ApoE- ϵ 4 is associated with reduced memory in long-standing intractable temporal lobe epilepsy

R.M. Busch, PhD; T.T. Lineweaver, PhD; R.I. Naugle, PhD; K.H. Kim, PhD; Y. Gong, MD; C.Q. Tilelli, MD; R.A. Prayson, MD; W. Bingaman, MD; I.M. Najm, MD; and R. Diaz-Arrastia, MD, PhD

Abstract—Objective: To investigate the relationship between the apolipoprotein (ApoE) ϵ 4 allele and memory performance (verbal and nonverbal) in patients with medically intractable temporal lobe epilepsy (TLE) who underwent temporal lobectomy. **Methods:** Presurgical and postsurgical memory performance was examined in 87 adult patients with TLE (ϵ 4 = 22; non- ϵ 4 = 65) to determine whether the expression of ApoE- ϵ 4 may be associated with memory performance in this population and to examine how this relationship may be affected by duration of epilepsy. **Results:** There was a significant interaction between ApoE- ϵ 4 status and duration of epilepsy such that ϵ 4 carriers with a long duration of epilepsy demonstrated the poorest memory performance on both verbal and nonverbal measures. This relationship was observed both before and after temporal lobectomy, with little change in test performance over time. **Conclusions:** The ApoE- ϵ 4 allele interacts with longstanding seizures to affect memory performance, both verbal and nonverbal, in patients with medically intractable temporal lobe epilepsy.

NEUROLOGY 2007;68:409–414

Memory decline, which is commonly associated with temporal lobe seizures, has been related to age at epilepsy onset,^{1,2} duration of disorder,^{1,3} chronological age,³ and etiology,^{4,5} but little is known about underlying biologic factors that may predispose patients to memory loss. Two studies have examined the relationship between apolipoprotein (ApoE) polymorphisms and cognitive performance in patients with epilepsy. One examined IQ and memory performance in patients with newly diagnosed partial epilepsy and found that ϵ 4 carriers had significantly lower IQ scores than patients without ϵ 4.⁶ Carriers also performed more poorly on a list-learning measure, although the difference was not significant. Another study, which examined memory of patients with mild, well-controlled nonlesional temporal lobe epilepsy (TLE),⁷ found that ϵ 4 carriers demonstrated lower performance on a verbal list-learning task than noncarriers, particularly among patients with duration greater than 25.5 years.

No published studies have examined the relation-

ship between ApoE- ϵ 4 and memory performance in patients with medically intractable epilepsy or the relationship between ϵ 4 and memory performance after surgical intervention for the treatment of epilepsy. This study was designed to investigate the relationships among the apolipoprotein ϵ 4 allele, duration of epilepsy, and memory performance in a group of patients with medically intractable TLE who underwent temporal lobectomy.

Methods. Participants. This study involved an institutional review board–approved review of previously collected and archived data from 89 patients treated at Cleveland Clinic. Participants were older adolescent and adult patients (aged 16 years and older) with medically refractory epilepsy who underwent temporal lobectomies for treatment of their seizure disorders. Patients were included in the study if they completed presurgical and postsurgical neuropsychological evaluations, had a Full Scale IQ of 70 or higher, and had frozen or paraffin-embedded tissue available for DNA analysis. Two patients were excluded because their memory data were outliers, resulting in a final sample size of 87. Participants ranged in age from 16 to 65 years (mean = 36.26, SD = 11.20) and in education from 8 to 20 years (mean = 13.25, SD = 2.18). The mean age of seizure onset for the group was 14.15 years (SD = 9.87), and the mean duration of epilepsy was 21.84 years (SD = 12.61). Twenty-two patients (25%) had at least one ϵ 4 allele (ϵ 4 group), and 65 patients (75%) did not have an ϵ 4 allele (non- ϵ 4 group). The distribution of ApoE genotypes was consistent with what is typically observed in the general population and did not deviate from Hardy–Weinberg equilibrium (table 1). There were no significant differences between the ϵ 4 and non- ϵ 4 groups with

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the February 6 issue to find the title link for this article.

