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Cerebral Metabolism and Sleep Homeostasis: A Comment on Vyazovskiy et al

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Vyazovskiy et al [23] recently reported that an analysis of deoxyglucose uptake in mice supports the prediction that cerebral metabolic rate (CMR) increases across waking and is reduced by sleep. This prediction derives from Tononi and Cirelli's synaptic weight model [21] which holds that the neural activity of waking increases, as a saturating exponential, overall synaptic activity, the main determinant of CMR along with action potentials [18]. CMR should therefore increase rapidly across a normal waking day and be somewhat further increased by sleep deprivation. The model also holds that CMR is high at sleep onset and declines homeostatically ("downscales") across sleep, paralleling the kinetics of non-rapid eye movement (NREM) delta EEG. NREM delta increases with increasing waking duration and declines across sleep, a pattern that has been interpreted since 1974 [7] as reflecting the kinetics of sleep homeostatic recovery processes. Tononi and Cirelli explicitly apply Borbely's [3] mathematical model for delta homeostasis; it is on this basis that they predict that synaptic weight increases as a saturating exponential during waking and decreases exponentially across NREM periods.

In their analysis, Vyazovskiy et al used deoxyglucose data available from 3 groups of mice with different wake/sleep histories: All 3 groups had been kept awake for 6 h. CMR was significantly lower in the group allowed to sleep for ~2.5 h than in the group tested immediately after the 6 h waking period or in a second group kept awake for an additional 2 h. Vyazovskiy et al cautioned that their study was not a definitive test of the Tononi-Cirelli model because the numbers were small (8 or 9 mice/group), the data were originally collected for a different purpose, and sleep and waking were not monitored by EEG.

We strongly agree with Vyazovskiy et al that metabolic investigations of sleep will contribute importantly to determining its function. However, we note here that existing CMR data with the deoxyglucose method in animals and with PET in humans argue against the Tononi-Cirelli hypothesis. Moreover, these results point to an alternative model of sleep-CMR relations that seems intuitively more plausible.

In a human PET study of 10 subjects, Buysse et al [6] found virtually identical absolute CMR levels in waking during the morning and in waking during the evening after a normal day; this result is squarely inconsistent with the Tononi-Cirelli proposition that CMR increases across the day at a saturating exponential rate. Sleep deprivation studies in humans also directly

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contradict this proposition: when waking duration is extended by a night of total sleep deprivation, CMR *decreases* rather than increases. Thus, Thomas et al [20] found that 24 h of sleep deprivation in 17 normal adults significantly reduced global glucose uptake, noting that “No significant increases in absolute regional CMR_{glu}, nor trends for significant increases, were noted with 24 h of sleep deprivation.” p 346. Similarly Wu et al [24] found in 32 normal subjects that a night of sleep deprivation reduced absolute CMR in several brain regions and did not increase it any structure. Thus, quantitative PET data in humans show no difference in brain metabolic rate after a normal day and CMR falls when waking is extended by sleep deprivation. This decline suggests that synaptic activity has been decreased, presumably because of depleted substrates. It is important to consider an apparent exception to these findings, one that is heavily emphasized by Tononi and Cirelli. Braun et al [4] (and Balkin et al [2] in the same subjects) found that cerebral blood flow (CBF) measured by PET was significantly lower shortly after morning awakening than in the evening prior to sleep. Because CBF is normally coupled to CMR, Tononi and Cirelli interpret this result as strong support for their hypothesis that metabolic rate increases across waking. However, the morning CBF measurements of Braun et al and Balkin et al were made 5–20 min after awakening and could have been influenced by sleep inertia (persistence of the low CMR of sleep into the initial waking minutes). The Buysse et al study cited above, which found no difference in CMR between the morning and evening, performed the morning measurements 2–4 h after wake onset eliminating the issue of sleep inertia. Moreover, while it is true that CBF and CMR usually vary in parallel, they are perfectly coupled and can dissociate as a result of hemodynamic and metabolic factors [17].

It is now well-established that CMR is 20–25% lower in NREM sleep than in normal waking [11,16,5,14,12,24]. CBF similarly declines [4,13]. This metabolic depression, which varies in different brain regions but is greatest in plastic brain structures, surely must be related to the restorative processes of sleep; it may directly reverse waking brain changes by neural inactivity or establish the metabolic preconditions for active homeostatic reversal processes. Tononi and Cirelli explicitly state that Borbely’s process S “describes the process of synaptic homeostasis” [21], p49. Therefore, CMR should be highest in NREMP1 and decline exponentially across NREMPs. Grouped data, indeed, show an exponential decline for high amplitude slow wave EEG (stage 4 [7] or delta power [1]); however, individual night’s data are far more variable [8] and delta power in the third NREMP may exceed that in the second. We could find no data for CMR as a specific function of time of night or delta power. We predict that CMR will be lowest in stage 4 sleep wherever it occurs during the night or, more generally, that CMR correlates negatively with delta power. The studies reporting that CMR is lower in NREM sleep than in waking usually measured NREM CMR in stage 4 sleep.

We believe that the available metabolic evidence supports a different and perhaps more straightforward model than that put forward by Tononi and Cirelli. In this alternative model, CMR is tightly regulated and does not change measurably over a normal day although there is ongoing depletion of the resources needed for plastic (synaptic) activity. This depletion is indicated by the growth of delta power in naps after increasing waking durations. In both our model and that of Tononi-Cirelli, the resources for plastic activities are replenished (i.e. waking effects are reversed) during the metabolic depression of NREM sleep. However, we hypothesize that replenishment/reversal (i.e. when CMR is lowest) is highest in stage 4 sleep (high delta power) wherever in the night it occurs. When waking is extended by a night of total sleep deprivation, CMR can no longer be maintained at its normal regulated level and falls significantly, with the greatest decline in the most plastic brain structures. It would be valuable to perform graded sleep deprivation studies to determine how long waking can be extended before CMR declines. This might define a maximum physiological “day”. It would also be interesting to determine whether a physiological day can be extended by putative waking-enhancement drugs. Answers to these questions might require measurements over more than

one recovery day since Wu et al reported that even after global CMR has been restored by one night of recovery sleep, relative CMR remains depressed in plastic structures like frontal cortex [24].

The notion that sleep contributes to plastic (synaptic) brain function has a long and distinguished history, dating to Hughlings Jackson [10] in the 19th century and Moruzzi [15] in the 20th. In modern sleep research, ontogenetic sleep patterns have been related to changing brain plasticity and synaptic density [7,9] and the relation of sleep to memory consolidation is an active, albeit controversial [19,22], field of inquiry. Nevertheless we still don't know how and when (in sleep) plastic waking brain changes (most likely synaptic, as Tononi and Cirelli aver) are reversed by sleep. Although we disagree with their model, we thank Tononi and Cirelli for raising the important question of the relation of sleep homeostasis to cerebral metabolism. We believe that the preponderant evidence better fits our alternative model but we recognize that more data are needed. We therefore enthusiastically endorse their call for more detailed and systematic studies of CMR and sleep homeostasis.

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