

Alcohol Reduces Prefrontal Cortical Excitability in Humans: A Combined TMS and EEG Study

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The effects of alcohol (0.8 g/kg) on the prefrontal cortex were studied in nine healthy subjects using the technique of transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG). A total of 120 magnetic pulses were delivered with a figure-of-eight coil to the left prefrontal cortex at the rate of 0.4–0.7 Hz. The EEG was recorded simultaneously with 60 scalp electrodes (41 electrodes were used for analysis); the TMS-evoked activation was estimated by the area under the global mean field amplitude (GMFA) time curve. TMS caused changes in EEG activity lasting up to 270 ms poststimulus. Alcohol decreased GMFA at 30–270 ms poststimulus (713 ± 303 vs $478 \pm 142 \mu\text{V ms}$; $p = 0.007$). Alcohol-induced differences were most pronounced at anterior electrodes. These results suggest that alcohol reduces the excitability in the prefrontal cortex.

Neuropsychopharmacology (2003) 28, 747–754. doi:10.1038/sj.npp.1300099

Keywords: alcohol; electroencephalography; prefrontal cortex; transcranial magnetic stimulation

INTRODUCTION

The mechanisms by which alcohol produces its mood-altering and behavioral effects are poorly understood. One approach for studying these mechanisms is to monitor neural activity after alcohol ingestion. A number of studies in humans have examined the effects of intoxication on different frequencies of brain electrical activity. Studies examining the effects of moderate doses of alcohol on spontaneous EEG have generally reported an increase of α -rhythm amplitude and a decrease of the dominant α frequency (Lukas *et al*, 1986). With larger doses, an increase in the lower frequencies is observed (Lehtinen *et al*, 1985). Low doses may produce alterations in θ (4–7 Hz) and in slow α activity (8–9 Hz) (Ehlers *et al*, 1989). However, no information about the brain structures underlying the EEG changes is available.

Other studies have examined the effects of alcohol on regional cerebral blood flow (rCBF) and glucose utilization (CMRglu) yielding conflicting results. Investigators have found decreased rCBF in cerebellum and increased rCBF in the parietal and prefrontal cortex (Volkow *et al*, 1990), increased rCBF in the frontal cortex only (Matthew and

Wilson, 1986), increased rCBF in the right prefrontal cortex (Tiihonen *et al*, 1994), and increased rCBF in all gray matter areas except the left anterior cortical areas (Newlin *et al*, 1982). Decreased CMRglu was found in frontal cortices (De Wit *et al*, 1990). The interpretation of rCBF data is complicated by the fact that alcohol has both vasodilatory and vasoconstrictive effects, which can change blood flow directly.

Transcranial magnetic stimulation (TMS) provides an experimental method for studying localized changes in the electrical properties of the human brain. In TMS, a time-varying magnetic field is generated by a current pulse through a stimulator coil placed above the head. This induces a flow of current in the brain, resulting in neural activation (Barker, 1991). Alcohol has been found to change motor cortex excitability studied by TMS (Ziemann *et al*, 1995).

Recently, TMS has been combined with electroencephalography (EEG) (Ilmoniemi *et al*, 1997; Kähkönen *et al*, 2001a, b; Komssi *et al*, 2002). With this approach, we have recently shown that acute alcohol ingestion is associated with alteration in excitability and functional connections of the motor cortex (Kähkönen *et al*, 2001a). Further, this study showed that the prefrontal cortex is affected by alcohol. TMS combined with EEG allows one to record responses to the stimulation of the prefrontal cortex (Kähkönen *et al*, 2001b). These responses are stimulus-intensity dependent, that is, higher intensities produce greater brain activation (Kähkönen *et al*, 2002). In the present study, we investigated whether alcohol intoxication changes TMS-evoked EEG activity when the prefrontal cortex is stimulated directly.

