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Mild cognitive impairment and structural brain abnormalities in a sexagenarian with a history of childhood traumatic brain injury

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Abstract

In this report, we present a case study involving an older, female patient with a history of pediatric traumatic brain injury (TBI). Magnetic resonance imaging and diffusion tensor imaging volumes were acquired from the volunteer in question, her brain volumetrics and morphometrics were extracted, and these were then systematically compared against corresponding metrics obtained from a large sample of older healthy control (HC) subjects as well as from subjects in various stages of mild cognitive impairment (MCI) and Alzheimer disease (AD). Our analyses find the patient's brain morphometry and connectivity most similar to those of patients classified as having early-onset MCI, in contrast to HC, late MCI, and AD samples. Our examination will be of particular interest to those interested in assessing the clinical course in older patients having suffered TBI earlier in life, in contradistinction to those who experience incidents of head injury during aging.

KEYWORDS
traumatic brain injury, mild cognitive impairment, aging

1 | INTRODUCTION

Despite reasonable chances of recovery and frequent evidence for cognitive reserve (CR) (Bigler & Stern, 2015), traumatic brain injury (TBI) experienced early in life may result in late-life cognitive decline and dementia (LoBue et al., 2017; LoBue, Wilmoth, et al., 2016; Plassman & Grafman, 2015). However, a direct cause-and-effect relationship has yet to be firmly established between pediatric TBI and early-onset Alzheimer disease (AD) (Mendez, Paholpak, Lin, Zhang, & Teng, 2015). Reports suggest that TBI during childhood may not necessarily cause dementia later in life per se but may result in earlier onset (Li, Risacher, McAllister, & Saykin, 2016). For example, in those who are genetically predisposed to dementia, the occurrence of TBI early in life may hasten AD onset. In contrast, neuropsychological studies of older adults who had recently suffered a TBI did not show any more or less amnesia or cognitive impairment (CI) than similarly aged patients suffering from mild CI (MCI) alone (Rapoport et al., 2008). In other words, late-life TBI may not necessarily result in MCI or AD. Additionally, TBI as a risk factor for MCI may also be confounded by other factors such as sex and clinical depression (LoBue, Denney, et al., 2016). Nevertheless, neuroimaging of older subjects who experienced TBI during their youth can provide valuable insights with potential diagnostic utility.

Magnetic resonance imaging (MRI) measurements of brain structure have been shown to demonstrate brain atrophy (which correlates with neuronal loss) in MCI and AD as well as increasing rates of brain atrophy as patients with MCI/AD become more impaired (Hua et al., 2008, 2011; Morra et al., 2009; Nestor et al., 2008; Thompson et al.,

Significance

Structural and diffusion measurements of the brain have been shown to demonstrate brain atrophy in mild cognitive impairment (MCI) and Alzheimer disease as well as increasing rates of brain atrophy as patients with MCI/AD become more impaired. Examining the long-term effects of pediatric traumatic brain injury (TBI), especially in cases of successful recovery, using neuroimaging may take on unique importance in the aging brain. Comparison of individual cases having suffered TBI against aging-specific disease cohorts can contribute insights into the clinical picture of early-life brain injury.

TABLE 1 Longitudinal gross morphological changes in the brain of patient IH

Structure	Volumes (mm^3) 5/27/2011	2/18/2014	% Change	% Annual
Total gray matter	624,685	629,350	−0.096	−0.035
Total cortical gray matter	452,898	453,531	0.507	0.186
Total cortical white matter	436,302	419,036	4.578	1.674
Intracranial volume	1,482,111	1,491,752		
Left thalamus proper	6272	6198	1.819	0.665
Right thalamus proper	6421	6140	4.994	1.827
Left lateral ventricle	16,282	18,480	−12.766	**−4.670**
Right lateral ventricle	16,067	17,167	−6.156	**−2.251**
Third ventricle	1384	1566	−12.419	**−4.542**
Fourth ventricle	1221	1541	−25.392	**−9.287**

Numbers in bold indicate changes exceeding 2% annual changes over time in cerebrospinal fluid containing brain spaces.

