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Distinct structural correlates of the dominant and nondominant languages in bilinguals with Alzheimer's disease (AD)

Denis S. Smirnov[a,*], Alena Stasenko[b,c], David P. Salmon[a], Douglas Galasko[a], James B. Brewer[a], Tamar H. Gollan[c]

[a] Shiley-Marcos Alzheimer's Disease Research Center, Department of Neurosciences, University of California, San Diego, United States
[b] San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, United States
[c] Department of Psychiatry, University of California, San Diego, United States

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ABSTRACT

Structural adaptations in brain regions involved in domain-general cognitive control are associated with life-long bilingualism and may contribute to the executive function advantage of bilinguals over monolinguals. To the degree that these adaptations support bilingualism, their disruption by Alzheimer's disease (AD) may compromise the ability to maintain proficiency in two languages, particularly in the less proficient, or *nondominant*, language that has greater control demands. The present study assessed this possibility in Spanish-English bilinguals with AD ($n = 21$) and cognitively normal controls ($n = 30$) by examining the brain correlates of dominant versus nondominant language performance on the Multilingual Naming Test (MINT), adjusting for age and education. There were no significant structural correlates of naming performance for either language in controls. In patients with AD, dominant language MINT performance was associated with cortical thickness of the entorhinal cortex and middle temporal gyrus, consistent with previous findings of temporal atrophy and related decline of naming abilities in AD. Nondominant language MINT performance, in contrast, was correlated with thickness of the left caudal anterior cingulate cortex (ACC), a central cognitive control region involved in error monitoring and task switching. The relationship between naming in the nondominant language and ACC in patients with AD but not in controls may reflect increased reliance on the ACC for nondominant language use in the face of atrophy of other control network components. The results are consistent with the possibility that the increased burden nondominant language use places on cognitive control systems compromised in AD may account for faster nondominant than dominant language decline in AD.

1. Introduction

Mounting evidence suggests that bilingualism is associated with the delayed onset of cognitive decline due to Alzheimer's disease (AD) by an average of 4–5 years (Bialystok et al., 2007; Craik et al., 2010; Chertkow et al., 2010; Schweizer et al., 2012; for review see Bak and Alladi, 2014; Guzmán-Vélez and Tranel, 2015). This type of cognitive reserve is often attributed to the executive control advantage of bilinguals compared to monolinguals, which may result from increased demands associated with needing to manage and switch between activation of two languages in a single cognitive system (Gold, 2015; Green and Abutalebi, 2013; for review see Bialystok, 2011, 2017; Kroll and Bialystok, 2013). In their seminal neurocognitive language control model Abutalebi and Green (2007) identified the domain-general control structures involved in the dynamic process of bilingual language production, including the anterior cingulate cortex (ACC), prefrontal cortex (PFC), inferior parietal lobule (IPL), and basal ganglia. In their more recent Adaptive Control Hypothesis, Green and Abutalebi (2013) suggested that this network is adaptive to specific language contexts – with control regions more involved in some than in other interactional contexts (e.g., they propose less control is needed in conversations with dense code switching). Nevertheless, the very need to monitor which type of language use is appropriate for each conversation could itself produce adaptations within control regions, in turn resulting in advantages compared to monolinguals in non-linguistic executive control functions such as response inhibition, working memory, and task-switching (e.g., a bilingual advantage on the flanker task was associated with more efficient functional activation of the

* Corresponding author. Shiley-Marcos Alzheimer's Disease Research Center, Department of Neurosciences, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA, 92093, United States.
E-mail address: dsmirnov@ucsd.edu (D.S. Smirnov).

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ACC; Abutalebi et al., 2012; for review see Dong and Li, 2015; but see Paap and Greenberg, 2013; Lehtonen et al., 2018).