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Received 26 April 2002; revised 11 October 2002; accepted 18 October 2002

Online publication: 23 October 2002 at <http://www.acnp.org/citations/Npp102302414>

METHODS

Subjects

Nine healthy right-handed nonsmoking male volunteers (25 ± 3.7 years) with no personal history of drug/ethanol abuse participated in the study. The subjects reported having no systemic, neurological, or psychiatric disorders; they used no medication. They were instructed to abstain from food for at least 3 h and from ethanol for at least 48 h prior to participation in the experiment. The study was approved by the local ethical committee. All subjects gave their written informed consent.

Experimental Design and Ethanol Challenge

Only males were included in this study to avoid sex-related differences in the alcohol challenge. Compared to men, women show a higher level of blood alcohol concentration (BAC) after the same dose of alcohol (Marshall *et al*, 1983). Subjects received the conditions in the same order: the baseline TMS-EEG study was followed by ethanol ingestion. They had 30 min to drink the ethanol (0.8 g/kg) dissolved in 10% lemon-flavored solution. After a further 30-min waiting period, the repeated TMS-EEG experiment was performed. The BAC was tested using the SD-2 breath analyzer (Lion Laboratories, Barry, UK) before the alcohol ingestion and after ingestion of alcohol and waiting period.

Magnetic Stimulation

The subjects were seated in a comfortable reclining chair. Studies were performed while they had their eyes open; they used earplugs to avoid possible adverse effects of the auditory click produced by the TMS coil. The stimulation was performed by a figure-of-eight coil, which consisted of two coplanar circular loops 40 mm in diameter. The coil was placed above the left hemisphere and was oriented so that the induced current was in the posterior-anterior direction during the rising phase of the biphasic 320- μ s pulse. After finding the optimal site for activating the right abductor digiti minimi (ADM), the stimulation intensity was adjusted to the motor threshold (MT). Motor evoked potentials were recorded with surface EMG with one electrode on the belly of the muscle and one on the proximal base of the phalange. The MT was determined as the intensity required to evoke the peak potential of at least 50 μ V in four out of eight trials. The left prefrontal cortex was defined as a point located 5 cm anterior and 2 cm lateral from the optimal ADM site. Magnetic pulses were delivered at a random interstimulus interval (ISI) of 1.5–2.5 s. Previous studies have shown that TMS evokes complex EEG responses, which can contain an auditory and possibly also a somatosensory component (Nikouline *et al*, 1999; Tiitinen *et al*, 1999). TMS pulses are accompanied by a click of up to 130 dB (Starck *et al*, 1996). Since part of the auditory response is due to bone-conducted sound (Nikouline *et al*, 1999), we used a piece of plastic between the coil and the scalp to maintain bone conduction in the control condition, while significantly reducing induced electric field by $\sim 70\%$. The experimental protocol consisted of two conditions before and after ethanol ingestion: (1) left prefrontal cortex

TMS ($n = 9$), with the coil pressed against the scalp; and (2) control prefrontal cortex condition (in six randomly selected subjects) with the coil 2 cm from the scalp, but with a piece of plastic connecting the head and the coil. A separate EMG control recording in one randomly selected subject was made in order to explore the possible muscle activity induced by the left prefrontal stimulation. In two conditions, two bipolar platinum needle electrodes were inserted to the main muscle mass of the left or right temporal muscle 3 cm apart. A separate electro-oculography (EOG) recording with two electrodes attached to the outer canthi of left and right eyes in one randomly selected subject was made to explore the possible artifacts related to eye movements. In each condition, at least 120 pulses were delivered.

EEG

The EEG was recorded from 60 scalp electrodes referred to the forehead. To avoid artifacts in the EEG caused by the TMS pulses, an EEG amplifier designed for TMS was used (Virtanen *et al*, 1999). Small Ag/AgCl C-shaped electrodes eliminated possible heating effects. Saturation of the EEG amplifiers during the TMS pulse was avoided by using a sample-and-hold circuit that pinned the amplifier output to a constant level during the brief pulse. The amplifiers were released from the constant output 5 ms after the end of the magnetic pulse. The signals were low-pass filtered at 250 Hz and sampled at the rate of 1450 Hz. After the rejection of epochs contaminated with eye movements and muscle activity, at least 100 responses were averaged.

