Is sleep-related consolidation impaired in focal idiopathic epilepsies of childhood? A pilot study

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1. Introduction

Children with epilepsy are at high risk of behavioral disturbances and cognitive deficits of multi-factorial origins [1, 2]. A way to isolate the possible effect of interictal epileptiform discharges (IED) on behavior and cognition from other contributive factors – overt seizures, underlying lesion, side effects of anti-epileptic drugs (AED) – is to study patients with focal idiopathic (genetic) epilepsy because (1) these epilepsies are not related to a structural lesion, (2) seizures are usually infrequent and of brief duration, making the use of AED often unnecessary, and (3) patients usually show on EEG very frequent IED, still present in the awake state but more abundant during non-rapid eye movement (NREM) sleep [3, 4].

Benign epilepsy with centro-temporal spikes (BECTS) and benign childhood epilepsy with occipital paroxysms (BCEOP) are two focal idiopathic epileptic syndromes of childhood called “benign” because outcome for seizures and cognition is usually favorable. However, a significant number of children with BECTS present heterogeneous cognitive deficits affecting language and memory functions that are associated with the intensity and the duration of IED, evolving to recovery with EEG normalization [5–9]. Since the publication of the International League Against Epilepsy (ILAE) classification of epileptic syndromes in 1989 [10], the group of focal idiopathic epilepsies has been enlarged to a subgroup of epileptic encephalopathies (EE) with continuous spike and waves during slow-wave sleep (CSWS), recall performance significantly decreased overnight, suggesting impairment in sleep-related declarative memory consolidation. Hydrocortisone treatment in one patient with EE with CSWS resulted in normalization of overnight memory performance, which was not the case in the other EE/CSWS patient whose sleep EEG was only partially improved. These preliminary results suggest that interictal epileptiform discharges in idiopathic focal epilepsies may disrupt the brain processes underlying sleep-related memory consolidation.

We investigated sleep-related declarative memory consolidation in four children with focal idiopathic epilepsy. In a population of healthy control children, recall of learned pairs of words was increased after a night of sleep, but not after a daytime wakefulness period. In children with epilepsy (1 case of benign epilepsy with centro-temporal spikes, 1 case of benign childhood epilepsy with occipital paroxysms, and 2 cases of epileptic encephalopathy (EE) with continuous spike and waves during slow-wave sleep, CSWS), recall performance significantly decreased overnight, suggesting impairment in sleep-related declarative memory consolidation. Hydrocortisone treatment in one patient with EE with CSWS resulted in normalization of overnight memory performance, which was not the case in the other EE/CSWS patient whose sleep EEG was only partially improved. These preliminary results suggest that interictal epileptiform discharges in idiopathic focal epilepsies may disrupt the brain processes underlying sleep-related memory consolidation.

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but also of distantly connected brain area [22,23]. As interictal spiking is most intense and diffuse during NREM sleep in those patients, it was hypothesized that this could interfere with the sleep-dependent physiological processes of neuronal plasticity supporting memory consolidation for recently learned information in children [24–26], thus contributing to impaired cognition [27–29]. In this study, we aimed first at characterizing sleep-related consolidation for a declarative memory task in a sample of 4 patients with different forms of focal idiopathic epilepsy, compared to an age-matched control population. In a second step, we investigated the potential role of IED on sleep-related memory consolidation impairment in comparing overnight memory performance in 2 of these 4 patients, diagnosed as EE with CSWS, before and after a corticosteroid trial aimed at reducing epileptic activity.

2. Subjects and methods

2.1. Patients

Four 7- to 10-year-old children with epilepsy (3 males; one female) and 24 healthy control children, and their parents, gave written informed consent to participate in this study approved by the Biomedical Ethics Committee of the Erasme Hospital-Université Libre de Bruxelles. Patients were diagnosed as focal idiopathic epilepsy (BECTS, patient 1; BCEOP, patient 2; and EE with CSWS, patients 3 and 4). Patients’ clinical and EEG data are summarized in Table 1. Patients’ declarative learning abilities were measured using the List Memory subtest (Learning of a 15 known Word List) of the Nepsy–French version [30]. All patients had declarative learning abilities within normality confidence limits (mean composite z score: patient 1: –0.33; patient 2: +0.33; patient 3: –1.33; patient 4: –1). Cerebral MRI was normal in all cases. None of the patients had pre- or perinatal problems. They were studied off-medication except session 3 that had been learned. Children were asked to recall orally the second word of the pair upon presentation of the first word (with no explicit time limit). If the answer was correct, the next pair appeared. If it was incorrect, feedback with the correct answer was given.

