Published in final edited form as:

Epilepsia. 2018 May ; 59(5): 1037–1047. doi:10.1111/epi.14072.

Does bilingualism increase *brain or cognitive reserve* in patients with temporal lobe epilepsy?

Anny Reyes^{1,2}, Brianna M. Paul^{3,4}, Anisa Marshall², Yu-Hsuan A. Chang², Naeim Bahrami², Leena Kansal⁵, Vicente Iragui-Madoz⁵, Evelyn Tecoma⁵, Tamar H. Gollan⁶, Carrie R. McDonald^{1,2,6}

¹San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

²Center for Multimodal Imaging and Genetics, University of California, San Diego, CA, USA

³Department of Neurology, University of California - San Francisco, San Francisco, CA, USA

⁴UCSF Comprehensive Epilepsy Center, San Francisco, CA, USA

⁵UCSD Comprehensive Epilepsy Center, San Diego, CA, USA

⁶Department of Psychiatry, University of California, San Diego, CA, USA

Abstract

Objective: Bilingual healthy adults have been shown to exhibit an advantage in executive functioning (EF) that is associated with microstructural changes in white matter (WM) networks. Patients with temporal lobe epilepsy (TLE) often show EF deficits that are associated with WM compromise. In this study, we investigate whether bilingualism can increase cognitive reserve and/or brain reserve in bilingual patients with TLE, mitigating EF impairment and WM compromise.

Methods: Diffusion tensor imaging was obtained in 19 bilingual and 26 monolingual patients with TLE, 12 bilingual healthy controls (HC), and 21 monolingual HC. Fractional anisotropy (FA) and mean diffusivity (MD) were calculated for the uncinate fasciculus (Unc) and cingulum (Cing), superior frontostriatal tract (SFS), and inferior frontostriatal tract (IFS). Measures of EF included Trail Making Test-B (TMT-B) and D-KEFS Color-Word Inhibition/Switching. ANCOVAs were conducted to compare FA and MD of the Unc, Cing, SFS, and IFS and EF performance across groups.

Results: In bilingual patients, FA was lower in the ipsilateral Cing and Unc compared to all other groups. For both patient groups, MD of the ipsilateral Unc was higher relative to HCs. Despite more pronounced reductions in WM integrity, bilingual patients performed similarly to monolingual TLE and both HC groups on EF measures. By contrast, monolingual patients performed worse than HCs on TMT-B. In addition, differences in group means between bilingual and monolingual patients on TMT-B approached significance when controlling for the extent of

Disclosure of conflicts of interest/ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflicts of interest to disclose.

WM damage ($p = 0.071$; $d = 0.62$), suggesting a tendency towards higher performance for bilingual patients.

Significance: Despite poorer integrity of regional frontal lobe WM, bilingual patients performed similarly to monolingual patients and HCs on EF measures. These findings align with studies suggesting that bilingualism may provide a protective factor for individuals with neurological disease, potentially through reorganization of EF networks that promote greater cognitive reserve.

Keywords

executive function; diffusion tensor; brain function; white matter integrity bilingualism

Introduction

Simultaneously managing two or more languages has been hypothesized to result in adaptive changes in the brain that contribute to enhanced cognitive functioning^{1–3}. In particular, bilingualism has been associated with enhanced cognitive control abilities in healthy individuals, such as task switching⁴, mental flexibility⁴ and inhibition^{5; 6}. These changes may, in part, be due to a more efficient executive control system that is involved in both nonverbal and verbal cognitive functions mediated by the frontal lobes³. The joint activation of languages may lead to long-term modification of the executive control system, which is continuously recruited to manage attention to the target language and simultaneously inhibit the non-target language⁷.

The bilingual population worldwide continues to increase, and therefore, understanding how bilingualism affects the brain and brain disorders is of utmost importance. Adaptive brain changes reported in bilingual individuals have been suggested to provide *cognitive reserve*, a protective mechanism that allows individuals to cope with brain pathology by using residual brain resources more efficiently^{1;8;9}. For example, researchers have found a delay in the onset of symptoms in bilingual patients with Alzheimer's disease (AD) relative to their monolingual counterparts. The bilingual advantage has also been hypothesized to mitigate cognitive decline in healthy aging^{1;2}. By contrast, *brain reserve* refers to individual differences in brain structure or microstructure (i.e., greater brain volume, more synaptic connections) that make some individuals more resistant to brain pathology than others⁹. Thus, individuals with higher brain reserve are less likely to exhibit cognitive impairment compared to those with less reserve. Although the mechanism(s) through which bilingualism promotes cognitive and/or brain reserve remains unclear, one hypothesis is that functional or structural neuroplasticity within white matter (WM) networks may lead to greater resilience against brain pathology, thus mitigating the effects of brain pathology on cognition^{8;10–12}.

Despite an emerging literature on the effects of bilingualism on structural and functional brain networks, the effects of bilingualism on structural neuroplasticity in patients with temporal lobe epilepsy (TLE) have not been well addressed. Electrical stimulation mapping and fMRI studies of bilingual patients with epilepsy have shown that primary (L1) and secondary (L2) languages differ in anatomical distribution, with language-specific sites activating for L2 but not for L1^{13;14}. Thus, bilingualism may lead to differences in

functional reorganization of language networks in individuals with epilepsy, and it is possible that bilingualism results in changes to other cognitive networks in TLE as well.

Structural and functional alterations within frontal networks have been well-documented in TLE, and these changes have been associated with executive dysfunction^{15–19}. Despite the well-known deficits in EF found in patients with TLE²⁰ and the noteworthy differences in EF between monolingual and bilingual individuals¹, only one study has examined the effects of bilingualism on EF in epilepsy²¹. Veenstra et al.²¹ found that bilingual children with epilepsy demonstrate advantages in working memory relative to monolingual children with epilepsy. The authors proposed that perhaps bilingualism offers a protective factor against epilepsy-related dysfunction. Although this study highlighted an important gap in the literature, the authors did not examine whether the advantage in working memory was associated with changes to underlying WM networks.

