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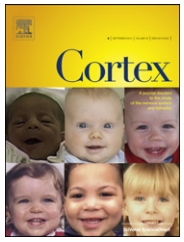

Research report

Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease

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ABSTRACT

Much of the research on delaying the onset of symptoms of Alzheimer's disease (AD) has focused on pharmacotherapy, but environmental factors have also been acknowledged to play a significant role. Bilingualism may be one factor contributing to 'cognitive reserve' (CR) and therefore to a delay in symptom onset. If bilingualism is protective, then the brains of bilinguals should show greater atrophy in relevant areas, since their enhanced CR enables them to function at a higher level than would be predicted from their level of disease. We analyzed a number of linear measurements of brain atrophy from the computed tomography (CT) scans of monolingual and bilingual patients diagnosed with probable AD who were matched on level of cognitive performance and years of education. Bilingual patients with AD exhibited substantially greater amounts of brain atrophy than monolingual patients in areas traditionally used to distinguish AD patients from healthy controls, specifically, the radial width of the temporal horn and the temporal horn ratio. Other measures of brain atrophy were comparable for the two groups. Bilingualism appears to contribute to increased CR, thereby delaying the onset of AD and requiring the presence of greater amounts of neuropathology before the disease is manifest.

1. Introduction

In the course of diagnosing patients with Alzheimer's disease (AD) and other forms of neurodegenerative disorders, clinicians often encounter individuals with substantial levels of brain atrophy but with relatively spared cognitive functioning. A recent review found that approximately 30% of individuals who exceed pathological criteria for AD at autopsy had shown no signs of cognitive impairment during life (Valenzuela and Sachdev, 2006). This mismatch between degree of brain

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atrophy and level of cognitive functioning has been attributed to the concepts of 'brain reserve' and 'cognitive reserve' (CR) (Stern, 2002, 2009), although the nature of these constructs is still poorly understood. Cases of brain reserve are thought to involve individuals whose greater reserve capacity reflects some structural features of the brain itself; suggested characteristics include greater brain size, increased number of neurons, and larger pyramidal neurons (Sachdev and Valenzuela, 2009; Valenzuela and Sachdev, 2006). CR, in contrast, emphasizes functional rather than structural benefits associated with a variety of intellectual, social and physical activities in a person's daily life. Thus, a large number of studies have now documented the beneficial effects of education, occupation and stimulating leisure activities in reducing or delaying the incidence of AD and other forms of dementia (Fratiglioni et al., 2004; Sachdev and Valenzuela, 2009; Stern, 2009; Valenzuela and Sachdev, 2006). One limitation on the usefulness of the concept of CR, however, is its correlational nature. It is often unclear whether individuals with high levels of attainment in education or occupation who show evidence of CR do so because their brains are genetically well endowed, thereby enabling them to succeed, or whether their elevated levels of CR are caused more directly by heightened levels of intellectual and social engagement.

The constant use of two languages over the lifespan is one type of mental activity that may also contribute to CR; if so, it is difficult to argue that some inherited brain characteristic leads a person to become bilingual. Rather, bilingualism occurs in the great majority of cases in response to such circumstances as emigration to a different country, differences between the family language and the language of school or workplace, and the need to communicate with neighboring groups (Diamond, 2010). Bilingualism thus seems a clear case of an environmental factor that acts to produce CR, although of course this environmental factor may well also affect the brain, its development and organization and contribute to brain reserve.

What is the evidence that bilingualism has an effect on mental functioning? Bialystok and colleagues have reported that bilingualism in children (Bialystok, 2001) and adults (Bialystok et al., 2004, 2006) enhances specific skills associated with cognitive and attentional control. The constant necessity to resist attending to a second language in favor of the one in use, and the need to switch between languages demands more effortful attention than does monolingual speech production, and this greater cognitive demand fosters the development of a higher level of attentional control (reviewed in Bialystok et al., 2009). These results prompted the question of whether such highly practiced and developed skills in bilinguals might have some neuroprotective function in older adults in the context of dementia. Preliminary evidence in favor of this outcome was reported in a study by Bialystok et al. (2007). They recorded the ages at which symptoms of dementia appeared in 184 patients, half of whom were bilingual, and reported a delay of over 4 years in the onset of symptoms in the bilinguals relative to the monolinguals. Cognitive level and other lifestyle variables were comparable, so the authors concluded that the bilingual group benefited from protection as a result of their lifelong experience in using two languages. These findings were subsequently replicated in a new study of 211 patients, all diagnosed with probable AD and half of whom were bilingual (Craik et al., 2010). Similar results were reported by Chertkow et al. (2010) who studied a sample of 632 patients who were diagnosed with probable AD and found a delay of almost 5 years in the diagnosis of AD in bilingual patients, although this result was found only in an immigrant group. However, a significant protective effect was found more generally in patients who spoke three or more languages. Thus, the conclusion that bilingualism (or multilingualism) is associated with a very significant delay (4–5 years) in the onset of symptoms of AD is well documented in total samples of over 1000 patients.

