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CASE REPORT

Brain Reserve in a Case of Cognitive Resilience to Severe Leukoaraiosis

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Abstract

Objective: Leukoaraiosis, or white matter rarefaction, is a common imaging finding in aging and is presumed to reflect vascular disease. When severe in presentation, potential congenital or acquired etiologies are investigated, prompting referral for neuropsychological evaluation in addition to neuroimaging. T2-weighted imaging is the most common magnetic resonance imaging (MRI) approach to identifying white matter disease. However, more advanced diffusion MRI techniques may provide additional insight into mechanisms that influence the abnormal T2 signal, especially when clinical presentations are discrepant with imaging findings. **Method:** We present a case of a 74-year-old woman with severe leukoaraoisis. She was examined by a neurologist, neuropsychologist, and rheumatologist, and completed conventional (T1, T2-FLAIR) MRI, diffusion tensor imaging (DTI), and advanced single-shell, high b-value diffusion MRI (i.e., fiber ball imaging [FBI]). **Results:** The patient was found to have few neurological signs, no significant cognitive impairment, a negative workup for leukoencephalopathy, and a positive antibody for Sjogren's disease for which her degree of leukoaraiosis would be highly atypical. Tractography results indicate intact axonal architecture that was better resolved using FBI rather than DTI. **Conclusions:** This case illustrates exceptional cognitive resilience in the face of severe leukoaraiosis and the potential for advanced diffusion MRI to identify brain reserve.

Keywords: Leukoaraiosis, White matter hyperintensities, Diffusion MRI, Cognition, Case study, Reserve

INTRODUCTION

Leukoaraiosis refers to neuroimaging findings of white matter disease, seen as hyperintense lesions on T2 magnetic resonance imaging (MRI) sequences. These may be circumscribed or confluent, typically found in periventricular or subcortical regions (Smith et al., 2017) and is often presumed to be of vascular origin (Wardlaw et al., 2019). It is a common finding in older adults, especially those with vascular risk factors (Abraham et al., 2016; Jeerakathil et al., 2004). The extent to which leukoaraiosis results in cognitive impairment remains unclear; it has been hypothesized that these effects are attributable to coincident neurodegeneration (e.g., Ross et al., 2005; Frisoni et al., 2007) or only confer modest but robust effects on cognition, particularly attention and executive functioning (Kloppenborg et al. 2014).

Leukoencephalopathies are diseases characterized by especially severe leukoaraiosis. These are diseases of white matter that are acquired following toxic exposure or infections (Filley et al., 2017), are inherited forms involving small vessel ischemia (Vanderver et al., 2015), or result from congenital disorders of myelin development or maintenance (Köhler et al., 2018). Leukoencephalopathies are typically functionally impairing and often progressive. The inherited forms are called "leukodystrophies," implying congenital etiologies regardless of age of symptom onset (Köhler, et al., 2018). In these cases, functional impairments are common, including dementia, emotional disturbance, motor incoordination, autonomic dysfunction, and other neurologic symptoms like chronic headaches and seizures (Di Donato et al., 2017; Hageman et al., 1995; Joutel et al., 1996; Nozaki et al., 2014).

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Remarkably, there are rare cases where neuropsychological functioning remains preserved despite severe leukoaraoisis (e.g., Duning, Kugel, & Knecht, 2005). Such findings are illustrations of the concepts of cognitive or brain reserve. Described in the white paper by Stern et al., 2018, cognitive reserve is defined as *"the adaptability (i.e., efficiency, capacity, flexibility) . . . of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult."* In contrast, brain reserve is conceptualized as more static "*neurobiological capital*," wherein greater brain integrity confers an advantage prior to the onset of disease or injury. Although both likely have shared mechanisms, cognitive reserve is often estimated using socio-behavioral proxies (e.g., IQ, occupational complexity, educational attainment, literacy, socioeconomic status, access to healthcare) or functional neuroimaging, whereas brain reserve is typically measured *in vivo* via neuroimaging-based measures of brain structure including cortical and regional volumetry and metrics of white matter microstructure. Current terminology precludes a specific method of assaying brain reserve (Stern et al., 2018), as the knowledge base on the extent to which these measures are totemic of the concept of brain reserve *versus* indicators of disease is still evolving. Nonetheless, advances in structural neuroimaging as applied to unusual cases may illuminate future innovations of its measurement.