The present study sought to provide preliminary data on the effects of bilingualism on WM structure and function in patients with refractory TLE. We tested whether 1) bilingualism increases *brain reserve*, mitigating WM compromise in bilingual patients compared to monolingual patients with TLE and 2) bilingualism increases *cognitive reserve* in bilingual patients, allowing for better EF performance despite the presence of frontal lobe pathology.

Methods

Participants

This study was approved by the Institutional Review Boards at UC San Diego and UC San Francisco, and informed consent was collected from all participants. Twenty-one bilingual and 26 monolingual patients with medically refractory TLE and 12 bilingual and 21 monolingual healthy controls (HC) were identified for inclusion in the study. All patients were recruited through referral from the UC San Diego or UC San Francisco Epilepsy Centers. Inclusion criteria for patients included a unilateral TLE diagnosis by a board-certified epileptologist, in accordance with the criteria defined by the International League Against Epilepsy, based on video-EEG telemetry, seizure semiology, and neuroimaging evaluation. The presence of mesial temporal sclerosis (MTS) and other pathologies was determined by inspection of MRI images by a board-certified neuroradiologist. In 27 patients, MRI findings suggested the presence of ipsilateral MTS, with no patients demonstrating dual pathology. HCs were included if they were between the ages of 18 and 65 and had no reported history of neurological or psychiatric disease. Bilingual patients with TLE and HCs self-identified as bilingual during a neuropsychological evaluation and provided information on the languages in which they were proficient. All patients were evaluated by a board-certified neuropsychologist as part of a pre-surgical evaluation, whereas HC were evaluated on the same battery of tests per a research protocol. Participants were included in the study if they reported English as L2 and/or reported learning a different language before age 6. Two TLE patients were excluded from the study based on these criteria. For the remaining 19 bilingual TLE patients, all but one learned English as an L2; patients learned English on average at age 8.46 (SD = 4.7, Range = 3–16). One additional bilingual who reported learning Arabic at age 3, and having Arabic speaking parents, was also included. All patients worked or attended school in English but spoke another language

at home, providing daily use of both languages. Table 2 includes age of exposure to L2, years of exposure to L2, and method of exposure to L2 for bilingual patients. The distribution of reported L1 among bilingual patients and controls was: Patients: 68.4% Spanish, 5.3% English, 10.5% Vietnamese, 5.3% Arabic, 5.3% Italian, and 5.3% Japanese; Controls: 58.8% English, 16.7% Spanish, 16.7% Cantonese, 8.3% Vietnamese.

MRI acquisition

All patients were seizure-free, per self-report, for a minimum of 24 hours prior to the MRI scan. Patient and HC data were acquired on either a General Electric (GE) Discovery MR750 3T scanner with an 8-channel phased-array head coil at the Center for Functional MRI at UC San Diego or the Surbeck Laboratory for Advanced Imaging at UC San Francisco (N = 68) or on a GE 1.5T EXCITE HD scanner at UC San Diego (N = 10). Image acquisitions on the 3T scanner were identical at both centers and included a conventional three-plane localizer, GE calibration scan, a T1-weighted 3D customized FSPGR structural sequence (TR = 8.08 ms, TE = 3.16 ms, TI = 600 ms, flip angle = 8°, FOV = 256 mm, matrix = 256 × 192, slice thickness = 1.2 mm), and for standard diffusion MRI, a single-shot pulse-field gradient spin-echo EPI sequence (TR = 8000 ms, TE = 82.9 ms, flip angle = 90°, FOV = 240 mm, matrix = 96 × 96 mm, slice thickness = 2.5 mm, echo-spacing = 588 ms). For the 3T scans, diffusion data used for standard DTI analysis were acquired with b-value = 0 and 1,000 s/mm² with 30 unique gradient directions. Image acquisition at the 1.5T scanner included a conventional 3-plane localizer, GE calibration scan, two T1-weighted 3D structural scans (TR = 10.7 ms, TE = 3.8 ms, TI = 1000 ms, flip angle = 8°, bandwidth = 31.25 Hz/pixel, FOV = 256 mm, matrix = 256 × 192, slice thickness = 1.0 mm) and for diffusion data, a single-shot echo-planar imaging with isotropic 2.5 mm voxels (TR = 12.3 s, TE = 75.6 ms, flip angle = 90°, FOV = 240 mm, matrix = 96 × 96, slice thickness = 2.5 mm, partial k-space acquisition). One volume series was acquired with 51 diffusion gradient directions using a b-value of 1000 s/mm² with an additional b=0 volume. For use in nonlinear B₀ distortion correction, two additional b=0 volumes were acquired with either forward or reverse phase-encode polarity.

DTI Processing

All data were processed at UC San Diego Center for Multimodal Imaging and Genetics using the same image processing pipeline. Preprocessing of the diffusion data included corrections for distortions due to magnetic susceptibility (B₀), eddy currents, and gradient nonlinearities, head motion correction and registration to the T1-weighted structural image. For B₀ distortion correction, a reverse gradient method was used²². A detailed description of the image processing is provided elsewhere²³. DTI-derived fractional anisotropy (FA) and mean diffusivity (MD) were calculated based on a tensor fit to the b = 1,000 data.

