

Ethical issues

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INTRODUCTION

In addition to being a valuable tool for basic research in neurophysiology, transcranial magnetic stimulation (TMS) has promising therapeutic uses for the treatment of conditions such as depression, obsessive compulsive disorder and epilepsy. Reports of epileptiform activity or seizures following single-pulse TMS in patients with epilepsy (Hufnagel *et al.*, 1990; Classen *et al.*, 1995) and the occurrence of seizures following repetitive transcranial stimulation (rTMS) in normal volunteers (Pascual-Leone *et al.*, 1992; Wassermann *et al.*, 1996) have provoked ethical discussion (Bridgers, 1990; Pascual-Leone *et al.*, 1993; Green *et al.*, 1997; Wassermann, 1998). TMS research and clinical applications will require investigators to be alert to the ethical constraints and specific risks in the use of this technology.

BASIC ETHICAL CONSIDERATIONS

Three ethical principles apply to all research on human subjects: the principle of respect for persons; the principle of maximizing benefit and minimizing harm (beneficence/non-maleficence); and the principle of justice (US National Commission, 1979). In the USA and most other nations, these principles underlie legal and other regulatory requirements to which all research involving human subjects must adhere (Department of Health and Human Services, 1991). The first two of these principles also apply to clinical settings not involving formal research. (Research is defined as systematic investigation aiming at generalizable knowledge. It usually has publication as a goal.)

Respect for persons

This principle comprises two specific norms. One is the requirement of respect for the patient-subject's autonomy; the other is the obligation to preserve the confidentiality of the patient-subject's personal information. That TMS is currently being studied for its value in relieving depression, obsessive compulsive disorder or other serious psychological or neurological disorders makes attention to both these norms especially important.

Respect for the patient's autonomy requires that neither treatment nor research proceeds without the informed consent of the patient-subject. The patient-subject's choice must be free and voluntary, and based on the provision of all relevant information. The experimental or non-experimental nature of the intended procedure should be made clear at the outset. The patient-subject should be fully informed of the balance of efficacy versus risk. Subjects must be told of 'any reasonably foreseeable risks or discomforts' (Department of Health and Human Services, 1991; § 46.116 (a) 2). This must include notification of the possibility of the kinds of seizure events that have occurred in some normal patient-volunteers in rTMS research. It must also include lesser risks, such as the possibility of damage to hearing or burns resulting from the magnetic coil (Counter *et al.*, 1990; Pascual-Leone *et al.*, 1990). At the cellular level, the risks of sustained exposure to TMS are unclear. Furthermore, despite the safety data available (see Chapter 4), the relative newness of this technology requires that patient-subjects be told that TMS may involve risks which are currently unforeseeable (Department of Health and Human Services, 1991; § 46.116 (b) 1).

A special problem arises in connection with the use of TMS for individuals suffering from refractory depression

or other psychiatric disorders. Informed consent has been analysed as having five discrete components: disclosure, comprehension, voluntariness, competence and consent (Appelbaum *et al.*, 1987). Depression and other psychiatric disorders may impair the voluntariness of consent by rendering the patient especially susceptible to coercion by researchers or family members. It may also undermine a patient's competence to consent. Competence has been defined as evidencing the awareness of choice, the ability rationally to manipulate information, appreciation of the nature of the situation and factual understanding of the issues (Appelbaum and Roth, 1982; Appelbaum and Grisso, 1988). In most cases, a diagnosis of depression does not call into question a patient's competence to consent to treatment or research. Depressed patients, like others experiencing acute pain, may validly seek relief from their distress. In some cases, however, depression results in altered mood states (hopelessness, feelings of worthlessness, anxiety or euphoria) that are so extreme as to call the patient's competence into question (Wettstein, 1995). In these instances, whether the patient accepts or rejects an offered treatment, third party consent (a relative or court-appointed guardian) is usually required. Some have argued that when patients of questionable competence are willing to undergo potentially beneficial treatment, clinicians may utilize a lower threshold for competence than would be the case where the patient refuses such treatment. This doctrine of 'therapeutic jurisprudence' attempts to accept the patient's decision as valid informed consent when it coincides with the physician's treatment recommendation (Brown and Brennan, 1995). However, others maintain that competence must be assessed independently of the patient's treatment decisions (Culver and Gert, 1982). Since TMS is not risk free, independent assessment of competence and resort to third party consent are advisable if there is reason to believe that the patient cannot validly offer consent to the procedure.