In this paper, we present a case study to demonstrate how an advanced diffusion MRI technique may identify potential structural mechanisms (i.e., "brain reserve") supporting a patient's cognitive resilience in the face of leukoaraiosis, so severe and extensive as to prompt workup for leukoencephalopathy. The technique, fiber ball imaging (FBI; Jensen et al., 2016; Moss et al., 2019), is a single-shell, high b-value diffusion MRI technique that can be implemented on 3-T MRI systems. It is distinguished from more conventional methods (e.g., diffusion tensor imaging [DTI]) in that it suppresses the extra-axonal signal such that axonal integrity can be independently imaged, which is the hypothesized mechanism for the preservation of this patient's cognitive functioning. In particular, FBI enables white matter fiber tractography that is unaffected by water in the extra-axonal space. In this way, FBI allows for an assessment of structural connectivity that is not confounded by microstructural changes external to axons, such as edema, gliosis, and myelin loss. Here, we provide data from the patient and a matched control with which to compare and contrast FBI results.

METHODS

For this case study, the patient completed the following over the course of 1 month: a neurological consultation, a neuropsychological evaluation, and a brain MRI on a research-dedicated 3-T Siemens Prisma^{fit} scanner with a 32-channel head coil, acquiring T1-weighted magnetization-prepared rapid gradient-echo sequence, T2-weighted fluid-attenuated inversion recovery sequence, T2-weighted susceptibility-weighted imaging, DTI, and FBI. Total scan time was 1 hr and 50 s (see Supplementary Material for acquisition parameters and image analysis procedures). Her images were reviewed by a neuroradiologist, who had the patient's scans from 1, 3, and 6 years prior for comparison.

Prior clinical and research data are also summarized here. Specifically, clinical evaluations from neurology, neuroradiology, and neuropsychology were reviewed from 6 years prior (when the participant was 68 years of age), and neuropsychological test results from another research study was reviewed from 3 years prior (when the participant was 71 years of age) in which an author (A. B.) was the principal investigator. This case study was approved by the Institutional Review Board (IRB) at the Medical University of South Carolina. The control FBI data were obtained from a separate IRB-approved study. Both were compensated for their participation in research.

RESULTS

Case Description

Presenting Problem

The patient is a 74-year-old Caucasian woman who denied any clinically significant cognitive decline other than greater difficulty recalling names that has worsened over the years. She denied any other memory, language, visuospatial, or executive functioning difficulties. Her neurologic complaints included balance difficulties confounded by pelvic pain which began several years prior and was treated via physical therapy. She occasionally stumbles and falls, with the last major fall 3 years prior to this study. There were two prior episodes of dizziness/vertigo. She endorsed occasional dull frontal headaches relieved by ibuprofen. She denied photophobia or phonophobia but had a baseline sensitivity to bright moving lights and loud noises. She also endorsed fatigue, hearing loss, urge incontinence, and constipation. Her husband concurred with her report, adding that he has noticed a subtle "mumbling" quality to her speech which has been stable over time. He otherwise denied any cognitive issues and confirmed that she remains independent in all routine activities.

Her brain MRI abnormalities were first noted 6 years prior at the age of 68 years, as she had experienced acute onset of dizziness and vertigo and was admitted to a hospital for possible stroke (she previously had an episode of vertigo, although this had resolved after 3–4 days with meclizine). Brain MRI was negative for acute stroke but showed extensive leukoaraiosis of bilateral subcortical white matter and increased T2 signal in the pons, with no enhancement. Neurology subsequently ordered an extensive workup including computed tomography angiogram (normal), and metabolic, autoimmune, and genetic testing, all of which were negative (see Table 1.a). A neuropsychological evaluation at the time identified normal performance overall except

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Table 1. Summary of the patient's past laboratory and genetic testing

Rheumatologic/antibody testing	Cerebrospinal fluid tests	Genetic/metabolic tests
a. From 6 years prior		
aCL	Cell count	CADASIL
ANAs (1:80)	Protein/glucose	CARASIL
cANCA	Bacterial culture	COL4A1
Anti-dsDNA	Oligoclonal bands	VLCFA
Anti-RNP	Immunoglobulin G index	Arylsulfatase A
Anti-SCL-70	Cytology	
Anti-SM	Flow cytometry	
Anti-SSA/SSB		
C3/C4		
ESR/CRP		
RF (23; indeterminate)		
b. Present evaluation		
Anticardiolipin	Cell count	
ANA (1:160; homogenous)	Protein/glucose	
Anti-B2GP	Bacterial and fungal culture	
Anti-CCP	Immunoglobulin G index	
Anti-dsDNA	Oligoclonal bands (1 CSF band)	
Anti-Jo 1	Neuronal cell antibodies	
Anti-RNP	Ribosomal P antibody	
Anti-SCL-70		
Anti-SM		
Anti-SSA: + (4.7)		
Anti-SSB		
dRVVT		

