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Invited review

TMS and drugs

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Abstract

The application of a single dose of a CNS active drug with a well-defined mode of action on a neurotransmitter or neuromodulator system may be used for testing pharmaco-physiological properties of transcranial magnetic stimulation (TMS) measures of cortical excitability. Conversely, a physiologically well-defined single TMS measure of cortical excitability may be used as a biological marker of acute drug effects at the systems level of the cerebral cortex. An array of defined TMS measures may be used to study the pattern of effects of a drug with unknown or multiple modes of action. Acute drug effects may be rather different from chronic drug effects. These differences can also be studied by TMS measures. Finally, TMS or repetitive TMS by themselves may induce changes in endogenous neurotransmitters or neuromodulators. All these possible interactions are the focus of this in-depth review on TMS and drugs.

Keywords: Transcranial magnetic stimulation; Neuropharmacology; CNS active drugs; Motor cortical excitability; Motor evoked potential; Corticospinal projection; Human

1. Introduction

What are the main topics that come to mind when thinking about transcranial magnetic stimulation (TMS) and drugs? First, drugs with a known mode of action may be used to explore physiological properties of TMS measures of motor excitability. The typical experimental setting is the administration of a single dose of the study drug and to obtain TMS measures before and at one or several time points after drug intake. This application proved to be extremely useful in promoting a better understanding of what is measured with TMS. Second, a single well-defined TMS measure may be used as biological marker of acute drug effects. Typically, this is tested in drug concentration—drug effect relationships. Third, an array of well-defined TMS measures may be used to identify modes of action of a study drug at the systems level of the human motor cortex, if these modes of action are not known or complex. Fourth, chronic drug effects on TMS measures may be different from acute ones. Knowledge about chronic versus acute drug effects is important, if drug effects in the setting of long-term treatment shall be predicted. Fifth, particular anaesthetics may acutely reduce corticospinal excitability. The knowledge, to which extent different anaesthetics are doing this, is very important in the setting of intraoperative monitoring of corticospinal tract integrity. Sixth, TMS and repetitive TMS (RTMS) by themselves may result in changes in the concentration and release of endogenous CNS active substances, such as neurotransmitters and neuromodulators. Knowledge about these effects would be important, if TMS and RTMS are used for therapeutic purposes. This review will present an in-depth survey on all of these topics. It will be limited to research in healthy subjects though because drug effects on TMS measures in patients with CNS disorders may deviate unpredictably from the effects obtained in the intact brain.

2. Effects of CNS active drugs with a known mode of action on TMS measures of motor excitability

The reviewed studies were always designed to compare TMS measures at one or several time points after drug intake with one baseline measure before drug intake. Some studies added a placebo control in a randomised and blinded parallel or crossover design to minimise experimenter bias.

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This chapter will review drug effects separately for the different TMS measures of motor cortical and corticospinal excitability.

2.1. Motor threshold

Motor threshold is most often defined as the minimum intensity that is necessary to elicit a small (usually $>50\ \mu V$) motor evoked potential (MEP) in the target muscle in at least half of the trials (Rossini et al., 1999). Motor threshold is lower in the voluntarily contracting muscle (active motor threshold, AMT) compared to the resting muscle (resting motor threshold, RMT), usually by about 10% of maximum stimulator output (Devanne et al., 1997). It may be expected that motor threshold depends on the excitability of those elements, which are activated by TMS. Most likely, these are cortico-cortical axons (Amassian et al., 1987; Shimazu et al., 2004), and their excitatory synaptic contacts with the corticospinal neurones. Voltage-gated sodium channels are crucial in regulating axon excitability (Hodgkin and Huxley, 1952), while ionotropic non-NMDA glutamate receptors are responsible for fast excitatory synaptic neurotransmission in neocortex (Douglas and Martin, 1998). Accordingly, it was found that drugs which block voltage-gated sodium channels (Boroojerdi et al., 2001; Chen et al., 1997; Mavroudakis et al., 1994; Ziemann et al., 1996c) elevate motor threshold, while the NMDA antagonist ketamine that may indirectly increase neurotransmission through the AMPA receptor decreases it (Di Lazzaro et al., 2003) (Table 1). Acute modulation of other neurotransmitter and neuromodulator systems (GABA, dopamine (DA), norepinephrine (NE), serotonin (5-HT) or acetylcholine (ACh)) has no significant effects on motor threshold (Table 1).

2.2. Motor evoked potential amplitude

Motor evoked potential (MEP) amplitude increases with stimulus intensity in a sigmoid fashion (Devanne et al., 1997). At low stimulus intensity, the corticospinal volley resulting in the MEP often consists of only one single wave (I1-wave if the current induced by TMS in the brain runs in posterior-to-anterior direction), while the corticospinal volley becomes more complex and consists of multiple I-waves (I2–I4 in addition to I1) at higher stimulus intensity (Di Lazzaro et al., 2004). In contrast to the I1-wave the later I-waves are modifiable by many processes, and it is very likely that they originate through a chain of cortical excitatory inter-neurones (Amassian et al., 1987; Ziemann and Rothwell, 2000). Accordingly, it may be expected that neurotransmitters (glutamate, GABA) and modulators of neurotransmission (DA, NE, 5-HT, ACh) influence MEP amplitude, particularly in the high-stimulus intensity range. It was found that MEP amplitude decreases after application of allosteric modulators of the GABAA receptor (benzodiazepines, barbiturates), DA agonists (cabergoline, own unpublished observation) and one NE antagonist (guanfacine). In contrast, MEP amplitude increases after application of DA antagonists (haloperidol, own unpublished observation), various NE agonists (methylphenidate, d-amphetamine, reboxetine, yohimbine), one serotonin re-uptake inhibitor (sertraline), and one muscarinic receptor (M1) antagonist (scopolamine) (Table 1). These effects are most likely explained by the complex and hitherto only incompletely understood modulating effects of DA, NE, 5-HT and ACh on inhibitory and excitatory synaptic transmission in neocortical neuronal networks (Hasselmo, 1995). In several instances, changes in MEP amplitude occurred without significant changes in motor threshold (Table 1), supporting the notion (see above) of a fundamental difference in physiology between the two measures.

