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Review

# TMS and drugs revisited 2014

Ulf Ziemann [a,*], Janine Reis [b], Peter Schwenkreis [c], Mario Rosanova [d,e], Antonio Strafella [f,g], Radwa Badawy [h,i], Florian Müller-Dahlhaus [a]

[a] Department of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Eberhard-Karls-University Tübingen, Tübingen, Germany
[b] Department of Neurology, Albert-Ludwigs-University Freiburg, Freiburg, Germany
[c] Department of Neurology, BG-University Hospital Bergmannsheil Bochum, Bochum, Germany
[d] Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy
[e] Fondazione Europea di Ricerca Biomedica, FERB Onlus, Milan, Italy
[f] Morton and Gloria Shulman Movement Disorder Unit & E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, Ontario, Canada
[g] Research Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada
[h] Department of Neurology, Saint Vincent's Hospital, Fitzroy, The University of Melbourne, Parkville, Victoria, Australia
[i] Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia

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HIGHLIGHTS

- Pharmaco-TMS improved our understanding of the effects of TMS on the human brain.
- Pharmaco-TMS-EEG is a new research field to measure directly drug effects on brain excitability and connectivity.
- Pharmaco-TMS can monitor and possibly predict drug responses in neurological and psychiatric patients.

ABSTRACT

The combination of pharmacology and transcranial magnetic stimulation to study the effects of drugs on TMS-evoked EMG responses (pharmaco-TMS-EMG) has considerably improved our understanding of the effects of TMS on the human brain. Ten years have elapsed since an influential review on this topic has been published in this journal (Ziemann, 2004). Since then, several major developments have taken place: TMS has been combined with EEG to measure TMS evoked responses directly from brain activity rather than by motor evoked potentials in a muscle, and pharmacological characterization of the TMS-evoked EEG potentials, although still in its infancy, has started (pharmaco-TMS-EEG). Furthermore, the knowledge from pharmaco-TMS-EMG that has been primarily obtained in healthy subjects is now applied to clinical settings, for instance, to monitor or even predict clinical drug responses in neurological or psychiatric patients. Finally, pharmaco-TMS-EMG has been applied to understand the effects of CNS active drugs on non-invasive brain stimulation induced long-term potentiation-like and long-term depression-like plasticity. This is a new field that may help to develop rationales of pharmacological treatment for enhancement of recovery and re-learning after CNS lesions.

This up-dated review will highlight important knowledge and recent advances in the contribution of pharmaco-TMS-EMG and pharmaco-TMS-EEG to our understanding of normal and dysfunctional excitability, connectivity and plasticity of the human brain.


* Corresponding author at: Department of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, Eberhard-Karls-University Tübingen, Hoppe-Seyler-Straße 3, 72076 Tübingen, Germany. Tel.: +49 7071 2982049.
*E-mail address:* ulf.ziemann@uni-tuebingen.de (U. Ziemann).

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**Contents**



## 1. Effects of CNS active drugs with a known specific mode of action on TMS-EMG measures of corticospinal and motor excitability

### *1.1. Introduction*

Pharmaco-TMS experiments to characterize TMS-EMG measures of corticospinal or motor cortical excitability are performed with CNS active drugs with a well-known single mode of action. Their effects or lack of effects on a given TMS measure will then allow conclusions on the physiological mechanisms underlying this measure. All studies reviewed here evaluated acute changes in TMS measures of motor excitability at one or several time points after application of a single dose of the study drug compared to a baseline obtained prior to drug intake. Randomized placebo-controlled double-blind parallel or crossover studies provide the best level of scientific evidence, but not all studies reported here, in particular the early ones, fulfill this standard. Another important issue is that CNS active drugs may have significant effects on cognition (e.g. attention) and vigilance that may have contributed to the observed drug effects on TMS-EMG excitability measures. Only a minority of the studies reviewed here have obtained measures on these behavioral effects and related them to the TMS-EMG excitability measures. It will be crucial for future pharmaco-TMS studies to integrate behavioral measures on cognition and/or vigilance into the study design. This section is restricted to studies in healthy subjects. Pharmaco-TMS in neurological disorders with focus on epilepsy is dealt with in Section 7. Even in healthy subjects, genetic polymorphisms, e.g. of proteins involved in regulation of neuronal excitability, such as dopamine or serotonin transporters may cause significant interindividual variability of drug effects on TMS measures of motor excitability (Eichhammer et al., 2003; Menzler et al., 2014). Other factors that may significantly affect the TMS measures of motor excitability at baseline, such as age (Moll et al., 1999; Oliviero et al., 2006; Peinemann et al., 2001; Pitcher et al., 2003; Silbert et al., 2006; Young-Bernier et al., 2012a), sex (Pitcher et al., 2003; Wassermann, 2002), phase of the menstrual cycle (Smith et al., 1999), or concomitant consumption of caffeine, ethanol, or nicotine (Lang et al., 2008; Orth et al., 2005; Ziemann et al., 1995) have so far not been systematically explored in pharmaco-TMS experiments.

Section 1 will review systematically the effects of CNS active drugs on several well-explored TMS-EMG measures of corticospinal and motor cortical excitability.

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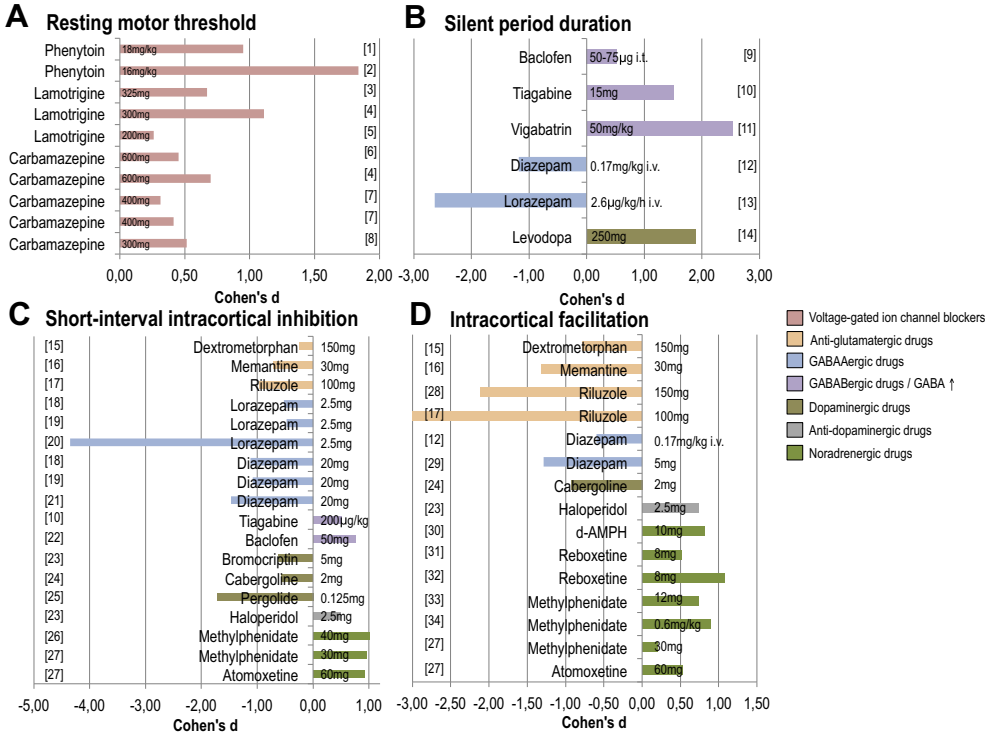


**Fig. 1.** Effect size of CNS active drugs on TMS measures of motor excitability as expressed by Cohen's *d* (effect size is weak if $d < 0.5$, moderate if $0.5 < d < 0.8$, and strong if $d > 0.8$). A positive Cohen's *d* means increase in motor threshold, lengthening of cortical silent period, decrease in short-interval intracortical inhibition or increase in intracortical facilitation. A negative Cohen's *d* means shortening of cortical silent period, increase of short-interval intracortical inhibition or decrease of intracortical facilitation. Plotted are data from those studies only that showed significant drug effects ($p < 0.05$). Drug doses and references are indicated. **(A)** Motor threshold. [1] (Chen et al., 1997); [2] (Mavroudakis et al., 1994); [3] (Tergau et al., 2003); [4] (Ziemann et al., 1996c); [5] (Boroojerdi et al., 2001); [6] (Sommer et al., 2012); [7] (Menzler et al., 2014), data show effects of carbamazepine on healthy subjects with SCN1A splice-site polymorphism rs3812718 (IVS5N+5G>A), homozygous for AA (top) or GG (below); [8] (Lang et al., 2013). **(B)** CSP duration. [9] (Stetkarova and Kofler, 2013); [10] (Werhahn et al., 1999); [11] (Pierantozzi et al., 2004); [12] (Inghilleri et al., 1996); [13] (Kimiskidis et al., 2006); [14] (Priori et al., 1994). **(C)** Short-interval intracortical inhibition (SICI). [15] (Ziemann et al., 1998a); [16] (Schwenkreis et al., 1999); [17] (Schwenkreis et al., 2000); [18] (Di Lazzaro et al., 2005c); [19] (Di Lazzaro et al., 2007); [20] (Teo et al., 2009); [21] (Müller-Dahlhaus et al., 2008); [22] (McDonnell et al., 2006); [23] (Ziemann et al., 1997); [24] (Korchounov et al., 2007); [25] (Ziemann et al., 1996a); [26] (Ilic et al., 2003); [27] (Gilbert et al., 2006). **(D)** Intracortical facilitation (ICF). [28] (Liepert et al., 1997); [29] (Mohammadi et al., 2006); [30] (Boroojerdi et al., 2001); [31] (Plewnia et al., 2002); [32] (Herwig et al., 2002); [33] (Moll et al., 2003); [34] (Kirschner et al., 2003). I.v., intravenous drug administration; i.t., intrathecal drug administration.

### *1.2.1. Motor threshold*

Motor threshold (MT) is most often defined as the minimum TMS intensity that is necessary to elicit a liminal (usually $\geqslant 50$ µV in peak-to-peak amplitude) MEP in the target muscle, either at rest (resting motor threshold, RMT) or during slight voluntary contraction (active motor threshold, AMT) (Awiszus, 2003; Qi et al., 2011; Rossini et al., 1999; Siebner and Ziemann, 2014). It has been hypothesized that motor threshold depends on the excitability of those neural elements, which are excited by TMS and propagate the elicited action potential. In the CNS, these are the cortico-cortical axons, their excitatory synaptic contacts with the corticospinal neurons and the initial axon segments of the corticospinal neurons (Amassian et al., 1987; Di Lazzaro et al., 2008). Voltage-gated sodium channels (VGSCs) are important for regulating axon excitability (Hodgkin and Huxley, 1952), while ionotropic glutamatergic non-N-methyl-D-aspartate receptors (non-NMDARs), in particular α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are responsible for fast excitatory synaptic neurotransmission in neocortex (Douglas and Martin, 1998).

