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Transcranial Magnetic Stimulation in the investigation and treatment of schizophrenia: a review

H. Magnus Haraldsson*, Fabio Ferrarelli, Ned H. Kalin, Giulio Tononi

Department of Psychiatry, University of Wisconsin, 6001 Research Park Blvd., Madison, WI 53719, USA

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Abstract

Transcranial Magnetic Stimulation (TMS) is a non-invasive method of stimulating the brain that is increasingly being used in neuropsychiatric research and clinical psychiatry. This review examines the role of TMS in schizophrenia research as a diagnostic and a therapeutic resource. After a brief overview of TMS, we describe the application of TMS to schizophrenia in studies of cortical excitability and inhibition, and we discuss the potential confounding role of neuroleptic medications. Based on these studies, it appears that some impairment of cortical inhibition may be present in schizophrenic subjects. We then review attempts to employ TMS for treating different symptoms of schizophrenia. Some encouraging results have been obtained, such as the reduction of auditory hallucinations after slow TMS over auditory cortex and an improvement of psychotic symptoms after high frequency TMS over left prefrontal cortex. However, these results need to be confirmed using better placebo conditions. Future studies are likely to employ TMS in combination with functional brain imaging to examine the effects produced by the stimulated area on activity in other brain regions. Such studies may reveal impaired effective connectivity between specific brain areas, which could identify these regions as targets for selective stimulation with therapeutic doses of TMS.

Keywords: Transcranial Magnetic Stimulation; Schizophrenia; Cortical excitability; Cortical inhibition; Antipsychotic medications; Functional brain imaging

1. Introduction

Transcranial Magnetic Stimulation (TMS), introduced almost two decades ago (Barker et al., 1985), is a non-invasive method of stimulating the brain. It is increasingly being used as a tool in basic neuroscience to study the function of the nervous system, and it has also entered the field of clinical psychiatry as a potential treatment option for a variety of mental illnesses (Burt et al., 2002). Comprehensive reviews of the role of TMS in basic neuroscience and neuropsychiatry have recently been published (Burt et al., 2002; Fitzgerald et al., 2002a; George et al., 1999; Hallett, 2000; Lisanby et al., 2000, 2002). In this paper, we focus on TMS as a neurophysiological tool in schizophrenia research and as a therapeutic resource for the treatment of schizophrenia. After a brief introduction about TMS, we describe the application of TMS for studying cortical excitability and assessing

* Corresponding author. Tel.: +1-608-263-6063; fax: +1-608-263-0265.
E-mail address: hmagnus@landspitali.is (H.M. Haraldsson).

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inhibitory mechanisms. The neurophysiological and clinical studies using TMS in schizophrenia are then reviewed.

2. Transcranial Magnetic Stimulation

TMS is based on Faraday's principle of electromagnetic induction. A rapidly changing magnetic field (2 T) is generated by passing a very brief (0.2–0.9 milliseconds (ms)) high-current alternating electric pulse through an insulated coil made of wire. When the coil is placed against the scalp the magnetic field passes readily through the skull and induces a weak electrical current in the superficial cortex of the brain lasting exactly as long as the current pulse in the coil (Barker, 2002). The induced electrical activity can cause cortical neurons to discharge action potentials. The strength of the magnetic field decreases exponentially with increasing distance from the coil and therefore stimulation of nervous tissue deeper than approximately 2 cm from the scalp is currently not possible (Lisanby et al., 2000).

TMS can be applied as a single stimulus pulse or repeated pulses for seconds or minutes (rTMS). Stimulation frequency of more than one pulse per second (1 Hz) is called rapid TMS. Single pulse TMS is generally safe and well tolerated (Wassermann, 1998). Its most common side effect is mild headache, which responds readily to analgesics. There is a low risk of inducing seizures with rTMS and the risk increases with higher stimulation frequencies and intensities (Wassermann, 1998). However, at slow rates (<1 Hz) and standard intensity the risk for healthy subjects is virtually nonexistent.

TMS can produce different effects depending on where and how it is applied. For example, single pulse TMS applied to the primary motor cortex induces muscle twitches that can be recorded with an electromyogram (EMG) (Barker et al., 1985), while single pulse TMS to the occipital cortex can produce subjective light flashes (Kammer, 1999). On the other hand, high frequency TMS applied to the prefrontal, left midtemporal and primary visual cortex produces short-term impairments in working memory (Pascual-Leone and Hallett, 1994), free recall of verbal material (Grafman et al., 1994) and visual stimuli identification (Amassian et al., 1989), respectively. In this way TMS can provide unique information about the temporal and topographic organization of various neurophysiological and cognitive processes.