The relation between brain pathology and cognitive functioning in the context of CR may be demonstrated in two major ways. First, if two groups, one with high and the other with low levels of CR are matched on degree of brain pathology, then the high CR group should show higher levels of cognitive functioning – their greater CR is protective and confers an advantage. The second approach is to match the two groups on cognitive level or on level of clinical severity, with the prediction that the high CR group should exhibit greater amounts of AD pathology. Again, the logic is that the group's higher levels of CR compensates for the advanced pathology, enabling them to function at a higher level than the pathology would normally predict. This second approach was one of the earliest methods used to test the CR hypothesis (Stern, 2009), and was also the method adopted in the present report.

In a series of studies in the 1990s, Stern and colleagues used resting regional cerebral blood flow (rCBF) as a surrogate measure of degree of AD pathology. This assumption was based on previous work showing that rCBF values are related to the underlying pathology; blood flow decreases as pathology increases. Using this logic with patients matched for clinical severity of AD (based on cognitive and functional measures) the investigators found negative correlations between years of education and resting rCBF levels in areas of the brain associated with AD. That is, more education was associated with reduced blood flow and higher levels of pathology. Parallel findings were obtained for occupation and engagement in leisure activities (reviewed in Stern, 2009). A similar approach was taken by Kidron et al. (1997); they found that individuals with more education showed more ventricular enlargement in the parietal region, indicating more atrophy. Thus it appears that more education allows individuals to function at a higher level than their degree of atrophy would predict. In the present study we measured brain atrophy directly with computed tomography (CT), with the prediction that bilingual patients, matched on cognitive level and clinical severity with monolingual patients, would show greater atrophy in brain regions associated with AD pathology.

As described below, we selected two groups of patients, one of monolinguals and the other of bilinguals, who had been diagnosed with probable AD, and who had received CT as part of the diagnostic process. Crucially, the groups were matched on level of cognitive functioning and also on degree of clinical severity. Pathological changes occur early in the disease process, with preferential atrophy observed in the Medial-Temporal Lobes (MTL). Several studies have identified measures derived from CT that best characterize MTL atrophy. Zhang et al. (2008) analyzed the CT images of 248 dementia patients and 59 controls using a series of ratio scores based on linear measurements that assessed global, local, cortical and

central atrophy. Increases in temporal horn ratio, third ventricle ratio and suprasellar cistern ratio were the most significant linear measurements of medial-temporal atrophy that differentiated AD patients from controls, with other measures (e.g., Evans ratio, Huckman's number and Bicaudate ratio) indicating more general frontal or central atrophy. Frisoni et al. (2002) reported 93% sensitivity and 97% specificity in differentiating patients with mild AD from healthy controls using a measurement of the radial width of the temporal horn (rWTH). When CT scans are acquired with a maximal view of the MTL (i.e., ~20° caudal to the orbitomeatal line) the rWTH is a very sensitive marker of AD. In fact, some practitioners have proposed that the measure be used routinely in the clinic, given its good inter- and intra-rater reliability (Frisoni et al., 2002; Rossi et al., 2004). In the present case we took a number of linear measurements of brain atrophy from the CT scans of monolingual and bilingual patients diagnosed with probable AD. Given that the groups were matched on cognitive level and on degree of clinical severity, we predicted that the bilingual group would show greater evidence of brain atrophy in the MTLs, with little or no difference in measures of frontal or central atrophy. More specifically, we predicted that measurements of rWTH, along with the temporal horn ratio and the third ventricle ratio would be greater in the bilingual group than in the monolingual group, given that these measures are indicative of MTL atrophy and AD.

