Focal ESES as a selective focal brain dysfunction: a challenge for clinicians, an opportunity for cognitive neuroscientists

To the Editor,
We have read with great interest the report by Kuki et al. (Epileptic encephalopathy with continuous spikes and waves in the occipito-temporal region during slow-wave sleep in two patients with acquired Kanji dysgraphia. Epileptic Disord 2014;16(4):540-5) who describe in two young Japanese boys (10 and 11 years old, respectively), the occurrence of an “encephalopathy related to electrical status epilepticus during sleep” (ESES) with a very peculiar clinical picture. In fact, the encephalopathy was very selective indeed since, through the evolution of ESES, both patients retained normal social behaviour and intelligence, and whereas they had no problems reading and writing in the Kana syllabic language, they developed a selective dysgraphia for ideographic Kanji language learnt at school, which, however, could be correctly read and copied. These two written languages are processed through different pathways. The Kanji system is mediated by the posterior inferior temporal cortex (PITC), thalamus, and parietal lobe (Sakurai et al., 2000; Usui et al., 2005). In the patients of Kuki et al., Kanji dysgraphia partially recovered after the disappearance of status epilepticus during sleep (SES). Since functional neuroimaging and MEG dipole clustering of spike activity during ESES suggested a dysfunction in the left posterior inferior temporal lobe, the authors concluded that a very selective impairment, such as the kanji dysgraphia, “may occur due to an electrocortical dysfunction of the left posterior inferior temporal cortex (PITC) in children with ESES”.

According to the study of Dehaene and collaborators (Nakamura et al., 2005), the left PITC is activated when a Japanese person is requested to write in Kanji, which requires visualization in space of the complex characters of this language (Tokunaga et al., 1999; Nakamura et al., 2000). Furthermore, since “the left occipito-temporal region is activated by written not pronounced words in every person who can read” (Dehaene, 2007), we can attempt to extend this unique information reported by Kuki et al. to other non-Japanese cognitive acquisitions. Some evidence provided by brain imaging and electrophysiological recording studies in humans has demonstrated that the posterior ventral temporal cortex, including the PITC, is composed of a complex mosaic of functionally discrete columns that respond preferentially to faces, objects, and letters (Puce et al., 1996; Ishai et al., 1999; Dehaene et al., 2002). The dysfunction of a very restricted patch of cortex or even of a limited number of cortical columns could result in such a selective impairment of functions, which could be easily overlooked on clinical grounds. This may well be the case in ESES, particularly at the onset of this condition.

The pathophysiological mechanisms underlying the appearance of cognitive and behavioural disorders in ESES are still poorly elucidated. It has been proposed that epileptic EEG paroxysms may interfere with physiological functions, and possibly, with neuroplasticity processes involved in higher cortical functions (such as learning and memory) that occur during sleep (Tassini and Rubboli, 2006). Indeed, several studies support a role of sleep in neuroplastic remodelling of neural networks mediating cognitive performances and behaviour, particularly in children. Recent experiments in humans showed that a learning task performed during the day can trigger a local increment of slow wave activity (SWA) during sleep, in correspondence with the cortical regions that were involved in the performance of that task (Huber et al., 2004). This local increase in SWA may imply direct or indirect local plastic changes mediating learning processes and demonstrates a correlation between local SWA homeostasis during sleep and learning/cognitive performances related to the cortical areas where SWA homeostasis was modulated, as postulated by the “synaptic homeostasis hypothesis” (SHY), proposed by Tononi and Cirelli (2006). In the SHY, it is accepted that the synapses are strengthened during wakefulness and weakened or rebalanced during sleep through a process of synaptic downscaling. In other words, strengthening of synapses corresponds to the neuronal process of learning. Occurrence of synaptic downscaling can be indirectly assessed by measuring changes in the slope of EEG slow waves throughout overnight sleep (Vyazovskiy et al., 2009). According to this hypothesis, ESES may represent a model of the clinical effects of the disruption, caused by prolonged focal epileptic activity during sleep, of local SWA homeostatic processes involved in the local plastic changes associated with learning and/or other cognitive functions performed at the site of the epileptic paroxysms. Learning is a process during which multiplex cognitive inputs are acquired and stored in the brain, during which the synaptic strength increases in response to new information. The strengthening of neural synaptic connections is the basis of learning and memory. During the last years, it has become increasingly clear that synaptic plasticity is a prominent mechanism by which learning occurs and is stored. Learning induces changes in synaptic strength (Hebb, 1949). Synapses that are activated during the performance of a task undergo long-lasting synaptic changes allowing the memory trace to be established. Changes in synaptic strength correspond to significant improvements in learning performance (Huber et al., 2004). A critical stage of the learning process is synaptic downscaling, which is a process of synaptic pruning that occurs during sleep (Karst et al., 2008). Synaptic pruning occurs in the development of the brain and is an essential aspect of the consolidation of memory.