2007; Wolz et al., 2011). For this reason, structural MRI can be used to quantify the rate of disease progression, and possibly as a measure of treatment effect, in AD treatment trials (Poulin & Zakzanis, 2002; Van Horn & Toga, 2009b). Moreover, interest exists in using neuroimaging data resources as a basis for comparison in studies of potentially degenerative syndromes (Van Horn & Toga, 2009a), including TBI (Li et al., 2016; Weiner et al., 2013).

In this report, we present a case study involving an older, female patient with a history of pediatric TBI. MRI and diffusion tensor imaging (DTI) volumes were acquired from the volunteer in question, her brain volumetrics and morphometrics were extracted, and these were then systematically compared against corresponding metrics obtained from a large sample of older healthy control (HC) subjects as well as from subjects in various stages of MCI and AD.

2 | METHODS

2.1 | Subject

Patient "IH" is a 67 year-old female who experienced a severe head injury in childhood (at 5 years of age) subsequent to a moving-vehicle traffic accident. After successful clinical recovery, the patient led an exemplary adult life that involved higher education achievements, philanthropy, and community service. When the patient was in her early 60s, however, her family members reported to clinicians that she was experiencing memory loss and other cognitive deficits.

The patient underwent clinical assessment at the University of California Los Angeles, where the following examinations were administered: Mini-Mental State Examination (MMSE); Wechsler Test of Adult Reading (WTAR); Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) selected subtests; California Verbal Learning Test–II (CLVT-II); Wechsler Memory Scale–3rd Edition (WMS-III) selected subtests; Trailmaking A & B; Stroop Color-Word Interference Test; Boston Naming Test (BNT); Rey-Osterrieth Complex Figure Test (ROCFT); Controlled Oral Word Association Test (FAS, animals); Geriatric Depression Scale (GDS); and the Wisconsin Card Sorting Test (WCST).

Genetic screening (30X, Illumina HQ, San Diego, CA, 2013) indicated that the patient was *APOE*-negative, although her genome did feature single-nucleotide polymorphisms associated with presenilin-encoding genes (*PSEN1*, *PSEN2*), which are recognized as having a putative role in familial AD (Lalli et al., 2014; Mathews et al., 2000). Clinical abnormalities were also observed on resting and task-oriented electroencephalographic recordings, suggestive of remnant morphological damage. Prior neuroimaging assessment using 1.5 T MRI over two occasions (Table 1) showed that Patient IH had experienced considerable percentage increases in the volume of the ventricular system over the roughly 3-year period during which symptoms of cognitive decline became noticeable by her close relatives.

2.2 | Neuroimaging

Patient IH provided informed consent and underwent brain imaging using the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI-2) neuroimaging protocol in a General Electric 3 T MRI scanner located at the Keck School of Medicine of USC. The MRI protocol consisted of four sequences: (1) inversion-recovery spoiled gradient echo T1-weighted structural MRI, (2) fluid-attenuated inversion recovery MRI, (3) gradient recalled echo T_2^* MRI, and (4) 64-direction DTI. Resting-state functional MRI was also collected, but we have chosen to defer analysis of this sequence to a later exploration. Here, we focus specifically on analyses of the T1 structural and DTI imaging data. The details of the ADNI-2 neuroimaging protocol are described in Jack et al. (2010), while various applications and a review of results obtained from this multisite trial are given in Weiner et al. (2012).

