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Electroencephalographic recording during transcranial magnetic stimulation in humans and animals☆

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Abstract

Objective: We report on the development of an EEG recording system, comprised of electrodes and amplifiers that are compatible with TMS (single and rapid-rate) in both human and animal studies.
Methods: We assembled a versatile multi-channel EEG recording system consisting of: (1) two types of electrodes that are safe during TMS or rTMS. (2) Low slew-rate EEG amplifiers that recover within a few milliseconds after the application of TMS pulses.
Results: The two electrode types: (a) a conductive-plastic surface electrode with a conductive-silver epoxy coat and (b) a subdermal silver wire electrode (SWE) are compatible to TMS pulses. The amplifiers recover within 30 ms, so that the EEG can be viewed online, essentially without interruption and/or blocking or excessive artifact.
Conclusions: Our TMS compatible electrode and EEG recording system allows safe and online viewing/recording of the subject's (human or animal) EEG/EP during experiments or studies involving TMS or rTMS applications. The TMS compatible electrode/amplifier system can be used with any EEG recording instrument.
Significance: A simple recording technique coupled with new electrodes permit safe and readable EEG records during TMS in humans and animals. Such online monitoring of the EEG would allow control of TMS/rTMS parameters based on EEG activity.

Keywords: Electroencephalogram (EEG); Transcranial magnetic stimulation (TMS); Electrode; Human; Animal; Safety; Epilepsy

1. Introduction

Transcranial magnetic stimulation (TMS) for human cortical stimulation was first demonstrated in 1985 by Barker et al. (1985). TMS can induce motor, perceptual, cognitive and behavioral effects, and repetitive TMS may have therapeutic applications in a variety of conditions (Pascual-Leone et al., 2002; Walsh and Pascual-Leone, 2003). However, the neural correlates of such effects are not clear. Concurrent monitoring of brain activity during TMS would allow one to relate behavioral with neurophysiologic effects of the stimulation. In addition, online monitoring of the neurophysiologic effects of TMS may help make it safer, and timing the TMS to coincide with specific physiologic

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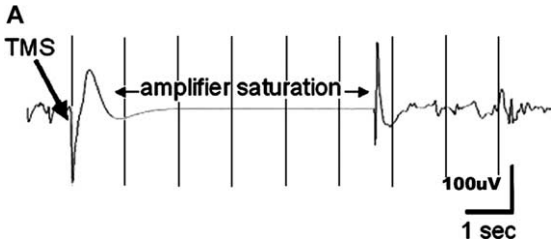

Fig. 1. This illustrates the recording characteristics of a typical EEG data acquisition system when a single TMS pulse is applied to the same rat recording setup shown in Fig. 3a. Generally all the EEG channels block for a period of time related to the strength of the TMS pulse and the front-end characteristics of the amplifiers.

events may make it more effective. Therefore, real-time recording of brain activity during TMS would be desirable. Unfortunately, recording the EEG during TMS is challenging (Thut et al., 2003a,b, 2005). TMS induces 'Eddy-currents' in traditional metal EEG electrodes causing heating and posing a risk of burning of the tissue under the electrode (Pascual-Leone et al., 1990,1993; Roth et al., 1992; Wassermann, 1998). Traditional EEG amplifiers were either blocked for many seconds (see Fig. 1) or minutes, and some amplifiers can even be destroyed by the short but intensive TMS energy burst. A solution to recording the EEG and evoked potentials (EP) during TMS was first demonstrated by Ilmoniemi et al. (1997) using a switching EEG amplifier circuit controlled by the initiation of the TMS pulse. In our approach, we used stand-alone, low slew-rate amplifiers (Epstein, 1995) with complimentary attenuation between the preparation and the existing EEG recording device (Ives et al., 1998). This simplified the setup, eliminates the need for complex integration and allows any EEG instrument to be used (gain, filter) as though it was directly connected to the electrodes. A discussion of this system and viable methodology to utilize if for studies in cognitive function in humans has been previously presented (Thut et al., 2003a,b, 2005). We focus now on the utility of the system in both humans and animal models to study the effects of TMS on the brain and the online monitoring of EEG activity.