From the Departments of Psychiatry & Psychology (R.M.B., R.I.N.), Neurology (R.M.B., R.I.N., C.Q.T., I.M.N.), Anatomic Pathology (R.A.P.), and Neurosurgery (W.B.), Cleveland Clinic, Cleveland, OH; Department of Psychology, Butler University, Indianapolis, IN (T.T.L.); School of Education, University of Pittsburgh, Pittsburgh, PA (K.H.K.); and Department of Neurology, University of Texas Southwestern Medical School, Dallas, TX (Y.G., R.D.-A.).

Supported by the Epilepsy Foundation through the Postdoctoral Fellowship Program: Research and Training Fellowships for Clinicians. Additional support for this research was provided by the NIH (RO1 HD4817 and UO1 HD42652) and the US Department of Education (H133A02052601).

Disclosure: The authors report no conflicts of interest.

Received June 14, 2006. Accepted in final form October 13, 2006.

Address correspondence and reprint requests to Dr. Robyn M. Busch, Department of Psychiatry & Psychology, Cleveland Clinic, 9500 Euclid Avenue, P57, Cleveland, OH 44195; e-mail: buschr@ccf.org

Table 1 Frequency of ApoE genotypes and alleles

ApoE polymorphism	Frequency	Percentage
Genotype (n = 87)		
ε2/ε2	0	0.00
ε2/ε3	13	14.94
ε3/ε3	52	59.78
ε2/ε4	1	1.14
ε3/ε4	17	19.54
ε4/ε4	4	4.60
Allele (n = 174)		
ε2	14	8.05
ε3	134	77.01
ε4	26	14.94

regard to sex, race, age, education, Full Scale IQ, age at seizure onset, duration of seizures, number of antiepileptic drugs (AEDs), side of surgery, or hippocampal pathology (table 2).

Measures. All participants in this study completed the Wechsler Memory Scale—Third Edition (WMS-III[®]) as part of their routine presurgical and postsurgical neuropsychological evaluations. The following WMS-III indices were used in the data analyses: Auditory Immediate Memory Index, Auditory Delayed Memory Index, Visual Immediate Memory Index, Visual Delayed Memory

Table 2 Demographic and seizure data for study patients

Variable	Patients with ε4 allele (n = 22)	Patients without ε4 allele (n = 65)
Age	35.41 (10.58)	36.55 (11.47)
Education	13.68 (2.63)	13.11 (2.02)
Full Scale IQ	97.95 (15.46)	94.60 (12.12)
Age at seizure onset	13.82 (9.29)	14.26 (10.13)
Duration of seizures	21.64 (12.23)	21.91 (12.83)
No. of AEDs	2.05 (0.50)	2.03 (0.53)
Sex		
Male	10 (45%)	27 (42%)
Female	12 (55%)	38 (58%)
Race		
White	22 (100%)	62 (95%)
Black	0 (0%)	2 (3%)
Side of surgery		
Left	13 (59%)	34 (52%)
Right	9 (41%)	31 (48%)
Pathology		
Hippocampal sclerosis	15 (71%)	49 (80%)
Gliosis	5 (24%)	9 (15%)
Perivascular inflammation	1 (5%)	0 (0%)
Glioneuronal hamartias	0 (0%)	2 (3%)
No abnormality	0 (0%)	1 (2%)

Data are mean (SD) or n (%). Pathology data were not available for three patients.

AED = antiepileptic drug.

Index, and General Memory Index. The mean interval between presurgical and postsurgical neuropsychological evaluation was 10.87 months (SD = 4.26; range 5 to 27 months), and the mean interval between surgery and postoperative testing was 7.64 months (SD = 3.89; range 4 to 24 months).