2.3 | Analyses

Tissue classification and anatomical parcellation of T1-weighted volume—together with DTI processing and connectogram creation (see Figure 1D–H)—were performed as described elsewhere (Irimia,

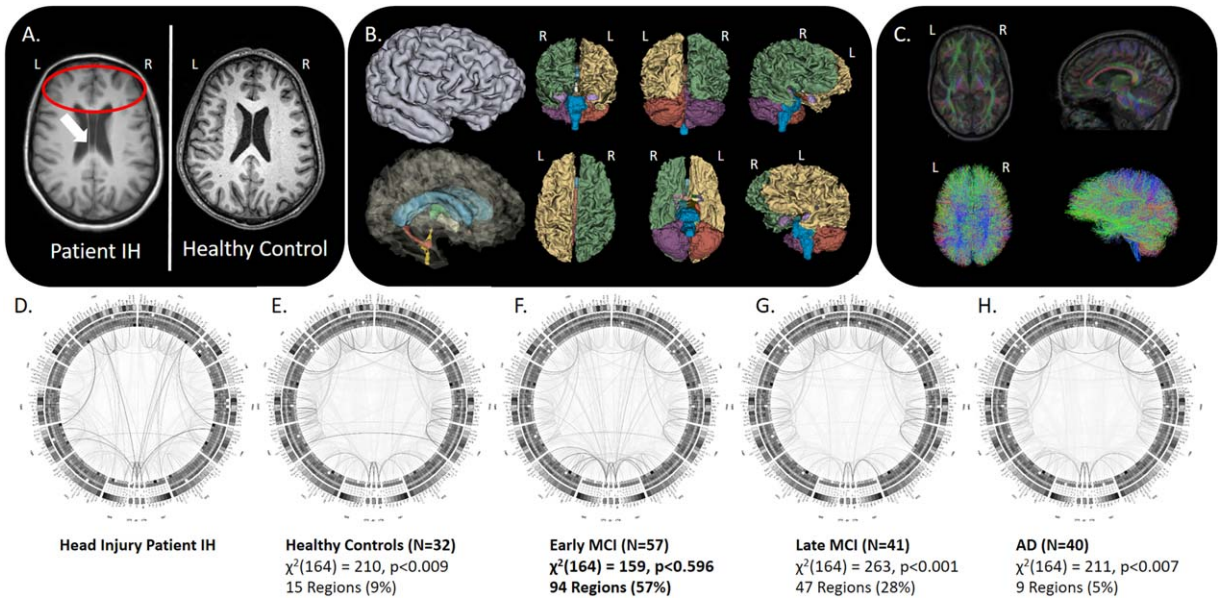

FIGURE 1 (A) Magnetic resonance imaging of Patient IH relative to an age-matched healthy control subject; (B) cortical parcellation and volumetric modeling; (C) diffusion imaging tractography; (D–H) group-specific connectograms for Patient IH, healthy older adults, early mild cognitive impairment (MCI), late MCI, and Alzheimer disease (AD), respectively, with accompanying "goodness-of-fit" assessment of Patient IH's group membership.

Chambers, Torgerson, & Van Horn, 2012). We identified patients from the ADNI-2 cohort of similarly aged females. These included HCs (N = 32), early MCI (EMCI, N = 57), late MCI (LMCI, N = 41), and AD (N = 40) with mean (± SD) ages of 75.00 ± 6.06, 75.00 ± 7.74, 73.87 ± 6.05, and 75.32 ± 8.28, respectively. In instances where multiple MRI scan session data were available from these subjects, we selected the scan session representing the date closest in age to Patient IH. We then assessed the overall pattern of connectivity density across the brain of Patient IH against these groups using a posteriori Bayesian probabilities of group membership (see Rencher, 2002, for description). Finally, we sought to assign Patient IH to the most likely group via chi-square "goodness-of-fit" test to enable us to classify her into one or more of the ADNI-2 patient cohorts and, thus, infer upon her a computational "diagnosis." In goodness-of-fit testing, one seeks the smallest χ^2 statistic when comparing across classes—thus, the largest probability for a particular comparison based on probabilistic similarity. In other words, this reflects the probability of a subject "belonging" to that particular group. This is in contrast to the more familiar seeking of a large χ^2 statistic against the associated degrees of freedom (and small *P* value), suggesting departure from the theoretical expectation (Johnston, Berry, & Mielke, 2006; Kvalseth, 2004).

