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Decrease in motor cortical excitability in human subjects after sleep deprivation

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Abstract

The effect of sleep deprivation on human motor cortical excitability was investigated by evaluating the changes in motor evoked potentials from the thenar eminence muscles of the right hand in seven subjects. Motor threshold, motor evoked potential amplitude, silent period, intracortical inhibition, intracortical facilitation and F wave were studied. Recordings were performed every 6 h during the day-time (from 09.00 to 21.00 h) and every 3 h during the night-time (from 21.00 to 09.00 h). Significant increases in motor threshold, intracortical inhibition and silent period were noted in the recordings during the night associated with a return to baseline values in the morning. No significant changes were observed in any of the other parameters. Enhancement of intracortical motor inhibition is suggested to explain the effect of sleep deprivation. © 2001 Published by Elsevier Science Ireland Ltd.

Keywords: Sleep; Sleep deprivation; Transcranial magnetic stimulation; Intracortical inhibition; Epilepsy

The mechanisms responsible for changes in brain function that occur during normal sleep and after sleep deprivation are not fully understood. Sleep deprivation can induce a number of physiological effects including alterations in systemic and brain energy metabolism [2,4,7], temperature regulation [10,12], and altered hormonal profiles [2]. Thus, sleep may have a facilitating or precipitating effect on seizures as well as protective effects against epilepsy [3]. It is well known that sleep deprivation leads to sensitization to seizures and represents an important activation test in clinical electroencephalography [3]. The EEG recorded in awake human subjects is the main objective measure of excitability of the central nervous system during sleep and sleep deprivation [1,5,6]. Transcranial magnetic stimulation (TMS) is widely used to investigate motor excitability. Several studies have shown that intracortical inhibition and intracortical facilitation assessed by paired magnetic stimulation, reflect the excitability of distinct inhibitory and excitatory interneuronal circuits within the motor cortex [9,13,14]. The aim of the study was to investigate the effect of sleep deprivation on motor excitability in normal subjects applying several TMS parameters across a number of recordings during 24 h of monitoring.

Seven subjects (three females and four males, ranging in age from 24 to 35 years) were included in the present study. Volunteers with night work or with a history of psychiatric or neurological disorders were excluded. All the subjects signed a consent form approved by the institutional ethical committee and were paid for their participation. Prior to the study, each subject was required to maintain a regular sleep schedule for at least 5 days. The subjects were monitored in the laboratory throughout the 24 h period. In each subject the recordings were performed every 4 h during the day-time (09:00, 13:00, 18:00 h) and every 3 h during the night-time (21:00, 24:00, 03:00, 06:00 h); the last recording was performed at 09:00 h. Throughout the night-time routine subjective sleepiness was evaluated every 3 h just before TMS recording using a 10 cm visual analog scale (VAS).

All subjects were seated in an armchair. During the recording the subjects kept their eyes open. MEPs (motor evoked potentials) were recorded from the right thenar eminence muscles by surface electrodes. The amplified and bandpass filtered (50–5 KHz) EMG signal was fed into a Basis Esaote Machine (Esaote Company, Florence, Italy) with a sampling rate of 5000 Hz. A circular coil was used for single and paired stimulation using two Magstim 200 magnetic stimulators

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(The Magstim Company, Whitland, Dyfed, U.K.) connected by means of a Bistim device. The 'motor threshold' intensity was defined as the lowest stimulator output intensity capable of inducing MEPs of at least 50 μV peak-to-peak amplitude in relaxed thenar eminence muscles in at least half of ten trials over the optimal scalp position. Stimulus intensities were expressed as a percentage of the maximum stimulator output. The peak-to-peak MEP amplitudes were measured in the resting muscles at a stimulus intensity of 120% over the resting motor threshold. The size of the MEPs induced by TMS was measured as a percentage of the compound motor action potential (cMAP) elicited by peripheral stimulation of the median nerve. The duration of the silent period was determined at stimulus intensities of 110, 120 and 130% of the motor threshold in the thenar eminence muscles performing maximum voluntary contraction. Intracortical inhibition and facilitation was studied by paired TMS. A subthreshold conditioning stimulus was set at 70% of the resting motor threshold and was delivered through the same magnetic coil at interstimulus intervals of 1, 2, 3, 4, 5, 10 and 15 msec before a suprathreshold test stimulus. The test stimulus intensity was adjusted to 120% of the resting motor threshold [9,16,17]. Conditioned MEPs in both paired TMS paradigms were recorded at randomly varying interstimulus intervals. Changes in the mean control MEP size produced by the conditioning stimulus were expressed as a percentage of the unconditioned mean. Early intracortical inhibition and intracortical facilitation were then calculated by averaging the ratios across interstimulus intervals of 1–4 and 10–15 msec, respectively. Finally, in order to evaluate spinal excitability we studied the F wave amplitude recorded from the thenar eminence muscles and elicited by seven supramaximal stimuli of the median nerve once a second.