2. Method

CT scans of 40 patients with a diagnosis of probable AD were obtained from the memory disorders clinic servicing older adults at St. Michael's Hospital in Toronto. All patients had received a comprehensive medical history, physical examination, mental status evaluation (MMSE, Behavioral Neurology Assessment (BNA), Clock Drawing), clinical CT scan and screening blood tests. On the basis of these interviews and tests, the examining physician rated each patient for severity of dementia in terms of the standard Clinical Dementia Rating (CDR) scale. Half of the subjects had been classified as bilingual by asking both the patient and a significant other (when available) if he/she was fluent in a second language and had used both languages consistently throughout most of his or her life. Bilingualism was confirmed by a spouse/caregiver in 16/20 bilingual AD patients. Monolingual and bilingual AD patients were matched on the BNA test of cognitive function. The BNA (Darvesh et al., 2005) measures memory, language, attention, visuospatial function, naming and executive function. In addition, the two groups were similar in terms of number of years of education, gender mix (six males and 14 females in each group) and two additional measures of cognitive status (MMSE and clock drawing). Functional status of all patients was assessed using the Katz Activities of Daily Living (ADL) index. The Katz ADL index measures the patient's ability to perform ADL independently. Occupational status was measured on a four-point scale developed by Human Resources and Skills Development Canada (2009). Details of these variables are provided in Table 1. This study received approval from the Hospital Research Ethics Board.

2.1. CT acquisition

All subjects underwent a non-contrast CT head scan. In 38 of the 40 scans analyzed in the current study the section orientation was parallel to the plane of the temporal lobe – ~20° caudal to the orbitomeatal line. This orientation was necessary to accurately measure the rWTH. All 40 scans were included when analyzing the other linear measurements. The LightSpeed QX/I scans had the parameters 120 kV at 2.5 mm and 5 mm slice thickness and a range of 170–340 mA at 2.5 mm slice thickness and 140–280 mA at 5 mm slice thickness.

2.2. CT measurements

CT linear measurements were derived using the digital calipers in Analyze 9.0 (2001). Linear measurements were taken as described by Zhang et al. (2008, 2009) (see Fig. 1): the maximal transversal intracranial width (A), the suprasellar cistern (B), the temporal horn diameter (C), the minimal intercaudate distance (D), the maximal frontal horn width (E), the maximal width of the third ventricle (F) and the maximal width of the frontal skull (G). With those measurements the following indices were calculated (see Table 2); suprasellar cistern ratio (B/A), temporal horn ratio (C/A), bicaudate ratio (D/A), Huckman's number (D + E), third ventricle ratio (F/A) and the Evans ratio (E/G). In addition to these, measurements of the rWTH were also obtained (left, right and greatest) using the methods outlined in Frisoni et al. (2002).

3. Results

The results for the demographic measures are shown in Table 1. The variables age at CT scan, age at diagnosis, and education are measured in years; occupation was measured on a four-point scale developed by Human Resources and Skills Development, Canada (2009) in which higher numbers signify higher status. There were no significant differences between groups in either

Table 1 – Demographic and behavioral characteristics of monolingual and bilingual patients.

	Monolingual ($n = 20$)		Bilingual ($n = 20$)		p-value
	Mean	SD	Mean	SD	
Age at CT scan	77.2	7	78.9	7.6	.45
Age at diagnosis	77.3[a]	6.8	78.9	7.7	.5
Education (years)	13.6	3.5	11.6	4.5	.12
Occupational status	3.2[b]	1.2	2.1[b]	1.2	.007
CDR	1.2	.4	1.2	.4	1.0
Katz ADL index (/6)	5.6	.8	5.6	.8	.91
Overall BNA (/114)	66.4	13.7	64.4[a]	17.7	.7
MMSE (/30)	23.2[a]	3	22.1[c]	5.1	.43
Clock Drawing Test (/15)	10	4.2	10.3	4.8	.83

a $n = 19$.
b $n = 18$.
c $n = 17$.