When all word-pair presentations had occurred, an immediate retrieval test was proposed to ensure that at least 60% of the material had been learned. Children were asked to recall the word pairs using the same cued recall procedure as during learning. Feedback was again provided in case of an incorrect answer. If the criterion was not reached, the unlearned word pairs were presented again in a second learning phase, after which all the word pairs were retested until 60% of the word pairs were learned.

Finally, a delayed retrieval testing occurred either after a sleep or a wakefulness interval of same duration, respectively. During this delayed retrieval session, subjects were asked again to recall the word pairs using the same cued recall procedure as during the immediate recall phase except that no criterion had to be reached and no feedback was given.

2.2. Experimental task

The declarative memory task was adapted from [24], using three parallel version lists composed of either 32 (for children aged 9–11 years) or 22 (for children aged 7 and 8 years) pairs of semantically associated French words (e.g. bath–shower) derived from a database [31]. All word pairs were standardized with respect to word frequency [no list effect for lexical frequency: F(1,193) = 0.206; p = 0.65 and no interaction between the factors list and lexical frequency: F(2,93) = 1.525; p = 0.22] and emotionality [no list effect of emotionality: F(1,93) = 2.67; p = 0.10; no interaction between the factors list and emotionality: F(2,93) = 0.327; p = 0.72]. The word pair at the beginning and at the end of the test served to buffer primacy and recency effects, and were not included in the analysis.

During the learning session, children were asked to memorize all the word pairs for further recall. The experimenter read out loud each word-pair of the list (1 word-pair/5 s). Each presentation was followed by a cued recall testing in which the child was asked to recall orally the second word of the pair upon presentation of the first word (with no explicit time limit). If the answer was correct, the next pair appeared. If it was incorrect, feedback with the correct answer was given.

In the sleep condition, learning occurred in the evening and retrieval after a night of sleep. In the wake condition, learning occurred in the morning and retrieval in the evening after daytime wakefulness.

Patients were tested in the sleep condition only at the sleep unit of Erasme Hospital under video-EEG control. Sleep EEG was analyzed qualitatively using a grading system, and quantitatively in calculating a spike–wave index (SWI) in stages 1 and 2 of NREM sleep, as previously published [18] (see Table 1). In patients 3 and 4, presenting EE with CSWS, the procedure was repeated 2 times using the 3

<table>
<thead>
<tr>
<th>Patient number/age (year)/sex</th>
<th>Epilepsy onset (year)</th>
<th>Cognitive profile</th>
<th>Previous AED trials</th>
<th>EEG wake (localization and SWI of IED)</th>
<th>EEG NREM sleep (grade and SWI of IED)</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 7, M</td>
<td>6</td>
<td>IQ = 100, ADHD</td>
<td>VPA, LEV</td>
<td>C4, O1; SWI = 18%</td>
<td>Grade 2; SWI = 40%</td>
<td>BECTS</td>
</tr>
<tr>
<td>2, 8, M</td>
<td>5</td>
<td>IQ = 87, ADHD</td>
<td>None</td>
<td>P4–02; SWI = 16%</td>
<td>Grade 1; SWI = 35%</td>
<td>BCEOP</td>
</tr>
<tr>
<td>3, 10, M</td>
<td>3</td>
<td>IQ = 77, SLI with periods of stagnation</td>
<td>VPA, TPM, PDN, ETS, LEV</td>
<td>CL, C4; SWI = 8%</td>
<td>Grade 4; SWI = 90%</td>
<td>EE with CSWS</td>
</tr>
<tr>
<td>4, 8, F</td>
<td>3</td>
<td>IQ = 66, global mental regression</td>
<td>VPA, LEV, ETS, CBZ, PDN</td>
<td>FP2, bursts of generalized spike–waves SWI = 19%</td>
<td>Grade 97%</td>
<td>EE with CSWS</td>
</tr>
</tbody>
</table>