2.3. Cortical silent period

Cortical silent period (CSP) refers to a TMS induced interruption of voluntary activity in the EMG of the target muscle. CSP duration increases approximately linearly with stimulus intensity and may reach 200–300 ms in hand muscles (Cantello et al., 1992). While spinal inhibition contributes to the early part of the CSP, the late part originates in supraspinal structures, most likely the motor cortex (Fuhr et al., 1991; Inghilleri et al., 1993; Ziemann et al., 1993). It was proposed that the late part of the CSP is caused by a long-lasting cortical inhibition mediated by GABAB receptors because the GABA re-uptake inhibitor tiagabine lengthened the CSP (Werhahn et al., 1999). This is consistent with the duration of the inhibitory post-synaptic potentials (IPSPs) elicited by GABAB receptor activation, which is in the range of several hundred milliseconds (Connors et al., 1988). The meta-analytic evidence from pharmacological TMS experiments in favour of a GABAB receptor mediated inhibition is relatively weak, though (Table 1). In two studies, the GABAB receptor agonist baclofen did not lead to a lengthening of the CSP (Inghilleri et al., 1996; Ziemann et al., 1996c). However, the applied dosages were probably too low to result in an effective drug concentration in the brain. One patient with generalised dystonia who was treated with incremental doses of intrathecal baclofen showed a significant lengthening of the CSP, starting at 1.000 μg/d (Siebner et al., 1998). However, a contribution by an increase in GABAB mediated spinal inhibition to that effect was not ruled out. Furthermore, L-DOPA and DA agonists appear to lengthen the CSP (Priori et al., 1994; Ziemann et al., 1996a), which is consistent with a dopamine-induced enhancement of post-synaptic sensitivity to GABA in animal preparations (Beauregard and Ferron, 1991), and the shortened CSP in patients with a cortical dopaminergic deficit, such as patients with Parkinson's disease (Cantello et al., 2002). One important potential confounding effect in CSP measurements is

Table 1
Acute drug effects on TMS measures of motor cortical excitability

Drug	Mode of action	MT	MEP	CSP	SICI	ICF	SICF	Literature
Carbamazepine	Na^+	▲○	○	○	○○	○▼	○	Ziemann et al. (1996c) Schulze-Bonhage et al. (1996)
Phenytoin	Na^+	▲▲	○○	○○				Chen et al. (1997) Mavroudakis et al. (1994)
Lamotrigine	Na^+	▲▲▲	▼	○	○○	○○	○	Ziemann et al. (1996c) Boroojerdi et al. (2001) Tergau et al. (2003)
Valproic acid	Na + /GABA	○		○	○	○		Ziemann et al. (1999)
Lorazepam	GABAA	○○○	▼▼	▲	▲▲○	▼○	▼	Ziemann et al. (1996b) Boroojerdi et al. (2001) Di Lazzaro et al. (2000a)
Diazepam	GABAA	○○	▼○	▼○	▲○	▼	▼	Inghilleri et al. (1996) Palmieri et al. (1999) Ilic et al. (2002b)
Thiopental	GABAA	○	▼	○				Inghilleri et al. (1996)
Ethanol	GABAA	○	○	▲	▲	▼		Ziemann et al. (1995)
Progesterone	GABAA	○			▲	○		Smith et al. (1999)
Flumazenil	GABAA antagonist	○	○	○	○	○		Jung et al. (2004)
Vigabatrin	GABA	○	○○	○○	○	▼	▼	Ziemann et al. (1996c) Mavroudakis et al. (1997)
Tiagabine	GABA	○	○	▲	▼	▲		Werhahn et al. (1999)
Baclofen	GABAB	○○	○○	○○	▲	▼	○	Ziemann et al. (1996c) Inghilleri et al. (1996)
Dextrometorphan	NMDA antagonist	○	○	○	▲	▼		Ziemann et al. (1998a)
Memantine	NMDA antagonist	○○	○	○	▲	▼	○	Ziemann et al. (1998c) Schwenkreis et al. (1999)
Riluzole	Anti-GLU	○○		○○	▲○	▼▼		Liepert et al. (1997) Schwenkreis et al. (2000)
Ketamine	NMDA antagonist	▼	▲	○	○	○		Di Lazzaro et al. (2003)
L-DOPA	DA precursor	○	○	▲	○	○		Priori et al. (1994) Ziemann et al. (1997)
Bromocriptine	DA agonist	○			▲	○		Ziemann et al. (1997)
Pergolide	DA agonist	○	○	▲	▲	○		Ziemann et al. (1996a)
Cabergoline	DA agonist	○	▼	○	▲	▼	▼	(own unpublished observations)
Selegiline	MAO-B inhibitor	○			○	○		Ziemann et al. (1997)
Haloperidol	DA antagonist	○○	▲	○	▼○	▲		Ziemann et al. (1997) (own unpublished observations) Daskalakis et al. (2003)
Sulipiride	DA antagonist	○			○	○		Ziemann et al. (1997)
Olanzapine	DA/5HT2A antagonist	○		○	○			Daskalakis et al. (2003)
Methylphenidate	NE agonist	○○	▲	○	▼○	○▲		Ilic et al. (2003) Moll et al. (2003)
d-Amphetamine	NE/DA agonist	○	▲		○	▲		Boroojerdi et al. (2001)
Reboxetine	NE re-uptake inhibitor	○▼	▲		▼○	▲▲		Plewnia et al. (2002) Herwig et al. (2002)
Yohimbine	α2 Antagonist	○	▲		○	▲		Plewnia et al. (2001)
Prazosin	α1 Antagonist	○	○		○	○		Sawaki et al. (2003)
Guanfacine	α2 Agonist	○	▼		▲	▼		Korchounov et al. (2003)
Sertraline	SSRI	○	▲	○	○	▼		Ilic et al. (2002a)
Citalopram	SSRI	○			▲	○		Eichhammer et al. (2003)
Zolmitriptan	5-HT1B/1D agonist	○	○	○	▼	○		Werhahn et al. (1998)
Atropine	M1/M2 antagonist	○	○	○	▼	▲		Liepert et al. (2001)
Scopolamine	M1 antagonist	▼	▲	○	○	○		Di Lazzaro et al. (2000b)

