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Acute effects of subclinical epileptiform EEG discharges on cognitive activation

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Summary
In this prospective, open, clinical comparative study we analyzed impairments of cognitive activation occurring during, immediately before and immediately after epochs with epileptiform EEG discharges of 3 seconds or longer, in an attempt to establish whether cognitive slowing occurs in direct association with an epoch with epileptiform EEG discharges and whether cognitive impairments precede or follow such an epoch. All children were assessed with EEG/video (Brainlab\textsuperscript{5}) simultaneously with computerized neuropsychological testing (FePsy\textsuperscript{5}): a test for cognitive activation (simple visual and auditory reaction time measurement). Thirty-seven epochs with epileptiform EEG discharges without clinical signs of a seizure (subclinical epileptiform EEG discharges) were evaluated. The results showed a statistically significant and clinically relevant slowing (35% compared to the overall reaction time), occurring during the epoch with epileptiform EEG discharges (repeated measurement analysis of variance $p<.05$; df=3; F-value: 3.293). No statistically significant slowing was found for the periods ‘post-discharge’ or ‘pre-discharge’. Type of discharge was important and effects on cognitive activation were found exclusively for generalized discharges. This effect was, however, also seen in the remaining period, outside the ‘peri-discharge’ periods and thus seemed to represent a more general effect of the type of epilepsy on cognitive activation.

Our results show that the acute effect of short epileptiform EEG discharges (duration 4.14 sec; sd 1.38) may be impressive, causing impairment (slowing) of cognitive activation. This effect was limited to generalized discharges. This effect was not observed for focal discharges, even during longer periods with discharges. However, it is reassuring that this impact on cognitive activation is limited to the actual period in which the discharges occur and does not have ‘post-discharge’ effects. The risk of accumulating effects that may have longer-lasting repercussions on higher-order cognitive functions therefore seems to be negligible.

KEY WORDS: cognitive impairment, epilepsy, subclinical epileptiform EEG discharges.

Introduction
Cognitive impairment is a frequently occurring secondary handicap of epilepsy and is often associated with the pathological sequelae of seizures (1). Serious and accumulating effects have been demonstrated in the cases of secondary generalized seizures (2) and recurrent complex partial seizures, when these persist for years (3). Conversely, some studies (4,5) reported improved intellectual functioning in patients with these seizure types who became seizure-free. Serious effects like these have not been reported in relation to short non-convulsive seizures such as absence seizures or short partial-onset seizures. Nonetheless the transient, ‘acute’ effects of these seizures are often underestimated and may accumulate, and have a severe cognitive impact in uncontrolled patients with high seizure frequency (6,7). Although these effects are generally reported to be reversible when the seizures are controlled, their impact on daily life may be greater than hitherto suspected, especially when the effects are not recognized or when the seizures persist for years. In a group of children with short and difficult-to-detect non-convulsive seizures, we reported sudden and unexpected decline of school performance as the first symptom of epilepsy, possibly a result of the accumulating effect of these seizures on cognitive function (8). In another study, we showed that the acute cognitive effect of these seizures concerned attentional and memory functions (9).

One complication when seeking to interpret the relationship between seizures and cognitive function derives from the fact that in most patients with epilepsy the electroencephalogram (EEG) shows the discharges (spikes and sharp waves, with or without slow waves) that represent the underlying cause of the epileptic seizures i.e., paroxysmal abnormal electric activity of the brain. This raises the diagnostic problem of differentiating between the cognitive impact of the seizures and the cognitive impact of interictal epileptiform activity. The cognitive im-
impact of epileptiform EEG discharges in the absence of seizures ('subclinical epileptiform EEG discharges') was established as early as 1939, when Schwab demonstrated a slowing of reaction time during such episodes, even in the absence of seizures (10). Aarts et al. (11) in a more recent study using EEG/video telemetry, showed that the cognitive effects of epileptiform EEG discharges may be very similar to those of short epileptic seizures. Consequently, accumulating cognitive impairment, and even a decline in IQ scores, is reported in patients with frequent episodes with epileptiform EEG discharges – a pattern very similar to that observed in patients with frequent non-convulsive seizures (12-14).

Previous research has suggested that the extent of cognitive impairment during epileptiform EEG discharges varies according to the type of discharges and, particularly, the number of spike components and the involvement of frontocentral regions (15). Moreover, most studies have found cognitive impairment to be more common during prolonged (> 3 sec) generalized (3 per/sec spike-wave discharges) activity than during focal activity (11). In general, therefore, the assessment of cognitive impairment is most difficult in cases of focal EEG discharges (16).

