

Altered information processing in children with focal epilepsies with and without intellectual disability

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Summary

The aim of this exploratory study was to investigate the relationship between focal interictal epileptiform discharges (IEDs), intellectual disability and cortical information processing in children with partial epilepsy. Two groups of patients – Group 1 (n = 9 patients) with focal IEDs and normal IQ and Group 2 (n = 10 patients) with focal IEDs and intellectual disability – were compared with 14 healthy control participants. A computerized choice reaction time task (go/no-go paradigm) was performed and event-related potentials (ERPs) were recorded. When an IED occurred during the period between the presentation of the stimulus and the response, the response was defined as a response with IED. Omission errors, commission errors and reaction time were evaluated in temporal relationship to IEDs. The Group 1 patients did not differ from the healthy children in neurophysiological functions and ERP amplitudes. The Group 2 children showed inferior

performances in verbal learning and memory, cognitive flexibility and selective attention, and were characterized by low ERP amplitudes compared with the epilepsy patients with normal IQ and the healthy children. We were not able to identify any significant relationship between IEDs and cognitive functions in either group of patients. Our findings suggest that the impact of IEDs on the overall intellectual abilities of epilepsy patients may not be as significant as previously thought. Moreover, it is likely that abnormalities in cognitive information processing as revealed by lower ERP amplitudes, occurrence of IEDs, and intellectual disabilities may represent common abnormal processes and may not be causally related to each other.

KEY WORDS: epilepsy, go/no-go, intellectual disability, mismatch negativity, visual evoked potentials.

Introduction

Although the influence of epilepsy on cognition and neuropsychological functioning is evident, the underlying mechanisms are still poorly understood. Identification of possible causes of neuropsychological deficits in single subjects is difficult because of the involvement of many interrelated factors. These include underlying genetics, pathophysiology, structural brain pathology, the effects of seizures, medication, social stigma and educational deprivation, and subclinical interictal epileptiform discharges (IEDs) causing transitory cognitive impairment (TCI) (Binnie, 2003). These factors are often related to each other – epilepsy syndromes are associated with morphological or functional pathology and/or genetics, and have social consequences – and they can influence the choice of medications. TCI is probably the only factor whose role in a given patient can be isolated and identified, since cognitive function during discharges can be compared with cognitive function in the intervals between discharges (Binnie, 2003).

In a first attempt to determine the effect of IEDs on information processing and cognitive abilities, Schwab (1939), employing behavioral testing and simultaneously recorded encephalograms, showed that subclinical EEG discharges were often accompanied by delayed reactions or even failure to respond to a stimulus. TCI has been observed in up to 50% of patients from different selected samples of adults and children with focal

or generalized IEDs (Aarts et al., 1984; González-Garrido et al., 2000). The probability of demonstrating TCI depends on the test employed and characteristics of subjects' IEDs. Tests that measure higher cortical function, such as choice reaction time, signal detection or working memory tasks, are more sensitive than simple motor tasks (measurements of reaction time and repetitive motor tasks) or tasks that measure basic attention functions (Binnie and Marston, 1992; González-Garrido et al., 2000). It remains unclear what other factors may influence the occurrence of TCI.

Event-related potentials (ERPs) constitute a promising method for the quantitative assessment of higher cognitive brain functions. The early ERP component, mismatch negativity (MMN), has been shown to characterize an automatic neurophysiological process in the discrimination of repetitive stimuli (Näätänen, 1995; Näätänen and Alho, 1995a,b; Näätänen et al., 1978; Alho, 1995). The response is automatically elicited when rare (deviant) stimuli occur in a sequence of frequent (standard) stimuli and it can be described as the cerebral representation of the orienting response. The late ERP component, P300, is another well-established parameter of cortical information processing which is considered to reflect information updating (Mäntysalo, 1987). The amplitude of P300 is related to the probability of stimulus occurrence and the subject's effort to manage the task being performed. Different ERP studies comparing early and late components between patients with epilepsy and age-matched healthy participants have found epilepsy patients to show: i) prolonged latency (Sun et al., 2007; Gokcay et al., 2006; Soyuer et al., 2006), ii) abnormal lateralization of components in relation to IEDs (Liasis et al., 2006; Rugg et al., 1991), and iii) abnormal amplitude of components, as well as their absence (Liasis et al., 2006; Grippo et al., 1996). In some of the studies, patients demonstrated poorer performances on neurophysiological testing, but few studies looked for correlations between behavioral performance, psychophysiological data (ERPs), and time of IED occurrence.

The aim of our study was to evaluate cognitive functions, especially selective attention, using neurophysiological and psychophysiological methods in children with focal IEDs and partial epilepsy (with and without intellectual disabilities) in comparison with healthy chil-

dren, and to determine the influence of IEDs on general cognitive functions. In order to investigate the influence of intellectual abilities on behavioral performance, the patients were divided in two groups: Group 1 - patients with intellectual status within normal range and Group 2 - patients with intellectual disabilities.

