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High-density electroencephalographic recordings during sleep in children with disorders of consciousness

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ABSTRACT

Introduction: A large number of studies have investigated neural correlates of consciousness in adults. However, knowledge about brain function in children with disorders of consciousness (DOC) is very limited. We suggest that EEG recordings during sleep are a promising approach. In healthy adults as well as in children, it has been shown that the activity of sleep slow waves (EEG spectral power 1–4.5 Hz), the primary characteristic of deep sleep, is dependent on use during previous wakefulness. Thus the regulation of slow wave activity (SWA) provides indirect insights into brain function during wakefulness.
Methods: In the present study, we investigated high-density EEG recordings during sleep in ten healthy children and in ten children with acquired brain injury, including five children with DOC and five children with acquired brain injury without DOC. We used the build-up of SWA to quantify SWA regulation.
Results: Children with DOC showed a global reduction in the SWA build-up when compared to both, healthy children and children with acquired brain injury without DOC. This reduction was most pronounced over parietal brain areas. Comparisons within the group of children with DOC revealed that the parietal SWA build-up was the lowest in patients showing poor outcome. Longitudinal measurements during the recovery period showed an increase in parietal SWA build-up from the first to the second sleep recording.
Conclusions: Our results suggest that the reduced parietal SWA regulation may represent a characteristic topographical marker for brain network dysfunction in children with DOC. In the future, the regulation of SWA might be used as a complementary assessment in adult and paediatric patients with DOC.

1. Introduction

After severe traumatic or non-traumatic brain injury surviving patients often show disorders of consciousness (DOC). Traditionally, DOC are categorized into coma, in which patients are completely unarousable and unresponsive, vegetative state (VS) defined by the re-emergence of spontaneous eye-openings and minimally conscious state (MCS), in which patients start to show non-reflexive responses to stimuli. In clinical practice, the gold standard for the diagnosis of DOC is the use of behavioural assessment scales like the Coma Recovery Scale — Revised (Giacino et al., 2004). Such assessments are very challenging as a lack of motor functions, receptive aphasia or fluctuations in arousal might lead to false negative results and consequently to a misdiagnosis (Giacino et al., 2009). Hence, much effort has focused on the development of complementary methods to detect neural correlates of consciousness. Functional neuroimaging and electrophysiological measurements in patients with DOC and healthy subjects have provided novel insights into neurobiological aspects of consciousness (for a review see Giacino et al., 2014). While functional MRI and PET may not always be available in the clinical setting, EEG measurements can easily be performed at the bedside. Another advantage of EEG is the possibility of long-duration measurements including sleep. Such long-duration measurements are especially convenient, when assessing patients with DOC, as these patients typically show frequent fluctuations in the level of arousal (Forgacs et al., 2014).

In patients with DOC the presence or absence of normal sleep features such as different sleep stages, sleep spindles and sleep slow waves has been associated with behavioural outcome and was hypothesized to reflect global functional brain integrity (Avantaggiato et al.,

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2015; Cheliout-Heraut et al., 2001; Cologan et al., 2013; de Biase et al., 2014; Landsness et al., 2011; Malinowska et al., 2013; Rossi Sebastiano et al., 2015). More specifically, sleep spindles and sleep slow waves are known to involve thalamocortical and corticocortical circuits (e.g., Riedner et al., 2011; Schabus et al., 2007) and thus, might be suitable markers for preserved thalamocortical and frontoparietal connectivity, which in turn has been related to consciousness (Laureys and Schiff, 2012).

While, in recent years, many complementary neurophysiological methods for the assessment of DOC have been investigated in adults, very few have been applied to children. In fact, the only studies reporting more than single cases, investigated the presence or absence of sleep stages and sleep spindles in children with DOC (Avantaggiato et al., 2015; Cheliout-Heraut et al., 2001). Compared to adult patients, paediatric patients hold the additional difficulty that differences in brain activity result not only from brain injury but also depend on brain maturation. During development, the brain undergoes critical anatomical and functional maturation processes, such as synaptic pruning and changes in functional network efficiency (e.g., de Bie et al., 2012; Huttenlocher and Dabholkar, 1997). Therefore, if applied in children, neurophysiological correlates of consciousness have to account for maturational differences.

