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CHAPTER 35

Progressive cognitive decline in adolescents and adults with epilepsy

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Abstract: The effects of an accumulation of single seizures upon mental abilities in adolescents and adults is explored through a selective review of the world's literature. The papers reviewed were divided up into cross-sectional and longitudinal studies. Of 16 investigations meeting all requirements for inclusion, 12 produced results pointing to a relationship between seizures and adverse cognitive change. The cross-sectional studies produced stronger results than the longitudinal ones, no doubt because the effects of co-existing factors not related to seizure effects were included in measures of cognitive decline. The longitudinal investigations showed mild but definite relationships between seizures and mental decline. However, relationships could be found only with generalized tonic–clonic seizures and not with partial attacks. Results of an original investigation were reported which were consistent with the literature review. Suggestions for future research were offered.

Introduction

The possibility that seizures may damage the brain has been entertained for decades, but the mere fact that this conference was scheduled is an indication that as of yet no clear answer to the question has been forthcoming. This chapter is specifically designed to address the question of cognitive decline due to seizures themselves with a particular emphasis upon multiple single seizures in adolescents and adults. The literature will first be reviewed, and some original data will also be presented.

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Review of the literature on cognitive effects of seizures

This review will take the form of citing selected studies done over the past 60 years rather than attempting to summarize all investigations which bear on the topic at hand. Studies most likely to contribute to the field were selected and others were omitted. Studies included here had the following features: (1) they routinely used formal measures of mental abilities which were typically intellectual and neuropsychological tests although ratings of mental status were permitted in two exceptional circumstances; (2) they were longitudinal rather than cross-sectional in nature, or, if cross-sectional, they included specific features which permitted inferences about changes in mental abilities over time; and (3) they evaluated adolescents and adults rather than children since studies of children were covered elsewhere in this conference. For all studies, providing an estimate of the numbers and types of seizures experienced as well as a non-seizure control group was desirable but not required for inclusion in this review. Studies

merely providing correlations between mental abilities and seizure history variables such as age at onset of seizures, duration of the disorder, and seizure type were omitted since these variables, even taken in combination, have been shown to have limited relationship with mental abilities, even with large samples (Dodrill and Matthews, 1992; Strauss et al., 1995).

The studies reviewed are divided into cross-sectional and longitudinal investigations as the differences between these types of inquiries are especially important.

Cross-sectional studies

The possibility has long been considered that monozygotic twins discordant for epilepsy might provide information about the effects of seizures. In an early work of this type, Lennox and Collins (1945) studied six twin pairs discordant for epilepsy and failed to identify any consistent intellectual differences between the twins who did and who did not have epilepsy, much less intellectual changes related to seizure frequency. However, they also noted that the number of seizures experienced by the affected twin were few in number or absence only, and thus this study did not produce definitive information.

Lennox and Lennox (1960), in an historically important paper, made clinical judgments of whether or not 1,471 patients seen in clinic were or were not 'mentally impaired,' and then related these judgments to estimates of lifetime numbers of epileptic seizures. Although they did not take the position that seizures cause mental deterioration, their data showed quite a direct relationship with the number of convulsions experienced and the probability of being identified as mentally impaired. With less than 10 convulsions experienced in their lifetimes, only 9% were considered mentally impaired, but with more than 1,000 convulsions experienced, 54% were considered impaired. Furthermore, having a second seizure type as well as generalized tonic–clonic seizures was associated with a slightly increased rate of mental impairment regardless of the lifetime number of convulsions experienced. Although this study suffers from being cross-sectional by nature and from not having a formal test of mental abilities, the reputation of the authors and the care in which these data were likely gathered require our attention. Not only is the type of seizure underscored as important in presaging losses in mental abilities, but the fact that they should be considered over the *lifetime* of the patient is drawn to our attention.

