

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 electroclinical 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 function-

ally 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 (Tassinari 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 epilep-

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 SES. 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.

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