Materials and methods

Participants

Overall, 19 children with epilepsy were recruited from the Northern German Epilepsy Center for Children & Adolescents, Schwentinal/OR Raisdorf, and the Neuropediatric Department of Christian Albrechts University in Kiel, Germany. All the children had focal IEDs on previously recorded EEGs. Epilepsy diagnoses were made according to the proposed classification scheme of the International League Against Epilepsy 2001 (Commission on Classification and Terminology of the International League Against Epilepsy, 2001). The patients were assigned to two different groups according to their neuropsychological development. Nine patients had an IQ within normal range [3 males, 6 females; IQ \geq 85; mean IQ: 95.75 (SD \pm 9.42); range of IQ: 85-109; Group 1], whereas ten had intellectual disabilities [7 males, 3 females; IQ < 85; mean: 61.67 (SD \pm 6.03); range of IQ: 56-68; Group 2]. The inclusion criteria for these groups were: i) presence of IEDs, ii) absence of seizures during testing, and iii) a developmental age of at least 6 years. Neurological examination and structural MRI (high-resolution T1-, T2-, FLAIR-T2 and diffusion-weighted imaging) were performed before inclusion in the study. Patients also underwent routine EEG prior to inclusion, in order to document the presence of IEDs. Patient data were compared with the data of 14 healthy control participants (11 males, 3 females; mean age: 154 \pm 26 months; Group 3). The healthy control children were recruited from Raisdorf primary school and Raisdorf high school. There were no significant differences in age between the three groups and the patient groups did not differ significantly in the number of medications used. Table I shows the demographic and clinical data of the patients.

Table I - Demographic and clinical characteristics of 19 patients with focal epileptiform discharges.

| Patient n. | Age at onset (yrs) | Group | Gender | Seizures/month | Diagnosis | AEDs | Seizure types | N. of IEDs | Localization of spikes |
|------------|--------------------|-------|--------|----------------|---------------------------|----------|----------------------------|------------|------------------------|
| 1 | 9.0 | 1 | M | None | Left polymicrogyria | STM, OXC | Focal motor seizures, CPSS | 179 | Right central |
| 2 | 15.3 | 1 | M | None | Right perisylvian gliosis | OXC | Focal motor seizures | 30 | Bilateral central |

continued

Table I - (cont.).

| Patient n. | Age at onset (yrs) | Group | Gender | Seizures/month | Diagnosis | AEDs | Seizure types | N. of IEDs | Localization of spikes |
|------------|--------------------|-------|--------|----------------|--|-------------------|--|------------|------------------------------|
| 3 | 10.7 | 1 | F | 1 | Rolandic epilepsy | STM | Focal motor seizures | 56 | Centrotemporal |
| 4 | 19.6 | 1 | F | 5 | Rasmussen's encephalitis | OXC, ZNS, LEV, PB | Focal motor seizures | 110 | Right centroparietal |
| 5 | 10.10 | 1 | F | 180 | Cryptogenic partial epilepsy | LTG, LEV | Atypical absences, CPSSs, SGTCSSs | 23 | Frontocentral |
| 6 | 17.0 | 1 | F | None | Idiopathic occipital epilepsy | None | Focal autonomic seizures, CPSSs | 276 | Occipital |
| 7 | 14.5 | 1 | F | None | Healthy IEDs | None | No | 20 | Right centroparietal |
| 8 | 10.5 | 1 | F | None | Rolandic epilepsy | STM, CLB | Focal motor seizures | 48 | Right centrotemporal |
| 9 | 8.6 | 1 | M | None | Rolandic epilepsy | None | Focal motor seizures | 86 | Right centrotemporal |
| 10 | 9.1 | 2 | M | 1 | Perinatal hemorrhage, HIE | LTG | Focal seizures, CPSSs | 166 | Frontal, bilateral |
| 11 | 11.0 | 2 | F | None | Perinatal hemorrhage, Bilateral parieto-occipital leukomalacia | LTG | Focal seizures, CPSSs | 102 | Left frontotemporo-occipital |
| 12 | 9.9 | 2 | M | None | Large polymicrogyria Left hemiparesis | LEV, ESM | Focal seizures, CPSSs, SGTCSSs | 114 | Centrotemporal |
| 13 | 10.10 | 2 | M | None | Periventricular leukomalacia | OXC, LTG | Focal seizures, CPSSs, SGTCSSs | 55 | Frontoparietal, bilateral |
| 14 | 12.2 | 2 | M | None | Atypical benign partial epilepsy | No | Atypical absences, focal seizures, CPSSs | 50 | Centrotemporal, bilateral |
| 15 | 8.8 | 2 | M | None | Traumatic brain injury | LTG | Focal motor seizures | 64 | Central |
| 16 | 14.6 | 2 | F | None | MAE | LTG, ESM | Myoclonic astatic, absences, FSs. | 35 | Multifocal |

continued

Table 1 - (cont.).

| Patient n. | Age at onset (yrs) | Group | Gender | Seizures/month | Diagnosis | AEDs | Seizure types | N. of IEDs | Localization of spikes |
|------------|--------------------|-------|--------|----------------|--|----------|------------------------|------------|------------------------|
| 17 | 18.7 | 2 | M | None | Brain tumor resection (in left temporo-occipital region) | LTG, LEV | Focal seizures, SGTCSS | 201 | Temporo-occipital |
| 18 | 14.2 | 2 | M | 3 | Cryptogenic focal epilepsy | LTG | Focal seizures, CPSs | 257 | Fronto-centroparietal |
| 19 | 14.01 | 2 | F | 42 | Left parieto-occipital gliosis | LTG | Focal seizures, CPSs | 159 | Left parieto-occipital |

