Cortical excitability and sleep deprivation: a transcranial magnetic stimulation study

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Abstract
The objective was to assess the changes in cortical excitability after sleep deprivation in normal subjects. Sleep deprivation activates EEG epileptiform activity in an unknown way. Transcranial magnetic stimulation (TMS) can inform on the excitability of the primary motor cortex. Eight healthy subjects (four men and four women) were studied. Transcranial magnetic stimulation (single and paired) was performed by a focal coil over the primary motor cortex, at the “hot spot” for the right first dorsal interosseous muscle. The following motor evoked potential features were measured: (a) active and resting threshold to stimulation; (b) duration of the silent period; (c) amount of intracortical inhibition on paired TMS at the interstimulus intervals of 2 and 3 ms and amount of facilitation at interstimulus intervals of 14 and 16 ms. The whole TMS session was repeated after a sleep deprivation of at least 24 hours. After the sleep deprivation, the threshold to stimulation (in the active and resting muscle), as well as the silent period, did not change significantly. By contrast, the paired stimulus study showed a significant (p<0.05) reduction in both intracortical inhibition and facilitation. Thus, TMS showed that sleep deprivation is associated with changes in inhibition-facilitation balance in the primary motor cortex of normal subjects. These changes might have a link with the background factors of the “activating” effects of sleep deprivation.

Keywords: sleep deprivation; cortical excitability; transcranial magnetic stimulation

Subjects and methods
Eight healthy volunteers (four men and four women, mean age 28.7 (SD 4.2) years; range 25 to 36 years) were studied. All gave their informed consent. The local ethics committee approved the experimental procedures. Awake subjects sat in a comfortable chair with their eyes open. Two monophasic electromagnetic stimulators (Magstim 200, Magstim Co, Whitland, Dyfed, UK) were used coupled with a Bistim device. The TMS was performed with a “figure of eight” or “butterfly” coil, delivering focal pulses over the left primary motor cortex, at the “hot spot” for the right first dorsal interosseous muscle. Motor evoked potentials (MEPs) were recorded from this muscle via surface Ag-AgCl cup electrodes (diameter=9 mm). A Viking 4 machine (Nicolet Biomedical, Madison, WI, USA) amplified (0.1–5 mV/cm) and filtered (20–5000 Hz) the signal, then stored it on hard disks. The sampling rate for digitisation was 25 kHz. Firstly, the following variables were determined with a single stimulator: (1) relaxed threshold (RT), defined as the minimum stimulator intensity that evoked at least 50% of responses with an amplitude of 50 µV or more (sensitivity 0.1 mV/division,
Figure 1  Sleep deprivation: results on paired pulse transcranial magnetic stimulation. (A) Comparison of the inhibitory and facilitatory effects. The results for ISIs 2 and 3 ms, then for ISIs 14 and 16 ms were averaged. A significant reduction of both inhibition (p=0.025) and facilitation (p=0.019) after sleep deprivation was found. Black column=before sleep deprivation; grey column=after SD; bars=standard deviation. (B) Effects of sleep deprivation on inhibitory (3 ms) and facilitatory (16 ms) interstimulus intervals. Each tracing represents the average of eight control (upper tracing) and eight conditioned (lower tracing) motor evoked potentials.

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Results

In all subjects, the average score on the Stanford sleepiness scale was equal to 1 before, and equal to 3.5 after the sleep deprivation. In other words, somnolent subjects were still sufficiently alert and able to follow the
Sleep deprivation and transcranial magnetic stimulation and anxiety, yet to activate the corticospinal tract. Some agonists were attributed a similar effect, whereas the reverse was true for dopamine antagonists.16

Whereas the reverse was true for dopamine antagonists,16 sleep deprivation seemed to alter none of its facilitation.9 Both arise from the cerebral circuitry in the primary motor cortex.13 17 In general, most of the conditions studied showed an inverse correlation between inhibition and facilitation. If the second decreased, the first increased, and vice versa. A partial exception to this rule might be the effects of vigabatrin, a typical GABAergic drug that reduced facilitation without affecting inhibition, or the serotonergic 5HT 1A agonist zolmitriptan,18 which reduced inhibition leaving facilitation unaffected. In general, the intimate pharmacological nature of the paired pulse effects seems to need further studies. In our present findings, however, loss of inhibition was unexpectedly coupled with reduction of facilitation. The coexistence of such apparently opposing phenomena is difficult to interpret. In theory, proepileptogenic and antiepileptogenic effects would seem to cancel each other. To us, it may be more useful to note that sleep deprivation was associated with a general hyporeactivity of cortical area 4 interneurons, reflected by the flattening of the paired pulse curve. Besides, excess excitation, and defective but also excessive inhibition, interact in a very complex manner to predispose the cortex to epileptiform discharges.19 Thus, we cannot exclude the possibility that our findings might be compatible with an “activating” net effect within the cortex.

As our method explored the primary motor cortex, the relevance of our data to those epileptiform activities which might affect the brain with a different topography may be questioned. Yet, area 4 excitability was found altered in various epileptic syndromes, not only generalised20 but also partial (for example, with hippocampal genesis of the condition). The observation that intracortical inhibition is related to a more severe EEG and clinical picture.21 Thus, area 4 physiology—in the epilepsy field—proved sensitive to phenomena that exceed its boundaries.

In conclusion, TMS disclosed some subtle changes in normal cortical physiology, which may serve as a model for studying the “activating” effects of sleep deprivation in patients with epilepsy.

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