Note: Positive findings are in **bold**. All other findings are in negative or equivocal. ACE = angiotensin converting enzyme; ANAs = antinuclear antibodies; cANCA = anti-neutrophilic cytoplasmic antibodies; Anti-B2GP = anti-beta 2 glycoprotein; aCL = anti-cardiolipin; Anti-CCP = anti-cyclic citrullinated peptide; Anti-dsDNA = anti-double stranded DNA; Anti-RNP = anti-U1 ribonucleoprotein; Anti-SCL-70 = anti-topoisomerase (scleroderma); Anti-SM = anti-Smith; Anti-SSA = anti-Sjögren's syndrome-related antigen A; Anti-SSB = anti-Sjögren's syndrome-related antigen type B; C3/C4 = complement proteins C3 and C4; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; COL4A1 = collagen type IV alpha 1; CSF = cerebrospinal fluid; dRVVT = dilute Russell viper venom time; ESR/CRP = erythrocyte sedimentation rate and C-reactive protein; RF = rheumatoid factor; VLCFA = very long-chain fatty acids.

for a select weakness in confrontation naming, consistent with her self-report (see Table 2, column 1).

Personal and Family Medical History

Relevant diagnoses included obstructive sleep apnea (managed with Continuous positive airway pressure (CPAP) therapy), mild depression, hypertension, and hyperlipidemia. The patient saw ophthalmology for dry eye syndrome, glaucoma, and cataracts. She had a past history of uveitis. She reported ulcers in her mouth for the previous 1–2 years, diagnosed as lichen planus. Surgical history included hysterectomy, oophorectomy for a noncancerous cyst, and knee replacement. She had severe measles with high fevers at the age of 6 years, prompting concerns about encephalitis but this was never diagnosed; she had no neurologic sequelae and returned to school without issue. She denied any history of anoxic episodes, known toxic exposures, or head injuries.

Current medications included a calcium channel blocker, aspirin, a statin, a selective serotonin reuptake inhibitor, a beta-3 adrenergic agonist, anastrozole for prophylaxis, an antihistamine, nasal spray for rhinitis, a steroidal nasal spray, a topical corticosteroid, eye drops (brimonidine, cyclosporine, and patanol), a stimulant laxative, a stool softener, vitamins and an omega 3 fatty acid supplement, as well as ibuprofen as needed. She endorsed good medication compliance overall and per her records she demonstrated a clear pattern of consistent engagement with various healthcare providers.

Her family medical history is noteworthy for neurological and psychiatric conditions. Her father had a history of alcoholism, depression, and dementia of unspecified etiology which reportedly first developed at the age of 59 years. Her mother had a stroke at the age of 95 years but was previously living independently. One sibling had a history of alcoholism and bipolar disorder with onset of cognitive decline and walking difficulties around the age of 60–70

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Table 2. Summary of the patient's neuropsychological test results by cognitive domain and assessment period

Test	Percentile (age 68 years)	Percentile (age 71 years)	Percentile (current; age 74 years)	Norms
Mental Status Examination				
MoCA (Form A)		Raw=27/30	Raw=27/30	
MMSE	Raw=30/30			
Premorbid IQ Estimate				
TOPF			14	ACS Manual
WTAR		55		WTAR Manual
Vocabulary	91			WAIS-IV Manual
Information	95			WAIS-IV Manual
Attention & Processing Speed				
Digit Span			37	WAIS-IV Manual
Symbol Span			25	WMS-IV Manual
Coding	95		63	WAIS-IV Manual
Digit-Symbol Coding		84		WAIS-III Manual
Trail Making Test, Part A	66	50	34	Heaton et al. (2004)
Stroop (Color)		72	35	Demick & Harkins (1997)
Stroop (Word)		13	0	Demick & Harkins (1997)
Grooved Pegboard, Dominant	61		2	Heaton et al. (2004)
Grooved Pegboard, Non-dominant	61		8	Heaton et al. (2004)
Expressive Language				
Boston Naming Test	14		1	Heaton et al. (2004)
Category Fluency (Animals)	92	24	54	Heaton et al. (2004)
Visuospatial Functions				
Clock Drawing				
Command	Raw=4/4		Raw=4/4	
Copy			Raw=4/4	
Block Design	84			WAIS-IV Manual
Executive Functions				
Trail Making Test, Part B	34	73	42	Heaton et al. (2004)
Verbal Fluency (FAS)		18	10	Heaton et al. (2004)
Design Fluency				
Filled Dots: Total Correct			25	D-KEFS Manual
Empty Dots: Total Correct			84	D-KEFS Manual
Switching: Total Correct			9	D-KEFS Manual
WCST-128				
Total Errors			82	WCST Manual
Perseverative Responses			77	WCST Manual
Perseverative Errors			77	WCST Manual
Conceptual Level Respons.			86	WCST Manual
Categories Completed			>16	WCST Manual
Failure to Maintain Set			Raw=0/21	
Stroop (Interference)		67	32	Demick & Harkins (1997)
Verbal Episodic Memory				
HVLT-R				
Total Recall			86	HVLT-R Manual
Delayed Recall			84	HVLT-R Manual
Retention			58	HVLT-R Manual
Recognition Discrim. Index			84	HVLT-R Manual
RAVLT				
Learning (Trials 1-5)		65		Schmidt et al. (1996)
Short Delay Free Recall (Trial 6)		62		Schmidt et al. (1996)
Delayed Recall		66		Schmidt et al. (1996)
Hits		68		Schmidt et al. (1996)
WMS-IV				
Logical Memory I	98			WMS-IV Manual
Logical Memory II	99			WMS-IV Manual