Dodrill and Troupin (1976) studied monozygotic twin girls from a family with a strong history of epilepsy. The twins were normal at birth and normal in development until the onset of seizures. Furthermore, at the age of 5 years, when Twin 2 had her first seizure, their EEGs were essentially identical with widespread synchronous polyspike wave discharges. Twin 2's first seizure was a generalized tonic–clonic seizure and in the 10 months that followed, she was inadequately treated with various drugs and consequently she had a number of generalized tonic–clonic seizures as well as many classical absence attacks. At the end of this time, Twin 1 spontaneously began to have generalized tonic–clonic and absence seizures, and the parents sought help from a specialized medical facility where the girls had similar drug treatments with better seizure control. Nevertheless, Twin 2 continued to have occasional generalized tonic–clonic seizures while Twin 1 had only rare tonic–clonic seizures. At the age of 19 years when they were examined neuropsychologically, Twin 2 had experienced a lifetime total of exactly 37 tonic–clonic seizures and Twin 1 a lifetime total of only seven tonic–clonic seizures. Neither twin had experienced status epilepticus at any time.

The neuropsychological testing results on the twins are presented in Table 1. Twin 1 was below average intellectually, somewhat behind academically, and she demonstrated mild but definite generalized impairment in brain functions. However, Twin 2 performed more poorly on all tests than Twin 1, was intellectually within the mildly retarded range, and had 100% of her scores on the neuropsychological test battery outside normal limits. Cognitive (and affective) differences were obvious between the twins which the parents insisted were not present before their seizures started. The data provided 'suggestive evidence' (Dodrill and Troupin, 1976, p. 607) of the adverse effects of single tonic–clonic seizures upon mental abilities.

Dikmen and Matthews (1977) studied the question of seizure frequency with regard to generalized tonic–clonic attacks in 72 patients. Patients were

TABLE 1

Comparison of Twins 1 and 2 at the age of 19 years on various neuropsychological measures (Dodrill and Troupin, 1976)

Test/variable	Twin 1	Twin 2
Wechsler Adult Intelligence Scale		
Verbal IQ	92	68
Performance IQ	81	64
Full scale IQ	86	64
Wide Range Achievement Test		
Reading, grade equivalent	7.5	5.4
Spelling, grade equivalent	7.0	4.0
Arithmetic, grade equivalent	6.5	2.3
Expanded Halstead–Reitan Neuropsychological Battery		
Category Test (errors)	96	98
Tactual Performance Test		
Total time (min/block)	0.6	9.0
Memory (number remembered)	6	5
Localization (number localized)	4	2
Seashore Rhythm (number correct)	23	17
Speech–sounds Perception (errors)	7	14
Finger Tapping, pref. (taps/10 s)	42	31
Halstead Impairment Index	0.71	1.0

classified as having low, moderate, or high seizure frequencies ". . . in consecutive time periods over the span of the disorder" (p. 22). The final index of seizure frequency consisted of the average of the ranks. By this method, a relative rather than an absolute estimate of lifetime generalized tonic–clonic seizure frequency was made. Results showed that higher seizure frequencies were associated with lower scores on the WAIS and on some but not all measures from the Halstead–Reitan Neuropsychological Test Battery. The differences were of moderate magnitude and achieved statistical significance at the 0.01 level on only two of 14 variables (WAIS FSIQ, Trail Making Test Part B).

Dodrill (1986) evaluated 310 adults with epilepsy in a comprehensive epilepsy center and intensively studied their lifelong histories of generalized tonic–clonic seizures (GTCs). He found that with a high level of confidence he could classify 94 of these patients (30%) into one of the following categories (the other patients had seizure histories which were too uncertain to permit confident classification): (1) 2–10 GTCs in lifetime (average of about 4) but no form of status epilepticus; (2) 11–100 GTCs in lifetime (average of about 30) but no status; (3) >100 GTCs in lifetime (average of 200–300) but no status; or (4) at least one episode of GTC status regardless of the total number of individual GTCs experienced in lifetime (about 40 on average not counting the episodes of status). The complete WAIS was administered to all patients as well as an expanded Halstead–Reitan neuropsychological battery. Statistically significant differences ($P < 0.001$) were found on all IQ scores and on the summary neuropsychological measures as well as on many subtest scores. Representative findings are presented in Fig. 1.