A number of variables influence how accurately a specific brain area can be stimulated with TMS. These variables include the intensity of stimulation, the shape and orientation of the stimulating coil and the excitability, type and orientation of the neurons in the area of stimulation (Brasil-Neto et al., 1992a). The two most common coil shapes are circular and figure-of-eight. Circular coils are powerful but may stimulate a large brain area. Figure-of-eight coils are made of a coil, which is twisted and flipped over onto itself forming a figure-of-eight. The cross point of the coil is the site of maximum stimulation intensity (Cohen et al., 1990). Mapping studies of the motor cortex have indicated that spatial resolution is approximately 0.5–1.0 cm with a figure-of-eight coil (Brasil-Neto et al., 1992b). It is hard to determine the spatial resolution of TMS in brain areas where no visible response such as a muscle contraction can be recorded. TMS has a high temporal specificity and allows for investigating changes of brain activity that occur over a few ms (see also for review of TMS: Hallett, 2000; Pascual-Leone et al., 1998).

3. Studying cortical excitability and inhibitory mechanisms with TMS

Researchers have utilized TMS of the motor cortex to study neuronal excitability, and cortical inhibitory mechanisms, both in patients and healthy subjects (Fitzgerald et al., 2002a). This has mainly been achieved by examining EMG recorded motor evoked potentials (MEPs). Here we briefly review several key TMS paradigms that are useful for evaluating cortical excitability and inhibition.

4. Motor threshold and MEP

A MEP is a synchronous muscle response evoked by a TMS pulse stimulating the motor cortex. It is a marker of cortical excitability and its size reflects the number of motor neurons that are activated by a TMS pulse. The latency from the time of motor cortex TMS to the onset of a MEP is a measure of corticospinal

conduction time. The threshold for inducing MEPs with TMS is called motor threshold. Motor threshold has been defined as the lowest stimulation intensity over the motor cortex needed to induce a MEP in an extremity muscle in at least 5 out of 10 consecutive trials (Rossini et al., 1994). The motor threshold is well established as an objective and standardized measure of corticospinal excitability in humans, and also is widely used to standardize stimulation intensities in various neurocognitive studies (Walsh and Rushworth, 1999). The motor threshold seems to be relatively stable within individuals (Mills and Nithi, 1997), although some minor hemispheric differences have been demonstrated (Cicinelli et al., 1997). A decrease in motor threshold indicates increased neuronal excitability, whereas an increased motor threshold reflects decreased excitability. TMS pulses also affect inhibitory neural processes both in the ipsilateral and contralateral motor cortex (Ferbert et al., 1992). Thus, TMS has been employed to investigate cortical inhibitory mechanisms by focusing on three main paradigms: (1) Cortical Silent Period, (2) Response to Paired Pulse TMS and (3) Single and Dual Pulse Transcallosal Inhibition.

Cortical silent period is a period of TMS-induced EMG suppression during a tonic voluntary contraction of a muscle. A cortical silent period can be induced by both supra- and sub-threshold stimuli and is therefore independent of the presence of a MEP (Triggs et al., 1992). This brief period of EMG silence, which starts approximately 30–40 ms after the TMS stimulus, reflects the effects of inhibitory interneurons in the motor cortex that are activated by TMS (Hallett, 1995; Sanger et al., 2001). A decreased level of EMG suppression and a reduced duration of the silent period are indications of disturbed cortical inhibition.

Paired pulse TMS involves stimulating the motor cortex with two successive TMS pulses—a conditioning pulse followed by a test pulse-delivered at a short inter-stimulus interval through the same stimulating coil. The motor response to the test pulse may be decreased (inhibition) or increased (facilitation) depending on the length of the inter-stimulus interval. If a sub-motor threshold conditioning pulse precedes a supra-motor threshold test pulse, the motor response is inhibited at inter-stimulus intervals of 1–6 ms and facilitated at intervals of 8–30 ms (Kujirai et al., 1993). Paired pulse inhibition can also be obtained with a supra-motor threshold conditioning pulse delivered 100–200 ms prior to the test pulse (Nakamura et al., 1997). A decreased level of MEP suppression by the conditioning pulse is an indication of disturbed cortical inhibition. In both the short and long interval inhibitory procedures the conditioning pulse is believed to activate inhibitory interneurons that suppress the effects of the test pulse (Sanger et al., 2001). Paired pulse facilitation is probably mediated by excitatory interneurons (Terao and Ugawa, 2002).

Transcallosal inhibition has been investigated both with a dual pulse and single pulse technique (Fitzgerald et al., 2002a). Dual pulse transcallosal inhibition is observed when one delivers a conditioning stimulus to the motor cortex of one hemisphere prior to giving a test pulse to the motor cortex of the opposite hemisphere, using two TMS coils. The conditioning pulse induces action potentials that pass through the corpus callosum to the contralateral motor cortex where they suppress corticospinal neurons being stimulated by the TMS test pulse (Ferbert et al., 1992). Inhibition of the test pulse response (decreased amplitude of the MEP) is seen when the inter-stimulus interval is between 5 and 20 ms, which is consistent with transcallosal responses recorded with frontal scalp electrodes following TMS over the contralateral homologous area (Cracco et al., 1989).

Single pulse transcallosal inhibition is observed when one stimulates the motor cortex with TMS while the subject performs a steady contraction of hand muscles on the same side as the stimulation. The TMS pulse triggers a volley of action potentials that pass through the corpus callosum and inhibit the corticospinal neurons controlling the contralateral hand muscles, which are voluntarily activated. In this way, transcallosal inhibition of voluntary muscle contraction can be measured. The suppression of EMG recorded hand muscle activity begins on average 30–40 ms following the TMS pulse and lasts approximately 25 ms (Meyer et al., 1995).