Structural neuroimaging studies in cognitively normal bilinguals support this view, suggesting that bilingualism may produce structural adaptations (i.e., increased grey matter density or volume) in a range of regions associated with domain-general cognitive control (Abutalebi and Green, 2016; Green and Abutalebi, 2013; Mechelli et al., 2004). Structural changes in the inferior frontal gyrus (IFG; part of the PFC) correlate with second language training (Stein et al., 2012), and thickness of the IFG is related to age of second language acquisition in bilinguals (Klein et al., 2014). Second language proficiency and bilingualism appears to similarly affect the left IPL in young adults (Mechelli et al., 2004) and cognitively normal older bilinguals (Abutalebi et al., 2015a, b). Aging bilinguals also have increased grey matter volume in the ACC (Abutalebi et al., 2015a, b), a structure whose grey matter density was previously reported to correlate with better conflict monitoring in bilinguals (Abutalebi et al., 2012). A recent study also identified greater temporal pole volume in aging bilinguals compared to monolinguals, and reported a correlation between volume of this structure and second language proficiency (Abutalebi et al., 2014). This is consistent with other reports of the protective effect of bilingualism on age-related temporal pole atrophy (Olsen et al., 2015). While not part of the domain-general control network (Green and Abutalebi, 2013; Niendam et al., 2012), the temporal poles function as general semantic hubs activated during lexical retrieval (Patterson et al., 2007).

Although structural advantages (e.g., thicker cortex and higher grey matter density) in domain-general control regions persist in multilinguals with AD or Mild Cognitive Impairment (MCI) (Duncan et al., 2018), many of these same brain regions are subject to atrophy as the disease progresses (McDonald et al., 2012; Sabuncu et al., 2011; Westman et al., 2011). If bilingualism is supported by these adaptations, their disruption by AD may compromise the ability to maintain proficiency in two languages, particularly in the less proficient, or *nondominant*, language (Ivanova et al., 2014; Mendez et al., 1999). Consistent with this possibility, it has been reported that bilinguals with AD gradually lose the ability to maintain fluency in two languages (Obler et al., 1986), regress to strongly preferring the language that is first-learned and dominant (Ardila and Ramos, 2008), and have increased unintended intrusions of the dominant language into the second-learned nondominant language (Mendez et al., 1999). In addition, Ivanova et al. (2014) found that non-balanced Spanish-English bilinguals with AD exhibited greater longitudinal decline in their nondominant language over a 3-year period. These effects may, however, be specific to bilinguals with a clearly dominant language since studies of balanced Spanish-Catalan bilinguals (i.e. who were similarly proficient in both languages) with AD showed similar declines in both languages cross-sectionally as well as longitudinally (Calabria et al., 2017; Costa et al., 2012).

Greater decline in the nondominant than dominant language in non-balanced bilinguals with AD may be related to atrophy of domain-general cognitive control regions and accompanying decline in executive control functions (Chang et al., 2010; McDonald et al., 2012; Pa et al., 2009; for review see Nowrangi et al., 2014). Retrieval of words in the nondominant language is more difficult and less automatic than in the dominant language, and therefore more likely to be affected by the well-known deficits in executive control that occur in AD (Balota et al., 1999; Nebes et al., 1984; Ober et al., 1995). The present study assessed this possibility in Spanish-English bilinguals with AD and cognitively normal controls by examining the brain correlates of dominant versus nondominant language performance on the Multilingual Naming Test (MINT), a picture naming task designed for use in multiple languages (Gollan et al., 2012; Ivanova et al., 2013). We hypothesized that naming ability in the nondominant language would be associated with structural integrity in cognitive control areas previously associated with bilingualism in healthy older adults. Naming ability in the dominant language, in contrast, would be less reliant on the domain-general control network and be more likely to correlate with the structural integrity of temporal lobe structures associated with semantic memory.

2. Methods

The research protocol was reviewed and approved by the Institutional Review Board (IRB) at the University of California, San Diego and informed consent to participate in the study was obtained at the point of entry into the ADRC longitudinal study from all patients or their caregivers consistent with California State law.

2.1. Participants

The study included 21 Spanish-English bilingual participants clinically diagnosed with AD and 30 cognitively normal (NC) Spanish-English bilingual participants from the University of California, San Diego (UCSD) Shiley Marcos Alzheimer's Disease Research Center (ADRC). Participants were diagnosed by a panel consisting of at least one neurologist and one neuropsychologist using systematic guidelines for clinical diagnosis based on the most up to date published research criteria (Albert et al., 2011; McKhann et al., 2011). Groups did not differ in age, gender distribution, APOE ε4 allele frequency, or dominant language spoken (see Table 1). Education, expressed continuously as the cumulative years of formal education, was greater in the NC group ($p < 0.001$). On average, the AD group had lower scores on global cognition measures such as the Mini-Mental State Exam (MMSE; $p < 0.001$) and the Mattis Dementia Rating Scale (DRS; $p < 0.001$), as well as a worse confrontation naming performance in their dominant and nondominant languages (MINT; $p < 0.001$ and $p < 0.01$ respectively). The bilingual index (a measure of degree of bilingualism that is described in detail below) revealed a small but significant difference between the groups such that the AD patients were relatively less bilingual ($p = 0.04$). Participants with AD were also more functionally impaired as judged by the Functional Assessment Questionnaire (FAQ; $p < 0.001$).

