Bilingualism and Structural Network Organization in Temporal Lobe Epilepsy

Resilience in Neurologic Disease

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Abstract

Background and Objectives

There is growing evidence that bilingualism can induce neuroplasticity and modulate neural efficiency, resulting in greater resistance to neurologic disease. However, whether bilingualism is beneficial to neural health in the presence of epilepsy is unknown. We tested whether bilingual individuals with temporal lobe epilepsy (TLE) have improved whole-brain structural white matter network organization.

Methods

Healthy controls and individuals with TLE recruited from 2 specialized epilepsy centers completed diffusion-weighted MRI and neuropsychological testing as part of an observational cohort study. Whole-brain connectomes were generated via diffusion tractography and analyzed using graph theory. Global analyses compared network integration (path length) and specialization (transitivity) in TLE vs controls and in a 2 (left vs right TLE) × 2 (bilingual vs monolingual) model. Local analyses compared mean local efficiency of predefined frontal-executive and language (i.e., perisylvian) subnetworks. Exploratory correlations examined associations between network organization and neuropsychological performance.

Results

A total of 29 bilingual and 88 monolingual individuals with TLE matched on several demographic and clinical variables and 81 age-matched healthy controls were included. Globally, a significant interaction between language status and side of seizure onset revealed higher network organization in bilinguals compared with monolinguals but only in left TLE (LTLE). Locally, bilinguals with LTLE showed higher efficiency in frontal-executive but not in perisylvian networks compared with LTLE monolinguals. Improved whole-brain network organization was associated with better executive function performance in bilingual but not monolingual LTLE.

Discussion

Higher white matter network organization in bilingual individuals with LTLE suggests a neuromodulatory effect of bilingualism on whole-brain connectivity in epilepsy, providing evidence for neural reserve. This may reflect attenuation of or compensation for epilepsy-related dysfunction of the left hemisphere, potentially driven by increased efficiency of frontal-executive networks that mediate dual-language control. This highlights a potential role of bilingualism as a protective factor in epilepsy, motivating further research across neurologic disorders to define mechanisms and develop interventions.

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Glossary

3D = 3 dimensional; **AD** = Alzheimer disease; **ANOVA** = analysis of variance; **B-LTLE** = bilingual LTLE; **B-RTLE** = bilingual RTLE; **dMRI** = diffusion-weighted MRI; **DRM** = dynamic restructuring model; **FOV** = field of view; **HC** = healthy control; **LTLE** = left TLE; **M-LTLE** = monolingual LTLE; **M-RTLE** = monolingual RTLE; **MTS** = mesial temporal sclerosis; **ROI** = region of interest; **RTLE** = right TLE; **TE** = echo time; **TI** = inversion time; **TLE** = temporal lobe epilepsy; **TR** = repetition time; **UC** = University of California; **UCSD** = UC San Diego; **UCSF** = UC San Francisco; **WASI** = Wechsler Abbreviated Scale of Intelligence.

One factor increasingly studied as a measure of resilience, particularly in neurodegenerative disease, is bilingualism—proficiency and/or active use of 2 or more languages. Extensive literature demonstrates that bilingualism is a unique process that leads to neuroplastic changes in the brain, presumably due to adaptation to the demands of dual-language use. This type of cognitive stimulation has been associated with increased resistance against cognitive aging and neurodegeneration[1-5] via mechanisms of cognitive and/or neural reserve.[3] Converging studies suggest increased efficiency of frontal-executive control networks in older bilinguals and bilinguals with Alzheimer disease (AD).[6-9] Other studies reported bilingualism-related modulation of connectivity within language-specific networks in AD[10,11] and in healthy bilinguals.[12-14] These findings suggest that the bilingual brain adapts to the demands of dual-language use, similar to a mental gym. Despite a large bilingual population worldwide and a growing number of bilingual individuals in the United States,[15] the potential role of bilingualism as a neuroprotective factor in epilepsy has been minimally investigated.

The broad and heterogeneous effects of focal epilepsy on the brain[16] have led to the conceptualization of epilepsy as a network-level disorder, often linked to devastating effects on cognition. The significant social and health care burden associated with cognitive dysfunction suggests a need to identify protective factors, such as bilingualism, to help maintain brain health for individuals with epilepsy. A previous study from our laboratory demonstrated that bilinguals with temporal lobe epilepsy (TLE) had comparable executive function but lower white matter integrity compared with monolinguals, providing evidence for cognitive reserve.[17] Here, we examine microstructural changes that may help explain function (i.e., neural reserve). Specifically, it is unknown whether the wiring among cortical regions increases due to bilingualism, thereby increasing whole-brain or subnetwork connectome organization in epilepsy.

A shift to understanding epilepsy as a network disorder has been accompanied by advances in quantifying whole-brain network connectivity, which provides the scaffolding for dynamic exchanges of information flow between brain regions.[18] A healthy brain network is thought to have an optimal balance of integration and specialization (i.e., high clustering of connections between neighboring brain regions, yet a short path between any 2 distant regions) that allows for rapid transfer and integration of information that supports complex cognitive functions. Previous studies have shown that integration and specialization of structural networks are disrupted in individuals with recurring seizures.[19] Network alterations have been associated with degree of cognitive impairment,[20-22] disease progression,[23] and postsurgical cognition,[24] demonstrating clinical relevance of whole-brain network topology in epilepsy.[25]

