

Cognitive Prognosis in Chronic Temporal Lobe Epilepsy

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Objective: First, to determine whether patients with chronic temporal lobe epilepsy have a different cognitive trajectory compared to control subjects over a prospective 4-year interval; second, to determine the proportion of patients who exhibit abnormal cognitive change and their profile of demographic, clinical epilepsy, and baseline quantitative magnetic resonance imaging characteristics; and third, to determine the most vulnerable cognitive domains.

Methods: Participants with chronic temporal lobe epilepsy ($n = 46$) attending a tertiary referral clinic and healthy control subjects ($n = 65$) underwent neuropsychological assessment and reevaluation 4 years later. Analysis of test–retest patterns identified individual patients with adverse cognition outcomes.

Results: The prospective cognitive trajectory of patients with chronic temporal lobe epilepsy differs from age- and sex-matched healthy control subjects. Lack of practice effects is common, but frank adverse cognitive outcomes are observed in a subset of patients (20–25%), particularly in vulnerable cognitive domains that include memory. Cognitive declines are associated with a profile of abnormalities in baseline quantitative magnetic resonance volumetrics, lower baseline intellectual capacity, as well as longer duration of epilepsy and older chronological age.

Interpretation: Cognitive prognosis is poor for a subset of patients characterized by chronicity of epilepsy, older age, lower intellectual ability, and more baseline abnormalities in quantitative magnetic resonance volumetrics.

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Temporal lobe epilepsy is common, often with an intractable course,^{1,2} and associated with cognitive morbidity that may not be limited to memory impairment.^{3–5} Still controversial is the degree to which abnormalities in mental status may progress over time⁶; this is an important issue because curative surgical treatments exist but are frequently delayed.^{1,7,8} When finally referred for surgical consideration, unfortunately sometimes after decades of unsuccessful medical management,^{9,10} significant cognitive morbidity may be apparent. However, whether this represents a static encephalopathy versus a progressive process remains an issue of interest and concern.¹¹

Prospective cognitive studies of epilepsy patients first appeared in the early twentieth century, but methodological limitations include limited assessment of cognition (often just intelligence), varying test–retest intervals, lack of control groups, and other problems.⁶ More common are cross-sectional studies^{5,12,13} that, although informative, have the obvious limitation of providing an indirect evaluation of neuropsychological change

over time, cohort effects, and other issues preventing an unequivocal characterization of the cognitive course of epilepsy.¹⁴

This controlled prospective investigation was designed to characterize the prognosis of cognition in patients with chronic temporal lobe epilepsy. The attendant methodology included an age- and sex-matched control group, a prospective 4-year test–retest design, comprehensive neuropsychological assessment, and analytic techniques designed to control for sources of error in test–retest assessment. In addition, we examined the association of change in neuropsychological performance with baseline quantitative magnetic resonance imaging (MRI) volumetric measurements of hippocampus and cerebrum. Volumetric measures predict cognitive course in other neurological conditions,^{15,16} and for the first time in epilepsy research, the relation between baseline volumetrics and prospective cognitive course is examined together with conventional epilepsy-related variables of interest (eg, duration of epilepsy).

The specific questions addressed include: (1) Do pa-

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tients with temporal lobe epilepsy as a group exhibit a different cognitive trajectory compared with healthy control subjects over a 4-year test–retest interval? (2) What proportion of patients with temporal lobe epilepsy exhibits an abnormal pattern of cognitive change, and what is their profile of demographic, clinical epilepsy, and baseline quantitative MRI characteristics? (3) Which cognitive domains are most vulnerable to abnormal change?