Research contexts impose especially stringent restrictions on the use of cognitively impaired patient-volunteers or those suffering from disorders of mood, emotion and perception. Unlike therapeutic clinical settings, the balance of benefit to risk may be unclear and, in some research, no patient benefit may accrue. A report by the (US) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978) proposed a tiered system of restrictions for research on 'those institutionalized as mentally infirm'. Where the research involves 'minimal risk', and the subject is deemed incompetent to consent, studies can go forward as long as the research is relevant to the patient's condition and the patient's assent is obtained. Minimal risk is defined as a magnitude of physical or psychological harm that is 'normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons' (Department of Health and Human Services, 1991; § 46.303). Assent was a novel

concept and created a duty on the part of researchers to communicate and elicit subjects' agreement to participate even though they are not deemed legally competent to consent. If no assent is possible or if the subject objects, minimal-risk research has to hold the prospect of direct benefit to the subject and explicit court authorization is needed. Research involving more than minimal risk requires either full consent by subjects or, if they are not competent to consent, that of a court-appointed guardian. The Commission also proposed an intermediate category of research involving a 'minor increase over minimal risk'. Research in this category requires the patient's consent or, failing that, the prospect of direct benefit to the subject, the absence of a better alternative treatment, and the patient's assent. If the patient could not assent or objected to the research, formal authorization by a court-appointed guardian was needed. Although these recommendations never formally became law in the USA, they serve as informal guidelines for investigational review boards (Cook-Deegan, 1996). Because TMS research in the treatment of psychiatric and neurological disorders ordinarily involves more than minimal risk, the requirements apply of direct benefit for the subject, the demonstrated absence of better alternative treatment, and third party approval in the absence of patient consent. Some TMS research may fall in the category involving 'a minor increase over minimal risk', with its specific requirements.

Finally, the principle of respect for persons requires clinicians and researchers to respect the privacy of patients or subjects. Since mental disorders can invite social stigmatization or discrimination in employment and insurance, efforts should be made to preserve the confidentiality of medical records. Where there is reason to believe that information relating to patient-subjects' medical records will be susceptible to disclosure, researchers should consider requesting a certificate of confidentiality or similar protection from legal disclosure of their research records.

Beneficence/non-maleficence

The moral principle requiring maximization of benefit and minimization of harm (beneficence/non-maleficence) means that there must be a favourable balance of benefit to risk in both treatment and research activities. In treatment contexts, this balance is normally determined by the competent patient in concert with his or her physician. In research, however, beneficence/non-maleficence imposes a further responsibility of independent assessment by both investigators and investigational research boards. Although current regulations privilege the autonomy of research subjects in determining whether they are willing to accept the balance of risks to benefits in a protocol (Levine, 1986), their judgements must nevertheless be deemed 'reasonable' in the eyes of the investigator and the review board. In making these judgements, where

competent patient-volunteers are involved, review boards are permitted to include benefits beyond those accruing to the research subject, such as the general advancement of medical or scientific knowledge. Among the risks of research, however, US regulations explicitly forbid review boards from considering the possible long-range negative effects of applying knowledge gained in the research (Department of Health and Human Services, 1991; § 46.111). Although this frees TMS researchers from any legal obligation to take into account the longer term social risks of TMS, such considerations cannot be entirely removed from their ethical purview.