A review of Fig. 1 reveals that there are no important differences in abilities with lifetime histories of fewer than 100 GTCs without a history of status. However, either a greater lifetime number of GTCs or a history of status epilepticus is associated with diminished cognitive capacity. While this fundamental conclusion is consistent with clinical experience, attention must be drawn to the fact that this is a cross-sectional study and that cohort factors are likely contaminated with the cognitive findings. The result may be an overstatement of seizure effects

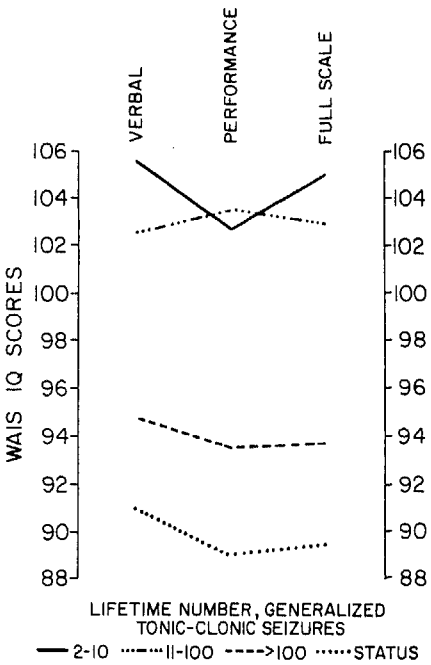

Fig. 1. Comparison of patients grouped by lifetime numbers of generalized tonic–clonic seizures on the Wechsler Adult Intelligence Scale.

despite the extensive efforts made not to do so in the study report.

Trimble (1988) reported on a study of 40 long term residents at the Chalfont Centre in the UK. Using psychological testing, an estimate was made of premorbid IQ, and when this was contrasted with IQ at the time of the study, it was determined that 21 of the 40 cases had lost more than 15 IQ points. Deteriorating cases had more generalized tonic–clonic seizures than non-deteriorating cases, had required medical attention more frequently for head injury, and were more commonly taking phenytoin and phenobarbital. All these factors were thought to be important. There were no differences on other EEG, seizure history, and medication variables. The subjects in this study apparently heavily overlapped those in the study of Thompson et al. (1987) and therefore that study will not be discussed independently.

Helmstaedter and Elger (1999) studied 63 left mesial temporal lobe epilepsy patients and compared them with 125 matched healthy control persons. Although the study was cross-sectional in nature, the investigators showed that the two groups demonstrated the same fundamental pattern of vocabulary increasing with age but with verbal learning and memory decreasing with age. They concluded that there was no accelerated deterioration of memory due to a progression of the disease.

Jokeit and Ebner (1999) evaluated 209 patients for epilepsy surgery and divided them up by duration of habitual seizures. Using the German form of the WAIS-R, they discovered in this cross-sectional study that longer durations of seizures were associated with diminished intelligence. Age, at onset of seizures, and other variables differed remarkably across the groups and complicated interpretation. Individuals with higher educational attainment were apparently brighter at the outset and typically had epilepsy longer before falling below the normal range in terms of FSIQ. However, the better educated persons in the successively longer seizure duration groups diminished intellectually as much as did the less educated groups, but perhaps not quite as rapidly. The authors concluded that uncontrolled temporal lobe epilepsy gradually exacts a cognitive toll if not brought under control.

Jokeit et al. (2000) evaluated 37 patients with refractory complex partial seizures with a measure of long-standing intellectual functioning (MWT-B) and compared results with the FSIQ from the German version of the WAIS-R. They found that the FSIQ on the WAIS-R was significantly lower (90.8) than the MWT-B (102) which suggested that an intellectual loss had occurred. In addition, they discovered a significant negative correlation ($r = -0.37$, $P = 0.012$) between the difference between the WAIS-R and the MWT-B and the duration of epilepsy.

Longitudinal studies

Arieff and Yacorzynski (1942), using the 1916 and 1937 forms of the Stanford–Binet Intelligence Scale, found that over a 1–9-year period, adolescents and adults deteriorated much more (an average loss of 6 IQ points) if they had a clearly identifiable cause of their epilepsy than if they did not have such a cause (average gain of 0.7 IQ points). This study is of value today by drawing our attention to the fact that intellectual deterioration cannot be expected to be the same in all groups of people with epilepsy. The study included no information on seizure frequency between testings.