DNA genotyping. DNA was extracted from 20 mg of frozen brain tissue obtained at surgery using a silica-based absorption method (Qiagen DNA minikit, Qiagen, Inc., Valencia, CA) following the manufacturer's instructions. Genotyping at the APOE locus was carried out by a modification of the method of Chapman et al.⁹ The upstream primer was 5'-TCCAAGGAGCTGC-AGGCGGCGCCA-3', and the downstream primer was 5'-ACAGAAATTCGCCCGGCCTGGTACACTGCCCA-3'. PCR was conducted at 150 nM concentration for each primer, 50 μM for each for each dNTP, 2 mM MgCl₂, 10% dimethyl sulfoxide, and 2 U Taq polymerase (New England Biolabs). Reaction was conducted for 40 cycles, using a melting temperature of 94 °C, a reaction temperature of 72 °C, and an annealing temperature of 65 °C. The 227-base pair (bp) PCR product was separately digested by Afl III (New England Biolabs), which digests ε2 and ε3 into 177- and 50-bp fragments but does not hydrolyze ε4, and by Hae II (New England Biolabs), which digests ε3 and ε4 into 195- and 32-bp fragments but does not hydrolyze ε2. PCR products were resolved by electrophoresis in 2% Agarose 1000 (Invitrogen) slab gels, and bands were visualized by staining with ethidium bromide.

Results. A doubly multivariate analysis of variance (MANOVA) was performed on memory scores as a function of ApoE genotype (ε4, non-ε4), duration of epilepsy (<22 years, ≥22 years—based on mean split), and time (presurgery, postsurgery). There were five memory indices included as dependent variables in the analyses: Auditory Immediate Memory Index, Auditory Delayed Memory Index, Visual Immediate Memory Index, Visual Delayed Memory Index, and General Memory Index. All assumptions of MANOVA were met. A summary of the mean memory scores for each group, as well as scores collapsed across groups, is provided in table 3.

Examination of the multivariate effects revealed that the pattern of differences on the memory indices between duration groups was different between the ε4 and non-ε4 groups: Pillai trace = 0.18, F(5,79) = 3.45, *p* < 0.01, partial η² = 0.18 for the duration by genotype interaction. There was a trend toward a difference in memory performance between patients who had seizures for <22 years (short duration) and those who had seizures for ≥22 years (long duration) averaged across ApoE genotype: Pillai trace = 0.12, F(5,79) = 2.07, *p* = 0.08, partial η² = 0.12. There were no differences in memory performance between the ε4 and non-ε4 groups averaged across duration of epilepsy: Pillai trace = 0.06, F(5,79) = 0.95, *p* = 0.454, partial η² = 0.06. The within-subjects main effect of time was not significant, and none of the within-subjects interactions effects were significant.

Examination of univariate between-subjects effects averaged across time revealed a significant interaction between ApoE group and duration of epilepsy on all five of the memory indices. Results of the univariate analyses are summarized in table E-1 on the Neurology Web site at www.neurology.org. Although some of the main effects associated with duration of epilepsy were also significant in the between-subjects univariate analyses, the multivariate main effects were not significant, and the univariate effects were mediated by the significant interactions between duration and genotype. Therefore, the univariate main effects for this variable were not interpreted.