A fundamental question is whether synaptic pruning is affected in children with ESES. Presumably, the disrupted sleep of the children with ESES is an important risk factor for cognitive impairment. The pathophysiological consequences induced by a disruption in sleep may have significant repercussions on cognitive development. In the child, the selective impairment of cognitive and behavioral functions associated with ESES may reflect a delayed development of synaptic pruning. This may have important clinical implications and may influence the approach to the treatment of the condition. Sleep and neuroplasticity are tightly connected. Sleep acts as a homeostatic process that synchronizes the activity of neuronal networks. Sleep is also involved in the regulation of plasticity processes, which underlie memory consolidation (Tononi and Cirelli, 2006). Sleep deprivation has been shown to impair learning and memory consolidation (Sastre-Garau et al., 2009). Therefore, sleep deprivation may lead to altered synaptic plasticity and a decrease in hippocampal neurogenesis, which is important for learning and memory consolidation. It is possible that a disruption in sleep homeostatic processes may lead to altered synaptic plasticity and a decrease in neurogenesis, which may be associated with the cognitive impairment observed in children with ESES.

Moreover, in the caption to the figure provided by the authors, the term “Epileptic encephalopathy with continuous spikes and waves in the occipito-temporal region during sleep (ESES)” is not defined. ESES is a rare and complex epileptic syndrome that is characterized by continuous spikes and waves in the occipito-temporal region during sleep, with a typical clinical picture of altered consciousness, automatisms, and myoclonic movements. The pathophysiological mechanisms underlying ESES are still poorly understood, and further research is needed to better understand the clinical implications of this syndrome. The recognition of ESES as a distinct clinical entity may lead to improved diagnostic accuracy and better management strategies for these patients.
tic focus (Tassinari and Rubboli, 2006; Tassinari et al., 2012). Indeed, recently, Bölsterli et al. (2011, 2014) observed, in a cohort of children with ESES, no significant change in slow wave slope overnight at the site of the epileptic focus. In addition, spike wave density was correlated with the impairment of the overnight slope decrease. These findings led to the conclusion of a local impairment of the synaptic downscaling process, caused by prolonged focal spike wave activity during sleep, as the potential mechanism underlying the development of neuropsychological deficits in ESES, as previously postulated (Tassinari and Rubboli, 2006). Interestingly, these concepts provide a new approach in the evaluation of the relevance of paroxysmal activities during sleep, not only for ESES, but for a large population of children with significant activation of focal paroxysmal activity during sleep (Cantalupo et al., 2011).

In the children described by Kuki et al. (2014), recovery was achieved in a relatively short time, likely because of the early detection of the selective impairment of Kanji reading, leading to a prompt effective treatment of the selective impairment of cognitive functions. In this context, EEG and other functional data, as in the cases of Kuki et al., can be particularly helpful in identifying, at an early stage, which functional area(s) might likely be affected by a SES-induced impairment of local SWA homeostasis. In addition, it raises the issue of the need for appropriate neuropsychological testing, individually tailored to specific deficits and interpreted in the light of the neurophysiology and functional neuroimaging data (Filippini et al., 2013). Lastly, these data suggest that, even in individual cases, adequate neurophysiological examination (i.e. electrical and/or magnetic source imaging to localize the “functional lesion”), combined with meticulous neuropsychological evaluation, can be an indirect way to study the cortical network subserving specific cognitive functions.

References