As network disruption presents a key target for resilience, the current study investigated the effect of bilingualism on whole-brain structural network organization in TLE. We hypothesized that being bilingual may provide a protective buffer against whole-brain white matter network dysfunction. In addition, we evaluated differences in local efficiency of frontal-executive and perisylvian (i.e., language specific) networks in bilingual and monolingual TLE given that bilingual language control is mediated by the coordination of language and executive control regions,[26] and epilepsy can alter language and executive function networks.[27] We also tested whether better network organization is related to higher executive function and/or language performance.
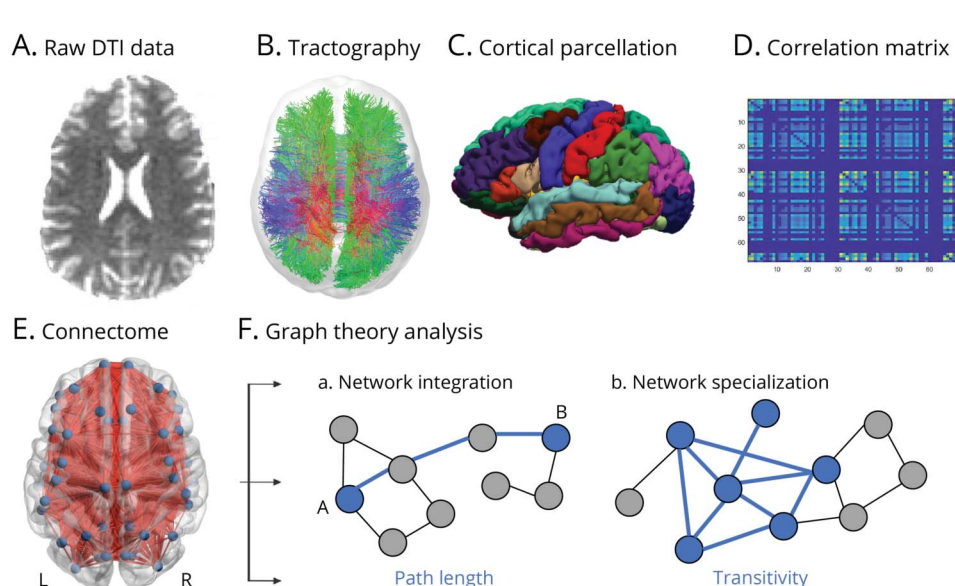
Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Review Board at the University of California (UC) San Diego (UCSD) or UC San Francisco (UCSF). All participants provided written informed consent.

Participant and Inclusion Criteria

Our initial sample had 133 patients with drug-resistant TLE and 84 neurologically healthy controls (HCs). A TLE diagnosis was established by epileptologists, based on video-EEG telemetry, seizure semiology, and neuroimaging. Inclusion criteria consisted of (1) age 18–65 years, (2) estimated premorbid IQ >70, (3) no evidence of large lesions or visible extratemporal pathology on MRI, (4) structural and diffusion-weighted MRI (dMRI) that passed visual quality inspection, and (5) sufficient evidence of bilingualism evidenced at follow-up interview. Sixteen patients were excluded for tumor (n = 3), bilateral seizure focus (n = 7), artifact and/or significant outlier in dMRI data (n = 4), and low bilingual proficiency (n = 2). Three HCs with incomplete demographic information were excluded.

Figure 1 Illustration of White Matter Connectome Generation and Graph Theory Analysis

A. Raw DTI data
B. Tractography
C. Cortical parcellation
D. Correlation matrix
E. Connectome
F. Graph theory analysis
a. Network integration
Path length
b. Network specialization
Transitivity

(A) Raw diffusion-weighted MRI data were preprocessed and registered to a T1 space. (B) Probabilistic whole-brain tractography was used to construct white matter fiber tracts connecting different brain regions (shown here is tractography from 1 participant for visualization). (C) Data were analyzed in a parcellated anatomic space with regions of interest (ROIs) selected from the Desikan-Killiany atlas, which were registered to each participant's diffusion tensor imaging space. (D) White matter connectivity matrices were generated by assessing pairwise connections between each pair of ROIs and input into a 2-dimensional matrix (shown here is an individual connectome) where each row and column represent an ROI, and the corresponding color is the strength of the structural connectivity between that pair of ROIs. (E) Network render of a structural connectome, which is equivalent to brain graphs, with ROIs representing nodes and white matter connections representing edges. For visualization, a matrix averaged across participants is imposed on a standard brain template using the BrainNet Viewer. (F) Connectivity matrices were analyzed with graph theory analysis to extract 2 global metrics of interest that reflect brain network organization—path length (a measure of network integration) and transitivity (a normalized clustering coefficient; a measure of network specialization).

Language Status Characterization

Bilingualism in TLE was established according to the following criteria: participants self-identified as bilingual and responded to a series of questions evaluating proficiency and the amount of active use of the non-English language spoken. All bilingual TLE (B-TLE) participants demonstrated English proficiency and completed a neuropsychological battery in English. Objective English proficiency was measured with the vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) or with letter fluency (F-A-S) when WASI was not administered. B-TLEs reported either learning English as their second language (L2; n = 23) or simultaneously learning English and another language before age 6 years (n = 6). Based on these criteria, 15 left TLEs (LTLEs) were classified as bilingual (B-LTLE) and 43 as monolingual (M-LTLE). Fourteen right TLEs (RTLEs) were classified as bilingual (B-RTLE) and 45 as monolingual (M-RTLE). Bilinguals learned English on average at 8.4 years (SD 9.0; range 0–35), typically considered just past the cutoff for early L2 acquisition (conventionally 6–7 years). Bilinguals used both languages for an average of 27.1 years (SD 8.9; range 5–46). Bilingual groups did not differ in age of English acquisition (p = 0.65) or duration of English use (p = 0.76). All B-TLEs received some education in English and were actively immersed in an English environment but used their other language at home. The most common other language was Spanish (n = 21). Although 19 of the HCs reported knowing a language other than English, we were confident in the bilingual status of only 11 (i.e., English as L2), as a detailed proficiency interview was not conducted with HCs.

Image Acquisition

Imaging at UCSD (n TLE = 61; n HC = 47) and UCSF (n TLE = 30) was performed with identical protocols on the same manufacturer and model—GE Discovery MR750 3 T with an 8-channel phased-array head coil. Thirty-six TLEs and 24 HCs were additionally scanned on a GE 1.5 T EXCITE HD scanner at UCSD. Image acquisitions at both 3 T centers included a conventional 3-plane localizer, GE calibration scan, a T1-weighted 3-dimensional structural scan (repetition time [TR] = 8.08 milliseconds, echo time [TE] = 3.16 milliseconds, inversion time [TI] = 600 milliseconds, flip angle = 8°, field of view [FOV] = 256 mm, matrix = 256 × 192, and slice thickness = 1 mm^3), and a single-shot pulsed-field gradient spin-echo EPI sequence (TE/TR = 96 milliseconds/17 seconds; FOV = 24 cm, matrix = 128 × 128 × 48; axial). Image acquisition at the 1.5 T scanner included a conventional 3-plane localizer, GE calibration scan, 2 T1-weighted 3D structural scans (TR = 10.7 milliseconds, TE = 3.8 milliseconds, TI = 1,000 milliseconds, flip angle = 8°, bandwidth = 31.25 Hz/pixel, FOV = 256 mm, matrix = 256 × 192, and slice thickness = 1.0 mm), and for dMRI, a single-shot echo-planar imaging with isotropic 2.5 mm voxels (TR = 12.3 seconds, TE = 75.6 milliseconds, flip angle = 90°, FOV = 240 mm, matrix = 96 × 96, slice thickness = 2.5 mm, and partial k-space acquisition). On all scanners, dMRIs were acquired with 30