Fiber tracts calculations

Fiber tract FA and MD values were derived using a probabilistic diffusion tensor atlas (AtlasTrack), which has been validated in healthy controls and patients with TLE²⁴. For each participant, T1-weighted images were used to nonlinearly register the brain to a common space, and diffusion tensor orientation estimates were compared to the fiber tract atlas to obtain a map of the relative probability of a voxel belonging to a particular fiber

tract, given the location and similarity of diffusion orientations. Voxels identified with FreeSurfer as cerebrospinal fluid (CSF) or cortical gray matter were excluded from the fibers of interest. Fiber tracts were segmented in this way for each individual, and mean FA and MD values were calculated based on that participant's diffusion data. A full description of the atlas and the steps used to create the atlas and extract fiber regions of interest are described elsewhere²⁵. In the current study, the method described above was used to reconstruct the following tracts because they are among the most frequently implicated in EF¹⁷: cingulum bundle (Cing), uncinate fasciculus (Unc), inferior frontostriatal tract (IFS), and superior frontostriatal tract (SFS). The Cing connects cingulate gyrus to entorhinal cortex and the Unc arcs through the lateral fissure, connecting orbital frontal cortex and the anterior temporal lobe. The IFS and SFS connect the striatum to the inferior and superior frontal cortices, respectively¹⁹ (Fig. 1).

Neuropsychological measures

Verbal set-shifting and response inhibition were measured with the Delis-Kapan Executive Function System Color-Word Interference Inhibition/Switching condition and visuomotor set-shifting was measured with the Trail Making Test B (TMT-B). To estimate premorbid intellectual functioning, the Wechsler Test of Adult Reading (WTAR) was administered. The Color-Word Interference Inhibition/Switching condition was selected because this condition places the greatest demands on executive functioning of the four task conditions, requiring both inhibition and set-shifting. These scores were corrected for age. For TMT-B, normalized scores were used, however, these scores were not corrected for any demographic variables.

Statistical analysis

In TLE, all left and right fiber tracts were designated as ipsilateral or contralateral relative to side of seizure onset. For HC, half of the controls were randomly selected to have the left tracts designated as ipsilateral and the other half had the right tracts designated as ipsilateral. Multiple analysis of covariance (ANCOVA) tests were conducted to compare FA and MD across all four groups, with covariates of education, age, sex, premorbid functioning (WTAR raw scores). In addition, scanner was entered as a covariate in all analyses to control for differences in field strength and acquisition protocols between the two scanners. ANCOVA were also conducted to compare EF measures across groups, with education, age, and premorbid functioning (WTAR raw scores) as covariates. When results from the ANCOVA were significant, group contrasts were assessed using post-hoc pairwise tests with Bonferroni correction. Independent *t*-tests and Fisher's tests were used to test differences in clinical and demographic variables. Effect sizes for group differences were computed with Cohen's *d*.

Results

Patient clinical variables and participant demographics

There were no differences in age across the four groups [Age: $F(3, 74) = 0.79, p = 0.501$]; see Table 1. There were differences in education across groups [Education: $F(3, 74) = 5.02, p = 0.003$]; monolingual patients were less educated than monolingual HC group ($p = 0.011$)

and differences in group means between monolingual patients and bilingual HC approached significance ($p = 0.055$). Bilingual patients did not differ from the monolingual TLE group ($p = 1.00$) or bilingual HC ($p = 0.204$), however differences between bilingual patients and monolingual HC on education approached significance ($p = 0.077$). There were differences in sex distribution across groups (Fisher's Exact = 17.721, $p = 0.001$), with the bilingual patient group having all females. There were no differences in duration of epilepsy between bilingual and monolingual patients ($t(43) = -1.08$, $p = 0.285$), however, differences between groups means on age of seizure onset approached significance ($t(43) = 1.991$, $p = 0.053$), with bilingual patients demonstrating an earlier age of seizure onset. There were no differences in the presence of MTS or side of seizure onset between the TLE groups [MTS: $\chi^2 = 2.566$, Fisher's Exact $p = 0.134$; Side of onset: $\chi^2 = 0.114$, Fisher's Exact $p = 0.770$].

White matter network integrity: Does bilingualism increase brain reserve?

Omnibus ANCOVA revealed group differences in FA of the ipsilateral Cing and ipsilateral Unc (Table 3). Pairwise comparisons revealed that bilingual patients had lower FA in the ipsilateral Cing compared with monolingual patients ($p = 0.047$), bilingual HC ($p = 0.031$) and monolingual HC ($p = 0.026$) (Fig. 2A). Ipsilateral Unc FA was lower in bilingual patients relative to bilingual HC ($p = 0.002$) and monolingual HC ($p = 0.003$) (Fig. 2B). No other group contrasts were significant (Fig. 2A-D). These differences were consistent without the covariates in the model. ANCOVA revealed group differences in MD of the ipsilateral Unc [$F(3,69) = 4.80$, $p = 0.004$], with bilingual patients having higher MD relative to bilingual HC ($p = 0.012$) and monolingual HC ($p = 0.020$); and monolingual patients having higher MD relative to bilingual HC ($p = 0.034$) and monolingual HC ($p = 0.046$). No other group differences were found (Table 3). In efforts to duplicate the results described above with a more homogenous bilingual patient sample, we conducted post-hoc analyses with a group of bilingual patient who reported English as L2 (see Supplementary Table 2). In addition, in order to determine whether scanner differences contributed to group differences in FA and MD, post-hoc analyses were conducted with 3T data only (See Supplementary Table). Both supplemental analyses revealed the same pattern of results described in the whole group analyses.

Because differences between monolingual and bilingual patients with TLE were of particular interest, ANCOVAs were also conducted with the two patient groups only for tracts that were significant in the omnibus analyses. This revealed significantly lower FA in the ipsilateral Cing [$F(1, 38) = 6.007$, $p = 0.019$] and ipsilateral Unc [$F(1, 39) = 7.625$, $p = 0.009$], of bilingual patients compared to monolingual patients. Estimated means revealed large effect sizes for the ipsilateral Cing ($d = 0.87$) and Unc ($d = 0.98$) between bilingual and monolingual patients. There were no significant differences in MD of the ipsilateral Unc between the two patient groups [$F(1, 38) = 0.610$, $p = 0.440$].