Most of these studies compared global cognitive and EEG data, i.e., they correlated average cognitive scores for a certain period with EEG data, sampled during more or less the same period. The accuracy of such global correlations is limited (although, in view of the clinical relevance of behaviour-EEG comparisons, it is unclear whether there is actually a need for greater accuracy). To date, no studies have evaluated the direct or 'acute' cognitive impact during the actual period with interictal epileptiform EEG discharges. In this study we analyzed impairments of cognitive activation occurring during, immediately before and immediately after epochs with epileptiform EEG discharges of three seconds or longer in an attempt to establish whether cognitive impairment (i.e., cognitive slowing) occurs in direct association with an epoch with epileptiform EEG discharges and whether 'peri-discharge' effects occur; i.e., whether cognitive impairments precede or follow such an epoch.

Materials and methods

All children were assessed using 32-channel EEG (BrainlabR). The EEG was time-synchronized with the FePsy (FePsyR) computerized cognitive test system (17,18), using a separate software program. This system, in turn, was connected with a precisely synchronized video-monitoring system, allowing a computer program to correlate cognitive performance with EEG and clinical symptoms. This three-way connection between videosystem, test computer and EEG was accurate to within a millisecond. Each epoch with epileptiform EEG discharges could therefore be exactly matched to the video-recording and the test results during that epoch. Only one cognitive test was used in this study: i.e., simple reaction time measurement following visual (a white square on the screen) or auditory (800 Hz tones) stimuli (60 stimuli in total), presented at random intervals by the computer. This test measures cognitive activation, the state known to affect general receptivity to input information, a function closely related to alertness and arousal (19,20). The score was the reaction time in milliseconds. This test was chosen on the basis of its sensitivity to epileptiform EEG discharges, established in previous studies (9,21).

Selection was determined by the need to include a sufficient number of epochs with epileptiform EEG discharges (see power analysis in the statistical section). Children with non-convulsive seizures, assessed with the aforementioned method were only included if:

- a) they had a reconfirmed diagnosis of epilepsy;
- b) they suffered from non-convulsive generalized or partial-onset seizures of which at least one was recorded during the combined EEG-recording/cognitive testing assessment;
- c) they had at least two episodes with epileptiform EEG discharge without any clinical sign of a seizure and lasting for 3 seconds or longer. The 3-second criterion was included as previous studies have shown only limited cognitive impairment in association with shorter epochs;
- d) they had no mental handicap and no malignant epilepsy syndromes with aetiology that may affect cognitive function.

We included in the analysis at least two (but no more than ten) episodes per individual child. Subsequently, cognitive activation was analyzed taking into consideration four periods (Fig. 1): three ‘peri-discharge’ periods (a and b, below) and one overall-comparison period (c, below):

- a) the actual period with epileptiform EEG discharges;
- b) the period before discharges;
- c) the period after discharges.

Figure 1 - Peri-discharge periods correlated with measures of cognitive activation.
b) periods of similar length immediately before and after the epoch with epileptiform EEG discharges. (Thus, if the period with epileptiform EEG discharges lasted 5 seconds, a period of 5 seconds before this epoch and a period of 5 seconds after this epoch were also analyzed);

c) the overall performance during the test, excluding the epochs mentioned above. Thus, a general measure of cognitive activation was generated by subtracting the epochs with epileptiform EEG discharges and the periods occurring immediately before and after these epochs. This measure served as a general indicator of cognitive activation, without the acute effect of the epileptiform EEG discharges.

All analyses were performed by one investigator (JB), a trained EEG lab technician and neuropsychologist, and checked by JA (neurologist/clinical neurophysiologist), I vd L (EEG lab technician) and by APA and LD (both neuropsychologists and neuropsychological lab technicians).

**Statistical analysis**

Power analysis suggested that a total of 30 epochs with epileptiform EEG discharges was sufficient to detect medium-size behavioural effects, i.e., changes > 0.7 standard deviation, according to Cohen’s conventions (22,23) with a 5% level of significance and assuming a Beta of type-2 error risk (β) of 20% – the visual reaction time task has a discriminative power around 80% or higher (17,18). The results from the four periods were analyzed using repeated measurements analysis of variance (MANOVA) to compare the change over time. Post-hoc analysis was performed using paired Student’s t-tests. Statistical analysis was performed using SPSS/PC V9.1.

