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

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ABSTRACT

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 the sleep EEG together with 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.

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) that associate severe global or task-specific cognitive regression and almost continuous and diffuse IED during slow-wave sleep. The existence of an idiopathic subgroup of EE with CSWS is supported by reported cases of evolution from BECTS to EE with CSWS, and by transitory cases of so-called "atypical rolandic epilepsy". This suggests that BECTS and EE with CSWS are at the opposite ends of a spectrum where the most frequent and diffuse IED during NREM sleep result in the more severe behavioral and cognitive deficits [11–17]. The impact of IED on cognition is recognized in EE with CSWS. Indeed, normalization of sleep EEG with drugs, particularly corticosteroids, results in considerable cognitive improvement, as well as normalization of epilepsy-related regional metabolic changes for glucose in these patients [18–21].

The pathophysiology of IED-induced cognitive deficits in patients with focal idiopathic epilepsy is not completely understood. The pathophysiology of IED-induced cognitive deterioration in EE with CSWS has been investigated using functional imaging techniques. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) and combination of electroencephalogram and functional magnetic resonance imaging (EEG-fMRI) studies suggested IED-induced dysfunction of brain areas involved by the epileptic discharges

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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 occurred under hydrocortisone treatment for patients 3 and 4. In all patients, the last seizure reported by the parents had occurred more than 1 year before the entry in the study. All patients were tested under video-EEG monitoring that started 6 h before the evening testing session and ended 30 min after the morning testing session. No clinical seizures occurred during these video-EEG sessions. However, in patient 4, occasional bursts of polymorphic generalized spike and waves of maximum 10 second duration, suggesting atypical absence seizures, occurred when awake at sessions 1 and 2.

Additionally, twenty-four control children recruited from public schools participated in this study. They had no known learning, language, or neurological problems, had a regular sleep–wake rhythm, and did not present any known sleep disorder. They were matched to patients for age and socioeconomic status. Two control groups of 12 children each were created: a Sleep-control group (mean age 9.3 ± 1.4 SD years; 8 boys), and a Wake-control group (mean age 9.9 ± 0.8 SD years, 7 boys).

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: $F(1,93) = 0.206$; $p = 0.65$ 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.

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.

2.3. Experimental procedure

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 1
Patient characteristics.

Patient number/age (year)/sex	Epilepsy onset (year)	Cognitive profile	Previous AED trials	EEG wake (localization and SWI of IED)	EEG NREM sleep (grade and SWI of IED)	Clinical diagnosis
1, 7, M	6	IQ = 100, ADHD	VPA, LEV	C4, O1 SWI = 18%	Grade 2 SWI = 40%	BECTS
2, 8, M	5	IQ = 87, ADHD	None	P4–O2 SWI = 16%	Grade 1 SWI = 35%	BCEOP
3, 10, M	3	IQ = 77, SLI with periods of stagnation	VPA, TPM, PDN, ETS, LEV	C3, C4 SWI = 8%	Grade 3 SWI = 90%	EE with CSWS
4, 8, F	3	IQ = 66, global mental regression	VPA, LEV, ETS, CBZ, PDN	FP2, bursts of generalized spike–waves SWI = 19%	Grade 4 SWI = 97%	EE with CSWS

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].