M = male; F = female; IQ = intelligence quotient; ADHD = attention deficit hyperactivity disorder; SLI = specific language impairment; VPA = valproate; LEV = levetiracetam; TPM = topiramate; PDN = prednisolone; ETS = ethosuximide; CBZ = clobazam; grade and SWI = spike and waves index, according to [18].
different lists of paired words. The second session occurred without any treatment to ensure stability in performances and IED on EEG. The third session occurred one month after initiation of a treatment with hydrocortisone at the dose of 5 mg/kg/d. This procedure, specific to patients 3 and 4 who had a CSWS pattern, was used to test the hypothesis that IED during sleep contributed to the impairment in memory consolidation.

Control children were tested at home. Sleep-controls were tested 3 times at one-month intervals in the sleep condition (i.e., evening learning and immediate testing, morning delayed testing) using the 3 different lists of paired words. This was implemented to ensure that the possible modifications of performance across the 3 sessions in the 2 children who had CSWS were not due to a habituation bias to the task with repeated practice. Wake-controls were tested one time only in the wake condition (i.e., learning in the morning and immediate testing, and delayed testing in the evening).

Vigilance was tested at each retrieval (delayed vs. immediate) session using the Psychomotor Vigilance Task (PVT [32]) to ensure that the memory performance at delayed retrieval was not confounded by a circadian effect (i.e. morning vs. evening sessions) [33]. In this task, subjects had to press a button as fast as possible each time a digital counter started, with a random interval between the onsets of the clock. Dependent measures were reaction times and lapses.

3. Results

3.1. Sleep and awake-related memory consolidation in controls

Sleep-control and Wake-control groups had similar performance levels (in terms of number of correctly recalled items) at immediate retrieval (unpaired t-test; p = 0.80). An analysis of variance conducted on recall performance disclosed a significant interaction effect between retrieval time (delayed vs. immediate) and group (Sleep-control vs. Wake-control) factors (F(1,22) = 13.357; p = 0.001). Post-hoc analyses showed higher delayed than immediate recall after sleep (see Fig. 1; 87.91 (± 8.01 SD) vs. 79.3 (± 11.35 SD); p = 0.001) but not after wakefulness (73.33 (± 8.28 SD) vs. 74.99 (± 7.97 SD); p = 0.83), showing sleep-dependent memory consolidation for the learned word pairs in healthy children. A separate ANOVA was conducted across the 3 repeated sessions at one-month intervals in the Sleep-control group (see Table 2). Results consistently disclosed an overnight improvement with higher delayed than immediate recall (main effect F(1,11) = 34.278; p = 0.001), but no interaction with the session factor (F(2,22) = 0.008; p = 0.99), indicating stability in memory consolidation over the 3 sessions.

![Fig. 1. Retention of word pairs at immediate and delayed retrieval in Sleep-control and Wake-control groups. Children had a significantly higher delayed than immediate recall after sleep (Sleep-control) than after wakefulness (Wake-control).](image)

3.2. Effect of hydrocortisone on sleep EEG in EE with CSWS

Both patients presenting EE with CSWS showed at session 2 the same EEG abnormalities found at session 1 (see Table 1). At session 3, one month after the initiation of hydrocortisone, wake EEG was normalized in both patients. Sleep EEG was normalized in patient 3 (from SWI of 90%, grade 4, to SWI=0%) and markedly improved but not normalized in patient 4 (from SWI of 97%, grade 4, to SWI<50%, grade 1).

3.3. Sleep-related memory consolidation in patients

Performances of Sleep-control children and individual patients at each sleep session are summarized in Table 2. Crawford’s analyses were used in order to assess whether changes in performance from immediate to delayed retrieval sessions in each single patient were within normality confidence limits for immediate to delayed retrieval changes in Sleep-controls, separately for each session [34]. Contrary to Sleep-controls, all 4 patients showed significant lower recall at delayed than immediate retrieval at session 1 (p≤0.005). Similar results were obtained one month later (session 2) in patients 3 and 4 with EE with CSWS tested again in the same conditions (p<0.001). At session 3, one month after initiation of the hydrocortisone treatment, overnight change in performance was not significantly different from Sleep-control children (p>0.2) in patient 3 whose sleep EEG had normalized. This was not the case for patient 4, who showed improvement but not normalization of his EEG; in this patient, overnight delayed recall remained different from controls (p<0.001) in the way of diminished delayed recall.