Analysis

After excluding all channels that appeared noisy at least in one subject, a set of 41 channels was used for the analysis. As prefrontal TMS activates ipsilateral and contralateral hemispheres (Kähkönen *et al*, 2001a,b), the global mean field amplitude (GMFA) was used as an indicator of the strength of an evoked field (Lehmann and Skrandies, 1980). The GMFA was calculated by the formula

$$\frac{\sqrt{\sum_{i=1}^N (v_i - \bar{v})^2}}{N},$$

where v_i is the potential at electrode i , \bar{v} is the average potential of electrodes, and N is their number. The TMS-evoked EEG activation was estimated by the area under the GMFA time curve, which was calculated by the trapezoidal rule from 30 to 270 ms. The time intervals for analysis were chosen on the basis of TMS responses being quickly varying (from 30 to 130 ms) and slowly varying (from 130 to 270 ms). Data were analyzed with two-factor (alcohol; before alcohol/after alcohol \times poststimulus interval; early/late period) repeated measures analyses of variance (ANOVAs), separately for real TMS and real minus control TMS. Pair-wise comparison was made by the two-tailed paired t -test with a Bonferroni correction. The results are expressed as mean \pm standard deviation (M \pm SD).

RESULTS

The baseline BAC was 0.0 ml/l in all subjects. At 30 min after the consumption of ethanol, the BAC was 0.76 ± 0.14 ml/l.

Left prefrontal TMS caused changes in GMFA activity lasting up to 270 ms poststimulus before alcohol ingestion. Figure 1 shows that the differences between before and after alcohol ingestion were largest in frontal and central electrodes.

Figure 2 shows alcohol-induced differences in GMFAs. ANOVA revealed a significant main effect on alcohol

($F(1,8) = 12.9$; $p = 0.007$). No significant interaction between alcohol \times poststimulus interval was observed. Paired t -test showed that the reduction of GMFA by alcohol was significant at 30–130 ms and at 130–270 ms (Table 1). After the subtraction of the control from the real TMS, ANOVA showed a significant main effect on alcohol ($F(1,5) = 8.9$; $p = 0.03$). No significant interaction between alcohol \times poststimulus interval was found. In this subtraction the reduction of GMFA by alcohol was significant at 30–130 ms but not at 130–270 ms (Table 1). Figure 3 demonstrates that alcohol-induced differences

