INVITED REVIEW

MEG and TMS combined with EEG for mapping alcohol effects

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Received 3 May 2005; received in revised form 24 November 2005; accepted 29 November 2005

Abstract

Magnetoencephalography (MEG) is a noninvasive method of studying magnetic fields from outside the skull that are generated by at least partially synchronized neuronal populations in the brain. The advantage of MEG over electroencephalography (EEG) is the transparency of the skull, scalp, and brain tissue to the magnetic fields, which facilitates easy localization of the cortical activity. In MEG, alcohol increased the relative power of the alpha rhythm and reduced the relative power of beta activity in parieto-occipital regions. In contrast, no changes were observed in EEG, indicating that these methods differently detect alcohol’s action on the cortex. Furthermore, MEG and EEG also differently detected the effects of alcohol on cognition. Alcohol reduced magnetic and electric auditory N1 and mismatch negativity amplitudes. P3a amplitudes were also reduced in EEG but not in MEG, suggesting that different cortical areas are responsible for alcohol’s action on involuntary attention. Transcranial magnetic stimulation (TMS) provides new possibilities for studying localized changes in the electrical properties of the human cortex, especially when combined with EEG. Different cortical areas can be stimulated and the subsequent brain activity can be measured, yielding information about cortical excitability and connectivity. Alcohol modulates EEG responses evoked by motor-cortex TMS, the effects being largest at the right prefrontal cortex (assessed by minimum-norm estimation), meaning that alcohol changed the functional connectivity between motor and prefrontal cortices. Furthermore, alcohol decreases amplitudes of EEG responses after the left prefrontal stimulation of anterior parts of the cortex, which may be associated with the decrease of prefrontal cortical excitability. Taken together, MEG and TMS combined with EEG provide new insight into the focal actions of alcohol on the cortex with a temporal resolution of milliseconds, giving information different from that given by other brain imaging modalities. © 2005 Elsevier Inc. All rights reserved.

Keywords: Alcohol; Electroencephalography (EEG); Magnetoencephalography (MEG); Transcranial magnetic stimulation (TMS)

1. Introduction

The direct approach to the study of the mechanisms of alcohol’s mood-altering and behavioral effects is to monitor neural activity after alcohol ingestion. A number of studies on humans have examined the effects of intoxication on different frequencies of brain electrical activity and evoked potentials with electroencephalography (EEG; Polich & Ochoa, 2004; Porjesz et al., 2005). Most studies have shown an increase of alpha oscillations (10 Hz) after ingestion of a moderate dose of alcohol (Ehlers et al., 1989; Ilan & Gevins, 2001; Noldy & Carlen, 1990). Biphasic changes in brain oscillations following alcohol administration have been also observed: an initial increase in alpha and similarly in beta activity during the absorption phase followed by a decrease of those oscillations after 1 h (Schwarz et al., 1981). EEG has been also used to study the effects of alcohol on neural bases of auditory information processing with a high temporal resolution in milliseconds. Alcohol has been shown to reduce mismatch negativity (MMN) and P3a amplitudes and to increase their latencies dose dependently (for a review, see Jääskeläinen et al., 1996). However, these studies do not provide information about the brain structures underlying the observed changes.

2. Magnetoencephalography for detecting cortical neuronal activity

When a neuron is active, small currents flow in the intracellular space. The synchronous activation of many neurons can be measured as a difference of potentials between two points on the scalp with EEG. Magnetoencephalography (MEG) is a neurophysiological technique that allows the recording of magnetic fields detected at the scalp with superconducting quantum interference device sensors generated by brain activity (Fig. 1; for a review, see Parra...
et al., 2004). The unique feature of the MEG technique is the transparency of the skull, scalp, and brain tissue to the magnetic fields. An EEG signal, on the other hand, is strongly influenced by the properties of the head. Both methods offer high temporal resolution, which provides a means to study the instantaneous neuronal effects in the brain with a timescale of milliseconds, which is presently not possible with any brain imaging method. However, the localization of MEG brain sources is less complicated by the irregular distortions caused by the skull and tissue than that of EEG sources. Another difference between EEG and MEG is that the latter measures mostly primary currents oriented tangentially with the surface of the head (sulcus dipoles). This property makes MEG ideally suited for the measurement of alcohol’s effects in sensory cortices. EEG is sensitive to both radial and tangential sources. MEG has been shown to be an important tool in the investigation of brain dynamics after the administration of central nervous system drugs (Kähkönen & Alveninen, 2002).

