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REVIEW

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Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders

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Abstract *Rationale:* Transcranial magnetic stimulation (TMS) is a noninvasive tool that directly stimulates cortical neurons by inducing magnetic and secondary electric fields. Traditionally TMS has been used to study the motor neurophysiology of healthy subjects and those with neurological disorders. *Objective:* Given the known motor dysfunctions in many psychiatric disorders supplemental usage of TMS to study the underlying pathophysiology of certain psychiatric disorders and to assess treatment outcomes is underway. Such studies include examination of motor neuronal membrane, corticospinal and intracortical excitability. Our objective is to overview the past findings. *Methods:* We review the past literature that used TMS as an assessment tool in psychiatric disorders such as schizophrenia, mood disorders, Tourette's syndrome, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, and substance abuse. *Results:* While the findings are still preliminary due to small sample-size, inconsistent patient population (diagnosis, medication), differences in methodology between research groups, studies restricted to the motor region and possible lack of sensitivity and specificity, the studies are yielding interesting results which could potentially lead to trait- and state-markers of psychiatric disorders. *Conclusions:* Future studies using TMS alone or in combination with other neuroimaging techniques promise to further expand the application of TMS from studies of motor excitability to higher cognitive functions.

Keywords Transcranial magnetic stimulation · Psychiatry · Trait-marker · State-marker · Cortical excitability · Neurophysiology

Introduction

Since its first demonstration in 1985 by Barker and his colleagues (1985a, 1985b) transcranial magnetic stimulation (TMS) has become increasingly popular, with its relative ease, very few side effects, and wide range of potential applications. It has been used to measure corticospinal excitability, to map motor and cognitive functions, to study neural networks, and to modulate brain function with a potential therapeutic aim (George and Belmaker 2000; Mills 1999; Pascual-Leone et al. 1999, 2000).

The most traditional use of TMS has been to study the central motor pathways in healthy subjects and in patients with neurological disorders. New findings of motor system abnormalities in neuropsychiatric disorders and greater insights into the mechanisms of action of various TMS techniques invite the systematic exploration of TMS for the study of the pathophysiology of psychiatric disorders and the assessment of treatment outcomes. This review focuses on TMS studies relevant to the pathophysiology of disorders such as schizophrenia, mood disorders, Tourette's syndrome, obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), and substance abuse and their modulation by pharmacological interventions or repetitive trains of TMS (repetitive TMS, rTMS). TMS techniques employed in such studies include measurements of the motor threshold, silent period and motor-evoked potentials (MEPs) to single pulse stimulation, and paired-pulse (PP) curve determinations. For a review on TMS and its role in neurological disorders refer to Boylan and Sackeim (2000), Rossini and Rossi (1998), or Ziemann et al.

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(1998). For a review on the therapeutic role of TMS in neuropsychiatric disorders refer to George et al. (1999), Post et al. (1999), or Pridmore and Belmaker (1999).

Basic mechanisms

TMS utilizes the principle of electromagnetic induction, which was first discovered by Michael Faraday in 1831. It involves the discharge of very large current (peak current: approximately 5,000 amps) from a bank of capacitors which rapidly flows through a simple LCR circuit and then through a copper-wire coil. A rapid time-varying magnetic field is induced (rise time: approximately 0.1 ms, field strength: approximately 2 T) at the level of the first conductor, the coil. When the coil is held to the head of a subject, and the magnetic field pulse penetrates the scalp and skull and induces a small current parallel to the plane of the coil in the adjacent second conductor, the brain. When the induced current is sufficient (several mA/cm^2), depolarization of neuronal membranes occurs, and hence generation of action potentials. When the coil is held tangentially to the scalp, the induced current flows parallel to the surface of the brain surface, thereby preferentially activating interneuronal elements that are oriented horizontally to the surface of the brain (Day et al. 1989). In the case of the hand area within the primary motor cortex, TMS is thought to predominantly activate the pyramidal cells transynaptically through excitatory interneuronal elements (Amassian et al. 1990; Day et al. 1989; Di Lazzaro et al. 1999a, 1999b; Nakamura et al. 1996). This is supported by several studies in humans (Day et al. 1989; Di Lazzaro et al. 1999a, 1999b; Nakamura et al. 1996) and monkeys (Amassian et al. 1990) that show that the difference in latency between electromyographic (EMG) responses or corticospinal volleys evoked by electrical and magnetic stimulation is due to synaptic transmission time in cortical circuits. This became known as the D and I wave hypothesis. D wave is the first volley of the multiple descending volleys in the spinal cord evoked by transcranial stimulation. This term comes from the assumption that it is evoked by direct excitation of pyramidal tract neurons. I waves are the subsequent volleys which appear to be generated by indirect excitation of the pyramidal tract neurons via cortical interneurons. Transynaptic activation of pyramidal cells seems true provided that the stimulation intensity is low, and the induced current is in a direction anterior and perpendicular to the central sulcus (Brasil-Neto et al. 1992; Kaneko et al. 1996a, 1996b; Mills et al. 1992; Sakai et al. 1997; Werhahn et al. 1994).

The spatial resolution of TMS is thought to be approximately 0.5–1.0 cm within the hand area of the motor cortex. The combination of neuroimaging studies have shown coinciding areas for the induction of finger movement using TMS and activated regions due to finger movement (Boroojerdi et al. 1999; Terao et al. 1998). Direct stimulation is thought to reach approximately 1–2 cm to achieve neuronal depolarization, hence allowing only the surface of the cortex to be stimulated (Barker 1999). This seems critical in the studies of neuropsychiatric disorders, in which subcortical regions play an important role. Transynaptic effects of TMS to remote areas of the brain, however, have recently been shown by simultaneous neuroimaging techniques (see "Future directions," below). The excellent temporal resolution (a magnetic pulse duration is approximately 0.3–1.0 ms) and unique applications make TMS complementary and able to compete with other neuroimaging techniques.

Measurements of corticospinal and corticocortical excitability

There are many available TMS techniques that have been used to measure corticospinal and corticocortical excitability. These measurements can be influenced by a large number of methodological factors (Pascual-Leone et al. 1998; Rossini and Rossi 1998). Individual characteristics and physiological state have a substantial effect on such measures (Maeda et al. 2000a, 2000b; Mills et al. 1992). For example, subjects' age (Matsunaga et al. 1998) or handedness (McDonnell et al. 1991; Priori et al. 1999; Triggs et al. 1999a), fatigue (Brasil-Neto et al. 1994; Hollge et al. 1997), hyperventilation (Priori et al. 1995), gender and time in the menstrual cycle (Smith et al. 1999), attention (Kiers et al. 1993), imagery (Fadiga et al. 1999; Hallett et al. 1994), and action observation (Fadiga et al. 1995; Maeda et al. 2002a; Strafella and Paus 2000) all affect corticospinal and/or corticocortical excitability. In addition, preceding stimulation to other neural elements can influence excitability of the motor cortex due to the afferent connections. For example, measures of motor excitability can be influenced by preceding stimulation of the cerebellum (Maeda et al. 2000f; Ugawa et al. 1999), the contralateral motor cortex (Di Lazzaro et al. 1999a, 1999b; Leipert et al. 1996; Schnitzler et al. 1996) or the peripheral nerves (Date et al. 1991; Ridding et al. 2000). Similarly, measures of corticospinal excitability are influenced by contraction of the target muscles or even neighboring muscles (Hess et al. 1986). Finally, of course a large number of drugs can markedly influence the results of TMS measures of excitability (for a review see Ziemann et al. 1998). Essentially, TMS delivers a constant stimulus to the subject's brain and any factor that changes, either the type of stimulus or the state of the brain region receiving the stimulus, influences the results.