Rodin (1968) reported data on 56 adolescents and adults who had been tested using (apparently) the Wechsler–Bellevue Intelligence Scale on two occasions at least 5 years apart and 7 years apart on average. At follow-up, 60% of patients who had been seizure free for 2 years or more had an increase in their Full Scale IQ scores. In contrast, 25% of patients who were improved in seizure frequency but not seizure-free had increased Full Scale IQ scores, and only 15% of patients whose seizure frequency was the same or worse had improved IQ scores. Overall, changes in seizure frequency were significantly correlated with changes in Full Scale IQ scores ($r = 0.33$, $P < 0.02$). This study is important because it was among the first to provide a longitudinal design with actual testing of mental abilities at the beginning and at the end of the study. Types of seizures experienced during the study were not clearly distinguished and the follow-up interval was somewhat variable, but the work is nevertheless an important one.

Seidenberg et al. (1981) used the WAIS to evaluate adults with epilepsy on two occasions approx-

imately 18 months apart. One group consisted of 22 patients who had improvement in their seizure frequencies over the interval, while a second group of 25 persons had essentially the same seizure frequency or got worse. The group with improved seizures had an improved VIQ of 3 points, an improved PIQ of 10 points, and an improved FSIQ of 7 points. Changes in the seizure-unimproved group were −1, +4, and +1 IQ points, respectively. The authors concluded that changes in scores on the WAIS are related to changes in seizure frequency. This investigation also shows that practice effects must be taken into account in evaluating the results of studies of this type; a failure to gain with retest may in fact constitute a loss, or at least an inability to keep up with other people.

Kalska (1991) evaluated 69 adults with epilepsy on two occasions approximately 10 years apart. These patients had various epilepsy diagnoses and were originally part of a group of 161 persons who had participated in a vocational rehabilitation program in Helsinki. The patients were extensively described. Administered at the beginning and at the end of the study were the Wechsler Adult Intelligence Scale (WAIS) and several other neuropsychological tests. Intellectually, 67% of the cases did not change on the typical test variable (performances within one standard deviation) while improvement was noted in 25% and deterioration in 8%. Similar results were found on other types of variables except for memory where losses were often found in 15–20% of the cases. The seizure frequency of patients who lost abilities was difficult to determine.

Dodrill and Wilensky (1992) administered the WAIS and the Neuropsychological Battery for Epilepsy to 36 adults on two occasions 5 years apart. The patients had experienced very few seizures between the testings and had been selected because they had been on exactly the same drug regimens throughout the 5-year period. No changes were found on the tests beyond that expected on the basis of chance and practice effects. In particular, no losses in mental abilities were noted.

Selwa et al. (1994) evaluated 28 adults with temporal lobe epilepsy on two occasions averaging 2.3 years apart. Typically, the second evaluation was requested due to patient complaints of memory dysfunction. Nevertheless, no changes were found from the first testing to the second on the WAIS-R or the Wechsler Memory Scale (Form I) beyond those that would be expected with normal adults.

Holmes et al. (1998) studied 35 adults with intractable partial seizures over a 10-year period and administered an extensive battery of neuropsychological tests at the beginning and the end of that period along with waking and sleep EEGs. The EEGs were quite similar over the 10-year period, although, in two cases, epileptiform patterns which were originally unilateral became bilateral by the end of the study. Also, during the course of the study, two patients who had never before experienced GTCs began to have them. On the WAIS-R, the Performance IQ was slightly increased upon retesting, likely due to practice or retest effects which can be found on the Wechsler scales even after several years (Dodrill, 1983). Of 17 neuropsychological variables from the Neuropsychological Battery for Epilepsy, it was noted that average scores were statistically significantly ($P < 0.05$) worse on six. Diminished scores were found in the areas of visual memory, attention, psychomotor problem solving, and perceptual functioning.