3 | RESULTS

The results of Patient IH's neuropsychological evaluation revealed no areas of significant cognitive or intellectual impairment (Table 2). Given her estimated high premorbid level of functioning, relative weaknesses were noted in selected aspects of processing speed (e.g., rapid number sequencing), as well as aspects of executive functioning, including mental flexibility, divided attention, and word generation. Patient IH did report some family-related stress, which could have adversely impacted cognitive function and which might have contributed to her more subjective complaints. However, many individuals demonstrate areas of relative weakness due to normal variability and aging that are not pathological in nature, and her performance on other measures in these domains were intact. Despite her childhood injury and reported declines in memory, her performance on measures of both verbal and nonverbal memory was intact and comparable with that of younger adults.

The brain imaging from Patient IH, however, was noted to exhibit a cavum septum pellucidum (Figure 1A), where the septal lamina have become detached and separated—a condition often associated with head trauma (see, for instance, the study of American football players by Gardner et al., 2016). Also present was a concave deformation of the lateral gray matter surface extending over the antero-superior portion of the temporal lobe (inferior, middle, and superior temporal gyri) and over the inferior portion of the right prefrontal cortex. No similar deformation was observed in the corresponding region of the right hemisphere. Patient IH's brain also exhibited reduced white matter volume in the right hemisphere in contrast to that of the left hemisphere. Interestingly, the left pallidum was noted to be ~47% larger than the right pallidum; such a large asymmetry is rare in healthy adults, though it has been observed frequently in patients with chronic TBI and dementia (Gooijers et al., 2016). More specifically, examining interregional brain connectivity (Figure 1B–C), we measured the multivariate Mahalanobis distance and a posteriori probabilities of group memberships between the connectogram-based patterns of white matter fiber density in Patient IH versus the same in the HC, EMCI, LMCI, and AD groups from the ADNI-2 cohort (Figure 1D–H). Patient IH's overall pattern of brain connectivity was most probabilistically different from that of AD patients, LMCI subjects, and HC subjects. Patient IH did, however, show a pattern of brain connectivity probabilistically most similar,

TABLE 2 The results of neuropsychological testing

Neuropsychological assessment	Score/outcome (percentile)	Comments
Mini-Mental State Examination (MMSE)	30/30	Suggesting intact cognitive functioning
Wechsler Test of Adult Reading (WTAR)	Verbal IQ = 122 (93rd)	In the superior range
Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) selected subtests	Digit Span = 7 forward, 5 backward (63rd) Digit-Symbol = 84th percentile Picture Completion = 91st percentile Block Design = 84th percentile	Average range
California Verbal Learning Test–II (CLVT-II)	Initial: • CVLT-II List Trials 1–5 = 55 (82nd) • Learning curve: 7, 9, 12, 14, 13 • CVLT-II Short Delay Free Recall = 12 (84th) • CVLT-II Short Delay Cued Recall = 11 (50th) Following 20-min delay: • CVLT-II Long Delay Free Recall = 12 (69th) • CVLT-II Long Delay Cued Recall = 13 (69th) • CVLT-II Total Hits = 15 (50th); false positives = 0 (84th)	Demonstrated a positive learning curve High average range for her age
Wechsler Memory Scale–3rd Edition (WMS-III) selected subtests	Logical Memory I = 55 (95th) Logical Memory II = 37 (98th) (95% retention) Visual Reproduction I = 78 (50th) Visual Reproduction II = 61 (75th) 78% retention	Average to superior range of memory
Trail Making A & B	Trails A = 14th percentile Trails B = 71 seconds, (36th), 0 errors	Average mental flexibility and divided attention
Stroop Color-Word Interference Test	EWord reading = 95th percentile Color naming = 83rd percentile	In the superior range
Boston Naming Test (BNT)	3-min delay = 17.5 (58th)	In the average range
Rey-Osterrieth Complex Figure Test (ROCFT)	ROCFT Copy = 33 (>16th)	Within limits, demonstrating overall gestalt
Controlled Oral Word Association Test (FAS, animals)	Animals = 19 (58th) FAS = 39 (40th)	In the average range for her age
Geriatric Depression Scale (GDS)	GDS = 4	In the normal range for mood
Wisconsin Card Sorting Test (WCST)	Categories = 6 (>16th) Perseverative Errors = 6 (61st)	In the average range

via chi-square goodness-of-fit test ($df = 164$), to that of the EMCI patients in the ADNI-2 cohort (see Figure 1F).