Motor evoked potential

The term MEP refers to the electrical potential recorded from muscle, peripheral nerve, or spinal cord in response to stimulation of the motor cortex or the motor pathways within the central nervous system (CNS). The technique most commonly used at present for TMS studies involves application of the stimulation to the scalp area overlying the primary motor cortex and recording of the compound

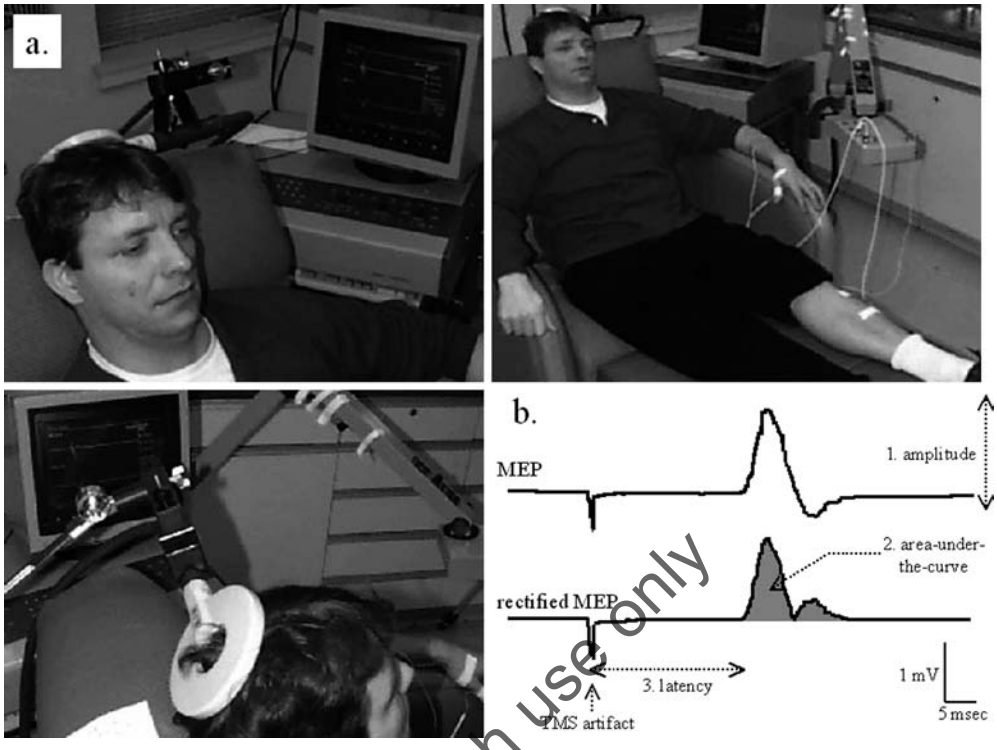

Fig. 1a, b Motor-evoked potential. **a** A magnetic stimulus is applied to the scalp area over the primary motor cortex with a circular coil and motor-evoked potentials (*MEPs*) are collected from the abductor pollicis brevis (*APB*) and anterior tibialis (*AT*). **b** The figure illustrates a rectified and nonrectified MEP. Amplitude (*1*), area under the curve (*2*), and latency (*3*) of MEPs can be measured

muscle action potential via surface electrodes. Stimulation can also be applied to the cervical spine overlying the cervical root that one desires to activate while recording form distal extremity muscles. The size of MEPs [peak-to-peak amplitude (Fig. 1, 1) or area under the curve of the rectified MEP (Fig. 1, 2)], and latency (Fig. 1, 3) from the TMS pulse to the onset of MEP are measures that reflect corticospinal excitability.

Motor threshold

Motor threshold, by convention, refers to the minimum intensity to evoke a small motor response of a given criterion amplitude with a set probability. Motor threshold can be defined when the target muscle is at rest or under sustained voluntary contraction. When the target muscle is at rest, motor threshold is generally defined as the lowest intensity that induces MEPs of 50 μV peak-to-peak amplitude in the target muscle in 50% of the trials given that TMS is applied to the "optimal site" (Rossini et al. 1994). The optimal site is the scalp position of the stimulation coil from which TMS induces MEPs of maximal amplitude in the target muscle. Optimal sites are different for different target muscles. The target muscle typically used to measure motor threshold is one of the intrinsic hand muscles (e.g., first dorsal interosseus or abductor pollicis brevis), which requires the lowest intensity for activation (Wassermann et al. 1992). This makes sense also given the relative lack of spinal circuitry contribution to the motor cortical projection to intrinsic hand muscles. One methodological factor to keep in mind in determining motor threshold is the importance of the interval intervals. When TMS is repeatedly applied to the same cortical region, the response to a given stimulus can be influenced by the effects of the preceding transcranial stimulus (this becomes the basis for the PP technique discussed below). Therefore it is important to allow sufficient time between stimuli during the determination of motor threshold. Generally 5- to 10-s intervals ought to be used (Chen et al. 1997). Another important methodological factor frequently overseen is the position of the limbs. Limb posture determines proprioceptive afferent input to the motor cortex and hence different postures can change cortical excitability (Landau 1952; Wassermann et al. 1998). It is therefore important to use a consistent placement of the limbs during and across motor threshold determination studies.

Motor threshold is related to the orientation, density, and electrical susceptibility of the corticocortical and thalamocortical axons on which the stimulus acts. Alterations in the threshold could hence reflect alterations at various levels: the neural membrane, axonal electronic property, the structure or the number of the excitatory projections onto the primary motor cortex, or upregulation of receptors in this region (Ziemann et al. 1998). Motor threshold is believed to represent a measure of membrane excitability of pyramidal neurons from studies that showed changes in motor threshold induced by antiepileptic drugs (single oral doses) with prominent sodium and calcium channel blocking activity but limited or absent neurotransmitter interaction (Ziemann et al. 1996b). This is consistent with the Hodgkin and Huxley (1952a, 1952b, 1952c) mathematical model that neuronal

membrane excitability is dependent mainly on ion channel conductivity. There are studies, however, that showed intravenous anesthetics that potentiate -aminobutyric acid (GABA) transmission (e.g., barbiturate thiopental sodium (Pentothal) or benzodiazepine midazolam) also decreased MEP amplitudes (Burke et al. 1993; Schonle et al. 1989). The relationship of this intravenous study and the studies of single oral doses is unclear since the means of administration and doses were different. The difference in motor threshold at rest and under contraction is thought to be indicative of the magnitude of the voluntary drive on the corticomuscular pathway (Tergau et al. 1999).

Motor threshold is known for its large interindividual variability. Two studies by University of South Carolina now indicate that a significant portion accounting for this variability is due to the distance from the TMS coil to the motor cortex (Kozel et al. 2000; McConnell et al. 2001). The intraindividual variability across time, on the other hand, is lower, which makes it useful in longitudinal studies (Ziemann et al. 1998). The reproducibility of the motor thresholds has been carefully tested by Mills and Nithi (1997). They found that motor thresholds are normally distributed and are independent of age, gender, and hemisphere. Repeatability estimates indicated an absolute change of more than 10% in motor thresholds in the same individual over 1–3 months that was significant at the 5% level in a study of 102 hands of 55 healthy subjects.

Determining threshold in the manner suggested can be time consuming and requires the use of EMG recording. Some have argued for the use of the presence of an evoked twitch as a marker of the TMS effects (Pridmore et al. 1998). They used a TMS device with the output intensity marked in 5° increments on an analog dial and found that the proportional difference measured by the EMG recording and visualization was up to 10% of total machine output. They concluded that, with the TMS device which they used and with their rigorous technique, the determination of motor threshold by neurophysiological and by visualization of movement methods produces similar results. Whenever possible, however, it seems well worth the effort to measure the motor threshold following the procedures recommended by the International Federation of Clinical Neurophysiology (Rossini et al. 1994) using EMG recordings especially when studying the pathophysiology or to monitor serially within and across subjects.

