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Preview

Just a sound: A non-pharmacological treatment approach in epilepsy

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Benign epilepsy with centro-temporal spikes is typically not treated by antiepileptic drugs, but it leads to cognitive disfunctions. In this issue, Klinzing et al.[1] demonstrate that closed-loop auditory stimulation delivered after paroxysmal spikes reduces the total number of paroxysmal spikes.

Benign epilepsy with centro-temporal spikes (BECTS) or benign rolandic epilepsy is not as benign as the name suggests. It occurs in 3–13-year-old children with partial seizures circumscribed to centro-temporal region. BECTS typically occurs at the onset or at the end of sleep, (mostly stage 2 of NonREM episodes) in 3–13-year-old children. Pharmacological treatment of this epilepsy is rarely recommended and offered mainly to patients having seizures while they are awake. Because this form of epilepsy is age-dependent and it disappears at the adolescence, it is considered benign. However, a number of patients with BECTS develop cognitive deficits such as impaired attention[2] and declarative memory[3,4] and as a consequence, young patients display language deficits, lower ability in arithmetic calculations, and lower academic success.[4,5] Therefore, new treatment options for BECTS patients are needed.

Given multiple side effects, the use of systemically applied pharmacological antiepileptic drugs is not justified in BECTS. In a paper published in this issue of *Cell Reports Medicine*, Klinzing et al.[1] applied closed-loop brief pink noise auditory stimuli triggered after paroxysmal EEG spikes and were able to reduce the total number of paroxysmal spikes. The largest spike suppression was found when auditory stimuli were applied 1.5–3.5 s after a detected paroxysmal spike. The idea to use closed-loop auditory stimuli to influence brain oscillations and cognitive performance comes from a previous work by this group.[6] In that study, the authors detected sleep slow waves, applied auditory stimuli during UP states of the slow oscillation, and by doing that, they enhanced slow-oscillation rhythm and phase-coupled spindle activity, thereby enhancing declarative memory. The exact mechanisms of in-phase auditory stimulation affecting slow-wave and spindle activity remains unknown, but it is absolutely clear that such stimulation during sleep affects thalamocortical function, because slow-wave activity originates in the neocortex,[7] and although spindles are generated in the thalamus, sleep-slow-wave-dependent corticothalamic drive controls spindle activities including onset and termination of spindles.[8] Therefore, auditory stimulation during sleep affects thalamocortical function well beyond the auditory system.

How exactly paroxysmal spikes are generated in benign rolandic epilepsy remains unknown. Klinzing et al.[1] point to several studies providing indirect evidence that the thalamocortical system is involved. Because these spikes are recorded over the central and temporal cortical areas, it is absolutely clear that these cortical areas are implicated. Both central and temporal cortical areas form extensive bidirectional connections with the thalamus. Therefore, by any measure the thalamocortical system must be involved in the generation of centro-temporal spikes. A part of the superior temporal gyrus forms auditory cortex that receive strong auditory input from medial geniculate body, a specific auditory thalamic nucleus. Thus, auditory stimulation directly affects at least a part of the thalamocortical system involved in the generation of centro-temporal spikes, and pink noise stimuli can directly affect physiological or pathological processes developed in this system. It is not clear what structure is leading in the generation of paroxysmal spikes: the cortex or the thalamus? Ascending thalamocortical connectivity has well-organized tonotopic organization with strict borders, but cortical efferents affect first and higher order thalamic nuclei and other cortical areas. Because paroxysmal spikes are recorded by an EEG in the centro-temporal region, which is much larger than the auditory cortex, it is unlikely that auditory thalamus plays a leading role in the generation of BECTS, but other thalamic structures via the cortico-thalamo-cortical loop can. The thalamus plays a major role in the generation of sleep spindles. The amplitude, duration, and density of spindles are decreased in BECTS patients[9] pointing to an important role of the thalamus. The amplitude of any EEG signal, including spindles, depends on the synchrony of depolarization and/or hyperpolarization of cortical neurons contributing to the production of an EEG signal. Thus, a reduction in amplitude can depend on either a less synchronous drive from higher order thalamic nuclei, nuclei receiving driving inputs from cortex, or intracortical abnormalities. Because the cortex controls onset and termination of the spindles, a reduction of spindle density and duration likely depends on the cortico-thalamic drive. Klinzing et al.[1] report significantly lower spindle frequency in BECTS patients as well as negative correlation of paroxysmal spikes with spindles, pointing to shared mechanisms. Although the known properties of

fast spindles are fully congruent with known thalamic mechanisms, several properties of slow spindles can be easily explained by intracortical processes.[10] The fact that spindles in patients with BECTS are slower than in control subjects does not mean that spindles in these patients originate in the neocortex, but it means stronger neocortical control of spindles. Klinzing et al.[1] suggest that the thalamocortical system is likely involved in the generation of paroxysmal spikes. Available data from different studies confirm such a likelihood, but possibly the accents should be different, and a better term would be that the cortico-thalamo-cortical network mediates paroxysmal spikes in BECTS patients. A clear generator of this pathological activity can be identified with intracranial recordings for which development of animal models could help.

There are at least three important developments that could span from the study by Klinzing et al.[1] (1) As the authors acknowledged, a very small number of patients were tested; thus, a larger cohort of patients is needed to confirm that closed-loop auditory stimulation can reduce the number of paroxysmal spikes. (2) Is it only auditory stimulation that can efficiently reduce paroxysmal spikes? The postcentral gyrus is a part of cortex involved in BECTS generation and it is also the home of the primary somatosensory cortex. It might be possible that closed-loop somatosensory stimulation could produce the same effects on paroxysmal spike reduction. (3) It would be important to evaluate whether paroxysmal spike reduction achieved via closed-loop stimulation actually reduces cognitive deficits observed in BECTS patients.

In conclusion, the study by Klinzing et al.[1] provides a new, non-pharmacological, and easily accessible approach to treat BECTS patients, a condition which is typically not treated.

DECLARATION OF INTERESTS

The author declares no competing interests.

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