Results of all subjects were tested for each TMS parameter over time by repeated-measures one-way ANOVA. In the case of overall group significance, single comparisons were made. A post-hoc Bonferroni correction was applied if $P < 0.05$.

Individual VAS scores obtained just before the TMS recordings showed a marked significant increase in sleepiness during the night (03:00, 06:00 h: ANOVA, $P < 0.005$, $P < 0.001$, respectively) with a mild decrease in the morning (Fig. 1). Table 1 summarizes the effect of sleep deprivation on different TMS parameters. Post-hoc comparisons indicate that the resting motor thresholds were significantly reduced during the late recordings in the night (ANOVA, $P < 0.05$) and showed a return to baseline values in the morning (Fig. 1). Oscillations in MEP amplitude were observed during the late recordings in the night but were not significantly different in comparison to baseline values. Intracortical inhibition at interstimulus intervals from 1 to 4 msec showed a significant enhancement of intracortical inhibition across all subjects during the night (ANOVA, $P < 0.001$), with a return to baseline values in the morning (Fig. 1). The intracortical facilitation showed a tendency to decrease in the late hours of the night, but because of inter-individual oscillations during the day-time and night-time, there were no significant changes in intracortical facilitation in comparison to baseline values.

The silent period at different intensities showed a tendency to lengthen during the night. Nevertheless, because of inter-individual variability and the frequent oscillations across the recordings only the silent period obtained with an intensity of 130% of the motor threshold, was significantly different in comparison to baseline values during the late recordings in the night (03:00 h) (ANOVA, $P < 0.05$) with a return to the initial values in the morning (Fig. 1). No significant changes in F wave amplitude were noted during the night-time in comparison to baseline values.

The main finding of the study was the decrease in motor excitability as tested by paired TMS in normal subjects during sleep deprivation. The subjective sleepiness during the night in sleep deprivation was associated with increases in motor threshold, silent period and intracortical inhibition, while no significant changes were observed in other parameters such as MEP amplitude and F wave amplitude. In the morning the slight decrease in sleepiness was associated with a partial recovery of TMS parameters to baseline values. Unlike the case of electroencephalography, the possibility of using TMS parameters enables us to investigate the effect of sleep deprivation on the different aspects of motor excitability. A progressive increase in motor threshold was observed across the subjects during maximal sleepiness. Since voltage-gated sodium- or calcium-channel blockers increase

Table 1
Mean and standard deviation of seven subjects

Recordings	09.00 h		14.00 h		21.00 h		24.00 h		03.00 h		06.00 h		09.00 h	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Motor threshold (%)	53.4	5	54.7	6	54.1	6	55.2	5	60	2	61.7	7	62.1	5
MEP amplitude (%)	13.5	11	13.2	10	13.8	12	13.6	12	12.9	10	14	11	14.1	11
Silent period 110% (msec)	43.1	28	47.3	30	40.6	31	50.6	29	53.3	30	46.7	39	43.4	25
Silent period 120% (msec)	76.4	34	78	36	76	36	81.7	44	96.5	38	92.3	55	86.6	41
Silent period 130% (msec)	118.7	32	127	33	123.8	33	123.6	32	140.3	32	133.2	31	121.6	30
Intracortical inhibition (%)	57.6	18	53.6	16	59.1	21	48.8	18	42.4	21	42.9	22	48.8	24
Intracortical facilitation (%)	148.7	35	143.1	32	148.6	35	142.7	35	126.7	38	129.9	40	147	27
Fwave (uV)	132.8	40	123.5	48	132.1	49	132.1	49	127.7	55	123.2	41	142	49

