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Letter to the editor “Cerebral Metabolism and Sleep Homeostasis: A Comment on Vyazovskiy et al”

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We thank Dr. Feinberg and colleagues for their thoughtful comments on [25]. In that paper we found that, in awake mice, the global brain uptake of 2-deoxyglucose (2-DG) was higher if the animals had been previously awake than if they slept prior to sacrifice. Our data were consistent with a human study showing reduced cerebral blood flow after a night of sleep [4]. In attempting to interpret these findings, we argued that lower brain metabolism after sleep might result from decreased levels of synaptic activity. This interpretation was suggested by the synaptic homeostasis hypothesis of sleep function, according to which net synaptic strength increases during wakefulness and is renormalized during sleep [22,23]. Since synaptic activity is responsible for up to 75–80% of brain energy metabolism [1,2], changes in brain metabolism as a function of sleep/wake history might be expected.

Feinberg et al. did not comment on the empirical results of our mouse study or our interpretation of the findings. However, they emphasized that the human data in [4] may be confounded by sleep inertia. Moreover, another study in humans appears to be inconsistent with the prediction that brain metabolism may change as a function of sleep/wake history [5]. Finally, sleep deprivation studies indicate that brain metabolism decreases, rather than increases, with extended wakefulness [21,29]. We consider each point in turn.

While sleep inertia could indeed be a factor in [4], we think it unlikely for several reasons. First, EEG studies indicate that sleep inertia is a transient phenomenon that is maximal immediately after awakening and dissipates within ~ 20 min [12,20]. Since cerebral blood flow in [4] was measured *at least* 15 min after awakening in the morning, the results should not have been affected significantly by sleep inertia. Second, late sleep (close to the morning) is particularly rich of REM sleep, which is characterized by high, not low metabolic activity. Third, blood flow changes from sleep (REM or stage 2) to post-sleep waking were not homogeneous across brain regions. Therefore, reduced blood flow after waking up in the morning is not easily explained by “the persistence of the low CMR of sleep into the initial waking minutes”.

In the study by Buysse et al. [5], no differences in cerebral metabolic rates were found between morning and evening, whereas the synaptic homeostasis hypothesis [23] explicitly predicts that if net synaptic weight increases during waking, metabolic demand should be higher in the evening compared to the morning. Concerning this study [5], several methodological aspects

should be considered before taking the negative results at face value. Apart from great interindividual variability and low overall values for slow wave sleep, a major concern is that factors other than sleep/wake history, most importantly the behavioral state at the time of testing (see below), must be strictly controlled before strong conclusions can be drawn. In [5] the order of scans was not randomized (with potential effects due to the novelty of the procedure) and, in general, the subjects were more alert in the morning compared to the evening. Also, the morning scans were performed 2–4 hours after arousal, a period of waking possibly long enough to result in increased synaptic strength (and thus cerebral metabolism), at least in some subjects. Such a possibility is suggested by our recent observation that, at least in rats, just one hour of spontaneous waking is sufficient to significantly increase electrophysiological indices of synaptic strength [24]. As emphasized by Feinberg et al, studies aimed specifically at investigating the effects of previous wakefulness and sleep on metabolic variables are sorely needed.

Indeed, apart from the studies by Braun et al. [4] and Buysse et al. [5] in humans, and our own study in mice, very little is known about whether and how metabolic variables may differ before and after periods of sleep or waking. However, a few other studies are worth mentioning. In particular, Madsen et al. [18] showed that learning a difficult task is associated not only with an increase in aerobic glycolysis during task performance, which was expected, but that the glycolytic increase persisted for as long as investigators could record it (several hours). Unfortunately, we do not know whether such a persistent metabolic trace would be renormalised by sleep. A study by Boyle et al. [3] reports that cerebral blood flow, oxygen and, more markedly, glucose consumption, increase over a period of wakefulness, suggesting an increase in aerobic glycolysis during wakefulness. Importantly, glycolytic values were much reduced after the first 3 hours of sleep (which is usually rich in slow wave activity; SWA, 0.5–4.0 Hz), and did not change much in subsequent sleep [3]. In one subject who did not sleep, glycolytic values did not decrease. Again, such results need to be confirmed to establish whether sleep does indeed renormalize metabolic demand, for example with respect to glycolysis, or whether instead the passage of time may be enough. Also, it will be important to determine which cellular processes – pre- and postsynaptic activity, anabolic processes and so on – may mediate the increase in metabolic demand.