3.4. Vigilance state in Sleep-controls and Wake-controls groups and patients at each retrieval session (delayed vs. immediate)

To ensure that improvement (Sleep-controls) or decrease in memory performance (patients) at delayed retrieval after sleep was not confounded by a circadian effect on the vigilance state, vigilance was tested at each retrieval (delayed vs. immediate) session using the PVT. An analysis of variance conducted on mean reactions times (RTs) did not disclose any significant main effect of the retrieval (delayed vs. immediate) (F(1,22) = 0.523; p = 0.47) and group (Sleep-controls vs. Wake-controls) (F(1,22) = 0.641; p = 0.431) factors and no interaction effect between retrieval (delayed vs. immediate) and group condition factors.

### Table 2

<table>
<thead>
<tr>
<th>Session</th>
<th>Immediate R</th>
<th>Delayed R</th>
<th>Immediate R</th>
<th>Delayed R</th>
<th>Immediate R</th>
<th>Delayed R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>79.30</td>
<td>(11.35)</td>
<td>87.91</td>
<td>(8.01)</td>
<td>78.60</td>
<td>(8.19)</td>
</tr>
<tr>
<td>Patient 1</td>
<td>66.66</td>
<td>56.66</td>
<td>0.003</td>
<td>Patient 2</td>
<td>100.00</td>
<td>70.00</td>
</tr>
<tr>
<td>p-value</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

R = retrieval; SD = standard deviation.
A = percentage of correct responses.
F = Crawford’s analysis assessing significance of immediate vs. delayed retrieval performance in each patient’s session as compared to changes in control group.

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(Sleep-controls vs. Wake-controls) factors ($F(1,22) = 0.074; p = 0.78$) at session 1.

Likewise, there were no significant interaction effects between retrieval (delayed vs. immediate) and session (session 1, session 2, session 3) factors in the Sleep-control population ($F(2,22) = 2.294; p = 0.12$).

Finally, Crawford’s analyses were used in order to assess whether changes in vigilance from immediate to delayed retrieval sessions in each single patient were within normality confidence limits for immediate to delayed retrieval changes in Sleep-controls, separately for each session [29]. Similarly to controls, all patients showed similar performance at the PVT at immediate and delayed retrieval at session 1 ($p > 0.05$). Similar results were obtained one month later (session 2) in patient 3 with EE with CSWS ($p = 0.199$) but not for patient 4 with EE with CSWS ($p = 0.029$). At session 3, one month after hydrocortisone administration, similarly to controls, all patients showed a similar performance at the PVT at immediate and delayed retrieval ($p > 0.05$). RTs are summarized in Table 3. These results indicate that vigilance parameters are not confounding factors in the evaluation of changes in sleep-related memory consolidation processes.

### 4. Discussion

Memory consolidation refers to a dynamic longitudinal time-dependent process converting labile memory traces into more permanent and/or enhanced forms [35]. These transformations are subtended by brain plasticity processes, i.e., the capacity of the brain to modify its structure and function over time [36]. Studies performed in adults suggest that both rapid eye movement (REM) and non-REM sleep stages participate in memory consolidation [37]. Some studies suggested that the different stages of sleep are involved in consolidation for specific memory systems, with consolidation of declarative memory mainly associated with slow-wave sleep and consolidation of procedural memories with REM sleep [38]. However, other studies have suggested that harmonious succession of all stages of sleep is mandatory for some memories to consolidate [39]. In children, the effect of sleep for consolidation of procedural memories is more disputed than for declarative memories [25,26,40]. Besides sleep-dependent consolidation, animal and human data indicate that post-training awake periods also may achieve the necessary conditions to consolidate novel memories in the nervous system [41,42], cognition- and consolidation-related cerebral activity being additionally modulated by complex interactions between circadian and homeostatic regulatory processes [33,43].