4 | DISCUSSION

In this brief article, we present a case study examination of a female sexagenarian patient who experienced TBI as a child but presented an admirable recovery, spending her life conducting philanthropic work before suffering cognitive decline. Neuropsychological assessments indicated an intelligent woman presenting no major deficits for her age but with minor weaknesses in executive function and divided attention, which might simply reflect normal age- or stress-related variation. Using structural and diffusion neuroimaging, we parcellated the brain and computed its interregional DTI connectivity. Our analyses find Patient IH's brain morphometry and connectivity most similar to those of patients from the ADNI cohort classified as having EMCI. Several points of discussion are worth considering relevant to Patient IH and our analyses of her neuroimaging data.

4.1 | Altered brain morphometry in Patient IH

Patient IH was noted here to exhibit cavum septum pellucidum, altered left temporal gray matter, frontal lobe white volume asymmetry, and a greater volume of the left than the right pallidum. Cavum septum pellucidum (CSP) variations are common in neurological patients (Akinola, Idowu, & Nelson-Paseda, 2014) and have been intermittently reported in retired professional athletes (Bodensteiner & Schaefer, 1997; Bogdanoff & Natter, 1989; Casson, Viano, Haacke, Kou, & LeStrange, 2014). In a study by Silk et al. (2013), there was no difference in the presence of CSP between patients with TBI and controls; however, there was larger and more severely graded CSP in the patient group, with the size of the CSP correlated positively with injury severity. Patient IH was unconscious for 2 weeks following her injury, suggesting a particular and sufficient level of severity. Greater degenerative white matter alterations have been reported in pediatric TBI patients (Keightley et al., 2014), where lowered white matter integrity may be more important in the pathophysiology of brain injury than indices of gray matter change, macroscopic lesions, and injury severity (Max

et al., 2012). MRI findings frequently identify frontal and temporal alterations in pediatric TBI groups relative to comparison samples (Wilde et al., 2005); however, temporal lobe injuries may not be associated with greater levels of anxiety (Vasa et al., 2004). Finally, subcortical volumetric alterations are frequently reported in TBI (Gooijers et al., 2016), are notable in MRI of pediatric head injury cases (Wilde et al., 2007), and can affect cognitive processes such as proactive inhibition (Hermans et al., 2016). Such alterations in this case, thus, are not uncommon with regard to other reported TBI studies in young and adult samples, and Patient IH's injury was likely the initiation of a process culminating in eventual cognitive decline later in life.

4.2 | Age as an important factor in TBI recovery but eventual cognitive decline

Outcome from TBI is a function of age at injury (Testa, Malec, Moessner, & Brown, 2005), with younger subjects tending to recover more fully than older individuals. Indeed, early intervention, surgical treatment, and/or intensive care for patients have been reported to produce excellent clinical results up to the age of 59 years, with favorable outcomes still possible for 39% of cases aged 60 to 69 years, without an excessive burden of severely disabled patients (Stocchetti, Paterno, Citerio, Beretta, & Colombo, 2012). Children suffering TBI, however, show cortical thickness changes measured using MRI at 3 and 18 months following injury in contrast to children with orthopedic injuries (Wilde et al., 2012). TBI in animal models has suggested increased motor and cognitive deficits in rats suffering injuries earlier in development, in contrast to greater anxiety in rats injured during adulthood (Rowe et al., 2016). So while structural and connectomic injuries may be clinically recoverable, their residual effects may be expressed later in life as cognitive decline. As such, an improved integration of major clinical and scientific effort needs to be made to improve any potential for posttraumatic recovery after TBI in neonates and young children (Maxwell, 2012).