(*Continued*)

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Table 2. (*Continued*)

Test	Percentile (age 68 years)	Percentile (age 71 years)	Percentile (current; age 74 years)	Norms
Recognition	>75			WMS-IV Manual
CERAD - List Learning and Memory	WNL			
Visual Episodic Memory				
BVMT-R				
Total Recall			24	BVMT-R Manual
Delayed Recall			38	BVMT-R Manual
Percent Retained			>16	BVMT-R Manual
Recognition Discrim. Index			>16	BVMT-R Manual
Copy			Raw=12/12	BVMT-R Manual
CERAD Constructional Praxis & Recall	WNL			
Mood/Anxiety				
GDS		Raw=2/30	Raw=1/30	Yesavage et al. (1982)
GAI-10			Raw=5/10	Segal et al. (2015)

Notes: MoCA = Montreal Cognitive Assessment; MMSE = Mini Mental State Exam; WAIS-IV = Wechsler Adult Intelligence Scale – Fourth Ed.; WMS-IV = Wechsler Memory Scale – Fourth Ed.; D-KEFS = Delis–Kaplan Executive Function System; WCST-128 = Wisconsin Card Sorting Test 128 Card Version; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; HVLT-R = Hopkins Verbal Learning Test – Revised; RAVLT = Rey Auditory Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test – Revised; GDS = Geriatric Depression Scale; GAI-10 = Geriatric Anxiety Inventory – 10 item

years, currently diagnosed with vascular dementia and is no longer able to ambulate independently. Two other siblings reportedly have no neurologic or cognitive impairments.

Psychosocial History

The patient obtained her doctorate (20 years of education) in a humanities field and has a premorbid IQ that is estimated to be in the superior range (Table 2, column 1), suggesting high cognitive reserve. She had trouble with reading and with foreign languages in school but was never diagnosed with a learning disability or ever received educational remediation. She is married and has no biological children. She has never smoked. In her 30s, she drank alcohol excessively until her late 40s (2–4 glasses of wine/daily) and has only drunk wine occasionally since. She denies any history of substance abuse.

Clinical Examinations

Neurology

On mental status exam, the patient was alert and fully oriented with normal attention, memory, and fund of knowledge. Evaluation of language identified mild anomia with frequent phonemic paraphasic errors. She was able to describe the objects shown and correctly identified objects given multiple choice options. Propositional speech was normal and fluent. She could read irregular words but was impaired when reading nonwords. On frontal executive motor tasks, fist-edge-palm was normal. She had impaired crossed response inhibition (5 errors out of 10 trials). The remainder of her neurologic exam was normal with the exception of right eye ptosis (present since childhood), 3+ reflexes in all extremities and bilateral crossed adductors (downgoing plantar reflex bilaterally), decreased sensation to pinprick and temperature in her feet and lower calves, a mild intention tremor (L > R) on finger to nose testing, and an impaired tandem gait.

Neuroradiology

A board-certified neuroradiologist reviewed all of the patient's MRI studies and described the following results. There was extensive scattered and confluent T2 prolongation, present in subcortical and periventricular white matter of both hemispheres including the temporal lobes as well as in the brain stem, nonspecific in appearance and distribution but most likely represent the sequelae of severe small vessel ischemic disease (Figure 1). These results were stable compared to images obtained 1 and 3 years prior, and only slightly progressed compared to exam 6 years prior, particularly in the peritrigonal region. Mild interval cerebral volume loss was noted compared to the study 6 years prior, but with no significant changes in the degree of volume loss over the last 3 years. In the left lateral precentral gyrus, an 8-mm area of T1 prolongation was observed in the subcortical white matter, stable since the first exam conducted 6 years prior. This was considered to be of uncertain etiology but may represent an area of encephalomalacia surrounded by gliotic changes. Her exam was otherwise unremarkable.

