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Executive function and sleep problems in childhood epilepsy

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ABSTRACT

Pediatric epilepsy has been reported to be associated with both sleep problems and cognitive deficits. In turn, in healthy children, poorer sleep has been associated with deficits in cognitive functioning. We hypothesized that poor sleep in childhood epilepsy may contribute to cognitive deficits. Using actigraphy, we objectively measured the sleep of children with epilepsy alongside that of healthy controls. In contrast to previous reports, we did not find any differences in objectively measured sleep between children with epilepsy and healthy controls. However, significant deficits in cognitive functioning were demonstrated that were not explained by differences in sleep.

1. Introduction

The relationship between sleep and epilepsy is complicated and reciprocal [1]. Sleep promotes seizure activity in specific seizure types such as frontal lobe and rolandic epilepsy. Not all stages of sleep are proconvulsant, with epileptiform discharges occurring most commonly in non-REM sleep when the EEG demonstrates synchronized background activity [2]. Furthermore, the drowsy wake state induced by sleep deprivation increases interictal epileptiform activity [3], a fact exploited in diagnostic EEG studies. While the proconvulsant nature of non-REM sleep is the main source of sleep-related seizures, obstructive sleep apnea and its associated intermittent hypoxia may also be a factor in some patients. In adult epilepsy, obstructive sleep apnea is a common [4] and treatable risk factor for seizures [5]. The literature is contradictory in childhood. Some authors have suggested prevalence rates of sleep-disordered breathing (SDB) in childhood epilepsy of almost 40% by parental report [6], although questionnaires are notoriously unreliable screening tools in this condition [7]. Importantly, treatment of sleep disorders including SDB in childhood epilepsy may reduce seizure frequency [4,8].

Sleep has developmental importance for cortical plasticity and memory consolidation [9]. Experimental sleep restriction in school children has a direct effect on teacher-rated academic performance and children's attention [10]. We have previously demonstrated that objectively measured total sleep time predicts measures of executive function in typically developing school-aged children [11]. These findings are extended by a recent meta-analysis, which indicated that shorter sleep is associated with poorer cognitive functioning and school performance [12].

A number of studies have sought to characterize sleep in children with epilepsy and have demonstrated increased problems in a variety of sleep domains such as bedtime resistance and parasomnias [13–15], although the majority rely on subjective parental report of child sleep. We have previously reported that parental report of child sleep does not always correspond to actigraphy data. Quantitative aspects of child sleep may be better measured using actigraphy, whereas qualitative aspects are better captured via questionnaires [13]. As such, some caution needs to be exercised in interpreting these data, as previous studies in clinical samples have found inconsistencies when parental report of sleep is compared with objective methods, for example, in children with ADHD [14,15]. A few studies using polysomnography, the gold standard to objectively measure sleep, have demonstrated significant differences in the sleep architecture of children with epilepsy compared with controls, including less sleep time and a reduction in sleep efficiency [16–18]. However, polysomnographic studies are typically undertaken over a single night in a laboratory setting, compromising the ecological validity of the data that are gathered. An alternative method to objectively measure sleep is actigraphy. An actigraph is a

Abbreviations: AWMA, Automated Working Memory Assessment; CSHQ, Child Sleep Habits Questionnaire; EF, Executive function; NEPSYA, Developmental Neuropsychological Assessment 1; SDB, Sleep-disordered breathing; TEA-Ch, Test of Everyday Attention for Children.

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small, watch-like device that quantifies body movements during wake and sleep and is considered a reliable method of sleep estimation. Validation studies using polysomnography have demonstrated high sensitivity (>90%) of actigraphy to detect sleep in healthy adults [19]. A number of studies have used this methodology to measure child sleep [20–22].

Hence, while there is subjective evidence of sleep disturbance in childhood epilepsy from parental report, to date, objective evidence gathered in the child's natural sleep environment is lacking. The fact that children are reported to have both behavioral insomnias and other disparate sleep disorders, such as parasomnias or SDB, suggests that causation may be multifactorial. Psychosocial factors such as parental anxiety may play a part [23].

Children with epilepsy are at risk of a variety of neurocognitive deficits, particularly those thought to represent 'executive functions'. Significant deficits across a broad range of functions have been found in children with epilepsy aged 6–12 years and were contributing factors to poorer school performance [24].

A recent meta-analysis [12] examined the differing effect of sleep time and sleep efficiency on various aspects of cognitive functioning in children without epilepsy. Sleep time was positively associated with cognitive performance and, more specifically, with executive functioning but did not show a significant relationship with sustained attention and memory. Sleep efficiency was not significantly associated with any cognitive domains. The authors suggest that developmental neurobiology (e.g., brain immaturity) may be responsible for their findings, some of which differ from those typically found in the adult literature.