Subjects and Methods

Subjects

Research participants (n = 111) included 46 patients with temporal lobe epilepsy and 65 healthy control subjects. Subjects were between 14 and 59 years of age with Wechsler Adult Intelligence Scale, third edition (WAIS-III) Full Scale IQ score greater than 69. Selection criteria for epilepsy patients included: (1) complex partial seizures of definite or probable temporal lobe origin based on consensus conference review of ictal and/or interictal electroencephalogram, clinical semiology, and clinical history; (2) no MRI abnormalities other than atrophy on clinical interpretation; and (3) no other neurological disorder. Control subjects were a friend or relative of epilepsy participants without histories of the following: (1) current substance abuse or medical or psychiatric condition that could affect cognitive functioning, and (2) episodes of loss of consciousness greater than 5 minutes, developmental learning disorder, or repetition of a grade in school. Complete details regarding subject selection are available elsewhere.¹⁷ The project was reviewed and approved by the University of Wisconsin-Madison institutional review board, and informed consent was obtained from all research participants.

Patients and control subjects were reassessed 4 years after their baseline evaluation. Over the interval, 3 subjects died (1 epilepsy patient and 2 control subjects), 4 were lost to follow-up (1 epilepsy patient and 3 control subjects), 6 refused retesting (1 epilepsy patient and 5 control subjects), and 16 epilepsy patients underwent surgery. Surgical patients did not differ from study patients in baseline age, sex, age of onset/duration of epilepsy, cerebral and hippocampal volumes, number of medications, and 13 of 16 cognitive measures indicating lack of bias. In addition to patient interview,

interval medical records were reviewed by an independent reviewer blinded to the test–retest findings, and interval medication changes, seizure-related complications (eg, episodes of status epilepticus), seizure frequency, and total interval generalized tonic-clonic seizures were documented.

The groups were comparable in age, education, and sex distribution. Temporal lobe epilepsy patients had a significantly lower Full Scale IQ, experienced recurrent seizures since childhood (mean, 11.1 years) with long duration (mean, 22.4 years), and were treated at baseline and follow-up with an average 1 to 2 antiepileptic drugs (Table 1).

Neuropsychological Assessment

A comprehensive test battery (Table 2) was administered at baseline and 4-year follow-up that assessed intelligence¹⁸ (seven subtest short form¹⁹), language (naming,²⁰ fluency²¹), visuoperceptual/spatial skills (facial discrimination,²¹ spatial orientation²²) memory (verbal and nonverbal²³), executive functions (novel problem solving,²⁴ response inhibition and working memory²⁴), speeded psychomotor processing and fine motor dexterity²⁵.

Magnetic Resonance Imaging Volumetrics

Images were obtained on a 1.5 Tesla GE Signa MR scanner (Milwaukee, WI). Sequences acquired for each participant included: (1) T1-weighted, three-dimensional spoiled gradient recalled acquisition in a steady state (SPGR) acquired with the following parameters: TE = 5, TR = 24, flip angle = 40 degrees, NEX = 2, field of view = 20, slice thickness = 1.5mm, slice plane = coronal, matrix = 256 × 256; (2) proton density; and (3) T2-weighted images acquired with the following parameters: TE = 36 (for proton density) or 96 milliseconds (for T2), TR = 3,000 milliseconds, NEX = 1, field of view = 26, slice thickness = 3.0mm, slice plane = coronal, matrix = 256 × 192, and an echo train length = 8. MRIs were processed using a semiautomated software package (BRAINS-2).^{26–29} MR processing staff were blinded to the clinical and neuropsychological characteristics of the participants. Details of the image processing have been described previously.¹⁷ Variables of interest were segmented volumes of total cerebral gray and white matter and cerebrospinal fluid. A neural network application²⁹ traced the hippocampus using established guidelines³⁰

Table 1. Demographic and Clinical Characteristics

Characteristics	Temporal Lobe Epilepsy Patients (N = 46)	Control Subjects (N = 65)
Age, yr	33.7 (10.2)	32.6 (12.1)
Sex, M/F	15/31	25/40
Education, yr	12.9 (2.1)	13.5 (2.5)
Full Scale IQ ^a	91.4 (18.2)	106.7 (13.8)
Age at onset, yr	11.1 (7.3)	
Duration of epilepsy, yr	22.4 (11.5)	
Number of AEDs at baseline	1.7 (.80)	
Number of AEDs at follow-up	1.8 (.83)	

^ap < 0.01.

IQ = intelligence quotient; AED = antiepileptic drug.