The principle of justice

This third basic principle requires a fair distribution of the burdens and benefits of research. The principle of justice is violated when research is conducted on categories of patients rendered vulnerable by economic, social or physical conditions and who are likely to bear only the burdens of research and not its benefits. Among those in this class are children, prisoners, pregnant women, mentally disabled people or economically and educationally disadvantaged individuals. Research violates the principle of justice when it involves these and other vulnerable classes of people in research without producing direct medical benefit for them.

SUITABLE CATEGORIES OF PATIENT-SUBJECTS

Against this ethical background, it is possible to identify those classes of patient-volunteers who, in view of the known and unknown risks, might be suitable subjects for TMS research. One broad group of admissible patient-subjects is individuals suffering from neurological or psychiatric disorders for whom TMS might provide significant clinical benefit. Both the risk-benefit and justice requirement of human subject research support the appropriateness of this patient category, which includes adult patients with progressive myoclonus epilepsy (PME) and children with juvenile myoclonus epilepsy (JME). These individuals must already deal with the physical and psycho-social risks of seizure on a recurrent basis as well as the risks associated with high dosages of anti-convulsive medication. Slow-wave rTMS might point the way to a new means of seizure control for these individuals (Weiss *et al.*, 1995) and other forms of TMS might provide a way of testing new seizure medications (Ziemann *et al.*, 1996). Patients with refractory depression also fit into this class of suitable subjects. Electroconvulsive therapy (ECT) is a therapeutic alternative for these patients (or has already been tried without success). The seizure risk of ECT is 100% and there are additional risks not present for rTMS, including use of a general anesthetic, memory loss, cardiac arrest, broken

teeth, reactions to drugs etc. The risk of seizure and its attendant complications with current or foreseen TMS regimens is therefore on a far lower scale of magnitude than this existing alternative therapy (Kirkcaldie *et al.*, 1997). Additional categories of patients might be identified among individuals suffering refractory obsessive compulsive disorder and other seriously disabling psychiatric conditions for whom there is evidence that TMS might provide direct benefit (Greenberg *et al.*, 1997). In all such cases, third party consent should be sought whenever patient-subjects' illness indicates that they lack the competence to consent to research or treatment. Although the close relatives of such patients should be involved in this decision-making (Hall, 1996), care should be taken that patients are spared coercion by family members.

Outside the category of patient-volunteers for whom TMS might provide clinical benefit, an additional category of suitable research subjects is patients with disorders which might not be treated by TMS but which TMS can help us better understand. Parkinson's patients fit into this category. Research suggests that TMS can have the short-lived effect of reducing Parkinson's symptoms (Pascual-Leone *et al.*, 1994, 1995), but these effects have been difficult to reproduce. Therefore, the primary benefit of TMS studies in Parkinson's disease lies in an improved understanding of the processes leading to this disease. It is this link between TMS and Parkinson's research that makes this patient class suitable, not the fact that Parkinson's patients already face substantial independent psycho-social risks that mitigate the impact of seizure events. Ordinarily, on grounds of justice, subjects' existing suffering and vulnerability are a justice-based argument *against* their inclusion in additionally risky research. In this case, this argument is overridden by the unfairness of denying these patients an opportunity to contribute, whether for themselves or others, to the future treatment or cure of a disease from which they suffer.

Identifying the category of suitable patient-subjects raises the question of whether normal volunteers should be allowed to participate in TMS research. Some might argue against permitting this, since TMS does not now appear to have the magnitude of scientific or clinical benefit that warrants imposing on healthy individuals the risks associated with even a single seizure event. Although there is no evidence suggesting that rTMS-induced seizures will recur in a non-epileptic individual, studies in animals involving electrical stimulation have shown permanent physiological changes in the brain, lowering the threshold of excitability, a phenomenon known as 'kindling' (Goddard *et al.*, 1969). It cannot be said with sufficient confidence, therefore, that a normal volunteer potentially susceptible to seizures will not be pushed over the edge by repeated rTMS excitation. Quite apart from the reality of further seizure risk, there is the risk of a subject's continued anxiety about seizure recurrence in the event of an rTMS-induced seizure (see Chapter 4).

