anterior temporal gyrus	0.17	*0.58*	0.44	*0.13*	0.00	*1.00*	0.12	*0.74*
Left inferior parietal lobule	− 0.36	*0.22*	0.40	*0.18*	0.70	*0.04*	0.23	*0.52*
Left supramarginal gyrus	0.23	*0.44*	0.62	*0.02*	− 0.17	*0.66*	0.25	*0.48*
Right supramarginal gyrus	0.01	*0.99*	0.25	*0.41*	− 0.10	*0.80*	0.34	*0.34*
Left cerebellum	0.18	*0.55*	0.50	*0.08*	0.38	*0.32*	0.02	*0.95*
Right cerebellum	− 0.24	*0.43*	0.43	*0.14*	0.46	*0.22*	0.12	*0.74*
Right cerebellar tonsil	0.20	*0.51*	− 0.07	*0.83*	− 0.36	*0.35*	0.55	*0.10*

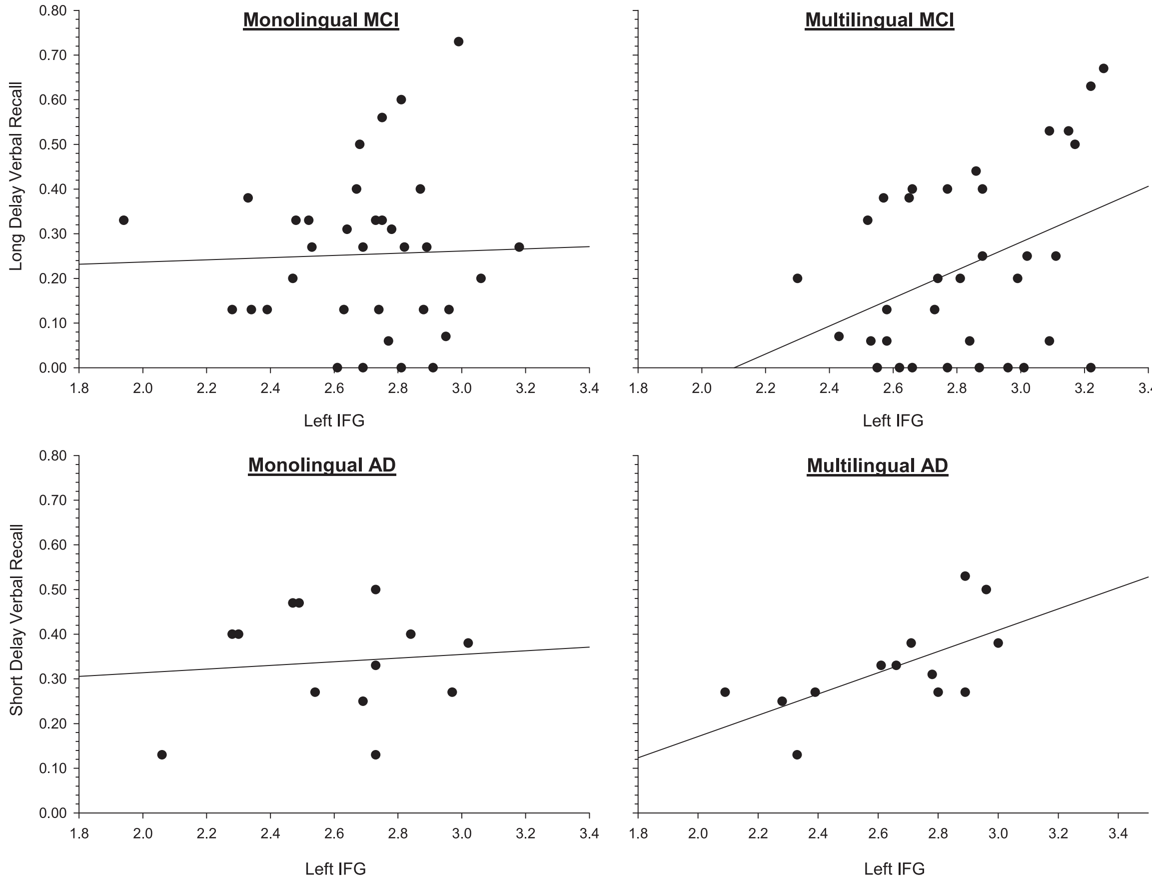

Fig. 5. Scatterplots of correlatetions between Verbal Recall scores (proportion of total possible score) and cortical thickness (mm) of the left inferior frontal gyrus for monolingual and multilingual MCI patients (upper left and right panels, respectively) and monolingual and multilingual AD patients (lower left and right panels, respectively). Note the significant correlations for the multilingual MCI and AD groups, which are absent in the monolingual groups. Note that we used short delay verbal memory scores for the AD participants rather than long delay verbal memory scores, to avoid floor effects. Abbreviation: IFG = inferior frontal gyrus.

language groups represent neuroplastic changes brought about by the experience of speaking more than one language (for reviews see, García-Pentón et al., 2015; Li et al., 2014). The adaptive control hypothesis (Green and Abutalebi, 2013) posits that language comprehension and production require the interaction of multiple discrete and overlapping control processes (e.g., goal maintenance, conflict monitoring) carried out by interconnected networks of brain regions and furthermore, that bilingual language functioning results in adaptive changes in the recruitment of, and interactions between, these networks. Functional neuroimaging studies have demonstrated that the regions recruited by bilinguals in the hypothesized series of networks are indeed involved in language processing and/or cognitive control (for a review see, Li et al., 2014). Our data contribute to the hypothesis that having two languages "exercises" specific brain regions implicated in various control processes, inducing neural changes that can be seen at the level of increased cortical thickness and grey matter density, and extends these findings by demonstrating that these structural differences can be seen in the brains of multilingual MCI and AD patients.