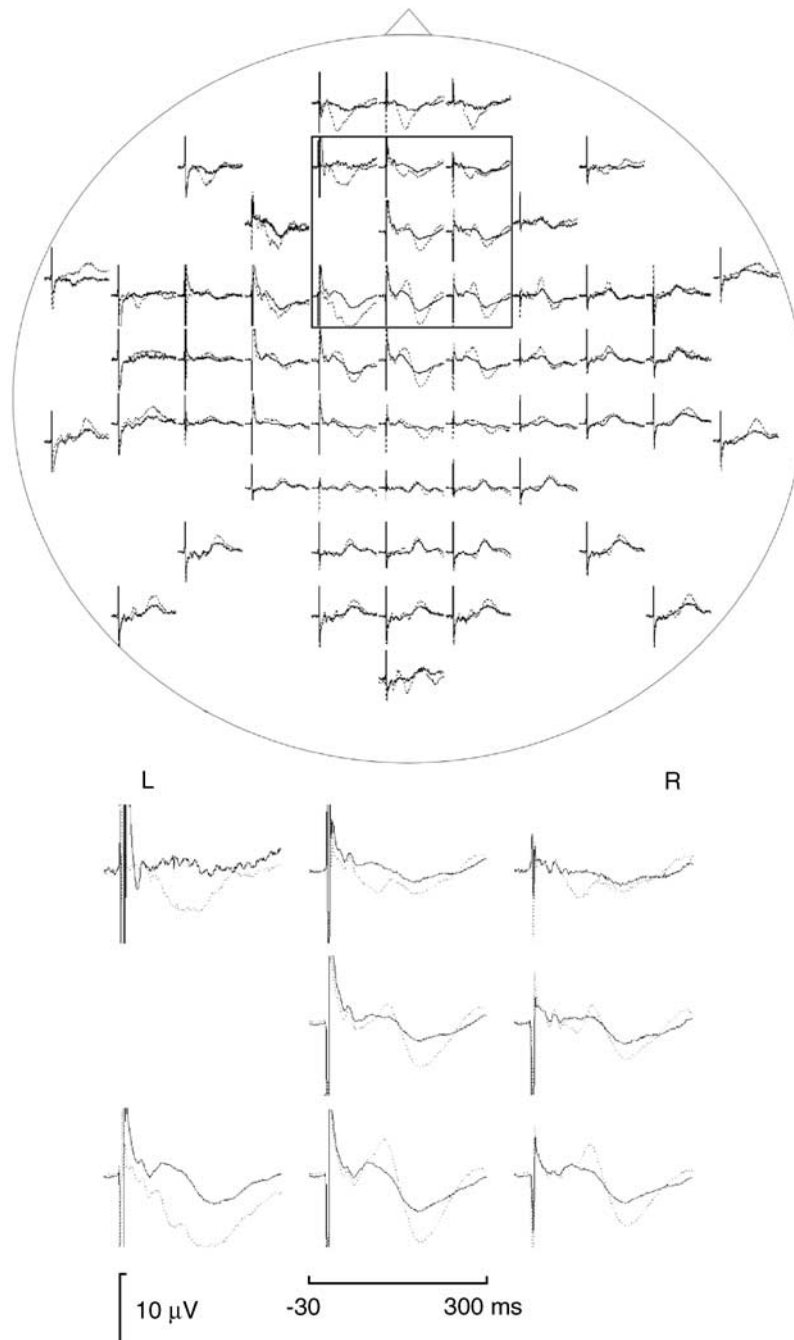
