

# Implications of Sleep Deprivation Experiments for Our Understanding of Sleep Homeostasis

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WE ARE WRITING IN RESPONSE TO THE INTERESTING AND PROVOCATIVE REVIEW BY RECHTSCHAFFEN et al. on "Effects of Method, Duration, and Sleep Stage on Rebounds from Sleep Deprivation in the Rat". The title of this review does not do it justice. The authors use their new data on method, duration, and stage-specificity of sleep deprivation as a springboard for a closely argued consideration of key issues in recent thinking about sleep homeostasis. They present some new and different interpretations of the effects of sleep deprivation on sleep recovery processes. The entire work is carefully reasoned and represents a sincere and thoughtful attempt to make sense of a great mass of data from a bewildering array of different types of sleep deprivations. We highly recommend this thought-provoking article to anyone with an interest in the function and/or homeostatic control of sleep. We temper this recommendation, however, with a caveat. We believe that the authors have made a small number of unwarranted assumptions that have caused them to arrive at conclusions which are, in our opinion, highly implausible.

One of the key issues considered in the review is whether an increase in slow-wave activity (SWA) in the NREM-sleep EEG during recovery from sleep deprivation is tied to the sleep recovery process. The main evidence in favor of a link between SWA and the sleep recovery process is that 1. Sleep deprivation (usually) causes an increase in SWA in recovery NREM sleep; 2. in normal sleep, SWA is greatest at the beginning of the night, when sleep need is greatest; 3. arousal threshold is (usually) positively associated with the incidence of SWA; and 4. selective deprivation of NREM sleep characterized by large amounts of SWA produces evidence of a sleep debt. The main confounding evidence presented by Rechtschaffen et al. is that 1. some sleep deprivation protocols produce large increases in REM sleep in the early stages of recovery sleep; 2. when there is a large REM-sleep rebound, increases in SWA may be reduced, delayed, or absent; 3. in the later

stages of recovery sleep, there is often actually a reduction in SWA activity in NREM sleep, below baseline levels a "negative rebound". To this evidence, we would also like to add the well-established observation that benzodiazepines produce what appears to be restorative sleep, while markedly reducing SWA in NREM sleep.<sup>2</sup>

The authors argue against the idea that the intensity of sleep, and therefore the rate of recovery of lost sleep, is a direct function of the amount of SWA in the NREM sleep EEG. This position may ultimately be a paper tiger, but it is nevertheless not unheard of in the sleep research community. What the authors have not considered, in our opinion, is the possibility that there could be an important link between SWA and sleep recovery even though SWA is not absolutely for recovery of sleep debt to occur. For example, even if the sleep periods characterized by the highest SWA are normally the most restorative, that does not necessarily imply that SWA will always occur during maximally restorative sleep. Even less does it imply the stronger conclusion that increased SWA is essential to the physiological recovery process. Neither of these two implications is well established by evidence, even though sleep researchers do often speak as if they were true.

We therefore applaud the authors for drawing attention to these issues, but the simple fact that sleep restoration and SWA can be experimentally dissociated in some circumstances is not incompatible with the conclusion that potentiation of SWA in recovery sleep following sleep deprivation is usually representative of "deeper," more restorative sleep. The well-established link between SWA and sleep recovery is still of considerable interest as a possible avenue for investigating the physiological mechanisms of sleep homeostasis. Researchers still do not fully understand why the level of SWA in NREM sleep is, under normal circumstances, so tightly correlated with the duration of prior waking, and determining the nature of this link should take us a step closer to discovering the homeostatically regulated function of sleep.

We cannot agree with the authors' suggestion that NREM-sleep and REM-sleep rebounds may be to some extent interchangeable, that REM sleep may be the functionally important sleep state with NREM sleep serving as a priming mechanism to permit the expression of REM

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sleep. In our opinion, Rechtschaffen et al. were led to these conclusions by overly simplistic conceptions of the effects of sleep deprivations and of the interactions between NREM-sleep and REM-sleep processes.

We posit two ideas that seem to us obvious based on our experience with sleep deprivations in rats. First, total sleep deprivation (TSD) in rats for more than a few hours is effectively impossible. By this we mean that rats will eventually and inevitably find ways to discharge some part of their accumulated sleep need, no matter what sleep deprivation protocol one uses. Second, complete and selective REM-sleep deprivation in rats is effectively impossible for more than an hour or two. By this we mean that in rats, drive to enter REM sleep increases so markedly in a relatively short period of time that the occurrence of short amounts of REM sleep cannot be prevented without virtually blocking sleep altogether. Moreover, increased REM-sleep drive during REM-sleep deprivations causes such frequent attempts to enter REM sleep that NREM sleep is markedly fragmented and high voltage SWA does not occur.