Abbreviations: IEDs=interictal epileptiform discharges; AEDs=antiepileptic drugs; HIE=hypoxic ischemic encephalopathy; CPSs=complex partial seizures, SGTCSS=secondary generalized tonic-clonic seizures; FSS=febrile seizures; STM=sulthiam; OXC=oxcarbazepine; ZNS=zonisamide; LEV=levetiracetam; PB=phenobarbital; LTG=lamotrigine; CLB=clobazam; ESM=ethosuximide; MAE=myoclonic astatic epilepsy

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Kiel, Germany. The study was explained to all the participants and their parents, and written informed consent according to the Declaration of Helsinki (current version, 1996) on biomedical research involving human participants (Tokyo amendment) was obtained.

Neuropsychological tests

All the participants underwent testing of neuropsychological functions and assessment of comorbid psychopathology. We used Luria's learning (acquisition) and memory test for words, in which the subjects were required to learn and memorize 10 common and unrelated nouns (e.g. "forest", "table", "house") (Luria, 1973). The task was continued until all words were immediately recalled. The learning session was terminated after the tenth unsuccessful trial. Thirty minutes later, the children were asked to recall the list of words. In order to evaluate intellectual status, all the participants were administered a short form of the Hamburg Wechsler Intelligence Scale for Children-Revised (HAWIK-R III), which is the German version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Tewes, 1983). Children with intellectual disabilities also performed further intelligence tests appropriate to their impairment (the Kaufman Assessment Battery for Children, the Columbia Mental Maturity Scale). The severity of intellectual disability was defined according to the international criteria proposed by the American Association on Intellectual and Developmental Disabilities: mild intellectual disability (IQ 50-69), moderate intellectual disability (IQ 35-49), severe intellectual disability (IQ 20-34). All the children with intellectual disability had the mild form. Comorbid psychopathology was assessed using the parents' rating on the German version of the Child Behavior Checklist (CBCL) (Remschmidt and Walter, 1990). The Trail-Making Test (TMT) was used to investigate sustained visual attention and task switch-

ing. In this test, subjects are required to connect the dots of 25 consecutive points on a sheet of paper. Two versions were performed: TMT A, in which the targets were just numbers (1, 2, 3, etc.), and TMT B, in which the subject had to alternate between numbers and letters (1, A, 2, B, etc.). The goal was to finish the test as quickly as possible, and the time taken to complete the test was used as the primary performance metric (Corrigan and Hinkeldey, 1987; Gaudino et al., 1995; Reitan, 1958).

Experimental procedure

A computerized choice reaction time task [go/no-go paradigm (Mäntysalo, 1987; Salisbury et al., 2004)] was designed and performed using the E-Prime software package (Psychology Software Tools Co., Sharpsburg, PA, USA). The stimuli consisted of pictures of different colored monsters and a yellow sun. The subject was instructed to press the spacebar of a computer keyboard in response to randomized presentation of frequent target pictures (red monster, 'go condition') and to withhold reaction upon presentation of infrequent stimuli (different colored monster or yellow sun, 'no-go condition'). The game was motivating and the task simple, namely, to shoot bad monsters (i.e. the red ones) but not good ones or the sun. During recording, the participants sat in a comfortable armchair in a dimmed room. After a practice trial of 12 stimuli, 150 trials were presented (50 no-go trials and 100 go trials). The stimuli were 600 ms in duration and were presented at randomized interstimulus intervals, which varied between 1500 ms and 3000 ms. The interval between the presentation of a target stimulus and the button press was measured as the reaction time (RT) for each response. Only responses given within the time limit of presentation, maximum 600 ms, were recorded. Two types of error could occur: omission errors, when participants failed to react in time upon presentation of target stimuli, and commission errors, when participants pressed the spacebar in a

no-go condition. The occurrence of the stimuli was automatically marked in the EEG by two different markers, indicating either a go or no-go condition.

ERP recording and analysis

Data on ERPs were recorded using the Neurofile EEG amplifier (IT-Med Co., France). Twenty-one sintered Ag/AgCl disk electrodes were attached to the scalp according to the international 10-20 system. Standard surface AgCl electrodes were affixed using conductive paste (Ten 20 paste, D.O. Weaver and Co., Aurora, United States.). Electrode impedance was kept below 5 kOhms. The reference was derived from coupled mastoids. Evoked potentials were sampled at 250 Hz and filtered with a bandpass of 0.01-102 Hz.

After recording, the EEG and markers were transferred to the BESA software package (Brain Electrical Source Analysis, MES Co., Munich, Germany) for further off-line analysis. The raw data were processed first with a high-pass filter with a border frequency of 30 Hz, and then using a line filter with a border frequency of 50 Hz. An average reference montage was used for the further analyses. The EEGs were corrected for eye movements using the algorithm of Gratton and Coles (Gratton et al., 1983). Movement artifacts were rejected automatically according to the following criteria: gradient increase $>75 \mu\text{V}$ per data point or amplitude $>120 \mu\text{V}$. For the remaining artifact-free trials, the EEG intervals of 100 ms before and after go and no-go trials were segmented for the further analyses. After baseline correction, visual evoked potentials (VEPs) were averaged. N2 peak was defined as the most negative point between 260 and 400 ms after the stimulus. MMN was defined as the amplitude derived by subtracting the N2s evoked by the go condition from those of the no-go condition. P300 was defined as the most positive point between 400 and 550 ms in the no-go condition. In order to investigate regional effects on VEP amplitudes, averaged VEP curves were grouped into three areas as described by Wessa et al. (2006) and Bender et al. (2005). Channels were grouped into three cortical areas (frontal: F3-Fz-F4-F7-F8, central: C3-Cz-C4; parietal: P3-Pz-P4).