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There is also a possibility that the subject may experience insurance and employment discrimination.

Although these risks raise a formidable barrier to the use of normal volunteers in rTMS research, they do not rule it out altogether. In ethical terms, normal volunteers can participate in research evidencing a favourable balance of benefit to risk, with benefit being understood to include general gains in scientific or medical knowledge. Because rTMS research carries a significant seizure risk, competent normal volunteers should be permitted to participate in it when the research is 'likely to produce generalizable knowledge of vital importance'. In such cases, research may go forward in conformity to the guidelines recommended below and subject to a further safety factor indicated in Guideline 7.

The governing phrase here is that research be 'likely to produce generalizable knowledge of vital importance'. This phrase is adapted from current US federal regulations governing research on children in which more than minimal risk is presented by interventions or procedures that do not hold out the prospect of direct benefit to the child-subject (Department of Health and Human Services, 1991; § 46.406.). The application of this language to rTMS research on adult subjects expresses the conviction that research posing significant neurological and social risks for normal subjects for whom the protocol promises no direct medical benefits must be of compelling scientific or therapeutic importance. This standard permits rTMS research that points the way to significant therapeutic advances and/or that strengthens (or weakens) significant hypotheses about brain function. It does not include research aimed at information that is merely of interest to a few researchers or that is likely to provide only incremental expansion of the knowledge base.

One example of permitted research is the use of rTMS to determine differences in the lateralization of mood response in depressed and normal subjects (George *et al.*, 1996; Pascual-Leone *et al.*, 1996). Such studies have major implications for our understanding of normal mood and depression. Another example is a study using rTMS in the visual areas of the brains of blind subjects to disrupt Braille reading (Cohen *et al.*, 1997). Such a study may help confirm earlier position emission tomography (PET) scan results indicating that supposedly specialized areas of the brain can take over functions in a completely different sensory domain. Research requiring the use of normal volunteers as control subjects and directly related to improved treatments for patients with serious disorders also fits into the category of research 'likely to produce generalizable knowledge of vital importance'.

RECOMMENDED GUIDELINES

The following guidelines for the conduct of all TMS research are meant to assist investigational research boards

and researchers. Further discussion of many issues raised is provided in Chapter 4. Guidelines 1–9 apply to the assessment of individual protocols. Guideline 10 applies to the TMS research community as a whole, to manufacturers of TMS equipment and to funding agencies sponsoring this research.

It goes without saying that all the usual requirements of valid scientific investigation should be met before investigational research board review. This includes provision of data from appropriate safety studies in animal models. In the case of TMS this requirement remains in force even though for specific applications of TMS in humans there may be significant limitations on the use of animal models. Differing brain volumes and configurations, different ratios between stimulation coil size and head size, and the need for patient self-reporting will often render animal models, including primates, inappropriate. Nevertheless, the burden rests on researchers to show why animal models cannot be used in specific TMS experiments.

Guideline 1

Researchers must demonstrate that they are using the lowest-risk form of TMS suitable for the research. Evidence suggests that seizure risk is greatest in the use of high-frequency rTMS with brief intertrain intervals. Because lower-frequency rTMS and even non-repetitive TMS may be equally suitable for inducing the desired effect in some circumstances, researchers should proceed from low-risk to higher-risk modalities. The burden of proof rests on them to justify each increment of risk.

Guideline 2

Researchers must adhere to well-developed exclusion criteria. Adverse events have occurred in subjects with family histories of epilepsy or who were taking medication that lowered their seizure threshold. The research community is responsible for developing, disseminating and applying exclusion criteria based on this and other information. Wassermann (1998) recommends that investigators consider the use of a standard questionnaire to screen for a history of head trauma or head surgery, seizures, implanted hardware, medications, neurological and medical illnesses, and family history of epilepsy.