A transcallosal inhibition paradigm can thus be used to measure transcallosal conduction time. That is calculated by subtracting the time it takes a TMS pulse to induce a contralateral MEP from the time it takes the same pulse to generate an EMG inhibition. The difference reflects the conduction time from ipsi- to contralateral motor cortex through the corpus callosum (Fitzgerald et al., 2002a).

Several studies provide evidence that these inhibitory mechanisms are primarily related to cortical but not peripheral processes (Ferbert et al., 1992; Fuhr et al., 1991; Inghilleri et al., 1993; Kujirai et al., 1993). For example, the duration of the silent period is altered in patients with unilateral cortical lesions (von Giesen et al., 1994). Moreover, the inhibition of MEP obtained with paired pulse TMS at short interstimulus intervals (2 and 3 ms) is due to a reduced corticospinal output as indicated by recordings with electrodes implanted in the cervical epidural space in awake subjects (Di Lazzaro et al., 2002).

5. Neurophysiological studies using TMS in patients with schizophrenia

Some histopathological and pharmacological studies have suggested that the pathophysiology of schizophrenia may involve dysfunction of excitatory (Selemon and Goldman-Rakic, 1999) and/or inhibitory neural function (Olney and Farber, 1995). In a number of recent studies, TMS of motor cortex has been used to evaluate both cortical excitability and inhibitory mechanisms in patients with schizophrenia. This research is still in its early days and most of the studies are limited to small sample sizes. Furthermore, due to methodological differences it is often difficult to directly compare the results of different studies. Table 1 summarizes the findings of studies using the previously described TMS paradigms for evaluating cortical excitability and inhibition in patients with schizophrenia.

5.1. Studies of cortical excitatory function

Overall, TMS studies provide little evidence for significant abnormalities in cortical excitability in patients with schizophrenia. Most investigations have failed to show any significant difference in motor threshold, MEP size or paired pulse facilitation between patients and healthy subjects (Boroojerdi et al., 1999; Fitzgerald et al., 2002b,c,d; Puri et al., 1996). One exception is a study by Abarbanel et al. (1996), which demonstrated larger MEP size and lower motor thresholds in 10 medicated patients with schizophrenia compared to 10 depressed and 10 healthy subjects. This increased excitability in schizophrenia patients may have been due to increased muscle tonus secondary to extrapyramidal side effects from neuroleptic medications.

A hemispheric difference in corticospinal excitability between patients with schizophrenia and healthy subjects was found in a recent study by Pascual-Leone et al. (2002). These authors found that a group of right handed patients taking conventional antipsychotic medications ($n=7$) and a group of unmedicated patients ($n=7$) had a 5–10% lower motor threshold in the right compared to the left hemisphere, while the opposite was found in a group of healthy subjects ($n=7$). Healthy right-handed people generally have a lower motor threshold in their dominant left hemisphere, which has been linked to facilitation due to more frequent use of their right hand (Triggs et al., 1994). The finding of a lower excitability threshold for the non-dominant hemisphere in schizophrenics may indicate that, compared to normal subjects, patients with schizophrenia have reversed asymmetry in corticospinal excitability.

TMS research has provided inconclusive results concerning corticospinal conductivity in schizophrenia (Abarbanel et al., 1996; Boroojerdi et al., 1999; Puri et al., 1996). In the first study of motor function in schizophrenia using TMS, Puri et al. (1996) detected a significantly shorter latency of MEPs in nine unmedicated patients with schizophrenia compared to nine healthy subjects. However, further studies measuring MEP latency did not find a difference between medicated schizophrenia patients and normal controls (Abarbanel et al., 1996; Boroojerdi et al., 1999).

5.2. Studies of cortical inhibition

Several findings indicate that a lack of cortical inhibitory control may be involved in the pathophysiology of schizophrenia (Frith et al., 2000). For example, studies using auditory evoked potentials have demonstrated that patients with schizophrenia lack normal suppression of the P50 auditory evoked response with a conditioning pre-pulse stimulus (Freedman et al., 1996; McCarley et al., 1991). Abnormal motor function such as incoordination, involuntary movements and impaired fine motor skills, which are not related to antipsychotic drug treatment, have been detected in approximately 80%

of patients with schizophrenia (Yager and Gitlin, 2000). These motor deficits could be explained by disturbances in central inhibition and fine-tuning of motor responses (Puri et al., 1996).

A number of recent TMS studies indicate that patients with schizophrenia have impairments of cortical inhibition. The main results of investigations using the silent period, paired pulse inhibition and transcallosal inhibition TMS paradigms are summarized in Table 1.

