Scalp recordings of the electroencephalogram (EEG) have been used in association with repetitive transcranial magnetic stimulation (rTMS) investigations as a safety measure in monitoring ongoing EEG activity and as a neurophysiologic tool in examining the specific effects induced by the magnetic stimulus on the EEG or evoked potentials (EPs). Medline review on the use of EEG or EPs with rTMS reveals that this area has been largely unexplored. Limited available studies attest to the potential for studies combining EEG/EPs and rTMS to be useful in further elucidating the normal brain physiology. Herein, we report on our experience with continuous EEG sampling combined with rTMS in patients with major depression (n = 14), schizophrenia (n = 7), and obsessive–compulsive disorder (n = 5). Our data support the practice of using continuous EEG monitoring when the stimulation parameters fall outside established safety guidelines. Depression and Anxiety, 12:166–169, 2000. © 2000 Wiley-Liss, Inc.

Key words: electroencephalogram; EEG; evoked potentials; repetitive transcranial magnetic stimulation; rTMS; depression; schizophrenia; obsessive–compulsive disorder

INTRODUCTION

In the last few years, repetitive transcranial magnetic stimulation (rTMS) has emerged as both a potential therapeutic modality and an investigative tool. RTMs seems to hold a significant promise for contributing to the understanding of the basic brain neurophysiology as well as the pathophysiology of neuropsychiatric disorders. To date, scalp recordings of the electroencephalogram (EEG) have been used in association with rTMS investigations in two ways: as a safety measure in monitoring ongoing EEG activity and as a neuro-physiologic tool in examining the specific effects induced by the magnetic stimulus on the EEG or evoked potentials (EPs). Herein, we will first review currently available literature on the coupling of EEG or EPs technology with rTMS. Additionally, we will present data from our experience with continuous EEG sampling in patients with major depression, schizophrenia, and obsessive–compulsive disorder (OCD).

EEG AND EPS AS TOOLS FOR EXAMINING THE EFFECTS OF RTMS

Examination of the effects of rTMS on the EEG and EPs remains in its infancy. Before this field can rapidly expand, some of the technical difficulties associated with the influence of magnetic stimulators on EEG recording systems need to be resolved. Information processing and stimulus conduction in the central nervous system (CNS) are extremely fast processes. Most of the neuronal communication within the CNS occurs in milliseconds. If standard EEG amplifiers are used during magnetic
stimulation, they become saturated and take 6 to 10 sec before returning to baseline. If the amplifiers are turned off the moment just before stimulation, amplifiers remain blocked for 2–3 sec, a time scale that still is six orders of magnitude slower than any cerebral activity of interest to researchers. For either EEG or EPs to be useful tools in association with rTMS investigations, the technical problems induced by the magnetic stimulus blocking and saturating the EEG amplifiers had to be dealt with first.

In the BioMag Laboratory at the Helsinki University Central Hospital, the saturation of the EEG amplifiers by the magnetic pulse was avoided by using a sample-and-hold circuit that pinned the amplifier output to a constant level during the pulse. The amplifiers recovered in just 100 µsec after the termination of the magnetic pulse [Ilmoniemi et al., 1997]. At the Harvard University Laboratory for Transcranial Magnetic Stimulation, Ives (unpublished data) devised a system that allows the amplifiers to recover within 15–20 msec after magnetic pulse. They used conductive plastic electrodes with short leads connected to low-power amplifiers and a special amplifier/analog multiplexor. Although the system developed in Helsinki has significantly better temporal resolution, allowing recording to resume within 1 msec of stimulus delivery, its technical complexity may limit its common use. On the other hand, the Harvard system, although unable to examine physiologic processes occurring during the first 30 msec after stimulation, its relative simplicity may make it cost effective in many studies.

In a demonstration of its utility, Ilmoniemi et al. demonstrated neuroanatomic connectivity with high temporal resolution [Ilmoniemi et al., 1997]. They stimulated the left sensorimotor hand area and demonstrated the immediate effects on the stimulated site. Activation spread to adjacent ipsilateral motor areas within 5–10 msec and to homologous regions in the opposite hemisphere within 20 msec. Similar activation patterns were observed with stimulation of the visual cortex. In earlier investigations, again with specially developed focal magnetic stimulation coils, researchers reported transcallosal responses in human subjects with a latency of 8.8–12.2 msec [Cracco et al., 1989]. Amassian et al. [1992] recorded a positive potential of 14–26-msec [Cracco et al., 1989]. Amassian et al. [1992] re-

EEG AND RTMS SAFETY

The most disconcerting side effect of rTMS is seizure precipitation [Wassermann et al., 1996; Wassermann, 1998]. Although there is no systematic acquisition of TMS-induced seizures worldwide, it is estimated that the incidence of seizures in association with TMS is less than 1%. Although the frequency of seizures is seemingly low, particularly when administered within safety guidelines [Wassermann, 1998], any seizure is a frightening event and should be avoided. Wang et al. demonstrated the induction of epileptiform spikes in rodents’ auditory cortex using rTMS [Wang et al., 1996]. Certain EEG changes may be indicative of an increased susceptibility to the occurrence of seizures. The presence of epileptiform discharges or persistent focal slow-wave abnormality on the EEG are such indicators [Neidermeyer and da Silva, 1993]. Whether the appearance of paroxysmal EEG activity, including epileptiform discharges, in the course of TMS is indicative of an impending seizure is not known. To date,
there is one published report of a seizure occurring while EEG was being monitored [Pascual-Leone et al., 1993]. They reported a normal subject developing a focal motor seizure with secondary generalization. No preseizure EEG changes were reported. Eighteen other normal subjects had no EEG changes with rTMS [Pascual-Leone et al., 1993]. EEGs performed immediately after the occurrence of seizures showed diffuse slowing consistent with a postictal state. These EEGs reverted to normal within 1 or 2 days [Wasser- mann, 1998]. Earlier studies found no observable effects of rTMS on EEGs of epileptic patients [Dhuna et al., 1991] or normal volunteers [Pascual-Leone et al., 1991]. Developing informed guidelines for when to stop a course of TMS to avoid a seizure would be very useful, particularly at this stage of searching for the most effective therapeutic parameters in varied neuropsychiatric disorders.