In our control children, delayed recall was improved after sleep but not wakefulness, confirming a role for sleep in declarative memory consolidation in children ([24–26]; see [44] for a review). Conversely and in line with our hypotheses, all four children with focal idiopathic epilepsy exhibited decreased memory retention after a night of sleep, suggesting that processes of memory consolidation are impaired in epilepsy. Suspecting that IED during sleep contribute to impair memory consolidation, we repeated the experiment in 2 children who had the CSWS pattern after 1-month hydrocortisone treatment and found that one of them, in whom sleep EEG was completely normalized under hydrocortisone treatment, showed normal consolidation of learning after sleep.

The mechanisms underlying impaired sleep-related memory consolidation in our patients with epilepsy remain hypothetical. Neuroimaging studies have shown delayed reactivation of learning-related activity during post-training sleep [45,46] and awake [42] periods, followed by transfer from early hippocampal activity toward delayed prefrontal [47] and basal ganglia [48] activity days to months later. At the cellular level, early reactivation during sleep of the cortical regions involved in a specific task learned when awake could be expressed, according to the synaptic homeostasis hypothesis, by an increase of synaptic strength [49] and by bursts of gamma oscillations [50]. We surmise that neuronal networks involved in memory consolidation processes are impaired in patients with epilepsy. A drug effect or a direct effect of epileptic seizures may be ruled out as our patients were studied off-medication in seizure-free periods. Impairment could be related to the occurrence of IED during slow-wave sleep, a sleep stage of crucial importance for consolidation of declarative memories [38,44], or from more irreversible neuronal changes related to the epileptic disease. Our data are in favor of the first hypothesis as memory consolidation was restored in that patient with CSWS whose EEG normalized in association with corticosteroids but not in the other patient whose EEG was improved but not normalized. A recent study analyzing the time course of the slope of EEG slow waves during the night in children with CSWS also supports a direct role of IED in showing the absence of the expected slope decrease, suggesting impaired synaptic homeostasis [51]. However, it should be kept in mind that, even after spontaneous or drug-induced EEG normalization, long-term cognitive sequelae are frequently found in EE with CSWS, suggesting irreversible brain damage [52]. Further studies are needed to confirm these data on a larger population of children with epilepsy, to evaluate the effects of treatments, and to approach the pathophysiology of impaired sleep-related memory consolidation in epilepsy.

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### Table 3

Reactions times at the Psychomotor Vigilance Task (PVT) before (immediate) and after (delayed) sleep in control group and patients.

<table>
<thead>
<tr>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate R</td>
<td>Delayed R</td>
<td>Immediate R</td>
</tr>
<tr>
<td>Sleep-controls (SD)$^a$</td>
<td>390.37 (39.27)</td>
<td>394.78 (48.65)</td>
</tr>
<tr>
<td>Wake-controls (SD)$^a$</td>
<td>393.45 (42.87)</td>
<td>391.31 (47.29)</td>
</tr>
<tr>
<td>Patient 1$^a$</td>
<td>373.67</td>
<td>0.0701</td>
</tr>
<tr>
<td>p-value$^ab$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2$^a$</td>
<td>438.83</td>
<td>447.83</td>
</tr>
<tr>
<td>p-value$^ab$</td>
<td>0.3817</td>
<td></td>
</tr>
<tr>
<td>Patient 3$^a$</td>
<td>432.54</td>
<td>443.46</td>
</tr>
<tr>
<td>p-value$^ab$</td>
<td>0.4389</td>
<td>0.1996</td>
</tr>
<tr>
<td>Patient 4$^a$</td>
<td>505.94</td>
<td>515.69</td>
</tr>
<tr>
<td>p-value$^ab$</td>
<td>0.17</td>
<td>0.0296</td>
</tr>
</tbody>
</table>

R = retrieval; SD = standard deviation.

$^a$ Reaction times.

$^b$ Crawford’s analysis assessing significance of immediate vs. delayed retrieval performance at the PVT in each patient’s session as compared to the control group.
None of the authors has any conflict of interest to disclose.

References