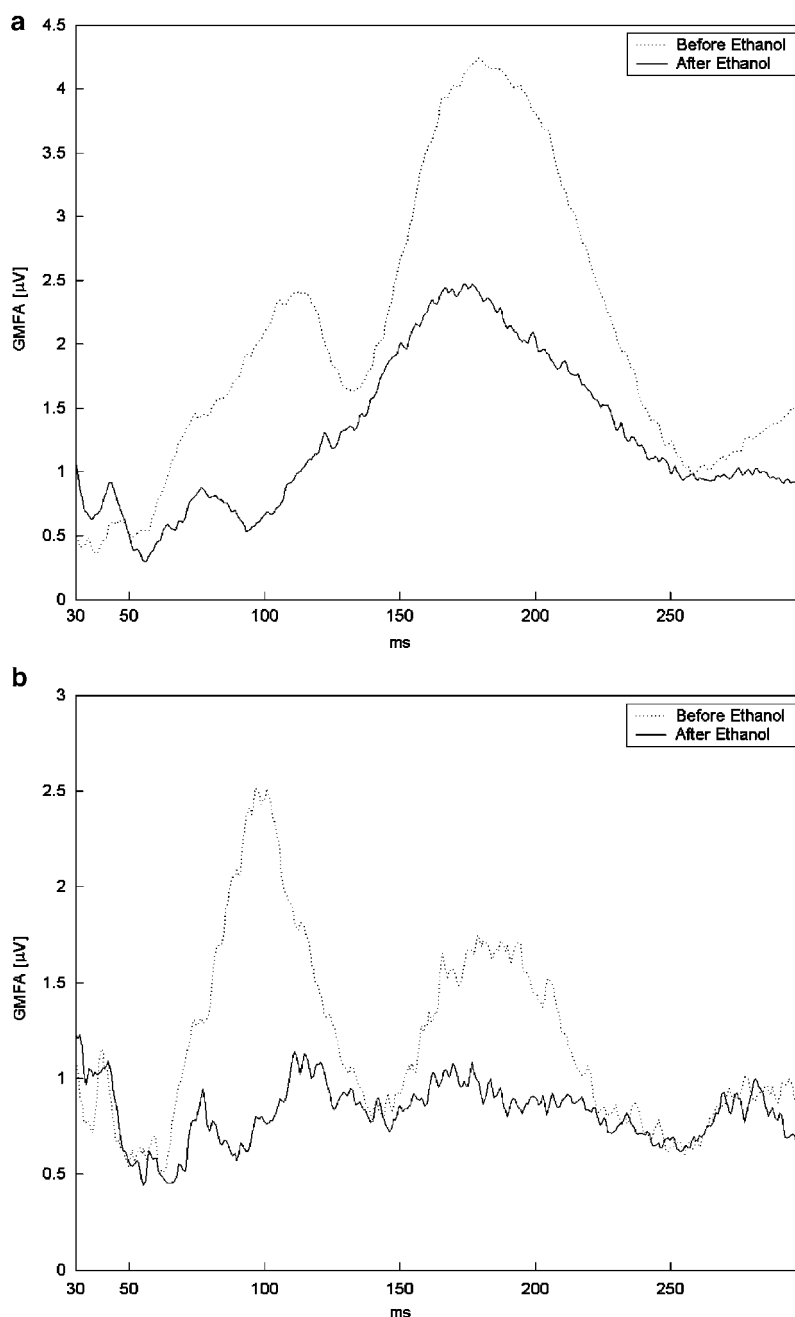