2. Methods

2.1. Methods (human)

EEG monitoring in humans is traditionally performed with metal disc electrodes made of tin, pure silver or pure silver with a gold coating. These 1 cm diameter metal disc electrodes have a considerable surface area and thus sufficient mass to permit 'Eddy-currents' to be generated during TMS or rTMS applications. The 'Eddy-currents' in turn, can cause heating and subsequent burning of the underlying tissue (Roth et al., 1992; Wassermann, 1998). Recently we have developed a conductive plastic electrode (Plastic One model 36562) with low mass and conductivity to reduce the effect of 'Eddy-currents'. However, conductive plastic electrodes did not record a high quality EEG or EP. Therefore, a thin layer of conductive silver-epoxy (Chemtronics model CW2200STP) was added to create a silver–silver chloride (Ag–Ag/Cl) electrode with 'excellent' recording characteristics (Tallgren et al., 2005).

Traditional EEG machines are usually designed with high quality, precision, wide-band, low noise operational amplifiers. The TMS pulse has a very high energy component, but only lasts for a very short time, in the order of 200 μs. Traditional amplifiers, because of their design and wide-band characteristics, respond to this fast, high-energy transient possibly saturating and thus blocking for a substantial period of time. One approach to dealing with this phenomenon is to block or shutoff the amplifier during the TMS pulse period (Ilmoniemi et al., 1997). This makes for a fairly complicated circuit design that requires integration of the timing of the TMS machine into the EEG amplifier circuit.

In our application we use a low slew-rate (0.07 V/μs) operational amplifier (LT2079, Linear Technology Corp., Milpitas, CA) with a relatively low gain-bandwidth product (200 kHz). By adjusting the gain, the bandwidth (or slew-rate) is a variable. Therefore, in our specific application, a gain of 2200 creates a high frequency cutoff of 90 Hz with significant slew rate limiting properties. In the demultiplexing unit we incorporate complimentary attenuation of 2200. Thus a low slew-rate EEG amplifier can be placed between the electrodes and any EEG recording device. The amplifier's internal low slew-rate prevents the circuit from responding to the very high slew-rate of the TMS pulse and thus prevents blocking and significantly reduces the artifact in the EEG associated with the TMS pulse.

2.2. Methods (animal)

EEG recording in animals is traditionally performed with either subdermal stainless steel or platinum needle electrodes (Pellegrino and Sica, 2004) or surgically placed epidural stainless steel skull screw electrodes, since traditional disc electrodes are not appropriate in animal preparations. However, if the electrodes have any magnetic properties they will be affected by the TMS pulse, and cause movement or influence the distribution of the applied magnetic field. A new subdermal wire electrode (SWE) has been developed that is ideal for animal biopotential signal recording. The SWE has been fully described as a chronic EEG electrode a neuro ICU application (Ives, 2005; Young et al., 2006) and has been adapted for use in animals. The SWE is essentially a 0.25 mm, Teflon insulated, Ag–Ag/Cl wire electrode (Tallgren et al., 2005) that is now placed using a 25 gauge, 16 mm hypodermic needle. The SWE has applications as a TMS compatible electrode in animals (Ives et al., 2005; Poma et al., 2005). For use in the small rodent (mouse, rat), the length of the SWE was reduced to 2 cm. The 5 cm SWE length worked best for the dog studies as the head was larger and the hair was longer.

In most circumstances, the SWEs could be placed in the awake dog. In the rodent, a gentle restraint works best and enables 3 SWEs to be placed in seconds without surgery. In this setting, the SWE records a better quality EEG than surgically placed epidural stainless-steel screw electrodes or needle electrodes. Again the amplifier/attenuator unit can be placed between the animal/electrode preparation and any EEG recording device.

3. Results

3.1. Results (human)

To date, two applications have been applied to human recording of the EEG (EP) during TMS. In the first application, 16 channels of EEG were recorded from standard 10–20 electrode locations during selected studies