Table 1 TLE and Healthy Control Demographics

	TLE (n = 117)	HC (n = 81)	Statistic	*p* Value
Age	36.05 (12.24)	35.49 (12.57)	$t = -0.31$	0.759
Education	13.49 (2.14)	16.02 (2.26)	$t = 8.01$	**<0.001**
Sex: female/male	66/51	49/32	$\chi^2 = 0.33$	0.661
Race: White/>1 race/Black or AA/Asian/American Indian or Alaska Native/Native Hawaiian or other Pacific Islander/unknown	73/23/8/7/2/1/3	60/1/6/9/2/0/3	$\chi^2 = 19.91$	**<0.001**
Ethnicity (NH/H/unknown)	87/29/1	73/6/2	$\chi^2 = 11.06$	**0.002**

Abbreviations: AA = African American; H = Hispanic; HC = healthy control; NH = non-Hispanic; TLE = temporal lobe epilepsy.
SDs are presented inside the parentheses for continuous variables. Significant *p* values are bolded.

diffusion gradient directions using a *b* value of 1,000 s/mm^2 with an additional $b = 0$ volume. For use in nonlinear B0 distortion correction, 2 additional $b = 0$ volumes were acquired with either forward or reverse phase-encode polarity. Field strength was not significantly associated with graph theory metrics ($ps > 0.05$). The proportion of patients scanned using 1.5 vs 3 T did not differ by language group or side of seizure onset ($p = 0.79$).

dMRI Processing, Tractography, and Connectome Generation

Detailed methods are provided in eAppendix 1 (links.lww.com/WNL/C665). T1-weighted and dMRIs were preprocessed using the multimodal imaging pipeline (Figure 1, A–E).[28]

(A) dMRI data were corrected for head motion, geometric susceptibility-induced distortions, and eddy current-induced artifacts. Postprocessing was performed using MRtrix3 tools.

(B) Probabilistic global tractography was performed using the default iFOD2 algorithm,[29] based on fiber orientation distributions derived from the dMRI signal using constrained spherical deconvolution.[30] Tractography parameters were informed by QSIprep's default tractography workflows.[31] Streamlines were refined using the anatomically constrained tractography framework using the T1-weighted image.[32] Those with anatomically plausible termination such as the gray-white matter interface were kept. Minimum and maximum fiber lengths were set to 30 and 250 mm. Streamlines were dynamically seeded using the SIFT model, until 10 million candidates were found. The SIFT2 algorithm in tcksift2 was used.

(C) Cortical parcellations derived from FreeSurfer (Desikan-Killiany, 68 regions of interest [ROIs]) were used to determine connectome edge weights and were defined as the sum of SIFT2 weights of all streamlines connecting a pair of nodes. Connectome edges were scaled by the inverse of the 2 node volumes.

(D) Undirected, binary graph matrices were created at multiple density levels.[33] Each ROI constituted a node in the network with each connection edge defined by traced fiber connections between nodes. Each density level was defined as the threshold at which the number of edges in the graph equaled from 10% to 65% of total possible edges. These were selected in concordance with similar methods with an equivalent number of ROIs.[34]

(E) This panel depicts a whole-brain structural connectome imposed on a standard brain template.

Global Graph Theory Metrics

Connectivity matrices were analyzed with the Brain Connectivity Toolbox[33] to yield 2 global graph theory metrics of interest (*F*) that reflect key organizational principles of the brain—network specialization (measured by transitivity) and network integration (measured by path length)—and are among the most commonly investigated and frequently aberrant in epilepsy.[19] We used 55 different density levels to calculate a single area under the curve for the resulting receiver operating characteristic curves for each participant for each measure.

1. Transitivity (or a normalized mean clustering coefficient) is defined as the ratio of the number of estimated connections among its first-degree neighbors to the number of all possible connections, ranging from 0 (no first-degree neighbors of a node link to each other) and 1 (all first-degree neighbors of the node also link to each other), which reflects the degree to which nodes tend to cluster together (higher = neighbors of a node are more densely interconnected). We chose transitivity instead of clustering coefficient because clustering coefficient is normalized individually for each node and may be disproportionately influenced by nodes with a low degree.[33]

2. Path length is defined as the minimum number of intermediate nodes needed to connect any 2 nodes. Networks with short path lengths indicate a higher global capacity of exchanging information across the whole network (lower = any 2 ROIs can be reached in a smaller number of steps).

Subnetwork Analysis

Mean local efficiency—that is, the average of global efficiency constrained to only the local neighbors of specific nodes—was computed for the following 2 subnetworks.

Table 2 Bilingual TLE Language Characteristics

Patient	Side of seizure onset	L1	L2	L2 AoA	Duration of L2 use	Method of L2 exposure	English proficiency
1	Left	Spanish	English	14	34	College	41
2	Left	Spanish/English	—	SB	33	Parents/grandparents	36
3	Left	Spanish	English	35	7	ESL classes	39
4	Left	Cantonese	English	9	19	Elementary-college	44
5	Left	Japanese/English	—	SB	28	Elementary-college	33
6	Left	Arabic	English	—	—	—	—
7	Left	Spanish	English	14	35	Middle school–college	40
8	Left	Spanish	English	4	21	Elementary-college	34
9	Left	Spanish	English	5	20	Elementary-college	37
10	Left	Spanish	English	12	20	Middle school–college	—
11	Left	Spanish	English	8	29	Elementary school	24
12	Left	Spanish	English	12	42	Middle school	24
13	Left	Vietnamese	English	4	24	Elementary-college	56
14	Left	Spanish	English	5	29	Kindergarten	39
15	Left	Spanish	English	6	29	Kindergarten/elementary	42
16	Right	Spanish/English	—	SB	24	Parents/siblings	50
17	Right	Spanish/English	—	SB	46	—	—
18	Right	Spanish/English	—	SB	36	Parents	54
19	Right	Spanish	English	31	19	Work	67[a]
20	Right	Spanish	English	—	—	Formal schooling	30[a]
21	Right	Spanish	English	13	18	Formal schooling	60
22	Right	Arabic	English	4	22	Elementary-college	33
23	Right	Tagalog	English	—	—	—	47[a]
24	Right	Tagalog	English	—	—	—	—
25	Right	Spanish	English	4	18	Elementary-college	43
26	Right	Spanish	English	3	28	Elementary-college	53
27	Right	Spanish	English	16	25	High school/college	37[a]
28	Right	Italian	English	11	33	Formal schooling	59
29	Right	Spanish/English	—	SB	24	Parents/siblings	49

Abbreviations: AoA = age of acquisition (missing for 4 participants); L1 = first language learned; L2 = second language learned; SB = simultaneous bilingual (i.e., acquired both languages from birth).
[a] English proficiency is based on the vocabulary subtest of the Weschler Abbreviated Scale of Intelligence and reported as T-scores; where vocabulary scores were not available, English letter fluency T-scores are reported instead and denoted with a superscript; missing for 4 participants.