Aikia and Kalviainen (1999) followed 58 new cases with epilepsy for 5 years and performed neuropsychological testing at the beginning and at the end of the study. All had partial seizures and all were well-controlled during the 5-year period with only occasional seizures at worst. Neuropsychological testing included the WAIS and a number of other measures. Results showed slight improvement over the 5 years on 12 of 24 test variables.

Helmstaedter et al. (2000) treated 47 adult temporal lobe epilepsy cases conservatively with medicine only and performed initial and follow-up neuropsychological testing an average of 56 months later (range 2–10 years). They found no changes in verbal memory over this period, but figural memory did show a loss ($P < 0.05$).

Bjornaes et al. (2001) evaluated 17 adults with refractory epilepsy with the WAIS on two occasions an average of 6.0 years apart (SD 4.8). These people were primarily individuals who were evaluated upon entrance into a major epilepsy program for assistance in dealing with their seizures and then at a later point when being considered for epilepsy surgery. On average, the IQ scores on the WAIS all improved

(VIQ 4 points, PIQ 8 points, FSIQ 6 points) with the changes being statistically significant for PIQ ($P < 0.01$) and FSIQ ($P < 0.05$). No losses in intelligence were indicated, and the improvements were likely the products of practice or retest effects.

One area outside the realm of epilepsy has often been thought to be relevant to the effects of convulsions upon cognition. This is the use of electroconvulsive therapy (ECT) for the treatment of depression. The effects of this treatment upon memory have been studied on multiple occasions, and one review nearly 20 years ago summarized 39 investigations, many of which had longitudinal components (Taylor et al., 1982). From this review and from other more recent papers (Squire and Slater, 1983; Hoch et al., 1994; Calev et al., 1995), it is evident that both memory and non-memory cognitive functions are adversely impacted by ECT. However, most of the cognitive concerns reportedly dissipate over a few months in the typical case and lessened depression counterbalances the cognitive losses to some degree in terms of cognitive efficiency. Nevertheless, most investigators are unable to rule out the possibility of very mild but persisting cognitive consequences of ECT, especially in the area of memory. Unfortunately, this overall finding does not assist us substantively in providing new insights into the cognitive effects of seizures; it is a finding which is not greatly different than that commonly arising from the study of epileptic seizures themselves.

Conclusions for literature review

The studies selected for review in this paper were deliberately chosen to be the best available. In three of these investigations (Lennox and Collins, 1945; Dodrill and Wilensky, 1992; Aikia and Kalviainen, 1999), the patients being studied had so few seizures that no changes in cognition could be expected, and in each case no changes were found. The results of the remaining 16 investigations are summarized in Table 2. Taken together, in 12 of the 16, results were reported which fundamentally supported the conclusion of a loss in mental abilities due to an accumulation of single seizures. These seizures were routinely GTC by nature.

A further review of Table 2 reveals that there are differences in outcome dependent upon study design. In general, cross-sectional studies produced results which were more strongly supportive of a relationship between the occurrence of single seizures and decline in mental abilities than longitudinal studies.

TABLE 2

Summary of selected studies of the relationships between accumulations of single seizures and adverse changes in mental abilities

Study type/investigators	Relationship between seizures and changes in mental abilities	Comments
Cross-sectional studies		
Lennox and Lennox (1960)	*Strong* relationship found	Ratings of abilities used
Dodrill and Troupin (1976)	*Strong* relationship found	Study of twins
Dikmen and Matthews (1977)	*Moderate* relationship found	Frequency of GTCs studied
Dodrill (1986)	*Strong* relationship found	Lifetime number of GTCs
Trimble (1988)	*Mild* relationship found	Estimated premorbid IQ
Helmstaedter and Elger (1999)	*No* relationship found	Normal changes in memory
Jokeit and Ebner (1999)	*Moderate* relationship found	Study of seizure duration
Jokeit et al. (2000)	*Mild* relationship found	Estimated premorbid IQ
Longitudinal studies		
Arieff and Yacorzynski (1942)	*Mild* relationship found	Approximately 5-year follow-up
Rodin (1968)	*Mild* relationship found	Approximately 7-year follow-up
Seidenberg et al. (1981)	*Mild* relationship found	1.5-year follow-up
Kalska (1991)	*No* definite relationship found	10-year follow-up
Selwa et al. (1994)	*No* relationship found	2.3-year follow-up
Holmes et al. (1998)	*Mild* relationship found	10-year follow-up
Helmstaedter et al. (2000)	*Mild* relationship found	4.7-year follow-up
Bjornaes et al. (2001)	*No* relationship found	6.0-year follow-up