Performance on measures of executive functioning: Does bilingualism increase cognitive reserve?

To validate that the fiber tracts selected in this study are associated with performance on the tests of executive function administered, Pearson r correlations were used to test for associations at the whole group level. Consistent with our previous studies^{19; 26}, higher FA

in the ipsilateral Cing, Unc, and IFS was associated with better performance on EF measures (all p -values < 0.05 ; Supplementary Table 1). Omnibus ANCOVA with education, premorbid functioning, and age as covariates, revealed group differences in TMT-B performance [$F(3, 71) = 5.002$, $p = 0.003$]. Pairwise comparisons revealed that monolingual patients had lower scores on TMT-B relative to monolingual HC ($p = 0.006$) and bilingual HC ($p = 0.009$). Bilingual patients did not differ from bilingual HC ($p = 0.116$), monolingual patients ($p = 1.00$), or monolingual HC ($p = 0.233$) (Fig. 3). Although group means on TMT-B for the monolingual and bilingual patient groups were within normal limits, 19.2% of monolingual and 21.1% of bilingual patients showed impaired performances (i.e., SS of 6 or less). The proportion of patients demonstrating impairment on TMT-B was not statistically different between the two groups ($\chi^2 = 0.023$, Fisher's Exact $p = 1.00$). There were no group differences for Color-Word Inhibition/Switching [$F(3, 40) = 1.545$, $p = 0.218$; marginal means: bilingual TLE = 8.346, monolingual TLE = 9.79, bilingual HC = 11.99, monolingual HC = 9.66).

Given that bilingual patients demonstrated greater pathology within the ipsilateral Cing and Unc relative to monolingual patients, but achieved similar performance on measures of EF, we conducted a secondary analysis to examine if bilingual patients would show a greater EF advantage when controlling for degree of WM pathology. As a measure of frontal lobe WM pathology, we included tracts that were significantly different across groups (i.e., FA of the ipsilateral Cing and Unc and MD of the ipsilateral Unc) as covariates in the model along with education, WTAR score, and age. The ANCOVA revealed group differences in TMT-B performance [$F(3, 69) = 3.75$, $p = 0.015$], with group contrasts revealing lower scores for monolingual patients with TLE relative to bilingual HC ($p = 0.037$) and monolingual HC ($p = 0.037$). Similar to the previous analysis, bilingual patients with TLE did not differ on TMT-B performance from either control group (Bilingual HC: $p = 1.00$; monolingual HC: $p = 1.00$). However, they also did not differ from monolingual patients ($p = 0.969$), despite a one scale score difference in group means (bilingual TLE TMT-B mean = 10.51; monolingual TLE TMT-B mean = 9.22). Nevertheless, ANCOVA between bilingual and monolingual patients with all co-variables included revealed that differences in group means approached significance in a direction suggesting higher TMT-B performance for the bilingual TLE group [$F(1, 39) = 3.435$, $p = 0.071$], with a medium effect size ($d = 0.62$) (Supplementary Figure 1). There were no group differences in Color-Word Inhibition/Switching performance when controlling for frontal WM pathology.

How do clinical variables and age of L2 acquisition influence EF in bilingual and monolingual patients with TLE?

To determine if any clinical variables (i.e., presence of MTS, side of seizure onset, age of seizure onset, and duration of epilepsy) influence differences in EF between bilingual and monolingual patients with TLE, a post-hoc analysis was conducted with these clinical variables as covariates. Although the groups did not *statistically* differ in these clinical variables, relative to the monolingual TLE group, there was a tendency for the bilingual TLE group to have an earlier age of seizure onset and a slightly greater proportion of patients with MTS that approached significance—both of which would be expected to lead to poorer EF and WM integrity in TLE²⁰. The ANCOVA revealed no group differences in TMT-B

performance [$F(1, 39) = 0.111$, $p = 0.741$; bilingual TLE TMT-B mean = 9.32; monolingual TLE TMT-B mean = 9.03] and there were no statistically significant covariates in the model.

In order to determine whether the age of L2 acquisition influenced WM integrity or EF performance, bilingual patients with TLE were divided into early and late bilinguals based on the age of L2 acquisition (i.e., age 6 or younger cut-off for early bilinguals). Post-hoc analyses revealed no differences in FA of the ipsilateral Cing or Unc, or on TMT-B performance between early and late bilingual patients (all p -values $> .05$; see Supplementary material).

Discussion

In this study, we explore whether bilingualism can increase *brain reserve* and/or *cognitive reserve* in bilingual patients with TLE relative to their monolingual counterparts. First, we demonstrate that bilingual patients show significantly lower ipsilateral frontal lobe WM integrity in two fiber tracts associated with EF (i.e., Cing and Unc) relative to HCs and monolingual patients. Second, despite greater disruption in frontal lobe WM networks, bilingual patients did not differ from HCs on measures of EF, while their monolingual peers performed worse than both HC groups on an EF measure involving visuomotor set-shifting. Third, when controlling for important clinical epilepsy variables such as age of onset, epilepsy duration, and MTS status, bilingual patients with TLE demonstrated comparable EF performance to monolingual patients. Finally, these findings remained the same after controlling for potential confounding variables such as education, age, sex, and a measure of premorbid functioning. Together, these findings suggest that in the presence of WM network pathology, bilingualism may increase *cognitive reserve* in patients with TLE. To the best of our knowledge, our study is the first to investigate the effects of bilingualism on both WM networks and EF in TLE, adding to a growing literature suggesting that bilingualism may offer a cognitive buffer to aspects of EF^{2;27} and potentially modifying the relationship between neuropathology and cognitive functioning¹²⁸²⁹.

Does bilingualism promote brain reserve?