Figure 1 Grand average with common averaged referencing prefrontal TMS-evoked EEG responses before (dotted lines) and after alcohol (solid) challenge. Signals from frontal and central electrodes are enlarged. Artifacts electrodes were removed. Negativity is upward.

Table 1 GMFA Before and After Alcohol Ingestion ($M \pm SD$)

Interval (ms)	Before alcohol ($\mu V ms$)		After alcohol ($\mu V ms$)	
	Real TMS	Real TMS–control	Real TMS	Real TMS–control
30–130	251 ± 83	210 ± 80	$160 \pm 49^{**}$	$156 \pm 44^*$
130–270	462 ± 230	277 ± 114	$318 \pm 104^*$	230 ± 87

$^{**}p < 0.01$; $^*p < 0.05$, paired t -test with a Bonferroni correction. Before and after alcohol ingestion tested.

**Figure 2** GMFA in the prefrontal real-TMS condition (a) and in the condition after subtracting the control from real TMS (b).

assessed by the paired t -test were most pronounced at anterior electrodes. EMG activity was observed up to 30 ms after stimulation (Figure 4a). No significant EOG activity was measured after TMS (Figure 4b).

DISCUSSION

We investigated with prefrontal magnetic stimulation combined with EEG whether alcohol challenge changes

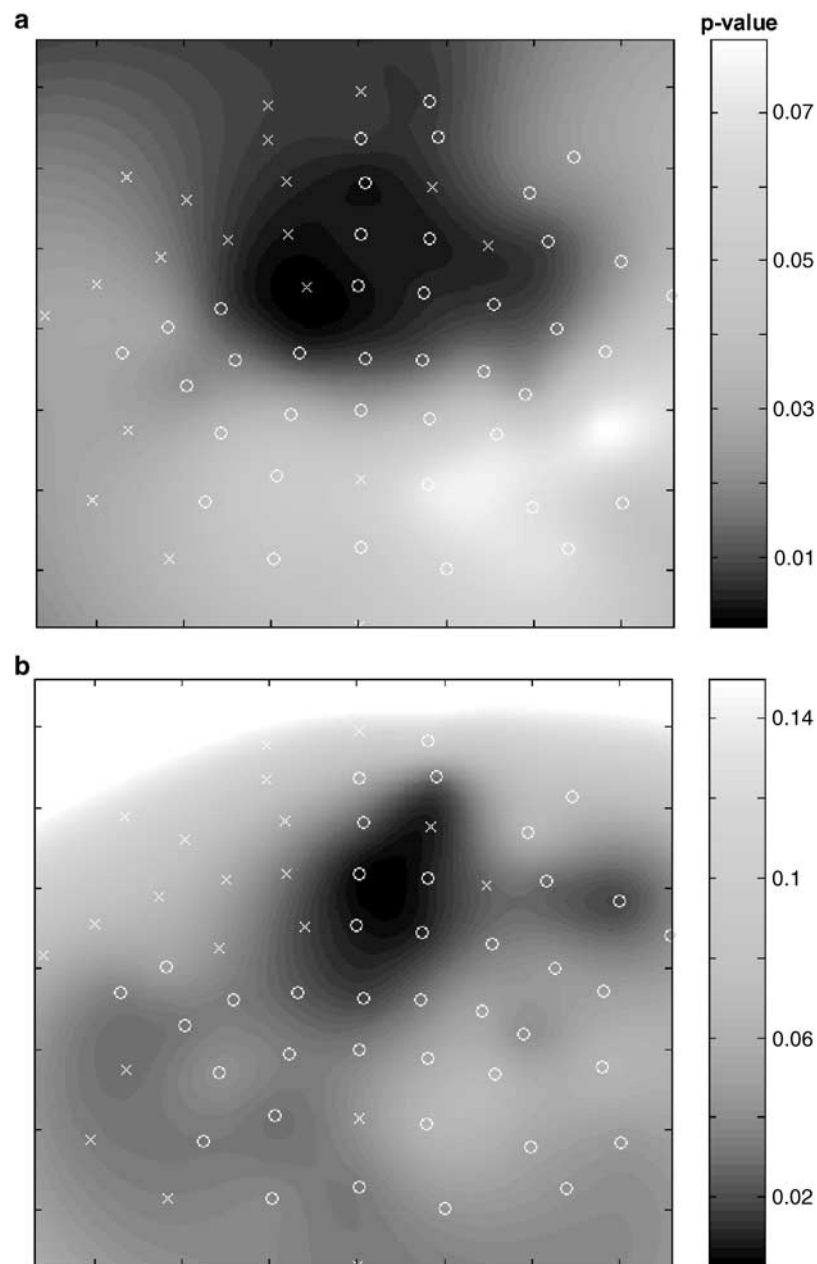


Figure 3 Paired *t*-test maps for the difference of time-integrated EEG responses from 30 to 270 ms (before and after alcohol ingestion) in the prefrontal real-TMS condition (a) and in the condition after subtracting the control from real TMS (b). Circles indicate electrodes used in analysis. Crosses indicate artifacted electrodes. The nose is upwards. Note the low *p*-values in anterior electrodes.

cortical reactivity. A novel finding was that acute alcohol ingestion decreases the GMFA after prefrontal cortex TMS, suggesting reduced cortical excitability. The reduction of GMFA was evident in the data also after the subtraction of the control from real TMS. This indicates that the results were not due to TMS-induced auditory activation. The strongest decrease was observed at anterior EEG electrodes. Other controls with EOG and EMG after TMS showed that the EEG changes did not result from eye movements or muscle twitches during the experiments.

Alcohol has been found to reduce motor cortex excitability by Ziemann *et al* (1995). In their study, TMS was combined with EMG, which gives only indirect evidence

about the excitability of the motor cortex, because these responses might be modulated by spinal mechanisms (Morita *et al*, 1999; Nielsen *et al*, 1999a,b). In contrast to this, we used the combination of TMS and EEG, which provides direct information about cortical excitability after stimulation of different sites (Ilmoniemi *et al*, 1997; Kähkönen *et al*, 2001a,b, 2002; Komssi *et al*, 2002).