Neuropsychology

Comprehensive testing revealed intact cognition with minimal deficits to correlate with her severe imaging results (Table 2) and three noteworthy findings. First, fine motor dexterity and coordination were in the impaired/borderline ranges bilaterally. This finding suggests non-lateralized slowing, although her overall presentation and intact performance

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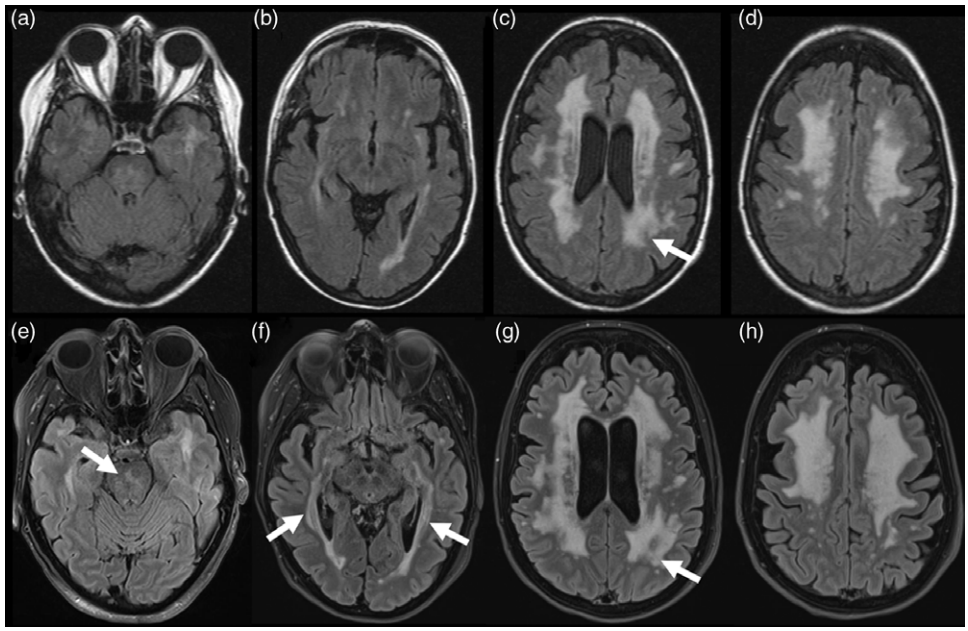

Fig. 1. Axial T2 FLAIR images of the patient 6 years earlier at the age of 68 years (Panels A–D) and during the present evaluation at the age of 74 years (Panels E–H). Images of the patient at the age of 74 years (Panels E–H) revealed extensive confluent white matter T2 prolongation, present in the subcortical and periventricular white matter of both cerebral hemispheres including the temporal lobes (see arrows at Panel F), as well as in the brain stem (see arrow at Panel E), nonspecific in appearance and distribution but deemed most likely to represent the sequelae of severe small vessel ischemic disease. Findings were only slightly progressed compared to images obtained 6 years earlier at the age of 68 years, especially in the parietal regions (see arrows at Panels C and G). Mild interval cerebral volume loss was noted when compared to the prior examination.

on other speeded tasks argue against globally diminished processing speed. Second, confrontation naming was impaired, but she correctly identified all missed items with phonemic or multiple choice cues. This finding suggests compromised lexical access with preserved semantic representations, which is consistent with her weaker performance on letter relative to semantic fluency. It is possible that these findings are consistent with deficits in rapid automatized naming seen in developmental dyslexia (Wolf & Bowers, 1999). Indeed, her performance on the word but not the color condition was impaired on the Stroop, and her ability to pronounce words with irregular grapheme-to-phoneme translation was low average, belying her high educational attainment. There was no evidence for clinically significant depression or diminished effort that may better account for her performance. Third, compared to her prior neuropsychological results for clinical and other research purposes 3 and 6 years previously, her current performance was remarkably consistent except for: a 1 standard deviation decline on confrontation naming, 2.5–3 standard deviation decline in fine motor dexterity bilaterally, and 1 standard deviation decline in aspects of processing speed, as above (i.e., coding and word reading speed).