VGSC blocking antiepileptic drugs (AEDs), i.e. carbamazepine (Lang et al., 2013; Menzler et al., 2014; Sommer et al., 2012; Ziemann et al., 1996c), phenytoin (Chen et al., 1997, Mavroudakis et al., 1994) and lamotrigine (Boroojerdi et al., 2001; Tergau et al., 2003; Ziemann et al., 1996c) increased MT, i.e. the corticospinal system became less excitable (Fig. 1**A**). The increase in MT correlated with study drug plasma concentration (Chen et al., 1997; Tergau et al., 2003). In contrast, ketamine, a NMDA receptor (NMDAR) antagonist that indirectly facilitates glutamate (GLU) neurotransmission through the AMPAR, dose-dependently decreased MT (Di Lazzaro et al., 2003). Acute pharmacological blockade of voltage-gated calcium channels (VGCCs) (Wankerl et al., 2010) or modulation of the major CNS neurotransmitter systems (gamma-aminobutyric acid, GABA; dopamine, DA; noradrenaline, NA; serotonin, 5-HT; acetylcholine, ACh) had inconsistent or no effect on MT (for review, see Table 1 in (Paulus et al., 2008)). This pharmacological profile strongly supports the concept that MT represents axon excitability, most likely of cortico-cortical axons directly excited by TMS at threshold intensity with the induced current oriented along the anterior-to-posterior axis (Di Lazzaro et al., 2008). The effect of ketamine possibly points to an additional contribution of fast ionotropic glutamatergic neurotransmission, most likely at the glutamatergic synapses of these axons onto corticospinal neurons. However, the effects of drugs with specific action on AMPARs, such as the recently developed non-competitive AMPAR antagonist perampanel for treatment of epilepsy (Hsu et al., 2013; Rogawski and Hanada, 2013) need to be tested by pharmaco-TMS to elucidate the role of fast ionotropic glutamatergic neurotransmission further.

### *1.2.2. Motor evoked potential (MEP) amplitude and MEP input–output curve*

MEP peak-to-peak amplitude increases with stimulus intensity in a sigmoid fashion (Devanne et al., 1997; Hess et al., 1987; Möller

**Table 1**
Overview of TMS studies using drugs with unknown/multiple mechanisms of action.

| Drug | Mode(s) of action | MT | MEP | CSP | SICI | ICF | LICI | SICF | Dose–response | Placebo-controlled | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Acamprosate | NMDAR antagonist<br>VGCC blocker | ⇧ | | | ○ | ○ | | | No | Yes | Wohlfarth et al. (2000) |
| Amantadine | NMDAR antagonist<br>Potassium channel blocker<br>DA reuptake inhibitor<br>DA release ↑<br>NA release ↑ | ○ | ○ | ○ | ⇗ | ⇩⇩ | ⇧ | | Yes | Yes | Reis et al. (2006) |
| Gabapentin | α2δ VGCC blocker<br>GABA synthesis ↑<br>Glutamate release ↓ | ○ | | ⇗ | ⇧⇧ | ⇩⇩ | | | No | No | Rizzo et al. (2001), Ziemann et al. (1996) |
| Pregabalin | α2δ VGCC blocker<br>VG potassium currents ↑<br>Glutamate release ↓<br>NA release ↓ | ○ | ○ | ⇧ | ⇩ | ○ | ⇧⇧ | ○ | No | Yes | Lang et al. (2006) |
| Lacosamide | VGSC blocker (slow inactivation) | ⇧ | ○ | ○ | ○ | ○ | | | Yes | Yes | Lang et al. (2013) |
| Losigamone | ? VGSC, VGCC blocker | ⇧ | | ○ | ○ | ○ | | | No | No | Ziemann et al. (1996) |
| Piracetam | ? GABA derivate | | | | | | | ⇘ | No | No | Wischer et al. (2001) |
| Quetiapine | ? NA, DA release ↑ | ○ | | ⇧⇧ | ○ | ○ | ○ | | Yes (1 vs. 5 days) | Yes | Langguth et al. (2008) |
| Theophylline | Adenosine antagonist | ○ | | ○ | ⇧⇧ | ○ | | | No | Yes | Nardone et al. (2004) |
| Topiramate | VGSC blocker<br>VGCC blocker (L-type)<br>GABAAR agonist<br>KA/AMPA receptor antagonist | ○ | | ○ | ⇧⇧ | ⇘ | | | Yes | Yes | Reis et al. (2002) |

?, Exact mechanism unknown; ⇧, increase; ⇩, decrease; ⇗, trend for increase; ⇘, trend for decrease; ○, no change; blank cells, not investigated; VG, voltage-gated; VGCC, voltage-gate calcium channel; VGSC, voltage-gated sodium channel; NA, noradrenaline; DA, dopamine; GABAAR, gamma-aminobutyric A receptor; KA, kainate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

et al., 2009). TMS at slightly suprathreshold intensity elicits a corticospinal volley typically consisting of only one single descending wave (I1-wave if the current induced by TMS in the brain flows in posterior-to-anterior direction), while the corticospinal volley becomes more complex and consists of additional late I-waves (I2–I4 waves) at higher stimulus intensity (Di Lazzaro et al., 2008). In contrast to the I1-wave the late I-waves are thought to originate by transsynaptic activation of corticospinal neurons through distinct excitatory interneuron circuits that are modifiable by many processes (Di Lazzaro and Ziemann, 2013), including regulation by GABAergic, glutamatergic and neuromodulating neurotransmitters (Hasselmo, 1995). For exploration of the effects of CNS active drugs specifically on MEP amplitude, it is important to adjust stimulus intensity in the post-drug measurements for changes in MT in order to identify changes in MEP amplitude over and above those in MT.

Positive allosteric modulators of the GABAAR decreased MEP amplitude as has been consistently demonstrated for the benzodiazepines midazolam (Schönle et al., 1989), lorazepam (Boroojerdi et al., 2001; Di Lazzaro et al., 2000a; Kimiskidis et al., 2006), diazepam (Heidegger et al., 2010; Ilic et al., 2002b), and the barbiturate thiopental (Inghilleri et al., 1996) decreased MEP amplitude, most prominently or selectively in the high-intensity part of the MEP input–output curve. The reduction of MEP amplitude by lorazepam was associated with a reduction of late I-waves amplitude (Di Lazzaro et al., 2000a). Ketamine increased MEP amplitude (Di Lazzaro et al., 2003). The NA agonists methylphenidate (Ilic et al., 2003), d-amphetamine (Boroojerdi et al., 2001), reboxetine (Plewnia et al., 2004, 2002) and yohimbine (Plewnia et al., 2001) and the 5-HT agonists sertraline and paroxetine (Gerdelat-Mas et al., 2005; Ilic et al., 2002a) increased MEP amplitude. In contrast, voltage-gated ion channel blockers and other neuromodulating neurotransmitters had inconsistent or nil effects on MEP amplitude (for review, see Table 1 in (Paulus et al., 2008)).

In summary, MEP amplitude elicited by stimulus intensity at clearly above threshold reflects transsynaptic activation of corticospinal neurons through a complex network of excitatory circuits controlled by inhibitory circuits. The pharmacological TMS-EMG profile indicates that this network is regulated by glutamatergic, GABAergic and neuromodulating (in particular noradrenergic and serotonergic) neurotransmitters.

### *1.2.3. Cortical silent period (CSP) duration*

The CSP is defined as a TMS-induced interruption of activity in the EMG of the voluntarily contracting target muscle. CSP duration increases with TMS intensity in a sigmoid fashion and, in hand muscles, it typically plateaus at 200–300 ms (Kimiskidis et al., 2005). Spinal inhibition contributes to the early part of the CSP (its first 50–75 ms), while the late part is of supraspinal, most likely motor cortical origin (Fuhr et al., 1991; Inghilleri et al., 1993; Ziemann et al., 1993). It has been hypothesized that the late part of the CSP is caused by a long-lasting cortical inhibition mediated by the GABABRs (Nakamura et al., 1997) because inhibitory postsynaptic potentials (IPSPs) elicited by GABABR activation in pyramidal cells of animal preparations can have a similar duration (Connors et al., 1988).

The GABAB hypothesis was not supported by three studies in healthy subjects where a single oral dose of 50 mg or an i.v. application of 0.6 mg/kg of the specific GABABR agonist baclofen had no effect on CSP duration (Inghilleri et al., 1996; McDonnell et al., 2006; Ziemann et al., 1996c). These nil findings may be explained by insufficient dosing, as baclofen does not easily penetrate the blood brain barrier. One longitudinal study in a patient with generalized dystonia demonstrated CSP lengthening at high doses ($\geqslant$1.000 μg/d) of intrathecal baclofen (Siebner et al., 1998). This was recently confirmed in patients with spinal cord injury or progressive multiple sclerosis in whom an intrathecal bolus application of baclofen lengthened the CSP but not the cutaneous silent period, an inhibition selectively mediated by spinal circuits (Stetkarova and Kofler, 2013).

The GABA reuptake inhibitor tiagabine and vigabatrin, an inhibitor of the GABA degrading enzyme GABA transaminase both increase extracellular GABA availability and resulted in significant CSP prolongation (Pierantozzi et al., 2004; Werhahn et al., 1999). To what extent this effect has been mediated by activation of GABABRs remains unknown. The effects of positive modulators at the GABAAR (i.e. benzodiazepines) on CSP duration seem to depend on TMS intensity: benzodiazepines prolonged short CSPs

(<100 ms) obtained in the low-intensity range of the CSP input–output curve (Kimiskidis et al., 2006; Ziemann et al., 1996b) whereas they shortened long CSPs (>200 ms) in the high-intensity range (Inghilleri et al., 1996; Kimiskidis et al., 2006). These findings strongly suggest that GABAAR activation contributes to short CSPs. The mechanism underlying the shortening of long CSPs by GABAAR activation remains speculative. One possibility is reduction of GABABR mediated slow IPSPs by concurrent activation of GABAARs (Lopantsev and Schwartzkroin, 1999).

Dopaminergic drugs lengthened the CSP in some but not all of the studies (Priori et al., 1994; Ziemann et al., 1996a) (Fig. 1**B**). This is consistent with a DA-induced enhancement of post-synaptic sensitivity to GABA in animal preparations (Beauregard and Ferron, 1991) and the abnormally short CSP duration in patients with a dopaminergic deficit, e.g. Parkinson's disease (Cantello et al., 2002).

The effects of other neuromodulating neurotransmitters or VGSC blockers on CSP duration were inconsistent or absent (for review, see Table 1 in (Paulus et al., 2008)).

In summary, CSP duration reflects motor cortical postsynaptic inhibition. Its pharmacological profile is consistent with the view that long CSPs are mediated by GABABR activation while GABAAR activation contributes to short CSPs.

