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AUTHOR(S):

Usami, Kiyohide

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Does simple stimulus elucidate complex sleep mystery?

Kiyohide Usami^{a,*}

^aDepartment of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan.
ukiyo@kuhp.kyoto-u.ac.jp

*To whom correspondence should be addressed.

Kiyohide Usami, MD, PhD

Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

Phone number: +81-75-751-3662

Fax number: +81-75-751-3663

E-mail: ukiyo@kuhp.kyoto-u.ac.jp

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Conflict of Interest

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1 Every morning human beings awake from an unmindful world, sometimes having had peculiar
2 experiences or probably having changed minutely from their previous selves. Why do livings
3 beings on earth sleep? What is the specific aspect of sleep in human beings? The mystery of
4 sleep has continued to attract people since ancient times. Researchers in the field of neuroscience
5 are no exception. Sleep per se and sleep-associated issues such as unconsciousness, memory
6 consolidation, and sleep-related epilepsy, which have been investigated by means of various
7 contemporary cutting-edge techniques, have remained unsolved (Bazil, 2019, Boly et al., 2013,
8 Diekelmann and Born, 2010).

9 Since around 1990, and especially early in the 21st century, single pulse electrical
10 stimulation (SPES) was introduced by researchers in multiple institutes across the world. SPES is
11 a simple technique to elicit responses at the cortices connected to the stimulus site possibly via
12 white matter (Matsumoto et al., 2017). Subsequently, we can analyze the induced responses
13 together with other variables such as the location of the response sites and areas with or without
14 epileptogenicity, to unveil brain connectivity (Entz et al., 2014, Lacruz et al., 2007, Matsumoto
15 et al., 2004, Wilson et al., 1990) and local epileptogenicity in the human cortex (Valentin et al.,
16 2005, Valentin et al., 2002, van 't Klooster et al., 2011), respectively. This unique perturbational
17 approach is limited to usage in patients who undergo invasive intracranial implantation. However,
18 it carries an advantage, in that, we can apply stimulation directly to the human cortex and look at

the responses from the rest of the implanted channels with high spatiotemporal resolution no matter what the patient's vigilance status is. Therefore, it was suitable to employ SPES for investigating sleep (Pigorini et al., 2015, Usami et al., 2015) across various brain areas.

In this line of research, to clarify the modulatory effect of sleep on cortical excitability, the study by Arbune et al. recorded cortico-cortical evoked responses, i.e., cortico-cortical evoked potentials (CCEPs) elicited by SPES during wakefulness and sleep stage N2, which are characterized by spindles and k-complexes (Arbune et al., 2019) in 25 patients with implanted stereo-EEG (SEEG). The authors focused on the amplitudes of the early components of the CCEPs (10-100 ms after stimulation). Then, they applied a graph-theory approach to the significant CCEPs to analyze the change in effective connectivity. They observed that sleep globally increased CCEP amplitudes with some variance between local and distant connections, and that frontal lobe connectivity was especially reinforced during sleep. The connectivity between the hippocampus and temporal neocortex increased in the non-epileptogenic areas during N2 sleep and some interhemispheric differences existed in the epileptogenic areas. CCEP amplitude is the most classical index to be analyzed, and some of their results are also in agreement with previous sleep studies (Pigorini et al., 2015, Usami et al., 2019, Usami et al., 2015). In part, their results can be explained by sampling bias in SEEG, which was exclusively done in clinical practice for patients. In this study, the electrodes of the left side were more

1 included than the right, and the hippocampus was possibly well investigated. These factors might
2 have emphasized statistical significance of the specific connections. However, their large dataset
3 and meticulous methodology (Donos et al., 2016) that excludes false-positive connectivity make
4 their results robust so that we can expand on constructive discussions.

5 First, what do increased amplitudes during sleep indicate? Evoked response in general is
6 believed to reflect synchronization of neurons. However, we should consider that the amplitude
7 is calculated relative to the baseline. Thus, the plausible interpretation is that sleep absolutely
8 depresses the baseline – probably through some biochemistry – to apparently show CCEP
9 amplitude increase during sleep. To clarify the true effect of sleep on the degree of neuronal
10 synchronization, it may be needed to also analyze absolute values such as neuronal firing rates.

11 In addition, the degree of CCEP change caused by sleep seemed to be smaller in the
12 epileptogenic zone than in the non-epileptogenic zone in this study (the mean differences of
13 sleep-wake responses were 4.6 μ V vs. 5.7 μ V), although large variability existed in the responses.
14 The seemingly counterintuitive result would be explained by the ceiling effect, which means that
15 CCEP is already large enough in the epileptogenic zone during wakefulness to attenuate the sleep
16 effect on CCEP augmentation. Second, from a clinical point of view, the predominance of sleep
17 modulatory effects on CCEPs at the frontal lobes would be vital to understand seizures of frontal
18 lobe epilepsy frequently occur during the non-rapid eye movement (REM) period (Herman et al.,

2001). Inherent nature of hypersynchrony in the frontal lobe may exist. Moreover, the physiology of the protective effect on seizures or interictal discharges during REM (Bazil, 2019), which were not analyzed in this article, and the characteristics of the other lobes (parietal, temporal, and occipital lobe) in terms of excitability need to be further explored in the future. Third, how the deep brain structure influences cortical network during sleep as well as the generation of CCEP itself remain unsolved (Matsumoto et al., 2017). It is possible that we have just scratched the surface by stimulating the cortex and focusing on the responses from the superficial layer. One of the important structures would be the thalamus (Gent et al., 2018). How could we reach the core that is a possible true conductor of the cortical symphony changed by sleep? Combining CCEPs with non-invasive techniques such as functional MRI or diffusion tractography imaging including deep brain structures could be an option.

We have been steadily accumulating data about sleep that deserve consideration as this study by Arbune et al., though sleep is not yet completely understood. To untangle the complicated mystery of sleep, we should think hard and maybe “sleep on it” (Hoffman and McNaughton, 2002), hoping to re-organize our way of thought.

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Kiyohide Usami^{a,*}

^aDepartment of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate

School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan.

ukiyo@kuhp.kyoto-u.ac.jp

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School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

Phone number: +81-75-751-3662

Fax number: +81-75-751-3663

E-mail: ukiyo@kuhp.kyoto-u.ac.jp