To find the pattern of differences in performance on the

Table 3 Summary of patient performance on memory measures

Memory measure	ApoE	Duration of epilepsy, years	Presurgery, mean (SD)	Postsurgery, mean (SD)	Collapsed, mean (SE)
Auditory immediate	$\epsilon 4$	<22	102.83 (12.21)	104.58 (15.45)	103.71 (4.33)
		≥ 22	84.60 (12.62)	83.10 (14.50)	83.85 (4.75)
	Non- $\epsilon 4$	<22	91.78 (13.66)	90.54 (19.96)	91.16 (2.47)
		≥ 22	91.29 (16.27)	93.36 (17.34)	92.32 (2.84)
Auditory delayed	$\epsilon 4$	<22	103.50 (11.24)	104.67 (13.31)	104.08 (4.34)
		≥ 22	82.20 (16.65)	80.40 (16.89)	81.30 (4.75)
	Non- $\epsilon 4$	<22	89.95 (16.57)	90.08 (18.70)	90.01 (2.47)
		≥ 22	93.21 (14.90)	95.14 (15.43)	94.18 (2.84)
Visual immediate	$\epsilon 4$	<22	103.17 (15.86)	98.67 (17.03)	100.92 (4.27)
		≥ 22	79.80 (14.67)	80.80 (13.06)	80.30 (4.68)
	Non- $\epsilon 4$	<22	90.49 (15.07)	90.35 (18.99)	90.42 (2.43)
		≥ 22	89.07 (15.18)	95.21 (16.57)	92.14 (2.80)
Visual delayed	$\epsilon 4$	<22	100.58 (17.70)	98.58 (12.87)	99.58 (4.51)
		≥ 22	80.50 (17.56)	83.80 (12.20)	82.15 (4.94)
	Non- $\epsilon 4$	<22	88.08 (16.59)	89.57 (20.19)	88.82 (2.57)
		≥ 22	90.07 (14.92)	92.57 (16.27)	91.32 (2.95)
General memory	$\epsilon 4$	<22	103.25 (13.94)	102.17 (10.29)	102.71 (4.35)
		≥ 22	79.20 (16.21)	80.80 (14.37)	80.00 (4.77)
	Non- $\epsilon 4$	<22	87.11 (15.39)	87.81 (18.52)	87.46 (2.48)
		≥ 22	90.39 (15.25)	92.89 (16.84)	91.64 (2.85)

memory indices between the short- and long-duration groups as a function of ApoE genotype, simple main effects of duration were performed for both $\epsilon 4$ and non- $\epsilon 4$ groups. Among $\epsilon 4$ patients, those with a long duration of epilepsy had significantly lower memory scores on all five memory indices than those with a short duration of epilepsy. However, there were no significant differences in memory performance on any of the memory indices among non- $\epsilon 4$ patients with short vs long duration of epilepsy (table E-2).

Bivariate correlations were calculated to examine the strength of the relationship between memory performance and duration of epilepsy among $\epsilon 4$ and non- $\epsilon 4$ groups. For the $\epsilon 4$ group, duration of epilepsy was significantly negatively correlated with memory performance on all of the WMS-III indices, with Pearson r values ranging from -0.51 to -0.67 (p values ranging from 0.015 to 0.001). In contrast, there were no correlations between duration of epilepsy and memory performance in the non- $\epsilon 4$ group, with Pearson r values ranging from -0.02 to 0.11 (p values ranging from 0.40 to 0.90). Scatter plots of the relationships between duration of epilepsy and memory among $\epsilon 4$ and non- $\epsilon 4$ groups are depicted in the figure, A and B.

Discussion. The ApoE- $\epsilon 4$ allele may play a major role in memory performance among patients with medically intractable TLE, and this relationship may be heavily influenced by the duration of time one has had epilepsy. Specifically, data from this study suggest that there is a significant interaction between $\epsilon 4$ status and duration of epilepsy such that $\epsilon 4$ carriers with a long duration of epilepsy demonstrate signifi-

cantly lower memory scores than $\epsilon 4$ carriers with a short duration of epilepsy. At the multivariate level, this interaction accounted for almost 18% of the variance in memory scores after accounting for other effects (partial $\eta^2 = 0.18$). Examination of the mean memory scores of $\epsilon 4$ carriers (table 3) reveals that those with a long duration of epilepsy consistently scored an average of 20 standard score points lower than the short-duration group on the memory measures. In contrast, memory performance among non- $\epsilon 4$ carriers did not vary as a function of duration of epilepsy. This pattern of relationships was observed on all WMS-III memory indices, including both verbal and visual memory measures, on both immediate and delayed memory trials.