Table 6
Demographic, neuropsychological, and cortical thickness data for non-immigrant MCI patients.

	Mono (n = 27)		Multi (n = 14)			
	M	SE	M	SE	t	*p*
Age at symptom onset	68.0	1.10	68.80	1.80	− 0.39	*0.70*
Age at scan	73.5	1.0	72.5	1.7	0.57	*0.58*
MMSE at scan	26.6	0.5	27.9	0.5	− 1.74	*0.09*
Education	12.4	0.8	12.6	1.0	− 0.13	*0.90*
Block design	28.8	2.1	27.7	2.0	0.33	*0.74*
Short delay verbal recall (%)	51.0	3.0	44.0	3.0	1.45	*0.16*
Long delay verbal recall (%)	25.0	4.0	18.0	6.0	1.04	*0.31*
Delayed recall visual reproduction	22.4	3.9	20.1	4.9	0.34	*0.73*
Clock (/10)	8.6	0.3	7.9	0.4	1.26	*0.22*
Stroop Interference	2.4	0.2	2.0	0.1	1.41	*0.17*
Orientation (%)	93.2	2.2	91.6	3.1	0.44	*0.66*
Trail A	48.9	3.7	44.1	4.5	0.80	*0.43*
Spatial span total	12.2	0.6	10.4	0.6	2.00	*0.05*

4.2. Cognitive reserve

4.2.1. Cognitive reserve in AD patients

We found that multilingual AD patients showed thinner cortex and lower tissue density in the posterior parahippocampal gyri and the rhinal sulci compared to their monolingual counterparts, suggesting more AD neuropathology in the memory-specific substrates. This suggests that their increased cognitive reserve (gained from a history of managing two languages) allowed them to perform at the level of their monolingual peers on several episodic memory tasks, despite having sustained more atrophy in areas related to memory processing. Note that cognitive reserve can be demonstrated through a number of different outcomes. One way is to compare the records of all eligible participants as a function of whether the cognitive reserve promoter is present or absent and determine whether the target group has delayed symptom onset or older age at diagnosis (e.g., Bialystok et al., 2007; Alladi et al., 2013). A second way, which is the one used in our study, is to hold those factors constant, and then observe whether there is evidence of brain differences which might allow the group with the higher hypothesized reserve to compensate for brain disease. This is the pattern that we observed, through the combined findings of a) reduced brain matter in posterior parahippocampal gyri and the rhinal sulci in multilingual AD patients compared to the monolinguals, and b) positive associations between LCC brain regions and episodic memory performance only in the multilingual patient groups.