Surface electrical stimulation of the motor cortex causes inhibitory postsynaptic potentials (IPSPs) through interneurons (Rosenthal *et al*, 1967). The IPSPs are probably γ amino butyric acid (GABA)-mediated; ethanol has been shown to potentiate this inhibition (for a review, see Korpi, 1994). GABA mechanisms may constitute one of the factors

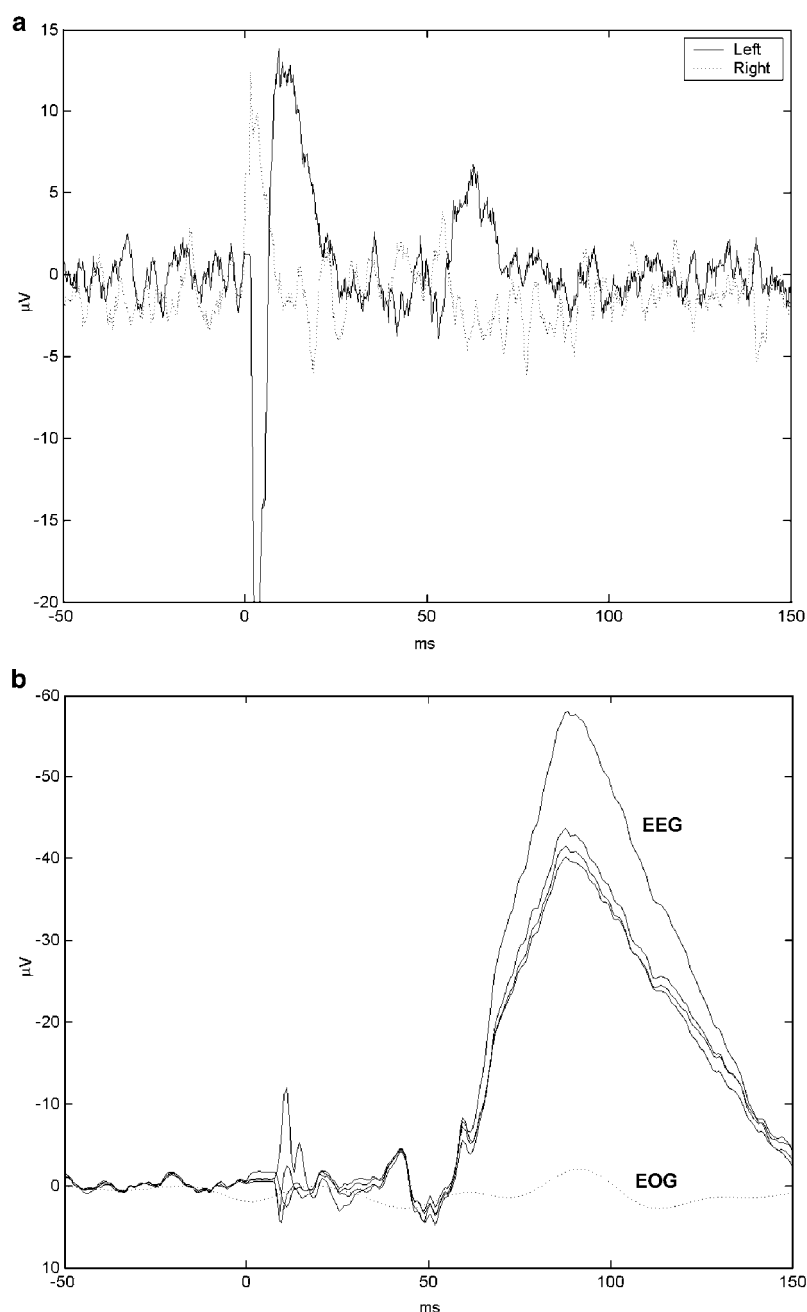


Figure 4 (a) Averaged EMG to the left prefrontal TMS pulses as recorded with the bipolar platinum electrodes in one subject from temporal muscles. (b) Horizontal electro-oculogram after prefrontal TMS in one subject (dotted line). EEG responses of the same subject from frontal electrodes (solid lines). Note that the EOG signal has been low-pass-filtered at 35 Hz.