*1.2.4. Short-interval intracortical inhibition (SICI)*

SICI is measured by paired-pulse TMS: a subthreshold conditioning stimulus and a suprathreshold test stimulus are applied at short interstimulus intervals of 1–5 ms through the same stimulating coil (Kujirai et al., 1993; Ziemann et al., 1996d). The conditioning stimulus leads to inhibition of test MEP amplitude. It has been hypothesized that SICI represents short-lasting IPSPs in corticospinal neurons through activation of a low-threshold cortical inhibitory circuit (Hanajima et al., 1998; Ilic et al., 2002b; Kujirai et al., 1993). Variation of conditioning stimulus intensity results in a U-shaped SICI intensity curve, suggesting that SICI is a net inhibition consisting of low-threshold inhibitory and higher-threshold facilitatory effects of the conditioning stimulus on test MEP amplitude (Ilic et al., 2002b; Peurala et al., 2008; Ziemann et al., 1996d). The duration of SICI is approximately 20 ms (Hanajima et al., 1998), compatible with the duration of GABAAR-mediated fast IPSPs (Avoli et al., 1997). Finally, refractoriness of cortico-cortical axons rather than synaptic inhibition is very likely responsible for reduction of the test MEP amplitude at very short intervals of <1.5 ms (Fisher et al., 2002).

Benzodiazepines, i.e. positive modulators of GABAARs containing α1-, α2-, α3- or α5-subunits increased SICI (Di Lazzaro et al., 2000a, 2007, 2006, 2005c; Ilic et al., 2002b; Müller-Dahlhaus et al., 2008; Teo et al., 2009; Ziemann et al., 1996b) (Fig. 1**C**). In contrast, the benzodiazepine antagonist flumazenil did not change SICI, providing evidence that there is normally no significant endogenous activity at the benzodiazepine GABAAR binding site in human motor cortex (Jung et al., 2004). Zolpidem, a benzodiazepine-like hypnotic with largely specific positive modulation of the α1-GABAAR also had no effect on SICI (Di Lazzaro et al., 2007, 2006; Teo et al., 2009) suggesting that SICI represents inhibition mediated by α2- or α3-GABAARs. This indicates that pharmaco-TMS-EMG allows pharmaco-physiological characterization of motor cortical excitability down to the level of specific receptor subtypes. The GABA re-uptake inhibitor tiagabine (Werhahn et al., 1999) and the GABABR agonist baclofen (McDonnell et al., 2006) decreased SICI (Fig. 1**C**), supporting the notion that SICI is controlled by presynaptic GABABR mediated autoinhibition of inhibitory interneurons (Müller-Dahlhaus et al., 2008; Sanger et al., 2001). Voltage-gated ion channel blockers had no effect on SICI (for review, see Table 1 in (Paulus et al., 2008)). The majority of studies showed that DA agonists increased SICI (Korchounov et al., 2007; Ziemann et al., 1996a, 1997), while DA antagonists (Ziemann et al., 1997) and NA agonists decreased it (Gilbert et al., 2006; Ilic et al., 2003) (Fig. 1**C**). Nicotine increased SICI in non-smokers (Grundey et al., 2013).

In summary, these data are consistent with the notion that SICI reflects short-lasting postsynaptic inhibition mediated through the GABAAR, positively modulated by DA and nicotine, and decreased by NA.

*1.2.5. Intracortical facilitation (ICF)*

ICF is measured by a similar protocol as SICI, but longer interstimulus intervals of 7–20 ms are tested (Kujirai et al., 1993; Vucic et al., 2006; Ziemann et al., 1996d). ICF likely reflects excitability of an excitatory motor cortical circuit distinct from the SICI network (Ziemann et al., 1996d). However, ICF is a net facilitation that amalgamates inhibition from the tail of the GABAAR-mediated SICI (Hanajima et al., 1998).

Accordingly, NMDAR antagonists (Schwenkreis et al., 1999; Ziemann et al., 1998a) and benzodiazepines, i.e. positive modulators at the GABAAR, decreased ICF (Inghilleri et al., 1996; Mohammadi et al., 2006; Ziemann et al., 1996b). Furthermore, NA agonists consistently increased ICF (Boroojerdi et al., 2001; Gilbert et al., 2006; Herwig et al., 2002; Kirschner et al., 2003; Moll et al., 2003; Plewnia et al., 2001, 2002) (Fig. 1**D**).

The pharmacological profiles of ICF and SICI are very similar (Fig. 1**C** and **D**). This confirms the notion that inhibition as reflected by SICI contributes to the net facilitation represented by ICF.

*1.2.6. Short-interval intracortical facilitation (SICF)*

SICF is tested with a special paired-pulse TMS protocol. The first pulse is above MEP threshold and the second pulse is subthreshold (Hanajima et al., 2002; Ziemann et al., 1998b), or both pulses are close to threshold intensity (Di Lazzaro et al., 1999; Tokimura et al., 1996). MEP facilitation occurs at very short and discrete interstimulus intervals of about 1.1–1.5 ms, 2.3–2.9 ms and 4.1–4.4 ms while intermediate intervals do not result in MEP change, i.e. the periodicity of the three peaks is about 1.5 ms (~660 Hz). This led to the hypothesis that SICF reflects generation of I-waves because I-waves occur at the same periodicity (Amassian et al., 1987; Patton and Amassian, 1954), and accordingly, SICF has also been termed I-wave facilitation (Avanzino et al., 2007; Ziemann et al., 1998b).

Benzodiazepines and barbiturates (Ilic et al., 2002b; Ziemann et al., 1998c), i.e. allosteric positive modulators of the GABAAR, and the DA agonist cabergoline (Korchounov et al., 2007) decreased SICF, while the indirect NA agonist methylphenidate increased it (Ilic et al., 2003). In contrast, VGSC blockers (Ziemann et al., 1998c) and the NMDAR antagonist memantine did not alter SICF (Ziemann et al., 1998c) (for review, see also Table 1 in (Paulus et al., 2008)).

These pharmaco-TMS findings support the view that the neuronal circuitry responsible for I-waves is controlled by GABAAergic inhibition and various neuromodulating neurotransmitter systems, a view consistent with the current hypotheses on the mechanisms underlying I-waves generation (Di Lazzaro and Ziemann, 2013).

*1.2.7. Long-interval intracortical inhibition (LICI)*

LICI is tested by paired-pulse TMS protocols that apply two suprathreshold stimuli at long interstimulus intervals of 50–200 ms (Di Lazzaro et al., 2002a; Nakamura et al., 1997; Valls-Sole et al., 1992). The conditioning pulse leads to inhibition of the test MEP. Magnitude and duration (longest effective interstimulus interval) of LICI increase with intensity of the conditioning pulse (Hammond and Vallence, 2007; Valls-Sole et al., 1992). LICI is followed by a recently described late cortical disinhibition (Cash et al., 2010, 2011). In accord with the long interstimulus

intervals effective in producing LICI it was proposed that LICI reflects slow IPSPs mediated through the GABABR (Werhahn et al., 1999). This implicates similarity with the CSP (see above). However, several study demonstrated dissociable features, indicating that these two measures are complementary rather than identical (Benwell et al., 2007; Hammond and Vallence, 2007).

The GABABR hypothesis was directly supported by the demonstration that the specific GABABR agonist baclofen increased LICI (McDonnell et al., 2006). Furthermore, tiagabine (Werhahn et al., 1999) and vigabatrin (Pierantozzi et al., 2004) increased LICI, very likely by GABABR activation through increased availability of GABA in the synaptic cleft. In contrast, benzodiazepines, i.e. positive GABAAR modulators, did not alter LICI (Mohammadi et al., 2006; Teo et al., 2009).

*1.2.8. Short-latency afferent inhibition (SAI)*

SAI refers to a MEP inhibition in a hand muscle produced by a conditioning afferent electrical stimulus applied to the median or ulnar nerve at the wrist approximately 20 ms prior to focal TMS of the hand area of the contralateral motor cortex (Tokimura et al., 2000). SAI increases with the intensity of the conditioning stimulus (Fischer and Orth, 2011). SAI decreases with normal aging (Young-Bernier et al., 2012a, Young-Bernier et al., 2012b) and in neurodegenerative disorders of the central cholinergic system, such as Alzheimer's disease (Di Lazzaro et al., 2005a, 2002b; Nardone et al., 2008, 2011) and Parkinson's disease (Celebi et al., 2012; Nardone et al., 2013; Rochester et al., 2012; Yarnall et al., 2013). Accordingly, it was proposed that SAI is a physiological marker of the integrity and excitability of central cholinergic pathways.

The benzodiazepine lorazepam decreased SAI but increased SICI (see also above and Fig. 1**C**) (Di Lazzaro et al., 2005b, 2007, 2005c; Teo et al., 2009), suggesting that SAI and SICI are mediated and controlled by different neuronal circuits. This was confirmed by showing that the ACh antagonist scopolamine reduced SAI while it did not affect SICI (Di Lazzaro et al., 2000b). On the other hand, ACh esterase inhibitors that increase the availability of ACh in the synaptic cleft normalized the abnormally reduced SAI in patients with Alzheimer's disease (Di Lazzaro et al., 2004, 2005a), and nicotine increased SAI in healthy non-smoking subjects (Grundey et al., 2013). These data are consistent with the view that SAI represents central cholinergic activity controlled by inhibitory circuits separate from those underlying SICI.

## 2. Effects of CNS active drugs with incompletely known or multiple modes of action on TMS-EMG measures of corticospinal and motor cortical excitability

Using TMS, drugs with a clear mode of action have shown typical electrophysiological signatures of their underlying mechanism in the human M1 (see Section 1). Such a signature may result from direct or remote effects of the drug on the cortical system. Moreover, the physiological correlates of particular TMS measures have been studied intensively in humans (Hallett, 2007; Reis et al., 2008), and less frequently in animals (Hsieh et al., 2014; Luft et al., 2001; Rotenberg et al., 2010). As a consequence, TMS measures of corticospinal and motor cortical excitability can by now be utilized as biomarkers to reflect the net effect of drug action on a physiological or even pathological system (see Section 7). Subsequently, TMS has offered the possibility to utilize particular TMS measures in a "screening mode" – to indicate the predominant mode of action of CNS active drugs with multiple or incompletely known mechanisms of action. A summary of these studies is presented in Table 1. It should be noted that except for studies on acamprosate (Wohlfarth et al., 2000) and quetiapine (Langguth et al., 2008), all of the cited studies tested a single oral application of the drug under investigation, hence only the acute effects on the motor system were explored.

First, we highlight an early study exploring the hypothesized mechanism of action of losigamone. Based on animal experiments it was postulated that losigamone acts via inhibition of the persistent presynaptic sodium influx and enhances chloride uptake (Luszczki, 2009). When studied with TMS in humans, a single oral dose of losigamone resulted in an increase in RMT and AMT, while paired-pulse measures reflecting GABAergic or glutamatergic transmission remained unchanged (Ziemann et al., 1996c) – a result in accordance with the proposed mechanism of action.