No doubt this is due to the fact that the effects contaminating factors (e.g., age at onset of seizures, duration of seizure disorder, antiepileptic medications, etc.) are likely to be included in the measurements of the effects of seizures in cross-sectional research especially. Investigators using cross-sectional designs have made extensive efforts to minimize these effects, but they are undoubtedly still present at least to a slight degree and to that degree they do inflate the apparent effects of seizures upon mental abilities.

The most accurate conclusions appear to arise from the longitudinal investigations. Routinely, mild relationships between GTC seizures and changes in mental abilities are reported. In one of the studies where this relationship was not found (Selwa et al., 1994), the test–retest interval was quite short (2.3 years) and may not have allowed for the effects of seizures to accumulate. Taken together, the best studies available today provide suggestive although not truly conclusive evidence for losses in mental abilities associated with the repeated appearance of single seizures. It may, of course, be that concomitant conditions such as the taking of AEDs may contribute to the diminished scores as well.

Why cannot more definitive conclusions be reached about the effects of single seizures upon cognition? The reasons relate to the limitations of existing studies which prominently include the following: (1) the common use of cross-sectional designs which can never definitively answer the question at hand; (2) the frequent omission of data on seizure type and frequency during the test–retest interval in longitudinal studies so that seizures cannot be tied to changes in test scores; (3) the routine omission of a normal control group in all types of studies so that it is not possible to clearly describe how people with epilepsy change over time differently than normals; and (4) the use of test–retest intervals in longitudinal studies which are too short to provide a reasonable estimate of the effects of seizures over the lifetime of an adult. In connection with this last point, probably 25 years or longer is needed to accurately evaluate the effects of seizures in humans, and the longest study that is currently available in the world's literature utilized a 10-year follow-up period.

Original investigation

To help address the deficiencies in the field, the author assembled data which he had at hand which were collected with the major assistance of a colleague (Linda M. Ojemann, M.D., Neurologist). These data have been unpublished heretofore. A summary of these data is presented here. A group of 35 adults with active partial seizures with or without secondary generalization was matched with a group of 35 normal controls with no history of any type of medical problem. The groups were highly similar for age, sex, and education, and both groups were evaluated with the Neuropsychological Battery for Epilepsy (Dodrill, 1978) both initially and then after 10 years (±6 months). The test battery included the complete WAIS and an expanded Halstead–Reitan neuropsychological test battery. A total of 20 test variables was obtained on each testing. Change scores from the first to the follow-up testing were compared across the two groups of subjects using the Student t statistic applied to each test variable.

The epilepsy cases had detailed evaluations of their seizure frequencies during the 10-year period and many had been treated by us throughout the 10 years. The mean number of partial seizures (SPS and CPS) recorded during that time was 1,109 (SD 2,512) and the median was 410. The mean number of GTCs recorded during that time was 61 (SD 103) and the median was 8. Four patients had experienced GTC status epilepticus (30 min of continuous or repetitive seizures without the regaining of consciousness) during the 10-year period.

Results on the neuropsychological battery showed that relative to the epilepsy group, the normal group had favorable and statistically significant changes in test scores on the Stroop Test (reading of color word names, $P = 0.040$), Trail Making Part A ($P = 0.043$), and WAIS PIQ (normal group improved 7 points, epilepsy group improved 3 points, $P = 0.005$). There were no changes favoring the epilepsy group over the normal group except for Finger Tapping where it appeared that an unusual set of scores obtained by the normal group on initial testing resulted in a change favoring the epilepsy group ($P = 0.012$). Whereas both groups were only approximately 30 years of age at the start of the study, both actually lost visual memory (Wechsler

Memory Scale Form I Visual Reproduction) over the next 10 years. Were not a normal control group included which showed a loss ($P = 0.001$), the loss in the epilepsy group ($P = 0.014$) might have been misinterpreted as being due to seizures.