Table 2. Neuropsychological Test Battery

Domain	Ability	Test
Intelligence	Verbal	WAIS-III Verbal IQ
	Nonverbal	WAIS-III Performance IQ
Language	Confrontation naming	Boston Naming Test ^a
	Verbal fluency	Controlled Oral Word Fluency ^a
Visuoperceptual	Facial discrimination	Facial Recognition Test ^a
	Spatial judgment	Judgment of Line Orientation ^a
Verbal memory	Auditory memory-immediate	WMS-III
	Auditory memory-delayed	WMS-III
Nonverbal memory	Visual memory-immediate	WMS-III
	Visual memory-delayed	WMS-III
Executive function	Problem solving	Wisconsin Card Sorting Test ^b
	Response inhibition	Stroop Interference Test ^a
	Complex psychomotor speed	Trail Making Test (B) ^c
	Working memory	WMS-III Working Memory
Motor	Simple psychomotor speed	Trail Making Test (A) ^c
	Speeded fine motor dexterity	Grooved Pegboard ^c

^aRaw scores.

^bPerseverative responses.

^cMeasured in seconds.

WAIS-III = Wechsler Adult Intelligence Scale, third edition; IQ = intelligence quotient; WMS-III = Wechsler Memory Scale, third edition.

with manual correction by a technician trained to criterion. All volumes were adjusted for total intracranial volume.

Statistical Analyses

Standardized regression-based *Z*-scores^{31–35} adjust for sources of measurement error inherent in test–retest designs (eg, practice effects, regression to the mean), as well as sociodemographic factors that may affect performance (eg, age, education, sex). Using control test–retest data as the benchmark, we first regressed baseline (time 1) test scores on retest scores, with age, sex, and education included as possible predictors. The resulting equations were used to derive predicted retest scores for the epilepsy patients. Differences between predicted versus observed retest scores for the epilepsy patients were subsequently transformed into standardized *Z*-scores [*Z*-score = *Y* (observed) – *Y* (predicted) divided by the standard error of the estimate from the regression equation]. All cognitive outcomes, therefore, were converted to a standard metric. Negative *Z*-scores reflect lower than expected retest scores.

The *Z*-scores first were used as continuous measures for comparison of cognitive outcomes between the epilepsy and control groups across the tests. A regression-based *Z*-score of less than or equal to –2.0 was then used to identify individual epilepsy patients and control subjects exhibiting adverse cognitive outcomes, so that the proportion of subjects with unfavorable versus favorable (all other *Z*-scores) outcomes could be identified with characterization of their clinical, demographic, and MRI features. Student's *t* test was used to compare continuous variables, and the χ^2 statistic was used to compare categorical variables.

Results

Overall Patterns of Cognitive Change

Control subjects exhibited significant test–retest improvement (practice effects) over the 4-year interval on

9 of 16 measures (56%) compared with 1 of 16 (6%) for the epilepsy group ($\chi^2 = 9.3$; degrees of freedom = 1; $p < 0.01$). There were no significant test–retest declines in either group.

Table 3 summarizes the regression-based *Z*-score results³⁵ for epilepsy subjects. Included are the cognitive tests (column 1), mean observed raw baseline and 4-year follow-up scores (columns 2 and 3), observed test–retest difference for each measure (column 4), predicted time 2 score based on the regression-based analyses of the control group (column 5), obtained versus predicted difference scores for the epilepsy group (column 6), and resulting *Z*-score and *p* values for the predicted versus obtained difference score for each measure (columns 7 and 8).

In general, the observed raw difference scores (see column 4 in Table 3) were minimal other than for speed-dependent measures (eg, Trail-Making Test [B] and Grooved Pegboard). However, once the difference between obtained versus predicted score is considered (see column 6 in Table 3), the differential cognitive course for the epilepsy group becomes evident. Observed scores fall significantly below predicted scores for 13 of 16 measures, the exceptions involving tasks of visuoperception (Facial Recognition) and executive function (Wisconsin Card Sort, Stroop Interference). Figure 1 shows that 12 measures fall at least –0.5 SD and 5 measures fall at least –1 SD below control subjects including naming, immediate and delayed auditory-verbal memory, executive function (Trail-Making Test [B]), and speeded motor dexterity. Thus, inclusion of a control group retested at the identical