Drugs are grouped according to main mode of action. ○, no effect; ▼, reduction; ▲, increase; Na^+, blockade of voltage-gated sodium channels; GABAA, agonist at the GABAA receptor; GABAB, agonist at the GABAB receptor; GABA, increase of GABA in the synaptic cleft; GLU, glutamate; SSRI, serotonin re-uptake inhibitor; M, muscarinic receptor. A study is included only when it was primarily devoted to the testing of drug effects on TMS measures of motor excitability.

the influence of motor set and motor attention (Classen et al., 1997; Mathis et al., 1998). This may explain the lengthening of the CSP by drugs, such as ethanol (Ziemann et al., 1995) or benzodiazepines (Ziemann et al., 1996b), which is most likely unspecific because these drugs do not act at GABAB receptors but may reduce motor attention. Other drug effects on CSP duration were inconsistent (Table 1).

2.4. Short-interval intracortical inhibition

Short-interval intracortical inhibition (SICI) is measured in a paired-pulse TMS protocol, using a sub-threshold first (conditioning) pulse followed after a short inter-stimulus interval of ~2–5 ms by a supra-threshold second (test) pulse (Kujirai et al., 1993). It is currently believed that the sub-threshold first pulse produces an IPSP at the corticospinal neurones through activation of a low-threshold cortical inhibitory circuit, which inhibits action potential generation by excitatory post-synaptic potentials (EPSPs) elicited by the supra-threshold second pulse (Ilic et al., 2002b; Kujirai et al., 1993). Consistent with this hypothesis, GABAA agonists enhance SICI (Di Lazzaro et al., 2000a; Ilic et al., 2002b; Ziemann et al., 1996b). The GABAA antagonist flumazenil does not alter SICI, suggesting that there is no tonic activity at the benzodiazepine binding site of the GABAA receptor in normal human motor cortex (Jung et al., 2004). Furthermore, in contrast, the GABA re-uptake inhibitor tiagabine decreases SICI (Werhahn et al., 1999). This is best explained by activation of pre-synaptic GABAB auto-receptors on nerve terminals of GABAergic inhibitory interneurones, resulting in auto-inhibition. SICI is a net inhibition consisting of strong inhibitory effects and weaker facilitatory effects of the conditioning pulse on the test MEP (Ilic et al., 2002b). A decrease of the facilitatory effects may best explain why glutamate antagonists lead to an apparent enhancement of SICI (Ziemann et al., 1998a; Schwenkreis et al., 1999, 2000). In agreement with animal experiments, which show that neuromodulators strongly influence GABA and glutamate neurotransmitter systems in the cerebral cortex (Hasselmo, 1995), most TMS studies demonstrate significant effects of neuromodulators on SICI (Table 1). DA agonists and NE antagonists (guanfacine) increase SICI, while DA antagonists (haloperidol) and NE agonists decrease SICI (Table 1). The effects of neuromodulators on TMS measures may depend on genetic polymorphisms of the receptors and transporters involved in the neuromodulator system under study, and this may explain some of the variability of findings reported in Table 1. One first study to support this notion demonstrates that the selective serotonin re-uptake inhibitor citalopram increases SICI, but only in those subjects who are homozygotic for the long variant of the 5-HT transporter gene (Eichhammer et al., 2003). This is explained by the fact that homozygosity for the long variant is associated with a two times more efficient 5-HT re-uptake compared to the short variant. Finally, it should be noted that all reported findings refer to SICI as tested at inter-stimulus intervals of 2–5 ms between conditioning and test pulse. Another type of inhibition at very short intervals of ~1 ms is most likely caused by different inhibitory circuits (Roshan et al., 2003), and by relative refractoriness of neural elements in the cortex activated by the conditioning pulse and the resulting desynchronisation of the corticospinal volley (Fisher et al., 2002; Hanajima et al., 2003). This process was found to be largely unaffected by neurotransmitter or neuromodulator systems in those studies which differentiated between SICI at 1 ms versus longer intervals of 2-5 ms.

2.5. Intracortical facilitation (ICF)

ICF is tested by the same protocol as SICI, but longer inter-stimulus intervals of 7–20 ms are used (Kujirai et al., 1993; Ziemann et al., 1996d). Compared to SICI, the physiology of ICF is less clear. The leading hypothesis is that ICF tests excitability of excitatory neuronal circuits in motor cortex, which are at least in part dissociable from the SICI network (Ziemann et al., 1996d). It is likely that ICF is a net facilitation consisting of prevailing facilitation and weaker inhibition. The inhibition probably comes from the tail of the GABAA mediated IPSP, which has a duration of approximately 20 ms (Connors et al., 1988). Consistent with this, the range of effective inter-stimulus intervals for inhibition of the I3-wave in human motor cortex reaches up to 20 ms (Hanajima et al., 1998). EPSPs in neurones of motor cortex may consist of a fast component mediated by non-NMDA receptors and a slower component mediated by NMDA receptors (Hwa and Avoli, 1992). The latency to onset of the EPSP mediated by the NMDA receptor is in the order of 10 ms, which would be consistent with the time course of ICF. This idea is supported by the majority of the pharmacological studies, demonstrating a decrease of ICF by NMDA antagonists (Schwenkreis et al., 1999; Ziemann et al., 1998a), although this was not a unanimous finding (Di Lazzaro et al., 2003). GABAA agonists also decrease ICF (Ziemann et al., 1995, 1996b), supporting a contribution of inhibition through the GABAA receptor to the magnitude of ICF. A synopsis shows (Table 1), that the pharmacological profiles of ICF and SICI are similar though not identical, indicating similarity but also dissociability of the underlying mechanisms.