Frontal-Executive

Considerable research demonstrates neural overlap across language and executive control in bilinguals, for example, in the dorsolateral prefrontal and anterior cingulate regions.[26] These regions have also been shown to be connected more efficiently in aging bilinguals or those with AD.[9,11] Thus, we averaged the following bilateral frontal-executive ROIs: caudal middle frontal gyrus, caudal anterior cingulate gyrus, and rostral anterior cingulate gyrus.

Perisylvian

Given evidence that bilingualism modulates network efficiency[12] and structural plasticity within language regions[35] or tracts that connect them,[36] the following ROIs were averaged:

Table 3 TLE Demographic and Epilepsy Characteristics by Side of Seizure Focus and Bilingual Status

	M-LTLE	M-RTLE	B-LTLE	B-RTLE	Statistic	*p* Value
n	43	45	15	14		
Age, y	36.07 (13.59)	35.49 (12.79)	37.00 (8.61)	36.79 (10.18)	0.98	0.806
Education, y	13.35 (2.25)	13.51 (2.05)	13.07 (1.79)	14.29 (2.46)	2.27	0.518
WASI block design[a]	48.23 (9.82)	44.33 (9.79)	47.92 (8.58)	49.80 (10.44)	3.43	0.330
Handedness: R/L/A	39/4/0	41/3/1	12/3/0	14/0/0	5.94	0.436
Sex: female/male	17/26	27/18	12/3	10/4	9.68	**0.021**
Age at seizure onset, y	19.65 (15.10)	21.16 (14.15)	20.40 (13.23)	12.21 (10.76)	3.87	0.276
Duration of epilepsy, y	16.42 (14.44)	14.33 (13.18)	16.60 (12.70)	24.57 (13.17)	7.19	0.066
No. of ASMs	2.40 (0.90)	2.29 (0.90)	2.07 (0.70)	2.29 (0.83)	1.58	0.664
Ipsilateral HCV[b]	0.24 (0.05)	0.24 (0.06)	0.24 (0.06)	0.23 (0.05)	1.57	0.666
MTS: yes/no	27/16	22/23	12/3	11/3	6.67	0.081
Other MRI findings						
Normal	13	14	2	3		
Cortical dysplasia	0	1	1	1		
Cavernoma	1	2	0	0		
Hippocampal atrophy	0	3	1	0		
Abnormal hippocampal signal	1	0	0	0		
Encephalomalacia/gliosis	1	1	0	0		
Meningoencephalocele	0	2	0	0		
Enlarged amygdala	1	0	0	0		

Abbreviations: A = ambidextrous; ASM = antiseizure medication; B = bilingual; HCV = hippocampal volume; L = left; LTLE = left temporal lobe epilepsy; M = monolingual; MTS = mesial temporal sclerosis; R = right; RTLE = right temporal lobe epilepsy.
SDs are presented inside parentheses. Bolded *p* values represent significant group differences. Statistics represent Kruskal-Wallis or Fisher exact test.
[a] Block design represented as T-scores; missing for 4 M-LTLEs, 6 M-RTLEs, 2 B-LTLEs, and 4 B-RTLEs.
[b] Ipsilateral hippocampal volume is divided by total intracranial volume and multiplied by 100.

left inferior frontal gyrus (pars opercularis, pars triangularis, and pars orbitalis), left middle temporal gyrus, left supramarginal gyrus, left inferior parietal lobe, and bilateral superior temporal gyrus.

Neuropsychological Measures

A subset of participants (n = 86) completed (1) WASI Block Design, a measure of perceptual reasoning, (2) Delis-Kaplan Executive Function System Category Fluency, a measure of semantic fluency, and (3) Trail Making Test-B, a timed task of nonverbal task switching (i.e., higher score = worse performance).

Statistical Analysis

Fisher exact or χ^2 tests and independent samples *t* tests or 1-way Kruskal-Wallis *H* analysis of variance (ANOVA) were used to examine group differences in demographic and clinical variables. Multivariate ANOVAs were used to compare graph metrics between TLE vs HC, and in a 2 (L- vs RTLE) × 2

(bilingual vs monolingual) model, with Bonferroni correction of *p* = 0.025. Q-Q plots were acceptable, and assumptions were met (i.e., graph metrics were normally distributed, homogeneity of variance-covariance, equality of variances, and no significant outliers). Group differences in local efficiency of subnetworks were assessed with a 2 (frontal-executive vs perisylvian) × 2 (bilingual vs monolingual) ANOVA. Simple main effects using the pooled variance were performed for significant interactions. Spearman bivariate correlations (limited to patient groups that showed significant modulation of graph metrics) tested associations between neuropsychological performance and graph metrics. Correlations between groups were compared using 95% CIs and Fisher *z* test.