This is the second study to use neuroanatomical measures to examine the impact of speaking more than one language in AD patients who are balanced on clinical severity/cognitive performance. Schweizer et al. (2012) found that bilingual AD patients showed greater medial temporal atrophy (as measured by several estimates of brain volume derived from CT scans) compared to a group of monolingual AD patients matched on age, education, and cognitive functioning. Importantly, our results, derived through the use of high-resolution whole-brain MRI scans and sophisticated pre-processing and analysis techniques, extend these findings by enabling the precise measurement of cortical thickness and tissue density within specific medial temporal lobe structures. Our results indicate that, in the early stages of AD, multilinguals were able to tolerate more atrophy in the posterior parahippocampal gyri and rhinal sulci than monolinguals, while maintaining a comparable cognitive level. Moreover, we were able to demonstrate that multilingual patients with MCI did not show similar decreases in medial temporal cortex relative to their monolingual peers; in fact, they showed the opposite pattern.

Interestingly, the results seen in the hippocampi proper are not in line with predictions made by the cognitive reserve hypothesis. Specifically, we would have expected to see decreased grey matter density in the left and right hippocampi in multilingual AD patients compared to monolingual AD patients, as we saw for the parahippocampal gyri. Instead, the hippocampi showed a main effect of Language Group suggesting greater hippocampal volumes for the multilinguals compared to the monolinguals, regardless of Diagnosis Group. The lack of a reserve-congruent pattern in the left and right hippocampi, although puzzling, may simply be due to the fact that our AD sample consists of mostly early-AD patients. Recent research shows that neurodegeneration often occurs in the parahippocampal gyrus before the hippocampus (Desikan et al., 2009; e.g., Echávarri et al., 2010). As such, the AD patients in this sample may not have experienced significant enough neurodegeneration in the hippocampus proper for the multilinguals to demonstrate the expected cognitive reserve pattern. The AD patients in our study did, however, show reliably smaller hippocampi compared to the MCI participants, which is a predictable pattern of results and indicates that our Diagnosis Groups conform to this often-replicated pattern.

4.2.2. Cognitive reserve in MCI patients

The current study is the first to use neuroanatomical measures to examine the impact of multilingualism in MCI patients who are balanced on disease-specific cognitive functioning. We hypothesized that the multilingual MCI patients would not differ from monolingual MCI patients in DR areas as they have not begun to experience substantial AD atrophy. Unlike our multilingual AD patients, who showed evidence of cognitive reserve (thinner cortex and decreased grey matter density compared to monolingual AD patients in DR areas), the multilingual MCI patients did not. They showed either thicker cortex/higher grey matter density or did not differ reliably from the monolingual MCIs. Our sample was composed of MCI patients whose primary deficits were in the memory domain, and these are the individuals who are more likely to convert to AD (Albert et al., 2011). Although the sample sizes were small, our results indicated that among the MCI patients who had as of yet not converted to AD, multilingual MCIs showed a pattern of thicker cortex and higher tissue density in vertices and voxels within both LCC and DR areas compared to monolingual MCIs, whereas there were no Language Group differences between monolingual and multilingual MCI patients that had converted to AD. Based on this pattern, it is possible that there is heterogeneity in the extent to which increased gray matter is expressed in multilinguals, with those who show evidence of it perhaps being delayed in their development of AD, or may not develop the disease at all. Those MCI patients who show lesser amounts of increased gray matter appear more likely to decline to dementia in the future.