Table 3. Mean Raw Score Performance and Regression-Based Z-Scores for Change for Epilepsy Patients

Test	Observed Time 1	Observed Time 2	Observed Difference	Predicted Time 2	Observed vs. Predicted Score	Z-Score	p
Performance IQ (WAIS-III)	45.59	45.93	0.34	50.05	-4.12	-0.71	0.001
Verbal IQ (WAIS-III)	49.89	49.84	-0.05	53.96	-4.12	-0.67	0.001
Boston Naming Test	47.04	47.80	0.76	50.54	-2.74	-1.72	0.000
Fluency	30.52	30.56	0.04	33.81	-3.25	-0.44	0.029
Facial Recognition Test	42.41	43.51	1.10	44.78	-1.27	-0.48	0.076
Judgment of Line Orientation	21.54	21.38	-0.16	23.30	-1.92	-0.78	0.014
Auditory memory-immediate	53.00	52.80	-0.20	62.43	-9.63	-1.14	0.000
Visual memory-immediate	69.20	72.44	3.24	79.05	-6.61	-0.84	0.002
Auditory memory-delayed	25.16	25.93	0.77	34.49	-8.56	-1.50	0.000
Visual memory-delayed	71.98	72.04	0.06	80.53	-8.49	-0.98	0.000
Working memory	24.46	23.57	-0.89	25.46	-1.89	-0.66	0.017
Trails A, sec ^a	35.09	32.53	2.56	26.19	-6.34	-0.91	0.004
Trails B, sec ^a	81.17	87.80	-6.63	69.33	-18.47	-1.11	0.007
Stroop Test Interference	96.46	98.04	1.58	103.75	-5.71	-0.39	0.062
Card Sorting Test (perseverations)	12.02	12.84	-0.82	10.96	-0.66	-0.39	0.301
Grooved Pegboard-Total ^a	193.84	198.53	-4.69	162.36	-36.17	-3.47	0.000

^aLower scores reflect faster performance (signs have been reversed to maintain consistency with deteriorated performance of other variables). IQ = intelligence quotient; WAIS-III = Wechsler Adult Intelligence Scale, third edition.

interval is critical in highlighting the differential cognitive trajectories between the two groups.

Individual Patterns of Cognitive Change

Figure 2 depicts the proportion of *individual* epilepsy and control subjects exhibiting significantly impaired ($Z \leq -2.0$) test-retest performances across the test battery. Generally, no more than 25% of epilepsy pa-

tients exhibited adverse changes, the exceptions being confrontation naming (40%), delayed visual memory (27%), delayed verbal memory (38%), and bilateral motor speed (64%).

Epilepsy patients exhibiting adverse cognitive change were compared with cognitively stable patients for de-

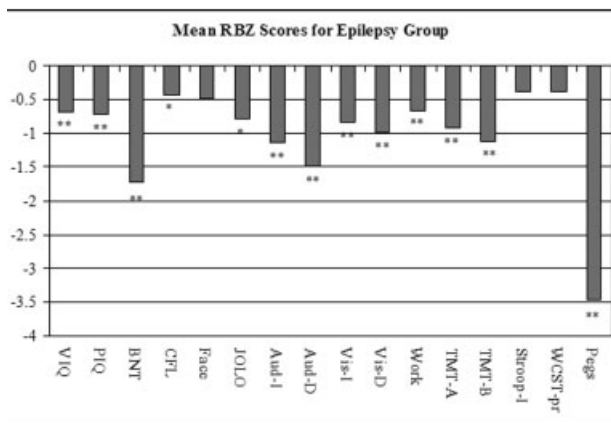


Fig 1. Mean regression-based Z-scores (RBZ) for the epilepsy group. * $p < 0.05$; ** $p < 0.01$. Aud-I = auditory immediate index; Aud-D = auditory delayed index; BNT = Boston Naming Test; CFL = Controlled Oral Word Association; Face = Facial Recognition Test; JOLO = Judgment of Line Orientation; Pegs = Grooved Pegboard; PIQ = Performance Intelligence Quotient; Stroop-I = Stroop Interference; TMT-A = Trail-Making Test (A); TMT-B = Trail-Making Test (B); VIQ = Verbal Intelligence Quotient; Vis-d = visual delayed index; VIS-I = visual immediate index; WCST = Wisconsin Card Sorting Test-perseverative responses; Work = working memory index.