Rheumatology

Due to her history of mouth ulcers and uveitis, she was also evaluated by rheumatology. A laboratory evaluation (Table 1.b) was significant for positive antinuclear antibodies and Sjogren's syndrome antibody (Anti-SSA). Given the combination of these results with her presenting symptoms, she was diagnosed with Sjogren's and started on hydroxychloroquine, with reported benefit. She was subsequently re-evaluated clinically by neurology and completed a lumbar puncture to assess for evidence of inflammation or autoimmunity. The results of this were negative (Table 1.b) and conservative management has since been maintained.

Advanced Diffusion MRI: Identifying a Potential Mechanism for Brain Reserve

Figure 2 depicts the results of tractography analyses to provide a qualitative depiction of the patient's white matter tracts using conventional (i.e., DTI) and advanced (i.e., FBI) diffusion MRI, vis-à-vis results from a well-matched cognitively unimpaired control (i.e., female, aged 77 years, 18 years of education). Figure 2A highlights FBI's ability to resolve crossing fibers in the frontal lobe of the control in an area with complex fiber orientations from well-validated fiber bundles (i.e., genu of the corpus callosum, anterior corona radiata). Similarly, the patient's FBI tractography resolves more fibers in this region (Figure 2B), suggesting a possible mechanism supporting the patient's cognitive resilience as particularly evident in her overall intact executive functions relative to the severity of her leukoaraiosis in the frontal lobes. FBI is able to resolve complex white matter architecture via

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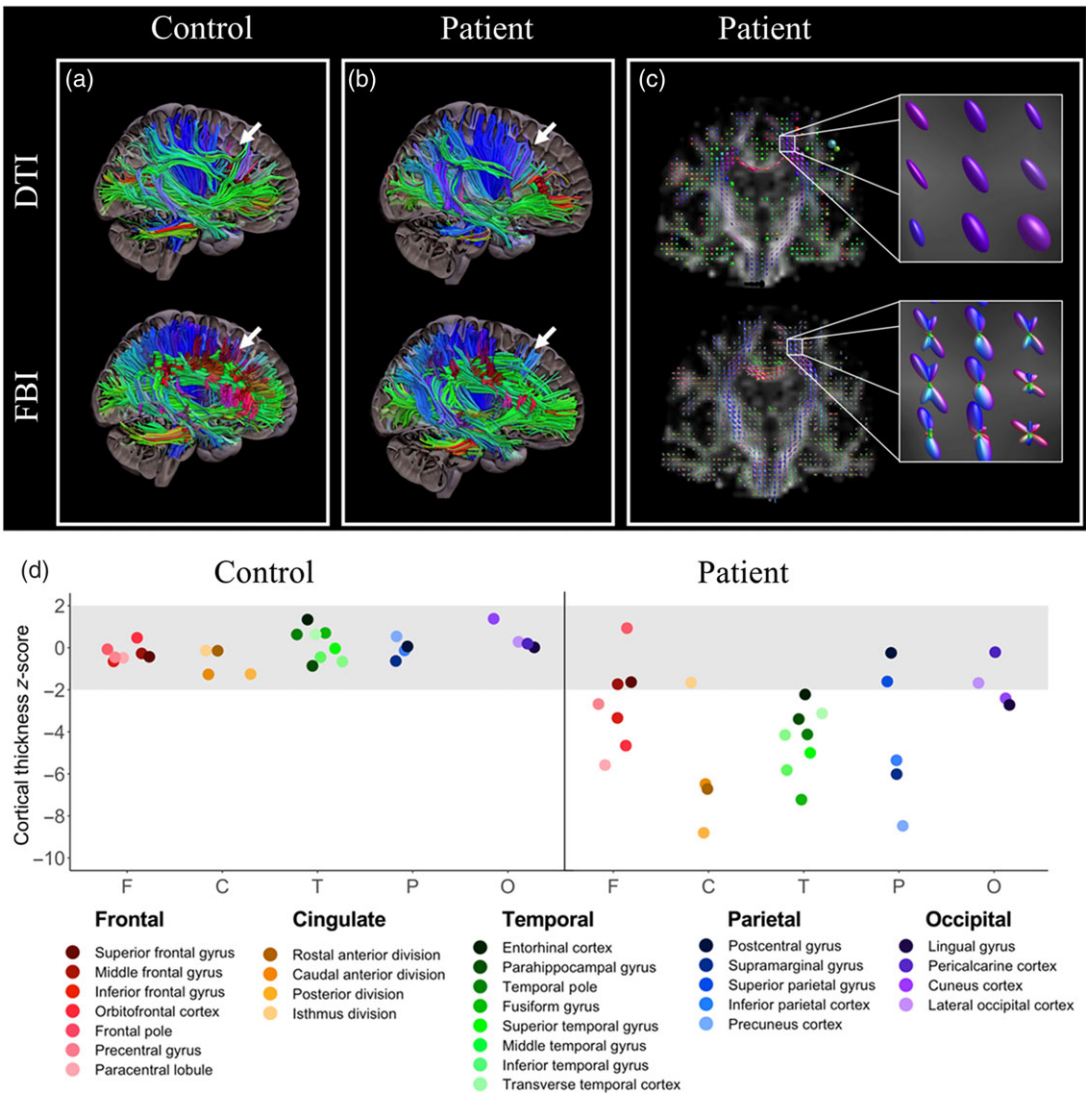