**Results**

Inclusion stopped after a total of at least 30 epochs with epileptiform EEG discharges had been collected (see power analysis). The total number included (37 epochs) was reached with nine children; five of these children had a diagnosis of localization-related epilepsy and 4 of idiopathic generalized epilepsy. The five children with localization-related epilepsy were all on monotherapy with carbamazepine (average daily dose: 325 mg/day; sd 54 mg/day); three of the four children with idiopathic generalized epilepsy were on valproate (average daily dose: 440 mg/day; sd 85 mg/day) and one was on lamotrigine (100 mg/day). On average 4.1 epochs per child were included (range 2-9). Table I shows the general characteristics of these epochs.

Table I - Characteristics of discharges.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n. of periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration*</td>
<td></td>
</tr>
<tr>
<td>3 seconds</td>
<td>15</td>
</tr>
<tr>
<td>&gt; 3 seconds</td>
<td>22</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
</tr>
<tr>
<td>Onset in the left hemisphere</td>
<td>16</td>
</tr>
<tr>
<td>Onset in the right hemisphere</td>
<td>6</td>
</tr>
<tr>
<td>Onset in both hemispheres</td>
<td>15</td>
</tr>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>24</td>
</tr>
<tr>
<td>Generalized</td>
<td>13</td>
</tr>
</tbody>
</table>

* total number of periods with epileptiform discharges=37; average duration: 4.14 sec (sd:1.38 sec.).

Table II - Results of simple measurement of reaction times.

<table>
<thead>
<tr>
<th>Period</th>
<th>Reaction times in milliseconds</th>
<th>Average length of period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction times during the epoch with epileptiform EEG discharges</td>
<td>450.19 (397.57)</td>
<td>4.14 sec. (1.38 sec.)</td>
</tr>
<tr>
<td>Reaction times in the period before the epoch with epileptiform EEG discharges</td>
<td>291.04 (78.36)</td>
<td>4.14 sec. (1.38 sec.)</td>
</tr>
<tr>
<td>Reaction times in the period after the epoch with epileptiform EEG discharges</td>
<td>336.72 (155.21)</td>
<td>4.14 sec. (1.38 sec.)</td>
</tr>
<tr>
<td>Reaction times during the remaining period of the test</td>
<td>333.18 (84.59)</td>
<td>An average of 13.46 sec.</td>
</tr>
</tbody>
</table>

1 period similar in length to the period with epileptiform EEG discharges. sd in brackets.
2 reaction time calculated as the average reaction time for the task after subtraction of the ‘peri-discharge’ periods (period with epileptiform EEG discharges and the periods immediately before and after the period with discharges).
using paired t-tests, is shown in Table III. The average duration of the period with discharge was 4.14 seconds. This shows that the reaction times in the period with epileptiform discharge were statistically significantly slower than those in the periods immediately before and immediately after discharge. The difference vs the remaining period was not statistically significant, even though there was a clear trend towards significance (p=.06). The remaining comparisons showed a statistically significant difference between the period immediately before discharge and the remaining period of the test. The effect of length of the epoch with epileptiform EEG discharges was statistically significant only for the period with discharge.

It can therefore be concluded that the length of discharge has an acute effect (during the discharge), but that this does not persist after the discharge. In addition, we analyzed, per epoch, the effect on reaction time of duration of the epoch with epileptiform EEG discharges. Short discharges (3 sec) were compared with longer discharges (> 3 sec) per epoch (Table IV). Figure 3 illustrates the effect on reaction time of duration of discharge during the period of discharge. We also investigated the effect of type of epileptiform EEG discharge on reaction time, comparing focal discharges with generalized discharges for each period (Table V).

Table III - Post-hoc T-test analysis of period with and period after discharge versus other periods.

<table>
<thead>
<tr>
<th>Period</th>
<th>T-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period with discharge vs period before discharge</td>
<td>-2.47</td>
<td>p=.02*</td>
</tr>
<tr>
<td>Period with discharge vs period after discharge</td>
<td>1.998</td>
<td>p=.05*</td>
</tr>
<tr>
<td>Period with discharge vs remaining period</td>
<td>1.943</td>
<td>p=.06</td>
</tr>
<tr>
<td>Period before discharge vs period after discharge</td>
<td>-1.918</td>
<td>p=.06</td>
</tr>
<tr>
<td>Period before discharge vs remaining period</td>
<td>-2.445</td>
<td>p=.02*</td>
</tr>
<tr>
<td>Period after discharge vs remaining period</td>
<td>.155</td>
<td>p=.88</td>
</tr>
</tbody>
</table>

Table IV - Effect on reaction time of duration of epoch with epileptiform EEG discharge (3 sec versus > 3 sec).

