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Cognitive Development in Epilepsy

The Relative Influence of Epileptic Activity and of Brain Damage

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Summary. A total of 37 children, aged between 12 and 18 years and resident in an epileptic colony, were assessed in several ways for the frequency of their epileptic discharging activity and for the extent of underlying brain pathology. In addition, the children were evaluated for their level of performance on various tests of cognitive and visuo-motor functions. The influence on test performance of the discharging activity and of the extent of pathology was then compared, taking other factors such as age at onset of the seizures, duration of the epileptic illness and level of medication into account as far as possible. Only two factors, namely certain indices of discharging activity and level of medication, were found to have significantly influenced particular aspects of cognitive performance; it was impossible to document an influence of brain pathology statistically.

Key words: Epilepsy – Brain damage – Cognitive development

Introduction

At least nine different variables have been implicated as relevant to the development of cognitive skills in patients suffering from epileptic attacks. Thus two authors [10, 16] on the basis of descriptive analysis, and two other studies [5, 13] on the basis of statistical comparisons, have claimed that underlying brain damage is one important factor in the genesis of cognitive deficit in epileptics, although other investigators [2, 4, 14] failed to support this view. Age at the time of occurrence of the brain pathology, and age at the time of onset of the seizures have been implicated either individually or together in several studies [10, 12, 13, 16], although two others [4, 23] failed to confirm the importance of these variables. That the nature of the epileptic attacks is of consequence for cognitive development has been argued by several authors [5, 12, 13, 16, 27]. Accordingly, the pattern of abnormality in the electroencephalogram (EEG) has likewise been implicated [5, 14, 16, 23, 25].

Two further factors, namely the duration of the epileptic illness and the frequency of attacks have often been treated as independent variables, although *sensu strictu* they may be interrelated. One or the other factor has been held to be important for cognitive development in epilepsy in several studies [2, 4, 5, 11, 12, 14, 16, 23]. Anti-epileptic medication has been found to influence cognitive development [7–9], both in terms of dosage levels and the specific agents administered, an area reviewed by Thompson and Trimble [24, 25]. Social factors must also be regarded as relevant [4, 15].

The multiplicity of these variables, which are not always independent, may account for the frequently contradictory outcomes of different investigations. An additional difficulty has been operational: how best can one assess, for instance, the extent of brain pathology or the level of cognitive achievement? In the present investigation we have sought to take account of these difficulties in asking the question: is the frequency of epileptic activity or the extent of the underlying pathology the more important determinant of cognitive deficit in epileptic subjects? In contrast to two previous studies asking this question [2, 4], we have used computer-tomographic (CT) evidence for the assessment of the extent of brain damage; and in contrast to the third [14] we have graded the CT findings more finely. The frequency of epileptic activity has been evaluated according to five different procedures; and account has been taken of several additional factors: age at the time of occurrence of brain damage, age at the onset of seizures, duration of illness, anti-epileptic medication and social environment. Cognitive performance has been assessed with a variety of standardised tests suitable for children performing at below average levels.

Method

Subjects

All 37 children aged 12.0–17.3 years (mean 15.4) had lived in two houses of the epileptic colony of Bethel on average for 40 months; they generally went home one weekend/month and during school holidays. The children lived in groups of 8–10 (5 groups/house) and all attended the same school; 19 were classified as backward ("lernbehindert") and 18 as retarded ("geistig behindert"). To be included, each child had to have certain evidence of epilepsy (if possible over a period of 5 years), and be testable. All except 6 of the subjects had lived in one of the two houses for at least 1 year, to allow full documentation of fit frequency. There were 23 boys and 14 girls. Table 1a shows the distribution of the different kinds of

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Table 1a. Nature of epileptic attacks

Attacks	*n*	(%)
Grand mal	2	5.4
Absences	4	10.8
Partial attacks	4	10.8
Combinations of attacks	20	54.1
No attacks[a]	7	18.9
Total	37	100.0

[a] No attacks while living in the epileptic colony of Bethel

Table 1b. Abnormalities indicative of discharging activity in the EEG

Finding	*n*	(%)
Focal	7	18.9
Generalised hypersynchronic activity	11	29.7
Focal and generalised hypersynchronic activity	3	8.1
Normal	16	43.2
Total	37	99.9

attack. Further details (e.g. in respect to aetiology of the seizures, physical disability, behaviour disorder, etc.) can be found elsewhere [18].

Assessment of Independent Variables

1. Fit frequency was assessed for 2 periods of time: firstly, for the whole time period from arrival at the epileptic colony to data analysis (FFQ1), and secondly for 15 days before and after the psychological testing (FFQ2). For both measures differing kinds of fit were summed, allowance was made for absence at home and a frequency per month was calculated (see ref. [18] for detail). FFQ1 and FFQ2 were found to correlate at rho = 0.84 (P = 0.001, two-tailed).