4.3 | Brain reserve capacity

Patient IH did not present pathological levels of cognitive decline despite subjective reports from herself and her family. Indeed, she showed above-average to superior performance on many of the measures assessed. Brain reserve capacity (BRC) refers to preinjury quantitative measures such as brain size that relate to outcome (Bigler & Stern, 2015). Higher degrees of BRC imply threshold differences when clinical deficits will become apparent after injury, where those individuals with higher BRC require more pathology to reach that threshold. CR, more specifically, pertains to how flexibly and efficiently the individual makes use of available brain resources even in the presence of advancing age (Whalley, Deary, Appleton, & Starr, 2004). The CR model suggests that the brain actively attempts to cope with brain damage resulting from TBI by using preexisting cognitive processing approaches or by enlisting compensatory approaches (Nunnari, Bramanti, & Marino, 2014). Standard contributors to CR include education and IQ (Carnero Pardo & del Ser, 2007; Elkana et al., 2016; Kowoll et al., 2016), including literacy, occupational attainment, engagement in leisure activities, and the integrity of social networks (Cheng, 2016; Henderson, 2014; Sakka, 2015; Moussard, Bermudez, Alain, Tays, & Moreno, 2016). Most research on BRC and CR has taken place in aging and degenerative disease (Sobral, Pestana, & Paul, 2015), but these concepts likely apply to the effects of TBI, especially with regard to recovery (Bigler, 2014; Miller, Colella, Mikulis, Maller, & Green, 2013; Scheibel et al., 2009; Schneider et al., 2014; Sumowski, Chiaravalloti, Krch, Paxton, & Deluca, 2013). Because increased incidence of TBI occurs in those under age 35, both CR and BRC factors likely relate to how the individual copes with TBI over the life span. Mild to moderate TBI during childhood, during a time of maximal neural plasticity, may show sufficient recovery when exposed to highly educational and psychosocial encouraging environments (Beauchamp & Anderson, 2013; Max et al., 1999). Such factors may be particularly relevant to the timing of cognitive decline in an individual who has sustained a TBI earlier in life, in contrast to an older adult suffering affected cognition as a consequence of head injury.

4.4 | Presence of presenilin proteins

Patients with AD with an inherited form of the disease may carry mutations in the presenilin proteins (*PSEN1*; *PSEN2*) or the amyloid precursor protein (APP). These disease-linked mutations result in increased production of the longer form of amyloid beta (Aβ). Presenilins are believed to regulate APP processing through their effects on gamma secretase, an enzyme that cleaves APP (Cruchaga et al., 2012). Moreover, presenilins contribute to the cleavage of the Notch receptor (Newman et al., 2014). They either directly regulate gamma secretase activity or themselves are protease enzymes. A number of alternatively spliced transcript variants have been identified for this gene; the full-length nature of only a handful have been determined (Bennet et al., 2011). The study of patients having *PSEN1/2* protein mutations provides unique opportunities to examine AD biomarkers in persons in whom the diagnosis is certain, as in the present case of Patient IH.

In a particular example, Ringman et al. (2011) describe a 55-year-old female patient with AD having a *PSEN1* mutation who underwent genetic, clinical, biochemical, and magnetic resonance and nuclear imaging assessments. They also explored neuropathological findings in her similarly affected male sibling. Neuropsychological testing confirmed deficits in memory, visuospatial, and language function. Cerebrospinal fluid–based t-tau and p-tau were markedly elevated, and Aβ levels were reduced. FDG-PET revealed hypometabolism in the left parieto-temporal cortex. FDDNP-PET revealed greater tracer binding in medial temporal and parietal lobes, in the head of the caudate nucleus, and in the anterior putamen bilaterally. Neuropathological examination of her brother showed the typical findings of AD, and the striatum demonstrated amyloid pathology and marked neurofibrillary pathology beyond that typically seen in late-onset AD. A novel S212Y substitution in *PSEN1* was present in the index patient and her affected brother but not in an older unaffected sister. An in vitro assay in which the S212Y mutation was introduced in cell culture confirmed that it was associated with increased production of Aβ. Their study helps to

validate the pathogenicity of this mutation as an index used to assess familial AD.