In summary, sleep problems are commonly reported in childhood epilepsy, are often overlooked in clinical practice [25], but may have a profound effect on children's daytime functioning and their epilepsy control. Despite a growing body of research using actigraphy with child populations and the advantage it offers of providing an objective measure of sleep in the child's usual sleep environment over a number of nights, we are not aware of any studies that have utilized this technology in pediatric epilepsy studies [26].

The aims of this study were as follows: 1) to objectively measure the sleep of children with epilepsy and compare with that of healthy school-aged children and 2) to ascertain if sleep problems were associated with impaired cognitive functioning. We hypothesized that children with epilepsy would have greater sleep problems and that this would be a risk factor for poorer cognitive functioning. Given the difficult and complex relationship between epilepsy and cognitive functioning, we restricted our sample to children with epilepsy of unknown etiology, attending mainstream schools and with no diagnosis of learning difficulties.

2. Methods

2.1. Participants

Children were eligible to take part if aged between 6 and 13 years with a diagnosis of epilepsy with no known cause, attending mainstream school, and not taking more than one antiepileptic drug. Children were identified by general pediatricians and pediatric neurologists in tertiary hospital settings. Invitations to participate were given or posted to eligible participants. Personal details were only passed to the research team if parents consented to receive further information. Sample size estimation was based on our data in healthy populations [27]. Using a global composite for neurocognitive measures and a total sleep disturbance score, where a median split categorized 50 children without epilepsy (6–12 years) into good and poor sleepers, we found that children in the poor sleep group had significantly worse global neurocognitive scores ($M = -1.58$, $SD = 4.48$) compared with children in the good sleep group ($M = +1.52$, $M = 4.14$) ($t = 2.58$, $p = .013$), effect size of .7. This existing cohort formed the control group [11]. For a similar effect size comparing this group with a group with epilepsy, we estimated a sample of 34 children. We aimed to recruit 40 children to allow for attrition and data loss due to equipment failure.

Children (cases and controls) were excluded if they had greater than mild learning difficulties or any significant visuoperceptual or motor disabilities likely to impair their physical ability to participate in neurocognitive testing. The cognitive tests were standardized for use with English-speaking children; therefore, English had to be the child's first or main language. Children were also excluded if they were being treated with more than one antiepileptic drug.

2.2. Materials

2.2.1. Actigraphy

Children wore actigraphs (Mini Motionloggers, Ambulatory Monitoring Inc.) on the nondominant wrist 24 h a day. It was requested that the device be worn for 7 days, although this was not always possible. These devices employ a piezoelectric beam sensor, which generates voltage each time the actigraph is moved. The actigraphs were initialized to record in zero-crossing mode, which records the number of times per epoch that the activity signal level crosses zero (or very near zero); hence, it is a measure of frequency of movement. The raw data were visually inspected to reject any epochs where the actigraph had been removed. A sleep diary was used to validate actigraphy sleep and wake times. Parents kept a record of the time the child went to bed, time of waking, and an estimate of the time it took the child to fall asleep. The activity data were analyzed using Action W2 software that employed an algorithm validated for use with children [28]. Actigraphy sleep measures of interest to this study were as follows:

1) Sleep time — total minutes scored as sleep during the sleep period. This measure excludes any periods of wakefulness.
2) Sleep efficiency — percentage of minutes scored as sleep during the sleep period (which is the time from sleep onset to sleep offset). This is a reflection of the proportion of time actually spent asleep during the sleep period and is considered the measure of sleep disturbance in this study.
3) Sleep period — total minutes from sleep onset to sleep offset and is a measure of time in bed from sleep onset.

2.2.2. Oximetry

To exclude the possibility that any deficits in executive function were the result of SDB-related hypoxia in children with epilepsy, overnight oxyhemoglobin saturation (SpO_2) was undertaken for one night using a Masimo Radical pulse oximeter (Masimo — Artemis, UK). Studies were performed at home in the child's familiar sleeping environment. Data analyses were performed with Download 2001 software (Stowood Scientific — Oxford, UK). Poor perfusion, low signal IQ, and movement artifact data were rejected. Any recordings comprising less than 5 h of artifact free data were rejected. This approach increased the likelihood that representative sleep cycles were sampled, in particular REM sleep episodes where obstructive events are most likely to occur, and is consistent with previously reported methods [29]. Analysis software yields a number of measures, but those of interest to this study were the following: mean SpO_2, minimum SpO_2 (SpO_2 nadir), number of desaturations > 4% per hour, and delta 12-s index (a measure of the variability in SpO_2). The latter is calculated as the absolute differences between successive 12-second intervals (sum of the absolute difference divided by the number of intervals measured).

For the purposes of this study, each child's oximetry reports were examined to determine the likelihood of SDB. Previously published data were used to obtain oximetry reference values [30]. Combining these data, we found that the thresholds for determination of SDB were as follows: two or more abnormal parameters = probable SDB diagnosis and one abnormal parameter (with the exception of abnormal nadir alone) = possible SDB diagnosis. The threshold oximetry values used to determine probable sleep-disordered breathing were the