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.
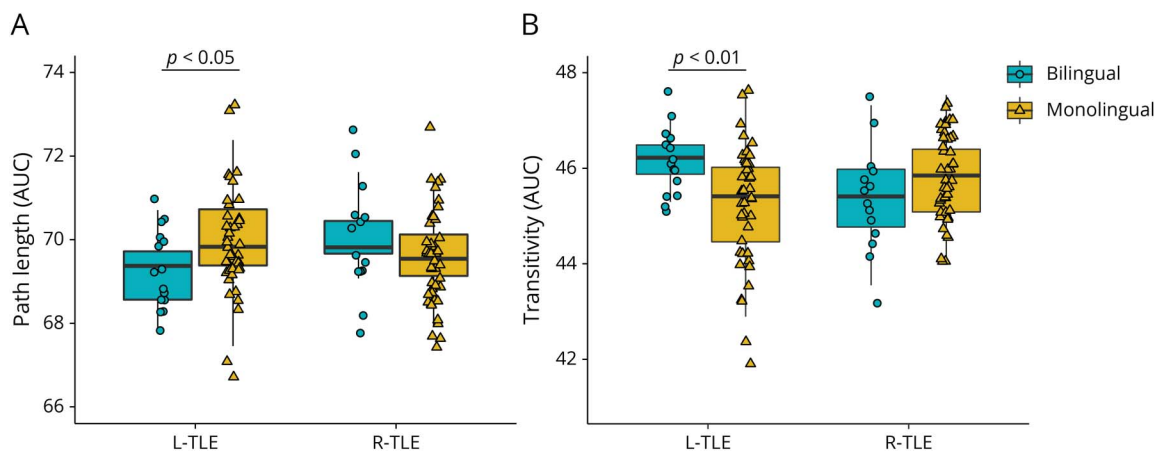
The effect of bilingualism on network organization was dependent on side of seizure focus such that bilingual LTLE showed increased network organization relative to monolingual LTLE. Plotted are AUC of path length and transitivity separately by side of seizure focus (L- vs R-TLE) and language status (bilingual vs monolingual). Boxplot denotes the median (bold bar), first and third quartiles (box limits), and ±1.5 times the interquartile range (whiskers). Bilingual and monolingual TLEs are coded as circles and triangles, respectively. AUC = area under the curve; LTLE = left TLE; RTLE = right TLE; TLE = temporal lobe epilepsy.

Results

Demographic and Clinical Variables

Our final sample included 117 TLE (n = 88 monolingual; n = 29 bilingual) and 81 HC (Table 1). Table 2 shows detailed language characteristics for B-TLE. Table 3 presents demographic and epilepsy-related variables for TLE (eTables 1 and 2, links.lww.com/WNL/C665, present this information by site). TLE groups did not significantly differ in age, education, handedness, perceptual reasoning, age at seizure onset, or number of medications. The distribution of sex significantly differed across groups such that M-LTLE had a lower proportion of female participants compared with B-LTLE (p = 0.015) and to a lesser extent compared with M-RTLE (p = 0.060). The distribution of mesial temporal sclerosis (MTS) showed a marginally significant difference across groups such that M-RTLE had a lower proportion of MTS compared with B-LTLE (p = 0.041). Bilinguals generally had a higher proportion of MTS than monolinguals, although not significantly. Other detailed MRI findings are presented in Table 3.

Global Graph Theory Metrics

TLE vs HC

To replicate previous work and understand the effects of TLE on network organization in our sample, we first examined global graph metrics in TLE vs HC. The omnibus group effect was significant ($F(2,195)$ = 5.01; p = 0.008; η_p^2 = 0.05; Wilks Λ = 0.95) such that TLE had (1) lower transitivity than HC ($F(1,198)$ = 8.56; p = 0.004; η_p^2 = 0.04; TLE: mean 45.58; 95% CI 45.40–45.77; HC: mean 46.01; 95% CI 45.79–46.23) and (2) longer path length than HC ($F(1,198)$ = 8.79; p = 0.003; η_p^2 = 0.04; TLE: mean 69.78; 95% CI 69.57–69.98; HC: mean 69.29; 95% CI 69.05–69.54). Group differences remained significant after controlling for age, education, and

sex (ps = 0.007 and 0.013, for transitivity and path length, respectively).

Language Status by Side of Seizure Onset

Figure 2 plots individual data. There was a significant language status by side of seizure onset interaction of a medium effect size ($F(2,112)$ = 5.46; p = 0.005; η_p^2 = 0.09; Wilks Λ = 0.91) and no significant main effects. The interaction was significant for each metric (transitivity: $F(2,116)$ = 11.01; p = 0.001; η_p^2 = 0.09; path length: $F(1,116)$ = 5.35; p = 0.022; η_p^2 = 0.05). For transitivity, the effect of bilingualism was present only in LTLE ($F(1,113)$ = 10.57; p = 0.002; η_p^2 = 0.09) and not RTLE (p = 0.147) such that B-LTLE had higher transitivity than M-LTLE (B-LTLE: mean 46.19; 95% CI 45.68–46.71; M-LTLE: mean 45.21; 95% CI 44.91–45.52). The effect of bilingualism on path length was present in LTLE ($F(1,113)$ = 4.79; p = 0.031; η_p^2 = 0.04) and not RTLE (p = 0.276) such that B-LTLE had shorter path length than M-LTLE (B-LTLE: mean 69.27; 95% CI 68.68–69.85; M-LTLE: mean 70.02; 95% CI 69.67–70.37). Direct comparison between B- and M-LTLE suggested differences of a large effect size (Cohen d = 0.89 and 0.63, for transitivity and path length, respectively). We also tested whether bilingual HC differed from monolingual HC by case-control matching M-HC on age, education, and sex to (1) 19 B-HC and (2) 11 B-HC whose bilingual status we were more confident in. Neither analysis revealed a trend toward group differences (ps > 0.05) (eAppendix and eFigure 1, links.lww.com/WNL/C665).

Control Analyses

The 2-way omnibus interaction between language status and side of seizure onset remained significant and of the same effect size when individually controlling for variables not closely matched across groups or variables that may affect network