5.2.1. Silent period

Four recent studies have found the silent period duration to be significantly shorter in medicated schizophrenic patients compared to healthy controls (Daskalakis et al., 2002; Fitzgerald et al., 2002b,c,d). One of these studies also included a group of unmedicated patients (Daskalakis et al., 2002) and found that these patients had a significantly shorter silent period duration than the medicated group. Only one smaller study failed to report a significant difference in silent period duration between patients on conventional antipsychotics and healthy controls (Davey et al., 1997).

5.2.2. Paired pulse inhibition

A study comparing 40 medicated schizophrenia patients with 22 normal subjects did not find a significant difference on measurements of paired pulse inhibition (Fitzgerald et al., 2002d). However, three smaller studies found less inhibition in schizophrenics compared to control subjects (Daskalakis et al., 2002; Fitzgerald et al., 2002c; Pascual-Leone et al., 2002). Two of these studies also included groups of unmedicated patients. In one study, unmedicated patients did not differ significantly from healthy subjects (Pascual-Leone et al., 2002); in the other one unmedicated patients had less paired pulse inhibition than healthy controls. In the latter study medicated patients did not differ significantly from either the unmedicated or the control group (Daskalakis et al., 2002). Furthermore, in this study a significant correlation ($r = 0.5$, $p = 0.01$) was found between the magnitude of paired-pulse inhibition and the severity of psychotic symptoms in the patient groups such that patients with higher scores on the Positive and Negative Symptom Scale (PANSS) exhibited decreased inhibition.

5.2.3. Transcallosal inhibition

Three studies found a reduction of the magnitude of transcallosal inhibition in schizophrenic patients (Daskalakis et al., 2002; Fitzgerald et al., 2002b,d). In one of these studies, the difference was seen between unmedicated patients and healthy subjects but a group of medicated patients did not differ significantly from the control and unmedicated groups (Daskalakis et al., 2002). A single pulse technique, used in one study, did not find significant differences in transcallosal inhibition between patients and controls (Fitzgerald et al., 2002b). In four studies, the duration of transcallosal inhibition was significantly longer in schizophrenics than in healthy subjects (Boroojerdi et al., 1999; Fitzgerald et al., 2002c,d; Hoppner et al., 2001).

Transcallosal inhibition has also been used to investigate inter-hemispheric interactions of homologous brain areas by measuring the latency of the inhibition. In the first TMS study of transcallosal inhibition in schizophrenia, Boroojerdi et al. (1999), using a single pulse paradigm, found a significant delay in the onset of transcallosal inhibition in 10 medicated schizophrenia patients compared to 10 controls. However, other investigators did not report a significant delay in the onset of transcallosal inhibition or indications of increased transcallosal conduction time in patients with schizophrenia (Fitzgerald et al., 2002c,d; Hoppner et al., 2001). Altogether, these reports suggest that stimuli mediating inhibition travel normally between hemispheres. However, contralateral inhibitory mechanisms activated by the transcallosal stimuli may be impaired in patients suffering from schizophrenia.

5.3. Effects of antipsychotic medications on cortical inhibitory mechanisms

The effects of antipsychotic medications on cortical inhibitory mechanisms are not well understood. However, there are some indications that conventional antipsychotic medications may disrupt cortical inhibition (Davey et al., 1997; Pascual-Leone et al., 2002; Ziemann et al., 1997), while atypical antipsychotic medications may enhance it (Fitzgerald et al., 2002c,d).

Ziemann et al. (1997) demonstrated using paired-pulse TMS that healthy subjects taking haloperidol had significantly less cortical inhibition while on the

Table 1
Neurophysiological TMS studies of patients with schizophrenia

Study	*n*	Medications	Motor threshold	MEP amplitude/ latency	Silent period	Paired pulse TMS	Transcallosal inhibition
Puri et al. (1996)	9 schizophrenics 9 controls	None	No group difference	Latency shorter in patients	Latency did not differ between groups	N/T	N/T
Abarbanel et al. (1996)	10 medicated schizophrenics 10 depressed 10 controls	Conventional anti-psychotics (7) or clozapine (3)	Significantly lower in patients	Larger MEP size in patients MEP latencies did not differ between groups	N/T	N/T	N/T
Davey et al. (1997)	20 schizophrenics 10 medicated 10 unmedicated	Conventional antipsychotics	No group difference	Latency did not differ between groups	Mean latency of maximal suppression was longer in medicated patients Total duration did not differ	N/T	N/T
Boroojerdi et al. (1999)	10 schizophrenics 10 controls	Atypical (7) and conventional (3) anti-psychotics	No group difference	Latency did not differ between groups	N/T	N/T	Single pulse technique: Latency and duration was longer in patients
Hoppner et al. (2001)	12 schizophrenics 12 controls	Atypical (6) and conventional (6) anti-psychotics	N/T	N/T	N/T	N/T	Single pulse technique: No difference in latency Duration was longer in patients
Fitzgerald et al. (2002b)	25 schizophrenics 20 controls	Atypical antipsychotics	No group difference	MEP size did not differ between groups	Shorter duration in patients	N/T	Single pulse technique: Patients had longer duration No difference in latency or reduction in MEP size Dual pulse technique: Patients had both smaller reduction in MEP size and silent period duration
Daskalakis et al. (2002)	30 schizophrenics 15 medicated 15 unmedicated	Atypical (14) and conventional (2) anti-psychotics	Lower MT over left hemisphere in patients compared to unmedicated patients	MEP size did not differ between groups	Shorter duration in unmedicated patients than in medicated patients and shorter duration in mediacted patients than controls	Less inhibition in unmedicated group than controls	Dual pulse technique: Less reduction in MEP size in ummedicated patients than controls Difference between medicated patients and other two groups was not significant