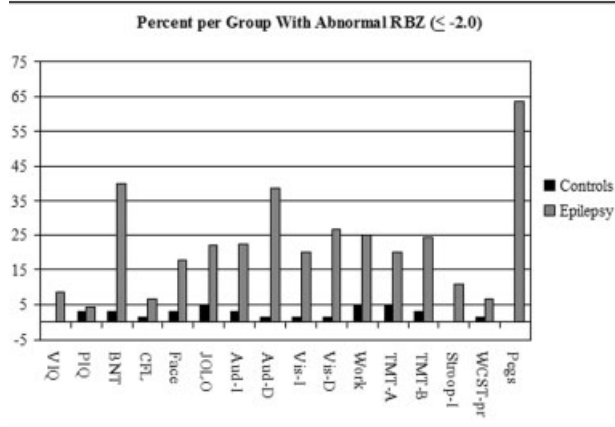


Fig 2. Percentage of epilepsy group with abnormal ($Z \leq -2.0$) test-retest performances across the test battery. Black bars represent control subjects; gray bars represent epilepsy patients. Aud-I = auditory immediate index; Aud-D = auditory delayed index; BNT = Boston Naming Test; CFL = Controlled Oral Word Association; Face = Facial Recognition Test; JOLO = Judgment of Line Orientation; Pegs = Grooved Pegboard; PIQ = Performance Intelligence Quotient; RBZ = regression-based Z-scores; Stroop-I = Stroop Interference; TMT-A = Trail-Making Test (A); TMT-B = Trail-Making Test (B); Vis-d = visual delayed index; VIS-I = visual immediate index; VIQ = Verbal Intelligence Quotient; WCST = Wisconsin Card Sorting Test-perseverative responses; Work = working memory index.

mographic variables (chronological age, sex, education, baseline IQ), seizure-related variables (age of recurrent seizure onset, duration of disorder, number of antiepileptic drugs), and MRI measurements (total intracranial volume-adjusted cerebral gray and white matter, cerebrospinal fluid, and left and right hippocampal volumes). Analyses were conducted for tests where more than 20% of epilepsy patients exhibited adverse cognitive change to ensure adequate statistical power and number of subjects for comparison (Table 4).

In general, epilepsy patients with adverse cognitive outcomes were older, with longer duration of epilepsy, lower baseline Full Scale IQ, and quantitative MRI abnormalities at baseline. Table 5 summarizes the significant correlates of abnormal course for each cognitive variable. Delayed memory examined as a continuous variable yielded comparable results, but increased power resulted in trends reaching significance (eg, age).

Medications, Clinical Seizure Variables, and Cognitive Change

Sixteen different medications were prescribed at baseline and follow-up with no statistically significant differences in drug distribution over time (*t* test for proportions). Trends existed for three drugs; carbamazepine was prescribed less often at follow-up (from 61 to 50% of patients; *p* = 0.058), whereas levetiracetam (4–13%; *p* = 0.10) and zonisamide (0–7%; *p* = 0.08) were used more often. There was no significant interval change in the proportion of patients receiving polytherapy (*p* = 0.10) or in the mean absolute number of

medications prescribed per patient (*p* = 0.47). There were no significant relations (all *p* values > 0.10) between cognitive decline on any measure and use of new medication at follow-up (all *p* values > 0.53) or change from baseline monotherapy to polytherapy at follow-up. We could not analyze the effects of specific medication changes during the interval because too few patients were placed on any one medication to perform reliable analyses (eg, five patients switched to levetiracetam and fewer than three subjects switched to any other medication).