2.6. Short-interval intracortical facilitation

Short-interval intracortical facilitation (SICF) is also measured in a paired-pulse TMS protocol, but in contrast to SICI and ICF the first pulse is supra-threshold and the second pulse is sub-threshold (Ziemann et al., 1998b), or both pulses are approximately of threshold intensity (Tokimura et al., 1996). SICF occurs at discrete inter-stimulus intervals of about 1.1–1.5 ms, 2.3–2.9 ms and 4.1–4.4 ms. The inter-peak latency between these facilitatory intervals is about 1.5 ms, which led to the hypothesis that SICF originates in those neural elements which are responsible for the generation of the I-waves (Tokimura et al., 1996; Ziemann et al., 1998b). It is currently thought that the second pulse directly excites the initial axon segments of those excitatory interneurones, which are depolarised by EPSPs from the first pulse but did not fire an action potential (Hanajima et al., 2002; Ilic et al., 2002b). Allosteric GABAA agonists reduce SICF (Ilic et al., 2002b;

Ziemann et al., 1998c), which is in accordance with the hypothesis that the first pulse elicits a GABAA dependent short-latency IPSP in corticospinal and/or first order excitatory interneurones, which inhibits the facilitatory interaction with the second pulse. Other drug effects on SICF are summarised in Table 1.

2.7. Long-interval intracortical inhibition

Long-interval intracortical inhibition (LICI) is tested in a paired-pulse TMS protocol by using two pulses of suprathreshold stimulus intensity (Claus et al., 1992; Valls-Sole et al., 1992). Duration and magnitude of LICI depend on the intensity of the conditioning and test stimulus. In healthy subjects, LICI typically occurs at inter-stimulus intervals between 50 and 200 ms, when stimulus intensity is adjusted to produce unconditioned MEP amplitudes of approximately 1 mV (Valls-Sole et al., 1992). This range of effective inter-stimulus intervals shows that LICI is a long-lasting inhibition, which is distinct from SICI (Sanger et al., 2001) but similar to the CSP (Valls-Sole et al., 1992). Accordingly, it was proposed that LICI is mediated by slow IPSPs via activation of the GABAB receptor (Werhahn et al., 1999). This is supported by an increase of the magnitude of LICI by the GABA re-uptake inhibitor tiagabine (Werhahn et al., 1999). However, LICI was not tested as of yet under exposure with a selective GABAB agonist.

2.8. Short latency afferent inhibition

Short latency afferent inhibition (SAI) is defined as an MEP inhibition produced by a conditioning afferent pulse applied to the median nerve at the wrist approximately 20 ms prior to TMS of the hand area of the contralateral motor cortex (Tokimura, 2000). Pharmacological experiments revealed that SAI is distinct from SICI because SAI is reduced by the ACh antagonist scopolamine, while SICI remains unaffected (Di Lazzaro et al., 2000b). The effects of scopolamine suggest that SAI may be useful to probe the integrity of cholinergic neural circuits. This idea is supported by an abnormal reduction of SAI in patients with Alzheimer's disease (Di Lazzaro et al., 2002). Effects of other drugs on SAI have as of yet not been tested.

2.9. Issues of study design and pitfalls

The typical study design includes a baseline measurement before drug application and at least one measurement after drug application. The statistical analysis uses a repeated measures test (usually a paired *t* test for two time points, and a repeated measures ANOVA with time as the within-subject effect for more than two time points) to evaluate the effect of drug. This is a valid procedure because the within-subject test–retest reliability of TMS measures is high (Maeda et al., 2002; Wassermann, 2002). Ideally, a study should be randomised and placebo-controlled to exclude or reduce experimenter bias. One important issue is to select an appropriate drug dose. A drug effect on a TMS measure increases with drug dose (see below, pt. 3). However, the minimal dose to reach a threshold drug effect may vary considerably between subjects (Tergau et al., 2003), and the individual relation between drug dose and drug effect may be non-linear due to complex drug pharmacodynamics (see below, pt. 3). Therefore, there is always the risk to miss a drug effect on TMS measures due to inappropriately low dosing. Another critical issue of drug dose is to produce 'unwanted' drug effects when a drug has more than one mode of action ('dirty drug'). Usually, these different modes of action come into play at different drug doses due to, for instance, differences in receptor density and/or drug-receptor affinity. This implies the risk to contaminate expected drug effects with unwanted drug effects due to inappropriately high dosing. A reasonable way to account for these potential problems in drug dosing is the inclusion of different or incremental doses into the study design (see below, pt. 3). Another critical issue is the timing of TMS measurements. While most studies chose timing according to the pharmacokinetics, i.e. the course of the plasma level of the drug under study, this may be inappropriate for drugs, which produce their effect through complex pharmacodynamic action. A good example is the antiepileptic drug vigabatrin. Its effect is exerted via irreversible inhibition of the GABA-degrading enzyme GABA-transaminase, which has a much slower and longer time course than the vigabatin plasma concentration (Ben-Menachem, 1995). GABA concentration in the brain peaks 24 h after intake of a single dose of vigabatrin (Petroff et al., 1996), while vigabatrin concentration in the plasma peaks after 1 h and the plasma half-life is 6–8 h (Ben-Menachem, 1995). Accordingly, a significant vigabatrin-induced decrease in ICF was observed 24 h after intake only, and not already after 6 h (Ziemann et al., 1996c). As a consequence, good knowledge about the pharmacokinetic/pharmacodynamic (PK/PD) actions of the drug under study is required in order not to miss drug effects by inappropriate timing of TMS testing. Finally, the selection of subjects may play a pivotal role on the study results. It is possible that the level of a TMS measure at baseline influences its responsiveness to experimental manipulation, although this was as of yet not directly explored in pharmacological TMS studies. The level of a TMS measure at baseline can be affected by many sources, such as anxiety-related personality trait (Wassermann et al., 2001), age (Peinemann et al., 2001) or phase of the menstrual cycle (Smith et al., 1999). As a consequence, a careful definition of the properties of the study population is important. Finally, it is very likely that subjects with neurological or psychiatric disease show drug effects on TMS measures that are different from healthy subjects. For instance, in patients with attention-deficit hyperactivity