Contrary to our first hypothesis, we found reductions in FA and increases in MD of fiber tracts implicated in EF in bilingual patients with TLE relative to the healthy control groups and monolingual patients with TLE. Greater WM integrity has been reported in bilinguals healthy adults^{2;8;10;30} children¹¹, and older adults^{12;27}; this could represent greater available neural substrates. The changes in WM structure in bilinguals have been proposed to lead to more widely distributed cognitive networks, resulting in more efficient communication between brain regions. In the presence of neurological disease, individuals with higher brain reserve may have a greater threshold for brain damage, mitigating the effects of brain disease⁹. This is particularly important for disease- or aging-related pathology, where increases in *brain reserve* may delay the expression of clinical symptoms or cognitive decline^{1;9;31}. We did not find evidence of increased brain reserve in the bilingual TLE group, but instead bilingual patients showed lower WM integrity in half of the fiber tracts queried. Consistent with our findings, Gold et al.²⁸ found that bilingual older adults matched on overall cognitive functioning to monolingual older adults, showed lower

FA in multiple WM tracts. The authors argued that bilingualism may not increase WM integrity (i.e., brain reserve) per se, but in the presence of pathology, bilingual individuals are able to compensate by leveraging a more efficient executive control network. Although it is not clear why our bilingual patients showed greater WM pathology relative to their monolingual counterparts, there was some tendency for bilingual patients to have an earlier age of seizure onset and a higher likelihood of having MTS—both of which have been linked to greater prefrontal WM damage and poorer EF²⁰. Thus, it is of interest that despite some evidence for a worse clinical phenotype, bilingual patients achieved equivalent performances on EF tasks.

Does bilingualism result in cognitive reserve?

In contrast to brain reserve, *cognitive reserve* refers to the ability of individuals to utilize brain resources more efficiently in order to circumvent the effects of neuropathology^{1;9;31}. In our study, bilingual patients with TLE demonstrated similar performance on measures of EF relative to all other groups, despite having lower WM integrity within frontal lobe tracts. In addition, there was a medium effect size for differences between bilingual patients and monolingual patients in EF when controlling for the extent of pathology within prefrontal WM networks, with bilingual patients demonstrating better performance. Lower FA and/or increases in MD are interpreted as representing axonal loss and demyelination within WM tracts and is frequently observed in patients with chronic TLE¹⁷. Our results suggest that bilingual patients with TLE may recruit other brain resources to perform EF tasks that may have been otherwise compromised due to a disrupted frontal lobe network. Similar to Gold et al.²⁸, Schweizer et al.²⁹ matched patients with probable AD on cognitive measures and degree of clinical severity and found that bilingual patients had greater brain atrophy in regions typically associated with AD pathology. In both studies bilingualism seemed to protect against the effects of pathology, as evidenced by comparable cognitive performance despite greater structural brain damage. Several studies have suggested that bilingualism may contribute to *cognitive reserve* by reorganizing the executive control network, which is constantly recruited when managing two languages simultaneously^{1;28;29}. The executive control network is believed to oversee the switching between the two languages and the inhibition of the non-target language in order to effectively communicate. This network can then be relied upon for other tasks, including nonverbal tasks, that require the same set of skills (i.e., task switching, inhibition), thus allowing individuals to compensate for the effects of pathology through use of these alternative cognitive resources. Our findings suggest that although bilingualism does not appear to increase *brain reserve*, it may help to mitigate the effects of epilepsy-related pathology on EF by increasing *cognitive reserve* via a more efficient executive control network.

TLE is now appreciated to be a network disorder associated with widespread structural and functional abnormalities^{17;32} including alterations in white matter microstructure^{19;33}, reduced regional brain activity³⁴, and cortical thinning¹⁵ within the frontal lobes. Disruptions within frontal lobe networks have been associated with executive dysfunction in numerous studies of TLE (for review see²⁰) and other neurological disorders³⁵. Approximately 20% of the patients in our study showed evidence of executive dysfunction compared to a normative sample, a percentage that falls at the lower end of estimates

reported in the literature, which range from 25–75% of TLEs impaired, depending on the patient sample and the tasks employed²⁰. The mechanisms by which TLE leads to disruption of frontal WM networks, and hence executive dysfunction, remains unclear. One hypothesis is that WM development is disrupted by the disease, leading to neurodevelopmental structural alterations within late-myelinating frontal lobe tracts³⁶. Learning a second language during the “critical period” of WM maturation may attenuate the functional manifestations of these changes by increasing cognitive reserve, thereby providing access to alternative, compensatory resources. The vast majority of the bilingual patients in our study were exposed to their second language during childhood or adolescence, thus it is possible that in this subset of patients, bilingualism offered compensatory resources helping mitigate the effects of the seizures. However, longitudinal studies are warranted to investigate the intersection between bilingualism and the effects of epilepsy on WM development.

Our study is unique in that it represents a first attempt at testing both the concepts of *brain reserve* and *cognitive reserve* within frontal lobe networks in bilingual patients with TLE compared to their monolingual counterparts, while controlling for important demographic and clinical variables. However, our study has several important limitations that should be noted and that we hope will motivate future work in this area. First, there are many factors that may influence cognitive reserve in bilinguals, such as level of education, IQ, occupational attainment, socioeconomic status, immigration, and language proficiency^{37–40}. Although our finding that bilingualism may lessen cognitive morbidity in the presence of epilepsy-related pathology, controlling for education, age, and premorbid functioning, the other aforementioned confounding factors could have influenced our results. Given the retrospective nature of this study, it was not possible to obtain a comprehensive language history in all the patients or objective measures of language proficiency in study participants. Since language proficiency has been shown to influence the relationship between bilingualism and cognitive outcome³⁹, collecting more quantitative data on language proficiency in future studies will be important. In addition, given that TLE is associated with deficits in language and semantic processing leading to impairments in auditory naming, visual naming and verbal fluency, developing methods to correctly quantify language proficiency in bilingual patients with known language deficits will aid in the classification of bilingualism in this clinical population. Second, although the lower FA found in the bilingual patients is most likely due to greater axonal loss and demyelination given evidence that this group represented a worse clinical phenotype (e.g., earlier age of seizure onset), it is possible that other factors (e.g., increased crossing fibers) may have contributed to lower FA in the bilingual patient group. Our study is cross-sectional and causal inferences about the relationship between bilingualism and WM networks in TLE cannot be inferred. Longitudinal studies could provide not only a better understating of how bilingualism modifies this relationship in the presence of TLE-related pathology, but they could also provide insight into the interplay of these factors during the process of aging in patients with TLE. Third, it is possible that our measures of EF or frontal lobe WM pathology were not comprehensive enough to capture other relationships within the data. We selected measures that are commonly used in the TLE and neuroimaging literature of EF, but ultimately, a broader examination of both brain and EF measures is warranted. Nevertheless, our study