Epilepsy patients experienced a mean of 2.8 (SD, 8.8) secondarily generalized seizures during the 4-year interval, which was not significantly associated with cognitive change. Seizure frequency ratings (ie, daily, weekly, monthly, yearly) for complex partial and total seizures yielded one significant association with adverse cognitive outcome (spatial orientation).

Discussion

This prospective study examined the nature and predictors of cognitive change in patients with temporal lobe epilepsy over a 4-year interval compared with healthy control subjects. Using a comprehensive neuropsychological battery, analytic procedures that control for sources of error in test–retest designs, and clinical-demographic and baseline quantitative MRI predictors, we discovered the following four primary findings: (1) The overall prospective cognitive trajectory for patients with temporal lobe epilepsy differs from healthy control subjects; (2) some cognitive do-

Table 4. Mean Demographic, Clinical Epilepsy, and Quantitative Magnetic Resonance Imaging Volumetric Findings in Epilepsy Patients Who Exhibit Abnormal Cognitive Outcomes ($Z \leq -2.0$) Compared to Epilepsy Patients with Stable Performance

	WMS-III Auditory Immediate		WMS-III Auditory Delayed		WMS-III Visual Delayed		WMS-III Working Memory		Trails A		Trails B		BNT		Pegboard Test		JOLO	
	Stable	Decline	Stable	Decline	Stable	Decline	Stable	Decline	Stable	Decline	Stable	Decline	Stable	Decline	Stable	Decline	Stable	Decline
Age, yr	33.1	39.0	32.5	37.5	33.0	37.4	33.0	39.0	32.0 ^a	40.1 ^a	30.8 ^b	42.6 ^b	33.0	34.7	33.1	33.9	34.7	30.0
Sex, M/F	12/22	3/7	6/21	9/8	12/22	3/8	11/22	4/7	12/24	3/6	12/22	3/8	10/17	5/13	8/15	5/15	12/23	3/7
Education, yr	13.1	12.4	13.2	12.6	12.9	13.0	13.2 ^a	12.3 ^a	13.1 ^a	11.7 ^a	13.0	12.0	13.1	12.3	13.0	12.6	12.9	12.3
Baseline FSIQ	93.8 ^a	78.9 ^a	96.3 ^b	81.1 ^b	93.0	82.8	93.4	82.8	94.8 ^b	77.3 ^b	94.1	82.7	97.6 ^b	81.9 ^b	95.7	86.7	94.7 ^a	79.4 ^a
Onset age, yr	11.6	10.3	12.3	9.6	11.5	10.3	12.8 ^b	7.2 ^b	11.9	7.0	10.9	11.2	11.5	10.1	10.1	12.2	11.6	8.7
Duration, yr	21.3	28.8	20.1 ^a	27.6 ^a	21.3	27.1	20.1 ^b	31.4 ^b	20.0 ^b	32.6 ^b	19.9 ^b	30.8 ^b	21.1	24.6	22.9	21.6	22.9	21.2
Number of AEDs	1.7	1.9	1.7	2.1	1.7	1.8	1.6	2.1	1.7	1.9	1.7	1.8	1.6 ^a	2.1 ^a	1.7	1.8	1.7	2.0
Total gray matter ^c	0.17	0.03	0.27	-0.08	0.17	0.11	0.19	-0.14	0.26	-0.05	0.36 ^a	-0.41 ^a	0.20	0.18	0.37	-0.04	0.07	0.72
Total white matter ^c	-0.54	-1.39	-0.56	-1.02	-0.46 ^b	-1.93 ^b	-0.38 ^a	-1.59 ^a	-0.45 ^b	-1.73 ^b	-0.52	-1.47	-0.38 ^a	-1.29 ^a	-0.71	-0.77	-0.64	-1.08
Total CSF ^c	0.34	1.15	0.23	1.04	0.29	1.48	0.16 ^b	1.61 ^b	0.18 ^a	1.49 ^a	0.11 ^b	1.73 ^b	0.26	0.80	0.44	0.51	0.50	0.30
Left hippocampus ^c	-0.63 ^a	-2.04 ^a	-0.50 ^a	-1.80 ^a	-0.78	-1.52	-0.74	-1.60	-0.82	-1.75	-0.94	-1.27	-0.72	-1.49	-0.94	-1.05	-1.08	-0.69
Right hippocampus ^c	-1.82	-1.17	-1.66	-1.69	-1.75	-0.90	-1.67	-1.56	-1.68	-1.35	-1.59	-1.69	-1.73	-1.41	-1.82	-1.26	-1.56	-1.83

^a*p* < 0.05; ^b*p* < 0.01.