						Medicated patients had less inhibition than controls but difference was not significant No group difference for paired pulse facilitation	
Pascual-Leone et al. (2002)	14 schizophrenics 7 medicated 7 unmedicated 7 controls	Conventional anti-psychotics	5–10% higher MT on left vs. right side in patients while the opposite was found in controls 5% higher MT on both sides in medicated compared to other groups	N/T	N/T	Less inhibition and more facilitation in medicated patients compared to other groups Unmedicated patients and controls did not differ	N/T
Fitzgerald et al. (2002c)	22 schizophrenics 21 controls	Atypical antipsychotics	No group difference	MEP size and latency did not differ between groups	Duration was shorter in patients than controls Latency did not differ between groups	Less inhibition in patients than controls No difference in facilitation	N/T
Fitzgerald et al. (2002d)	40 schizophrenics 22 normals	20 on olanzapine 20 on risperdone	Higher MT in risperidone group than in olanzapine group	No group differences	Duration was shorter in medicated groups Risperidone group did not differ from olanzapine group	No group differences on inhibition or facilitation	Single pulse technique: Longer duration of inhibition in olanzapine group than in risperidone group and controls No group difference in latency Dual pulse technique: Reduction in MEP size was less in olanzapine and risperidone groups than controls but the medication groups did not differ

MEP, Motor Evoked Potential; MT, Motor Threshold; TMS, Transcranial Magnetic Stimulation, N/T = not tested.

drug. Similarly Pascual-Leone et al. (2002) found that a group of patients with schizophrenia taking conventional antipsychotics had less paired pulse inhibition than groups of unmedicated patients and healthy control subjects.

The effects of conventional antipsychotic medications on the cortical silent period in patients with schizophrenia were studied by Davey et al. (1997). They found that in most of the patients taking medications, the cortical silent period was divided into an early part with weak suppression of voluntary EMG and a later component with strong suppression. No such division was seen in any of the non-medicated patients in the study, who all had an abrupt onset of maximum EMG suppression. The delay in maximal suppression in the medicated patients may be explained by disruption of basal ganglia inputs to the inhibitory circuitry in the motor cortex induced by the medications. Studies of patients with Parkinson's disease, where dopamine is depleted, demonstrate a similar reduction in the strength of EMG suppression in the early part of the silent period (Ridding et al., 1995).

The effects of the newer atypical antipsychotic medications on cortical inhibitory mechanisms may be different from the effects of typical antipsychotics. In a recent study by Fitzgerald et al. (2002d), where the effects of olanzapine and risperidone were compared on several measures of cortical inhibition in patients with schizophrenia, the two medications were found to differ. Schizophrenia patients taking olanzapine (mean dose 12.25 mg) had a significantly higher level of transcallosal inhibition than patients taking the risperidone (mean dose 4.1 mg). Olanzapine may therefore have enhancing effects on cortical inhibitory mechanisms. Moreover, the length of transcallosal inhibition was significantly longer in subjects taking olanzapine and the increased duration correlated with the dose of olanzapine (Fitzgerald et al., 2002c). Future studies of schizophrenia subjects both on and off medications will increase the understanding of the effects of antipsychotic medications on cortical inhibitory processes.

6. Treatment of schizophrenia with TMS

Since the mid 1990s, it has been suggested that TMS may play a role in the treatment of several neurological and psychiatric disorders (Pridmore and Belmaker, 1999). Indeed, there is increasing evidence suggesting that both slow and high frequency TMS trains applied to the left or right prefrontal cortex have antidepressant effects, although the effect sizes are variable between studies and few studies have shown high rates of strong response or remission (Burt et al., 2002). There is less data on the effectiveness of TMS in treating other psychiatric disorders such as mania (Grisaru et al., 1998b), post-traumatic stress disorder (Grisaru et al., 1998a), obsessive–compulsive disorder (Greenberg et al., 1997) and schizophrenia.

The optimal stimulation parameters for treating any psychiatric disorder with TMS, such as the frequency, intensity, duration and location of stimulation, as well as the total number of stimuli and treatment sessions, have not yet been determined. Furthermore, various types and shapes of stimulation coils have been used and they have been positioned and oriented in different ways. A direct comparison of treatment studies is therefore difficult.

A major concern in controlled TMS trials is the lack of a reliable placebo (sham) condition. An optimal sham TMS should induce the same somatic sensations (scalp twitches) as active TMS without stimulating the brain. The most commonly used sham condition today involves tilting the coil 45° or 90° off the head in order to direct the magnetic field away from the brain. However, it has been found that the brain may still be affected and subjects may be able to discriminate between active and sham conditions (Lisanby et al., 2001). A promising solution to this problem is the development of a new TMS coil that induces both active and sham stimulation without having to be moved or tilted. This coil has a special sham mode where the intensity of the magnetic field is below the threshold for activating cortical neurons but strong enough to induce stimulation of the scalp (Ruohonen et al., 2000).