The difficulties in achieving TSD for considerable periods are obvious even to people who have no familiarity with sleep research. If you keep subjects awake long enough, they will nod off if not carefully watched. And even if they manage to remain awake, their waking state is by no means identical to normal vigilant waking. In both humans and experimental animals, NREM sleep-like slow waves appear in the waking EEG after just 24 hours of total sleep deprivation (TSD).

In sleep deprivation experiments on humans, it is possible to get their voluntary cooperation to try to stay awake. In sleep deprivation experiments on animals, however, the animal will consistently attempt to overcome the manipulation and obtain some sleep. Therefore, animals are even more prone than human subjects to nod off during the sleep deprivation period.

Rats and other experimental animals must be kept constantly busy or they will go to sleep. Rechtschaffen et al. discuss this issue at some length in their review, but they do not in our opinion adequately grasp the implications. One such implication is that any TSD protocol lasting more than a few hours will inevitably allow a certain amount of sleep. Some researchers have reported the amount of sleep that occurred during their deprivation period, but most do not. Even reporting duration of sleep may not fully express the non-total nature of the sleep deprivation protocol, since twilight states having characteristics of both sleep and waking are well known to occur, especially when normal sleep-wake expression is experimentally perturbed.

We must keep these considerations in mind when evaluating different sleep deprivation methodologies. The "constant forced locomotion" protocol is often compared unfavorably with other, more gentle methodologies, but it may

in fact be the ideal technique for depriving rats of sleep, since it arguably permits the least sleep and sleep-like states during the deprivation period. As the authors acknowledge, the forced locomotion in most applications of this method is neither constant nor more exhausting than a rat's normal daily routine.

By comparison, the "disk over water" (DOW) protocol which Rechtschaffen et al. use almost certainly permits considerably more sleep and sleep-like states during the deprivation period. The advantage of this technique vs. constant forced locomotion is that the disk only starts turning when the subject falls asleep. In fact, we can personally attest to how exquisitely gentle this protocol is, one of us (J.H.B.) having witnessed it in operation at Rechtschaffen's laboratory in Chicago. In this protocol the animal is allowed to lie down and prepare itself for sleep, then achieve an indeterminate amount of relaxed, drowsy waking followed by one 30-second epoch of a state that is algorithmically scored as sleep before the disk even starts rotating, and then continue to sleep for an additional few seconds before waking up.

By accumulating such brief episodes of sleep and sleep-like brain activity, the subject is able to discharge a non-trivial fraction of its accumulated sleep drive as the deprivation continues. As a result, it would not be surprising if this protocol produces less pronounced rebounds in SWA than constant forced locomotion does. Similarly, when, Feinberg and Campbell report anomalously low rebounds of SWA following 24 hours of sleep deprivation by gentle handling,<sup>3</sup> we must ask whether their subjects had managed to discharge more sleep need during the deprivation period than in other studies using constant forced locomotion, thereby causing a reduction in the intensity of rebound nonREM sleep.

Another very important implication of animals' tendency to fall asleep during TSD is that they are much more likely to express NREM sleep and NREM sleep-like activity than REM sleep, since even in rats there is almost always 5–10 minutes of NREM sleep before the first REM-sleep episode. Therefore, total sleep deprivation is actually more total for REM sleep than for NREM sleep. As the duration of the sleep deprivation period increases, causing a more and more profound sleepiness and therefore a greater and greater tendency to drop off during the deprivation period, the differential between the totality of REM-sleep deprivation and the totality of NREM-sleep deprivation will increase. Each brief sleep episode will discharge some small amount of the accumulated NREM-sleep need but none of the accumulated REM-sleep need.

The occurrence of NREM sleep and NREM sleep-like activity during the deprivation is especially significant in light of the well-established correlation between duration of sleep deprivation and occurrence of a REM-sleep rebound during the early part of the recovery period (see

reference 4 for review). In rats, three or six hours of TSD by constant forced locomotion was followed by no REM-sleep rebound, 12 hours of TSD produced a very small REM-sleep rebound, and 24 hours of TSD produced a marked REM-sleep rebound. In the experiments of Rechtschaffen et al., the relative magnitude of the REM-sleep rebound was greater following 96 hours of TSD than after just 24 hours. In humans, 40 hours of TSD consistently produces no REM-sleep rebound in the first recovery night, while 112 hours of TSD produces a marked REM-sleep rebound early in the recovery period.