Table 1
Demographics and cognitive function in participants with AD and in cognitively normal controls.

	AD (n = 21)	NC (n = 30)	P value
Age (years)	72.0 ± 12.5	72.5 ± 8.2	0.89
Gender:			0.15
Male	11 (52%)	9 (30%)	
Female	10 (48%)	21 (70%)	
Education (years)	10.0 ± 4.4	14.2 ± 3.4	< **0.001**
APOE ε4 allele number [a]			0.22
0 ε4 alleles	11 (55%)	21 (70%)	
1 ε4 alleles	7 (35%)	9 (30%)	
2 ε4 alleles	2 (10%)	0 (0%)	
Dominant Language:			0.27
English	9 (43%)	18 (60%)	
Spanish	12 (57%)	12 (40%)	
MMSE (/30)	20.6 ± 4.5	28.3 ± 1.6	< **0.001**
DRS Total (/144)	109.8 ± 14.8	136.5 ± 4.8	< **0.001**
Dominant MINT (/68)	57.4 ± 6.5	63.8 ± 3.3	< **0.001**
Nondominant MINT (/68)	29.2 ± 17.4	42.1 ± 16.3	**0.01**
Bilingual Index (/1)	0.50 ± 0.3	0.70 ± 0.3	**0.04**
FAQ [a] (/30)	18.5 ± 7.9	0.6 ± 1.6	< **0.001**

Values presented as Mean ± SD for continuous variables or n (%) for discrete variables.
Abbreviations: MMSE = Mini Mental State Exam, DRS = Mattis Dementia Rating Scale, FAQ = Functional Assessment Questionnaire, MINT = Multi-Lingual Naming Test, AD = Alzheimer's Disease, NC = Cognitively Normal Controls.
Bold indicates significance at a $p < 0.05$ threshold.
[a] Missing Data: 1 AD subject missing APOE genotype, 1 NC subject missing FAQ.

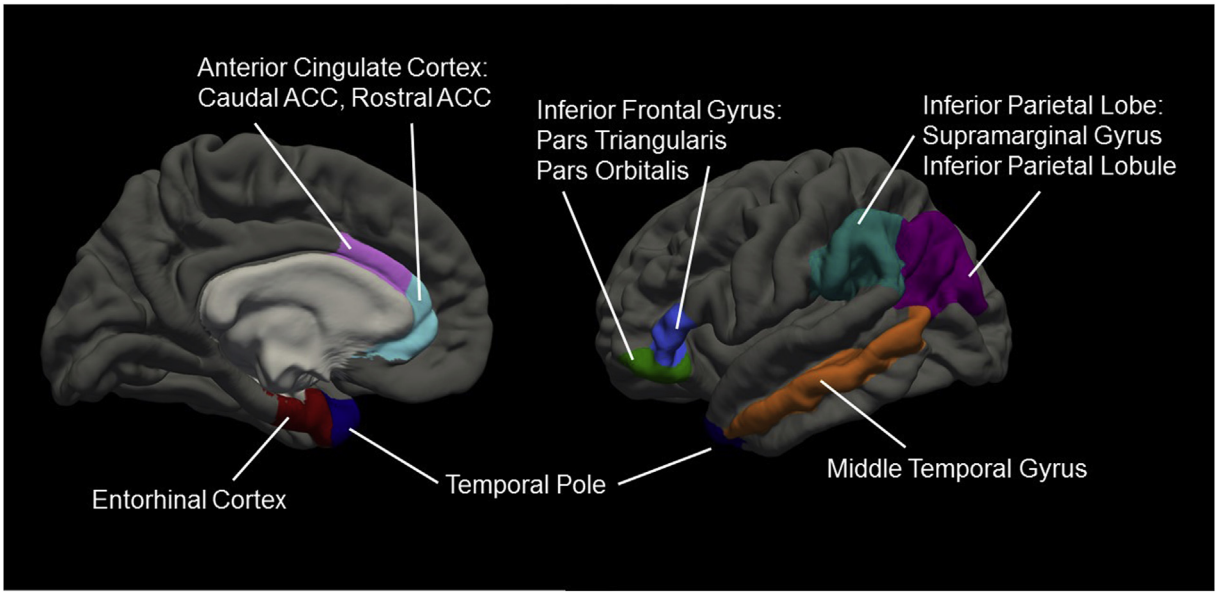


Fig. 1. Regions of interest selected for the analysis overlaid on the pial surface of the standard FreeSurfer "fsaverage" brain.