Many studies over the years have established a relationship between ApoE- $\epsilon 4$ and memory performance in healthy aging¹⁰ as well as in a number of clinical populations,¹¹⁻¹⁴ including patients with mild, nonlesional TLE.⁷ The majority of these studies have examined verbal memory performance with rather consistent findings. The current study provides evidence that a relationship between ApoE- $\epsilon 4$ and memory also exists in patients with medically intractable TLE. However, the relationship between ApoE- $\epsilon 4$ and memory performance in this population is rather complex and largely dependent on the duration of time one has had epilepsy. That is, examination of simple memory score differences between $\epsilon 4$ and non- $\epsilon 4$ groups does not reveal any significant

Figure. (A) Relationship between duration of epilepsy and General Memory Index score among $\epsilon 4$ patients. (B) Relationship between duration of epilepsy and General Memory Index score among non- $\epsilon 4$ patients.

findings. It is only when duration of epilepsy is considered in conjunction with $\epsilon 4$ status that significant differences in memory performance become apparent. Although they did not directly examine interaction effects between $\epsilon 4$ status and duration of epilepsy, a recent study found the strongest relationship between $\epsilon 4$ and verbal word list-learning in patients with TLE and long disease duration (i.e., ≥ 25 years).⁷ These results are similar to the current study, suggesting that the relationship between $\epsilon 4$ and memory performance among patients with TLE is strongly related to duration of epilepsy.

As expected, examination of the simple main effects of duration revealed that $\epsilon 4$ patients with a short duration of epilepsy had significantly higher memory scores than $\epsilon 4$ patients with a long duration of epilepsy. However, $\epsilon 4$ patients with a short duration of epilepsy also demonstrated significantly higher memory scores than non- $\epsilon 4$ patients with a short duration of epilepsy, a finding we did not anticipate. To better understand this finding, we examined differences between the $\epsilon 4$ short-duration group and the other three groups (i.e., non- $\epsilon 4$ short duration, non- $\epsilon 4$ long duration, and $\epsilon 4$ long duration) to rule out potential factors that may have contributed to differences in the observed memory scores. These analyses revealed that the $\epsilon 4$ short-duration group had somewhat more education (14.42 years vs 13.05 years; $t(47) = 1.99$, $p = 0.05$) and higher Full Scale IQ scores (104 vs 95; $t(47) = 1.93$, $p = 0.06$) than the

non- $\epsilon 4$ short-duration group. The $\epsilon 4$ short-duration group also had higher Full Scale IQ scores (104 vs 91; $t(20) = 2.22$, $p < 0.05$) than the $\epsilon 4$ long-duration group. To ensure that IQ and education were not related to the significant differences in memory performance between these groups, we reran all analyses with education and Full Scale IQ as covariates. The pattern of findings did not change after controlling for preexisting differences in education and IQ, suggesting that the differences in memory performance between the groups cannot be explained by overall intellectual function or educational experience. It is possible that this unexpected finding may simply be due to chance given the relatively small sample included in the study or may reflect the effects of some unmeasured confounding factor (e.g., seizure frequency, number and frequency of generalized tonic-clonic seizures, number of antiepileptic medications).

Duration of epilepsy was correlated with both chronological age (Pearson $r = 0.66$, $p < 0.001$) and age at seizure onset (Pearson $r = -0.52$, $p < 0.001$) in this sample, which makes it difficult to separate the independent contributions of these variables to memory performance. To understand how these variables may have impacted the significant interactions found between $\epsilon 4$ status and duration of epilepsy, we conducted a series of t tests to determine whether there were significant differences in chronological age or age at seizure onset between the short- and long-duration groups. Among $\epsilon 4$ carriers, those with a long duration of epilepsy had an earlier age at seizure onset than those with a short duration (7.80 vs 18.83 years; $t(20) = 3.40$, $p < 0.01$), but there was no difference in chronological age between the two groups (39.30 vs 32.17; $t(20) = 0.12$, $p = 0.18$). These findings confirm that duration of epilepsy is confounded by age at seizure onset. However, the high correlation between these two variables precluded us from statistically controlling for age at seizure onset. Instead, the doubly MANOVA analysis was rerun using age at seizure onset (> 14 years, ≤ 14 years—based on mean split) in place of duration of epilepsy. Findings were similar, demonstrating a significant interaction between $\epsilon 4$ status and age at seizure onset such that $\epsilon 4$ carriers with an early age at seizure onset (i.e., ≤ 14 years) demonstrated significantly lower memory scores than $\epsilon 4$ carriers whose seizures began later in life (i.e., > 14 years). This relationship was evident on all memory index scores except the Visual Delayed Memory Index.