4.3. Correlational results

In order to explore how patients could demonstrate equivalent performance on memory tests, despite evidence of reduced medial temporal matter, we examined the potential relationship between brain areas related to bilingualism and performance on memory tests. Interestingly, we found that multilingual patients showed significant correlations between episodic memory measures and a number of brain regions typically associated with language processing and cognitive control, while monolingual patients did not. It has been previously suggested that increased white matter density in older bilinguals compared to monolinguals may form the neural basis for bilingualism's contribution to cognitive reserve (Luk et al., 2011a). Similarly, we suggest that the cognitive reserve experienced by our multilingual AD patients may be made possible by the thicker cortex in frontal and parietal cognitive control areas. In other words, we take the correlation between cognitive control regions and episodic memory performance as evidence towards the hypothesis that multilingual patients are able to utilize alternate networks (i.e., the neural compensation subtype of cognitive reserve) for memory processing and that they are able to do so because of their increased grey matter in brain regions exercised by being bilingual. However, these results are based on post-hoc correlational analyses and should be interpreted with caution. A stronger test of this hypothesis would be to examine white matter tracts and functional connectivity between these regions, which is a current area of research for us.

4.4. Non-immigrant MCI sub-sample

Another unique strength of the current study is that we found similar results with a subgroup of non-immigrant MCI patients. Given the potential confounding effect of immigration with bilingualism, we replicated our analyses with a monolingual and multilingual non-immigrant subgroup of MCI patients. Disease-relevant ROI results show that monolingual and multilingual MCI patients do not differ significantly in these regions. The pattern of results from the LCC ROIs largely mirror those seen with the overall sample: multilingual patients show reliably thicker cortex in frontal, temporal, parietal, and cerebellar regions. Results for the medial frontal lobe (pre-supplementary motor/ventromedial prefrontal areas) and the supramarginal gyri were in the same direction but were found to be non-reliable differences, likely due to the lower statistical power in this subgroup analysis. Unfortunately, we were not able to conduct similar analyses for the AD participants due to the smaller sample sizes. Nevertheless, if we were to extrapolate from our findings with the MCI participants, our results generally suggest that the important potential confound of immigration may not be playing a role in our results.

4.5. Limitations

This study has its limitations. Firstly, as data in this study were gathered retrospectively, the information that we had on language history and use was limited. As noted in recent reviews (e.g., Calvo et al., 2016; Duncan and Phillips, 2016), important variables related to bilingualism (e.g., age of acquisition, degree of proficiency, contextual uses of language) may have an influence in the contribution to cognitive reserve expression. Secondly, this study was limited by a lack of data from healthy older adults that could have provided appropriate baselines to compare the level of neurodegeneration in the Diagnosis

Groups. Relatedly, larger sample sizes would allow us the ability to split our multilingual group into bilinguals and multilinguals to determine whether there is any linear or dose-response to speaking multiple languages. This is important given that previous research suggests that the two groups may differ in terms of the cognitive impact of AD neuropathology (Chertkow et al., 2010). It is important to note that, although our sample sizes, especially for the MCI group, are at or in excess of those reported in the younger and older healthy adult literature (for a review see García-Pentón et al., 2015), these results should still be considered preliminary and require confirmation with more stringent voxelwise approaches and larger sample sizes.

4.6. Summary

Our data contribute to the growing literature that there may be subtle differences in brain structure related to multilingualism. These results add new information to the individual and intersecting bodies of literature on the hypothesized protective effect of bilingualism against the cognitive effects of dementia (CR) and neuroplasticity associated with bilingualism (where past studies have typically been limited to healthy young and old adults). Ours is the first study to use structural MRI data to examine cognitive reserve in MCI patients and in AD patients, the first to assess structure in LCC regions in MCI and AD patients, the first to demonstrate an association between LCC regions and memory function in these groups, and the first to control for immigration status in these groups. Overall, our results contribute to the research findings that indicate that speaking more than one language is one of a number of lifestyle factors that contributes to reserve and supports the notion that multilingualism and its associated cognitive and sociocultural benefits are associated with brain plasticity.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.12.036

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