2. Fit duration was assessed by adjusting the measures FFQ1 and FFQ2 for the typical duration of each kind of attack observed for a particular child. Thus, for instance, a grand mal attack was allocated a typical duration of 120 s, an absence 3 s, a complex partial attack 120 s, or a simple partial attack 20 s, etc. The two measures thus derived, FD1 from FFQ1 and FD2 from FFQ2, were found to correlated at rho = 0.84 (P = 0.001).

3. EEG abnormality was assessed on the basis of the last EEG recorded (on the average at 7.2 months) before testing. Interictal abnormalities were explicitly included. The kinds of abnormality observed are shown in Table 1b. For each child the intenstiy of the abnormality was evaluated by one of us (H.E.B.) on a 10 point scale (see ref. [18] for details). This measure correlated at rho = 0.55, 0.50, 0.57 and 0.54 (all at P = 0.002) with FFQ1, FFQ2, FD1 and FD2 respectively).

4. A rating of the extent of brain damage was undertaken by one of us (R.C.S.) and by a second neuroradiologist on a 7 point scale, and repeated after 1 week. The CTs on which these ratings were based had been taken with a Philips Tomo Scan 210 at an average of 11.8 months before testing. Since the inter-rater and the test-retest reliabilities correlated at rho =0.76, 0.81, 0.93 and 0.73 (all at P = 0.001), the four ratings were collapsed to produce a composite rating CTM. The findings were positive in 27 children and only marginally abnormal or normal in 10. All 27 showed atrophy, and 7 additionally indicated focal lesions.

5. The extent of brain damage was additionally determined by ventricular measurements [20]: firstly, the ratio of maximal ventricular width to maximal inner skull diameter was calculated for one slice (VQ1); and secondly the ratio of the minimal width of the cella media to maximal inner skull diameter was calculated (VQ2). These measurements were repeated after 3 weeks (test-retest reliabilities at $P = 0.001$). The means of the original and repeat values were used in the further analyses, now identified as VQ1M and VQ2M; they correlated at rho = 0.61 and 0.75 with CTM (P = 0.001). There were no significant correlations between indices of the extent of brain damage (viz. CTM, VQ1M or VQ2M) and indices of fit frequency (FFQ1, FFQ2), fit duration (FD1, FD2) or EEG abnormality.

6. The family situation was categorized as "disturbed" in 14 children (= 38%) if the child-authority ("Jugendamt") had become involved as a result of potential neglect or abuse; if either parent was mentally ill or addicted to alcohol; or if either parent had attempted suicide. In 23 other cases the family situation was categorized as "undisturbed".

7. The time of occurrence of the brain damage was categorized as "early" in 11 children if there were indications for severe complications during pregnancy or at birth, or if there was relevant injury, illness or evidence of brain damage during the first year of life (for instance, Sturge-Weber syndrome, encephalitis, meningitis, cyst, trauma or v.a.); as "late" in 22 children if there were known to be no such indications, illness or injury in the first year after birth. Excluded were 4 children with insufficient information, and children with evidence of both early complications and of brain damage after the first year.

8. Age at seizure onset was determined as that age at which regular attacks began. (Fits during infancy, followed by a fit-free period of 1 year, did not qualify.) In 19 children fits began up to age 2.0 years; in 5 between 2.1 and 4.0; and in 11 between 4.1 and 10.0 years. No information was available for 2 children.

9. Duration of epileptic illness was calculated as age at time of testing less age at time of seizure onset. The mean was 12.1 (SD 2.96) years for the 35 children for whom information was available.

10. The levels of anti-epileptic medication were classified by one of us (H.E.B.) as 1. "sub-therapeutic" in 25 children, 2. "therapeutic" in 11 children and 3. "toxic" in one child on the basis of the latest blood level determination preceding (at an average of 8.2 months) the testing. The classification was based on Schmidt [22]. In 14 (= 36%) children the medication at the time of testing had been changed subsequent to the previous blood level determination (decreased in 12, slightly increased in 2), but was unchanged in 23. As only one child was allocated to group 3. "toxic", it was re-classified to group 2, leaving only the categories of "sub-" and "therapeutic".

11. Handedness was assessed by requiring the child to show how he/she threw a ball, combed the hair, used a toothbrush, and drank from a cup. If all four items were not executed with the same hand the child was classified as ambidextrous (n = 4). 28 were right-, 5 were left-handed. This index was only used for categorising the performance on one test (FTT—see later) respectively as with the preferred/non-preferred hand.