Because of non-normality in seizure frequencies, the frequencies were converted to ranks prior to analysis. Correlations of 10-year partial seizure totals with changes on the 20 test score variables in the epilepsy group did not render a single statistically significant Pearson correlation coefficient. GTCs correlated with changes in test scores rendered statistically significant relationships for Trail Making Part B ($r = -0.48$, $P = 0.028$) and for WAIS FSIQ ($r = 0.44$, $P = 0.047$) with adverse changes in test scores being associated with increasing numbers of convulsions. Although only four patients had definitely experienced generalized tonic–clonic status epilepticus, it was of interest to note that this small group suffered statistically significant losses in both verbal memory (WMS-I Logical Memory, immediate: $P = 0.018$) and visual memory (WMS-I Visual Reproduction, immediate: $P = 0.037$).

Taken together, the results of this study provide evidence for inferring a mild but only a mild relationship between changes in mental abilities and GTCs, especially when they occur in clusters. No evidence was found for relationships between changes in mental abilities and partial seizures, but attention is drawn to the fact that this study was only for a 10-year period of time and that this period may not have been long enough to evaluate the true effects of partial seizures. Also, even though seizure counts were done as accurately as possible, in many cases they were estimates rather than precise counts and especially so for partial seizures. Thus, the full effects of partial seizures may not have been appreciated in this investigation.

Conclusions and recommendations

Based on all the information at hand, it is concluded that losses in mental abilities do occur with an accumulation of isolated GTCs. It is likely that the number that must accumulate varies from one patient to the next and that cognitive deficits likely occur more quickly in some patients than in others. The reason for this is unknown. In many patients, it is believed that there is evidence for some deficit when 100 convulsive episodes have been experienced. There is a general consensus that convulsive status epilepticus produces at least some cognitive deficits. Although it is possible that a very large number of seizures other than generalized tonic–clonic attacks might eventually be associated with cognitive loss, there is no clear evidence for this at the present time.

To more definitively answer the major questions in the field in the future, the major limitations in existing studies will need to be addressed directly and deliberately. In particular, *longitudinal prospective investigations* are needed which include recording the numbers of GTC and other seizures experienced throughout the study. It is also of importance that such studies include normal groups closely matched with the epilepsy samples for age and education at the beginning of the study. Finally, it is likely that long study periods (at least 25 years) will be required before the true cognitive effects of single seizures in the lifetime of our patients can be adequately assessed. While these investigations will certainly prove to be laborious, their value to our patients will be great, and it is essential that they be undertaken.

References

Aikia, M. and Kalviainen, R. (1999) Five-year follow-up of cognitive performance of adult patients with well-controlled partial epilepsy. *Epilepsia*, 40(Suppl. 2): 100–101.

Arieff, A.J. and Yacorzynski, G.K. (1942) Deterioration of patients with organic epilepsy. *J. Nerv. Ment. Dis.*, 96: 49–55.

Bjornaes, H., Stabell, K., Henriksen, O. and Loyning, Y. (2001) The effects of refractory epilepsy on intellectual functioning in children and adults. A longitudinal study. *Seizure*, 10: 250–259.

Calev, A., Gaudino, E.A., Squires, N.K., Zervas, I.M. and Fink, M. (1995) ECT and non-memory cognition: a review. *Br. J. Clin. Psychol.*, 34: 505–515.

Dikmen, S. and Matthews, C.G. (1977) Effect of major motor seizure frequency upon cognitive–intellectual functions in adults. *Epilepsia*, 18: 21–29.

Dodrill, C.B. (1978) A neuropsychological battery for epilepsy. *Epilepsia*, 19: 611–623.

Dodrill, C.B. (1983) Long-term reliability of the Wonderlic Personnel Test. *J. Consult. Clin. Psychol.*, 51: 316–317.

Dodrill, C.B. (1986) Correlates of generalized tonic–clonic seizures with intellectual, neuropsychological, emotional, and social function in patients with epilepsy. *Epilepsia*, 27: 399–411.