While a causal relationship due to the presence of *PSEN* gene variants is difficult, if not impossible, to establish, a potential linkage between genetic susceptibility and Patient IH's head injury early in life is compelling. Patient IH was determined here to have cortical anatomy and white matter connectedness most similar to those of the ADNI EMCI cohort; however, it remains to be seen if she might later convert to full AD, and a more detailed examination of her family history would be warranted.

4.5 | Statistical similarity

We have systematically compared Patient IH's brain morphometry and connectivity to the distributions of the various cohorts of the ADNI-2 sample via multivariate modeling, a posteriori probabilistic classification, and goodness-of-fit assessment. This approach is distinguished from machine learning classification since we wish to compute a "distance" between the observed values obtained from Patient IH against those expected from each ADNI patient cohort relative to underlying random classification error to obtain a probabilistic statement about group membership (Boyle, Flowerdew, & Williams, 1997; Choi & McHugh, 1989; Fisher, Marshall, & Mitchell, 2011; Reijneveld, 1990). Related methods have been widely applied in neuroimaging voxel pattern analysis (Walther et al., 2016), structural connectivity (Gupta et al., 2015), and functional MRI time series data (Friston et al., 2008). While machine learning methods might also have been appropriate here (e.g., Apostolova et al., 2010), this approach serves a parsimonious purpose —showing the degree of similarity of Patient IH to each of the ADNI patient groups. It is unclear whether the computational efforts of a machine learning approach would provide additional information about Patient IH's similarity to the EMCI group, per se. Regardless, the availability of the ADNI neuroimaging data set as a basis for comparison represents a highly useful resource for computationally assessing the status of independently collected data in patient samples in health as well as in disease.

In general, Patient IH's brain morphometry and white matter connectivity density were determined to be statistically most similar to those of patients having been diagnosed with EMCI as indicated under the ADNI-2 study protocol. This agrees with what has been documented about MCI (Celsis, 2000) and its potential connections with TBI earlier in life (Plassman & Grafman, 2015). Still, the use of computational approaches for subject classification in this manner has important implications for the proactive utilization of neuroimaging data from leading databases for such purposes. It is important to note, however, that while the role of early-life TBI on neurocognitive changes in later life is an important topic, a number factors beyond Patient IH's injury could also be at play over her lifetime, which complicates making broad sweeping statements about her experience compared with those of other TBI sufferers. However, such subject classification approaches may be useful for providing key insights into the distinctions between patients having early versus later-life TBI and the clinical outcomes thereof.

5 | CONCLUSIONS

Examining the long-term effects of early-life TBI, especially in cases of apparent recovery, may take on particular importance as the brain ages. This may be particularly true in military veterans (Weiner et al., 2014), as well as in former professional and collegiate athletics (Hart et al., 2013). In the case presented here, Patient IH presented suffering from symptoms and a pattern of brain degeneration consistent with EMCI with a suggested link to head injury during youth. While a causal relationship between the presence of the *PSEN* gene variants is difficult to establish, a potential linkage between genetic susceptibility and Patient IH's head injury early in life is possible. Most likely, her injury during childhood began a degenerative process sufficient to culminate in cognitive decline and MCI in later adulthood. Our examination will be of particular interest to those assessing the clinical importance of patients who are "aging after having suffered TBI" in contradistinction to those who experience "incidents of TBI during aging" (Peters, 2016).

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DATA ACCESSIBILITY

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) is freely available, with permission, from http://adni.loni.usc.edu/. As a multisite consortia, ADNI researchers systematically obtain, rigorously validate, and promote the utilization of MRI and PET images, genetics, cognitive tests, cerebrospinal fluid, and blood biomarkers as predictors from patients with the disease. Data from the North American ADNI's study participants, including patients with Alzheimer disease (AD), subjects with mild cognitive impairment (MCI), and healthy elderly controls (HC), are available. Neuroimaging and other metadata from Patient IH are available upon written request to the lead author of this study.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the Journal of Neuroscience Research, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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