2.2. Procedures

Participants were tested on the Multilingual Naming Test (MINT) as part of their annual standardized ADRC neuropsychological evaluation. Testing was performed by a Spanish-English bilingual psychometrician. The MINT (Gollan et al., 2012; Ivanova et al., 2013) consists of 68 black-and-white line drawings of objects that are presented one at a time to be named. The drawings are graded in difficulty, with the easiest drawings presented first. The MINT was designed to assess both dominant and nondominant languages; thus it includes a greater proportion of medium to high frequency items than is typical for naming tests designed for monolinguals (e.g., the Boston Naming Test; Kaplan and Goodglass, 1983). Participants first named all the pictures in their dominant language, and then in their nondominant language. If an individual encountered difficulty identifying an object, a semantic or phonemic cue was provided. Testing was discontinued after six consecutive failed naming trials. The number of spontaneous correct responses and correct responses following a semantic cue were summed to give a total score (which ranges from 0 to 68).

Bilingualism Index scores were calculated by dividing the score in whichever language produced the lower score (*nondominant language*) by the score in the language which produced a higher score (*dominant language*). Index scores range from 0 to 1 and measure the extent to which knowledge of each language is similar, ignoring direction of dominance and absolute ability level (Gollan, Salmon, Montoya, & da Pena, 2010; Gollan et al., 2012).

2.3. Image analysis

2.3.1. MRI acquisition

High-resolution, three-dimensional, T1-weighted images were acquired for each subject (TE: 2.8 ms/3.8 ms; TR: 6.5 ms/8.5 ms; TI: 600 ms/500 ms; flip angle: 8°/10°; matrix: 256 × 256; voxel size: 0.9375 mm × 0.9375 mm × 1.2000 mm; values separated by '/' are for 3.0 T data/1.5 T data). Respiratory effort and heart rate were monitored with a pressure transducer (BioPac Systems Inc., Goleta, CA) and a pulse oximeter (BioPac Systems and InVivo, Orlando, FL), respectively.

2.3.2. MRI processing

A model of each subject's cortical surface was reconstructed from the T1-weighted MRI scan using FreeSurfer (version 6.0), an automated image processing pipeline that is documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these methods have been described in prior publications (e.g., Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2001, 2002; 2004; Fischl et al., 1999a, b). Following completion of the automated FreeSurfer pipeline, all scans were reviewed to assess the quality of skull stripping and ensure that cortical surfaces followed the grey and white matter boundaries. Where needed, manual edits were performed to improve accuracy of segmentation. This involved correction of pial surface misplacement (e.g., inclusion of non-brain tissue) and errors in white matter segmentation. This editing procedure was conducted by operators blinded to the diagnostic status of the participants. Final surfaces were visually inspected to search for gross errors; none were found in the present data set.

The surface cortical model was then anatomically parcellated using the Desikan-Killiany atlas and standard FreeSurfer tools (Desikan et al., 2006; Fischl et al., 2004). This process assigns each point (vertex) on the native surface to the most probable anatomical label (e.g., inferior parietal, precentral, parahippocampal, etc.) based on registration to a probabilistic atlas of surface folding patterns and on the observed surface geometry at that location of the native surface (Fischl et al., 2004). Automated parcellation by this method has been shown to be comparable to manual labeling (Fischl et al., 2004). The parcellation for each subject was visually inspected to search for gross errors; none were found in the present data set.