In order to detect TCI, IEDs were identified and marked in the EEG by an experienced neurophysiologist. When an IED occurred during the period between the presentation of the stimulus and the response, the response was defined as a response with IED. If no IED occurred in this period, the response was considered to be a response without IED [see procedure used by González-Garrido et al (2000)]. The association of an error with the IED was defined as TCI (Aarts et al., 1984).

Statistical analysis

Statistical analysis was carried out using SPSS 18.0 for Windows (SPSS Inc., Chicago). All data were normally distributed (Kolmogoroff-Smirnoff test) and characterized by homogeneous variances (F-test). Neuro-

psychological and behavioral performances, as well as the ERP parameters, MMN and P300, of the three groups were compared by separate analyses of variance (ANOVAs). Neuropsychological variables were analyzed using ANOVA with the between-subject factor *Group* (children with IEDs and normal intelligence vs children with IEDs and intellectual disabilities vs healthy participants). Statistical analysis of ERP components followed a multifactorial design with a within-subject factor *Area* (frontal vs central vs parietal) and a between-subject factor *Group*. Post-hoc analyses were carried out using Scheffe tests and t-tests for independent samples. The significance level was kept at $p < 0.05$. Because of the exploratory nature of the study, no Bonferroni alpha adjustment was performed.

Each EEG recording was analyzed to look for associations between errors and the occurrence of IEDs. Statistical comparison of behavioral data (RTs, omission errors, commission errors) in the go/no-go condition in relation to the presence or absence of IEDs in the EEG was done for each patient group by two-tailed t-tests for paired samples. Separate, 2 x 2 contingency tables were drawn up showing the incidence of correct and incorrect trials with and without epileptiform activity. χ^2 was calculated and compared to the critical determinate for each contingency table with a definitive association.

Results

Patients

Overall, nineteen patients with focal epileptiform discharges were studied. They were divided into two groups. Nine children (3 males and 6 females) with focal epileptiform abnormalities and normal IQ were included in Group 1; ten patients (7 males and 3 females) with focal IEDs and low IQ (< 85) were included in Group 2. The mean age of the patients was 154 (SD \pm 46) months in Group 1 and 147 (SD \pm 37) months in Group 2. The mean number of seizures in the last month prior to the study was 22.63 (SD \pm 63.59) in the patients in Group 1 and 5.60 (SD \pm 13.17) in those in Group 2. The mean number of antiepileptic drugs used per day was 1.11 (SD \pm 0.93) in Group 1 and 1.30 (SD \pm 0.675) in Group 2. In Group 1, four patients were diagnosed with idiopathic focal epilepsy, one with cryptogenic focal epilepsy, and three with symptomatic focal epilepsy; one child had focal epileptiform abnormalities without a diagnosis of epilepsy. In Group 2, two patients were diagnosed with cryptogenic focal epilepsy, and seven with symptomatic focal epilepsy; one patient was diagnosed with generalized epilepsy with focal epileptiform discharges in EEG. The clinical and demographic data are presented in more detail in table I.

Neuropsychological data

Table II presents the neuropsychological data recorded in the two patient groups. ANOVA revealed signifi-

cant group differences in TMT A ($F(2)=19.166$, $p<0.001$) and TMT B ($F(2)=5.086$, $p=0.013$), Luria acquisition ($F(2)=10.197$, $p<0.001$), Luria immediate recall ($F(2)=11.804$, $p<0.001$), and Luria delayed recall ($F(2)=5.246$, $p=0.011$).

The post-hoc tests provided evidence of poorer performances on all neuropsychological tests in the children with IEDs and intellectual disabilities compared with the healthy children (TMT A: mean difference=25.67, $p<0.001$; TMT B: mean difference=59.89, $p=0.016$; Luria acquisition: mean difference=-21.07, $p=0.001$; Luria immediate recall: mean difference=-2.97, $p<0.001$; Luria delayed recall: mean difference=-1.67, $p=0.011$). As expected, the patients in Group 2 (epilepsy and low IQ) demonstrated longer performance times on TMT A and B and were able to learn and remember fewer words on the Luria memory test for words.

There were no significant differences in performance between the healthy participants and the children with IEDs and normal intelligence, either on TMT A (mean difference=5.58, $p=0.42$) and B (mean difference=1.16, $p=0.942$) or on Luria acquisition (mean difference=-3.42, $p=0.79$), immediate recall (mean difference=-0.792, $p=0.50$) and delayed recall (mean difference=-0.60, $p=0.54$).