offers preliminary data supporting the notion that bilingualism may promote *cognitive reserve*, but not *brain reserve*, in patients with TLE. These findings contribute to a growing literature exploring how individual differences (e.g., age, vascular health, premorbid functioning) can alter the response to pathology and influence the relationship between brain pathology and clinical phenotype. Longitudinal designs with more sophisticated imaging and enriched clinical information will hopefully improve our understanding of the myriad of factors that promote brain and cognitive reserve in epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors would like to acknowledge funding support from the National Institute of Health (R01 NS065838 to C.R.M.).

References

1. Guzman-Velez E, Tranel D. Does bilingualism contribute to cognitive reserve? Cognitive and neural perspectives. *Neuropsychology* 2015;29:139–150. [PubMed: 24933492]
2. Grundy JG, Anderson JAE, Bialystok E. Neural correlates of cognitive processing in monolinguals and bilinguals. *Ann N Y Acad Sci* 2017;1396:183–201.
3. Bialystok E, Craik FI, Green DW, et al. Bilingual Minds. *Psychol Sci Public Interest* 2009;10:89–129. [PubMed: 26168404]
4. Macnamara BN, Conway AR. Novel evidence in support of the bilingual advantage: influences of task demands and experience on cognitive control and working memory. *Psychon Bull Rev* 2014;21:520–525. [PubMed: 24092496]
5. Bialystok E, Craik FI, Klein R, et al. Bilingualism, aging, and cognitive control: evidence from the Simon task. *Psychol Aging* 2004;19:290–303. [PubMed: 15222822]
6. Bialystok E Cognitive complexity and attentional control in the bilingual mind. *Child Dev* 1999;70:636–644.
7. Jubin Abutalebi DG. Bilingual language production: The neurocognition of language representation and control. *J Neurolinguistic* 2007;20:242–275.
8. Li P, Legault J, Litcofsky KA. Neuroplasticity as a function of second language learning: Anatomical changes in the human brain. *Cortex* 2014;58:301–324. [PubMed: 24996640]
9. Stern Y What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002;8:448–460.
10. Pliatsikas C, Moschopoulou E, Saddy JD. The effects of bilingualism on the white matter structure of the brain. *Proc Natl Acad Sci US A* 2015;112:1334–1337.
11. Mohades SG, Struys E, Van Schuerbeek P, et al. DTI reveals structural differences in white matter tracts between bilingual and monolingual children. *Brain Res* 2012;1435:72–80. [PubMed: 22197702]
12. Luk G, Bialystok E, Craik FI, et al. Lifelong bilingualism maintains white matter integrity in older adults. *J Neurosci* 2011;31:16808–16813. [PubMed: 22090506]
13. Lucas TH 2nd, McKhann GM 2nd Ojemann GA. Functional separation of languages in the bilingual brain: a comparison of electrical stimulation language mapping in 25 bilingual patients and 117 monolingual control patients. *J Neurosurg* 2004;101:449–457. [PubMed: 15352603]
14. Polczynska MM, Japardi K, Bookheimer SY. Lateralizing language function with pre-operative functional magnetic resonance imaging in early proficient bilingual patients. *Brain Lang* 2017;170:1–11. [PubMed: 28343082]