2.3.3. Selection of regions of interest

Regions of interest (ROIs) for this analysis were selected from the literature, targeting: 1) cognitive control regions demonstrating a bilingualism effect in older adults including the rostral and caudal ACC (Abutalebi et al., 2015a, b), temporal poles (Abutalebi et al., 2014; Olsen et al., 2015), inferior parietal lobule (angular gyrus) and supramarginal gyrus (Abutalebi et al., 2015a, b; Mechelli et al., 2004), and inferior frontal gyrus (pars orbitalis and triangularis per Klein et al., 2014; Stein et al., 2012); 2) the middle temporal gyrus whose volume has been shown to correlate with confrontation naming in AD (Grossman et al., 2004); and 3) entorhinal cortex which shows the greatest degree of cortical thinning in early AD (Bakkour et al., 2009; Dickerson et al., 2009, 2001; McEvoy et al., 2009; Ries et al., 2008). Fig. 1 visually displays these regions per the Desikan-Killiany atlas on the pial surface of the FreeSurfer "fsaverage" brain.

2.4. Statistical analysis

Demographics, clinical characteristics, and cognitive performance were compared using ANOVA for continuous variables and Fisher Exact Tests for categorical variables. Average cortical thicknesses for each ROI were extracted from FreeSurfer and subjected to a linear regression with dominant MINT score, nondominant MINT score, years of education, and age in years as predictors. The Kolmogorov-Smirnov test demonstrated that within each group, our variables did not deviate from normality (D range 0.10–0.14; all $p > 0.6$), while a variance inflation factor (VIF) of less than 3 for each covariate indicated that no significant co-linearity was present. For each of the models used, no autocorrelation was observed with the Durbin-Watson test (d range 1.72–2.27, all $p > 0.16$), and heteroscedasticity was ruled out with the Goldfeld-Quandt test (GQ range 0.38–1.20, all $p > 0.34$). Partial correlations were calculated for each variable, controlling for the others, from the regression model. We sampled 18 regions (9 ROIs bilaterally), with corrections for multiple comparisons carried out using the Benjamini-Hochberg procedure to adjust for a false discovery rate (FDR) < 0.05 (Benjamini and Hochberg, 1995; Storey et al., 2004). Results that survived this correction are bolded in tables. Analyses were performed using the R statistical software package (v 3.5.1, R Core Team, 2015).

3. Results

3.1. Cortical thickness differences between AD and NC

Compared to the cognitively normal bilingual controls, bilinguals with AD exhibited cortical thinning in bilateral entorhinal, middle temporal, temporal pole, and inferior parietal and supramarginal cortices. In addition, bilateral pars orbitalis and the right pars triangularis of the IFG, as well as the left rostral ACC were significantly thinner among patients (all FDR-adjusted $p < 0.05$, Table 2).

3.2. Partial correlations for dominant and nondominant MINT

Partial correlations were used to examine the unique contributions of dominant and nondominant MINT scores, adjusted for age and education, to cortical thickness in each of our target ROIs in AD patients and NC controls separately. In the NC group, despite a larger sample size, no significant correlations emerged with any regions sampled (Supplemental Table 1). In the AD group (Table 3), dominant language MINT performance showed a robust positive correlation with left entorhinal cortical thickness (partial $r = 0.63$, FDR adjusted $p < 0.05$; Fig. 2A) and left middle temporal thickness (partial $r = 0.63$, FDR adjusted $p < 0.05$). In contrast, nondominant language MINT was positively associated only with left caudal ACC thickness (partial $r = 0.68$, FDR-adjusted $p < 0.05$; Fig. 2B).

Table 2
Regional cortical thicknesses of patients with AD and cognitively normal adults.

	AD *Mean ± SD*	NC *Mean ± SD*	*p*-value
Temporal Lobe			
L. Entorhinal	2.8 ± 0.5	3.2 ± 0.3	**0.001**
R. Entorhinal	2.9 ± 0.4	3.3 ± 0.3	< **0.001**
L. Middle Temporal	2.5 ± 0.2	2.7 ± 0.2	< **0.001**
R. Middle Temporal	2.4 ± 0.2	2.7 ± 0.1	< **0.001**
L. Temporal Pole	3.2 ± 0.3	3.4 ± 0.3	**0.002**
R. Temporal Pole	3.2 ± 0.4	3.5 ± 0.3	**0.005**
Inferior Frontal Gyrus			
L. Pars Orbitalis	2.4 ± 0.2	2.6 ± 0.2	**0.005**
R. Pars Orbitalis	2.4 ± 0.2	2.6 ± 0.2	**0.030**
L. Pars Triangularis	2.2 ± 0.2	2.2 ± 0.1	0.363
R. Pars Triangularis	2.2 ± 0.1	2.3 ± 0.2	**0.015**
Anterior Cingulate Cortex			
L. Rostral ACC	2.4 ± 0.2	2.6 ± 0.3	**0.008**
R. Rostral ACC	2.7 ± 0.2	2.8 ± 0.3	0.318
L. Caudal ACC	2.6 ± 0.3	2.5 ± 0.3	0.396
R. Caudal ACC	2.4 ± 0.3	2.5 ± 0.3	0.074
Inferior Parietal Lobe			
L. Supramarginal	2.2 ± 0.2	2.3 ± 0.2	**0.005**
R. Supramarginal	2.1 ± 0.2	2.3 ± 0.1	< **0.001**
L. Inferior Parietal	2.1 ± 0.2	2.2 ± 0.1	**0.002**
R. Inferior Parietal	2.1 ± 0.2	2.3 ± 0.2	< **0.001**