MEP latency and motor conduction time

The duration between the TMS pulse and the onset of the MEP is another measure of corticospinal excitability (Fig. 1, 3). As the stimulation intensity increases, the latency is known to become shorter. Motor conduction time has been the most traditional use of TMS. This is measured by combining TMS as described above and percutaneous magnetic (electric) stimulation to the dorsal

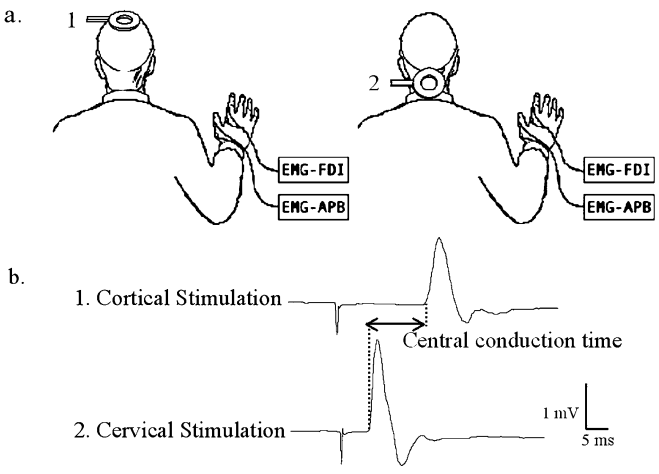

Fig. 2a, b Central conduction time. **a** The two top illustrations demonstrate applications of magnetic stimulation to the scalp area overlying the primary motor cortex (*1*) and the cervical spine targeting dorsal cervical roots (*2*). Motor-evoked potentials (*MEPs*) can be recorded from intrinsic hand muscles such as the first dorsal interosseous (*FDI*) or abductor pollicis brevis (*APB*). **b** The top electromyographic (*EMG*) tracing is acquired by cortical stimulation, and the bottom by cervical stimulation. Central conduction time is calculated as the difference of the two latencies

cervical root or F-wave recordings (Rossini et al. 1987). The transcranial stimulation measures the total conduction time between the motor cortex and the muscle (Fig. 2a), and the spinal stimulation (or F-wave latency) measure the spine-to-muscle conduction time (Fig. 2b). Although stimulation to the cervical root is at the level of intervertebral foramen and hence leaves us with some inaccuracy (Chokroverty et al. 1991; Mills and Murray 1986), subtraction of these two measures may be a reasonable measure of central conduction time (Fig. 2).

Silent period

Whereas the measurements described above are known to be a measure of excitatory effects, the silent period may be utilized to measure the inhibitory effects. This refers to the period of silence in the EMG activity of a voluntarily contracted muscle induced by a stimulus (in our case applied transcranially to the motor cortex). It consists of two components in which the first component is thought to be predominantly spinal in its origin and the latter to be specifically cortical in its origin (Brasil-Neto et al. 1995; Fuhr et al. 1991; Inghilleri et al. 1993; Ziemann et al. 1993). The possibility of inducing silent periods in the absence of a preceding MEP has led to the understanding that the excitatory and inhibitory descending pathways are at least independent or have different thresholds (Rossini et al. 1995; Wassermann et al. 1993). Although it has been proposed that the duration of the cortical spinal period reflects the function of GABAergic and dopaminergic cortical inhibitory mechanisms (Hallett 1995;

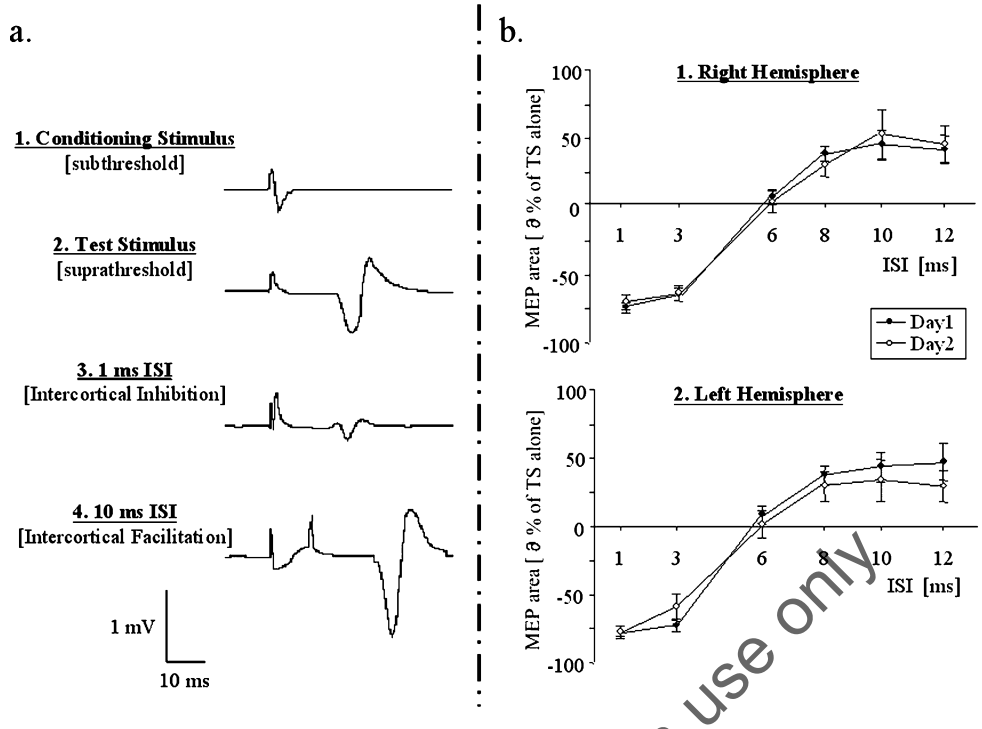

Fig. 3a, b Paired-pulse curve. **a** Electromyographic (*EMG*) tracings collected when a subthreshold magnetic stimulus is applied alone (conditioning stimulus, *CS*), a suprathreshold stimulus is applied alone (test stimulus, *TS*) or two pulses (CS followed by TS) are applied with an interstimulus-interval (*ISI*) of 1 ms (typical ISI for determination of intracortical inhibition, *ICI*) or 10 ms (intracortical facilitation, *ICF*). The size of all MEPs obtained during paired stimulation at different ISIs is expressed as proportional change (*∂%*) from the size of the MEPs to TS alone. **b** Paired-pulse curves of the right (*1*) and left (*2*) hemispheres (day 1 and day 2 superimposed). *Bars* Standard errors. There are no significant differences between right and left hemispheres or between day 1 and day 2

Ziemann et al. 1998), its physiology is yet to be fully understood.

MEP size in the paired-pulse technique

One of most popular techniques for the study of intracortical excitability is the PP technique. The PP technique investigates primarily intracortical excitability (Pascual-Leone et al. 1998). In this technique two magnetic stimuli are delivered in close sequence to the same cortical region through a single stimulation coil (Kujirai et al. 1993). The first (conditioning) stimulus (CS) is considered to condition the response to the second (test) stimulus (TS). The effects obtained depend on the intensity of the CS, the interval between the stimuli (interstimulus interval, ISI), the intensity of the TS and MEP size induced by TS (Pascual-Leone et al. 1998; Fig. 3 a). The intensities of the CS and TS influence the effects as different circuits are recruited by different intensities of stimulation. The ISI influences the results as the time constant of each activated circuit may differ. At very short ISI (<1 ms), neural time constants of the stimulated elements may be studied; at an ISI of 1–4 ms interactions between I-wave inputs to the corticospinal neurons may be studied; and at an ISI of 1.5–20 ms corticocortical inhibitory (ICI) and facilitatory (ICF) circuits may be studied.

All these effects appear to be cortically mediated (Kujirai et al. 1993; Valls-Solé et al. 1992; Ziemann et al. 1996d), and ICI (at ISIs between 1 and 4 ms) and ICF (at ISIs between 8 and 12 ms) appear to be due to activation of separate circuits (Ziemann et al. 1996d). Inhibition seems to reflect the activity of inhibitory interneurons or inhibitory connections between cortical output cells (Wassermann et al. 1996). Facilitation seems to be partially due to facilitatory interaction between I waves, and is thought to take place in the motor cortex at or upstream from the corticospinal neuron (Ziemann et al. 1998).