<table>
<thead>
<tr>
<th></th>
<th>Reaction time for short epoch (3 sec)</th>
<th>Reaction time for long epoch (&gt; 3 sec.)</th>
<th>T-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction times for the period before the epoch with epileptiform EEG discharges</td>
<td>281.27 (78.47)</td>
<td>297.70 (79.41)</td>
<td>-0.62</td>
<td>p=.05</td>
</tr>
<tr>
<td>Reaction times during the epoch with epileptiform EEG discharges</td>
<td>308.56 (95.66)</td>
<td>546.74 (490.69)</td>
<td>-2.22</td>
<td>p=.03*</td>
</tr>
<tr>
<td>Reaction times for the period after the epoch with epileptiform EEG discharges</td>
<td>331.61 (169.25)</td>
<td>340.20 (148.98)</td>
<td>-0.16</td>
<td>p=.87</td>
</tr>
<tr>
<td>Reaction times during the remaining period of the test</td>
<td>319.57 (83.62)</td>
<td>342.47 (85.92)</td>
<td>-0.81</td>
<td>p=.42</td>
</tr>
</tbody>
</table>

* Statistically significant (p-values < .05); in parentheses: standard deviations.
Only for the period before the epoch with epileptiform EEG discharges was this comparison not statistically significant. In all cases the differences showed longer reaction times (slowing) for the generalized discharges. The average scores showed that the effects occurred only for generalized discharges.

Discussion

In this study we assessed the direct or ‘acute’ cognitive impact of interictal epileptiform EEG discharges in 37 epochs lasting at least 3 seconds and not accompanied by clinical signs of seizures (‘subclinical epileptiform activity’). We analyzed impairments of cognitive activation ‘peri-discharge’, i.e., during, and immediately before and after epochs with epileptiform EEG discharges and compared these to one another, as well as to the remaining period of the test. This was performed through simple reaction time measurement coupled with simultaneous 32-channel EEG-recording and use of the EEG/video telemetry system. The issue of EEG-behaviour correlates was first raised in the 1930s (10,24), and reintroduced in the 1960s (25,26). Current technology, which allows exact synchronization of digital EEG, video and computerized cognitive testing, guarantees the precision needed for the linking (with millisecond precision) of short epochs and for the valid assessment of cognitive slowing. We have argued in earlier studies (9,21) that only this type of infrastructure guarantees the absence of subtle seizures during the epoch with epileptiform EEG discharge, and makes it possible to assess the cognitive effects of ‘subclinical epileptiform activity’, the subject of the present study.

The results show a statistically significant slowing occurring exclusively during the epoch with epileptiform EEG discharges. The clinical relevance of this finding is best illustrated when considering percentage slowing, which is 35% during the epoch with epileptiform EEG discharges compared to the overall reaction time recorded during the task. This seems to be only an ‘acute’ effect as no slowing was seen ‘post-discharge’. An intriguing finding was the moderate tendency towards faster reaction times immediately before the occurrence of the discharge, but this was not statistically significant. Although this effect increased with increased duration of the period with discharge, even with longer epochs the effect was not found to spread to the period after or before the discharge.

Our finding that the effects occurred only for generalized discharges and not for focal discharges is in line with previous research that has found cognitive impairment to be more common during prolonged (> 3s) generalized (3 per/sec spike-wave discharges) activity than during focal activity (11). In addition, however, there seems to be an underlying factor that is related to the type of epilepsy. In patients with generalized seizures, prolongation of reaction time was also observed in the remaining period, outside the ‘peri-discharge’ periods, resulting in a slower baseline. The effect during the discharges, thus, seems to be an interaction between the ‘ictal’ activity (the occurrence of discharges) and the interictal factor ‘type of epilepsy’.

To summarize our results, the acute effect of short periods (on average about 4 seconds) of epileptiform EEG discharges may be impressive, causing a slowing of cognitive activation in the order of approximately 35%. This effect was only observed for generalized discharges. For focal discharges this effect was not found, even during longer periods with discharges. It is reassuring that this impact on cognitive activation is limited to the actual period in which the discharges occur and does not have ‘post-discharge’ effects, i.e., does not spread. The risk of accumulating effects that may have longer-lasting repercussions on higher-order cognitive functions therefore seems to be negligible. Of course, the validity of this conclusion is limited to the effects of ‘subclinical’ epileptiform EEG discharges and it may not apply when clinical seizures occur.

Acknowledgments

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