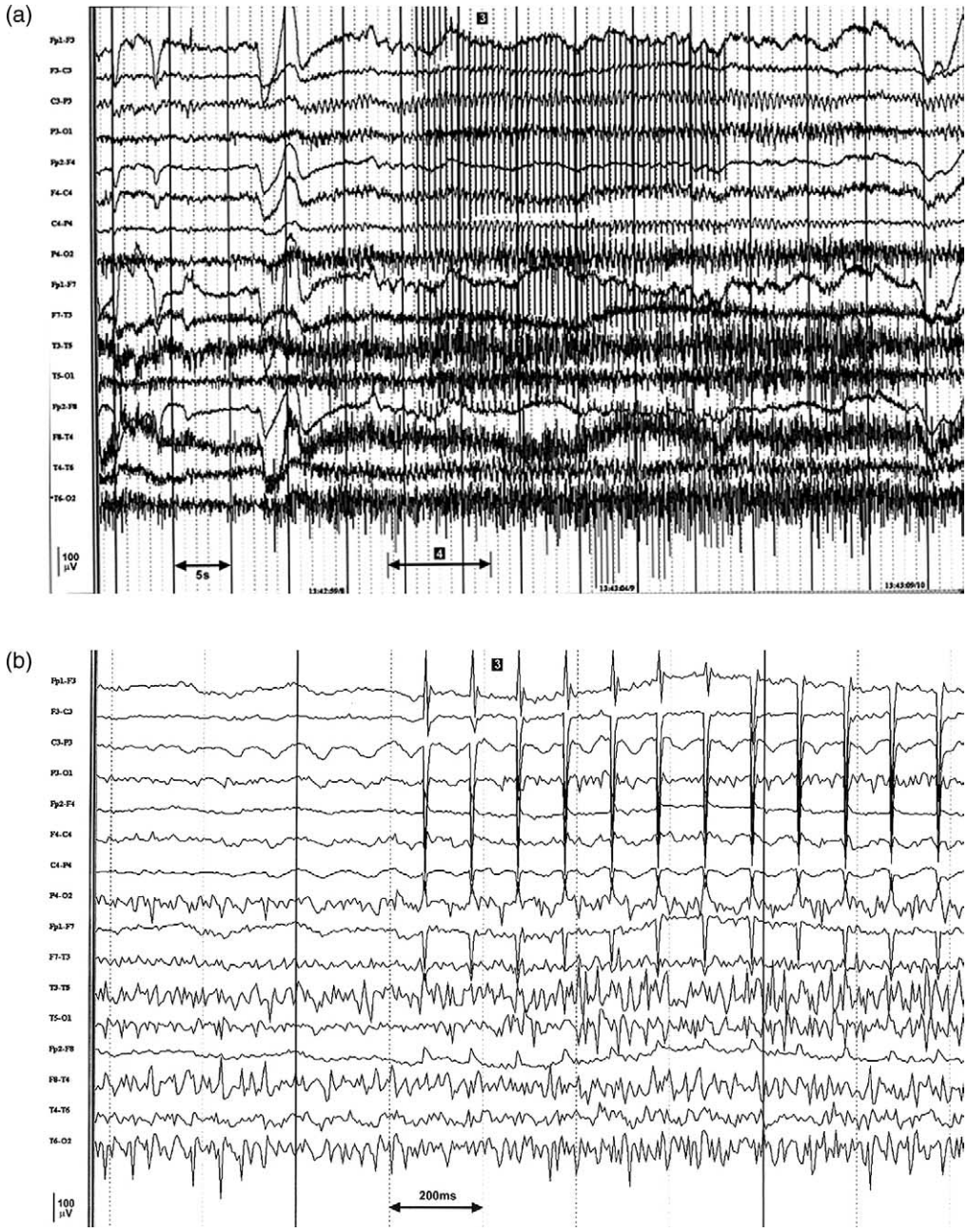

Fig. 2. (a) Illustrates a section of EEG obtained during the application of rTMS from a MagStim (Magstim Company US LLC, Woburn, MA) at 80%, at a rate of 10 Hz for 20 s using the low slew-rate amplifier/attenuator system. The duration of the TMS pulse is in the order of 200 μs and generates a peak magnetic field of 2.3 T. This is an unprocessed EEG and shown as recorded. The subject's EEG can be clearly seen during the application of the rTMS since the artifact's blocking is minimal. The marked section of EEG (4), between the arrows has been expanded in Fig. 1b. (b) This shows the expanded section (4) of EEG in Fig. 1a. The details of the TMS artifact can be clearly seen and are maximal over the left frontal-central area where the Fig. 8 coil was located. Some channels that are physically farther from the coil are not affected at all.

investigating the influence of rTMS on patients with depression. In the second application, EP recordings from up to 48 electrode sites in subjects during TMS studies were conducted (Thut et al., 2003a,b, 2005). Similar amplifiers were used, but with a more complicated, integrated data acquisition method to further reduce the effect of the TMS artifact using post-analysis techniques. A multi-channel EEG from a patient during 10 Hz, rTMS is shown in Fig. 2a. An expansion of the time-based during the presentation of the individual rTMS pulses are illustrated in Fig. 2b.