The effects of different disorders and medications on the inhibitory and facilitatory phases of the PP curve suggest that GABAergic, dopaminergic, and glutamatergic mechanisms are involved. Medications that enhance GABAergic activity have been shown to increase the degree of ICI and decrease ICF evoked by paired TMS stimuli (Inghilleri et al. 1996; Werhahn et al. 1998; Ziemann et al. 1996b, 1996c). Conversely, in Parkinson's disease, the dopamine deficiency is associated with reduced ICI at short ISIs (<5 ms; Berardelli et al. 1996; Ridding et al. 1995). Dopaminergic drugs have been shown to enhance ICI in normal subjects (Berardelli et al. 1996; Priori et al. 1994; Ridding et al. 1995; Ziemann et

al. 1996a). Furthermore, studies suggest that an early phase of relative facilitation in the PP curve at ISI of approximately 3 ms as well as ICF is related to glutamatergic excitatory intracortical modulation (Detsch and Koech 1997; Liepert et al. 1997; Ziemann et al. 1996d).

This technique is becoming increasing popular as the mechanism is becoming fairly well understood, the inter- and intraindividual variability is fairly small (Maeda et al. 2002b), and it is thought to study specifically the intracortical circuits (Ziemann 1999; Fig. 3b).

Cortical excitability studies in psychiatric disorders

Clinical observation and classification of symptoms are crucial facets comprising psychiatric diagnosis. In the age of objective findings as well as in the wake of increasing biological thinking about psychiatric disorders; however, it is not surprising that many valiant attempts have been made to define neurophysiological markers. Think, if you will, about the very large body of work carried out with electroencephalography (EEG) that already in its invention was indeed aimed at understanding psychiatric conditions. It is not within the scope of the present contribution to review this literature. Suffice to point out that many studies have examined neurophysiological patterns of various neuropsychiatric disorders before and after treatment. For example, Gunther et al. (1989) examined EEG patterns of schizophrenic and endogenous depressed patients during motor activation. They found signs of "diffuse hyperactivation" in the delta and alpha frequency bands, which tended to "normalize" with drug treatment. Davidson et al. (1999) has made, using topographic analysis of EEG power and patterns, compelling advances into the neurobiology of emotion and its pathophysiology in depression. Others have looked at diurnal fluctuations (Moffoot et al. 1994), metabolic changes (Goodwin et al. 1993), cerebral blood flow (Bench et al. 1995), dexamethasone suppression test (Arana et al. 1985), and auditory P3 event-related potentials (Blackwood et al. 1987) and have found changes or "normalization" on recovery from the disease episode. None of these measures, however, has thus far become a practical measure to support assessment or to follow the clinical course of patients with psychiatric disorders due to its low sensitivity or specificity. Along this line of research to define neurophysiological markers to support the assessment of psychiatric disorder or to find correlates with treatment outcome, some research groups, although not many, have begun to examine motor excitability of neuropsychiatric disorders using TMS.

Schizophrenia

Motor deficit is a known feature in patients with schizophrenia with or without medication. Such features include difficulty with saccadic inhibition (e.g., Curtis et al. 2001; Funahashi et al. 1990; Maruff et al. 1998; McDowell and Clementz 2001; Ross et al. 1998), abnormal involuntary movements (e.g., Ismail et al. 1998; Manschreck et al. 1990), abnormalities of grip strength and finger dexterity (e.g., Lohr and Caligiuri 1995), abnormalities of grip-induced muscle tension (e.g., Rosen et al. 1991), generalized incoordination and clumsiness (e.g., Chen et al. 2000), and impaired psychomotor activity (e.g., Walker 1994).

One of the first studies of motor excitability in schizophrenia was carried out by Puri et al. (1996). They studied nine drug-free schizophrenia patients (seven were drug-naive) with age-matched healthy controls and measured the motor threshold, latency of MEP, and latency of suppression under slight contraction of the target muscle of their dominant hand. Although there were no significant difference in motor thresholds or latency of suppression, the patients had significantly shorter mean latency of MEPs than controls (Fig. 4b, 1). It was concluded that this finding could be due to relative lack of corticospinal inhibition of motor responses, a change in the site of TMS activation, or an abnormality of peripheral nervous function. This study was followed up by the same group studying the effect of antipsychotic medications on EMG responses to TMS (Davey et al. 1997). They compared a group of nine neuroleptic-free schizophrenic patients with a group of nine schizophrenic patients on a stable antipsychotic regimen. There was no significant difference in their symptom ratings and duration of illness. There was no significant difference in the motor thresholds, latencies of MEPs, or total duration of silent periods. Patients on medication, however, exhibited significantly weaker EMG suppression in their early component of the silent periods and hence longer latency to reach maximum silent period-suppression (Fig. 4b, 2 and 3). The authors suggest that this finding may have resulted from medication disrupting the dopaminergic system within the basal ganglia, which in turn projects to the inhibitory circuit within the motor cortex. The amount of abnormality has not been studied in relation to motor dysfunctions or other symptoms. In contrast, a more recent study by Boroojerdi et al. (1999) did not find such latency difference in schizophrenic patients (on medication) as compared with age- and gender-matched healthy controls. This negative finding suggests the importance of differentiation between pathophysiological mechanisms of the disorder and the actions of medication (Davey and Puri 2000). Boroojerdi et al. (1999) found, however, transcallosal conduction time and duration of the inhibition to be significantly longer in the patient group.

Another study examined motor thresholds, MEP amplitude, and central motor conduction time of both hemispheres in ten patients with major depression, ten with chronic schizophrenia, and ten controls (Abarbanel et al. 1996). All the patients were on various psychotropic medications. There was no significant difference in central motor conduction time or interhemispheric difference in any of the measures across the groups. However,

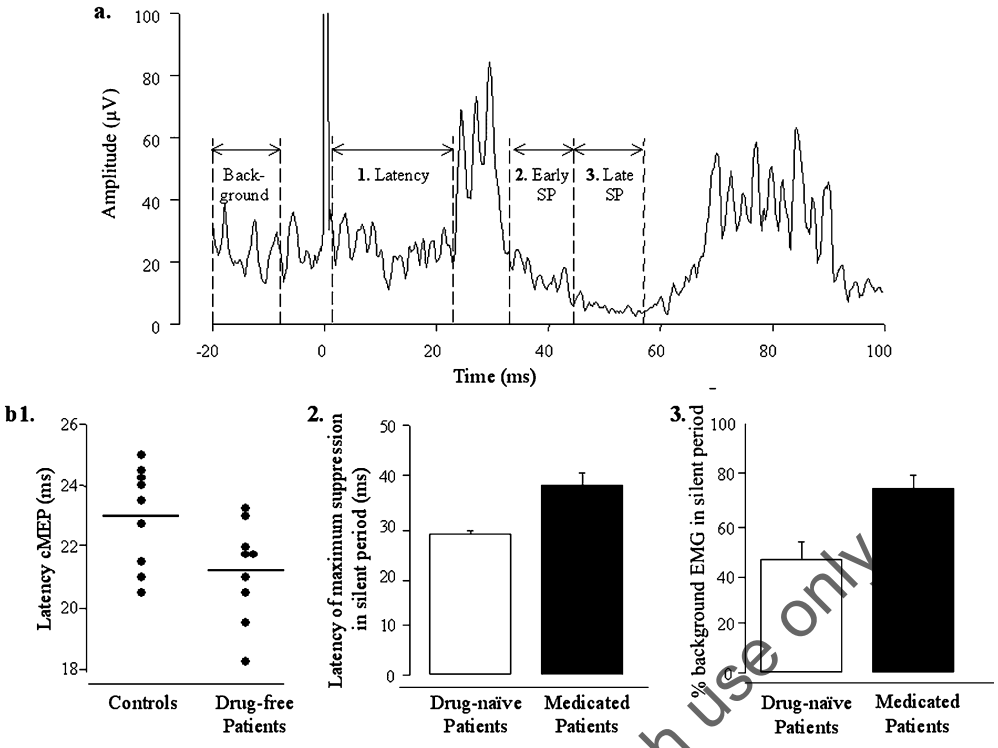

Fig. 4a, b Motor excitability studies of patients with schizophrenia. **a** A figure showing the rectified motor response to TMS during weak voluntary contraction of thenar muscles. **b***1* Mean latency of compound motor evoked potentials (*cMEPs*) is significantly shorter in drug-free schizophrenic patients compared to normal controls ($P<0.05$). When drug-naive patients are compared with those on neuroleptic medication, the latter are found to have: *2* a significantly longer latency of maximum suppression ($P<0.01$); *3* a significantly higher percentage of background electromyographic (*EMG*) suppression during early silent period (*SP*; $P<0.05$). *Bars* Standard errors. (Slightly modified with permission from the Royal College of Psychiatrists, BMJ Publishing Group, and authors: *1*, *2* from Puri et al. 1996; *3* from Davey et al. 1997)

the authors found a significant increase in MEP amplitude and decrease in motor thresholds in patients with schizophrenia compared to patients with depression or controls. They attributed this "increased brain excitability" to possible GABA deficiency in schizophrenia. Unfortunately, the possible confounding effect of the medications may account for the findings without having to invoke the underlying disease.