motor thresholds [16] the motor threshold parameter is thought to reflect the excitability of the neuronal membranes. The significant changes in motor threshold observed in normal subjects during sleep deprivation therefore suggest possible changes in membrane excitability. The MEP amplitude parameter, though showing a tendency to decrease, did not present significant changes. This may be attributable to the adaptation of the magnetic stimulation intensity to the individual motor threshold during each session. MEP amplitude, in fact, is thought to be related to the number of corticospinal neurons activated at a given stimulus intensity [11,16]. The main finding of the study was the effect of sleep deprivation on intracortical inhibition in normal subjects. Early intracortical inhibition by paired TMS mainly depends upon γ-aminobutyric acid (GABA)-ergic mechanisms. Neuropharmacological TMS studies in normal subjects have shown that early intracortical inhibition can be enhanced by single oral doses of several GABA-ergic drugs (benzodiazepines and baclofen) [16,17].

On the other hand, intracortical facilitation did not show a

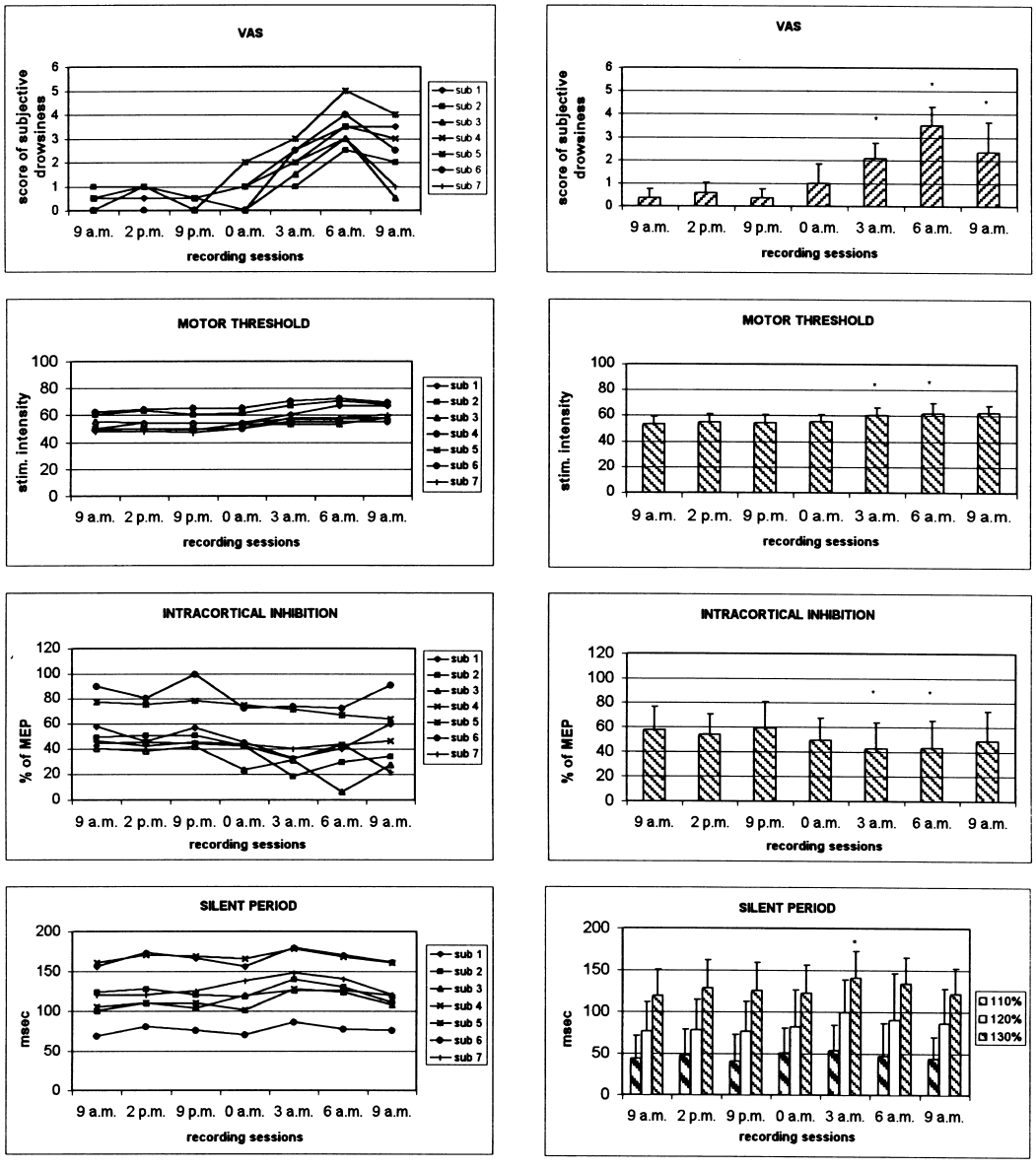


Fig. 1. Time course of subjective sleepiness and of different TMS parameters (motor threshold at rest, intracortical inhibition, silent period) during day and night periods of sleep deprivation. On the Y-axis are expressed the measures of the different parameters (scores for subjective drowsiness for VAS, stimulation intensity as percentage of maximal stimulator output for the motor threshold, percentage of the unconditioned MEP amplitude for intracortical inhibition and msec for the silent period). The recording sessions are indicated on the X-axis. On the left, individual data of the seven subjects examined (for silent period are showed only the data obtained at 130% of motor threshold). Each symbol represents individual values. The symbols are the same in all figures. On the right, each value is the mean of seven subjects. Vertical bars are standard deviations. Asterisks indicate a statistically significant difference versus baseline values.