Individuals with pacemakers, cochlear implants, medication pumps, surgical clips and similar devices are at direct risk of physical injury. Where appropriate precautions are possible, such individuals may participate in research when it has the prospect of relief of serious medical conditions (e.g. treatment of severe and refractory depression). Because seizures in a woman can endanger a child she is carrying, researchers must not permit a fertile woman to participate in research if, in the opinion of trained medical personnel, there is a significant chance

she may be pregnant. Exceptions to this may be made in cases where there is a clear medical benefit to the subject, as in the treatment of severe and refractory depression.

Guideline 3

Researchers are responsible for insuring full and informed consent on the part of research subjects. This includes discussion of lesser risks (headache, muscle pain, possible burns) as well as the history and consequences of adverse outcomes. Subjects must be made aware of the possible psycho-social risks of seizure, including risks to employment and insurability and the risk of continuing anxiety. They must be reminded frequently that they are permitted to withdraw from research at any time. Only evidence of full and voluntary consent and procedures to guarantee it can justify the use in TMS research of students or colleagues whose careers may depend on the researcher.

Guideline 4

There should be careful attention to the immediate risks of research. Researchers must be well trained and experienced in the use of TMS and research should only take place in clinical settings equipped for seizure control. Researchers must be familiar with the warning signs of seizure and at least one on-site member of the research team must be a medical doctor able to predict, forestall and treat seizures. At rTMS frequencies greater than 1 Hz and single-pulse TMS of 1 Hz, subjects and investigators should use earplugs (Pascual-Leone *et al.*, 1993). In the presence of electrodes, special precautions should be taken to prevent scalp burns (Roth *et al.*, 1992). Each laboratory should have a policy on action to be taken in the event of changes after TMS, such as delayed reaction time that might lead to an automobile accident.

Guideline 5

There must be continuous monitoring of subjects during TMS research. Appropriate use of electromyography (EMG) and electroencephalography (EEG) must accompany all TMS studies. Efforts must be made to develop ways of ensuring continuous monitoring even when stimulation makes the placement of electrodes difficult (Wassermann, 1998). Concurrent video recording of stimulation sessions is an important aid in determining the causes of adverse events (Pascual-Leone *et al.*, 1993).

Guideline 6

Research must be conducted within the best multi-dimensional limits of safety for the intensity, frequency

and duration for trains of TMS. It is the responsibility of the TMS research community to develop evidence-based safety limits for the conduct of TMS research. These safety limits must be constantly reviewed and updated with reference to reports of adverse events (see Guideline 10).

Guideline 7

When normal volunteers and other individuals not likely to receive direct medical benefit from the research are involved, additional margins of safety must be imposed on research. These safety margins would be created by lower intensities, frequencies and durations of stimulation than those identified as safe by previous experience with TMS. The research community is responsible for developing and applying quantitative standards for safety in studies on the various subject groups. Additional safety margins should be proportionate to the perceived value of the research. Studies likely to produce less valuable generalizable knowledge require a larger additional margin of safety than studies of greater value. Presuming the full and informed consent of subjects, studies pointing the way to significant therapeutic advances and/or that test significant hypotheses about brain function may approach more closely to established safety limits.

Guideline 8

There must be *objective* assessment of patient condition following TMS. Apart from those instances where adverse events have occurred, there have been no reports to date of significant or enduring side-effects of TMS. However, such side-effects cannot be ruled out, including possible cognitive alterations or impairments. Where cognitive effects are involved, it is not sufficient for investigators to rely on subjects' reports of their mental state, since the ability to assess one's condition may be impaired. Objective assessment of patient condition by competent clinicians is required on a continuing basis (as per Guideline 9).

