

SHORT REPORT

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 inter-stimulus 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.

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Sleep deprivation is a powerful activator of seizures in nearly all types of epilepsy.¹ It is also the best method for provoking EEG epileptiform abnormalities, or enhancing those induced by intermittent light stimulation and hyperventilation.² Few workers³ attributed the epileptic activation to drowsiness alone, and most concluded that sleep deprivation has a specific activating effect on its own.⁴ However, its intrinsic mechanisms are still obscure. In

animals, sleep deprivation results in a lowering of the thresholds to electroshock convulsions⁵ and for kindling to occur.⁶ This could relate to a change in the balance between excitatory and inhibitory neurotransmitters.⁷

Transcranial magnetic stimulation (TMS) is a safe probe of neuronal excitability of the primary motor cortex. Several variables contribute to assessment, of which the threshold to stimulation and the silent period may be assessed by the single pulse technique. Then, the paired pulse method allows measurement of the so called intracortical (corticocortical) inhibition and facilitation curve.⁸ This describes the effects that a weak (submotor threshold) conditioning magnetic shock induces on a test stimulus set to produce a motor evoked potential (MEP) of 0.5–1 mV. Intracortical inhibition and facilitation are thought to reflect the excitability of separate populations of interneurons intrinsic to cortical area 4.⁹ Thus, we used these TMS methods to detect possible changes in the cortical physiology of normal subjects induced by a sleep deprivation of at least 24 hours.

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 μ V or more (sensitivity 0.1 mV/division,

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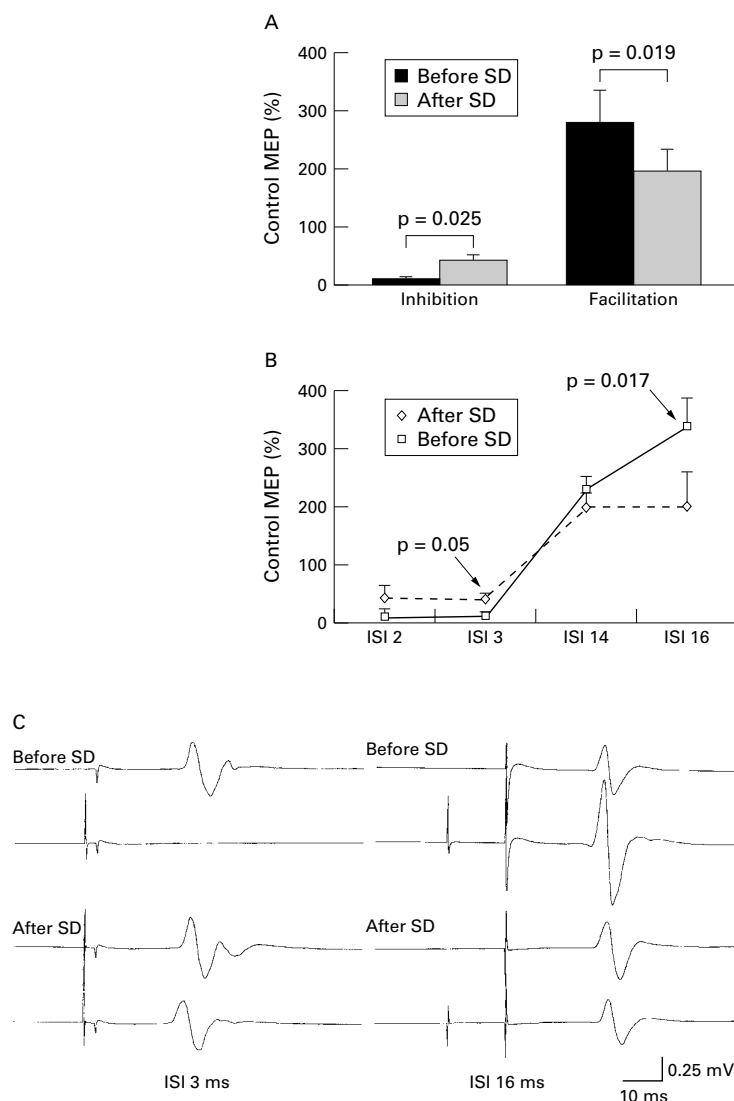


Figure 1 Sleep deprivation: results on paired pulse transcranial magnetic stimulation. (A) Comparison of the inhibitory and facilitatory effects. The results for ISIs 2 and 3 ms, then for ISIs 14 and 16 ms were averaged. A significant reduction of both inhibition ($p=0.025$) and facilitation ($p=0.019$) after sleep deprivation was found. Black column=before sleep deprivation (SD); grey column=after SD; bars=standard deviation. (B) Effects of sleep deprivation on the single ISIs of the inhibition and facilitation curve. Squares=before SD; diamonds=after SD; bars=standard deviation. (C) Typical example (subject 3) of the 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

analysis time 100 ms), after 16 consecutive stimuli in the relaxed FDI¹⁰; (2) active threshold (aT), the same as above but during 10% of maximum voluntary contraction (MVC) of the target muscle; (3) duration of the silent period (sensitivity 5 mV/division, analysis time 500 ms). This represented the period of suppression of the EMG activity produced by a magnetic shock set as $1.5 \times rT$ in the preactivated right first dorsal interosseous muscle (10% of MVC). The duration of the silent period went from the stimulus artefact to the reappearing of the EMG activity in eight superimposed, non-rectified trials. A sphygmomanometer was used for the monitoring of the appropriate level of muscle preactivation. The subjects squeezed the partially inflated cuff between their extended first and second