That the TMS approach can also yield unexpected results was consecutively shown for gabapentin and pregabalin. These drugs were originally synthesized as GABA analogues; however they failed to show direct GABAergic receptor action in animal experiments. Instead, gabapentin and pregabalin act via $\alpha 2\delta$ voltage-dependent calcium channel subunits. In addition, gabapentin has been found to increase GABA synthesis and turnover (Löscher et al., 1991), and it seems to elevate GABA levels in the human brain, possibly through competitive inhibition of the system-L-branched-chain-amino acid transporter or through reversal of the GABA-uptake transporter (Errante et al., 2002). Moreover, both gabapentin and pregabalin seem to decrease the release of several excitatory neurotransmitters, such as glutamate (for a review, see (Taylor et al., 2007)). In two independent TMS studies using different doses, gabapentin increased SICI and decreased ICF, while RMT remained unaffected and CSP was only marginally prolonged (Rizzo et al., 2001; Ziemann et al., 1996c). Interestingly, these results point to a GABAergic or anti-glutamatergic net effect of the drug on the motor system. Hence, it was proposed that not calcium channel inactivation but rather the action of gabapentin on GABA synthesis may be responsible for its clinical efficacy, e.g. as an anticonvulsant or as an antinociceptive drug. Of note, these earlier studies did not use a placebo-controlled study design. Recent studies now incorporate crossover designs in healthy volunteers, so that a distinction between drug related changes in cortical excitability and placebo-and/or time effects on excitability is possible. In a subsequent placebo-controlled TMS study (Lang et al., 2006), the pharmacological effects of pregabalin were carefully investigated testing several TMS markers of motor excitability. In contrast to the overall GABAergic net effect that had been observed for gabapentin (Rizzo et al., 2001; Ziemann et al., 1996c), the authors observed opposite effects of pregabalin on different types of GABAergic inhibition: While LICI and CSP (GABABergic) were increased, SICI (mostly GABAAergic) was decreased after pregabalin intake, a result similar to that observed for the GABA reuptake inhibitor tiagabine (Werhahn et al., 1999). Hence TMS allowed further dissecting drug effects even on subtypes of inhibition. It is currently unclear why there is an opposing effect of gabapentin and pregabalin on SICI. However one can speculate that differences in neuromodulatory action or the additional effects of pregabalin on voltage gated potassium currents may have contributed to this disparity.

Nardone and colleagues investigated the net effects of theophylline on motor cortical excitability (Nardone et al., 2004). They used a similar experimental approach as those previous studies but the hypothesis of this experiment was slightly different for two reasons: First, theophylline has a known mechanism of action as an adenosine antagonist. However, the exact mechanism by which adenosine modifies cortical excitability at the systems level is completely unknown. Second, theophylline has shown proconvulsive potential in clinical settings, thus an excitatory instead of inhibitory effect of the drug on TMS measures of motor excitability was anticipated. Endogenous adenosine hinders excitatory synaptic transmission through inhibitory modulation in various brain regions including the hippocampus and striatum *in vitro* and

*in vivo*. In accordance, adenosine antagonists lead to increased synaptic efficacy in brain slices (Centonze et al., 2001; Dunwiddie and Diao, 1994; Haas and Greene, 1988). When probed with TMS in humans, oral intake of theophylline led to a significant reduction of intracortical inhibition (SICI), while motor thresholds, CSP and ICF remained unchanged (Nardone et al., 2004). These findings are in line with the suppressive effect of adenosine antagonists on inhibitory transmission, with a resulting disinhibitory net effect on M1– a finding that may explain the proconvulsive effects of the drug.

Lastly, subsequent studies have probed the predominant mode of action of "dirty drugs" – compound drugs that demonstrate a wide spectrum efficacy and bind to several different receptors or target structures in the CNS. For instance, the broad spectrum antiepileptic drug topiramate has shown at least four different modes of action that may explain its seizure suppressing efficiency: sodium channel blockade, blockade of voltage-gated L-type calcium channels, enhancement of GABAergic transmission, blockade of non-NMDA receptor mediated glutamatergic transmission (Shank et al., 2000). Strikingly, in a placebo-controlled human TMS study, oral intake of topiramate led to a significant increase of SICI and an attenuation of ICF (Reis et al., 2002). Together with the lack of effect on motor thresholds and the CSP duration these results strongly support a predominant action via GABAAergic and and/or anti-glutamatergic mechanisms. It is important to note that the effects of topiramate on cortical excitability were dose-dependent.

Hence, studies investigating only one particular dosage bear the risk of missing significant effects. Dose-dependent effects on cortical excitability (decrease of ICF, increase of LICI) have also been shown for amantadine (Reis et al., 2006), a drug with a multitude of modes of action, including NMDAR antagonism, blockage of potassium channels, dopamine receptor agonism, enhancement of noradrenergic release, and anticholinergic effects. These effects correlated with the subjects' serum levels of amantadine.

Given the ongoing refinement of TMS-EMG measures, the growing evidence on their underlying physiological mechanisms and the improvement of study designs with placebo control and dose response curves, it is likely that future investigations will be even more helpful to unravel drug mechanisms at the systems level in humans.

## 3. Effects of anesthetics and analgesics on TMS-EMG measures of corticospinal and motor cortical excitability

Most data concerning the effects of anesthetics and analgesics on TMS measures of corticospinal and motor cortical excitability result from studies in patients undergoing surgery of brainstem or spinal cord. Although MEP recordings after TMS are regularly employed to monitor corticospinal tract integrity in this intraoperative setting, transcranial electrical stimulation (TES) is more often used than TMS for practical reasons. However, it appeared that the sensitivity of TES and TMS to detect changes in motor excitability induced by anesthetics is not different (Kalkman et al., 1992). In the majority of the studies, the MEP amplitude was used as measure for the excitability changes induced by anesthetics. Only the TMS studies have been selected here for review. For a more extensive review including TES studies, refer to Table 4 in (Ziemann, 2004). MEP amplitude was tested before (baseline) and after introduction of the study drug, or as a function of drug dose, using the same stimulus parameters throughout. Although TMS-induced motor responses seem to be more sensitive to nitrous oxide than TES-induced responses (Ubags et al., 1999), it has been shown that it is possible to elicit relatively stable MEP under maintenance anesthesia with nitrous oxide (Schmid et al., 1992). In contrast, most volatile (isoflurane) or intravenous anesthetics (propofol, etomidate, thiopental, pentobarbital, methohexital, midazolam) led to severe depression of the MEP. The MEP depression under intravenous anesthesia was much more profound compared with the MEP decrease observed after a single non-aesthetic dose of benzodiazepines or barbiturates. This difference was 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 was that the MEP depression by intravenous anesthetics could be rescued, at least to some extent, by using high-frequency (200–500 Hz) trains of stimuli instead of single-pulse TMS, whereas this was not achieved, or only to a lesser extent, when volatile anesthetics were used (Hargreaves and Watt, 2005; Rohde et al., 2003; Scheufler and Zentner, 2002). It is very likely that this difference was caused by differences in the main modes of action of intravenous versus volatile anesthetics. Intravenous anesthetics strongly enhance neurotransmission through the GABAAR while blockade of VGSCs is less prominent (Lingamaneni and Hemmings, 2003). Intravenous anesthetics (propofol, thiopental) resulted in suppression of late I-waves whereas the D-wave remained unaffected (Woodforth et al., 1999). This is consistent with previous observations that late I-waves were suppressed by the GABA system (Di Lazzaro et al., 2000a). In contrast, preservation of the D-wave suggested that axon excitability was 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 anesthetics are essentially equipotent at VGSCs and GABAARs (Lingamaneni and Hemmings, 2003). Accordingly, volatile anesthetics also led to strong suppression of late I-waves (Burke et al., 1993; Hicks et al., 1992; Kitagawa et al., 1995). The D-wave was 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 were less affected (Hicks et al., 1992; Woodforth et al., 1999). Another elegant demonstration that volatile anesthetics (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 anesthetics to maintain MEP amplitude. However, even among the intravenous anesthetics, there were differences with respect to the suppressive effect on MEP amplitude. MEP amplitudes were more profoundly depressed by propofol as compared to etomidate, although both drugs are thought to act mainly by activation of GABAARs (Sihle-Wissel et al., 2000). On the other hand, combining ketamine with propofol seemed to diminish the depressant effect of propofol (Sihle-Wissel et al., 2000). This might be explained by the fact that the intravenous anesthetic ketamine alone did not suppress MEP amplitude, but even led to MEP facilitation (Di Lazzaro et al., 2003). Besides blocking the NMDAR, ketamine exerts multiple other actions in the CNS, in particular by increasing the release and inhibiting the re-uptake of glutamate, NA and 5-HT. These latter actions could explain the increase in MEP amplitude observed with ketamine in sub-anesthetic dosages. Opioid analgesics (fentanyl) did not alter MEP amplitude. The analgesic acetaminophen increased MEP amplitude (Mauger and Hopker, 2013). Although its mode of action is not fully understood, multiple pharmacological effects such as inhibition of the cyclooxygenase and

interference with 5-$HT_3$ and cannabinoid 1 (CB1) receptors and the transient receptor potential cation channel (TRPA1) have been identified, which might enhance corticospinal excitability. Given the widespread use of this drug in the general population, it is important to control this possible confounding factor even in TMS studies with "healthy" subjects.

In contrast to the extensive studies on MEP amplitude, the effects of anesthetics and analgesics on MT was not explicitly examined in most studies performed in the intraoperative setting. Instead, in these studies usually a defined stimulation intensity was used, most often 100% of maximum stimulator output. However, since most volatile and intravenous anesthetics showed a complete MEP depression with higher dosages (for review, see Table 4 in (Ziemann, 2004)), it can be assumed that the decrease in MEP amplitude is paralleled by an increase in MT. In sub-anesthetic dosages, RMT was increased by propofol and sevoflurane, whereas AMT was increased by sevoflurane only (Kammer et al., 2002). Voluntary contraction increased the number and size of I-waves (Di Lazzaro et al., 1998). Therefore, the suppressive effect of propofol on I-waves (via GABAARs) might be antagonized by voluntary contraction, whereas this mechanism might not be able to antagonize the sevoflurane effect due to a decreased corticospinal axonal excitability. In contrast, ketamine decreased RMT in sub-anesthetic doses, which might also be explained by an enhancement of glutamatergic transmission (Di Lazzaro et al., 2003).

There are only few studies that examined the effect of analgesics and analgesics on CSP duration. Ketamine in sub-anesthetic doses prolonged the CSP (Di Lazzaro et al., 2003), whereas acetaminophen and thiopental did not significantly influence CSP duration (Inghilleri et al., 1996; Mauger and Hopker, 2013). The CSP prolongation under ketamine was explained by an increased GABABR-mediated slow inhibition activated by increased fast glutamatergic transmission (Di Lazzaro et al., 2003). Finally, SICI and ICF were studied with sub-anesthetic doses of racemic ketamine and its S-enantiomer (Di Lazzaro et al., 2003; Höffken et al., 2013). The racemate and the S-enantiomer reduced SICI, whereas ICF was not significantly changed. Again, this was explained by an activation of non-NMDA glutamate receptors by ketamine at sub-anesthetic doses, leading to diminished GABA release (Di Lazzaro et al., 2003; Höffken et al., 2013).