3.2. Results (animal)

We have recorded the EEG during TMS and rTMS on mice, rats and dogs (Ives et al., 2005) using the same designed amplifiers, but arranged in a smaller configurations to achieve miniaturization and thus, have limited the number of channels to 8. This has resulted in a very small (2×2 cm), 8-channel amplifier/multiplexer configuration that accepts the input from the TMS compatible electrodes. The multiplexed signal can then be demultiplexed, and

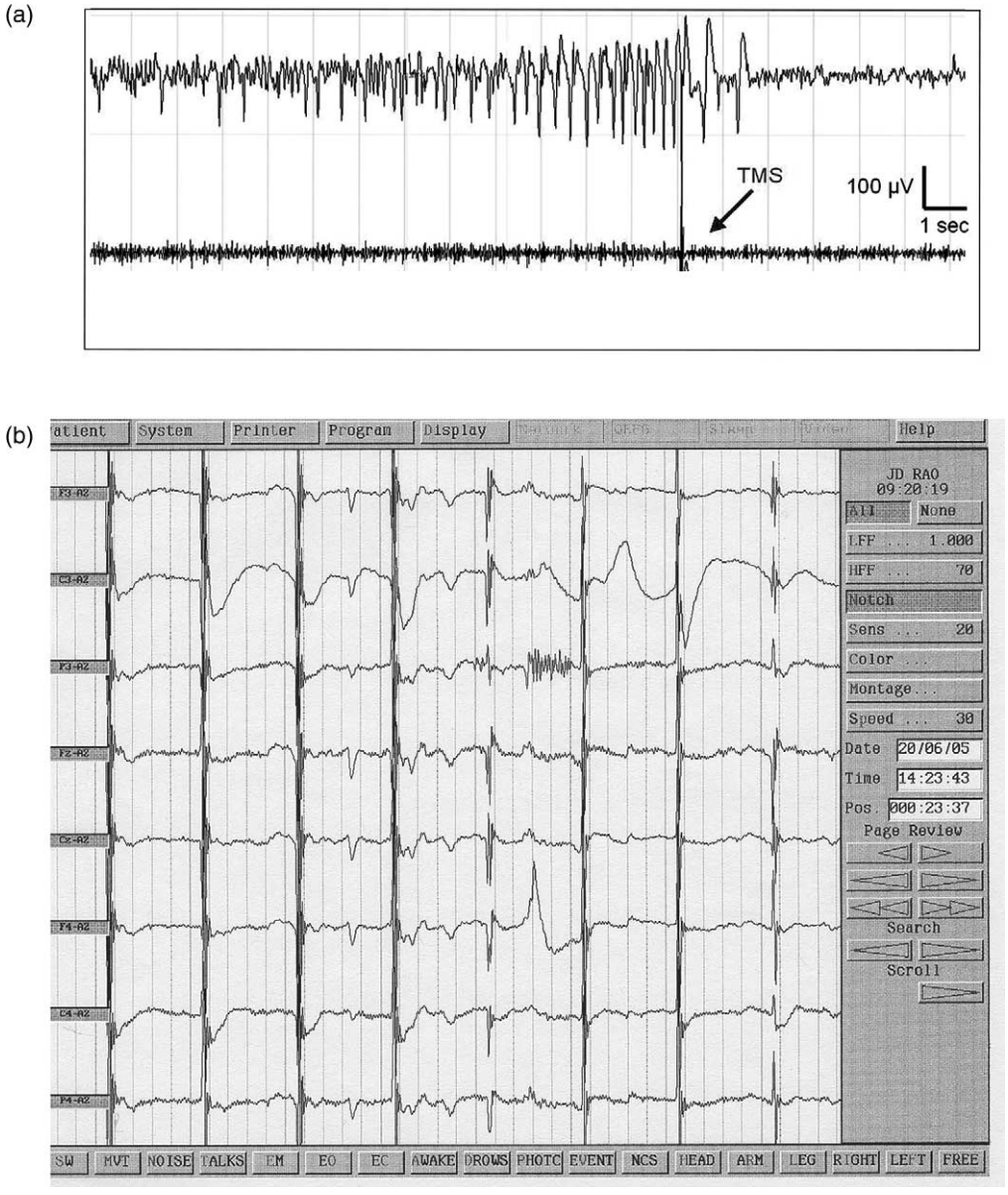

Fig. 3. (a) EEG recorded from a rat during a kainate (KA) induced seizure. The bottom tracing is an open channel that is used to detect the TMS artifact (antenna effect). The top tracing shows EEG obtained from two subdermal wire electrodes. Just after the spontaneous seizure discharge starts a single-pulse TMS at 70% is delivered that disrupts both the morphology and the progression of the seizure. The TMS device used was a Cadwell unit (Cadwell Laboratories, Inc., Kennewick, WA). (b) This shows the EEG recorded from a dog during the application of single pulse TMS repeated every second. The TMS device used in this case was also a Cadwell unit at 70% of peak.

attenuated to serve as inputs to any EEG machine. The short, 2 cm length SWE works well in the small rodent applications, while the longer 5 cm length works better in the canine application where the fur/hair is longer and the head larger. Fig. 3a shows a bipolar EEG recorded from a rat during a kinase induced seizure that was interrupted by a single TMS pulse. Fig. 3b shows a multi-channel EEG from a dog during 1 Hz single pulse TMS.

4. Discussion

Our data demonstrate the newly developed ability to record EEG during TMS in humans and experimental animals without blocking and with less artifact than conventional recording systems. The described method of recording EEG during TMS or rTMS places a simple amplifier/attenuator system between the recording site and any EEG recording device. Therefore the recording is straightforward and the EEG looks unaltered since it permits all the usually front-end controls (gain, low, high and notch frequency filtering) to be operational. Our methods' advantage is that the expected artifact and blocking seen with commercial EEG amplifiers is eliminated or significantly reduced so that the underlying EEG can be seen. The artifact generated in our EEG recording system varies with the magnitude of the TMS pulse, but is in the order of 30 ms at a TMS level of 100% in the worst case electrode/channel directly under the TMS transducer. However, with electrodes/channels farther away from the TMS field the artifact becomes less and at a few >5 cm, no artifact is seen. Also, using slew-rate limiting amplifiers while it reduces the amount of TMS artifact in the EEG, these amplifiers in turn limit the bandwidth of the biological signal of interest. In the case of routine EEG recordings this is in the order of 90 Hz, which is adequate.