Duration of epilepsy and age at seizure onset have been demonstrated to be important factors because they relate to cognitive functioning in patients with TLE irrespective of $\epsilon 4$ status. Patients with longstanding epilepsy generally perform more poorly on cognitive measures than patients with shorter epilepsy duration.^{15,16} Similarly, patients with early seizure onset tend to have more significant intellectual and cognitive dysfunction than patients who develop seizures later in life.^{17,18} Therefore, it is not surpris-

ing that these two variables interact with $\epsilon 4$ status to affect memory functioning in patients with TLE. Given the limitations of a cross-sectional study, it is impossible to definitively conclude that duration of epilepsy, rather than age at seizure onset, is the factor accounting for cognitive problems in $\epsilon 4$ carriers. Larger prospective studies will be required to investigate the independent contribution of each of these factors.

The ever-growing literature on ApoE and cognitive functioning has suggested that $\epsilon 4$ carriers who sustain a traumatic brain injury (TBI) are at higher risk for cognitive impairment than non- $\epsilon 4$ carriers who sustain comparable injuries. More specifically, memory performance has been demonstrated to be more impaired in $\epsilon 4$ -positive than $\epsilon 4$ -negative TBI patients, even when genotype groups do not differ on demographic or injury variables.¹⁴ In fact, it has been found that subjects without an $\epsilon 4$ allele performed more poorly on memory tests after a more severe head injury than after a milder head injury, whereas subjects with an $\epsilon 4$ allele performed as poorly as the severely injured subjects without $\epsilon 4$, regardless of injury severity.¹⁴ In cases of repetitive head injury (e.g., boxing, football), $\epsilon 4$ has been associated with severity of injury and impaired cognitive functioning,^{19,20} and survivors of head trauma who possess an $\epsilon 4$ allele have a tenfold increased risk for developing Alzheimer disease than those without this allele.²¹ It has been hypothesized that these cognitive difficulties are largely the result of ApoE isoform-specific neuropathologic changes in the brain to which memory systems are highly susceptible.¹⁴

Medically refractory seizures may be considered a form of repetitive brain injury, which would explain why $\epsilon 4$ seems to play a similar role in memory deficits associated with TLE. The current study suggests that ApoE- $\epsilon 4$ carriers with a young age at seizure onset and a long duration of medically intractable epilepsy demonstrate the lowest performance on memory measures likely because of the cumulative effects of early and repetitive seizure activity. We hypothesize that neuronal recovery after seizures is impeded by the presence of $\epsilon 4$, perhaps resulting in accumulation of amyloid β protein within the mesial temporal structures contributing to neuronal damage and eventually leading to memory dysfunction. This conjecture is supported by the finding of Gouras et al. that senile plaques were associated with the presence of an $\epsilon 4$ allele in patients with TLE.²² Future studies will be required to substantiate this hypothesis.

Reduced hippocampal volumes are often observed among $\epsilon 4$ carriers^{12,23} as well as among patients with TLE.²⁴ Preliminary investigations have found no association between $\epsilon 4$ and hippocampal damage in newly diagnosed patients with partial epilepsy.⁶ However, no published studies have investigated the relationships among ApoE- $\epsilon 4$, hippocampal volumes, and histopathology in patients with medically intractable epilepsy. We are in the process of conducting

research in an effort to understand the relationships among these factors and memory performance in patients with TLE.

One would expect that the left TLE patients would show verbal memory difficulties and the right TLE patients would show visual memory problems. In this study, the significant interaction between $\epsilon 4$ status and duration of epilepsy was consistent across all memory measures, both verbal (i.e., story recall and verbal paired associate learning) and nonverbal (i.e., face recognition and recall of details from pictured scenes). The small sample size did not allow for separate analysis of patients with right vs left TLE. Nevertheless, it is interesting that significant findings were apparent despite our inability to control for side of seizure onset. ApoE- $\epsilon 4$ interacted with duration of epilepsy to explain a significant amount of variance in all memory scores, verbal and nonverbal alike. These effects would be anticipated to be even more apparent when memory data from left and right TLE patients are examined separately; however, a study with significantly larger sample size will be required to conduct such investigations.