Another important variable in clinical TMS studies is the frequency of stimulation. Several studies have found that after high frequency TMS (>1 Hz) there is increased excitability in various brain areas, while after low frequency stimulation (< 1 Hz) cortical excitability is decreased (Wu et al., 2000; Chen et al., 1997; Wassermann et al., 1998). Changes in cortical excitability also depend on stimulation intensity and duration. Higher intensity is more likely to

induce activation and long stimulation trains correlate with longer lasting modification of cortical excitability (Pascual-Leone et al., 1998). In principle, such findings can help designing rational treatment trials for various psychiatric symptoms. For example, to the extent that hypoactivity of prefrontal cortex plays a role in the pathophysiology of negative symptoms of schizophrenia (Andreasen et al., 1997), high frequency TMS of prefrontal cortex should help reversing such hypoactivity and related symptoms. Conversely, positive symptoms such as hallucinations, which are associated with hyperactivity of temporoparietal areas (Silbersweig et al., 1995), should benefit from low frequency TMS to these regions.

Table 2 summarizes the design, stimulation parameters and main effects of TMS in therapeutic trials of schizophrenia. The studies can be separated into two groups according to the brain region being stimulated. Left and right dorsolateral prefrontal cortex stimulation has been applied when investigating TMS effects on positive and negative symptoms of schizoprhenia and the left temporoparietal cortex was stimulated when studying the effects of TMS on auditory hallucinations.

7. TMS of prefrontal cortex

The first two studies of TMS aimed at treating patients with schizophrenia were open trials using slow repetitive stimulation of the prefrontal cortex with circular coils (Feinsod et al., 1998; Geller et al., 1997). Transient improvement in mood was described in 2 of 10 schizophrenia patients treated with 15 TMS pulses over each side of the prefrontal cortex (Geller et al., 1997). Feinsod et al. (1998) treated 10 patients with right prefrontal TMS at 1 Hz in two 1-min daily sessions for 10 days. There was a significant reduction in scores on the Brief Psychiatric Rating Scale (BPRS) in seven patients, but this improvement was linked to a reduction in symptoms of restlessness, tension and anxiety and not to an improvement in psychotic symptoms.

The effects of slow-repetitive TMS on positive and negative symptoms of schizophrenia were studied in 31 medicated hospitalized patients with schizophrenia or schizoaffective disorder who had an exacerbation of psychotic symptoms (Klein et al., 1999). It should be noted that this was a double-blind sham controlled study (subjects were randomized to receive either TMS or sham TMS). In this study, the right prefrontal cortex was stimulated with a circular coil at a rate of 1 Hz in 20-min sessions for 10 days. The patients were evaluated using the PANSS, the BPRS and the Hamilton Depression Rating Scale (HDRS) at the end of each treatment week and then 1 and 4 weeks post-treatment. Both groups displayed a similar mild improvement over time on all rating scales but there was no significant difference between the TMS and sham treated groups.

Three small trials have demonstrated promising effects of high frequency prefrontal TMS for treatment of symptoms of schizophrenia. In a study of 12 medicated acutely psychotic patients with schizophrenia, Rollnik et al. (2000) performed high frequency (20 Hz) pulse trains with a figure-of-eight coil to the left or dominant dorsolateral prefrontal cortex at 80% of motor threshold for 10 days. In this study a crossover design was used in which subjects were randomized to receive 2 weeks of active TMS and 2 weeks of sham TMS. The patients were rated at the end of each week using the BPRS, Beck Depression Inventory (BDI), State-Trait-Anxiety Inventory and a number connection test to monitor frontal lobe function. The BPRS values were significantly lower for active treatment than sham treatment at the end of the second week. This effect was not explained by an improvement of depressive symptoms, since measures on the BDI were not significantly decreased with active TMS. Other ratings did not differ significantly between active and sham TMS.

The effects of rapid TMS of the prefrontal cortex on negative symptoms were studied by Cohen et al. (1999). They found a significant reduction in negative symptoms, measured with the PANSS, in an open trial of six patients treated with 20 Hz to the left prefrontal cortex for 2 weeks with a figure-of-eight coil. The patients in this study were not evaluated for symptoms of depression. In a double-blind sham controlled trial of eight schizophrenia patients, Nahas et al. (1999) reported an improvement of negative symptoms the day after a single session of 20 Hz TMS to the left dorsolateral prefrontal cortex.