These new methods are likely to compliment diagnostic and therapeutic TMS in several respects. For instance, TMS-compatible EEG can contribute to TMS safety, and may facilitate FDA acceptance of the procedure. That is, if the EEG could be more easily monitored during the application of TMS, then the EEG state may help to identify recruitment in the background EEG and thus prompt the operator to stop the TMS before clinical seizures are manifested. This would be analogous to EEG recording policy and procedures applied to hyperventilation and photic-stimulation to immediately terminate the external stimulation if adverse activity is seen in the patient's EEG. In a continuous EEG the expected TMS artifact may be very subtle and easy to confuse with epileptic-specific potentials and therefore as demonstrated in Fig. 3a, a non-cephalic monitor of the TMS discharge, may be an essential element of the recording.

The electrodes designed for use in these studies were essentially Ag–Ag/Cl electrodes and thus had all the same recording properties as any other Ag–Ag/Cl electrode in terms of DC capability, long-term stability, and low intrinsic noise. Other electrode types have been suggested for use with TMS to avoid the 'Eddy-current' problem. We did not try the cut-ring metal electrodes as we find these awkward to use and the sharp edges a problem; however, we do not see any problem in using these cut-ring electrodes with this amplifier design.

Also, in experimental animal studies where the effects of the TMS on epileptic seizure are of interest, the ability to accurately record the EEG in a simple, timely manner is essential. This provides the capacity to test EEG-guided TMS where the real-time effects of the TMS on seizures can be evaluated.

Among future directions for our methods may be the development of an automated closed-loop system where seizures are detected to trigger the TMS device, and rapidly re-analyzed to determine whether another pulse should be delivered. Another application may be to develop a system for EEG-coupled TMS where the stimulating pulse is delivered at a constant phase of a normal EEG oscillation or a seizure discharge. We are actively exploring these and other applications.

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