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Human way of thinking to overcome electrically induced cortical hyperexcitability

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Conflict of Interest

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

8 Functional brain mapping by electrical cortical stimulation plays a cardinal part in
9 presurgical invasive evaluation using chronic subdural electrodes for epilepsy surgery. It is often
10 preceded by recording multiple seizures to identify seizure onset zone. Typically, the cortex is
11 stimulated electrically via a pair of adjacently placed electrodes at a frequency of 50 Hz in a few
12 seconds to intervene the function related to the cortex beneath the electrodes (Ritaccio et al.,
13 2018). Summary data serve as blueprint for decision-making in epilepsy surgery team – whether
14 they could or should resect the area, balancing between the resultant likelihood of the seizure
15 improvement and the risk of residual neurological deficit. The advent of cortical stimulation
16 technique has brought about AD, epileptiform activity which occurs during or after the offset of
17 stimulation. ADs are in every occasion unwanted and stressful for all people who are engaged in
18 the testing room, including electrophysiological technologists and doctors in charge, not to

1 mention the patient. ADs cause further testing to be postponed and even evolve to epileptic
2 seizures regardless of stimulus sites.

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

11 At the dawn of the corticogram and electric cortical stimulation in epilepsy surgery,
12 there was a patient whose continuous slow spike-and-slow discharges were completely
13 suppressed by solving arithmetical problem (Penfield and Jasper, 1954). Since then, mental
14 activation by AST or simple questions has been commonly used to arrest ADs in clinical practice.
15 Hitherto, however, their mechanisms have been unproved while their robust proof has remained
16 scarce. Lesser et al. analyzed the electrocorticography before and after the cognitive tasks during
17 functional brain mapping in patients with subdural electrodes (Lesser et al., 2019). Then the
18 authors investigated whether the brain states relate with abortion rates of ADs using wavelet

1 cross-coherence analysis. The main observations include that, regardless of the areas where ADs
2 were induced, mean coherence in theta-to-beta frequency ranges significantly decreased
3 throughout the brain when ADs were terminated. Functional MRI during taken after resective
4 surgery revealed that the similar tasks activated wide regions in the brain, indicating their
5 participation in controlling mental effort. In the trials when ADs stopped, the low frequency
6 bands around delta-to-theta also showed significantly higher coherence during baseline
7 compared to those when ADs sustained. Additionally, the abortion rates of ADs by AST were
8 comparable with that by BPS (57% vs. 59%). The present data should be an important beacon for
9 managing the vexing ADs. The caveats are impossibility to assess the direct effect of AST on
10 ADs because control data without therapeutic intervention (AST or BPS) were unavailable, and
11 possible contamination of the raw electrocorticography by AD-related activities that can affect
12 coherence.

13 The present study by Lesser et al. has raised three major issues to be revealed. Firstly,
14 what kind of cognitive task is the most effective to influence a certain area where ADs are
15 generated? Elucidation of mechanisms for emergence, evolution, and extinction of ADs needs to
16 keep pace with the knowledge of network employed in each kind of tasks. Then it is necessary to
17 optimize and tailor the list of efficient cognitive tasks for each patient. Secondly, who are at risk
18 of unfavorable effects on ADs by cognitive tasks? Contrary to the intention to suppress ADs and

1 hopefully spontaneous epileptic seizures, it is assumable that a kind of cognitive task can incite
2 ADs to overgrow, considering similarity of ADs to interictal or ictal discharges. There are
3 various types of reflex epilepsies, whose seizures are induced by more complicated cognitive and
4 praxis tasks than simple visual or tactile stimuli. Examples are calculation by abacus (Yamamoto
5 et al., 1991), mahjong playing (Fukuma et al., 2016), and Lego[®] construction (Zylicz et al.,
6 2013). Thirdly, how can we prove the role of subcortical structures on occurrence and
7 suppression of ADs? Stereotactic electrocorticography, which a growing number of institutes use
8 in clinical practice, may expand our horizons on understanding the role of deep brain structure
9 (Chassoux et al., 2018). Especially, the thalamus has been thought to orchestrate the alpha/beta
10 frequency oscillations in the human cortex (Hawasli et al., 2016, Lopes da Silva et al., 1980,
11 Steriade et al., 1987). The cortical response to input from the other areas may be reduced in some
12 cortical areas when the power of the low frequency bands is diminished in the background
13 (Usami et al., 2019) possibly under the control of the deep brain structure, constructing a vital
14 part of engaged network hubs. Based on this proposed brain physiology, it would be effective to
15 prohibit spread of detrimental input like ADs or interictal discharges by approaching the
16 supposed hubs and transiently separating them from the normal network.

17 Cognitive task, which requires patients' cooperation and efforts, was equivalent to BPS,
18 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.

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