Figure 3 Local Efficiency of Predefined (A) Frontal-Executive and (B) Perisylvian Subnetworks in B-LTLE and M-LTLE
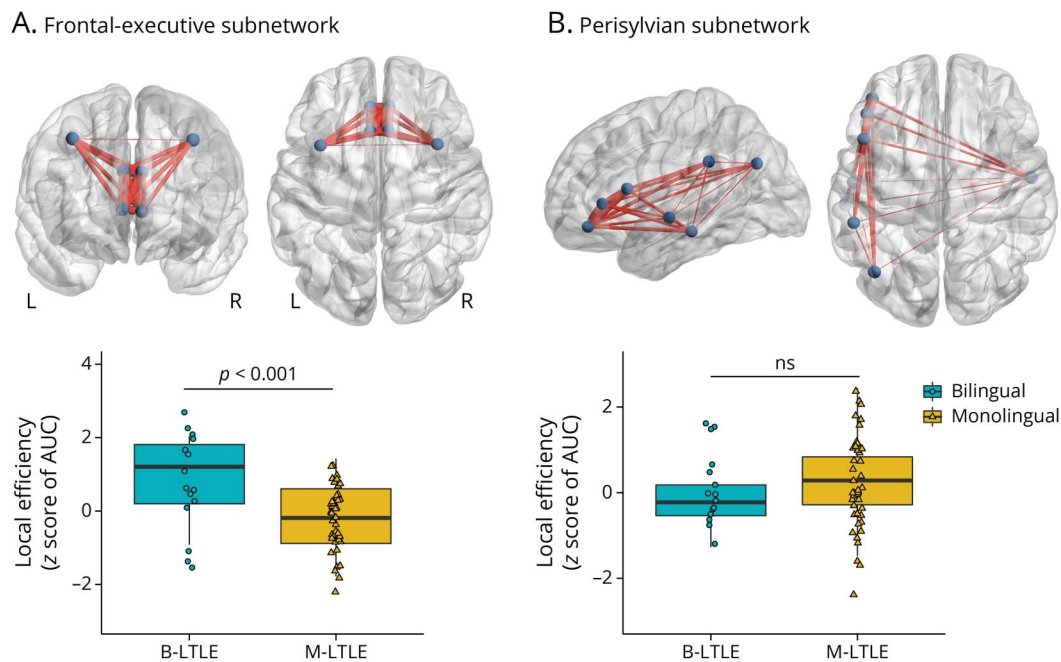
A significant interaction between subnetwork and language status such that B-LTLE had higher frontal-executive, but not perisylvian, local efficiency relative to M-LTLE. Panel A visualizes nodes that comprised the frontal-executive subnetwork in coronal and axial views. Panel B visualizes nodes that comprised the perisylvian (i.e., language) subnetwork in sagittal and axial views. Plotted are z scores (relative to healthy controls) of the mean subnetwork efficiency. B-LTLE and M-LTLEs are coded as circles and triangles, respectively. AUC = area under the curve; B-LTLE = bilingual left temporal lobe epilepsy; M-LTLE = monolingual left temporal lobe epilepsy.

organization—age, sex, MTS, and duration of epilepsy (all $ps < 0.05$; $\eta_p^2 = 0.08$–0.09). Excluding 6 simultaneous bilinguals (2 B-LTLE; 4 B-RTLE) did not change the interaction ($p = 0.013$; $\eta_p^2 = 0.08$). We repeated the analysis with clustering coefficient as it may be a more commonly reported global metric—the interaction remained significant with a similar effect size ($p = 0.008$; $\eta_p^2 = 0.08$).

Site and Scanner Effects
The main findings were consistent and of the same effect size when (1) examining only the main site (UCSD; n = 87), (2) including site as a covariate and (3) examining 3T participants scanned on an identical scanner and protocol (eAppendix 1 and eFigure 2, links.lww.com/WNL/C665).

Additional Atlas Comparison
We reanalyzed the data using a functionally derived atlas, the HCP Glasser 360 (eFigure 3, links.lww.com/WNL/C665). The 2-way interaction was observed across each global metric ($ps < 0.05$; $\eta_p^2 = 0.04$), with a similar pattern of results as reported above (see eAppendix 1).

Local Efficiency of Subnetworks in LTLE
In a secondary analysis, we examined whether improved whole-brain network organization in B-LTLE is related to local efficiency of subnetworks underlying language and/or executive control. A model with z scores (relative to HC) of local efficiency showed a robust subnetwork by language status interaction of a large effect size ($F(1,56) = 12.35$; $p < 0.001$; η_p^2

= 0.18). The interaction revealed that B-LTLE had higher mean local efficiency than M-LTLE in the frontal-executive subnetwork ($F(1,56) = 14.18$; $p < 0.001$; $\eta_p^2 = 0.20$), with no group difference in the perisylvian subnetwork ($p = 0.319$) (Figure 3). See eAppendix 1 (links.lww.com/WNL/C665) for the HCP atlas analysis.

MTS Subsample Analysis
We repeated the analyses in 68 TLEs with lesion evidence of only MTS (see eAppendix 1 and eFigure 4, links.lww.com/WNL/C665). The overall 2-way interaction remained significant across global metrics ($p < 0.005$; $\eta_p^2 = 0.16$) such that B-LTLE had increased network organization relative to M-LTLE. Local efficiency of subnetworks also revealed a consistent interaction ($p < 0.001$; $\eta_p^2 = 0.31$) such that B-LTLE had increased frontal-executive but not perisylvian sub network efficiency relative to M-LTLE, suggesting that findings are independent of lesion differences between groups.

Correlations Between Cognition and Network Organization
Because B-LTLE was the only group evidencing modulation of graph theory measures, we examined whether increased network organization in B-LTLE was associated with higher executive function and/or language performance, and whether these associations differed from M-LTLE (Figure 4). In B-LTLE, better Trails B performance was significantly associated with shorter path length ($\rho(13) = 0.64$; $p = 0.020$;