consistent pattern across the subjects during sleep deprivation. The enhancement of intracortical inhibition with no consistent changes in intracortical facilitation suggests involvement mainly of GABA-ergic mechanisms during sleep deprivation. The increase in subjective sleepiness during the night paralleled the increase in intracortical inhibition in all subjects. The silent period obtained at maximal stimulation showed a lengthening during the night in sleep deprivation associated with the increase in sleepiness. The late part of the silent period evoked is suggested as being mainly due to activation of GABA-ergic cortical interneurons [8,13,16]. The oscillations of silent period during sleep deprivation may be in keeping with the increase in early motor inhibition observed by paired TMS suggesting potentiation of both early and late GABA inhibition during sleepiness in subjects in conditions of sleep deprivation.

No significant changes were noted in F wave amplitude in any of the subjects, thus ruling out any major contribution of the spinal level to the modifications of TMS parameters during sleep deprivation. Nevertheless, since early intracortical inhibition has been found to be reduced in patients with basal ganglia pathology (Parkinson's diseases) [11], we cannot exclude the possibility of involvement of subcortical structures which may partially influence the excitability of the motor cortex during sleep deprivation.

The significant changes in motor inhibition measured by paired TMS, during sleep deprivation may depend on changes in cortical excitability modulated by an ascending neurotransmitter system such as GABA-ergic and cholinergic mechanisms. GABA-ergic and cholinergic systems are closely related in hypnogenic mechanisms. In addition, the cholinergic system including a number of regions (e.g. brainstem, hypothalamus, amygdala, temporal and cingulate cortex) can increase slow wave sleep and REM sleep [15].

The oscillatory behaviour of the TMS parameters suggests the influence of circadian rhythms on motor excitability as observed for subjective vigilance [5,14]. The return of motor inhibition to baseline values in the morning was associated in fact, with a slight reduction in subjective sleepiness. In conclusion, sleep deprivation, produced a slight but significant decrease in motor excitability in normal subjects, probably related to enhancement of inhibitory mechanisms. The different sensitivities of the TMS parameters to sleep deprivation suggest interesting research possibilities in the field of sleep and motor excitability, which is particularly important in the study of epilepsy.

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