Table 2. Correlations (Spearman-rho) between five measures of epileptic activity and test performance

Test	*n*	FFQ1 r	FFQ2 r	FD1 r	FD2 r	EEG r
WIPKI-IQ	37	−0.44*	−0.35	−0.43	−0.31	−0.30
Digit span	27	−0.14	−0.11	−0.15	−0.10	−0.13
GFT	37	0.21	0.18	0.18	0.15	0.36
D2	25	−0.27	−0.16	−0.24	−0.04	−0.28
FTT-preferred	37	−0.27	−0.25	−0.26	−0.22	−0.30
FTT-non-preferred	36	−0.26	−0.25	−0.23	−0.23	−0.43
TMT-A	32	−0.64**	−0.56**	−0.61**	−0.55**	−0.38
TMT-B	27	−0.33	−0.32	−0.32	−0.29	−0.11

* $P = 0.006$, ** $P = 0.001$

Assessment of Dependent Variables

1. Intelligence was assessed with a shortened version (the WIPKI) [1] of the German version (HAWIK) of the WISC. There are four sub-tests: general information, similarities, picture arrangement and block design, which can be given in 25–40 min. The age norms are 6.0–15.11, but norms for the 15.11 year olds were also used without extrapolation for the 17 children older than 15.11 years in this investigation since the German version (HAWIE) of the WAIS does not differentiate well for retarded children in the age range 10–18, and our procedure is conservative (i.e. does not favour rejection of the null hypothesis).

2. Verbal short-term memory was assessed with the digit span sub-test of the German version (HAWIK) of the WISC.

3. Visual co-ordination was assessed with the Göttinger Form Reproduction Test (GFT [21]), a German version of the Bender Visual Motor Gestalt Test, with age norms for 6.0–15.11 years. However, raw scores (errors) were used, to differentiate better at the lower performance levels.

4. Attention was assessed with the D2 test of Brickenhamp [3] which indicates the speed and accuracy of discriminating between many similar visual stimuli. This test correlates significantly only with the digit symbol sub-test of the HAWIE, therefore assessing an ability other than general intelligence. Raw scores were again used.

5. Finger dexterity was assessed with Halstead's Finger Tapping Test (FTT). Only two runs of 10 s/index finger were required, unless the runs differed by 5 or more points (when a third run was required, and only the best 2 runs were scored). Scores for preferred and non-preferred hands were treated individually.

6. Visual-motor speed and flexibility were assessed by use of the child version of the Trail Making Test (TMT). Only children who could write the numbers 1–15 and letters A-G correctly were tested. Times taken to complete the A and the B tests were individually converted to speed measures to obtain a normal distribution of the scores.

The tests were given in the order: writing of numbers and letters; WIPKI; D2; GFT; FTT; Digit Span; TMTA; TMTB. The test session lasted 60–120 min.

Results

Preliminary analyses showed no significant effects of sex on any dependent variable except for FTT (where boys differed from girls at $P = 0.02$ with the preferred hand). Therefore, the data were collapsed across sex. Likewise there were no significant correlations with age, so that age groups have been combined. (Non-parametric tests have been used throughout as the data were not always normally distributed. Calculations were made with SPSS 8, using only two-tailed P values corrected for type 1 error by the formula $\alpha_{PE} = 1-(1-\alpha_{PV})^{C^*}$, where α_{PE} is the probability of obtaining an incorrect value for all tests under one hypothesis, α_{PV} is the adjusted P value for a single test, and C* is the number of comparisons per hypothesis [6]. In this study eight tests were performed for each hypothesis. As α_{PE} should not exceed the 5% level, α_{PV} was set at 0.006. Corrections were made for ties when using the Mann-Whitney U-test.)

Influence of Epileptic Activity

In Table 2 the correlations between test performance and five indices of epileptic activity are shown. Performance on the WIPKI is significantly correlated with FFQ1; and on TMT-A with all epileptic indices except EEG. In all other cases the correlations do not differ significantly from chance.

Influence of Extent of Brain Damage

In Table 3 the correlations between test performance and three indices of the extent of brain damage are shown. These correlations do not differ significantly from chance.

Table 3. Correlations (Spearman-rho) between three measures of the extent of brain damage and test performance

Test	*n*	CTM r	VQ1 r	*n*[a]	VQ2 r
WIPKI-IQ	37	−0.22	−0.04	36	−0.15
Digit span	27	0.04	0.17	26	0.15
GFT	37	0.09	−0.10	36	0.10
D2	25	0.00	−0.18	25	−0.20
FTT-preferred	37	−0.14	0.08	36	−0.19
FTT-non-preferred	35	−0.09	0.05	34	−0.04
TMT-A	32	0.08	0.11	31	0.08
TMT-B	27	0.28	0.48	27	0.39

[a] It proved impossible to determine the width of the cella media for one child

Influence of Other Variables

Comparing groups of children with "disturbed" and "undisturbed" family situation, and with "early" and "late" occurrence of brain damage, the groups do not differ significantly from chance on any test performance. Correlating age at seizure onset with test performance, and duration of epileptic illness with test performance, the coefficients do not differ significantly from chance. Comparing groups of children with their anti-epileptic medication at a "sub-therapeutic" and "therapeutic" level, the groups do not differ significantly from chance except on the D2 test. Here the "sub-therapeutic" group performed significantly better ($P = 0.0037$) than the "therapeutic" group, indicating an adverse effect of medication on attention and concentration.