Bold indicates significant differences after adjustment using the Benhamini-Hochberg procedure for a false discovery rate (FDR) < 0.05.
Abbreviations: AD = Alzheimer's Disease, NC = Cognitively Normal Controls, ACC = Anterior Cingulate Cortex.

Table 3
Partial correlations of dominant and nondominant language with cortical thickness in AD.

	Dominant MINT		Nondominant MINT	
	Partial *r*	*p*- value	Partial *r*	*p*- value
Temporal Lobe				
L. Entorhinal	**0.63**	**0.005**	−0.38	0.115
R. Entorhinal	0.54	0.021	−0.37	0.134
L. Middle Temporal	**0.63**	**0.005**	−0.36	0.142
R. Middle Temporal	0.28	0.257	−0.29	0.248
L. Temporal Pole	0.34	0.162	0.12	0.640
R. Temporal Pole	0.42	0.082	−0.10	0.707
Inferior Frontal Gyrus				
L. Pars Orbitalis	0.09	0.718	−0.10	0.701
R. Pars Orbitalis	−0.03	0.903	−0.22	0.376
L. Pars Triangularis	0.34	0.164	−0.16	0.519
R. Pars Triangularis	0.21	0.405	−0.35	0.151
Anterior Cingulate Cortex				
L. Rostral ACC	0.19	0.452	−0.03	0.900
R. Rostral ACC	−0.08	0.761	0.02	0.946
L. Caudal ACC	0.07	0.782	**0.68**	**0.002**
R. Caudal ACC	−0.47	0.048	0.03	0.906
Inferior Parietal Lobe				
L. Supramarginal	0.47	0.049	−0.36	0.144
R. Supramarginal	0.27	0.273	−0.34	0.165
L. Inferior Parietal	0.45	0.062	−0.39	0.109
R. Inferior Parietal	0.50	0.037	−0.42	0.082

Bold indicates significant differences after adjustment using the Benhamini-Hochberg procedure for a false discovery rate (FDR) < 0.05.
Abbreviations: AD = Alzheimer's Disease, ACC = Anterior Cingulate Cortex.

3.3. Correlations with the bilingual index

The bilingual index provides a measure of relative degree of bilingualism by taking the ratio of nondominant to dominant naming ability. When using the bilingual index measure in place of the nondominant MINT in the regression, the pattern of results was unchanged, such that there was a correlation with only left caudal ACC thickness (partial $r = 0.68$, FDR-adjusted $p < 0.05$; Supplemental Fig. 1). Three AD patients had bilingual index scores that were less than 10%, lower than any NC participants. When excluding these three cases, the correlation strengthened to a partial r of 0.70 (FDR-adjusted $p < 0.05$; Supplemental Fig. 2).

4. Discussion

The goal of this study was to examine the distinct structural correlates of dominant and nondominant picture naming ability in bilinguals with AD. Previous work suggested that bilingualism is associated with increased grey matter density, thickness, or volume in cognitive control regions in healthy individuals (Abutalebi and Green, 2016), but it is unknown if decline in language ability in either or both languages is related to the integrity of these regions in AD.