Fig. 2. DTI and FBI tractography (A–C) and cortical thickness normed *z*-scores (D) of the control and the patient. (A and B) The sagittal slices include tracts with anterior-to-posterior (green), inferior-to-superior (blue), and left-to-right (red/magenta) directional orientations. Compared to DTI, FBI is better able to resolve crossing fibers particularly in the frontal regions (see tracts indicated by white arrows in A, particularly the red/magenta tracts using the FBI data). Compared to DTI, FBI resolves the potential presence of intact axons in the frontal regions (see tracts indicated by white arrows in B, particularly the green and red/magenta tracts using the FBI data). (C) This figure shows coronal slices of DTI and FBI fiber orientation distribution functions (ODFs) with a zoomed-in 3 × 3 matrix of voxels highlighting FBI's ability to generate ODFs with multiple directions, thereby resolving crossing fibers. (D) This figure depicts the normed *z*-scores (y-axis) of the cortical thickness regions of interest within the F = Frontal, C = Caudate, T = Temporal, P = Parietal, and O = Occipital lobes (x-axes) for both the control and the patient, showing more aberrant cortical thickness measurements in the patient than the control across most regions. DTI = diffusion tensor imaging; FBI = fiber ball imaging.

multi-directional diffusion orientation distribution functions (Figure 2C) and assesses diffusion within axons (i.e., via suppressing extra-axonal water), thereby revealing white matter tracts that are likely present and unresolved using DTI.

Figure 2D depicts the cortical thickness measurements of lobar regions of interest segmented using FreeSurfer. FreeSurfer outputs were converted to *z*-scores using a large normative database accounting for age, sex, and estimated total intracranial volume (Potvin et al., 2017) to provide a qualitative comparison of individualized deviation scores for each region of interest for both the control and patient (cf. Supplementary Material). Compared to the control, the majority of the patient's cortical thickness measurements were below the normative range (i.e., z = ±2.0), providing less support for cortical compensation and the relevance of cortical thickness as a measure of brain reserve in this particular case.

DISCUSSION

This case study illustrates cognitive resilience in the presence of severe leukoaraiosis and demonstrates how an advanced

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diffusion MRI method (i.e., FBI) can identify a potential mechanism of brain reserve. That is, as illustrated by tractography in both a control and the patient, FBI resolves white matter tracts with complex orientations and in areas where axonal architecture may remain intact despite alterations in the extra-axonal space (i.e., due to gliosis, myelin rarefaction, etc.). While advanced techniques such as this are still under development, individual case studies serve as powerful examples of their future potential to ascertain resilience *in vivo*. These findings have the following implications with regard to the patient, the concept of brain reserve, and the potential clinical use of advanced diffusion MRI.

This case illustrates the startling finding of intact functioning despite severe brain disease. While this patient demonstrated some declines over time (i.e., in processing speed and confrontation naming) that may reflect advancing vascular or rheumatologic disease, her overall intact abilities are remarkable given her severe leukoaraiosis. In contrast to conventional structural imaging, data from FBI suggest intact axonal architecture, revealing white matter that is not too discrepant from that of a similarly cognitively intact control. As implied by her cognitive resilience, these findings also suggest a favorable prognosis given her brain reserve.

This study adds to the literature by illustrating how an advanced diffusion MRI technique can yield other measures of brain reserve, specifically indicators of axonal architecture. However, the broader field of diffusion MRI has yet to achieve consensus regarding acquisition and analysis parameters for clinical use. Many developers agree that neuroscience is best served by going beyond DTI, but as to which advanced diffusion MRI technique to use remains up for debate (Le Bihan, 2013). It is especially important to analyze these data judiciously given the potential sources of bias and error endemic to all diffusion techniques from DTI to advanced ones like FBI (Jones & Cercignani, 2010), including when subjecting these data to tractography analyses (Campbell & Pike, 2014). Achieving consensus on how best to acquire, analyze, and validate diffusion data will be critical for its eventual application as a measure of brain reserve.