Guideline 9

There must be continuous clinical assessment of subjects at regular intervals following research. The longer-term risks of TMS must be investigated continuously. At higher levels of stimulation, enduring neurological and histological changes are a possibility, leading to alterations of seizure threshold or cognitive changes in subjects. Provision must be made in all protocols for continuing contact with subjects and the maintenance of a record of subject reports and assessment. No time limit should be placed on this responsibility. Investigational research boards can determine whether this requirement may be waived for some very low-risk TMS research.

Guidelines

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LARGE

Because of the potential for adverse events, the TMS research community has to take special precautions. In particular, the use of TMS in research must be carefully monitored and controlled. The research community is responsible for developing and applying quantitative standards for safety in studies on the various subject groups. Additional safety margins should be proportionate to the perceived value of the research. Studies likely to produce less valuable generalizable knowledge require a larger additional margin of safety than studies of greater value. Presuming the full and informed consent of subjects, studies pointing the way to significant therapeutic advances and/or that test significant hypotheses about brain function may approach more closely to established safety limits.

Guideline 10

The TMS research community is responsible for developing and maintaining an international registry for adverse outcomes and, in the longer term, a database of TMS research. Such a registry should be up to date and immediately available to researchers throughout the world. Internet access is essential. Investigational research boards must see to it that researchers have utilized this registry in developing their exclusion criteria and safety parameters. In the absence of full information about the total number of protocols and subjects involved, however, reports of adverse outcomes alone are not an accurate measure of risk. For this reason, a full database of TMS research is needed. Such a database would certainly be of great value and should be developed, even on a pilot basis. The research community, including manufacturers of TMS equipment and funding agencies, should assist in the development of this resource. However, delays in funding and establishing such a database should not impede the immediate development of an adverse outcomes registry, since this registry can help investigators identify newly discovered risk factors of which they should be aware.

LARGER ETHICAL ISSUES

Because of its promise and the risks of this technology, society as a whole has a stake in the future directions it takes. This suggests two additional areas of concern and responsibility for the TMS research community. One has to do with the immediate risks of abuse of this technology. TMS has been shown to have both positive and negative effects on mood (George *et al.*, 1996; Pascual-Leone *et al.*, 1996). Because of its non-invasiveness and apparent harmlessness at low intensities of stimulation, irresponsible researchers or others inside or outside the laboratory may be tempted to use TMS for unauthorized research or recreational purposes. Researchers and manufacturers must work together now to prevent this by developing adequate laboratory security procedures and, when necessary, by working with governments or regulators to prevent this equipment from falling into inappropriate hands. In the laboratory, the use of TMS by researchers on themselves must be subject to investigational research board review in accordance with the guidelines for all TMS research.

A second area of concern is the unknown and speculative longer-term risks and benefits associated with society's future development and employment of this technology. TMS holds out the prospect of a powerful new, non-invasive way of monitoring or influencing brain states. Many larger issues were raised in the 1960s and 1970s by the work of Delgado and others (Delgado, 1965, 1969) in connection with the direct electrical

stimulation of the brain (ESB). Delgado's well-publicized demonstrations of the ability to induce a rage response in cats or to terminate aggression in bulls via remote control ESB led to speculation that this technology might similarly be used, with or without people's consent, to induce dramatic changes in their behaviour or cognition. On the negative side, fears about the risks involved here were accentuated by popular fiction, especially Michael Crichton's (1972) novel *Terminal man*, whose main character has a stimulator placed in his brain to control epileptic seizures and who turns violent as a result. On the positive side, Delgado (1965, 1969) offered the hope of advances in the control of crime or war through ESB. These ideas raised complex questions of who would employ this technology for these purposes and what controls would be placed on their use.

There is no evidence to date that TMS can be used in any of these ways. Nevertheless, the TMS research community should be alert to these issues. In the area of genetics, which also has wide-reaching implications for society, the research community has taken a pro-active stance by helping develop various private and federally funded programmes devoted to study the ethical, legal and social implications of the Human Genome Project. Although it is probably too soon to initiate similar programmes for TMS, efforts should be made in TMS-related conferences and publications to include discussion of these larger social and ethical issues.

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