

Transcranial Magnetic Stimulation: Safety Considerations

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Transcranial Magnetic Stimulation, or TMS, is a technique in which a brief electrical current passes through a coil of wires, thereby generating a strong magnetic field that is perpendicular to the axis of the coil. The magnetic field can pass through tissues such as skin, muscle, and bone and extend into the brain. The rapidly rising and falling magnetic field generates a brief electrical discharge in the underlying tissues, including the brain. The brief, localized electrical discharge of brain tissue has the capacity to treat brain disorders such as aphasia, neglect and depression as well as to cause harmful side-effects. This brief manuscript focuses on the potential adverse effects of TMS.

Known Risks of TMS

1. **Seizure Induction:** The risk of greatest concern with TMS is the induction of seizures. The neurophysiological excitability induced even by focal rTMS can spread beyond the site of stimulation, causing seizure activity. In most instances, seizures have been relatively localized, causing only movements of the hand or arm, for example. Generalized seizures leading to loss of consciousness have also been observed, however.

The risk of seizures is influenced by a number of factors. Perhaps the most important factor is the state of the subject's brain. Seizures are far less likely to occur in normal, healthy subjects than in subjects with neurologic disease such as stroke, brain tumor, or Multiple Sclerosis. For this reason, most studies employ strict guidelines in an attempt to exclude subjects with a neurologic disorders or other condition that would be associated with an increased risk of seizures (e.g., certain medications).

Other factors that influence the risk of seizures include the frequency, intensity and duration of TMS. TMS may be delivered as a single pulse or as repeated pulses; the latter is termed repetitive TMS (rTMS). Seizures have not been reported with single pulse TMS in normal subjects but have

been observed with single pulse TMS in subjects with brain lesions. Many studies used rTMS with pulses delivered at 1/second (1 Hz); this paradigm appears to carry a very low risk of seizures in healthy subjects when stimulated with the appropriate stimulus intensity. In fact, emerging data suggests that low frequency rTMS may actually be helpful in preventing seizures (Kinoshita and colleagues, 2005). It is now known that frequencies between 5 and 20 Hz increase the motor cortex excitability and, therefore, the risk of seizures (Berardelli et al., 1998). The risk of seizures is also increased when stronger discharges are induced or when the duration of stimulation is long.

Another variable specific to rTMS is the interval between trains of stimulation. This variable also seems to play an important role in triggering any convulsive focus. Intervals below 1 second between stimuli seem to increase significantly the risk of producing a convulsion, whereas intervals above 20 seconds appear to be extremely safe (Wassermann et al, 1996b).

On the basis of deliberations at the “International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation (June 5–7, 1996), Wasserman (1998) proposed guidelines for the safe use of TMS. These guidelines specify the three dimensional space defined by the variables of stimulus intensity, duration and frequency within which seizures are very unlikely to be observed. These guidelines should be consulted when designing a TMS study.

2. Effects on Mood

Studies of language localization using rTMS have reported crying due to inability to speak, dysarthria, and pain (Michelucci et al., 1994; Pascual-Leone et al., 1991). Crying was also observed in a subject receiving intense stimulation of the motor speech area who subsequently experienced a seizure (Wassermann et al., 1996a). The crying episodes are consistent with reports of dysphoria with milder left-sided stimulation in normal subjects (George et al., 1996; Pascual-Leone et al., 1996b), although one subject (Wassermann et al., 1996c) noted that the crying was out of proportion to the degree of emotion or pain that was experienced. In contrast, in another rTMS study (Epstein et al., 1996) that was performed on the investigators themselves, speech arrest was accompanied by laughter. High frequency stimulation of left prefrontal cortex may transiently improve mood. Some studies have reported that rapid rate rTMS

has been shown to be a safe and effective treatment in patients with depression that was unresponsive to other types of treatment (See Gershon et al., 2003 for a recent review).

Nedjat et al. (1999) report the induction of hypomania in 3 of 50 neurologically normal subjects after high-frequency rTMS over the left dorsolateral prefrontal cortex. These symptoms lasted until the day following the rTMS. This is the first (and only) report of rTMS-induced hypomania in healthy volunteers without any past medical history. Mania has been induced in a number of patients with Bipolar Disorder (Garcia-Toro, 1999, Dolberg et al., 2001, Huang et al., 2004, Hausman et al., 2004) and Post Traumatic Stress Disorder (Cohen, et al., 2004). In all cases, manic symptoms were associated with high-frequency rTMS. To our knowledge there are no cases of mania induced by 1-Hz stimulation.

3. Effects on Hearing: Animals have shown permanent increases of the auditory threshold after single pulse TMS (Counter et al, 1990) and humans have shown transient increases (Pascual-Leone et al., 1992). Foam earplugs were effective in avoiding changes in the auditory threshold in a safety study of TMS (Pascual-Leone et al, 1993).

4. Effects on Tinnitus: Pascual-Leone (personal communication) noted that tinnitus increased in one subject who received TMS to the dorsolateral prefrontal cortex and that tinnitus recurred in a second subject after a three-year absence with stimulation to the same location. The mechanism by which tinnitus may be provoked remains obscure. In fact, some data suggest that TMS may be effective as a treatment for tinnitus (see Pridmore S, Kleinjung T, Langguth B, et al., 2006) for a recent review). [FULL REF:]

5. Scalp Burns: Rapid rate and high stimulus intensity TMS may cause the coil to heat, resulting in scalp burns (Roth, 1992). Most recent TMS machines incorporate a temperature sensor in the coil and will cease operation should the coil exceed 40° C.