Interestingly, there were no significant effects of surgery in the current study, suggesting that the observed relationships between $\epsilon 4$ and duration of epilepsy on memory were not significantly impacted by temporal lobectomy. One possible explanation for our lack of interaction effects involving time is the short test-retest interval. Six months may not be sufficient for ApoE genotype to have a significant impact on memory outcome after a surgical intervention. Additional studies with larger samples and longer test-retest intervals will be needed to confirm our findings. However, if an interaction between $\epsilon 4$ status and duration of epilepsy is again observed with no significant changes in individual memory scores, corrected for potential practice effects, after surgical intervention in independent samples, this would have a number of important implications. If replicated, these findings would not only assist in identifying patient subgroups at high risk for cognitive decline, but may suggest a role for pharmacotherapeutic prevention or early surgical intervention in TLE patients who are $\epsilon 4$ carriers to prevent declines in memory that accompany longstanding epilepsy among this group of patients.

References

1. Dikmen S, Matthews C, Harley J. The effect of early versus late onset of major motor epilepsy upon cognitive-intellectual performance. *Epilepsia* 1975;16:73-81.
2. Hermann B, Seidenberg M, Haltiner A, Wyler A. Relationship of age at onset, chronological age, and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. *Epilepsia* 1995;36:137-145.
3. Hermann BP, Seidenberg M, Dow C, et al. Cognitive prognosis in chronic temporal lobe epilepsy. *Ann Neurol* 2006;60:80-87.
4. Dodrill C. The relationship of neuropsychological abilities to seizure factors and to surgery for epilepsy. In: Engel J, ed. *Surgical treatment of epilepsies*. New York: Raven Press, 1993:106-110.
5. Klove H, Matthews C. Psychometric and adaptive abilities in epilepsy with differential etiology. *Epilepsia* 1966;7:330-338.
6. Kalviainen R, Partanen K, Aikia M, et al. Apolipoprotein E polymorphism in relation to hippocampal cell damage and memory impairment in newly diagnosed partial epilepsy. *Neurology* 1998;50. Abstract.

7. Gambardella A, Aguglia U, Chifari R, et al. ApoE epsilon4 allele and disease duration affect verbal learning in mild temporal lobe epilepsy. *Epilepsia* 2005;46:110–117.
8. Wechsler D. WMS-III test administration and scoring manual. San Antonio, TX: The Psychological Corporation, 1997.
9. Chapman J, Estupinan J, Asherov A, Goldfarb L. A simple and efficient method for apolipoprotein E genotype determination. *Neurology* 1996; 46:1484–1485.
10. Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging* 2004;19:592–600.
11. Haan M, Shemanski L, Jagust W, Manolio T, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* 1999;282:40–46.
12. Lind J, Larsson A, Persson J, et al. Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: relation to chronological age and recognition memory. *Neurosci Lett* 2006;396:23–27.
13. Caselli RJ, Reiman EM, Osborne D, et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE epsilon4 allele. *Neurology* 2004;62:1990–1995.
14. Crawford F, Vanderploeg R, Freeman M, et al. APOE genotype influences acquisition and recall following traumatic brain injury. *Neurology* 2002;58:1115–1118.
15. Jokeit H, Ebner A. Effects of chronic epilepsy on intellectual functions. *Prog Brain Res* 2002;135:455–463.
16. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Ann Neurol* 2003;54:425–432.
17. Saykin AJ, Gur RC, Sussman NM, Gur RE, O'Connor MJ. Memory deficits before and after temporal lobectomy: effect of laterality and age of onset. *Brain Cogn* 1989;9:191–200.
18. Strauss E, Hunter M, Wada J. Risk factors for cognitive impairment in epilepsy. *Neuropsychology* 1995;9:457–463.
19. Teasdale G, Nicoll J, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet* 1997;350: 1069–1071.
20. Kutner K, Erlanger D, Tsai J, Jordan B, Relkin N. Lower cognitive performance of older football players possessing apolipoprotein E epsilon4. *Neurosurgery* 2000;47:651–658.
21. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon4 in patients with Alzheimer's disease. *Neurology* 1995;45:555–557.
22. Gouras G, Relkin N, Sweeney D, Munoz D, Mackenzie I, Gandy S. Increased apolipoprotein E epsilon4 in epilepsy with senile plaques. *Ann Neurol* 1997;41:402–404.
23. Soininen H, Partanen K, Pitkanen A, et al. Decreased hippocampal volume asymmetry on MRIs in nondemented elderly subjects carrying the apolipoprotein E epsilon4 allele. *Neurology* 1995;45:391–392.
24. Trenerry MR, Jack CR, Ivnik RJ, et al. MRI hippocampal volumes and memory function before and after temporal lobectomy. *Neurology* 1993; 43:1800–1805.