In summary, this synopsis shows that there are differences between volatile and intravenous anesthetics with respect to their MEP depressant properties, and the possibility to overcome this depression by high-frequency multi-pulse stimulation. This supports the known differences in the main mode of action of these two classes of anesthetics 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 anesthetics should be preferentially used.

## 4. Effects of CNS active drugs on TMS-EEG measures of motor cortical excitability and connectivity

### *4.1. TMS-EEG to measure key parameters of cortical functioning in humans*

Despite a highly static structure, the human brain generates a large repertoire of behavioral and psychological phenomena spanning from simple motor acts to cognition and consciousness. This ability relies on the activation of highly specialized thalamic and cortical structures that interact on a subsecond timescale by means of long-range bundles of fibers (Park and Friston, 2013; Sporns, 2013). Hence, the electrical reactivity of the cerebral cortex to a direct, local stimulation (cortical excitability) and the ability of distant cortical regions to causally interact (cortical effective connectivity) are key parameters of cortico-thalamic circuits functioning. Since recently, by combining navigated TMS with EEG (TMS-EEG), it is possible to record the immediate response of the human brain to a cortical perturbation. In this way, TMS-EEG allows to measure directly and non-invasively changes of cortical excitability and effective connectivity occurring in physiological, pharmacological and pathological conditions. TMS-EEG measurements performed in healthy subjects showed, for instance, that cortical areas tend to oscillate at a preferential frequency (natural frequency; occipital cortex: 8–12 Hz; parietal and motor cortex: 13–20 Hz; premotor cortex: 21–50 Hz) after a single TMS pulse (Rosanova et al., 2009). Notably, TMS-EEG measurements showed that these intrinsic oscillatory properties of cortical areas are altered in schizophrenic patients. Specifically, premotor cortical areas showed decreased oscillations in the gamma frequency band together with a reduction of effective connectivity (Ferrarelli et al., 2008).

TMS-EEG has been employed to study the neural correlates of consciousness. When consciousness is lost, such as in non-REM sleep, deep sedation and vegetative state (VS), TMS-EEG measurements revealed that cortical areas lose their ability to effectively interact, despite being still excitable. On the contrary, recovery of consciousness in wakefulness, dreaming, minimally conscious state (MCS) and emergence from MCS (EMCS) were associated with resurgence of cortical effective connectivity (Ferrarelli et al., 2010; Massimini et al., 2007, 2005; Ragazzoni et al., 2013, 2012). Theoretical neuroscience suggests that consciousness requires the coexistence of integration and information in thalamo-cortical networks, otherwise defined as brain complexity (Seth et al., 2006; Sporns, 2011; Tononi, 2004; Tononi and Edelman, 1998). Casali and colleagues developed a synthetic index to measure the complexity of cortical responses to TMS based on the calculation of algorithmic complexity. This index, called Perturbational Complexity Index (PCI), was always high in wakefulness, irrespectively of TMS stimulation site and intensity, but dropped drastically when subjects lost consciousness in NREM sleep, in deep sedation with midazolam, and during general anesthesia with propofol and xenon. In all these conditions, PCI was invariably reduced resulting in a clear-cut distinction between the distributions of the conscious and unconscious states. Notably, PCI in patients with a stable clinical diagnosis of VS was as low as in NREM sleep and anesthesia, but was invariably higher in subjects who regained consciousness, including MCS, EMCS and locked-in syndrome patients (Casali et al., 2013).

### *4.2. Technical aspects and advantages of TMS-EEG*

The combination of TMS with EEG required the development of dedicated hardware. The first fully TMS-compatible EEG amplifiers were implemented almost twenty years ago (Ilmoniemi et al., 1997; Virtanen et al., 1999) and, by obliterating the large and long-lasting EEG electromagnetic artifact induced by the TMS coil discharge, allowed to reliably record artifact-free TMS-evoked potentials (TEPs) within a few milliseconds after the TMS pulse (Ilmoniemi et al., 1997; Massimini et al., 2005; Paus et al., 2001). Since then, other research groups have developed and employed both online and offline methods to effectively deal with the EEG electromagnetic artifact induced by TMS (Bonato et al., 2006; Iramina et al., 2003; Litvak et al., 2007; Thut et al., 2005). However, TEPs can be confounded by spurious responses to TMS other than the electromagnetic artifact, such as muscle electrical responses due to the direct activation of scalp muscles and auditory evoked potentials induced by the TMS "click" (Ilmoniemi and Kicic, 2010). Provided that specific experimental procedures or off-line TEPs preprocessing analysis steps are applied to reduce or abolish

muscle and auditory artifacts, TMS-EEG offers the following advantages when compared to other, more established techniques: (i) it directly assesses cortical excitability in humans non-invasively and with a temporal resolution (in the order of milliseconds) that is commensurate with neuronal responses to external inputs and synaptic interactions; (ii) due to the intrinsically causal nature of the cortical activations evoked by the TMS (Paus, 2005), and in contrast to methods based on temporal correlations between neural, metabolic or hemodynamic signals, TMS-EEG allows a straightforward assessment of cortical effective connectivity, provided that cortical generators of TEPs are computed by cortical source modelling algorithms; (iii) it bypasses sensory pathways and subcortical structures and, hence, unlike peripherally evoked potentials and motor evoked potentials, TMS-EEG does not depend on the integrity of sensory and motor systems and can access any patient (deafferented or paralyzed); (iv) it is well suited to assess cortical excitability and cortico-cortical effective connectivity independent of behavior as it does not depend on the subject's involvement in a task, on the subject's willingness to participate or on his/her attentional effort and performance; (v) finally, it can be performed at the patient's bedside. Furthermore, under the guidance of MRI-based neuronavigation systems, TMS-EEG can be precisely applied over individual cortical targets. In this way, neuronavigated TMS-EEG allows measuring excitability and connectivity of virtually any cortical area, including associative cortices.

#### 4.2.1. Reliability of TMS-EEG measurements

Ideally, TEPs, recorded across separate sessions in a healthy brain, should always change significantly every time stimulation parameters are varied (100% sensitivity) and should not change when stimulation parameters are kept constant (100% repeatability). Studies in which stimulation parameters of TMS were systematically varied, such as cortical target (Kähkönen et al., 2005; Rosanova et al., 2009), intensity (Kähkönen et al., 2005; Rosanova et al., 2009), and direction of the induced current with respect to the cortical surface (Bonato et al., 2006) indicated that TEPs have a certain degree of sensitivity to these changes. Moreover, as will be reported in Section 4.3., several studies demonstrated that TEPs can detect changes in the state of cortical circuits, as induced by alcohol intake (Kähkönen et al., 2001), sleep (Bergmann et al., 2012; Massimini et al., 2005), or administration of benzodiazepines (Ferrarelli et al., 2010; Premoli et al., 2014). TEPs exhibit meaningful test–retest reliability (Lioumis et al., 2009). Findings of another study further indicated that TEPs reflect deterministic properties of the stimulated neuronal circuits as opposed to stereotypical responses or uncontrolled variability (Casarotto et al., 2010). Moreover, this study confirmed the high repeatability of TEPs over time. To the extent that TEPs are sensitive to changes and repeatable over time, they may be employed to detect longitudinal changes in the state of cortical circuits and measure excitability and connectivity of cortical circuits in physiological, pathological and pharmacological conditions.

### 4.3. Physiology and pharmacology of primary motor cortex TEPs

In healthy and awake subjects, single-pulse TMS over the primary motor cortex – at suprathreshold intensity and with the induced current orthogonally oriented relative to the precentral gyrus – results in TEPs characterized by a sequence of positive and negative deflections occurring at remarkably preserved latencies. This has been reproduced by several studies in which different TMS-compatible EEG amplifiers were employed (see Section 4.2.) (Bergmann et al., 2012; Bonato et al., 2006; Del Felice et al., 2011; Ferreri et al., 2011; Ilmoniemi et al., 1997; Iramina et al., 2003; Paus et al., 2001).

#### 4.3.1. Early components of motor cortex TEPs

Ilmoniemi and colleagues were able to record early (within the first 40 ms) TEPs components following M1 stimulation and to compute the underlying cortical activations. They showed that the motor cortical area ipsilateral to the stimulation responded within 3–7 ms, while contralateral motor areas responded with longer latencies (17–28 ms) (Ilmoniemi et al., 1997; Komssi et al., 2002). More recent studies demonstrated that the amplitude of early components of motor cortex TEPs undergoes significant changes after the application of rTMS or transcranial Direct Current Stimulation (tDCS), two brain stimulation techniques that are thought to modulate synaptic strength and cortical excitability (Esser et al., 2006; Pellicciari et al., 2013; Veniero et al., 2012, 2010). Finally, it has been shown that the peak-to-peak amplitude of the N15-P30 complex (composed by a negative deflection at 15 ms followed by a positive deflection at 30 ms) correlated with MEP amplitude on a single-trial basis (Mäki and Ilmoniemi, 2010) and was strongly affected by the TMS coil orientation (Bonato et al., 2006).

#### 4.3.2. Late components of motor cortex TEPs

Early components of motor cortex TEPs are followed by two highly reproducible (Lioumis et al., 2009), EEG negative deflections peaking at around 45 ms (N45) and 100 ms (N100) (Paus et al., 2001). Cortical generators of the N45 are localized either ipsilaterally to the stimulation site or to more central and contralateral cortical areas (Komssi et al., 2004; Litvak et al., 2007; Paus et al., 2001). The amplitude of the N45 significantly increased after 1 Hz rTMS delivered at subthreshold intensity over M1 (Van Der Werf and Paus, 2006). Similarly, rising the intensity of TMS or performing rTMS at 5 Hz and at subthreshold intensity over M1 produced a significant increase of the global EEG response to TMS at latencies corresponding to N45 and earlier components (Esser et al., 2006; Huber et al., 2007). Other studies further showed that amplitude and topography of the N45 can be modulated by paired-pulse TMS protocols (Ferreri et al., 2011; Paus et al., 2001) and by ethanol administration (Kähkönen et al., 2001). Although the N100 component has been observed in many TMS-EEG studies (for review, (Rogasch and Fitzgerald, 2013)), so far only one study has successfully computed the cortical sources of this late component of the M1 TEPs and localized them ipsilaterally to the stimulation site (Komssi et al., 2004). Several studies suggested that the modulation of the N100 amplitude relies on different factors. For instance, preparation for voluntary hand movements resulted in a significant reduction of N100 amplitude (Kicic et al., 2008; Nikulin et al., 2003; Yamanaka et al., 2013). A reduction of the N100 amplitude has also been observed when the delivery of a TMS pulse over the M1 hand area is shortly (25 ms) preceded by a somatosensory stimulus applied to the contralateral hand (Bikmullina et al., 2009), in accord to short-latency afferent inhibition in MEP recordings (Tokimura et al., 2000). The N100 was almost abolished when the TMS coil is rotated by 90° relative to the optimal orientation (Bonato et al., 2006) and after alcohol ingestion (Kähkönen and Wilenius, 2007). Furthermore, the N100 amplitude was significantly increased after 1 Hz rTMS applied over M1 (Casula et al., 2014), and significantly correlated with the duration of the cortical silent period (Farzan et al., 2013), which is thought to reflect cortical inhibitory processes (see Section 2.2.3.). Premoli and colleagues have recently tested further the pharmacological underpinnings of TEPs. As shown in Fig. 2, alprazolam, diazepam, and zolpidem, positive allosteric modulators at the GABAAR, significantly increased the N45 amplitude (Premoli et al., 2014). Alprazolam and diazepam also resulted in a significant reduction of the N100 amplitude. In contrast, the GABABR agonist baclofen selectively increased the N100 amplitude (Fig. 2) (Premoli et al., 2014). Moreover, the analysis of the EEG scalp topographies