Correlations Between Global Network Integration (Path Length) and Specialization (Transitivity) and (A) Executive Function and (B) Language Performance in LTLE
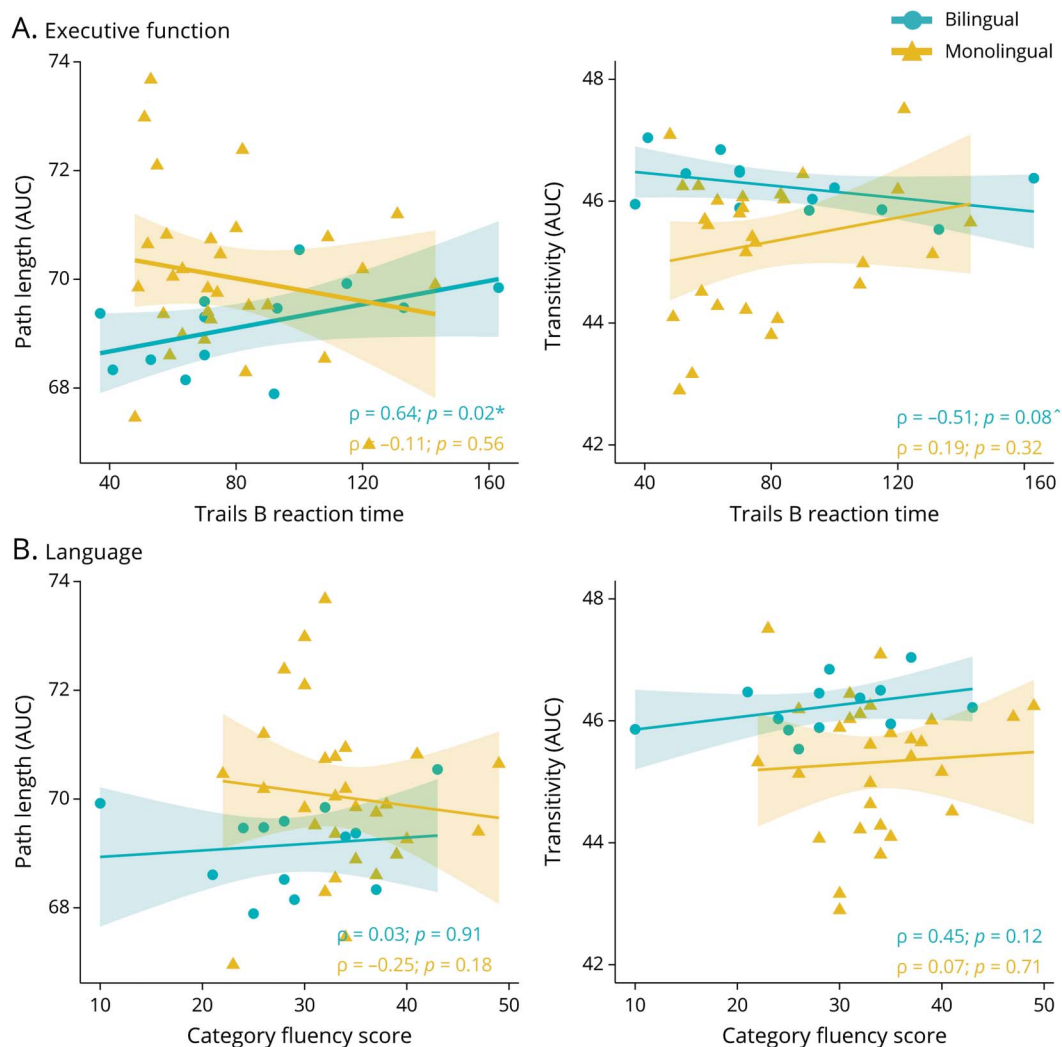
Spearman bivariate correlations between executive function measured by Trails B (panel A) and language function measured by category fluency (panel B) and (left panels) and (right panels) for 13 bilinguals and 30 monolinguals with LTLE. Significant correlations are denoted with *, and marginally significant correlations are denoted with ˆ. Bilingual and monolingual LTLEs are coded as circles and triangles, respectively. AUC = area under the curve; LTLE = left temporal lobe epilepsy.

95% CI 0.14–0.88) and with higher transitivity, although this did not reach significance ($\rho(13) = -.51$; $p = 0.076$; 95% CI -0.83 to 0.06). Category fluency was not associated with either metric in B-LTLE ($ps > 0.05$). No associations were significant in M-LTLE ($ps > 0.05$). Comparing correlations between network organization and Trails B performance for B- vs M-LTLE revealed a reliable group difference (path length: difference 0.75; 95% CI 0.13–1.17; transitivity: difference -0.70; 95% CI -1.15 to -0.02). Correlations with subnetwork efficiency were not significant in either group ($ps > 0.05$).

Discussion

An exciting discovery is that bilingualism may serve as a neuroprotective factor in neurologic disease.[3,37] There is converging evidence of delayed diagnosis of dementia in bilinguals relative to monolinguals by an average of 4–5 years[2,4,5] (but see reference 38), as well as neuroprotective effects of bilingualism in primary progressive aphasia[39] and stroke.[40] However, little is known about the underlying neurobiological mechanisms. There are strong reasons to believe that bilingualism can act as reserve in other neurologic disorders[41] including epilepsy. We previously demonstrated increased cognitive reserve in bilinguals with TLE.[17] The current study builds on this and shows that bilingualism may help retain a well-organized global information transfer between highly interconnected regions. These findings are important given reports that focal epilepsy decreases efficiency of whole-brain networks.[19]

Our work demonstrated that bilingualism increased network organization relative to monolingualism, with this increase evident only in individuals with a left-sided seizure focus. That

is, bilinguals with LTLE showed a pattern of network integration and specialization that most closely resembled that of HC. Second, B-LTLE had increased local efficiency of frontal-executive but not language-related networks compared with M-LTLE. Third, better network organization was related to better executive functioning in B-LTLE, whereas the same pattern was not observed in M-LTLE. Together, these findings suggest that bilingualism may attenuate and/or compensate for network inefficiency in individuals with a left hemisphere seizure focus, likely related to increased efficiency of frontal-executive networks and task-switching performance modulated by dual-language experience.

Our findings point to a neuroprotective effect of bilingualism on network integration and specialization in TLE. A likely mechanism for these results is neural reserve. Neural (or brain) reserve is conceptualized as neurobiological hardware (e.g., number of neurons or synapses), allowing some individuals to better cope with pathology.[42] Bilingualism may act as consistent training for the brain due to a complex process of managing 2 simultaneous languages that are always coactive. This invokes a widespread language control network, requiring activation of the spoken language, inhibition of the other language, monitoring to prevent cross-language interference, and switching between languages. This process may strengthen general executive control networks[43] and may lead to greater overall efficiency, particularly when these networks are affected by TLE. This idea is supported by increased neural efficiency in older bilinguals, evidenced by lower activation of regions supporting executive function,[6] increased connectivity within related networks,[7] and more preserved cortical thickness of these regions and white matter tracts that connect them.[8,36,44] Our novel findings suggest that bilingualism may reinforce regions affected by epilepsy as well as the white matter connections among them, leading to better organized global information transfer between highly interconnected regions.

The epileptogenic focus is often lateralized, whereas neurodegeneration (e.g., in dementia) is typically bilateral. This unique aspect of epilepsy interacted with bilingualism in that we observed enhanced global network organization in bilinguals with LTLE only. Although it is not fully clear why bilingualism was only protective in LTLE, a possible explanation is that dual-language use is only protective in the face of disruption to the left side of the brain, demonstrating the interaction between language networks and disease. Dysfunction of the left hemisphere may invoke increased compensatory processes in the bilingual brain, potentially drawing on resources from the contralateral hemisphere and/or in nonlanguage regions. We previously reported that language was frequently reorganized to the right hemisphere in bilinguals with LTLE,[45] suggesting that neuroplasticity related to bilingualism is most pronounced when the left hemisphere is affected. Another possible contributor to the bilingualism effect in LTLE only could be related to B-RTLE having a worse epilepsy phenotype, evidenced by approximately a

decade longer duration of epilepsy and higher proportion of MTS. However, we observed the same interaction when we controlled for these factors.