The results of the CBCL showed significant differences in global performance ($F(2)=5.20$; $p=0.01$), internalization problems ($F(2)=4.19$, $p=0.03$), and social competence ($F(2)=10.51$, $p<0.001$). The children in both patient groups showed more behavioral problems [global score: mean difference (group 1)=9.94, $p=0.04$; mean difference (group 2)=9.80, $p=0.04$] and poorer social competence compared with the healthy children [mean difference (group 1)=-14.03, $p=0.02$; mean difference (group 2)=-20.49, $p<0.001$]. The Group 2 children also showed more internalizing behavior problems than did the healthy children (mean difference=11.27, $p=0.04$). The internalizing score showed no group differences.

Behavioral data and event-related potentials

Figure 1 shows the mean RTs and the percentages of omission and commission errors recorded in the three groups. The children with intellectual disabilities (Group

2) made more omission errors than did the children of the other groups ($F(2)= 5.276$, $p=0.011$). Post-hoc tests showed a significant difference in omission errors between the healthy children and the Group 2 children ($t(23)=-2.763$, $p=0.011$). Furthermore, there emerged a tendency towards a difference in mean RT between all three groups ($F(2)=1.982$, $p=0.1$). Descriptive data show that the children with IEDs and normal cognitive abilities had the longest mean RT compared with the other two groups. Post-hoc tests showed a tendency towards a prolonged RT in Group 1 and healthy children ($t(22)=-1.887$, $p=0.072$). There were no differences between the groups with regard to commission errors ($F(2)=0.779$, $p=0.459$) (Fig. 1).

Figure 2 illustrates the differences in mean MMN amplitude and mean P300 amplitude between the three groups. ANOVA revealed a significant *Group* effect for MMN ($F(2)=3.775$, $p=0.034$). Post-hoc tests showed a significant difference between the control group and the children with IEDs and intellectual disabilities (mean difference=-1.86, $p=0.038$), whereas no significant difference in MMN was found between Groups 1 and 2 (mean difference=-1.08, $p=0.33$) or Groups 2 and 3 (mean difference=0.78, $p=0.61$). There was also no significant main effect for *Area* and no significant *Group x Area* interaction.

Regarding P300, the main effect for *Area* was significant ($F(2)=7.83$, $p=0.001$). Moreover, there was a significant *Group x Area* interaction, reflecting further group differences in the topographical distribution of P300 ($F(4)=2.710$, $p=0.038$). In all the groups, the maximum of P300 was observed over parietal regions. The children from Group 1 showed the largest mean P300, followed by the healthy children and the Group 2 children. P300 was observed over the frontal regions only in healthy children and children from Group 2, whereas P300 over the central sites was observed only in healthy children and children from Group 1. Post-hoc tests revealed a tendency towards differences in the amplitude of P300 over frontal regions between healthy children and children with IEDs and normal cognitive abilities (mean difference=2.97, $p=0.09$) and between both the patient groups (mean difference=-3.33, $p=0.08$). Observable group differences in mean amplitude did not reach significance ($F(2)=1.56$, $p=0.22$).

Table II - Neuropsychological data in 19 patients with focal epileptiform discharges.

| Test | Control group Mean (SD) | Group 1 Mean (SD) | Group 2 Mean (SD) |
|------------------------------------|----------------------------|----------------------|----------------------|
| HAWIK-R III – short-form | 106.20 (±8.83) | 95.75 (±9.42) | 61.67 (±6.03) |
| Luria learning acquisition | 92.87 (±4.44) | 89.44 (±8.52) | 71.80 (±19.56) |
| Luria immediate recall | 6.67 (±1.20) | 5.87 (±1.81) | 3.70 (±1.64) |
| Luria delayed recall | 9.27 (±0.70) | 8.67 (±0.87) | 7.60 (±2.01) |
| TMT A (seconds) | 16.87 (±6.98) | 22.44 (±9.72) | 42.33 (±13.68) |
| TMT B (seconds) | 41.40 (±21.91) | 47.56 (±20.82) | 101.29 (±81.50) |
| CBCL Total (T-value) | 53.31 (±9.08) | 63.25 (±8.31) | 63.11 (±6.99) |
| CBCL internalizing scale (T-value) | 55.23 (±9.82) | 66.50 (±9.67) | 63.11 (±7.72) |
| CBCL externalizing scale (T-value) | 51.15 (±8.38) | 59.13 (±9.73) | 53.44 (±5.90) |

Abbreviations: HAWIK-R III=German version of the Wechsler Intelligence Scale for Children-Revised; TMT=Trail-Making Test; CBCL=Child Behavior Checklist

Behavioral data in relation to IEDs

Figure 3 illustrates the findings on RT and omission and commission errors in relation to the occurrence of IEDs. Overall, the mean number of trials with IEDs was $n = 526$ and the mean number of trials without IEDs was $n = 1382$. There was therefore an asymmetry in the number of trials towards trials without IEDs. Behavioral performance did not differ within the groups of children with and without IEDs in their EEG, or within the groups with normal intelligence. In the group of children with intellectual disabilities, there was only a tendency ($p=0.100$) towards more omission errors in trials with IEDs, whereas the mean RT and commis-

sion errors did not differ between trials with or without IEDs. We observed a significant association between error rate and IEDs in only one patient with intellectual disability using the Chi² test ($\text{Chi}^2=8.25, p<0.01$). In two patients with normal intellectual development, we only found a tendency towards more errors ($\text{Chi}^2=2.92, p<0.1$; $\text{Chi}^2=2.86, p<0.1$).