This case study has some limitations. First, tractography is inherently a qualitative technique that serves as an *in vivo* estimate of white matter architecture. Only postmortem validation could verify our assertions. We also only had FBI data for one time point. Having multiple acquisitions and comparing their progression (ideally vis-à-vis a control's progression) would strengthen the argument that her sustained cognitive resilience is mediated by the stability of her brain reserve. Another valuable extension of this work would be to examine the FBI results in another matched patient with similarly severe leukoaraiosis *but with severe cognitive deficits*. If the preserved axonal architecture highlighted by the FBI findings in our patient were absent in this cognitively impaired leukoaraiosis "control," then we would have more compelling evidence supporting FBI as a brain reserve marker. At present, these data represent a preliminary demonstration of how an advanced technique resolves axonal architecture in a patient whose neuropsychological functioning belies what can be inferred from conventional techniques (i.e., DTI, cortical thickness).

Furthermore, the patient's neurologic diagnosis remains unknown. As best we can ascertain, she has a rheumatologic condition, and although white matter lesions can be seen in Sjogren's syndrome, the severity of her leukoaraiosis would be very atypical (Morgen et al., 2004; McCoy & Baer, 2017). It is also possible that vascular disease, such as hypertension and hyperlipidemia, are the main drivers of her white matter pathology. However, while data from a large observational study (i.e., UK Biobank) suggest that hypertension is associated with diffusion MRI findings indicating alterations in axonal structure (Suzuki et al., 2017), abnormal cholesterol was not shown to be uniquely associated with any MRI marker (Cox et al., 2019). It is perhaps more likely that these risk factors are additive and synergistic in their impact (Cox et al., 2019; Maillard et al., 2015), and it remains difficult to ascertain these effects on an individual patient basis, particularly in this case where medication and treatment compliance was high and perhaps contributing to her reserve. Given the absence of a known etiology, we are unable to more definitively comment on the suspected pathology underlying her imaging findings, which is likely complicated given her history (i.e., possible childhood encephalitis, remote history of alcohol use disorder).

The extent to which FBI findings are both sensitive and specific to this patient's unique set of circumstances or to a particular disease remains unknown. Nonetheless, this study serves to illustrate how an advanced technique such as FBI may improve upon the characterization of white matter integrity. Indeed, Figure 2 demonstrates better resolution of fiber architecture in both the control and the patient compared to DTI, which has significant implications for the investigation of white matter integrity as a method of quantifying brain reserve. A recent study demonstrated that greater occupational complexity (an index of cognitive reserve) in earlier adulthood was associated with better white matter microstructure and cognitive performance in mid-life, suggesting that reserve may attenuate cognitive and brain decline (Kaup et al., 2018). Importantly, this study did not find an association between occupational complexity with gray matter volume (another investigational measure of brain reserve), introducing the hypothesis that reserve may be conferred via white matter-mediated processes (e.g., axonal and myelin maintenance and plasticity) rather than changes to neuronal cell bodies or synaptic density approximated *in vivo* via gray matter morphometry (including cortical thickness, such as in this study). Utilizing advanced diffusion approaches in similar investigations may further explore this possibility given the greater fidelity with which it characterizes white matter microstructure, particularly if contrasted with other candidate measures of brain reserve. Future validation studies would ideally be longitudinal in design, given the importance of disentangling innate neurobiological capital ("brain reserve") from resilience to age-related or pathological changes that may be modifiable ("brain maintenance") (Nyberg et al., 2012; Stern et al., 2018). In addition, future applications of

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diffusion MRI must be mindful of the fact that this technique is inherently an indirect estimation, and work integrating physical, numerical, and histological validation strategies are necessary to substantiate the biological inferences made in clinical studies (Dyrby et al., 2018; Fieremans & Lee, 2018).

Despite these limitations, this study adds to the literature by introducing a clinical application of an advanced technique that may illuminate mechanisms of brain reserve. The current findings suggest that reserve may not only be implied based on discrepant cognitive and neuroimaging findings, but could potentially be quantified using advanced diffusion MRI. This project has also offered our patient some insight into her diagnostic conundrum as well as some hope, given that her previous diagnosis (i.e., leukoencephalopathy) had a far worse prognosis. Future work remains necessary to verify the application of this novel technique across individuals and populations and to further develop the construct of brain reserve for clinical use.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617720000569

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