^cZ-scores derived from intracranial volume-corrected baseline magnetic resonance imaging volumes.

WMS-III = Wechsler Memory Scale, third edition; Trails A = Trail-Making Test (A); Trails B = Trail-Making Test (B); BNT = Boston Naming Test; JOLO = Judgment of Line Orientation; FSIQ = Full Scale Intelligence Quotient; AED = antiepileptic drug; CSF = cerebrospinal fluid.

Table 5. Significant Predictors of Adverse Cognitive Change

Cognitive Test	Demographics	Clinical Epilepsy	MR Volumetrics
Auditory memory-immediate	Lower baseline IQ		Smaller baseline L hippocampus
Auditory memory-delayed	Lower baseline IQ	Longer duration	Smaller baseline L hippocampus
Visual memory-delayed			Smaller baseline white matter
Working memory	Lower education	Longer duration	Smaller baseline white matter
		Earlier age of onset	Larger baseline CSF
Simple psychomotor speed	Older age	Longer duration	Smaller baseline white matter
	Lower education		Larger baseline CSF
	Lower baseline IQ		
Complex psychomotor speed	Older age		Smaller baseline gray matter
	Longer duration		Larger baseline CSF
Confrontation naming	Lower baseline IQ	Polytherapy	Smaller baseline white matter
Speeded fine motor dexterity			
Spatial orientation	Lower baseline IQ		

MR = magnetic resonance; IQ = intelligence quotient; CSF = cerebrospinal fluid.

mains are more vulnerable to adverse change than others (memory, cognitive/psychomotor speed, some executive functions, naming); (3) a subset of epilepsy patients, about 20%, exhibit substantial adverse cognitive outcomes; and (4) adverse cognitive outcomes are associated with distinct baseline demographic, intellectual, clinical epilepsy, and quantitative volumetric features. These findings are reviewed below.

Cognitive Change in Temporal Lobe Epilepsy

Previous prospective investigations of test–retest cognitive change in epilepsy have yielded mixed findings.⁶ Examining only raw test–retest scores (see the second and third columns of Table 3), one might conclude that the cognitive course of temporal lobe epilepsy is benign. Only 1 of 16 test measures changed significantly after a 4-year test–retest interval, and this was a test–retest improvement (see the fourth column of Table 3). However, incorporation of a healthy control group alters this impression significantly because 57% of this group’s test measures improved significantly over the interval compared with 6% for the temporal lobe epilepsy group. Therefore, at a basic level, differences are evident in the test–retest trajectories of patients with temporal lobe epilepsy.

Test–retest cognitive change can be affected by a variety of factors including practice, regression to the mean, and demographic factors (age, sex, education). The statistical procedures used in this study, standardized regression-based norms for change, adjust for these factors and contrast *expected* retest scores (based on control group performance) with *obtained* retest scores in the epilepsy group. In such analyses, epilepsy patients exhibited significantly poorer than expected retest performance across all but three tests (see the seventh column in Table 3 and Figure 2), with substantial differences in memory, speeded cognitive functioning, and confrontation naming. These appear to be the

more vulnerable cognitive domains as operationally defined here. In summary, the overall pattern of obtained versus expected prospective cognitive performance is different in patients with chronic childhood/adolescent-onset temporal lobe epilepsy compared with control subjects.

Measures of central tendency are useful in characterizing the overall pattern of cognitive outcome, but information regarding the proportion of *individuals* who exhibit adverse cognitive trajectories, and their characteristics, is important. Figure 2 demonstrates that a sizable minority of epilepsy patients, generally 15 to 25%, exhibited adverse cognitive trajectories over the 4-year interval, again with greater vulnerability in certain cognitive functions, by operationally defining adverse change as a regression-based Z-score of -2.0 and lower (worse). These individuals did not just show lack of learning associated with practice effects, but also actual decline in performance over the interval.