disorder, where there is pathologically reduced SICI, the indirect DA and NE agonist methylphenidate resulted in an increase of SICI towards normalisation (Moll et al., 2000), whereas a significant decrease in SICI was observed in healthy subjects (Ilic et al., 2003). Therefore, results in healthy subjects do not predict drug effects in patients with brain disease.

2.10. Summary

TMS now offers a broad array of measures of motor cortical excitability, which covers various aspects of excitability, such as axon excitability, and inhibitory and excitatory synaptic excitability. Synaptic excitability can be dissected into, for instance, distinct forms of cortical inhibition, such as SICI (GABAA dependent), CSP and LICI (GABAB dependent) and SAI (ACh dependent). Further experiments showed that these forms of inhibition interact in a complex manner (for recent review, (Chen, 2004)). Pharmacology has helped to characterise these measures and it can be expected that the combination of TMS and drugs will further advance this field in the near future.

3. TMS measures as biological markers of drug effects

A biological marker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Biomarkers Definitions Working Group, 2001). The relation between drug plasma concentration and drug effect may be complex, for instance due to characteristics of the drug related to plasma protein binding, crossing of the blood brain barrier, or kinetics of drug–receptor interaction. The relation is usually sigmoid and can be described by pharmacokinetic/pharmacodynamic (PK/PD) modelling (e.g. (Della Paschoa et al., 2000)).

Only few TMS studies in humans have explored the relation between drug dose or drug plasma concentration and drug effects on TMS measures. These data are summarised in Table 2. Most of the studies provided only semi-quantitative data, which show that a given drug effect increased with drug dose (Table 2). Only two studies have so far provided quantitative correlation analyses between drug plasma concentration and drug effect. One study showed that RMT increases linearly with phenytoin plasma concentration (Chen et al., 1997), the other demonstrated that ICF decreases linearly with riluzole plasma concentration (Schwenkreis et al., 2000). One limitation of both studies is that the correlation analyses were calculated not within individuals, but at the group level, i.e. all individuals received the same dose and only a single data point per individual entered the analysis.

One recent study found a linear increase in RMT with lamotrigine plasma concentration at the group level, if the drug was taken in incremental divided doses (Tergau et al., 2003). Multiple data points per individual, one at each of the incremental doses entered the analysis. This study is of particular interest because, in a *post-hoc* analysis, subjects were divided into four groups depending on the minimal cumulative dose, which produced a significant increase in RMT. This analysis revealed that all groups had a sigmoid relationship between cumulative dose and RMT increase, while the relation between cumulative dose and lamotrigine plasma concentration was linear (Tergau et al., 2003). This strongly suggests that the *individual* relationship between drug plasma concentration and drug effect on RMT is sigmoid. A good explanation for this characteristic provides

Table 2
Acute drug effects on TMS measures of motor cortical excitability as a function of drug dose

Drug	Dose	Plasma concentration	RMT	MEP	CSP	SICI	ICF	Literature
Phenytoin	18 mg/kg	12–23 μg/ml	LIN▲	○	○	○	○	Chen et al. (1997)
Lamotrigine	Incremental dose 25,50,100,150 mg	430–2500 ng/ml	LIN▲[a] SIG▲[b]					Tergau et al. (2003)
Ethanol	0.35 l wine	0.3 ml/l	○	○	▲	▲	▼	Ziemann et al. (1995)
	0.70 l wine	0.8 ml/l	○	○	▲▲	▲▲	▼▼	
Tiagabine	5, 10, 15 mg		○	○	LIN▲	NO▼	LIN▲	Werhahn et al. (1999)
Riluzole	100 mg/7d	10–440 ng/ml	○		○	NO▲	LIN▼	Schwenkreis et al. (2000)
Ketamine	0.01–0.04 mg/kg/min		LIN▼	LIN▲	LIN▲	○	○	Di Lazzaro et al. (2003)
Reboxetine	4 mg	102 ± 20 ng/ml	○	▲		○	▲	Plewnia et al. (2002)
	8 mg	250 ± 88 ng/ml	○	▲▲		○	▲▲	
Yohimbine	20 mg		○	○		○	○	Plewnia et al. (2001)
	40 mg		○	▲		○	▲	
Atropine	1 mg		○	○	○	▼	○	Liepert et al. (2001)
	2 mg		○	○	○	▼▼	▲	

LIN, linear correlation between drug dose and change in TMS measure; SIG, sigmoid correlation between drug dose and change in TMS measure; NO, drug effect, but no correlation with drug dose; ○, no drug effect; ▲, increase; ▲▲, strong increase; ▼, decrease; ▼▼, strong decrease.

[a] Correlation analysis at the group level.

[b] Correlation analysis at the individual (sub-group) level.

the model of PK/PD relationship, which may lead to a non-linear transformation of drug concentration into drug effect (see above). With the individual correlation analysis between drug plasma concentration and drug effect on a TMS measure it may become possible to predict the individual therapeutic effect of this drug. This vision needs to be explored in systematic future trials. If it becomes reality then TMS measures will develop into surrogate endpoints. These are defined as biomarkers that are intended to substitute for a clinical endpoint (e.g. decrease in seizure frequency in response to anti-epileptic drug treatment) (Biomarkers Definitions Working Group, 2001). Such a development would be extremely helpful for the clinician because it is currently often impossible to predict an individual's therapeutic response.