Finally, high frequency TMS of prefrontal cortex has been employed to treat two subjects with prominent catatonic symptoms (Grisaru et al., 1998c; Saba

Table 2
Studies of TMS for treatment of schizophrenia

Study	*n*	Design	Stimulation location	Treatment	Evaluation	Effects	*p* value
(I) TMS of prefrontal cortex							
Geller et al. (1997)	10	Open	Prefrontal cortex bilaterally	One session. 14 cm circular coil 15 stimuli (1 every 30 s) at 100% stimulus intensity	BPRS	Two patients had transient improvement in mood	
Feinsod et al. (1998)	10	Open	Right prefrontal cortex	Ten sessions over 2 weeks. 9 cm circular coil Two 1 min stimulus trains at 1 Hz at 100% of motor threshold	BPRS	Significant improvement after 2 weeks compared to baseline	<0.01
Klein et al. (1999)	31	Sham controlled 16 patients rTMS 15 patients sham	Right prefrontal cortex	Nine sessions over 2 weeks. 9 cm circular coil. Two 1 min stimulus trains at 1 Hz and 110% of motor threshold Sham: Coil perpendicular to skull	CGI PANSS BPRS HDRS	No significant group differences No significant group differences No significant group differences	NS NS NS NS
Cohen et al. (1999)	12	Sham controlled crossover	Dominant dorsolateral prefrontal cortex	Ten sessions over 2 weeks. 7 cm figure 8 coil. Twenty 2 s trains at 20 Hz over 20 min at 80% of MT Sham: Coil 45° away skull	BPRS BDI	Significant improvement after 2 weeks in active group compared to sham	0.015 NS
Nahas et al. (1999) (Abstract)	8	Sham controlled crossover	Left dorsolateral prefrontal cortex	One session of forty 2 s trains at 20 Hz and 100% MT + 1 day sham Sham: Not described.	SANSS	Trend of improvement immediately following active TMS and the following day	NS
Rollnik et al. (2000)	6	Open	Left dorsolateral prefrontal cortex	Ten sessions over 2 weeks. 7 cm figure 8 coil. Twenty 2 s trains at 20 Hz over 20 min at 80% of MT	PANSS	Negative symptoms improved	<0.02

Grisaru et al. (1998c)	1	Case report	Right dorsolateral prefrontal cortex	Ten sessions over 2 weeks. 9 cm circular coil Twenty 2 s trains at 20 Hz over 20 min at 80% of MT		Full remission in 4 weeks	
Saba et al. (2002)	1	Case report	Left dorsolateral prefrontal cortex	Ten sessions over 2 weeks. 1600 stimuli/session at 10 Hz and 80% of MT		Almost all catatonia symptoms had disappeared at the end of the treatment	
(II) TMS of temporoparietal cortex (auditory hallucinations)							
Hoffman et al. (1999, 2000)	12	Sham controlled crossover	Left temporoparietal cortex	Randomly four daily TMS and four daily sham sessions. 7 cm figure 8 coil 4–16 min at 1 Hz and 80% of MT Sham: Same parameters but coil 45° away from skull	HSS PANSS	Significant improvement following 12 and 16 min of active rTMS compared to sham	<0.006 NS
d'Alfonso et al. (2002)	8	Open	Left medial/superior temporal gyri	Ten 20 min sessions during 2 weeks at 1 Hz and 80% of MT	VRS	Significant improvement between baseline and end of treatment	0.034
Hoffman et al. (2003)	24	Sham controlled 12 patients rTMS 12 patients sham	Left temporoparietal cortex	Nine sessions. 7 cm figure 8 coil 8–16 min at 1 Hz and 90% of MT Sham: Same parameters but coil 45° away from skull	HCS	Significant improvement between baseline and end of treatment for active group but not for sham group	0.003

BPRS, Brief Psychiatric Rating Scale; BDI, Beck Depression Inventory; CGI, Clinical Global Impression; HDRS, Hamilton Depression Rating Scale; HCS, Hallucination Change Scale; HSS, Hallucination Severity Scale; MT, Motor Threshold; PANSS, Positive and Negative Symptom Scale; SANSS, Scale of Assessment of Negative Symptoms; VRS, Voice Rating Scale.

et al., 2002). In this case, the TMS effects may resemble those induced with electroconvulsive therapy, which is known to be an effective treatment for catatonia. In summary, although these studies indicate that high frequency TMS to prefrontal cortex may be effective for treating certain symptoms of schizophrenia, larger controlled trials using consistent stimulation parameters are necessary to establish the efficacy of TMS in the treatment of schizophrenia.