Predictors of Adverse Cognitive Change

This study represents the first attempt to integrate the contribution of baseline MR volumetrics, clinical seizure characteristics, and demographic variables in the understanding of cognitive outcomes in temporal lobe epilepsy. Tables 4 and 5 summarize these findings. Abnormalities in baseline MR volumetrics have shown that the ability exists to predict adverse cognitive outcomes. For example, smaller baseline hippocampal volumes are associated with increased risk for conversion from amnesic mild cognitive impairment to Alzheimer’s disease.¹⁵ Among patients with chronic temporal lobe epilepsy, volumetric abnormalities have been reported in hippocampus, extrahippocampal mesial temporal lobe, temporal neocortex, and extratemporal regions.^{36–38} Our findings demonstrate that baseline volumetric abnormalities are prognostic of adverse cognitive changes in epilepsy. A specific relation was iden-

tified between decline in immediate and delayed verbal memory and smaller adjusted baseline left hippocampal volume. In addition, abnormalities in baseline volumetric measurements of other regions of interest were predictive of adverse changes in other cognitive abilities (see Table 5). Thus, volumetric abnormalities identified in prior cross-sectional research appear to be of prognostic significance for cognitive course.

The relation between so-called cerebral reserve^{39–41} and risk for cognitive decline in epilepsy has been discussed in previous investigations.^{5,12,42} The finding here that patients who exhibit significant adverse cognitive outcomes (in immediate and delayed auditory memory, psychomotor processing, confrontation naming, spatial orientation) were characterized by significantly lower baseline Full Scale IQ is consistent with the general notion of increased cognitive vulnerability among those with lower intellectual capacity. More directly, however, are the findings that baseline MRI volumes are significant predictors of cognitive course that provide a direct connection between cerebral reserve and cognition.

Changes in antiepileptic drugs appear not to be associated with the cognitive changes observed in this study including interval administration of new medications, change from monotherapy to polytherapy, and relations with specific medications. This does not rule out the possibility that decades of use of particular medications or combinations of medication may be associated with an adverse cognitive course, but that issue goes beyond what can be reliably addressed here.

Several methodological limitations should be recognized. First, it is uncertain whether the cognitive changes observed here are fixed/permanent versus transitory in nature. Multiple assessments at several points in time would be required to determine this. Second, the test–retest interval (4 years) is modest in duration, recognizing that these patients have had recurrent seizures for decades (26-year average duration at follow-up). It is not yet clear whether the cognitive changes are linear in nature or whether there are “critical periods” for cognitive change, for instance, after two to three decades of epilepsy and aging. Although we are able to provide a characterization of the cognitive course of these subjects, it occurs in the context of severe chronic epilepsy. Nevertheless, the finding of significant differences in cognitive trajectory over this time period is important. Third, the patients investigated in this study are attending a tertiary care clinic, and whether these findings generalize to community-based samples remains to be determined. Finally, the issue of cognitive change in relation to volumetric change remains to be characterized in the future.

In conclusion, the prospective cognitive trajectory of patients with chronic early-onset temporal lobe epilepsy differs from that of age- and sex-matched healthy

control subjects. Lack of traditional practice effects is evident, but adverse cognitive outcomes are observed in a subset of patients (approximately 20–25%), particularly in vulnerable cognitive domains (memory, speeded psychomotor/motor abilities, naming, some executive functions). Vulnerable patients are characterized by a profile of abnormalities in baseline quantitative MR volumetrics and lower baseline intellectual capacity and, to a somewhat lesser degree, by longer duration of epilepsy and increasing chronological age. Most patients (70–75%) appear to have an unproblematic prospective cognitive course as operationally defined in this article. These results should help characterize those individuals requiring close attention and monitoring to maximize their quality of life and cognitive health. Finally, this sample, in their 30s, on average, has yet to face the adverse neurocognitive effects of normal aging across subsequent decades of life, an important issue for future investigation.

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