4. Effects of CNS active drugs with incompletely known or multiple modes of action on motor cortical excitability

Many of the TMS measures are by now well defined in terms of their physiological and pharmacological properties (see pt. 2 and Table 1). This knowledge may be used to identify the most prominent actions of CNS active drugs with multiple or incompletely known mechanisms at the systems level of human motor cortex. The available data of this approach are summarised in Table 3.

As a clear example along this avenue, one study tested the effects of the novel anti-epileptic drug topiramate on a broad array of TMS measures (Reis et al., 2002). Topiramate demonstrated a wide spectrum of anti-epileptic activities in pre-clinical animal experimental models of epilepsy and in clinical studies. Several different modes of action were identified at the cellular level (for review, (Shank et al., 2000)). These include: (1) blockade of voltage-gated Na^+ channels; (2) enhancement of neurotransmission through the GABAA receptor; (3) inhibition of neurotransmission through non-NMDA glutamate receptors of the kainate and AMPA subtypes; (4) inhibition of voltage-gated Ca^{++} channels of the L-type. It was found that a single oral dose of 50 or 200 mg of topiramate dose-dependently increased SICI and tended to decrease ICF, while RMT and CSP remained unaffected (Reis et al., 2002). From this distinct pattern of effects it was concluded that a single dose of topiramate exerts significant effects at the level of human cortex through enhancement of GABAA and/or suppression of glutamate dependent mechanisms without detectable action on voltage-gated Na^+ channels or GABAB receptors (Reis et al., 2002). A vision for future investigations may be that, through refinement of TMS protocols, measures become even more specific towards particular mechanisms to facilitate further the identification of drug mechanisms at the systems level in humans.

5. Chronic versus acute effects on TMS measures of motor cortical excitability

Chronic drug effects may be fundamentally different from acute ones. There are several processes, which can potentially alter the response of the human brain to a drug, if chronically administered: (1) pharmacokinetic tolerance. This refers to changes in the distribution or metabolism of a drug induced by repeated application. The most common mechanism is an increase in the rate of metabolism; (2) pharmacodynamic tolerance. This refers to adaptive changes within the system affected by the drug. In the CNS, the most common mechanism are drug-induced changes in

Table 3
Effects of CNS active drugs with incompletely known or multiple modes of action on motor cortical excitability

Drug	Mode(s) of action	MT	MEP	CSP	SICI	ICF	SICF	Literature
Losigamone	? Na^+, ? Ca^{++}	▲		○	○	○		Ziemann et al. (1996c)
Gabapentin	Ca^{++}	○		▲	▲	▼		Ziemann et al. (1996c)
	Increase of GABA synthesis Increase of GLU release	○		▲	▲	▼		Rizzo et al. (2001)
Levetiracetam	Reversal of negative allosteric modulators at GABAA ? High voltage-gated Ca++ ? Inhibition I_k	○	▼	○	○	○		Sohn et al. (2001)
Piracetam	?						▼	Wischer et al. (2001)
Acamprosate	NMDA antagonist Ca^{++}	▲			○	○		Wohlfarth et al. (2000)
Topiramate	Na^+, GABAA Non-NMDA antagonist Ca^{++} (L-type)	○		○	▲	(▼)		Reis et al. (2002)
Theophylline	Adenosine antagonist	○		○	▼	○		Nardone et al. (2004)

?, mode of action unclear; Ca^{++}, blockade of voltage-gated calcium channels; I_k, delayed rectifier potassium current. For other abbreviations, see legend to Table 1.

receptor density, or efficiency of receptor coupling to signal transduction pathways; (3) sensitisation. This refers to an increase in drug effect with repeated application.

Naturally, only very few studies have investigated chronic drug effects on TMS measures in healthy subjects. The anti-glutamate drug riluzole results in an increase in SICI (Schwenkreis et al., 2000) and a decrease in ICF after a single oral dose of 100–150 mg (Liepert et al., 1997; Schwenkreis et al., 2000). Both effects are maintained if riluzole is administered daily over a period of 1 week (Schwenkreis et al., 2000). In addition, a slight but significant increase in RMT occurs after 1 week that was not seen after the first day (Schwenkreis et al., 2000). These data suggest that pharmacodynamic tolerance does not develop during chronic riluzole treatment. This is an important piece of information for the clinical setting, where riluzole is used for treatment of various neurodegenerative disorders, such as amyotrophic lateral sclerosis. More such studies are desirable in order to learn more about chronic versus acute drugs effects at the systems level of the human motor cortex. This may also help to understand better the contribution of chronic drug treatment to abnormal TMS measures in neurological or psychiatric patients.

Drug effects on TMS measures may be evaluated also outside of the motor system. One first example is a study on the effects of chronic ecstasy use on phosphene threshold in the visual cortex (Oliveri and Calvo, 2003). Phosphene threshold was found to be lower in ecstasy users than controls and correlated negatively with frequency of ecstasy use. Furthermore, those ecstasy users with visual hallucinations had a lower phosphene threshold compared to those without hallucinations (Oliveri and Calvo, 2003). Extension of TMS measures into visual cortex can provide substantial additional information because a within-subject comparison showed no correlation of phosphene threshold with motor threshold (Stewart et al., 2001), indicating assessment of different systems, and because, on the grounds of regional differences in cytoarchitecture and distribution of receptor binding sites, it is likely that the drug under study affects the different regions of the human cerebral cortex rather differently.