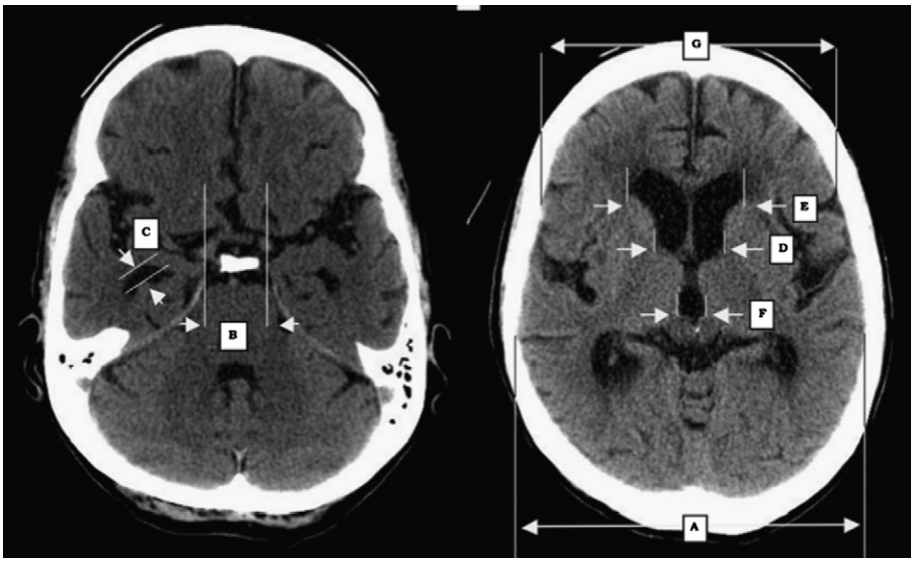

Fig. 1 – Linear measurements obtained from the axial CT slices. Maximal transversal intracranial width (A), the suprasellar cistern (B), the temporal horn diameter (C), the minimal intercaudate distance (D), the maximal frontal horn width (E), the maximal width of the third ventricle (F) and the maximal width of the frontal skull (G). With those measurements the following indices were calculated (see Table 2); suprasellar cistern ratio (B/A), temporal horn ratio (C/A), bicaudate ratio (D/A), Huckman's number (D + E), third ventricle ratio (F/A) and Evans ratio (E/G).

age at CT scan or age at diagnosis. The groups were also statistically similar in cognitive status as indicated by years of education, BNA, MMSE, and Clock drawing, all p-values $> .10$. Given that the breakdown of memory processes is a signature of AD we separately analyzed the memory subscores of the BNA and found that the groups did not differ; monolinguals scored 15.3 and bilinguals scored 14.3 out of a possible 25 ($p = .53$). Monolinguals and bilinguals also performed equivalently on the Katz ADL index ($p = .91$). The groups were significantly different in terms of occupational status ($p = .007$), with the monolinguals having higher job status than the bilinguals.

Table 2 – Brain ratios and scores of monolingual and bilingual patients.

	Monolingual ($n = 20$)		Bilingual ($n = 20$)	
	Mean	SD	Mean	SD
Bicaudate ratio	.17	.03	.18	.05
Huckman's number	60.01	7.82	64.30	12.18
Evans ratio	.36	.05	.35	.07
Suprasellar cistern ratio	.20	.02	.20	.02
Temporal horn ratio	.03***	.01	.05***	.02
Third ventricle ratio	.06**	.02	.07**	.01
Radial width of the temporal horn (rWTH) [a]				
Left	4.16***	1.09	7.23***	3.21
Right	4.04*	1.56	6.48*	3.64
Largest	4.69***	1.31	7.87***	3.53

*$p < .05$.
**$p < .01$.
***$p \leq .001$.
a $n = 19$/group.

The results for the calculations from the CT scans are shown in Table 2. Measurements of the bicaudate ratio, $t(20.21) = -.81$, $p = .43$, Huckman's number, $t(19.89) = -1.36$, $p = .19$, Evans ratio, $t(26) = .38$, $p = .70$, and the suprasellar cistern ratio, $t(26) = -.69$, $p = .50$, did not differ significantly between bilingual and monolingual patients. The first three of these measures are indications of general brain atrophy although the suprasellar cistern ratio may have some diagnostic utility in AD (Zhang et al., 2008). However, bilingual patients had significantly higher values than the monolingual patients in the temporal horn ratio, $t(18.49) = -2.64$, $p = .02$, and third ventricle ratio measures, $t(26) = -3.45$, $p = .002$, indicating more atrophy in the MTLs. The rWTH, arguably the best measure of temporal lobe atrophy and AD (Frisoni et al., 2002), was significantly larger in bilingual AD patients than in monolingual AD patients (all p's $< .05$) (see Table 2).