Our analysis was specifically designed to address this question by subjecting the average cortical thickness for each *a-priori* defined region

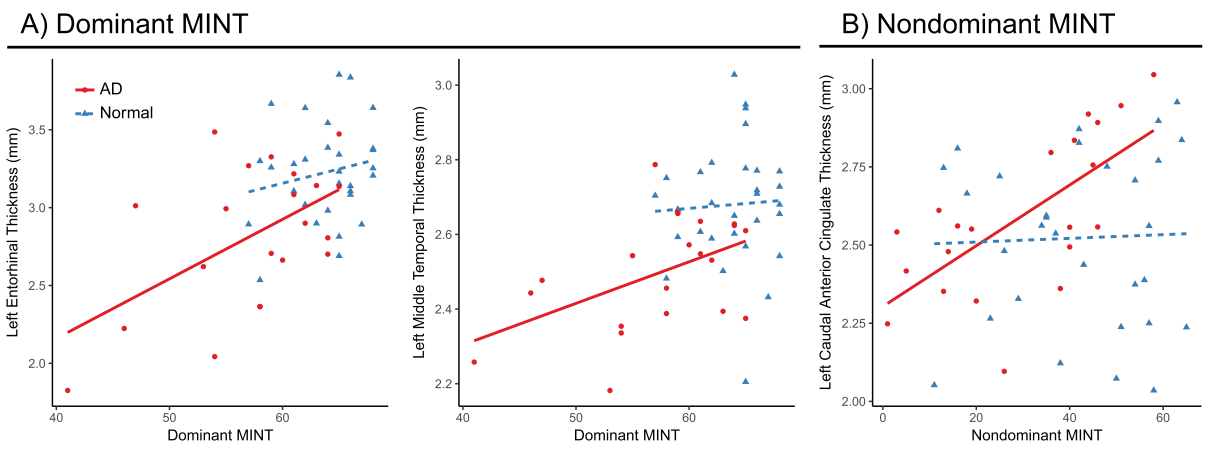


Fig. 2. Relationship with Cortical Thickness. Scatterplots of the significant correlations of A) dominant MINT with cortical thickness of left temporal regions, and B) nondominant MINT with cortical thickness of the left caudal ACC. Patients with AD are red circles with a solid regression line, while normal controls are blue triangles with a dashed regression line. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of interest to a regression analysis with both dominant and non-dominant confrontation naming performance on the MINT, controlling for age and education. This approach allowed us to examine correlates of naming ability in the two languages in the AD brain, and revealed reliable differences between them.

As expected, thickness of the left entorhinal cortex and left middle temporal cortex correlated with dominant MINT performance. This result suggests that ability to name pictures in the dominant language primarily taps semantic processes that are known to be impaired in AD in conjunction with early atrophy and decreased metabolic activity in the temporal lobes (Domoto-Reilly et al., 2012; Galton et al., 2001; Melrose et al., 2009). The middle temporal gyrus in particular has been shown to be the common correlate of confrontation naming in AD, frontotemporal dementia, and corticobasal degeneration (Grossman et al., 2004). This region, along with the entorhinal cortex, exhibited significant thinning in AD compared to healthy controls (Table 2), suggesting that atrophy of these structures may compromise dominant language naming abilities. Our finding of a robust association between dominant MINT scores and cortical thickness in patients, but not in elderly control participants (Fig. 2A), further suggests that inability to name pictures in the dominant language may reflect global cognitive impairment.

The nondominant language, in contrast, was positively correlated with thickness of the left caudal ACC in AD patients. The ACC has been postulated to be a common locus for domain-general cognitive control, particularly related to task monitoring and conflict/error detection (Aarts et al., 2008; Carter and van Veen, 2007; Kerns et al., 2004). The ACC is recruited in tasks that require bilingual language control—e.g., language switching in production (e.g., Branzi et al., 2016; Guo et al., 2011; for review see Abutalebi and Green, 2007) and in auditory comprehension (Abutalebi et al., 2007; Blanco-Elorrieta and Pylkkänen, 2016, 2017), and has increased volume in aging bilinguals compared to monolinguals (Abutalebi et al., 2015a, b). Branzi et al. (2016) reported increased ACC activity when using the nondominant language in comparison to the dominant language, and Abutalebi et al. (2008) specifically identified activation in the *left* ACC during use of the non-dominant language. These fMRI studies suggest that the dorsal ACC region may be more engaged when processing a weaker language. Previous literature also suggests overlap between language control and cognitive control functions, with bilinguals showing activation in the ACC across both verbal and non-verbal tasks (e.g., Anderson, Chung-Fat-Yim, Bellana, Luk and Bialystok, 2018; Weissberger et al., 2015; for review see Hervais-Adelman et al., 2011). For example, Abutalebi et al. (2012) found that bilinguals used the ACC more efficiently than monolinguals on a flanker task (a visual test of response inhibition), and bilinguals' flanker task performance correlated with both grey matter density and BOLD response in the ACC.