finger. The amount of contraction was expressed as mm Hg. The inhibitory and facilitatory interstimulus intervals (ISIs) were studied with the paired pulse technique⁸. The intensity of the conditioning stimulus was $0.8 \times rT$; and the intensity of the test stimulus was $1.2 \times rT$. The second was adjusted to evoke test MEPs 0.5–1 mV in amplitude. Attention was focused on the two most inhibitory (2 and 3 ms) and facilitatory (14 and 16 ms) ISIs (sensitivity 0.5 mV/division; analysis time 100 ms). For each ISI, we recorded eight control and eight conditioned MEPs in a random order. The effect of the conditioning was expressed as a ratio of the averaged conditioned MEP at each ISI to the averaged control MEP. Averaged MEPs were from non-rectified EMG signals. Inhibition occurred when the ratio was less than one, facilitation when it was greater than one. For determination of the relaxed threshold and the paired pulse curve, full relaxation of the interosseous muscle was necessary. To facilitate this, subjects were given audio feedback of the background activity in the high gain EMG signal through a loudspeaker. If an undue EMG background appeared in these experiments, the given signal was discarded. To test the peripheral and spinal motor excitability the maximum M wave (Mmax) and F wave amplitude was determined by supramaximal stimulation of the ulnar nerve at the wrist in the resting condition. Sixteen responses were collected for each test.

Sleep deprivation consisted of a period of total sleep loss of at least 24 hours, and was performed according to the routine suggested by Naitoh and Dement.¹¹ To avoid any hypothetical “order effect”, the baseline TMS study was performed before the one that followed sleep deprivation in five subjects, whereas the sequence was reversed in the remaining three. In this last group, at least three sleep/wake cycles represented the recovery from sleep deprivation, which was held sufficient for the “baseline” test. In theory, somnolence might interfere with the degree of subject cooperation during the experiments. Thus, the level of sleepiness before and after sleep deprivation was determined with the Stanford sleepiness scale.¹²

For statistical analysis the SPSS program (release 8.0.0) for Windows 95 was used. Data on rT, aT, and the silent period were compared by means of Mann-Whitney *U* tests, with a Bonferroni correction of *p* values. For the paired pulse curve, a repeated measure analysis of variance (ANOVA) model was used, where the main factor “time” included the different ISIs. The fixed factor was the sleep deprivation. Provided the *F* was significant ($p < 0.05$), paired *t* tests with a Bonferroni correction of *p* values were used to compare the single ISIs.

Results

In all subjects, the average score on the Stanford sleepiness scale¹² 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

experimental instructions. After sleep deprivation, the threshold to stimulation (in the resting and active muscle), as well as the silent period did not change significantly. Moreover, there were no significant changes in the Mmax and F wave amplitude. Subsequently the intracortical inhibition and facilitation index were estimated, as previously done by others.¹³ The inhibitory ratios for the interstimulus intervals of 2 and 3 ms, and the facilitatory ratios for intervals of 14 and 16 ms were combined. After the sleep deprivation, there was a significant ($F(1,7)=5.59, p<0.05$) reduction of both inhibition (Bonferroni $p=0.025$) and facilitation (Bonferroni $p=0.019$, fig 1 A). Next, the effects of the sleep deprivation on the single ISIs (fig 1 B) were analysed. The inhibitory effect was more evident at ISI 3 ms (Bonferroni $p=0.05$), whereas facilitation had a maximum at ISI 16 ms (Bonferroni $p=0.017$). Figure 1 (panel C) shows a typical example of the MEP tracings in a paired pulse experiment.

Discussion

Sleep deprivation induced changes in some of the TMS variables studied, which we attribute to alterations of the primary motor cortex excitability. In fact, indexes of spinal (F waves) or neuromuscular (M waves) excitability remained unaltered. Changes in TMS, however, did not affect the motor threshold or the silent period. Motor threshold most likely reflects axon membrane excitability, because drugs acting on voltage and frequency dependent sodium and calcium channels modulate it.¹³ Thus we assume that sleep deprivation had no direct effect on the membrane of the nerve cells presynaptic to the corticospinal neuron; these largely represent the primary excitation site of TMS.¹⁰ The silent period has a more complex, and perhaps obscure, pathophysiology,¹⁴ yet sleep deprivation seemed to alter none of its many putative generators. The sensitive variable was the intracortical inhibition and facilitation curve, both phases of which were depressed. The first (1–5 ms) phase, inhibition, is thought to rely on a different interneuron circuit from the second one (7–16 ms)—that is, facilitation.⁹ Both arise from the cerebral cortex, as the conditioning pulses are too weak to activate the corticospinal tract.⁸ Some authors made inferences to the transmitters implied in these phenomena. Antiepileptic GABAergic drugs were able to reduce facilitation, and, to some extent, enhance inhibition.¹³ NMDA-receptor antagonists¹⁵ and dopamine agonists were attributed a similar effect, whereas the reverse was true for dopamine antagonists.¹⁶ On this basis, paired pulse TMS was proposed as an assay of both excitability and pharmacology of the interneuronal 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,¹³ a typical GABAergic drug that reduced facilitation without affecting inhibition, or the serotonergic 5HT_{1B/1D} 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 hypoactivity 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 temporal foci).²¹ In the last condition, loss of 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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