Given the above, we sought to determine the feasibility of continuous EEG monitoring during rTMS and whether or not EEG changes that can be observed with non-computer-aided visual inspection of the records develop in association with rTMS.

METHODS

Patients who enrolled in rTMS efficacy studies at the Yale TMS Program underwent continuous EEG sampling as part of the Humans Investigations Committee (HIC)-approved procedure for each study. Patients with history of epilepsy or any other neurologic disorders were excluded from the study. The analyzed sample included patients with major depression (n = 14), schizophrenia (n = 7), and OCD (n = 5). All patients had baseline EEGs that included 30-40 min of recording using the 10/20 international electrode placement system, using both bipolar and referential montages. The majority of the records contained at least a brief period of sleep. Recordings were not repeated if sleep was not obtained and the awake record was normal. Hyperventilation was performed for 3 min. Additionally, EEG tracings were obtained for at least 2 min before each rTMS session. During 20-Hz stimulation sessions, all include 58-sec rest intervals between trains, and the intertrain EEG was monitored for approximately 45 sec. At the end of each rTMS session, the EEG was monitored for at least 2 additional min. A 16-channel Grass Model 8 (Astro-Med, West Warwick, RI) was used for all EEG recordings. All EEG interpretations, whether during monitoring or at a later date, were performed by a trained electroencephalographer.

RTMS PROTOCOLS

RTMS protocols for depression [Berman et al., 1998] and schizophrenia [Hoffman et al., 1999] have been described elsewhere. All protocols used a Cadwell Magnetic Stimulator with a water-cooled figure-of-eight coil. In brief, unmedicated patients with depression had been enrolled in a blinded, controlled trial of active (20 Hz, 80% motor threshold [MT]; 2-sec trains; 20 trains/session; during 10 weekdays; over left prefrontal dorsolateral cortex). MT was taken as the lowest stimulus amplitude that caused a visible movement of the contralateral thumb in at least three of six trials with the hand muscles relaxed. Although all patients underwent EEG monitoring, EEG interpretations are analyzed and presented only on those completing active treatment. Patients with schizophrenia were stable with neuroleptic medications and received four sessions of 1-Hz stimulation to the dominant posterior temporoparietal region [Hoffman et al., 1999]. Sessions were 4, 8, 12, and 16 min, respectively. Patients with OCD participated in a blinded four-arm, balanced crossover design in which they received 5 days of stimulation to the dorsolateral prefrontal cortex (20 Hz, 80% MT; 2-sec trains; 30 trains/session; right dorsolateral prefrontal cortex as defined as 5 cm anterior to point of optimal stimulation to left hand muscles), lateral cortex (1 Hz; up to 160% MT; 10-sec trains with 5-sec intervals; 120 trains; 2 cm lateral to previous stimulation site), orbitofrontal cortex (1 Hz; up to 160% MT; 10-sec trains with 5-sec intervals; 120 trains; over right orbitofrontal cortex as defined as 1 cm superior to brow ridge and 2 cm lateral from midline), and sham (20 Hz, 80% MT; angulated away from scalp with trailing methyl methacrylate paddle margin applied to midpoint of above locations).

RESULTS

None of the seven patients with schizophrenia, receiving 1-Hz stimulation, showed any EEG changes. Among the 14 patients with depression who received active rTMS, 10 showed no EEG changes. One patient started with a diffusely slow EEG background (7.5 Hz) and showed no changes during the course of rTMS. This subject was admitted to the study because he showed no clinical evidence of any organic cerebral disorder. A second patient exhibited rare slow wave transients (theta activity) on the left temporal lobe region during and after the fourth session. The patient had no clinical complaints. This minimal abnormality was not noted during the subsequent sessions. One additional patient complained of a severe migraine on the morning of the third session. The EEG showed minimal slowing (theta activity) on the occipital regions. The study was postponed for 1 day and resumed the following day with normal EEG. There was no recurrence of the migraine throughout the remainder of the study period. It should be noted that this patient has chronic migraines and the reported migraine episode was typical of his usual attacks. Another subject exhibited minimal slowing on the left temporal region on baseline recording. A decision was made to include the patient based on the absence of evidence of organicity or history of neurologic disorders including head injury. This minimal abnormality did not change during the stimulation period.

Among the patients with OCD, three of the five
CONCLUSIONS

Subjects had no EEG changes during the entire procedure. One subject had no changes during a week of Hz stimulation. On the third day of 20-Hz stimulation, a slight increase of the theta activity on the left temporal region was noted. This theta increase was not apparent the following day. A second patient also exhibited increased theta activity on the left temporal region the week after the 20-Hz stimulation and during a sham stimulation period. The changes were seen before sham stimulation and tended to become less observable as the week progressed. Finally, one patient had a minimal left temporal slowing at baseline. The decision was made to admit the patient to the study because of the minimal nature of the abnormality, the lack of personal or family history of seizures, and the lack of any evidence of an organic cerebral problem. The minimal focal slowing was noted throughout the procedure without any significant change or worsening.

REFERENCES