NeuroImages

Figure. The fluid-attenuated inversion recovery image (A) shows bilateral hyperintensities in the basal ganglia and the occipitopolar cortex. The latter and the globus pallidus internus are also hyperintense on the T1-weighted image (B), indicating hemorrhagic transformation. The T2-weighted image of the mesencephalon (C) shows hyperintense substantia nigra similar to the basal ganglia.

Acute parkinsonism with corresponding lesions in the basal ganglia after heroin abuse

Walter Mätzler, MD; Thomas Nägele, MD; Thomas Gasser, MD; Rejko Krüger, MD, Tübingen, Germany

Parkinsonian syndromes with encephalopathy after heroin abuse are rare. We report a 41-year-old Caucasian woman presenting with symmetric akinetic-rigid parkinsonism. Twenty-four hours after snorting heroin, the patient exhibited a

generalized dyskinetic syndrome and impaired vision, and severe parkinsonian symptoms developed within 2 weeks. The akinetic-rigid syndrome showed good response to levodopa therapy with motor fluctuations over the course of treatment. Previous studies on heroin-induced parkinsonism have reported leukoencephalopathy with diffuse white matter hyperintensities on brain MRI corresponding to spongiform degeneration.^{1,2} However, gray matter lesions of the basal ganglia and, to a lesser extent, the cerebral cortex, due to heroin abuse have not been reported before in drug-induced parkinsonism (figure, A–C). We speculate that the affected brain regions reflect a noxious effect of heroin or used additives on metabolical active neurons.

Copyright © 2007 by AAN Enterprises, Inc.

Address correspondence and reprint requests to Dr. Rejko Krüger, Center of Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany; e-mail: rejko.krueger@uni-tuebingen.de

Disclosure: The authors report no conflicts of interests.

1. Wolters EC, van Wijngaarden GK, Stam FC, et al. Leukoencephalopathy after inhaling "heroin" pyrolysate. *Lancet* 1982;2:1233–1237.
2. Kriegstein AR, Shungu DC, Millar WS, et al. Leukoencephalopathy and raised brain lactate from heroin vapor inhalation ("chasing the dragon"). *Neurology* 1999;53:1765–1773.

Neurology®

Acute parkinsonism with corresponding lesions in the basal ganglia after heroin abuse

Walter Mätzler, Thomas Nägele, Thomas Gasser, et al.

Neurology 2007;68;414

DOI 10.1212/01.wnl.0000250230.86581.ea

This information is current as of February 5, 2007

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/68/6/414.full>

Supplementary Material

Supplementary material can be found at:
<http://n.neurology.org/content/suppl/2007/07/27/68.6.414.DC1>

References

This article cites 2 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/68/6/414.full#ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

All Toxicology

http://n.neurology.org/cgi/collection/all_toxicology

Opiates

<http://n.neurology.org/cgi/collection/opiates>

Parkinson's disease/Parkinsonism

http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.