In a recent study schizophrenia patients on neuroleptic medications were compared with those off medications (for at least 4 months) and controls (Pascual-Leone et al. 2002). Schizophrenic patients (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th edition), seven unmedicated and seven on conventional neuroleptics, were compared with seven age- and gender-matched normal controls. Motor threshold for induction of MEPs in the fully relaxed right and left first dorsal interosseus and bihemispheric ICI and facilitation using the PP technique were measured with TMS. Medicated patients showed higher motor thresholds in both hemispheres than unmedicated patients and control subjects. Both patient groups showed a reversed pattern of interhemispheric motor threshold differences. While normal controls had a higher threshold for the right than the left hemisphere, the opposite was true for the patient groups. Medicated patients also showed significantly decreased ICI relative to unmedicated patients and control subjects (Fig. 5a). This difference was more pronounced for the right than the left hemisphere. Therefore, while unmedicated patients appear normal on these measures, treatment with conventional neuroleptics is associated with increased motor threshold and decreased ICI. Schizophrenic illness may also be associated with a reversed pattern of interhemispheric motor threshold.

In a follow-up study Freund et al. (1999) examined cortical excitability of six nonschizophrenic patients with tardive dystonia and compared them with healthy controls and with three groups of schizophrenic patients without motor symptoms that differed in their exposure to neuroleptic medications. All groups were matched for age and gender. Patients with tardive dystonia showed a significantly lower ICI than controls and medication-naive patients (Fig. 5b). There was, however, no significant difference in ICI or ICF between nonschizophrenic tardive dystonia patients and schizophrenic patients formally treated with neuroleptics despite absent motor symptoms. These findings suggest that an additional predisposition rendering some patients vulnerable is required for the manifestation of tardive dystonia in patients treated with conventional neuroleptics.

Kubota et al. (1999) studied movement-related cerebral potentials (MRCPs) and motor conduction times in

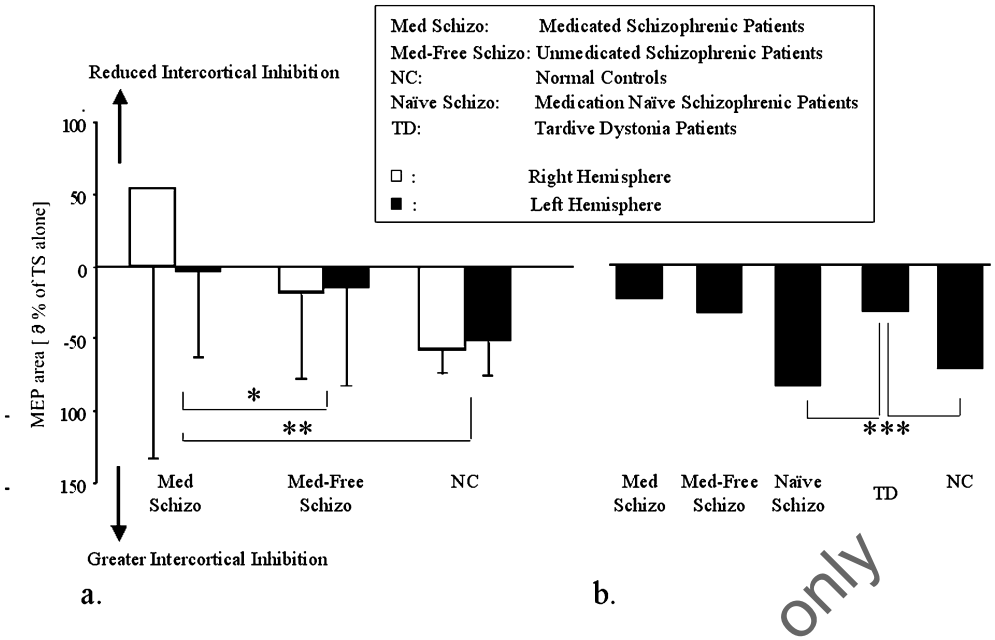

Fig. 5a, b Intracortical inhibition (*ICI*) of the right and left hemispheres in patients with schizophrenia, tardive dystonia (*TD*) without schizophrenia, and normal controls (*NC*). Negative values indicate greater ICI. **a** ICI of medicated schizophrenic patients, unmedicated schizophrenic patients and NC (n=6). Medicated patients (n=6) have significantly lower ICI than unmedicated patients (n=6, medication-naive patients: n=3, *P=0.0002) and NC (**P<0.0001). **b** ICI of medicated schizophrenic patients, unmedicated schizophrenic patients, medication-naive schizophrenic patients, TD patients, and NC. TD patients have a significantly lower ICI than medication-naive patients or NC (P=0.02). (With permission from the authors: **a** from Pascual-Leone et al. 2002; **b** from Freund et al. 1999)

27 schizophrenic patients on medication and 27 healthy controls. They found significant difference in the incidence of MRCPs among the two groups without significant difference in motor conduction time, either root or central. Although the exact brain region of the generation of MRCP is unknown, it is generally accepted to generate somewhere in the frontal lobe (Shibasaki et al. 1980). This finding led them to conclude that motor abnormality in schizophrenic patients does not originate from the motor corticospinal tract but in the motor-integrating system in the frontal lobe.

Taken together, these findings seem to provide some evidence of GABA deficiency or abnormal dopamine function in subcortical regions projecting to the motor system in schizophrenia. Studies on medicated patients suggest the main influence of disruption of the dopaminergic system. It should be noted, however, that all the above studies suffer either from small sample size or confounding effects of medication.

Depression

Some have attended to the shared symptoms between chronic fatigue syndrome and depression, such as cognitive disturbance, depression, and anxiety. Samii et al. (1996) studied postexercise MEP facilitation and suppression in 12 patients with chronic fatigue syndrome, 10 unipolar or bipolar depression, and 18 healthy controls. All the patients were medication free. They found that postexercise facilitation but not suppression was significantly lower in patients with chronic fatigue syndrome and depression than in controls. The characteristics of the reduced postexercise facilitation were different, however, in that patients with chronic fatigue syndrome had a primary deficiency in facilitation whereas the pattern in the depression patients was more similar to that of controls but decayed faster than controls. This may explain some of the symptoms in depression such as fatigue and motor retardation. However, another study has reported somewhat conflicting findings. In 16 patients with major depressive disorder (unipolar and bipolar), most of them on medication, Steele et al. (2000) found longer duration of silent period than in normal controls. This finding does not support the notion of a relative dopamine deficit in depressed patients with clinical retardation. Future studies with different approaches are necessary to address these issues further.