6. Local Pain and Headache: Muscles and nerves near the stimulating coil are activated by TMS. As a result, rTMS can be uncomfortable for some subjects, particularly with stimulation over frontal areas, where there is more muscle overlying the skull. This discomfort appears to

be related to the intensity and frequency of the stimulation (Wasserman 1998). Headache occurs in approximately 10% of subjects participating in rTMS studies; the headaches are self-limited and usually treated with minor analgesics.

7. Dental Pain: Ropohl et al. (2004) report the case of a patient who experienced dental pain in association with rTMS stimulation to the left dorsolateral prefrontal cortex. The presumed cause is local irritation of the superficial temporal portion of the trigeminal nerve and its projection via the N. buccalis into the dental region. All patients will be comprehensively informed about all possible rTMS side-effects, including dental pain, prior to rTMS therapy.

Potential Adverse Effects

In this section, a number of possible adverse effects for which there are theoretical but, at this juncture, unsubstantiated concerns are discussed.

1. Effects on Cognition: A number of studies have been performed to identify possible adverse neuropsychological consequences of TMS in neurologically normal subjects. Several studies in which a number of cognitive tasks were administered before and after TMS (Pascual-Leone et al, 1993; Wasserman et al, 1996c) have been reported. In these studies there were no adverse effects of TMS; in fact, both studies demonstrated a trend for performance to be better on measures such as delayed story recall. The data from Wasserman et al (1996) may be of particular relevance as they employed 1 Hz. rTMS (but with an amplitude higher than what we propose to use). Several additional safety studies have not reported adverse long-term effects or sustained changes in cognitive function in subjects receiving rTMS (Flitman et al., 1998; Hufnagel et al., 1993; Jennum et al., 1995; Padberg et al., 1999; Speer et al., 2000; Valzania et al., 1994; Wassermann, 1998). In several studies, performance on standard neuropsychological tests was not adversely affected by rTMS sessions; instead, verbal memory tended to improve and motor reaction times tended to decrease (Jahanshahi et al., 1997; Loo et al., 2001; Padberg et al., 1999; Pascual-Leone et al., 1993; Wassermann et al., 1996c).

2. Histotoxicity: Studies in animals (Mano et al., 1988) as well as study of subsequently resected anterior temporal lobes of humans (Gates et al., 1992) subjected to direct cortical stimulation or

TMS have failed to demonstrate evidence of histotoxicity. For reasons reviewed by Wasserman (1998), there appears to be very little chance of histotoxicity. Specifically, existing stimulators appear to be incapable of generating sufficient charge per phase or charge density to induce tissue injury (Wasserman, 1998)

3. Kindling: Kindling is a process by which repeated administration of an initially subconvulsive stimulus results in a progressive intensification of induced neuroelectrical activity resulting in a seizure. This has not been reported with TMS and appears unlikely for several reasons. Kindling is most readily obtained with high rate repetitive stimulation (e.g., 60 Hz), requires a pulse duration of 1 ms (longer than that of TMS) and is easiest to produce in the amygdala and hippocampus. Kindling of neocortex in animal models of epilepsy is very difficult to achieve. There is no evidence that kindling can be produced by TMS.

4. Exposure to Magnetic Fields

The maximal field strength generated by commercially available stimulators is in the 2 Tesla range. The field is induced for a brief period only and the strength of the field falls off rapidly with distance from the coil. There is no evidence of adverse effects from magnetic field exposure during TMS.

5. Endocrine Effects

The endocrine system has been another focus of safety studies. While Pascual-Leone et al. (1993) did not find that rTMS affected hormonal levels in humans, Wassermann et al. detected a decrease in serum prolactin levels following rTMS, which is opposite the effect seen after a seizure (Pascual-Leone et al., 1993; Wassermann et al., 1996b). George et al. (1996) found that an improved mood resulting from rTMS was accompanied by an increase in thyroid-stimulating hormone level. At present, there is no convincing evidence of a clinically relevant change in endocrinologic function after TMS.

Who Should Participate in TMS Studies?

In light of the risks outlined above, it is important to carefully screen subjects for conditions that would put them at higher risk for complications of TMS. Although inclusion and exclusion

criteria vary in different sites and studies, Exclusion criteria for studies involving normal subjects employed by most investigators would be likely to include the following:

1. History of seizures
2. History of seizures in first-degree relatives
3. History of any illness involving the brain
4. Consumption of medications known to lower the seizure threshold
5. History of tinnitus
6. Presence of cardiac pacemaker or intracardiac lines of any sort
7. History of bipolar disorder
8. Presence of any metal in the head (except the mouth)
9. Traumatic brain injury with loss of consciousness for greater than 5 minutes
10. Pregnancy
11. History or presence of increased intracranial pressure
12. Presence of medication pumps
13. Significant cardiac disease

Finally, subjects should be monitored carefully during the administration of TMS. In some centers, EEG may be performed while TMS is administered; in other centers, subjects may be monitored visually for the occurrence of muscle contractions or change in alertness that could be evidence of a seizure. A Neurologist or other physician trained in the management of seizures should be present during TMS administration.

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