Our finding of the association of nondominant language performance with thickness of the ACC in AD patients lends support to the idea that the same brain regions that are enhanced by bilingual language use are also important for the maintenance of bilingualism in AD. Indeed, the bilingual index (an objective measure of bilingualism) is at least as strongly related to ACC thickness as the nondominant language (Supplemental Figs. 1 and 2). However, the correlation between bilingual ability and ACC thickness is apparent only in patients and not controls, despite the lack of a difference in the mean ACC thicknesses between the groups. This suggests that this region did not exhibit significant atrophy in our AD patients. Because all of the other major hubs of the cognitive control network (namely the IFG and IPL) did show severe atrophy in AD (Table 2), we speculatively interpret these findings as evidence that atrophy in these alternate control structures places a greater burden on the ACC, such that integrity of this last control hub becomes essential for the maintenance of bilingualism (and specifically nondominant language use). This relationship is masked by intact cognitive systems in normal controls. This is in line with the suggestion of Gold (2015) that bilingualism confers cognitive reserve through effects on the cognitive control networks rather than explicit memory systems, either through direct structural changes (see Abutalebi and Green, 2016) or development of alternative pathways which could be recruited to compensate for early disruptions.

Several limitations of the present study should be noted. First, the sample size was relatively small, precluding a voxel-wise whole-brain analysis. We instead chose to focus on regions of interest from the literature which may introduce bias and miss unexpected results. Given this smaller sample size, caution should be taken in interpreting any null findings, and future replication with different groups of bilinguals is warranted. Second, the AD and NC groups differed in education by approximately 4 years. While we adjusted for education in regression analyses, the potential for non-linear interactions between brain changes, education and bilingualism warrants further study. This point is emphasized by the results of Gollan et al. (2011) who found that degree of bilingualism was associated with age of AD diagnosis only for participants with low education level. This suggests an upper limit to the extent to which cognitive reserve can function to delay dementia.

In contrast to these limitations, the sample was a well-characterized group of Spanish-English bilinguals who had undergone thorough clinical and neuropsychological evaluations that included objective measures of language ability in both languages. The use of the MINT administered in both languages allowed measurement of language ability as a continuous variable for each language, and allowed degree

of bilingualism to be measured in an objective manner on a continuous scale. This approach provides significant advantages over most previous studies that performed group comparisons by treating bilingualism as a dichotomous variable based upon the participant's self-report of their proficiency (which is not as powerful or reliable as the MINT in measuring language proficiency; Tomoschuk et al., 2018).

5. Conclusions

We examined cortical structural correlates of dominant and nondominant language abilities in patients with AD and cognitively normal adults, controlling for age and education. Correlations between dominant language naming performance and measures of cortical thickness were identified in the left entorhinal cortex and left middle temporal gyrus. These results are consistent with the temporal lobe atrophy and decline in naming that occur in AD. In contrast, we found a robust correlation between nondominant language naming performance and thickness of the left caudal ACC, a region associated with conflict monitoring and language switching. This association was only apparent in bilinguals with AD, and suggests that AD-related atrophy may increase reliance on the ACC for the control requirements of nondominant language use.

Declarations of interest

DSS reports no disclosures. AS reports no disclosures. DPS serves as a consultant for Aptinx, Inc. and Biogen MA, Inc. DG serves as editor for Alzheimer's Research and Therapy, and as a paid consultant on Data Safety Monitoring Boards for Pfizer, Inc., Elan, Inc., and Balance Pharmaceuticals, Inc. JBB has served on advisory boards for Elan, Bristol-Myers Squibb, Avanir, Novartis, Genentech, and Eli Lilly and holds stock options in CorTechs Labs, Inc and Human Longevity, Inc. THG reports no disclosures.

CRediT authorship contribution statement

Denis S. Smirnov: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Visualization. **Alena Stasenko:** Conceptualization, Investigation, Writing - original draft. **David P. Salmon:** Conceptualization, Writing - original draft, Supervision. **Douglas Galasko:** Resources, Writing - original draft. **James B. Brewer:** Methodology, Software, Resources, Supervision. **Tamar H. Gollan:** Conceptualization, Investigation, Writing - original draft, Supervision, Project administration.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2019.107131.

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