Discussion

In our study we found that epilepsy patients with IEDs and IQ within normal range did not differ from healthy children in neurophysiological functions and MMN

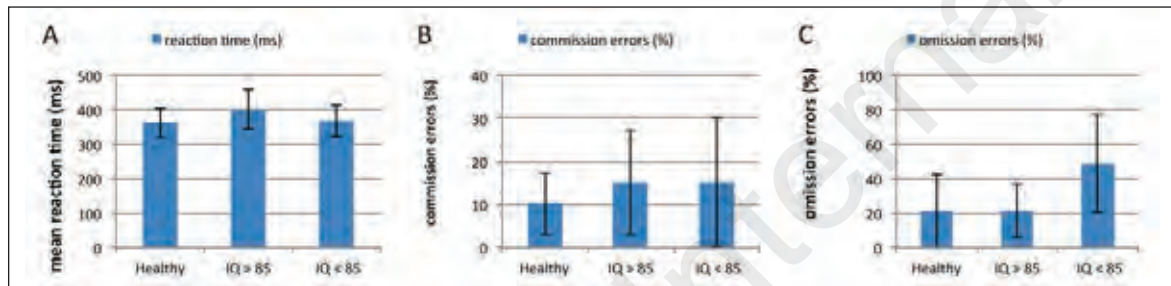


Figure 1 - Mean reaction time and percentage of omission and commission errors in healthy children and children with focal epileptiform discharges with/without learning disabilities.

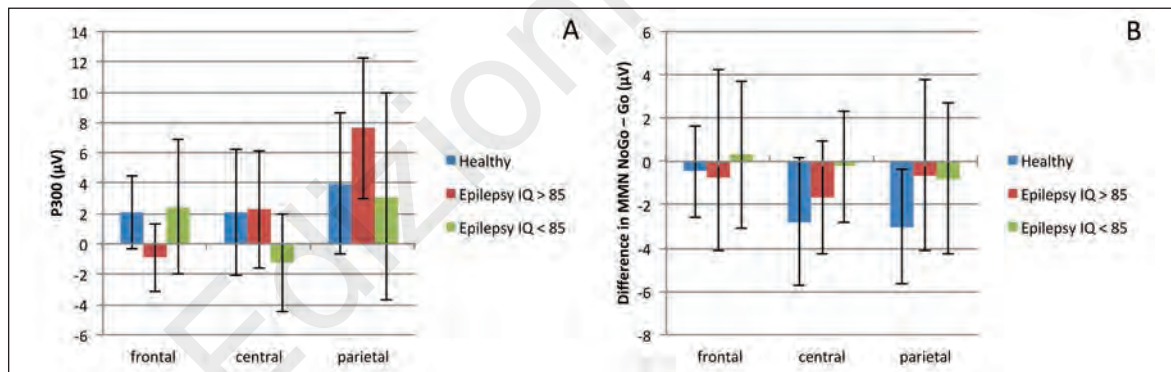


Figure 2 - Differences in mean MMN amplitude and mean P300 amplitude in frontal, central and parietal regions between epilepsy patients with/without learning disability and healthy controls.

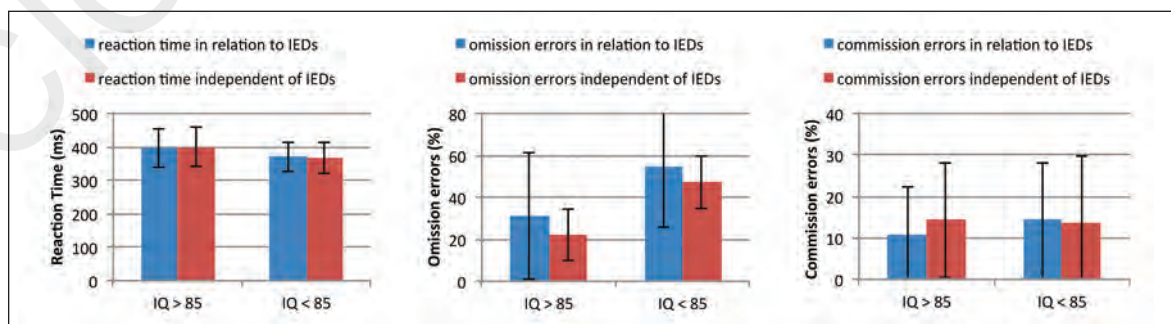


Figure 3 - Reaction times and omission and commission errors in relation to the occurrence of IEDs in epilepsy patients with low and normal IQ.

and P300 amplitudes. They did, however, show a tendency towards prolonged reactions in the selective attention task compared with the healthy children. In the group of patients with intellectual disabilities we found a tendency to commit more omission errors in go/no-go tasks in the presence of IEDs. However, the mean RT and mean number of commission errors did not differ between trials with or without IEDs. We demonstrated that children with intellectual disabilities and IEDs show inferior performances in verbal learning and memory, cognitive flexibility and selective attention, and low amplitudes of MMN and P300 compared with epilepsy patients with normal IQ and healthy children.