A key criticism by Feinberg et al. stands from the observation that, in several human studies, brain metabolism decreased after sleep deprivation (e.g, [21,29]). We are (and were) well aware of these findings. We add that a decrease in cerebral metabolic rates after prolonged waking is also found in rats deprived of sleep for several days [11]. Feinberg et al. argue that if the synaptic homeostasis hypothesis is correct, brain metabolism should increase, not decrease, after sleep deprivation. In fact, the hypothesis predicts that metabolic demand should increase with extended wakefulness, but not that brain metabolism would necessarily do so [23]. Specifically, we predicted that sleep deprivation may result in metabolic overload, which in turn could trigger compensatory responses such as reduced neuronal excitability and increased synaptic failure ([22,23]), which might paradoxically reduce metabolic rates.

In general then, when attempting to evaluate metabolic demand (as a reflection of synaptic efficacy), it is crucial to ensure that behavioural state be accurately controlled and that EEG activity be comparable. For example, during NREM sleep metabolic activity is inversely correlated with slow EEG activity [8,9,16], presumably because larger and more frequent slow waves are associated with longer and more frequent periods of neuronal silence [7,10,26]. In this respect, it should be mentioned that SWA and/or theta-activity (5–8 Hz) in the waking EEG increase during sleep deprivation in both humans and rodents [6,13,14,17,28]. The slowing of the wake EEG correlates with sleepiness and with the subsequent rebound of SWA in recovery sleep.

An intriguing possibility is that the slowing of the wake EEG with extended wakefulness may arise from an altered pattern of cortical neuronal firing. To test this possibility directly, we recently recorded multiunit activity (MUA) from the barrel cortex of freely behaving rats during sleep deprivation and recovery sleep. As shown in Figure 1A, we observed that neuronal firing rates during waking were consistently high at the beginning of sleep deprivation, but much less so as sleep pressure increased after several hours of continuous waking. In fact, sometimes during prolonged waking many units exhibited sudden, synchronous periods of silence. As a result, the overall pattern of neuronal activity in waking under high sleep pressure occasionally resembled more the burst firing typical of deep NREM sleep than the tonic firing observed during rested waking (Fig. 1A). Such changes in neuronal firing were associated with a relative predominance of slower frequencies in the waking EEG at the end of sleep deprivation. Thus, as shown in Figure 1B, the waking EEG power in the low frequencies (1–6 Hz) progressively increased across 4 hours of sleep deprivation, and so did the occurrence of periods of neuronal silence (>20 ms). Moreover, the two phenomena were positively correlated. Reduced metabolic rates after sleep deprivation [21,29], then, rather than demonstrating a decreased metabolic demand, may indicate neuronal “tiredness” that may be associated with performance decrements when neurons go “off-line.” That such off-line periods may be due to metabolic overload, of course, remains to be demonstrated.

Finally, Feinberg et al. suggest that the depletion of resources needed for synaptic activity during waking may be the reason why SWA increases during subsequent sleep. That may very well be the case, although it remains to be established whether a depletion of membrane lipids, glycogen, and/or proteins does indeed occur during wakefulness, and how such a depletion would result in increased SWA. The synaptic homeostasis hypothesis is already supported by both molecular and electrophysiological evidence indicating that a net increase in synaptic strength does indeed occur during wakefulness [24]. Moreover, the hypothesis suggests a precise mechanism by which increased synaptic potentiation would result in increased SWA. As indicated by computer models and confirmed by experimental studies in both rodents and humans, stronger cortico-cortical connections can lead to longer and more hyperpolarized neuronal down states and thus to slow oscillations of increased amplitude [10,15,19,23,27].

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Figure 1.

A. Representative example of the cortical electroencephalogram (EEG) from the right parietal area (referenced to the cerebellum) and neuronal multiunit activity (MUA) recorded simultaneously with a microwire array from the left barrel cortex in a Sprague-Dawley rat. The 4-second windows depict typical EEG and neuronal activity for wake before and after 4 hours of sleep deprivation (SD), and during subsequent recovery sleep (NREM). Each vertical bar represents a spike. Raster plots of spike activity are shown separately for five channels. Note that slow theta or delta waves in the EEG are associated with neuronal silent periods in both wake after sleep deprivation and in recovery sleep (arrows). B. Top panels: time course of mean spectral EEG power in waking (1.0–6.0 Hz) during 4 hours of sleep deprivation (% of 4-hour mean) and the number of the neuronal population silent periods defined as zero spiking activity for >20 ms (as % of the total number of silent periods of any duration). Bottom panel. The relationship between waking EEG power in the 1.0–6.0 Hz range and the number of neuronal silent periods in waking during 4 hours of sleep deprivation. Scatter plot represents mean values of the two variables computed over 15-min intervals (16 time points). The line depicts linear regression (Pearson correlation coefficient and the corresponding p-value are shown inside the panel).