6. Effects of anaesthetics and analgesics on motor cortical excitability

MEP recordings are increasingly employed to monitor corticospinal tract integrity during surgery of brainstem and spinal cord. In the intraoperative setting, transcranial electrical stimulation (TES) is more often used than TMS because it is less bulky and the electrodes can remain on the scalp once they have been fixed there so that continuous access to the patient's head is no longer necessary. It appeared that the sensitivity of TES and TMS to detect changes in motor excitability induced by anaesthetics or analgesics is not different (Kalkman et al., 1992) (Table 4). This review is limited to studies of healthy subjects and patients without significant affection of the corticospinal system before surgery. Only those studies are selected that allow assessment of the effects of a given anaesthetic or analgesic on MEP amplitude. This requires a comparison of MEP amplitude before (baseline) and after introduction of the study drug, or an analysis of MEP amplitude as a function of drug dose (Table 4), using the same stimulus parameters throughout. Many studies added the anaesthetic under study to a maintenance regimen of other anaesthetics (usually nitrous oxide, cf. Table 4). Most studies agree that it is possible to elicit relatively stable MEP under maintenance anaesthesia with nitrous oxide. In contrast, most volatile (isoflurane) or intravenous anaesthetics (propofol, etomidate, thiopental, pentobarbital, methohexital, midazolam) lead to severe depression of the MEP (Table 4). The MEP depression under intravenous anaesthesia is much more profound compared with the MEP decrease observed after a single non-aesthetic dose of benzodiazepines or barbiturates (cf. pt. 2.2. and Table 1). This difference is due to a dose effect as shown by a progressive decline of MEP amplitude during continuous infusion of midazolam associated with a continuous increase in midazolam blood level (Schönle et al., 1989).

One important finding is that the MEP depression by intravenous anaesthetics can be rescued, at least to some extent, by using high-frequency (200–500 Hz) trains of stimuli instead of single-pulse TMS or TES, whereas this is not possible, or only to a lesser extent, when volatile anaesthetics were used ((Pechstein et al., 1998; Scheufler and Zentner, 2002; Rohde et al., 2003), Table 4). It is very likely that this difference is caused by differences in the main modes of action of intravenous versus volatile anaesthetics. Intravenous anaesthetics strongly enhance neurotransmission through the GABAA receptor while blockade of voltage-gated Na^+ channels is less prominent (Lingamaneni and Hemmings, 2003). Intravenous anaesthetics (propofol, thiopental) result in suppression of late I-waves whereas the D-wave remains unaffected (Woodforth et al., 1999). This is consistent with previous observations that late I-waves are suppressed by the GABA system (Di Lazzaro et al., 2000a). In contrast, preservation of the D-wave suggests that axon excitability is maintained. High-frequency pulse trains imitate the multiple corticospinal discharges (D- and I-waves) and their temporal summation at spinal alpha-motoneurones (Pechstein et al., 1996; Taylor et al., 1993). Therefore, it is very plausible that high-frequency pulse trains help to elicit stable MEPs in a context of preserved axon excitability but suppressed I-waves. In contrast, volatile anaesthetics are essentially equipotent at voltage-gated Na^+ channels and GABAA receptors (Lingamaneni and Hemmings, 2003). Accordingly, volatile anaesthetics also lead to strong suppression of late I-waves (Burke et al., 1993; Hicks et al., 1992; Kitagawa et al., 1995).

Table 4
Effects of anaesthetics and analgesics on MEP amplitude

Drug	Mode of action	Dose	Stimulation	MEP	Literature
IFL	Na^+ >GABAA	1.9–3.7% ETC	TMS, 1P	▼ (100%)	Schmid et al. (1992)
N_2O(66%) + IFL		0.24% ETC	TES, 1P	▼ (100%)	Kalkman et al. (1991)
N_2O(66%) + IFL		0.5% ETC	TES, 1P	▼ (93%)	Calancie et al. (1991)
N_2O(70%) + IFL		0.5% ETC	TES, 1P	▼ (100%)	Woodforth et al. (1996)
N_2O(50%) + IFL		0.2/0.4/0.6% ETC	TES, 1-5P 500 Hz	▼ (78%)	Ubags et al. (1998)
N_2O(60%) + PFL + IFL		0.5% ETC	TES, 5P 200 Hz	▼ (91–100%)	Zhou and Zhu (2000)
IFL		1.2% ETC	TMS, 4P 200–333 Hz	▼ (100%)	Rohde et al. (2003)
N_2O	Opioid peptide release	N_2O(66%)	TES, 1P	▼ (91%)	Zentner et al. (1989)
N_2O		N_2O(79%)	TMS, 1P	▼ (20%)	Schmid et al. (1992)
PFL	GABAA, Na^+	2 mg/kg B	TMS, 1P	▼ (100%)	Schmid et al. (1992)
PFL		2 mg/kg B[a]	TES/TMS, 1P	▼ (99/93%)	Kalkman et al. (1992)
PFL		13 mg/min[b]	TMS, 1P	▼ (98%)	Taniguchi et al. (1993)
N_2O(50%) + PFL		0.7 → 1.4 μg/ml	TES, 6P 500 Hz	▼ (30–50%)	van Dongen et al. (2000)
PFL		6 μg/ml	TMS, 1P	▼ (97%)	Scheufler and Zentner (2002)
PFL		6 μg/ml	TMS, 2P 500 Hz	▼ (99%)	Scheufler and Zentner (2002)
PFL		6 μg/ml	TMS, 4P 500 Hz	▼ (94%)	Scheufler and Zentner (2002)
N_2O(50%) + KET + PFL		2 μg/kg/h	TES, 1P	▼ (100%)	Kawaguchi et al. (2000)
N_2O(50%) + KET + PFL		2 μg/kg/h	TES, 5P 500 Hz	▼ (72%)	Kawaguchi et al. (2000)
ETM	GABAA	0.3 mg/kg B[a]	TES/TMS, 1P	▼ (70/53%)	Kalkman et al. (1992)
ETM		2.18 mg/min[b]	TMS, 1P	▼ (63%)	Taniguchi et al. (1993)
ETM		0.25–0.5 mg/kg/h	TMS, 1P	▼ (64%)	Herdmann et al. (1993)
N_2O(50%) + ETM		0.1 mg/kg B	TES, 2P 333 Hz	▼ (28%)	Ubags et al. (1997)
TP	GABAA	25.6 mg/min[b]	TMS, 1P	▼ (96%)	Taniguchi et al. (1993)
TP		10 mg/kg CD	TMS, 1P	▼ (100%)	Kawaguchi et al. (1993)
MHX	GABAA	12.3 mg/min[b]	TMS, 1P	▼ (72%)	Taniguchi et al. (1993)
PB	GABAA	8 mg/kg B	TMS, 1P	▼ (96%)	Schmid et al. (1992)
MZL	GABAA	0.3 ml/kg/h[c]	TMS, 1P	▼ (90%)	Schönle et al. (1989)
MZL		0.4 ml/kg B	TMS, 1P	▼ (83%)	Schmid et al. (1992)
MZL		0.05 mg/kg B[a]	TES/TMS, 1P	▼ (73/73%)	Kalkman et al. (1992)
KET	NMDA-ant, NE-agonist	3 mg/kg	TMS, 1P	○	Kothbauer et al. (1993)
KET		1 mg/kg B	TMS, 1P	○ /▲	Kalkman et al. (1994)
N_2O(50%) + KET		0.5 mg/kg B	TES, 2P 333 Hz	○	Ubags et al. (1997)
FEN	Opioid agonist	8 μg/kg B	TMS, 1P	○	Schmid et al. (1992)
FEN		3 μg/kg B[a]	TES/TMS, 1P	○	Kalkman et al. (1992)