underlying the observed reduction of electrical activity by alcohol in the prefrontal cortex. Neurochemical effects other than GABA are also likely to exist, for example, the inhibition of *N*-methyl-D-aspartate-activated (NMDA) currents by ethanol (Lovinger *et al*, 1989). The NMDA antagonists memantine and riluzole have been shown to enhance intracortical inhibition and to reduce intracortical facilitation in comparison to placebo studied by TMS (Schwenkreis *et al*, 1999, 2000). Alcohol has also been shown to modulate dopamine function in the prefrontal cortex (Boone *et al*, 1997; Nielsen *et al*, 1999a, b). Recently, Strafella *et al* (2001) showed that 10-Hz high-frequency

rTMS of the prefrontal cortex induces the release of endogenous dopamine from subcortical nuclei. Further, alcohol may change the function of serotonin (Yukhananov *et al*, 1992). Prefrontal TMS may modify the function of serotonin (Gur *et al*, 2000). Summarizing, the effects of alcohol after prefrontal TMS may be mediated through its interaction with GABA, NMDA/glutamate, dopamine, and/or serotonin.

One confounding factor may be related to the test-retest study design (separated from each other by at least 1.5 h) used by us. The suppression of motor cortex excitability after low-frequency rTMS has been shown to exert effects

lasting beyond the time of stimulation (Wassermann *et al*, 1996; Chen *et al*, 1997), but was not supported by Siebner *et al* (1999). In the latter study motor cortex TMS did not change motor-evoked-potential input-output curves after 30 min of 1-Hz stimulation. Furthermore, the excitability of the prefrontal cortex is lower than that of the motor cortex (Kähkönen *et al*, submitted). It is unlikely that in our study 0.4–0.7 Hz TMS with 120 stimuli (lasting for 4 min only) could decrease the excitability of the prefrontal cortex after 1.5 h. However, the single-pulse technique used by us does not allow the separation of cortical inhibition and facilitation. In the future, placebo-controlled studies with a paired-pulse technique will allow one to take into consideration the possible confounding factors and expand our understanding on the effects of alcohol on different cortical processes.

The reduction of TMS-evoked electrical activity following alcohol ingestion is in line with the results of glucose metabolism studies in humans and animals. These studies have shown that alcohol decreases CMRglu in the cortex, in particular in the prefrontal areas. Whole-brain CMRglu, studied by positron emission tomography, was decreased after the administration of alcohol, in particular at a dose of 0.8 g/kg (the dose we used in this study). The decreased CMRglu was marked in frontal cortices bilaterally (De Wit *et al*, 1990). At a higher dose (1 g/kg), alcohol decreased cortical (including prefrontal areas) and cerebellar CMRglu with relative sparing of the basal ganglia and corpus callosum (Volkow *et al*, 1990). The decrease of CMRglu after alcohol administration was also documented in *in vivo* autoradiographic studies in rats (Eckardt *et al*, 1988). In these studies, changes in brain functions after alcohol administration were detected with a time resolution of minutes. In contrast to this, TMS allowed us to excite the prefrontal cortex locally and to monitor changes of neuronal activity directly by high-resolution EEG in millisecond accuracy.

In conclusion, alcohol-reduced cortical excitability was detected by focal prefrontal magnetic stimulation combined with high-resolution EEG. The reduction of prefrontal excitability may be associated with symptoms of alcohol intoxication such as mood lability and impairments in attention, memory, and judgement.

ACKNOWLEDGEMENTS

This work was supported by Helsinki University Central Hospital Research Funds and the Academy of Finland. We thank Matti Holli, MD and Jari Karhu, MD, PhD for helping with the experiments, and also Jarmo Ruohonen, PhD for calculations of the induced field by the TMS coil.

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