Discussion

We have found significant correlations between one or more indices of epileptic activity and the test performance of our children on WIPKI (intelligence) and TMT-A (i.e. part A of the Trail Making Test, a test indicative of skill at visual searching and motor speed and their co-ordination). Given that a significant difference was not found between FFQ1 and FFQ2 (Wilcoxon Test) and a trend is also present for a correlation between WIPKI and FFQ2, fit frequency must apparently by evaluated over a longer period of time than 30 days for significant effects on intelligence to emerge. Our findings accord with those of others [2, 4, 11, 12, 14, 27], although their tests and their epileptic samples differed in part from ours. Particularly convincing is one investigation [4] since this is one of the few longitudinal studies: groups with constant/deteriorating intelligence were found to differ in fit frequency and EEG abnormality. The failure of our variable EEG abnormality to correlate significantly with test performance may be related to the relatively long average time interval (7.2 months) between the recording of the last EEG and the testing. In other studies [4, 5, 14, 17, 23, 26] EEG abnormality proved a significant variable for test performance, though in one [12] the authors failed to obtain a significant effect.

Only three previous studies have taken account of the extent of underlying brain damage in assessing the cognitive performance of epileptics. Chaudhry and Pond [4] compared cases of unilateral and bilateral lesions; Blakemore et al. [2] compared the removal of five differing extents of temporal lobe; and Ladavas et al. [14] compared groups with and without evidence of damage on CT. In all three studies, as in our own in which damage was evaluated more finely, no significant associations with test performance were obtained. In our children the pathology was relatively heterogeneous and occurred while the brain was still developing and "plastic". In addition, the indices of the extent of brain damage may not have been optimal. Furthermore, in principle the CT scan may not reveal subtle or small pathological alterations. Nonetheless our findings are in accordance with all three previous relevant studies. It would, however, seem premature to conclude that the extent of brain damage has no effect on test performance in epileptic subjects.

Likewise to what extent the fit frequency can be held accountable for the cognitive changes remains unresolved. It is possible that epileptic discharges are themselves disruptive of cognitive performance; however, associated factors such as hospitalization, absence from school or other social factors may be more directly responsible for the cognitive changes.

We obtained no significant effect of a disturbed family situation, which accords with earlier findings [23]. The epileptic subjects in the study of Sohns were comparable to ours, i.e. residents of a colony. Lempp [15] obtained a significant effect of this variable, but with children who lived mainly at home. Similarly, we obtained no significant difference between children with early as opposed to late occurrence of brain damage. Freudenberg [10] claimed a clear effect but without statistical evaluation, and her classification between early and late comprised a greater time span than ours. In agreement with other finding [4, 22], age at seizure onset did not correlate significantly in our sample with test performance. However, this variable was significant in certain other studies [5, 12, 13]. Probably the narrow spread of this variable (mean = 3.4 years, SD = 2.96) accounts for our failure to obtain a significant effect, since Klove and Mathews [13] found the clearest difference when comparing groups with onset ages on the one hand between 0 and 25 years, on the other between 17 and 50 years. Thus, in effect, all of our children may have had an early onset age. An analogous account may explain our failure to obtain a significant effect of duration of epileptic illness: our mean duration was 12.1 years (SD = 2.96, minimum = 4.8), whereas authors [14, 16] who have obtained significant effects of this variable compared groups with a duration of only 1 year with groups having a longer duration.

Children with anti-epileptic medication at a "therapeutic" level were significantly impaired on our D2 test, indicative of their poorer attention and concentration. These findings are in agreement with those of Nobis [19] who also administered the D2 test, and in general with those of Thompson and Trimble [25] and of Sohns [23] Thus it appears that an inverse relationship may exist between level of medication and ability to pay attention and to concentrate (although caution is indicated since we were not able to test for an interaction between level of medication and fit frequency, and there was a non-significant trend for the group with the higher level to have more fits). Additionally, we obtained a non-significant trend for an inverse association between level of medication and motor speed (as assessed on Finger Tapping), in agreement with Dodrill [7]. Further work is needed to ascertain which cognitive skills are primarily affected by medication.

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