Dodrill, C.B. and Matthews, C.G. (1992) The role of neuropsy-

chology in the assessment and treatment of persons with epilepsy. *Am. Psychol.*, 47: 1139–1142.

Dodrill, C.B. and Troupin, A.S. (1976) Seizures and adaptive abilities: a case of identical twins. *Arch. Neurol.*, 33: 604–607.

Dodrill, C.B. and Wilensky, A.J. (1992) Neuropsychological abilities before and after 5 years of stable antiepileptic drug therapy. *Epilepsia*, 33: 327–334.

Helmstaedter, C. and Elger, C.E. (1999) The phantom of progressive dementia in epilepsy. *Lancet*, 354: 2133–2134.

Helmstaedter, C., Kurthen, M., Lux, S., Johanson, K., Quiske, A., Schramm, J. and Elger, C.E. (2000) Temporal lobe epilepsy: longitudinal clinical, neuropsychological and psychosocial follow-up of surgically and conservatively managed patients (in German). *Nervenarzt*, 71(63): 629–642.

Hoch, D.B., Hill, R.A. and Oas, K.H. (1994) Epilepsy and mental decline. *Neurol. Clin.*, 12: 101–113.

Holmes, M.D., Dodrill, C.B., Wilkus, R.J., Ojemann, L.M. and Ojemann, G.A. (1998) Is partial epilepsy progressive? Ten-year follow-up of EEG and neuropsychological changes in adults with partial seizures. *Epilepsia*, 39: 1189–1193.

Jokeit, H. and Ebner, A. (1999) Long-term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross-sectional study. *J. Neurol. Neurosurg. Psychiatry*, 67: 44–50.

Jokeit, H., Luerding, R. and Ebner, A. (2000) Cognitive impairment in temporal-lobe epilepsy. *Lancet*, 355: 1018–1019.

Kalska, H. (1991) Cognitive changes in epilepsy: a ten-year follow-up. *Commentationes Scientiarum Socialium*, 44, Societas Scientiarum Fennica, Helsinki, pp. 1–85.

Lennox, W.G. and Collins, A.L. (1945) Intelligence of normal and epileptic twins. *Am. J. Psychiatry*, 101: 764.

Lennox, W.G. and Lennox, M.A. (1960) *Epilepsy and Related Disorders*. Little, Brown, Boston.

Rodin, E.A. (1968) *The Prognosis of Patients with Epilepsy*. Charles C. Thomas, Springfield, IL.

Seidenberg, M., O'Leary, D.S., Berent, S. and Boll, T. (1981) Changes in seizure frequency and test–retest scores on the Wechsler Adult Intelligence Scale. *Epilepsia*, 22: 75–83.

Selwa, L.M., Berent, S., Giordani, B., Henry, T.R., Buchtel, H.A. and Ross, D.A. (1994) Serial cognitive testing in temporal lobe epilepsy: longitudinal changes with medical and surgical therapies. *Epilepsia*, 35: 743–749.

Squire, L.R. and Slater, P.C. (1983) Electroconvulsive therapy and complaints of memory dysfunction: a prospective three-year follow-up study. *Br. J. Psychiatry*, 142: 1–8.

Strauss, E., Loring, D., Chelune, G., Hunter, M., Bermann, B., Perrine, K., Westerveld, M., Trenerry, M. and Barr, W. (1995) Predicting cognitive impairment in epilepsy: findings from the Bozeman Epilepsy Consortium. *J. Clin. Exp. Neuropsychol.*, 17: 909–917.

Taylor, J.R., Tompkins, R., Demers, R. and Anderson, D. (1982) Electroconvulsive therapy and memory dysfunction: is there evidence for prolonged defects?. *Biol. Psychiatry*, 17: 1169–1193.

Thompson, P.J., Sander, J.W.A.S. and Oxley, J. (1987) Intellectual deterioration in severe epilepsy. In: P. Wolf, M. Dam, D. Janz and F.E. Dreifuss (Eds.), *Advances in Epileptology*, Vol. 16, Raven Press, pp. 611–614.

Trimble, M.R. (1988) Cognitive hazards of seizure disorders. *Epilepsia*, 29(Suppl. 1): S19–S24.