B, bolus; CD, cumulative dose; ETC, end tidal concentration; ETM, etomidate; FEN, fentanyl; IFL, isoflurane; KET, ketamine; MHX, methohexital; MZL, midazolam; N_2O, nitrous oxide; P, pulses; PFL, propofol; PT, pentobarbital; TP, thiopental. The anaesthetic in bold indicates the test agent (the other anaesthetics are used for maintenance of anaesthesia and are not changed during introduction of the test agent). Doses and/or stimulation settings in bold indicate those to which the given reduction in MEP amplitude refers to. ▼(n%), reduction in MEP amplitude by n% from baseline. ○, no significant change in MEP amplitude. For other abbreviations, see legend to Table 1.

[a] Measured 1–2 min after bolus application.

[b] Mean infusion rate at the time of anaesthesia induction.

[c] Infusion given at this rate for 30 min.

The D-wave is also suppressed, if tested at stimulus intensity around threshold (liminal D-wave) (Hicks et al., 1992), while D-waves tested at far above threshold stimulus intensity are less affected (Hicks et al., 1992; Woodforth et al., 1999). Another elegant demonstration that volatile anaesthetics (sevoflurane) decrease corticospinal axon excitability was provided by strength–duration curves, which show a decrease of the strength–duration time constant and an increase in rheobase (Burke et al., 2000). Both findings are consistent with a depression of Na^+ currents at corticospinal axons (Bostock and Rothwell, 1997; Burke et al., 2000). The depression of axon excitability in addition to I-wave excitability may explain why high-frequency pulse trains are less effective under volatile anaesthetics to maintain MEP amplitude. The intravenous anaesthetic ketamine does not suppress MEP amplitude, but may even lead to MEP facilitation (Table 4). Besides blocking the NMDA receptor, ketamine exerts multiple other actions in the CNS, in particular by increasing the release and inhibiting the re-uptake of NE and 5-HT. These latter actions would explain the increase in MEP amplitude (cf. 2.2 and Table 1). Opioid analgesics (fentanyl) do not alter MEP amplitude (Table 4). In summary, this synopsis shows that the differential potential of high-frequency multi-pulse stimulation to overcome MEP suppression by intravenous versus volatile anaesthetics supports the known differences in the main mode of action of these two classes of anaesthetics at the systems level of human motor cortex. In the setting of intraoperative monitoring of the corticospinal tract,

high-frequency trains of pulses (~500 Hz) and intravenous anaesthetics should be preferentially used.

7. TMS/RTMS induced changes in endogenous neurotransmitters and neuromodulators

Endogenous neurotransmitters such as GABA and glutamate, and neuromodulators (DA, NE, 5-HT, ACh) play a fundamental role in the regulation of the neuronal activity in the cerebral cortex (for review, (Hasselmo, 1995; McCormick et al., 1993)). The basis of many neurological and psychiatric disorders is thought to lie in abnormal neuronal network activity as a consequence of altered neurotransmitter or neuromodulator systems. For instance, DA is implicated in the control of fundamental processes such as movement, attention and learning. Dysfunction of DA plays a pivotal role in disorders such as Parkinson's disease, schizophrenia or drug addiction (Carlsson and Carlsson, 1990).

Conceptually, TMS and RTMS may result in changes in endogenous neurotransmitters and neuromodulators of potentially therapeutic interest. A wealth of studies has explored RTMS effects in the rat brain by using ex vivo analysis of brain homogenates or in vivo microdialysis techniques. For instance, several studies showed that RTMS leads to a DA increase in the striatum (Belmaker and Grisaru, 1998; Ben-Shachar et al., 1997; Kanno et al., 2004; Keck et al., 2002). In healthy human subjects, by using [^{11}C] raclopride positron emission tomography, a focal increase of DA in the striatum was demonstrated after sub-threshold 10 Hz RTMS applied to the ipsilateral primary motor cortex (Strafella et al., 2003) or dorsolateral prefrontal cortex (Strafella et al., 2001). To which extent this RTMS induced corticostriatal modulation of DA release has therapeutic implications in Parkinson's disease requires further investigation, given the so far only moderate or inconsistent RTMS treatment effects in this disorder (for review, (Cantello et al., 2002)). In summary, exploration of the effects of TMS and RTMS on endogenous neurotransmitters and neuromodulators in the human brain is a completely new field that may open a window to look closely at the physiological mechanisms of RTMS effects, and—in the clinical setting—possibly even to predict RTMS treatment effects in individual patients.

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