In both rats and humans, a REM-sleep rebound becomes more pronounced only following longer sleep deprivations in which there is likely to be a more marked differential between the totality of REM-sleep deprivation vs NREM-sleep deprivation. Moreover, evidence suggests that rats accumulate sleep need just over twice as fast as humans, which would imply that 40 hours of TSD in a human actually represents a less marked sleep debt than 24 hours of TSD in a rat.<sup>5,6</sup> Human subjects are likely to maintain a more nearly normal state of vigilant waking during one night without sleep than rats will during 24 hours of TSD (see above). Therefore, 24 hours of TSD in a rat, which is followed by a greater REM-sleep rebound than is 40 hours of TSD in a human, is also likely to be associated with more selective NREM-sleep expression during the deprivation period.

If you believe that the need for REM sleep accumulates during waking, in parallel with accumulation of the need for NREM sleep, then the differential between NREM-sleep deprivation and REM-sleep deprivation may not seem especially large. But we have hypothesized (not for the first time) that the need for REM sleep accumulates during nonREM sleep, that REM sleep episodes occur at fairly regular intervals because REM sleep occurs once a certain amount of REM-sleep need has accumulated in nonREM sleep, and therefore that REM sleep serves some function related to NREM sleep rather than waking (see reference 4 for review). This hypothesis is in fact abundantly supported by evidence, and it is our opinion that if the contrary view (that REM-sleep need accumulates during waking) had not come to dominate the field shortly after the discovery of REM sleep, then the idea that NREM sleep is homeostatically and functionally related to NREM sleep rather than waking would appear as obvious to most sleep researchers as it does to us (see ref. 7 for a review of the history of theorizing about REM sleep).

The hypothesis that REM-sleep need accumulates during nonREM sleep fits neatly with the observed effects of total sleep deprivation. During more prolonged TSD, an accumulation of brief NREM-sleep episodes and sleep-like brain activity in twilight states of waking cause a substantial REM-sleep debt to accumulate. Using an exceptionally gentle technique for selective REM-sleep deprivation in

rats, we found that after just two hours of nonREM sleep, drive to enter REM sleep is markedly increased.<sup>8</sup> This is not surprising according to the hypothesis that REM sleep is homeostatically related to NREM sleep, since REM-sleep episodes in rats normally occur every 10 minutes or so. If the equivalent of several hours of NREM sleep is permitted during 96 hours of TSD (whether or not all of it is scored as NREM sleep), then there should be a considerable REM-sleep rebound during the early stages of the recovery period, as is observed. Since we have hypothesized that REM sleep is necessary to permit further expression of normal NREM sleep, then it makes perfect sense that this REM sleep debt would also interfere with the expression of SWA in NREM sleep during the early stages of recovery. Rechtschaffen et al. in fact present evidence that this may be the right explanation for REM-sleep rebounds when they note that the magnitude of the REM-sleep rebound following TSD is highly correlated with EEG delta power during the deprivation period (which is indicative of the amount of SWA in NREM sleep and/or waking).

Rechtschaffen et al. raise two main objections to our hypothesis, neither of which, in our opinion, has much substance. Their first objection concerns our supposition that a significant amount of NREM sleep and sleep-like brain activity in drowsy waking occurs during sleep deprivation, and that accumulation of REM-sleep need in these states underlies the REM-sleep rebound that occurs early in the recovery period (as discussed above). They dispute the possibility that the totality of sleep deprivation could be incomplete enough to allow an accumulation of REM-sleep debt through expression of NREM sleep, without being incomplete enough to prevent the morbidity and mortality that is the observed result of long term sleep deprivation by the DOW methodology.

Our response is twofold. First, we don't see why it seems implausible to suppose that some amount of NREM sleep as well as nonREM sleep-like activity occurs during total sleep deprivation by the DOW technique. The alternative—that sleep deprivation is absolutely perfect—seems far more implausible. If it is agreed that sleep deprivation is not total but that only NREM sleep is likely to occur during sleep deprivation, then according to our model it would follow naturally that total sleep deprivation can produce a substantial REM-sleep debt even though REM-sleep need normally accumulates during NREM sleep.