8. TMS of temporoparietal cortex to treat auditory hallucinations

Recent studies have provided interesting findings on the effectiveness of TMS applied to one particular brain area to specifically treat auditory hallucinations (d'Alfonso et al., 2002; Hoffman et al., 1999, 2000, 2003). A previous study suggested that auditory hallucinations may stem from abnormalities in brain areas that are involved in the perception of speech. Silbersweig et al. (1995) performed PET scans on six patients with schizophrenia who were hallucinating at the time and demonstrated increased blood flow in the left temporoparietal auditory linguistic association cortex. Based on the finding that long trains (15–30 min) of low frequency (1 Hz) TMS decreases activity in stimulated brain areas (Wassermann et al., 1998), Hoffman et al. (1999, 2000) treated patients with schizophrenia that had frequent auditory hallucinations with 1 Hz TMS at 80% of motor threshold to the left temporo-parietal cortex using a figure-of-eight coil. In a double-blind crossover designed pilot study, 12 medicated patients underwent TMS and sham TMS each for 4 days. The stimulation duration was gradually increased from 4 to 16 min/day. Auditory hallucinations were rated every day using a scale that assessed the loudness, frequency, content and level of distress from the hallucinations. Eight of the patients reported a significant improvement in auditory hallucinations with TMS and the improvement reached significance following the third and fourth days of stimulation. Four of the patients had negligible or no improvement. Other symptoms of schizophrenia did not significantly change with the treatment. In follow up assessments, the auditory hallucinations were found to recur from 1 day to 2 months post-treatment. It was interesting in this study that five patients taking anticonvulsive medications had less of a treatment effect than patients who were not taking these medications. Several previous studies have indicated that various anticonvulsants can increase cortical inhibition and the threshold for cortical excitation measured with TMS (Manganotti et al., 1999; Rizzo et al., 2001; Ziemann et al., 1996).

Hoffman et al. (2003) recently followed their pilot study with a trial of 24 patients with medication resistant auditory hallucinations. Again, the left temporoparietal cortex was stimulated at 1 Hz but the intensity and total number of stimulations was higher than in the previous studies. Twelve patients received active TMS at 90% of motor threshold for 8 min on day 1, 12 min on day 2 and 16 min on days 3 to 9. The other 12 patients had sham stimulation with the stimulation parameters but the coil was angled 45° away from the head. Nine of the sham patients received a subsequent unblinded trial of active TMS. The active group had a significant linear decrease in hallucination frequency during the study and they also reported a significant decrease in distraction caused by the hallucinations. These measures did not change significantly in the sham group. Other hallucination ratings such as loudness, duration of voices and level of distress did not differ between the groups. All patients receiving active TMS who reported more than 20% improvement in the hallucination rating scale score were followed by telephone for 1 year. At 15 weeks, 52% of patients had sustained improvement but at week 52 they were down to approximately 25%. No significant changes were found on measures of general psychopathologic symptoms (PANSS) or neuropsychological tests.

A recent open trial of eight schizophrenia patients with medication resistant auditory hallucinations demonstrated a modest improvement in seven patients after 2 weeks of daily 20 min TMS of the auditory cortex (middle and superior temporal gyri) at 1 Hz and 80% of motor threshold (d'Alfonso et al., 2002).

9. Conclusions and future directions

The application of TMS in basic neurophysiological and neuropsychiatric research has been rapidly expanding since its introduction in 1985. TMS is a noninvasive method that can be employed to study

motor cortex excitability and cortical inhibitory mechanisms. A growing number of studies using TMS-based paradigms support the notion that cortical inhibition may be deficient in patients with schizophrenia. However, the use of TMS as a diagnostic tool for psychiatric disorders is still in its infancy and confounding factors related to the variability of stimulation parameters, the severity and duration of the disease, and the use of medications need to be resolved before compelling conclusions can be drawn.

On the therapeutic side, initial studies using TMS on subjects with schizophrenia have provided some disappointing as well as some encouraging results. The latter include the reduction of auditory hallucinations with slow TMS over auditory cortex and an improvement of psychotic symptoms after 2 weeks of high frequency TMS over left prefrontal cortex (Hoffman et al., 2003; Rollnik et al., 2000). It will be interesting to see whether these studies will be confirmed with more patients and longer follow-up periods. Moreover, it will be important to compare the therapeutic benefits of TMS with those of standard treatments, although a truly ideal placebo condition for TMS remains difficult to envision.

One of the most promising new developments is the ability to combine TMS with functional brain imaging. In such paradigms, TMS pulses are delivered over a cortical region while simultaneously recording brain activity patterns using PET (Fox et al., 1997; Paus et al., 1997; Kimbrell et al., 2002), fMRI (Bohning et al., 1998, 1999, 2000a,b; Nahas et al., 2001) or high-resolution EEG (Ilmoniemi et al., 1997; Komssi et al., 2002). These approaches make it possible to assess not only the cortical activity induced under the TMS coil but also the influence that the stimulated area exerts onto other brain areas—its *effective connectivity*.

The initial studies probing the effective connectivity of cortical regions have so far been performed in healthy subjects. However, studies of effective connectivity may be especially revealing when applied to psychiatric disorders to explore the possibility of disease-related alterations in connectivity between critical brain regions. For example, a number of recent neurobiological and neuroimaging studies indicate that some symptoms of schizophrenia may result from impaired functional integration of multiple brain areas rather than from a malfunction of one single area (Glantz and Lewis, 1997; Karson et al., 1999; Selemon and Goldman-Rakic, 1999; Tononi and Edelman, 2000). If a combination of TMS and neuroimaging were to uncover a dysfunction in the connections between specific brain areas in patients with schizophrenia, a potential treatment would be to selectively stimulate these connections with therapeutic doses of TMS. As suggested by studies of TMS for treating auditory hallucinations, stimulation of specific brain sites for targeting different symptoms (cognitive, positive and negative) may become an effective treatment for this complex disorder.

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