



Editorial

Mental activation to overcome electrically induced cortical hyperexcitability



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Human beings can suffer from epileptic seizures induced by abstract thinking (Geschwind and Sherwin, 1967, Senanayake, 1989). Meanwhile, more than half a century has passed since Penfield and Jasper shed light on the role of mental tasks in modulating epileptiform activity (Penfield and Jasper, 1954). In this issue of *Clinical Neurophysiology*, Lesser et al. demonstrate that cognitive activation, i.e., an arithmetic or spelling task (AST), results in diffuse brain changes which can lead to termination or modification of epileptiform activities, in particular afterdischarges (ADs) induced by electrical cortical stimulation (Lesser et al., 2019).

Functional brain mapping by electrical cortical stimulation plays a cardinal part in presurgical invasive evaluation using chronic subdural electrodes for epilepsy surgery. It is often preceded by recording multiple seizures to identify the seizure onset zone. Typically, the cortex is stimulated electrically via a pair of adjacently placed electrodes at a frequency of 50 Hz for a few seconds to intervene with the function related to the cortex beneath the electrodes (Ritaccio et al., 2018). Summary data serve as blueprints for decision-making by the epilepsy surgery team – whether they could or should resect the area, balancing between the resultant likelihood of seizure improvement and the risk of residual neurological deficit. The advent of the cortical stimulation technique has brought about ADs, epileptiform activity which occur during, or after the offset of, stimulation. ADs are in every occasion unwanted and stressful for all the people who are engaged in the testing, including electrophysiological technologists and doctors in charge, not to mention the patient. ADs can cause further testing to be postponed, and even evolve to epileptic seizures regardless of stimulus sites.

Although the underlying physiology of ADs remains elusive, ADs are considered to be artificially-induced localized epileptic activity associated with the mechanism of seizure generation. Two decades ago brief pulse stimulation (BPS) was discovered to be an effective method in terminating ADs (Lesser et al., 1999), which led epileptologists to explore methodologies to suppress interictal/ictal activity by electrical cortical stimulation (Kinoshita et al., 2005, Yamamoto et al., 2006). This line of research led to clinical application of electric stimulation devices for the treatment of epilepsy, including responsive neurostimulation currently in practical use in the United States (Geller et al., 2017, Morrell et al., 2011).

At the dawn of the corticogram and electric cortical stimulation in epilepsy surgery, there was a patient whose continuous slow spike-and-slow discharges were completely suppressed by solving arithmetical problems (Penfield and Jasper, 1954). Since then, mental activation by AST or simple questions has been commonly used to arrest ADs in clinical practice. Hitherto, however, the underlying mechanisms have remained unproven. Lesser et al. analyzed the electrocorticography before and after the cognitive tasks during functional brain mapping in patients with subdural electrodes (Lesser et al., 2019). Then the authors investigated the brain states related to AD abortion rates, using wavelet cross-coherence analysis. The main observations include that, regardless of the areas where ADs were induced, mean coherence in theta-to-beta frequency ranges significantly decreased throughout the brain when ADs were terminated. Functional MRI taken after resective surgery revealed that similar tasks activated several regions in the brain, indicating their participation in controlling mental effort, but also showed that these regions often did not correspond with where AST had stopped ADs. In the trials when ADs stopped, activity in the delta-to-theta frequency bands showed significantly higher coherence during baseline among channel pairs, compared to the findings when ADs continued. Additionally, the abortion rates of ADs by AST were comparable with those by BPS (57% vs. 59%). The present data should be an important beacon for managing the vexing ADs. The caveats are the impossibility to assess the direct effect of AST on ADs because control data without therapeutic intervention (AST or BPS) were unavailable, and the possibility of contamination of the raw electrocorticography by AD-related activities that can affect coherence.

The present study by Lesser et al. has raised three major issues to be further explored. Firstly, what kind of cognitive task is the most effective to influence a certain area where ADs are generated? Elucidation of mechanisms for emergence, evolution, and extinction of ADs needs to keep pace with the knowledge of the networks employed in each kind of task. Then it is necessary to optimize and tailor the list of efficient cognitive tasks for each patient. Secondly, are there patients who are at risk of unfavorable effects on ADs by cognitive tasks? Contrary to the intention to suppress ADs and hopefully spontaneous epileptic seizures, it is possible that a cognitive task can incite ADs to increase, considering similarity of ADs to interictal or ictal discharges. There are various types of

reflex epilepsies, whose seizures are induced by cognitive and praxis tasks that are more complicated than simple visual or tactile stimuli. Examples are calculation by abacus (Yamamoto et al., 1991), mahjong playing (Fukuma et al., 2016), and Lego® construction (Zylicz et al., 2013). Thirdly, how can we address the role of subcortical structures on occurrence and suppression of ADs? Stereotactic electrocorticography, which a growing number of institutes use in clinical practice, may expand our horizons on understanding the role of deep brain structures (Chassoux et al., 2018). Especially, the thalamus has been thought to orchestrate alpha/beta frequency oscillations in the human cortex (Hawasli et al., 2016, Lopes da Silva et al., 1980, Steriade et al., 1987). The cortical response to inputs from other areas may be reduced in some cortical areas when the power of low frequency background activity is diminished (Usami et al., 2019) possibly due to control by deep brain structures, which may themselves be vital network hubs. Based on this proposed brain physiology, it would be potentially effective to prohibit spread of detrimental input like ADs or interictal discharges by approaching the supposed hubs in thalamus or brainstem and transiently separating them from the normal network.

Cognitive task, which requires patients' cooperation and efforts, was equivalent to BPS, which uses mechanical and technological devices, in terminating ADs. It is very interesting that such a “human” way has attracted attention again in this era. It is very possible that the principle of mental activation will develop in the near future into an intrinsic neuromodulation therapy for epilepsy, using the human way of thinking to overcome both electrically induced cortical hyperexcitability and spontaneous epileptic seizures.

Declaration of Competing Interest

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