Second, the above supposition does not imply that there is enough discharge of sleep need during the deprivation period to preclude the accumulation of a greater and greater sleep debt with each day of the deprivation period. In other words, there is no reason why non-total sleep deprivations wouldn't eventually cause the morbidity and mortality observed in the Rechtschaffen et al. experiments. But even if the increasing intensity of sleep drive causes an animal

eventually to discharge as much nonREM-sleep need in a given day of sleep deprivation as it was accumulating as a result of the deprivation protocol, the total sleep deprivation by the DOW technique would still cause that animal to accumulate an increasing and entirely undischarged REM-sleep debt. In fact, it is possible that what kills the animal could be the REM-sleep debt rather than the NREM-sleep debt.

The second objection of Rechtschaffen et al. to our hypothesis is that the magnitude of REM-sleep rebound following 24 hours of TSD is the same as following 24 hours of selective REM-sleep deprivation. They note that if, as we have hypothesized, REM-sleep need accumulates during nonREM sleep, then there should certainly be more REM-sleep rebound following 24 hours of REM-sleep deprivation, since much more NREM sleep occurred in that condition than in a TSD condition even if that TSD were imperfect. This is a reasonable expectation if and only if it is assumed that REM-sleep deprivation is complete.

In fact few REM-sleep deprivation methodologies eliminate all REM sleep. In the DOW method used by Rechtschaffen et al., animals are aroused only once a certain amount of REM sleep is scored by the computer. In other words, animals, are by definition, able to discharge a certain amount of their REM-sleep debt during the deprivation period.

The actual amount of REM-sleep need discharged is not fully expressed by the amount of computer-scored REM sleep that occurs during the deprivation. REM sleep is preceded by a state called pre-REM sleep that exhibits characteristics of both REM sleep and NREM sleep and lasts up to 60 seconds per REM-sleep transition. Dement et al. reported that REM-sleep rebound is greater when animals are aroused at the onset of the pre-REM sleep period vs when animals are aroused only once they express REM-sleep itself.<sup>9</sup> This finding strongly suggests that a certain amount of REM-sleep need is discharged during the pre-REM-sleep period, before any REM sleep would actually be scored by a computer.

During 24 hours of REM-sleep deprivation, a considerable amount REM-sleep need is discharged during the deprivation period. So if we want to compare 24 hours of TSD with 24 hours of REM-sleep deprivation in terms of how much REM-sleep rebound is expected to occur, we should be mindful that what we are really comparing is a 24-hour period in which a greatly reduced but non-zero amount of NREM sleep is allowed to occur vs a 24-hour period in which NREM sleep is allowed to occur ad lib and REM-sleep expression is partly, but not entirely, impaired. In TSD, less REM-sleep need accumulates but none of it can be discharged. In REM-sleep deprivation, more REM-sleep need accumulates but some of it is discharged in brief bouts of REM sleep and REM sleep-like activity in pre-REM sleep. The ultimate REM-sleep debt could therefore

be approximately the same in both conditions.

In sum, neither of the observations noted by Rechtschaffen et al. are incompatible with the hypothesis that REM-sleep need accumulates during NREM sleep, as long as one bears in mind that neither total sleep deprivations nor selective REM-sleep deprivations perform exactly as intended. If one is sensitive to this, the seemingly paradoxical results noted by Rechtschaffen et al. need not lead to the conclusion that NREM-sleep and REM-sleep rebounds are functionally interchangeable or that the only functional role of NREM sleep is to serve as a priming mechanism for REM sleep.

As we have stressed previously, we are by no means the first researchers to propose that REM sleep may be homeostatically regulated in relation to prior nonREM sleep rather than prior waking, and therefore that the function of REM sleep relates to NREM sleep rather than to waking. We have advocated this hypothesis because, in our opinion, it much more readily explains the phenomenology of nonREM-sleep and REM-sleep expression. We continue to have a high degree of confidence in the validity of this hypothesis.

In our opinion, the main reason the concept that REM-sleep need accumulates during nonREM sleep has not enjoyed a broader acceptance is that sleep researchers have become accustomed to interpreting REM-sleep phenomena in terms of a waking-related function. Yet, this interpretation was originally decided upon almost reflexively, with little circumspection (see ref. 7 for review), presumably because REM sleep is a sleep state and therefore (it was thought) must serve some function related to waking. We hope that the recent observations of Rechtschaffen et al. draw renewed attention to this issue and thus encourage more sleep researchers to reconsider, without preconceptions, the relative merits of these hypotheses.

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