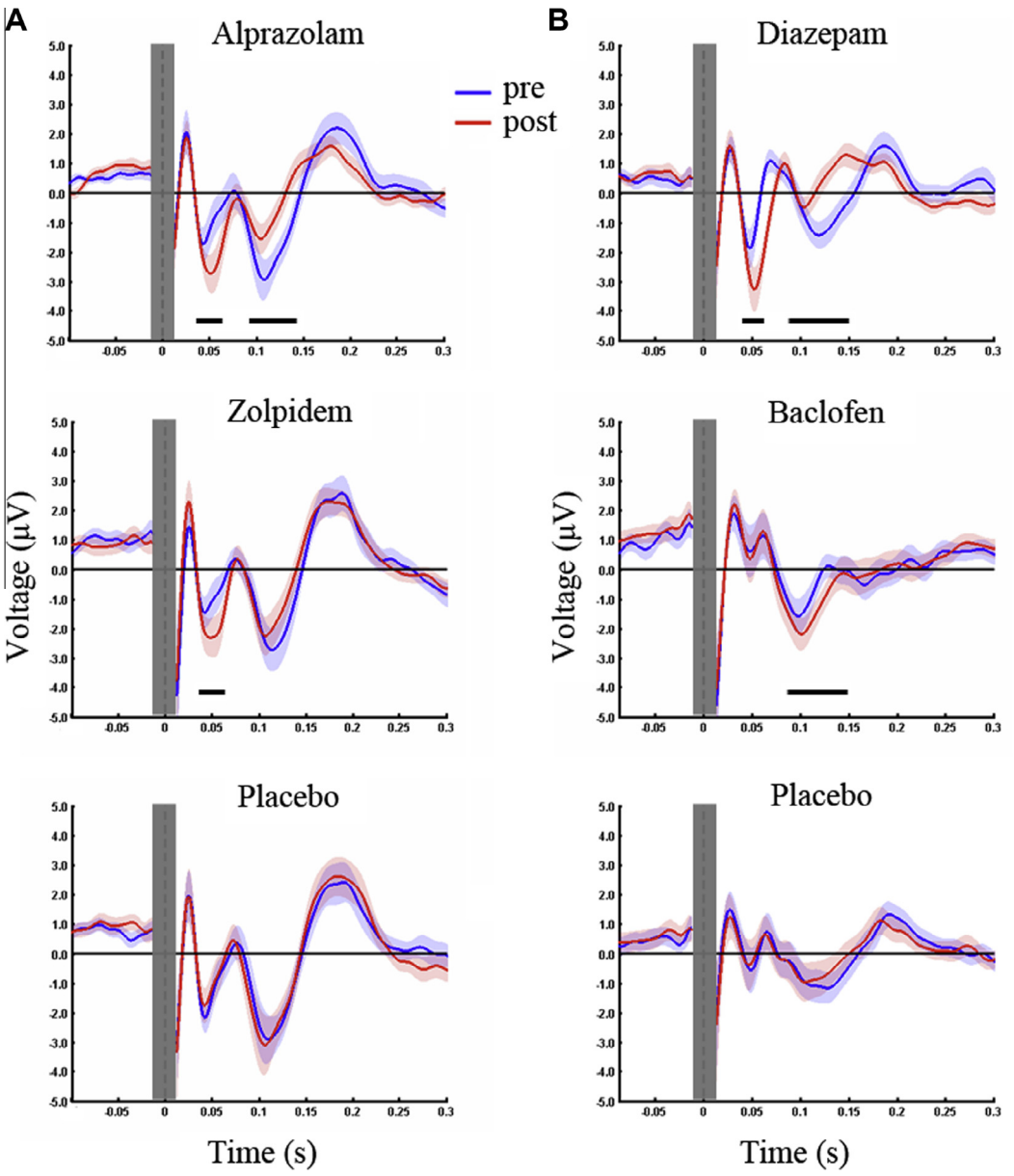


**Fig. 2.** Drug-induced modulation of TMS-evoked EEG potentials (TEPs). TEPs were recorded before (Pre, blue) and after (Post, red) intake of a single oral dose of 1 mg of alprazolam, 10 mg zolpidem, or placebo **(A)**, and 20 mg of diazepam, 50 mg of baclofen, or placebo **(B)**. Whilst alprazolam increased the N45 and reduced the N100 amplitude, zolpidem increased the N45 only. Diazepam increased the N45 and decreased the N100 similarly to alprazolam, whereas baclofen increased the N100. Black bars underneath highlight significant drug-induced changes in TEPs. To illustrate drug-induced changes of TEP components, representative EEG channels were chosen for each drug condition. Shades represent ±1 SEM (modified from (Premoli et al., 2014), with permission). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

indicated that across subjects the modulation of the N45 and the N100 amplitudes following administration of the positive modulators at the GABAAR was statistically significant at EEG channels contralateral to the stimulated M1, whereas the N100 amplitude increase induced by baclofen was confined to the EEG channels close to the stimulation site (Premoli et al., 2014). However, due to the relatively poor spatial resolution of EEG, further studies employing cortical source modeling of TEPs are needed in order to reliably localize the cortical areas that contribute to the pharmacological modulation of TEPs.

*4.3.3. TMS-evoked EEG oscillations of the motor cortex*

Besides single EEG deflections time-locked with the TMS pulse, TMS of M1 induces an increased synchronization of the EEG oscillations in the beta/gamma (15–30 Hz) and alpha frequency range (8–12 Hz) (Fuggetta et al., 2005; Paus et al., 2001). In the former case, TMS led to a phase-resetting of the EEG rhythms spontaneously generated by cortical motor circuits, which resulted in a short-lasting but specific and consistent enhancement of EEG oscillations in the beta band after the TMS pulse compared to pre-stimulus EEG (Paus et al., 2001; Van Der Werf and Paus, 2006). On the contrary, the amplitude of beta oscillations associated with TMS of M1 was reduced during a paired-pulse protocol employing an interstimulus interval of 12 ms (Paus et al., 2001). Notably, these oscillations were also dampened in Parkinson patients with unilateral surgical lesion of motor thalamic nuclei when TMS targeted the M1 on the operated side compared to the TEPs recorded over the intact hemisphere or in healthy subjects (Van Der Werf et al., 2006). Furthermore, TMS induced an increase of the interhemispheric coherence of oscillations in the alpha frequency range

(Fuggetta et al., 2005), which lasted up to 175 ms and linearly correlated with anatomical integrity of the thalamus contralateral to the stimulation site, and of the thalamo-cortical and transcallosal fibers (Groppa et al., 2013).

#### 4.3.4. Towards an understanding of the neurophysiological underpinnings of TEPs

The neural events that underlie TMS-evoked EEG deflections and oscillations are still largely unknown. However, by integrating the experimental evidence reviewed above with modelling studies, animal studies, and intracerebral recordings in humans a plausible scenario accounting for the neurophysiological correlates of motor cortex TEPs may be outlined as follows: (i) TEPs components occurring within the first 10 ms after the pulse are most likely contributed by the activation of local excitatory and inhibitory neuronal networks. In a very recent study, for the first time, single neuron responses to TMS were recorded from the cerebral cortex of awake monkeys (Mueller et al., 2014). It was demonstrated that very early (<5 ms) cortical responses to TMS are caused by action potentials generated by local axons, and excitatory and inhibitory neurons close to the recording electrode; (ii) TEP components falling between 10 and 40 ms possibly reflect the response of ipsilateral and contralateral cortical areas of the motor system as their latencies are consistent with the time delays of cortico-cortical potentials recorded at intrahemispheric (Matsumoto et al., 2007) and interhemispheric sites (Terada et al., 2008) after intracerebral stimulation of M1 in epileptic patients; (iii) both the N45 and the TMS-evoked beta oscillations may rely either on the activation of cortical or cortico-thalamic circuits involving local populations of inhibitory cortical neurons (Markram et al., 2004) or the motor sector of the thalamic reticular nucleus (Guillery et al., 1998) activated, respectively, by layer V and layer VI pyramidal neurons. GABAARs are crucial in sustaining recurrent activity in neocortical networks (Sanchez-Vives and McCormick, 2000) and have been specifically linked to the generation of EEG oscillations in the beta band (Porjesz et al., 2002). Similarly, as suggested by intracerebral recordings of the activity of the subthalamic nucleus in patients with Parkinson's disease during single-pulse TMS of M1, TMS-evoked EEG oscillations in the beta frequency range might be associated also with the interplay between M1 and basal ganglia (Gaynor et al., 2008; Strafella et al., 2004); (iv) finally, the N100 together with the TMS-evoked EEG oscillations in the alpha frequency band (frequency 10 Hz; period 100 ms) might be underpinned by locally generated inhibitory phenomena, such as the long-lasting (100–300 ms) inhibition of pyramidal cells firing following the delivery of electrical shocks over the cerebral cortex in anaesthetized mammals (Krnjevic et al., 1966a). This prolonged cortical inhibition periods are probably sustained by GABAergic circuits (Krnjevic et al., 1966b). The generation of the N100 could also be underpinned by interhemispheric interactions involving inhibitory circuits contralateral to the site of TMS application. A recent animal in vivo study has shown that transcallosal inputs inhibit layer V cells firing by means of a direct action on apical dendrites via layer 1 interneurons and GABABRs (Palmer et al., 2012).