Cognitive impairment is a frequent secondary consequence of epilepsy in children (Aldenkamp et al., 1990a,b; Dodrill and Wilensky, 1992; Aldenkamp et al., 1995), however, the exact cause of cognitive impairment in epilepsy is still poorly understood. The question of whether the cognitive impairment in epilepsy patients is caused by the epilepsy syndrome itself, epileptic seizures or IEDs remains to be answered (Aldenkamp and Arends, 2004). Numerous studies have set out to identify a possible contribution of IEDs to cognitive and behavioral problems in epileptic children (e.g. Fastenau et al., 2009). Two hypotheses had been proposed. The first theory is that each IED induces a transient inhibition of brain networks (Aarts et al., 1984), while the second proposes more long-lasting effects of IEDs on brain functioning and plasticity (Van Bogaert et al., 2012). Previous studies have demonstrated that epileptiform EEG discharges might have an additional and independent effect, but that this effect is mild and limited to transient mechanistic cognitive processes (alertness, mental speed) (Aldenkamp and Arends, 2004). Only in exceptional cases are epileptiform EEG discharges the dominant factor explaining the cognitive impairment (Aldenkamp and Arends, 2004). It has previously been reported that children with epilepsy, compared with normal control children, show significant slowing of RTs and inattention during the execution of psychological tasks (González-Garrido et al., 2000; Mitchell et al., 1992).

It has been shown that a substantial number of children with benign epilepsy with centrotemporal spikes present with heterogeneous cognitive deficits affecting language and memory functions that are associated with the intensity of interictal spiking and evolve towards recovery with EEG normalization (Baglietto et al., 2001; Deonna et al., 2000; Massa et al., 2001; Metz-Lutz et al., 1999; Nicolai et al., 2007). Binnie and Marston (1984) also detected TCI in the majority of the patients in their study on benign childhood epilepsy with Rolandic spikes. EEG-fMRI performed in a child with continuous spikes and waves during slow sleep disclosed a combination of activation in the presumed epileptogenic zone and extensive deactivation in the lateral and medial frontoparietal cortices and posterior cingulate gyrus, which was interpreted as reflecting an impact of IEDs on normal brain function leading to neuropsychological regression (De Tiège et al., 2007).

However, further behavioral studies aiming to identify TCI in focal epilepsies failed to replicate this TCI phenomenon in a large majority of patients and suggested that the effects of paroxysmal epileptic activity may accumulate over time and consequently affect the more stable aspects of cognitive function, such as educational achievement (Aldenkamp and Arends, 2004). Early reports have shown the type of discharge to be an important determinant of TCI, which may be more frequently detected during generalized, 3/s spike-and-wave discharges of at least 3-s duration than during focal IEDs (Binnie, 2003; Kooi and Hovey, 1957; Davidoff and Johnson, 1964; Goode et al., 1970; Mirsky and Vanburen, 1965; Browne et al., 1974; Schwab, 1941). Indeed, focal and generalized epileptiform discharges may differently influence neuronal networks responsible for cognitive abilities. It has been suggested that disruption of the resting state activity in the default mode network (DMN) by pathological processes (e.g. those that give rise to spikes) may be related to alterations in cognitive function, and this may be a mechanism underlying cognitive deficits in epilepsy (Gotman et al., 2005). The DMN constitutes a necessary and favorable neurometabolic environment for cognitive functions, represents a physiological baseline for processes of attention and working memory, and supports the dynamic integration of cognitive and emotional processing (Raichle and Mintun, 2006). Abnormal activity in the DMN and disrupted connectivity between the structures involved may influence task performance and contribute to the pathogenesis of neuropsychiatric disorders such as attention-deficit hyperactivity disorder, Alzheimer's disease, autism, schizophrenia and depression (Eichele et al., 2008; Broyd et al., 2009). Moreover, altered activity in the DMN has been associated with fluctuations and disturbance of consciousness (Boly et al., 2008). As revealed by functional MRI, decreases in the blood oxygenation level-dependent signal in the precuneus, retrosplenial cortex, and parietal and anterior medial frontal cortex (regions of the DMN) were consistently found in patients with primary and secondary generalized epileptiform discharges, such as absence seizures, as well as in participants with continuous spikes and waves during slow sleep (Gotman et al., 2005; Aghakhani et al., 2004; Hamandi et al., 2006; Moeller et al., 2008a,b; Siniatchkin et al., 2010). In group analysis, an influence of IEDs on activity in the DMN was found only in patients with temporal lobe epilepsy (Laufs et al., 2007). No other types of focal epilepsy were associated with consistent disruption of activity in the DMN (Jacobs et al., 2007, 2009). It is likely that generalized (and not focal) paroxysms are more able than focal IEDs to disturb resting state activity. This may explain why the focal IEDs in our study did not substantially influence cognitive abilities. However, disruption of the DMN is not the only mechanism leading to TCI. In a recent case report, we demonstrated that long, 3/s spike-and-wave discharges, which are very characteristic of absence seizures, did not cause cognitive impairment but were able to decrease activity in the DMN (Moeller

et al., 2010). Moeller et al. (2010) demonstrated that even generalized discharges are not always associated with cognitive deficits and that there could be another factor which may differentiate between discharges with TCI and IEDs without cognitive impairment. However, this factor is still unknown.