15. McDonald CR, Hagler DJ Jr., Ahmadi ME, et al. Regional neocortical thinning in mesial temporal lobe epilepsy. *Epilepsia* 2008;49:794–803. [PubMed: 18266751]
16. Riley JD, Moore S, Cramer SC, et al. Caudate atrophy and impaired frontostriatal connections are linked to executive dysfunction in temporal lobe epilepsy. *Epilepsy Behav* 2011;21:80–87. [PubMed: 21507730]
17. Leyden KM, Kucukboyaci NE, Puckett OK, et al. What does diffusion tensor imaging (DTI) tell us about cognitive networks in temporal lobe epilepsy? *Quant Imaging Med Surg* 2015;5:247–263. [PubMed: 25853083]
18. Mueller SG, Laxer KD, Cashdollar N, et al. Voxel-based optimized morphometry (VBM) of gray and white matter in temporal lobe epilepsy (TLE) with and without mesial temporal sclerosis. *Epilepsia* 2006;47:900–907. [PubMed: 16686655]
19. Reyes A, Uttarwar V, Chang YA, et al. Decreased neurite density within frontostriatal networks is associated with executive dysfunction in temporal lobe epilepsy. *Epilepsy Behav* In Press 2017.
20. Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. *Epilepsy Res* 2012;98:1–13. [PubMed: 22100147]
21. Veenstra AL, Riley JD, Barrett LE, et al. The impact of bilingualism on working memory in pediatric epilepsy. *Epilepsy Behav* 2016;55:6–10. [PubMed: 26720703]
22. Holland D, Kuperman JM, Dale AM. Efficient correction of inhomogeneous static magnetic field-induced distortion in Echo Planar Imaging. *Neuroimage* 2010;50:175–183. [PubMed: 19944768]
23. McDonald CR, Leyden KM, Hagler DJ, et al. White matter microstructure complements morphometry for predicting verbal memory in epilepsy. *Cortex* 2014;58:139–150. [PubMed: 25016097]
24. Hagler DJ Jr., Ahmadi ME, Kuperman J, et al. Automated white-matter tractography using a probabilistic diffusion tensor atlas: Application to temporal lobe epilepsy. *Hum Brain Mapp* 2009;30:1535–1547. [PubMed: 18671230]
25. Holland D, Brewer JB, Hagler DJ, et al. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci US A* 2009;106:20954–20959.
26. Kucukboyaci NE, Girard HM, Hagler DJ Jr., et al. Role of frontotemporal fiber tract integrity in task-switching performance of healthy controls and patients with temporal lobe epilepsy. *JIntNeuropsycholSoc* 2012;18:57–67.
27. Olsen RK, Pangelinan MM, Bogulski C, et al. The effect of lifelong bilingualism on regional grey and white matter volume. *Brain Res* 2015;1612:128–139. [PubMed: 25725380]
28. Gold BT, Johnson NF, Powell DK. Lifelong bilingualism contributes to cognitive reserve against white matter integrity declines in aging. *Neuropsychologia* 2013;51:2841–2846. [PubMed: 24103400]
29. Schweizer TA, Ware J, Fischer CE, et al. Bilingualism as a contributor to cognitive reserve: evidence from brain atrophy in Alzheimer's disease. *Cortex* 2012;48:991–996. [PubMed: 21596373]
30. Felton A, Vazquez D, Ramos-Nunez AI, et al. Bilingualism Influences Structural Indices of Interhemispheric Organization. *J Neurolinguistics* 2017;42:1–11. [PubMed: 28579694]
31. Grant A, Dennis NA, Li P. Cognitive control, cognitive reserve, and memory in the aging bilingual brain. *Front Psychol* 2014;5:1401. [PubMed: 25520695]
32. Bell B, Lin JJ, Seidenberg M, et al. The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nat Rev Neurol* 2011;7:154–164. [PubMed: 21304484]
33. Loi RQ, Leyden KM, Balachandra A, et al. Restriction spectrum imaging reveals decreased neurite density in patients with temporal lobe epilepsy. *Epilepsia* 2016;57:1897–1906. [PubMed: 27735051]
34. Reyes A, Thesen T, Wang X, et al. Resting-state functional MRI distinguishes temporal lobe epilepsy subtypes. *Epilepsia* 2016;57:1475–1484. [PubMed: 27374869]
35. Elliott R Executive functions and their disorders: Imaging in clinical neuroscience *British Medical Bulletin* 2003;65:49–59. [PubMed: 12697616]
36. Lee CY, Tabesh A, Benitez A, et al. Microstructural integrity of early- versus late-myelinating white matter tracts in medial temporal lobe epilepsy. *Epilepsia* 2013;54:1801–1809. [PubMed: 24032670]

37. Stern Y The concept of cognitive reserve: a catalyst for research. *J Clin Exp Neuropsychol* 2003;25:589–593. [PubMed: 12815497]
38. Meng X, D’Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One* 2012;7:e38268. [PubMed: 22675535]
39. Gollan TH, Salmon DP, Montoya RI, et al. Degree of bilingualism predicts age of diagnosis of Alzheimer’s disease in low-education but not in highly educated Hispanics. *Neuropsychologia* 2011;49:3826–3830. [PubMed: 22001315]
40. Watson CW-M, Manly JJ, Zahodne LB. Does bilingualism protect against cognitive aging? Methodological issues in research on bilingualism, cognitive reserve, and dementia incidence. *Linguist Approaches Biling* 2016;6:590–604. [PubMed: 30505373]

Key points

- Bilingual patients with TLE show lower ipsilateral frontal lobe WM integrity in fiber tracts associated with EF relative to HCs and monolingual patients
- Despite reductions in frontal WM integrity, bilingual patients with TLE demonstrated comparable performance on EF measures to HCs
- There was a medium effect size difference between bilingual and monolingual patients in TMT-B when controlling for the extent of WM damage

Figure 1.

A) Coronal and B) Sagittal rendering of the cingulum bundle (Cing), uncinate fasciculus (Unc), superior frontostriatal tract (SFS), and inferior frontostriatal tract (IFS) derived from probabilistic diffusion tensor atlas (i.e., AtlasTrack) projected onto a T1-weighted image. The corpus callosum is portrayed in light gray in order to provide additional spatial information. The four white matter tracts of interest are shown for a single individual.

Figure 2.

Y-axis represents estimated marginal means $\pm$ standard error for FA, controlling for education, age, sex, WTAR scores, and scanner differences. A) Bilingual TLE had lower FA in ipsilateral Cing relative to monolingual patients, monolingual HC, and bilingual HC. B) Bilingual TLE had lower FA in ipsilateral Unc relative to monolingual HC and bilingual HC. C-D) No differences in IFS or SFS FA were found. FA: fractional anisotropy; Ipsi: ipsilateral; Contra: contralateral; Cing: cingulum; IFS: inferior frontostriatal; SFS: superior frontostriatal. Single asterisk represents Bonferroni-corrected significance at 0.05; double asterisk represents Bonferroni-corrected significance at 0.01.

Figure 3.

Y-axis represents estimated marginal means controlling for education, age, sex, and WTAR scores. Lower scores indicate longer time to completion on TMT-B. Bilingual patients with TLE did not differ from monolingual patients with TLE or either HC groups. Monolingual patients had lower scores relative to monolingual HC and bilingual HC. Double asterisks represents Bonferroni-corrected significance at 0.01.