A later study examined postexercise facilitation and suppression in ten patients with major depressive disorder (unipolar and bipolar) on various medication and in ten healthy controls (Shajahan et al. 1999a). Initial facilitation was observed in both groups. In patients, however, this facilitation returned to baseline level of MEP responses significantly faster than in controls. They followed up on their study by examining depressed patients who recovered from depression (Shajahan et al. 1999b). They compared ten depressed patients, ten patients (five of which included those in the depressed group) who had recovered with medication within the

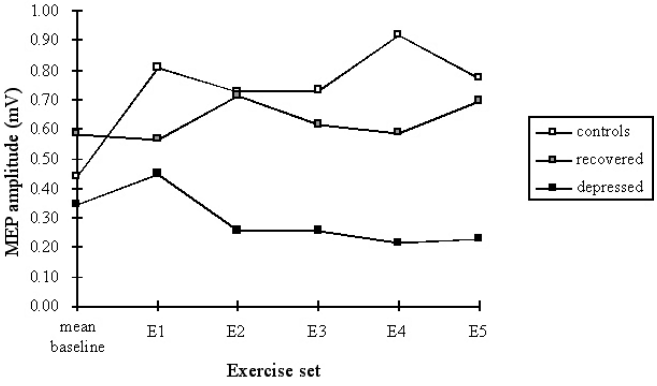

Fig. 6 Postexercise motor evoked potentials (*MEPs*) in patients with depression. While there was no significant difference in baseline MEP size, and between normal controls and recovered patients in postexercise MEP size, there was a significant difference between depressed patients and the other two groups (vs. normal controls, P=0.005; vs. recovered patients, P=0.012). (Slightly modified with permission from the publishers and authors, from Shajahan et al. 1999b)

previous 6 months and ten healthy controls. All the patients were on medication. The currently depressed patients showed reduced mean postexercise facilitation compared to the other two groups, whereas the recovered patients and controls had no significant difference in facilitation (Fig. 6). They found no significant difference in psychomotor performance between the depressed group and the recovered group. The authors suggest that this measurement is more sensitive than clinical measurements.

In the past several years there has been accumulating interest and evidence that rTMS has antidepressant effects over and beyond placebo contributions (George et al. 1999; Lisanby and Sackeim 2000). Although far from established, and its clinical utility unknown, "blinded" studies suggest that low-frequency (equal to or less than 1 Hz) rTMS to the right dorsolateral prefrontal cortex (Klein et al. 1999) or high-frequency rTMS (greater than 1 Hz) to the left dorsolateral prefrontal cortex (Berman et al. 2000; George et al. 1997, 2000; Grunhaus et al. 2000; Pascual-Leone et al. 1996) exerts antidepressant effects. Low-frequency and high-frequency rTMS is thought to depress and excite the cortex, respectively (Pascual-Leone et al. 1998; Wassermann et al. 1998), although recent studies suggest that the "frequency-dependent effects rule" cannot be easily generalized, and a high variability can be found by measurements of MEP size (Maeda et al. 2000e). With rTMS clinical trials, in addition to other interventions, there is rising evidence of reversal or alteration in brain activity after successful treatment of depression. Some have examined cerebral glucose metabolism and found that there is a negative correlation of antidepressant response after low-frequency (1 Hz) compared to high-frequency (20 Hz) rTMS to the left prefrontal area (Kimbrell et al. 1999). Additionally, they found that a better response to 20 Hz rTMS was associated with the degree of baseline hypometabolism, whereas antidepressant response to 1 Hz rTMS tended to be associated with baseline hypermetabolism. They concluded that antidepressant response may vary as a function of stimulation frequency and may depend on pretreatment cerebral metabolism. Another study examined cerebral blood flow before and after rTMS treatment (Teneback et al. 1999). They found a negative correlation between the severity of depression and blood flow in the bilateral medial temporal lobes, left prefrontal cortex, and caudate. Responders showed increased inferior frontal lobe activity, and this became more significant after treatment. There is also evidence on reversal of dexamethasone suppression test with successful antidepressant rTMS treatment (Pridmore 1999; Reid and Pridmore 1999). In normal subjects Schutter et al. (2001) recently reported significant increase in the contralateral EEG theta activity after low frequency rTMS to the right prefrontal cortex and a reduction in anxiety.

Using TMS as a motor neurophysiological tool, Triggs et al. (1999b) studied ten depressed patients who underwent high-frequency (20 Hz) rTMS treatment to the left prefrontal area for 2 weeks and found it to be associated with a decrease in motor threshold of the ipsilateral hemisphere (i.e. increase in cortical excitability). There was significant decrease after each rTMS session compared to before the session and on the second week of rTMS treatment compared to the first. The authors, however, did not report on the possible correlation of this change in motor threshold to their severity of the depression. Triggs et al. (1999b) have suggested, based on these results, that rTMS to the prefrontal area alters brain activity at sites remote from the stimulation, which is consistent to functional imaging data (Peschina et al. 2001; Teneback et al. 1999), spectral EEG analysis (Tormos et al. 1998), and motor excitability (Rollnik et al. 2000). This study on motor threshold, however, should be interpreted with caution since it was an open study, hence leaving the possibility that the observer's bias could have influenced the results. In a clinical trial of rTMS in medication-free patients with treatment-resistant major depressive disorder we applied high-frequency (10 Hz) rTMS to the left dorsolateral prefrontal area for 2 weeks but failed to find any significant decrease in motor threshold (Ng et al., unpublished data).

In a different study where medication-free patients with treatment-refractory major depressive disorder was compared to healthy controls, cortical excitability was found to be asymmetric in (Maeda et al. 2000c). We used the PP technique and found that the left primary motor cortex showed significantly lower intracortical excitability at 6 ms interstimulus interval, which is presumed to be affected by both inhibitory and facilitatory interneuronal circuits (Fig. 7a). There was no significant asymmetry in healthy controls. We conducted another study and examined intracortical excitability before and after high-frequency (10 Hz) rTMS to the left dorsolateral prefrontal area (Maeda et al. 2000d). The patients' baseline excitability (i.e., the lower the left and the higher the right relative to their contralateral motor cortex) was associated

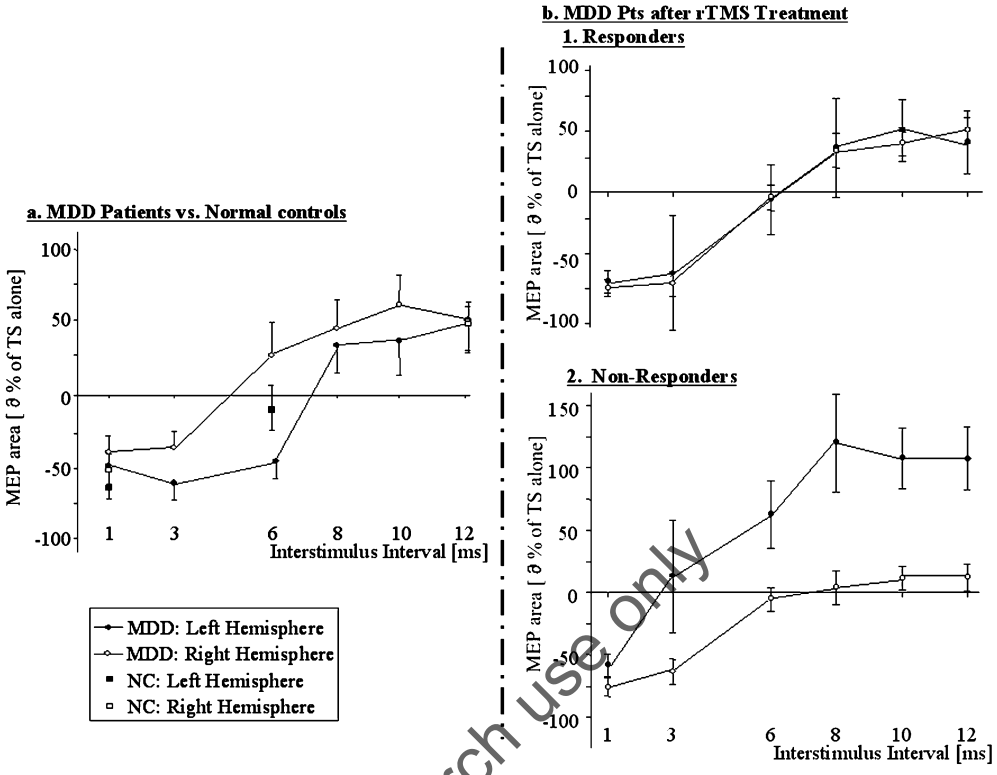

Fig. 7a, b Paired-pulse curves of medication-free patients with treatment-refractory major-depressive disorder (*MDD*) and normal controls (*NC*). **a** The MDD group has a significantly greater interhemispheric asymmetry in intracortical excitability (6 ms) than the NC group ($P<0.001$). (With permission from the Royal college of Psychiatrists, from Maeda et al. 2000c). **b** A further study demonstrates that after high-frequency (10 Hz) rTMS to the left dorsolateral prefrontal area (90% of motor threshold, 8 s/train, 52 s intertrain interval, 20 trains/day, 9 days), responders (*1*) have no significant interhemispheric asymmetry in intracortical excitability ($P>0.05$) whereas nonresponders (*2*) have a significant asymmetry ($P<0.001$)