4. Discussion

The present study has shown that a group of bilingual patients with AD exhibited substantially greater amounts of brain atrophy in regions associated with disease pathology than monolingual patients when the two groups were matched for level of overall cognitive and memory performance and for years of education. Specifically, bilingual patients had significantly more cerebral atrophy, and the atrophy was most marked in areas traditionally used to distinguish AD patients from normal controls – the temporal horn ratio (Zhang et al., 2008), third ventricle ratio and the rWTH (Frisoni et al., 2002). The groups did not differ in measures of central and frontal atrophy, however, none of which is associated with AD. To our knowledge, this is the first study to demonstrate significant

objective neuroanatomical differences between monolingual and bilingual AD patients matched for cognition, education and disease severity.

Is it possible that the observed group differences in brain atrophy are attributable to factors other than bilingualism? The differences between the groups in education and occupation work against our hypothesis, since both years of education and occupational status were greater in monolinguals. Another possibility is that bilingual patients are often immigrants to the country of testing and that people who emigrate may have more drive than those who remain. In the present samples, nine of 20 monolinguals and 16 of 20 bilinguals were immigrants, in line with typical trends. However, in two previous studies (Bialystok et al., 2007; Craik et al., 2010) the delay in onset of AD associated with bilingualism was not affected by immigrant status. With regard to the non-significant difference in age at time of scanning, it is well established that cerebral atrophy increases with age (Raz et al., 1995). There were no differences between the groups in measures of central and frontal atrophy, however (i.e., in the bicaudate ratio, Huckman's Number or the Evans ratio), so we conclude that the differences in the medial-temporal regions are specifically attributable to AD pathology.

Prior work in this area has shown that the onset of AD is significantly delayed by as much as 5 years in patients who are bilingual (Bialystok et al., 2007; Craik et al., 2010). In both studies, differences in education, occupation or immigration status were ruled out as the source of the effect. What remains to be determined is the precise mechanism by which bilingualism confers its advantage. As demonstrated in numerous past studies, certain factors appear to contribute to increased CR, potentially delaying the onset of AD and requiring the presence of more advanced neuroanatomical changes before the disease is manifest. Using the distinction between CR and brain reserve described above, the present findings clearly conform to the first description – the bilingual patients showed substantially greater atrophy than their monolingual counterparts, yet performed at the same cognitive level.

It has been well documented that neuropathology in the brains of patients with AD correlates strongly with the degree of atrophy, suggesting that the brains of the bilingual patients not only suffered more degeneration but were also likely to have exhibited more neuropathology. In spite of this, the two groups of patients were found to function cognitively at the same level, including their levels of memory performance, supporting the CR hypothesis and also the idea that bilingualism acts as one source of CR. Previous studies have shown accelerated brain atrophy in certain subtypes of AD patients, specifically patients with psychosis or a frontal variant. However, such patients typically demonstrate a worse clinical course in addition to showing greater cerebral atrophy. Prior studies have also shown a dissociation between clinical disease expression, brain volume and neuropathology suggesting that this discrepancy may be mediated by factors linked to CR (Mortimer et al., 2004; Wolf et al., 1999).

The results from the current study suggest that bilingualism is one factor that provides CR and thereby modulates the behavioral expression of the underlying neuropathology associated with AD. These findings should be interpreted cautiously given the relatively small sample sizes. Nevertheless, the group differences are highly significant statistically, and are in line both with existing behavioral results (Bialystok et al., 2007; Craik et al., 2010; Chertkow et al., 2010) and with expectations from a CR perspective. Many puzzles remain however; how does CR work, for example? In general, it seems most likely that such factors as education, social, physical and intellectual activity modify some other aspects of brain function (e.g., vascular supply or neuronal connectivity) that serve to compensate for the accumulated pathological brain burden. In that sense, all types of reserve are ultimately 'brain reserve.' An alternative possibility is that CR acts like a highly practiced skill, enabling the cognitive system to make more efficient use of reduced or impaired cerebral resources. Future studies using advanced neuroimaging techniques are needed to elucidate the responsible mechanisms and to compare neuropathological disease burden in larger samples of patients matched for multiple confounding variables.

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