3. Effects of alcohol on involuntary attention and cortical oscillations studied with simultaneous MEG/EEG

Recently, we studied the effects of alcohol on the neural bases of involuntary attention with combined whole-head MEG and EEG (Kähkönen et al., 2005b). Healthy subjects ingested 0.8 g/kg alcohol or juice in a double-blind, placebo-controlled, cross-over study design. Auditory evoked potentials and magnetic fields elicited by infrequent deviant tones differing in frequency (5 and 20% change) and novel sounds in a passive odd-ball paradigm were recorded with 306-channel MEG and 60-electrode EEG. Subjects watched a silent video and were instructed not to attend to the stimuli. Stimuli were presented separately to the left and right ears. Results showed that alcohol bilaterally reduced magnetic and electric N1 and MMN amplitudes. P3a amplitudes were also reduced in EEG but not in MEG. Hemisphere differences were not observed in amplitude reductions, and neither did alcohol affect the latencies of components. The EEG results regarding the reductions of N1, MMN, and P3a amplitudes after alcohol ingestion are well in line with those obtained by Jääskeläinen et al. (1996). MEG was able to detect the alcohol-induced reduction of amplitude only in magnetic MMN and N1 in the auditory cortices.

The dissociation of the MEG and EEG results after alcohol administration may be partly due to the different sensitivity of EEG and MEG to detect the alcohol-related changes during auditory processing. MEG mainly detects the tangential cortical sources (Hämäläinen et al., 1993) and therefore measures the electromagnetic activity in the cortical fissures.

Fig. 1. Measurements of magnetic auditory responses by whole-head magnetoencephalography. The magnetic field surrounding the head is measured with a superconducting quantum interference device (SQUID) magnetometer in a magnetically shielded room while the subject is listening to the sounds. The SQUIDs are kept superconducting at a temperature of 4 K by liquid helium contained in a thermally isolated Dewar vessel. (A) Auditory evoked magnetic fields of mismatch negativity (MMNm) to frequency change indicated by the difference wave obtained by subtracting the responses to standard tones from those to deviant tones. According to the principles of auditory parallel processing (Kelly, 1994), the left ear stimulation elicits the largest MMNm over the right and left temporal areas, indicating that both auditory cortices process the sound. Enlarged responses present the channel showing the largest responses over the temporal areas. (B) The isofield contour map from the same subject for MMNm. Solid lines represent areas where magnetic flux exits and dotted lines represent areas where it enters the head. The arrows depict the strength and location of a single equivalent current dipole of MMNm applied to the data.
EEG in turn detects both tangential sources and particularly the radial currents generated by the cortical gyri. MMN and P3a have bilateral generators in the auditory cortex. Alcohol similarly reduced the change detection in the auditory cortex independently of the site of stimulation. As the reduction of P3a was present only in EEG, this suggests that sources other than supratemporal regions were involved in this process. It is most probable that the frontal cortex was responsible for this change. When all data are taken together, alcohol has various effects on the neural base of involuntary attention detected by MEG and EEG, reflecting their different sensitivity to cortical sources.

In another study, healthy subjects ingested 0.8 g/kg alcohol or juice in a double-blind, placebo-controlled, crossover study design (Nikulin et al., 2005). Spontaneous brain activity was measured with MEG and EEG in eyes open and eyes closed conditions. Alcohol significantly increased the relative power of the alpha rhythm (8–10 Hz) and reduced the relative power of beta activity (17–25 Hz) recorded over the parieto-occipital regions of the left and right hemispheres in MEG, but only in the eyes closed condition. No changes were observed in EEG rhythms. However, the power of the alpha and beta rhythms was positively correlated in MEG and EEG recordings, indicating that MEG and EEG reflect similar processes. A distinct sensitivity of MEG and EEG to the sources of cortical oscillations as well as the strong spatial blurring of potentials in EEG are most likely the reasons for the observed differences in the effects of alcohol on spontaneous oscillations.