EEG recordings during sleep might be a promising approach to investigate patients with DOC. It has been shown that the activity of sleep slow waves (EEG spectral power 1–4.5 Hz), the primary characteristic of deep sleep (Borbely and Achermann, 1999), is dependent on use during previous wakefulness. This use-dependent regulation of slow wave activity (SWA) is best seen on a local level. Studies investigating SWA across the scalp found local increases over brain areas that had been used extensively (Kattler et al., 1994) or were involved in a learning task, prior to sleep (Huber et al., 2004; Wilhelm et al., 2014). Accordingly, when the use of specific brain areas was prevented (i.e., arm immobilization) SWA was locally decreased (Huber et al., 2006).Thus, the local regulation of SWA might serve as an indirect measure of the activity level of specific brain areas during wakefulness. Interestingly, the scalp distribution of SWA also shows regional differences in the course of development (Kurth et al., 2010). From early childhood to late adolescence the location of maximal SWA undergoes a shift from posterior towards anterior brain regions. These changes were proposed to reflect cortical brain maturation.

In our study, we recorded sleep in ten children with acquired brain injury (five with DOC, five without DOC) using high-density EEG. We investigated the regulation of SWA across the scalp and compared children with DOC to both, healthy children and children with acquired brain injury without DOC. For such comparisons high-density EEG is especially convenient, as the high spatial resolution allows us to detect local alterations in brain activity (Lustenberger and Huber, 2012). We hypothesized that local differences in sleep SWA regulation might represent markers for brain network dysfunction in children with DOC. Longitudinal measurements in children with DOC could further support our hypothesis and might even provide prognostic information.

2. Materials and methods

2.1. Patients

Ten children with acquired brain injury due to traumatic brain injury or stroke participated in the study, including five children with DOC (mean age 10 years, SD 4.3 years, range 4–14 years of age, two girls and three boys) and five age- and gender-matched children with acquired brain injury without DOC (mean age 10 years, SD 4.3 years, range 4–14 years of age, two girls and three boys). Demographic and clinical characteristics of the patients with DOC are shown in Table 1. Patients without DOC are described in Supplementary Table 1. Medication is documented in Supplementary Tables 2 and 3. All patients were recruited from the Rehabilitation Centre for children and adolescents in Affoltern am Albis in Switzerland over a period of three years. The participation rate was high. During the recruitment period, six patients with DOC were admitted to the rehabilitation centre. Five of them participated in the study. Parents from all patients gave written informed consent. Patients with acquired brain injury without DOC gave verbal consent. The study was approved by the local ethics committee.

2.2. Healthy subjects

We selected ten age- and gender-matched healthy children (mean age 10 years, SD 4.1 years, range 4–14 years of age, four girls and six boys) from earlier studies (Kurth et al., 2010; Pugin et al., 2015).

2.3. Behavioural assessment

Patients with DOC were assessed by a trained neuropsychologist (ALM with clinical training at the Coma Science Group in Liège, Belgium) using the Coma Recovery Scale-Revised (Giacino et al., 2004). This scale provides scoring rules for observable behaviour during auditory, visual, motor, oromotor, communication and arousal testing and categorizes patients into VS, MCS and emergence from MCS. During the week of the sleep recording, the Coma Recovery Scale-Revised was performed daily. The diagnosis was based on the best result (Table 1).

Table 1
Demographic and clinical characteristics of patients with DOC.

Patient: age, gender	Aetiology·pathology	S1 time since insult	S1 CRS-R diagnosis (total score)	Time interval S1–S2	S2 CRS-R diagnosis (total score)
DOC 1: 4 y, F	Shiga-like toxin-producing *E. coli* haemolytic-uremic syndrome, stroke (bilateral anterior and middle cerebral artery including basal ganglia)	5 months	MCS (9)	16.1 months (S2 not analysed due to epileptic activity)	MCS (9)
DOC 2: 7 y, F	Tumour resection (hypothalamic pilocytic astrocytoma), stroke (right basal ganglia, right internal capsule, left pons)	1.1 years	MCS (16)	Deceased	Deceased
DOC 3: 12 y, M	Diabetic ketoacidosis, generalized cerebral oedema, brain herniation, stroke (bilateral basal ganglia, bilateral internal capsule, bilateral cerebral crus, bilateral thalamus)	4 months	Emergence from MCS (22)	1.5 months	Fully conscious
DOC 4: 13 y, M	Traumatic brain injury, right frontoparietal and frontotemporal subdural haematoma, contusion (right cerebellum), cerebral oedema (midbrain, basal ganglia), haemorrhage (corpus callosum, brain stem), shearing injuries (subcortical, basal ganglia)	4 months	MCS (11)	4 months	Emergence from MCS (18)
DOC 5: 14 y, M	Traumatic brain injury, multiple shearing injuries (right corpus callosum, right basal ganglia, right thalamus, right midbrain), bilateral frontopolar and right frontobasal contusions	3 months	MCS (13)	4.9 months	Fully conscious

S1 = sleep recording first night; S2 = sleep recording second night; CRS-R = Coma Recovery Scale Revised; F = female; and M = male.