Clinical Neurophysiology

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--Manuscript Draft--

Manuscript Number:	
Article Type:	Editorial
Section/Category:	Epilepsy
Keywords:	
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Human way of thinking to overcome electrically induced cortical hyperexcitability

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Conflict of Interest

The Department of Epilepsy, Movement Disorders and Physiology, which KU belongs to, is an Industry-Academia Collaboration Course supported by a grant from Eisai Company, NIHON KOHDEN CORPORATION, Otsuka Pharmaceutical Co., and UCB Japan Co., Ltd. MK has nothing to disclose.

Human beings are thinking reeds, and as such 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 task in modulating epileptiform activity (Penfield and Jasper, 1954). In this issue of *Clinical Neurophysiology*, Lesser et al. demonstrated that cognitive activation, i.e., arithmetic or spelling task (AST), result in diffuse brain changes which can lead to termination or modification of epileptiform activities called as 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 seizure onset zone. Typically, the cortex is stimulated electrically via a pair of adjacently placed electrodes at a frequency of 50 Hz in a few seconds to intervene the function related to the cortex beneath the electrodes (Ritaccio et al., 2018). Summary data serve as blueprint for decision-making in epilepsy surgery team – whether they could or should resect the area, balancing between the resultant likelihood of the seizure improvement and the risk of residual neurological deficit. The advent of cortical stimulation technique has brought about AD, epileptiform activity which occurs during or after the offset of stimulation. ADs are in every occasion unwanted and stressful for all people who are engaged in the testing room, including electrophysiological technologists and doctors in charge, not to mention the patient. ADs 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 as artificially-induced localized epileptic seizures 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 successive epileptologists to explore for methodology to suppress interictal/ictal activity by electrical cortical stimulation (Kinoshita et al., 2005, Yamamoto et al., 2006). This line of research bore clinical application of electric stimulation devices for the tratment of epilepsy, i.e., responsive neurostimulation currently in practical use in the United States (Geller et al., 2017, Morrell and Group, 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 problem (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, their mechanisms have been unproved while their robust proof has remained scarce. 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 whether the brain states relate with abortion rates of ADs 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 during taken after resective surgery revealed that the similar tasks activated wide regions in the brain, indicating their participation in controlling mental effort. In the trials when ADs stopped, the low frequency bands around delta-to-theta also showed significantly higher coherence during baseline compared to those when ADs sustained. Additionally, the abortion rates of ADs by AST were comparable with that by BPS (57% vs. 59%). The present data should be an important beacon for managing the vexing ADs. The caveats are impossibility to assess the direct effect of AST on ADs because control data without therapeutic intervention (AST or BPS) were unavailable, and possible 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 revealed. 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 network employed in each kind of tasks. Then it is necessary to optimize and tailor the list of efficient cognitive tasks for each patient. Secondly, 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 assumable that a kind of cognitive task can incite ADs to overgrow, considering similarity of ADs to interictal or ictal discharges. There are various types of reflex epilepsies, whose seizures are induced by more complicated cognitive and praxis tasks 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 prove 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 structure (Chassoux et al., 2018). Especially, the thalamus has been thought to orchestrate the 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 input from the other areas may be reduced in some cortical areas when the power of the low frequency bands is diminished in the background (Usami et al., 2019) possibly under the control of the deep brain structure, constructing a vital part of engaged network hubs. Based on this proposed brain physiology, it would be effective to prohibit spread of detrimental input like ADs or interictal discharges by approaching the supposed hubs 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 such a “human” way has attracted attention again in this era. Given that human brain is the last to be deciphered, myriad seeds of the method should still lie hidden in the highly complicated matrix of the gray and white matter inside us. The principle of BPS was succeeded in production of the new technique of neuromodulation. Likewise, the principle of mental activation would achieve development of intrinsic neuromodulation therapy for epilepsy – by thinking through the human way of thinking to overcome electrically induced cortical hyperexcitability and spontaneous epileptic seizures in the near future.

Acknowledgement

This work is partially supported by JSPS KAKENHI 19K21210 to KU. We thank Dr. Kentaro Tamura, Department of Neurosurgery, Nara Medical University, for his kind assistance for literature search.

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