One possible approach in order to characterize this factor is to investigate the direct correlation between behavioral performance, psychophysiological data, timing of IED occurrence in patients with different IEDs (focal and generalized), and different pathologies. However, very few studies have thus far attempted to do this. In our study, behavioral performance was not found to depend on the temporal relationship with IEDs in the group of children with IEDs and normal intelligence. Possible explanations for this are the dependence of the task on the frontal circuits together with the very few patients found to have frontal discharges, and the brevity of the IEDs. Moreover, we cannot exclude an influence of the low statistical power on the negative results of this study, and a type II statistical error. Indeed, the groups of patients in our study were small. Given the small to medium effect sizes obtained in the comparisons done and the $p < 0.05$ significance level adopted, the groups of patients should have numbered 25 or more. Given this limitation, the results of the study have to be interpreted with caution.

In the group of children with intellectual disabilities, there emerged a tendency ($p = 0.100$) towards more IED-related omission errors, whereas the mean reaction time and commission errors did not differ between trials with or without IEDs. Patients with IEDs and intellectual disabilities also had smaller MMN values than healthy children and tended to show TCI characterized by inferior attention performance showing a temporal relationship with IEDs. It is likely that the cognitive deficits in patients with intellectual disability are related more to a common pathogenetic pathway responsible for both epilepsy and cognitive status than to each particular IED or to the number of seizures (lower in Group 2 than in Group 1). This notion may be supported by the fact that changes (primarily, omission errors) observed in this study are not specific for epilepsy and IEDs, but appear to be characteristic of intellectual disabilities. For example, Eliason et al. (1987) investigated 30 children with intellectual disability and healthy controls on a computerized test of attentional skills. Similar to the results of our study, they showed that the group of children with intellectual disabilities made more omission errors, but did not differ from controls on commission errors. The results were interpreted from a signal detection perspective and it was suggested that the intellectual disability group showed inefficient allocation of processing resources rather than an intentional deficit. Moreover, Buchmann et al. (2011) demonstrated that intellectual disability is an important moderator variable determining success in go/no-go tasks. Only patients with attention deficit hyperactivity disorder and intellectual disability demonstrated both neuropsychological deficits and low amplitude of P300 (Buchmann et al., 2011), similarly to the results of our study.

The relationship between IEDs and task errors was not statistically significant, which, as mentioned, may be explained by the brevity of the IEDs or by the fact that the task depended on frontal circuits and only a small group of patients had frontal epileptiform discharges; indeed, it should be considered that TCI is not necessarily a consequence of a general impairment of attention but can reflect disruption of specific psychological functions located in the region or regions where the epileptiform discharges arise. The selective nature of the impairment also raises the possibility that when TCI was not demonstrable by the present tests, the discharges involved structures different from those tested by the go/no-go task. The possible effects of such discharges, including TCI, might have been better detected by other tests (Aarts et al., 1984).

Additional evidence for these hypotheses may be derived from the P300 results. The late ERP component, P300, is a well-established parameter of cortical information processing which is considered to reflect information updating (Mäntysalo, 1987). The amplitude of P300 is related to the probability of stimulus occurrence and the effort made by a person to manage a task (Salisbury et al., 2004). We observed group differences in the amplitude of P300. In all the groups, the maximum P300 amplitude was observed over parietal regions, while the largest mean P300 amplitude was observed in the children from Group 1, followed by the group of healthy children. The children from Group 2 had the smallest mean P300 amplitude. Recent years have seen numerous investigations of ERPs in patients with epilepsy (Fukai et al., 1990; Zgorzalewicz, 2006; Zgorzalewicz and Nowak, 2000; Chayasirisobhon et al., 2007; Bocquillon et al., 2009; Duncan et al., 2009), and different ERP studies have compared early and late components between patients with epilepsy and age-matched healthy participants, finding epilepsy patients to show: i) prolonged latency (Sun et al., 2007; Gokcay et al., 2006; Soyuer et al., 2006), ii) abnormal lateralization of components in relation to IEDs (Liasis et al., 2006; Rugg et al., 1991), and iii) abnormal amplitude of components, and absence of the same (Liasis et al., 2006; Grippo et al., 1996). Therefore, our study is in line with previous research which has revealed impaired information processing in patients with focal epilepsy, irrespective of epileptic activity in the EEG. Patients with IEDs and intellectual disability are characterized by altered information processing, which is more likely to be related to common pathological processes underlying epilepsy and cognitive deficits than to interictal epileptic activity. In conclusion, our study was not able to identify TCI in a group of patients with IEDs and normal IQ, however we detected a tendency towards omission errors related to IEDs in the group of patients with intellectual disabilities. We must state, however, that the size of the effect was modest, and we can only speculate that a direct impact of single IEDs on intellectual abilities of epilepsy patients may not be as significant as previously thought. Our findings would support the theory of a more long-lasting, cumulative effect of IEDs on

brain functioning, especially considering the abnormally high prevalence of IEDs in several developmental disorders, like specific language impairment, and of cognitive and behavioral deficits in epileptic children after excluding confounding factors such as underlying structural brain lesions, drug effects, or the occurrence of frequent or prolonged epileptic seizures (Van Bogaert et al., 2012). However, as the groups investigated were small and the power of the statistical analysis was insufficient, the conclusions we have drawn from our results have to be considered with caution and need further confirmation in studies with larger samples and more homogeneous groups of patients.

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