4. Transcranial magnetic stimulation combined with simultaneous EEG

Transcranial magnetic stimulation (TMS) is a noninvasive tool to study a localized part of the human brain (Barker, 1991; George et al., 2003). In TMS, a time-varying magnetic field is generated by driving current pulses through a stimulator coil placed above the head. This induces an electric field in the brain, resulting in membrane depolarization and neuronal activation. TMS has been used widely in pharmacological studies to investigate the effects of different drugs on the motor cortex with a simultaneous recording of motor evoked potentials (Kähkönen & Ilmoniemi, 2004; Ziemann, 2004). TMS has been combined with brain imaging methods such as single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) to study the excitability and connectivity of the cortex (for a review, see Sack & Linden, 2003). However, fMRI, SPECT, and PET measure changes in cerebral blood flow giving only indirect evidence about neuronal activation. Direct effects of TMS on brain blood vessels cannot be ruled out, which is important for alcohol research. Recently, TMS has been combined with EEG, which allows direct evidence to be obtained about TMS-evoked transient changes in neuronal activation in a time resolution of milliseconds in different conditions (Bender et al., 2005; Fuggetta et al., 2005; Ilmoniemi et al., 1997; Kähkönen et al., 2001, 2003; Paus et al., 2001; Thut et al., 2003) (Fig. 2).
For example, stimulation of the left sensorimotor hand area elicited an immediate intensity-dependent response at the stimulated site and a subsequent spread of activation about 20 ms after stimulation to the contralateral hemisphere (Ilmoniemi et al., 1997; Komssi et al., 2004). TMS combined with EEG has also been applied to nonmotor cortical areas, such as the prefrontal cortex. Prefrontal TMS caused an intensity-dependent increase in EEG responses, but the extent of activation varied at different intervals after stimulation (Kählönen et al., 2005a, b). TMS/EEG allows the differences in excitability between cortical areas to be studied. Cortical reactivity after prefrontal TMS was lower compared with that after motor-cortex TMS. However, reactivities after prefrontal TMS and motor-cortex TMS correlated positively (Kählönen et al., 2004, 2005a).

5. Effects of alcohol studied with TMS/EEG

We studied the effects of alcohol on EEG responses evoked by magnetic stimulation, demonstrating the potential of combined TMS and EEG in neuropsychopharmacological studies. A dose of 0.8 g/kg alcohol was given to healthy subjects; EEG responses to left motor-cortex TMS were recorded before and after the alcohol challenge (Kählönen et al., 2001). Alcohol changed the EEG responses mainly at 45 ms after stimulation at the site of stimulation and at the right frontal areas. An inverse solve procedure called minimum-norm estimation was used to locate the effects more precisely. Activation of the right prefrontal area seemed to be most clearly affected, meaning that alcohol would have changed the functional connectivity between the left motor cortex and the right prefrontal cortex. In another study, EEG responses after left prefrontal TMS were measured before and after alcohol intake (Kählönen et al., 2003). Alcohol decreased the global mean field amplitude, the effect being greatest in the anterior EEG electrodes. These studies provide direct evidence that alcohol could change local cortical excitability and functional connectivity to remote sites.

6. Conclusions

MEG and TMS combined with EEG in a temporal resolution of milliseconds with high spatial accuracy give new insight into the actions of alcohol on cerebral dynamics. Alcohol effects on different cortical areas with functionally connected areas can be studied to obtain direct information about alcohol effects on neural activity. These studies revealed that alcohol has multiple actions on resting and activated brain. Alcohol decreased the activity of auditory and frontal cortices, probably mediating alcohol-induced cognitive dysfunction. Alcohol also decreased the activity of motor and frontal cortices. These changes may contribute to the symptoms of acute alcohol intoxication such as motor incoordination, mood lability, and impairments in attention, memory, and judgment. In future, studies with multiple alcohol doses with pharmacokinetics are necessary for further testing of the usefulness of neuromagnetic methods.

Acknowledgments

This work was supported by the Helsinki University Central Hospital Research Funds and the Academy of Finland.

References