## 5. TMS/RTMS induced changes in endogenous neurotransmitters and neuromodulators

Dopamine (DA) plays an important role in learning, reward, motor control, emotion and executive functions. Thanks to the development of neuroimaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), it is now possible to quantify dopaminergic activity in the living human brain. The combination of these technologies with rTMS offers great potential in that it is capable of tackling questions regarding region-specific/function-specific neurochemical activity both in healthy conditions and brain disease (Ko and Strafella, 2012). Animal studies have revealed that there are three major dopaminergic pathways: nigrostriatal, mesolimbic and mesocortical. Nigrostriatal DA plays a crucial role in the cortico-striato-pallido-thalamo-cortical circuitry (Alexander et al., 1986). It is thought that DA in this pathway facilitates the selection of an optimal response from competing motor programs by balancing activity within and between a direct and an indirect pathway, i.e., DA acts to excite the relevant motor program while inhibiting irrelevant ones (Mink, 2003). The mesolimbic and mesocortical dopaminergic pathways originate in the ventral tegmental area (VTA) of the midbrain and project to the limbic system (via the nucleus accumbens) and the frontal cortex, respectively. The former is proposed to be important for reward-related learning and emotion while the latter is involved in various executive functions (Ko and Strafella, 2012). Neuroimaging studies corroborate this functional network in the human but are limited by the fact that they cannot determine if an area is an essential mediator of a particular brain function or one that is merely activated in tandem with other essential components (Walsh and Cowey, 2000). Animal and human studies have demonstrated that subcortical dopamine can be modulated by the frontal cortex via dense interconnections between the two areas (Murase et al., 1993; Taber and Fibiger, 1993, 1995). Dysfunction of the frontal-striatal dopamine circuit is thought to be involved in several neurological impairments, such as depression, Parkinson's disease (PD) and schizophrenia. Thus, frontal-striatal connectivity may be a therapeutic target in order to manipulate DA activity in deeper brain regions and improve functions that rely on this circuit (Ko and Strafella, 2012).

Repetitive TMS in combination with PET can be used to probe the frontal-striatal network. When applied over the dorsolateral prefrontal cortex (DLPFC) or M1, high-frequency rTMS induced DA release in the ipsilateral caudate nucleus (Strafella et al., 2001) or putamen (Strafella et al., 2003), respectively, using the PET ligand [$^{11}$C]raclopride. Further, these studies demonstrated spatial-specific DA release, in line with the topographic order of corticostriatal projections (Alexander et al., 1986). DA changes in extrastriatal regions can be explored using the [$^{11}$C]FLB 457 ligand, which allows for clearer depictions of DA outside the striatum (Cho and Strafella, 2009). The DLPFC has dense connectivity with other prefrontal areas, such as the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). Following high-frequency rTMS of the left DLPFC, there was an increase in DA levels in the ipsilateral ACC and OFC, but no changes occurred following right DLPFC stimulation (Cho and Strafella, 2009). It is likely that stimulated prefrontal cortex projections activated dopaminergic neurons in the ventral tegmental area (VTA) and, in turn, caused dopaminergic changes in the ACC and OFC. Taken together, these studies support the influence of the human frontal cortex on DA release, which can be manipulated by using rTMS.

This approach may be used to investigate functional outcomes of striatal DA release using cognitive or behavioral tasks following rTMS. Repetitive TMS over left DLPFC disrupted striatal DA release and performance on a card-sorting task, known to involve executive function (Ko et al., 2008). In another study participants were imaged before and after rTMS of M1 while performing a cognitive switching task that is known to depend on a specific striatal substructure (van Schouwenburg et al., 2012). Frontal stimulation perturbed task-specific functional signals in the putamen, while reducing fronto-striatal functional connectivity. Recent research suggests that rTMS over the left DLPFC may influence learning as well, thought to involve striatal DA (Ahn et al., 2013; Ott et al., 2011). Thus, growing evidence suggests that cognitive function and behaviour may be altered via rTMS-induced striatal DA neurotransmission. It is likely that rTMS-induced DA release acts via

glutamatergic projections that originate in the area of stimulation and directly modulate dopaminergic neurons.

Brain DA activity induced by rTMS may have clinical relevance. Dysfunction of frontal-striatal connectivity is thought to underlie symptoms in psychiatric and neurological disorders. One approach is to enhance the frontal-striatal connections with rTMS, thereby influencing the activity of abnormal dopaminergic systems. Conceptually, this may serve as a potential treatment strategy for disorders such as depression, drug addiction, PD and schizophrenia, in which abnormalities of the dopaminergic systems have been demonstrated. Such studies may aid clinicians and scientists to disentangle neural circuitries within the human brain, and thereby help them to understand the underlying mechanisms of a given function in relation to brain diseases. Further, it may also aid the development of alternative treatment approaches for various neurological and psychiatric conditions (Ko and Strafella, 2012). Neuroreceptor imaging using PET/SPECT is highly recognized for its capability to investigate the neurobiology of diseases due to its unique ability to quantify in-vivo neurochemical abnormalities with high spatial-resolution. There is a continuing effort to develop new radio-ligands that tackle different neurochemical systems and bind to specific receptor subtypes. The combination of TMS or rTMS with PET/SPECT neuroreceptor imaging allows for investigation of the integrity and manipulation of specific cortical-subcortical neuromodulation neurotransmitter pathways. Such progress continues to increase knowledge of how different neurotransmitters contribute to brain function.

## 6. Effects of CNS active drugs on TMS-EMG measures of motor cortical LTP- and LTD-like plasticity

### 6.1. Introduction

CNS active drugs are used in a variety of neurological and psychiatric diseases with the intention to interfere with mechanisms of synaptic plasticity. NIBS offers the possibility to study the effects of CNS active drugs on cortical plasticity in humans non-invasively [for review see e.g., (Nitsche et al., 2012)]. This is possible because tDCS and TMS can induce alterations in cortical excitability, which outlast the stimulation period and map onto synaptic plasticity (Ziemann et al., 2008). This section will first provide a short introduction to mechanisms of synaptic plasticity as studied at the cellular level, followed by an overview from animal studies how synaptic plasticity can be modulated pharmacologically. This knowledge will then be linked to the current evidence on mechanisms and modulation of plasticity in the human motor cortex by CNS active drugs.

### 6.2. Mechanisms of synaptic plasticity

Plasticity in the motor cortex involves Hebbian-type long-term potentiation (LTP) of excitatory, i.e. glutamatergic synaptic transmission (Rioult-Pedotti et al., 1998, 2000). Induction of this form of LTP depends on activation of N-methyl-D-aspartate receptors (NMDARs) and subsequent calcium influx through the NMDAR channel (Bliss and Lomo, 1973; Morris et al., 1986). Alternatively, calcium may flow into the postsynaptic neuron through voltage-gated calcium channels (VGCCs), which have also been implicated in the induction of LTP (Westenbroek et al., 1990). Both mechanisms can act cooperatively, i.e. calcium influx through VGCCs depolarizes the postsynaptic membrane enough to release the magnesium block from NMDARs, thus facilitating induction of NMDAR-dependent LTP. In addition to NMDARs, metabotropic glutamate receptors (mGluRs) have a role in induction of LTP (Bashir et al., 1993).

The intracellular signaling pathways triggered by (strong) increases in postsynaptic calcium include activation of protein and tyrosine kinases, which result in phosphorylation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPAR) in the postsynaptic membrane and insertion of new AMPARs into it (Malinow and Malenka, 2002). In contrast, LTD which is triggered by lower levels of postsynaptic calcium is mediated by AMPAR internalization (Beattie et al., 2000). Thus, LTP and LTD are primarily expressed as an increase and decrease in AMPAR-mediated transmission, respectively, although plasticity of NMDAR-mediated transmission has also been described (Bashir et al., 1991).

GABA acts as the main inhibitory neurotransmitter in the mammalian brain and operates through two classes of receptors, an ionotropic GABAAR and a metabotropic GABABR. It has long been recognized that excitatory synaptic plasticity is under control of GABAergic inhibition since GABAAR blockers promote LTP of glutamatergic neurotransmission in the hippocampus (Wigstrom and Gustafsson, 1983) and neocortex (Artola and Singer, 1987). GABAAR-mediated inhibitory control of excitatory synapses is released during high-frequency synaptic transmission by autoinhibition via GABABRs, thus allowing for sufficient postsynaptic depolarization to permit NMDAR activation and induction of LTP (Davies et al., 1991).

In addition to controlling excitatory synaptic plasticity, inhibitory synapses are also highly dynamic and capable of activity-dependent long-term plasticity (Gaiarsa et al., 2002). Plasticity of excitatory and inhibitory synaptic transmission interacts in a complex manner and tunes the excitation-inhibition balance in cerebral networks, which is critical for physiological functioning.

### 6.3. Modulation of synaptic plasticity – cellular evidence

#### 6.3.1. The dopaminergic system

Dopamine has major modulating effects on excitatory synaptic plasticity. However, the role of dopamine as a neuromodulator is very complex and depends on a variety of factors, including non-linear dose–response profiles and dependence on the duration of dopamine receptor stimulation (Seamans and Yang, 2004). With regard to dopamine receptors, bidirectional effects following stimulation of D1-receptors (D1Rs) and D2-receptors (D2Rs) have been described: whereas D1Rs enhance the activity of both NMDARs and GABARs, D2Rs reduce their activity (Seamans and Yang, 2004). However, whilst D1R activation was shown to enhance LTP and LTD (Gurden et al., 2000; Otmakhova and Lisman, 1996), D2R activation was found to increase as well as decrease both LTP and LTD (Gurden et al., 2000; Manahan-Vaughan and Kulla, 2003). Thus, the modulatory effects of dopamine on excitatory synaptic plasticity are complex and may also depend on the balance of D1R and D2R stimulation.

#### 6.3.2. The cholinergic system

The cholinergic system has also a prominent impact on synaptic plasticity. For NMDAR-dependent LTP, a permissive function of the cholinergic system could be demonstrated: cholinergic activation promotes LTP, whereas cholinergic antagonists block it (Bröcher et al., 1992; Hasselmo and Barkai, 1995). Similarly, cholinergic activation enhances NMDAR-dependent LTD (Huerta and Lisman, 1995; Kirkwood et al., 1999). However, although a plasticity-enhancing effect of cholinergic activation has been demonstrated in the majority of studies, other studies showed a dose-dependent reduction of synaptic plasticity by activation of acetylcholine receptors, which may also depend on the level of muscarinic M1 vs. M2 receptor activation (Maeda et al., 1993; Sugisaki et al., 2011).

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*6.3.3. The serotonergic system*

The effects of serotonin (5-hydroxytryptamine, 5-HT) on excitatory synaptic plasticity in animal experiments are very heterogeneous. A number of studies showed an LTP-reducing or -abolishing effect by serotonin enhancement or 5-HT receptor activation (Kojima et al., 2003; Stäubli and Otaky, 1994), but others reported a nil effect (Normann and Clark, 2005) or even showed enhanced LTP under serotonergic activation (Kojic et al., 1997; Mori et al., 2001). However, also 5-HT receptor antagonists have been shown to abolish LTP (Huang and Kandel, 2007; Sanberg et al., 2006). For LTD it has been reported that 5-HT receptor activation blocks LTD or even converts it into LTP (Kemp and Manahan-Vaughan, 2005; Normann and Clark, 2005), whereas 5-HT receptor antagonists enhance LTD in brain slices of adult animals (Kemp and Manahan-Vaughan, 2005). However, in the visual cortex of juvenile cats serotonin may enhance LTD (Kojic et al., 1997), which shows that cortical area and/or age play a role in the modulatory effects of serotonin on synaptic plasticity.