with treatment outcome. In addition, we found "normalization" (i.e., their PP curves was no longer significantly different) in responders whereas nonresponders had greater "asymmetry" than before pretreatment (Fig. 7b). In all of these studies on depression patients, the TMS administrators were blind to the patients' severity of depression, there was only one TMS administrator who administered this technique, and the data were analyzed using an automated system. Hence it is unlikely that the TMS administrators were biased, or that the findings were due to interindividual variability in TMS administration. In addition, these results are comparable to a study in normals in which the PP curves of the left and right hemispheres, and of two separate days, were not significantly different (Maeda et al. 2002b). The ICI, but not the ICF, showed a good correlation across days within the individuals.

Taken together, these studies suggest that rTMS to the prefrontal area alters brain activity remote from the site of stimulation (see above). In addition, these studies are consistent with the literature on left hemispheric hypoactivity in depressed patients and 'normalization' with successful antidepressant treatment, and theories regarding hemispheric lateralization in the regulation of mood (Davidson 1998; Wheeler et al. 1993). With regards to evidence of motor abnormalities in depression, psychomotor retardation has long been known as a cardinal feature, and the motor component of psychomotor retardation has been reported to be most predictive of therapeutic outcome (Sobin and Sackeim 1997) and to be correlated to the severity of depression (Austin et al. 1992). Laterality effects have not been examined partly due to the limitation of available rating scales (CORE: Hadzi-Pavlovis et al. 1993; MARS: Sobin and Sackeim 1997). High rates of depression in motor disease such as Parkinson's disease, supranuclear palsy, Huntington's disease, Meige's syndrome, and Wilson's disease provide further evidence linking common dysfunctions of motor functions and mood. Hence it may not be too surprising to find abnormal motor excitability patterns as measured by TMS.

Tourette's disorder

Tourette's disorder is characterized by fluctuating motor and vocal tics. Currently, reduced motor impulse control is thought mainly to be due to enhanced dopaminergic transmission at the level of the striatum, causing deficient inhibitory control through the cortical-striatal-pallidal-thalamic-cortical sensorimotor loop. Ziemann et al. (1997) examined 20 patients with Tourette's disorder and 21 healthy controls with TMS to investigate the possible mechanism of deficient motor impulse control in Tourette's disorder. They measured motor threshold, cortical silent period, and ICI and facilitation. They found a shortening of silent period (Fig. 8a) and reduction in ICI (Fig. 8b). These findings were prominent especially when tics were present in the EMG target muscle or in patients without neuroleptic treatment. These findings were consistent with their hypothesis that tics in Tourette's disorder originate either from a primarily subcor-

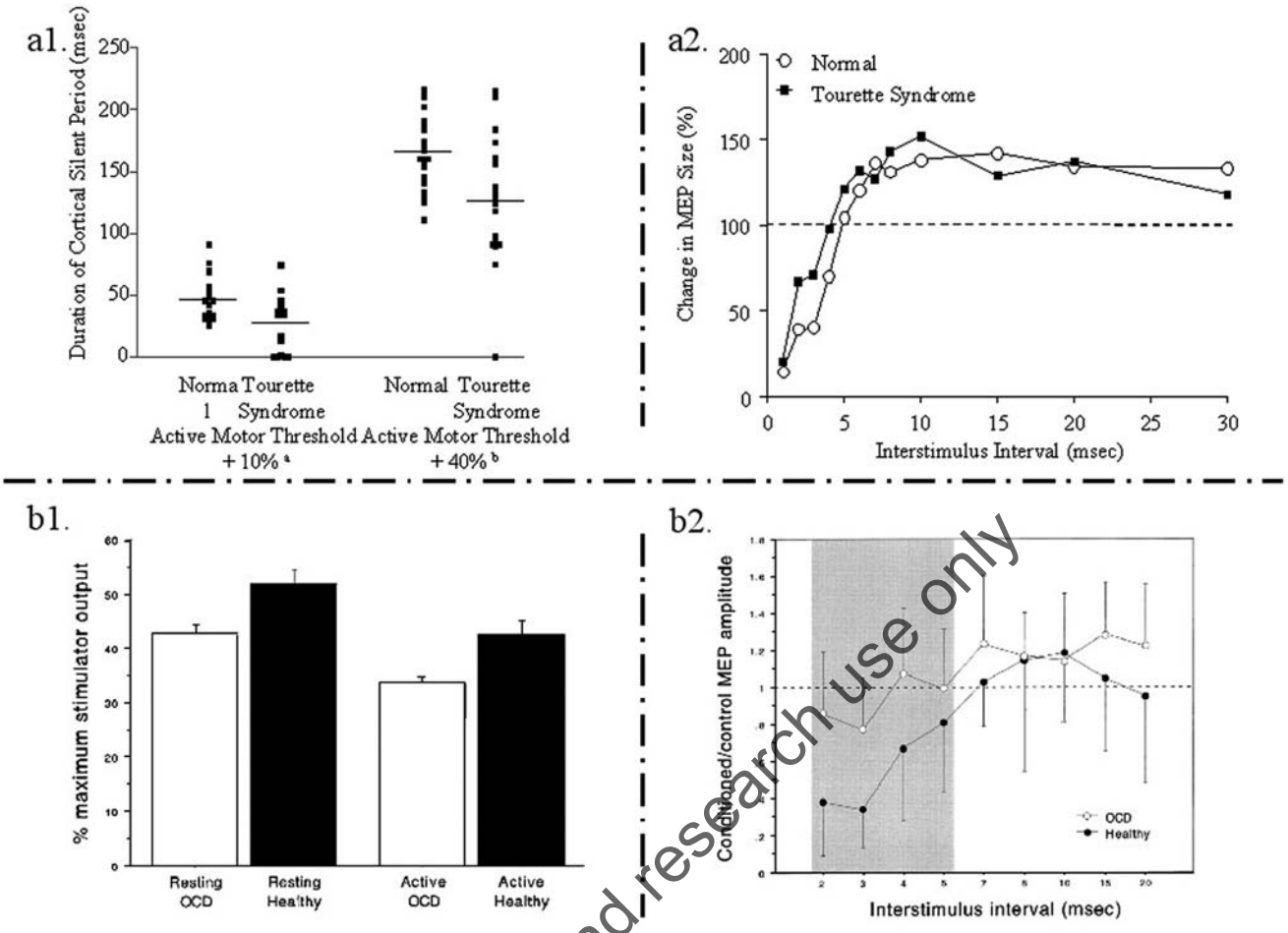

Fig. 8a, b Motor excitability studies in patients with Tourette's disorder and obsessive-compulsive disorder. **a** Patients with Tourette's disorder as compared to normal controls have a dysfunction in intracortical inhibitory mechanisms as measured by the duration of cortical silent period (*1*; $^{a,b}P$>0.01; *horizontal bars* mean), and interstimulus interval (*2*, ICI: 1–4 ms) of the paired-pulse curve (P<0.005). (With permission from American Psychiatric Press and authors, from Ziemann et al. 1997). **b** Patients with obsessive-compulsive disorder as compared to normal controls have significantly lower motor thresholds (*1*; resting: P=0.006, active: P=0.0007), and significantly less ICI (*2*, *shaded area*,P=0.0002). *Bars* Standard error mean. (With permission from the publisher and authors, from Greenberg et al. 2000)

tical disorder affecting the motor cortex through disinhibited afferent signals or from impaired inhibition directly at the level of the motor cortex or both.