Table 1:

Demographics and clinical variables

Demographics and clinical variables				
	Bilingual TLE	Monolingual TLE	Bilingual HC	Monolingual HC
N	19	26	12	21
Age (years)	34.79 (8.97)	38.18 (11.44)	32.58 (12.46)	37.14 (12.95)
Education (Years)	14.10 (2.33)	13.81 (2.00)	15.83 (2.82)	15.86 (1.77)
Sex: M/F	0/19	15/11	6/6	11/10
MTS: Yes/No	14/5	13/13		
Side of seizure onset: L/R	10/9	15/11		
Age of Onset	<i>13.36 (11.42)</i>	<i>21.50 (14.87)</i>		
Duration (years)	21.57 (12.23)	16.65(16.84)		
Neuropsychological variable				
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
WTAR	28.26 (8.99)	34.46 (7.15)	42.92 (6.96)	43.90 (4.59)

TLE: temporal lobe epilepsy; HC: healthy controls; F: females; M: males; L: left; R: right; MTS: mesial temporal sclerosis; WTAR: Wechsler Test of Adult Reading; standard deviations are presented inside the parentheses; bold signifies differences across groups; italics signifies group means approaching significance

Table 2:

Bilingual patient characteristics

Patient	L1	L2	Age at L2 first exposure	Years of exposure to L2	Method of L2 Exposure	English Category Fluency*	Side of seizure onset	Age of seizure onset	Wada	fMRI LI
1	Cantonese	English	9	19	Elementary - College	15	Left	11	Bilateral	Right
2	Japanese	English	SB	28	Elementary - College	12	Left	18	Left	Left
3	Spanish	English	14	35	Middle School-College	21	Left	40	Right	Right
4	Spanish	English	4	21	Elementary - College	14	Left	17	Left	-
5	Spanish	English	-	-	-	21	Right	2	Left	-
6	Spanish	English	-	-	-	13	Right	12	NW	-
7	Spanish	English	5	20	Elementary - College	17	Left	1	NW	-
8	Spanish	English	12	20	Middle School-College		Left	2	NW	-
9	Spanish	English	12	25	Middle School-High School	14	Left	7	NW	-
10	Spanish	English	13	18	Formal Schooling	15	Right	6	Left	Left
11	English	Arabic	3	33	Parents	12	Left	1	Left	Left
12	Arabic	English	4	22	Elementary - College	19	Right	21	NW	Left
13	Spanish	English	4	18	Elementary - College	12	Right	2	Left	Left
14	Spanish	English	-	-	-	13	Left	9	NW	-
15	Spanish	English	3	28	Elementary - College	18	Right	17	NW	Left
16	Spanish	English	16	25	High School/College	12	Right	29	NW	Left
17	Italian	English	11	33	Formal Schooling	18	Right	31	NW	Left
18	Vietnamese	English	4	24	Elementary - College	15	Left	23	NW	Left
19	Spanish	English	6	27	Elementary - High School	15	Right	5	NW	Mixed

L1: First language; L2: Second language; SB: simultaneous bilingual; NW: Wada was not performed

* Category Fluency total raw score in English

Table 3:

FA and MD group comparisons

	Bilingual TLE	Monolingual TLE	Bilingual HC	Monolingual HC	ANCOVA		Effect size
	Mean * (SD)	Mean * (SD)	Mean * (SD)	Mean * (SD)	F-value	P-value	η^2
Cing							
Ipsilateral							
FA	0.401 (0.074)	0.457 (0.061)	0.478 (0.062)	0.474 (0.064)	3.582	0.018	0.111
MD	0.789 (0.100)	0.759 (0.081)	0.744 (0.083)	0.750 (0.091)	0.594	0.621	0.019
Contralateral							
FA	0.437 (0.061)	0.465 (0.051)	0.454 (0.052)	0.448 (0.055)	1.102	0.354	0.031
MD	0.764 (0.078)	0.758 (0.066)	0.740 (0.066)	0.746 (0.069)	0.300	0.825	0.006
Unc							
Ipsilateral							
FA	0.363 (0.044)	0.393 (0.036)	0.424 (0.038)	0.417 (0.041)	5.503	0.002	0.149
MD	0.862 (0.074)	0.839 (0.061)	0.775 (0.062)	0.785 (0.064)	4.798	0.004	0.095
Contralateral							
FA	0.387 (0.043)	0.405 (0.035)	0.407 (0.038)	0.417 (0.041)	1.341	0.268	0.039
MD	0.825 (0.091)	0.817 (0.076)	0.795 (0.076)	0.800 (0.082)	0.344	0.794	0.008
IFS							
Ipsilateral							
FA	0.348 (0.025)	0.357 (0.031)	0.374 (0.027)	0.368 (0.027)	1.978	0.125	0.056
MD	0.792 (0.048)	0.781 (0.076)	0.744 (0.055)	0.752 (0.059)	1.764	0.162	0.029
Contralateral							
FA	0.356 (0.035)	0.365 (0.025)	0.366 (0.028)	0.365 (0.032)	0.335	0.80	0.012
MD	0.771 (0.069)	0.772 (0.056)	0.756 (0.059)	0.762 (0.064)	0.190	0.903	0.004
SFS							
Ipsilateral							
FA	0.433 (0.035)	0.425 (0.025)	0.430 (0.028)	0.427 (0.032)	0.284	0.837	0.010
MD	0.753 (0.052)	0.737 (0.046)	0.717 (0.045)	0.720 (0.046)	1.393	0.252	0.026
Contralateral							
FA	0.432 (0.035)	0.424 (0.030)	0.427 (0.031)	0.424 (0.032)	0.226	0.878	0.009
MD	0.742 (0.061)	0.729 (0.051)	0.715 (0.052)	0.728 (0.055)	0.518	0.672	0.013

* Estimated means were calculated using the following covariates: scanner differences, education, age, sex, WTAR; SD: standard deviation; Unc: uncinate; Cing: cingulum; SFS: superior frontostriatal; IFS: Inferior frontostriatal