In subnetwork comparisons, B-LTLE showed higher efficiency within the bilateral frontal-executive but not the primarily left-lateralized perisylvian regions compared with M-LTLE. An epilepsy-specific speculation is that left hemisphere seizures may reduce perisylvian network efficiency, with bilinguals relying more on networks outside of the typical perisylvian network to handle dual-language demands more efficiently. This interpretation is consistent with several studies that reported increased functional and/or metabolic connectivity in bilinguals compared with monolinguals with AD in frontoparietal/executive networks.[7,9,11] A more transdiagnostic explanation is a mechanism of executive control compensation in the presence of bilingualism. This explanation fits with the prevailing view that the greatest benefits of bilingualism in dementia tend to be observed in executive control rather than in language or in medial temporal lobe networks directly affected by AD.[37,46,47]

In B-LTLE, a modulated whole-brain network organization was associated with better task switching performance—a relationship not present in M-LTLE or in language performance. This lends additional support to the proposal that executive function is the domain that may be the most affected by dual-language experience and provides a functional correlate to whole-brain white matter network topology. Furthermore, this suggests that the efficacy of neural reserve varies across patients in a way which we hypothesize could be due to specific features of each individual's bilingual experience. Although we do not have sensitive measures available to ground this hypothesis, we believe that this should motivate prospective research on the mechanisms of neural resilience and bilingualism.

Much work remains to be done to elucidate bilingualism's protective mechanisms and its potential for intervention in neurologic disease.[41] Notably, our sample of bilingual TLEs was relatively small, requiring future replication. Given the cross-sectional design, it is unknown whether increased network organization in B-LTLE stems from preserved network organization (i.e., an attenuating effect) or a reparation of decreased network organization as a result of chronic seizures. In addition, although we propose neural reserve as the most likely mechanism, a recent concept of brain maintenance could apply[42]—a reduced development of pathology over time based on genetics or lifestyle experiences.[42] That is, ongoing bilingual language use may have attenuated epilepsy-related reduction of network organization. Although we did not observe increased network organization in healthy bilingual controls—suggesting that a neuroprotective effect of bilingualism may only be present in the face of neurologic disruption—future inclusion of a better-characterized bilingual control group will help to disentangle the effects of disease and bilingualism. In addition, it is possible that

unmeasured lifestyle factors other than language experience may have differed between groups. For example, it is well accepted that occupational history, diet, physical exercise, and cognitive and social stimulation are proxies for cognitive reserve[42] and should be examined in future studies along with bilingualism. On a methodological level, although we replicated our global findings across 2 commonly used atlases, it is possible that results could differ when other atlases are used. Therefore, future studies should further test the reproducibility of graph theory metrics across atlases.

Importantly, bilingualism is not a dichotomous phenomenon. It is increasingly recognized that neuroanatomic differences are shaped by factors such as proficiency, age of L2 acquisition (i.e., learned early and simultaneously with L1 vs much later than L1), amount of language exposure, frequency of language switching, and typological similarity between languages.[48] Two recent graph theory studies with healthy adults found that several of these bilingual language factors modulated whole-brain and regional network organization.[13,14] In addition, bilingualism's effects on the brain likely follow a dynamic nonlinear pattern. This is outlined in a number of models including the Dynamic Restructuring Model (DRM[49]), which proposes a specific time course for the effect of bilingualism on structural neuroplasticity. Notably, almost all our B-LTLEs used their L2 for 2 decades or more, likely having reached a more efficient level of language control. As this was a retrospective study, we had limited variability in duration and amount of L2 use to fully test the DRM. Future studies would benefit from detailed exploration of bilingual language factors to deconstruct bilingualism and understand how these factors influence network organization in TLE.

Finally, longitudinal studies that examine the interplay between when L2 is learned relative to when seizures begin would be helpful for understanding the time course of bilingualism-related neuroplasticity. This could have clinical implications for prevention and early intervention for network dysfunction. In addition, although the majority of studies that reported delayed onset of dementia included lifelong bilinguals, even late L2 learning (i.e., past childhood) has been associated with increased white matter integrity,[35,44] which invites the question of whether immersion and/or L2 learning in monolinguals with epilepsy can also attenuate network abnormalities.

In conclusion, our findings suggest that bilingualism is relevant to brain health in epilepsy. We provide evidence of a neuroprotective role of bilingualism on white matter network organization in LTLE and suggest that this may be related to the integrity of frontal-executive networks. Enhanced network organization in bilingual individuals with LTLE may be explained by the phenomenon of neural reserve. As some epilepsies represent progressive disorders, potentially leading to reduced structural integrity over time,[50] it will be important to test whether bilingualism may slow the progression of network dysfunction in epilepsy and/or whether it may lead to more efficient recovery of networks after surgery. Our preliminary findings support future studies examining bilingualism as an important resilience factor and testing of interventions aimed at increasing bilingual usage in individuals with neurologic disease.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Alena Stasenko, PhD	Center for Multimodal Imaging and Genetics, and Department of Psychiatry, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Erik Kaestner, PhD	Center for Multimodal Imaging and Genetics, and Department of Psychiatry, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Donatello Arienzo, PhD	Center for Multimodal Imaging and Genetics, and Department of Psychiatry, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Adam Schadler, MA	Center for Multimodal Imaging and Genetics, and Department of Psychiatry, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Anny Reyes, MS	Center for Multimodal Imaging and Genetics, and Department of Radiation Medicine & Applied Sciences, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jerry J. Shih, MD	Department of Neurosciences, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Jonathan L. Helm, PhD	Department of Psychology, San Diego State University, CA	Analysis or interpretation of data; additional contributions: statistical consultation
Monika Połczyńska, PhD, DLitt	Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, University of California, Los Angeles	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
Carrie R. McDonald, PhD	Center for Multimodal Imaging and Genetics, Department of Psychiatry, and Department of Radiation Medicine & Applied Sciences, University of California, San Diego	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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