Obsessive-compulsive disorder

Greenberg et al. (2000) studied 16 OCD patients some on medication and 11 matched healthy controls. They measured resting motor threshold, active motor threshold, cortical silent period duration, and ICI and facilitation. Similar to the findings in Tourette's disorder and focal dystonia, this study found significantly reduced ICI relative to controls (Fig. 8d). In addition, decreased resting and active motor thresholds were observed (Fig. 8c), all of which indicated abnormal increase in cortical excitability. Patients with comorbid tics had an even greater abnormality. This study suggests that the similar and frequently overlapping symptoms and hereditability of OCD and Tourette's syndrome may reflect a common pathophysiology in the circuits involving the frontal cortex, striatum, globus pallidus, and thalamus. The authors carefully state that the deficit they found may predispose to illness, but that subsequent pathophysiological events are necessary for symptom emergence.

Attention-deficit hyperactivity disorder

Another psychiatric disorder that was recently studied using TMS and motor neurophysiology is ADHD (Ucles et al. 2000). Ucles et al. (2000) studied 27 children and adolescents aged 4–18 years with ADHD. The mean value of central conduction time in the subjects was significantly higher than that in a group of normal controls, case-matched for IQ, age, and sex. In addition, they found a significant interhemispheric asymmetry of central conduction time. The authors suggest that these findings

are associated with the delay in the maturation of the corticomotoneuronal system.

Substance abuse

Chronic cocaine abuse is known for its influence on a number of neurotransmitters that are involved in the excitatory/inhibitory balance of the cerebral cortex. A pilot study measuring bilateral motor thresholds was conducted by Boutros et al. (2001) in ten cocaine-dependent subjects abstinent from cocaine use for at least 3 weeks, and normal controls. They found that both right and left resting motor thresholds were significantly higher in cocaine-dependent subjects than in matched control subjects. As they point out, brain atrophy associated with cocaine-use was not accounted for in their results. Nevertheless, their data suggest that chronic cocaine use significantly alters cortical excitability in the direction of increased inhibition or decreased excitability. The authors hypothesized that this observation reflects adaptation to those effects of cocaine intoxication that promote cortical excitability and seizures.

Cortical excitability studies in other relevant states

One issue that has been pointed out by Smith et al. (1999) is the cortical excitability changes during the menstrual cycle. They used the PP technique to measure cortical excitability of 13 healthy women during the follicular (low-progesterone) and luteal (high-progesterone) phases of the menstrual cycle. They found significant increase in ICI in the luteal phase than in the follicular phase, similar to the reported effect of benzodiazepine (BZP) drugs. There was no significant change in ICF or motor thresholds. It has been shown in animal studies that progesterone metabolites enhance the action of GABA, producing BZP-like physiological effect and reducing neuronal excitability. Estradiol has excitatory effects on measures of neuronal excitability, possibly through the glutamate system. This has been difficult to show in humans using conventional techniques. Previous studies on cortical excitability have not considered possible confounds due to differences in gender and phase of menstrual cycle. Some studies had more female subjects (Kubota et al. 1999: 12 male patients/15 female patient 16 male normals/15 female normals; Shajahan et al. 1999a, 1999b: 2 male patients/8 female patients among the depressed, 1 male patient/9 female patients among the recovered, 3 male normals/7 female normals; Steele et al. 2000: 4 male patients/12 female patients, 6 male normals/13 female normals), or the male-female ratio is unknown (Samii et al. 1996). Although the effect of menstrual cycle on motor excitability other than PP and motor thresholds is unknown, studies with a greater proportion of females may have been vulnerable to this confound.

This study not only provides the potential confound for using TMS in populations including menstruating women but may also provide interesting information on the relationship between menstrual cycle, cortical excitability, and neuropsychiatric disorders and patients who are affected by their hormonal state.

Future direction

We have reviewed the past literature of motor excitability studies using TMS in neuropsychiatric disorders. These studies have just begun, and the findings are still preliminary. As in the "traditional" neurophysiological studies, limitations in the interpretation of these data arise from the small sample-size, inconsistent patient population (diagnosis, medication), differences in methodology between groups, and possible lack of sensitivity and specificity. The studies conducted on measures of cortical excitability using TMS have predominantly employed EMG (hence the motor system) as output measures. This is the logical consequence of the history of TMS and the ease of MEP induction using TMS. For the purpose of applying TMS to the study of the pathophysiology of neuropsychiatric disorders, however, the motor system is not the primary cortical projection of interest. Indeed, the evaluation of cortical excitability in prefrontal cortex and other multimodal association cortices would be more desirable. Even in the current form, measuring motor effects, the studies reviewed illustrate the potential of TMS to become a valuable tool not only as a therapeutic instrument in neuropsychiatry but also in the study of the underlying pathophysiology (particularly for disorders with known motor dysfunction).

Nevertheless, TMS can be associated with other measures of brain activity and such studies promise to further expand the application of TMS in the study of the pathophysiology of neuropsychiatric disorders. This novel application of combining TMS and other neuroimaging techniques is already becoming popular in the field of cognitive neuroscience to investigate the brain-behavior relationship. One can investigate the relationship between focal cortical activity and behavior, to study the timing at which activity in a particular cortical region contributes to a given task and to map the functional connectivity between brain regions (for reviews see Pascual-Leone et al. 2000; Walsh and Rushworth 1999).

For example, TMS can be combined with EEG to investigate corticocortical connectivity (Ilmoniemi et al. 1997). TMS in combination with evoked potentials or steady-state EEG can be used to measure the excitability of nonmotor cortical regions (imagine, for example, measures of modulation of the P300 in response to TMS to prefrontal cortical regions; Kahkonen et al. 2001; Ilmoniemi et al. 1997; Izumi et al. 1997; Nikouline et al. 1999; Schurmann et al. 2001; Tiitinen et al. 1999; Virtanen et al. 1999). TMS in combination with positron emission tomography can highlight functional connectivity of cortical with subcortical and other cortical regions but can also provide information about the level of excitability of the targeted cortical region (Fox et al.

1997; Mottaghy et al. 2000; Paus and Wolforth 1998; Paus et al. 1997, 1998; Siebner et al. 1998, 1999, 2001; Strafella and Paus 2001). The use of specific ligands, for example, GABA or dopaminergic receptors, can be employed to determined neurochemical measures in vivo in response to TMS of specific brain regions (Strafella et al. 2001). Single photon emission computed tomography can be used to investigate regional ^{99m}Tc-hexamethyl-propyleneamine oxime uptake simultaneously during rTMS. Studies have shown local and distinct modulation of regional cerebral blood flow (Catafu et al. 2001; Peschina et al. 2001; Teneback et al. 1999; Zheng 2000). Combination of rTMS with transcranial Doppler sonography can demonstrate modulation of the cerebral hemodynamics within the site of stimulation as well as remote regions by measuring mean cerebral blood flow velocity, pulsatility index, and oxygen consumption (Pecuch et al. 2000; Sander et al. 1995, 1996). This change can be detected even in the absence of behavioral changes (Sander et al. 1995, 1996).

Finally, upon solution of substantial methodological problems (Bohning et al. 1998), the combination of TMS with functional MRI can be used to study the direct and transynaptic responses of the brain to TMS of specific brain target (Bohning et al. 1998, 1999, 2000a, 2000b; George 1999).

All these techniques combining TMS with simultaneous neurophysiological motor excitability measurements together with brain imaging methods (including future combination of tools such as optical brain imaging, magnetic resonance spectroscopy), near-infrared resonance spectroscopy, and magneto-encephalogram) not only allows a coherent modeling of human brain higher functions but may greatly expand the potential of using TMS with diagnostic aims in neuropsychiatry.

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