*6.3.4. The adrenergic system*

The overall effect of adrenergic activation seems to be an enhancement of LTP (Hu et al., 2007; Korol and Gold, 2008; Tully et al., 2007). With regard to adrenergic receptors, activation of β-adrenergic receptors enhances LTP and moreover shows importance for the conversion of early- to late-phase LTP (Gelinas and Nguyen, 2005). In accordance, blockade of these receptors prevents the induction of LTP (Kemp and Manahan-Vaughan, 2008). In contrast, activation of α1- and α2-adrenergic receptors reduces LTP (Mondaca et al., 2004), and therefore counteracts the effects of ß-adrenergic receptors on plasticity. For LTD, the effects of ß-adrenergic receptor activation are conflicting: whereas some studies found an enhancement of LTD (Kemp and Manahan-Vaughan, 2008; Lemon et al., 2009), others reported a diminution or prevention of LTD (Katsuki et al., 1997). For α-adrenergic receptors it was shown that α1-receptor activation enhances LTD (Marzo et al., 2010), whereas α2-receptor activation reduces LTD (DeBock et al., 2003).

*6.4. Effects of CNS active drugs on human motor cortical plasticity*

Several NIBS techniques such as tDCS (Nitsche and Paulus, 2000, 2011; Stagg and Nitsche, 2011), paired associative stimulation [PAS] (Carson and Kennedy, 2013; Müller-Dahlhaus et al., 2010; Stefan et al., 2000), and theta-burst stimulation [TBS] (Cardenas-Morales et al., 2010; Huang et al., 2005) can induce changes in cortical excitability, which outlast the stimulation period. Cortical excitability was quantified in these studies by the size of the MEP elicited by single-pulse TMS over M1, which represents a complex measure of excitatory interneurons and projection neurons in M1 (Di Lazzaro et al., 2008). Although the cellular and molecular mechanisms of NIBS-induced after-effects are not well understood [for review see, (Müller-Dahlhaus and Vlachos, 2013)], pharmacological studies suggest a close link between synaptic plasticity mechanisms as studied at the cellular level and the physiology underlying tDCS-, PAS-, and TBS-induced cortical plasticity. Conversely, these studies have provided important evidence on the effects of CNS active drugs on cortical plasticity. Table 2 summarizes the current knowledge of the effects of CNS active drugs on NIBS-induced LTP- and LTD-like plasticity in M1, which is reviewed below.

*6.4.1. The glutamatergic system*

Memantine, an NMDAR antagonist, abolished the LTP-like plasticity induced by intermittent TBS (Huang et al., 2007) and by laser-PAS, i.e. LTP-like plasticity induced by associative pairing of painful laser stimuli and TMS of M1 (Suppa et al., 2013), and the LTD-like plasticity induced by continuous TBS (Huang et al., 2007). Likewise, PAS- and tDCS-induced LTP-like and LTD-like plasticity were blocked by the NMDAR antagonist dextromethorphan (Liebetanz et al., 2002; Nitsche et al., 2003; Stefan et al., 2002; Wolters et al., 2003). In contrast, the partial NMDAR agonist D-cycloserine enhanced LTP-like plasticity induced by anodal tDCS (Nitsche et al., 2004b), but shifted iTMS-induced LTP-like plasticity to LTD-like plasticity in a different study, possibly due to strengthening of inhibitory actions induced by iTBS (Teo et al., 2007). These studies provided evidence for an NMDAR-dependence of NIBS-induced cortical plasticity, thus linking NIBS-models of plasticity to synaptic mechanisms of plasticity as reviewed above.

*6.4.2. Voltage-gated ion channels*

Blockade of L-type VGCCs by nimodipine abolished TBS-induced LTP-like plasticity (Wankerl et al., 2010) and eliminated PAS-induced LTD-like plasticity (Wolters et al., 2003). Likewise, the T-type VGCC antagonist flunarizine abolished anodal tDCS-induced LTP-like plasticity (Nitsche et al., 2003). No effect of flunarizine on cathodal tDCS-induced LTD-like plasticity was found (Nitsche et al., 2003). As LTP is an activity-dependent process, a role of voltage-gated sodium channels (VGSCs) in induction of LTP can be assumed. In line with this notion, the VGSC blocker lamotrigine reduced PAS-induced LTP-like plasticity (Heidegger et al., 2010), and carbamazepine abolished anodal tDCS-induced LTP-like plasticity (Nitsche et al., 2003). Again, no effect of carbamazepine on LTD-like plasticity induced by cathodal tDCS was found (Nitsche et al., 2003). This nil effect on LTD-like plasticity is most likely explained by the fact that cathodal tDCS hyperpolarizes neuronal membranes, which precludes an additional impact of VGSC blockers on membrane polarization. In summary, these studies showed that NIBS-induced LTP- and LTD-like plasticity is an activity- and calcium-dependent process.

*6.4.3. The GABAergic system*

The GABAergic drugs diazepam and tiagabine reduced PAS-induced LTP-like plasticity (Heidegger et al., 2010). Likewise, the GABABR agonist baclofen led to suppression of PAS-induced LTP-like plasticity (McDonnell et al., 2007). In contrast, lorazepam, a positive allosteric modulator at the GABAAR reduced LTP-like plasticity in the early phase after anodal tDCS, but enhanced and prolonged LTP-like plasticity in the late phase (Nitsche et al., 2004c). There was no effect of lorazepam on cathodal tDCS-induced LTD-like plasticity (Nitsche et al., 2004c). The relatively minor effects of lorazepam on tDCS-induced plasticity might be explained by the observation that anodal and cathodal tDCS resulted in a decrease of GABA concentration in the stimulated cortex when measured with MR spectroscopy (Stagg et al., 2009). In line with the cellular studies reviewed above, these studies provided evidence that NIBS-induced LTP-like plasticity is under tight control of the GABAergic system.

*6.4.4. The dopaminergic system*

Among the modulatory neurotransmitter systems, the impact of dopamine on NIBS-induced plasticity has been explored most extensively. These studies revealed rather complex effects of dopamine on cortical plasticity, depending on drug dosage and receptor specificity as well as the NIBS protocol used to induce cortical plasticity. The findings suggested a dose-dependent inverted U-shape-like effect of dopamine on LTP-like cortical plasticity. Low (25 mg) and high (200 mg) doses of L-Dopa abolished anodal tDCS-induced LTP-like plasticity (Monte-Silva et al., 2010), and even turned PAS-induced LTP-like plasticity into LTD-like plasticity (Thirugnanasambandam et al., 2011b). These effects were largely reproduced by selective stimulation of D1Rs (Fresnoza et al., 2014) or D2Rs (Monte-Silva et al., 2009). In contrast, a medium

**Table 2**
Acute effects of CNS active drugs on TMS measures of human motor cortical plasticity.

| System/Drug | Mode of action | Protocol | Effect | Literature |
|---|---|---|---|---|
| *1. The glutamatergic system* | | | | |
| Cycloserine | Partial NMDAR agonist | atDCS | ▲ | Nitsche et al. (2004b) |
| | | $iTBS_{600}$ | ►LTD | Teo et al. (2007) |
| Memantine | NMDAR antagonist | $iTBS_{600}$ | ▼ | Huang et al. (2007) |
| | | $cTBS_{600}$ | ▼ | Huang et al. (2007) |
| | | Laser-PAS | ▼ | Suppa et al. (2013) |
| Dextromethorphan | NMDAR antagonist | atDCS | ▼ | Liebetanz et al. (2002), Nitsche et al. (2003) |
| | | ctDCS | ▼ | Liebetanz et al. (2002), Nitsche et al. (2003) |
| | | PAS-LTP | ▼ | Stefan et al. (2002) |
| | | PAS-LTD | ▼ | Wolters et al. (2003) |
| *2. Voltage-gated ion channels* | | | | |
| Nimodipine | L-type VGCC antagonist | $cTBS_{300}$ | ▼ | Wankerl et al. (2010) |
| | | PAS-LTD | ▼ | Wolters et al. (2003) |
| Flunarizine | T-type VGCC antagonist | atDCS | ▼ | Wolters et al. (2003) |
| | | ctDCS | – | Nitsche et al. (2003) |
| Lamotrigine | VGSC antagonist | PAS-LTP | ▼ | Heidegger et al. (2010) |
| Carbamazepine | VGSC antagonist | atDCS | ▼ | Nitsche et al. (2003) |
| | | ctDCS | – | Nitsche et al. (2003) |
| *3. The GABAergic system* | | | | |
| Lorazepam | GABAAR agonist | atDCS | ▼▲ | Nitsche et al. (2004c) |
| | | ctDCS | – | Nitsche et al. (2004c) |
| Diazepam | GABAAR agonist | PAS-LTP | ▼ | Heidegger et al. (2010) |
| Tiagabine | SGRI | PAS-LTP | ▼ | Heidegger et al. (2010) |
| Baclofen | GABABR agonist | PAS-LTP | ▼ | McDonnell et al. (2007) |
| *4. The dopaminergic system* | | | | |
| L-Dopa (low/high dose) | DR agonist | atDCS | ▼ | Monte-Silva et al. (2010) |
| | | ctDCS | ▼ | Monte-Silva et al. (2010) |
| L-Dopa (medium dose) | | PAS-LTP | ►LTD | Thirugnanasambandam et al. (2011b) |
| | | PAS-LTD | ▼ | Thirugnanasambandam et al. (2011b) |
| | | atDCS | ►LTD | Monte-Silva et al. (2010) |
| | | ctDCS | – | Monte-Silva et al. (2010) |
| | | PAS-LTP | ▲ | Thirugnanasambandam et al. (2011b) |
| | | PAS-LTD | ▲ | Thirugnanasambandam et al. (2011b) |
| L-Dopa (low/high dose) + Sulpiride | D1R stimulation | atDCS | ▼ | Fresnoza et al. (2014) |
| | | ctDCS | ►LTP | Fresnoza et al. (2014) |
| L-Dopa (medium dose) + Sulpiride | | PAS-LTP | ▼ | Fresnoza et al. (2014) |
| | | PAS-LTD | ►LTP | Fresnoza et al. (2014) |
| | | atDCS | – | Fresnoza et al. (2014) |
| | | ctDCS | ▼ | Fresnoza et al. (2014) |
| | | PAS-LTP | ▼ | Fresnoza et al. (2014) |
| | | PAS-LTD | ►LTP | Fresnoza et al. (2014) |
| Ropinirole (low/high dose) | D2/D3R agonist | atDCS | ▼ | Monte-Silva et al. (2009) |
| Ropinirole (medium dose) | | ctDCS | ▼ | Monte-Silva et al. (2009) |
| | | PAS-LTP | ►LTP | Monte-Silva et al. (2009) |
| | | PAS-LTD | ▼ | Monte-Silva et al. (2009) |
| | | atDCS | – | Monte-Silva et al. (2009) |
| | | ctDCS | – | Monte-Silva et al. (2009) |
| | | PAS-LTP | – | Monte-Silva et al. (2009) |
| | | PAS-LTD | ▼ | Monte-Silva et al. (2009) |
| | | | ▼ | |
| Sulpiride | D2R antagonist | $iTBS_{600}$ | ▼ | Monte-Silva et al. (2011) |
| | | $cTBS_{600}$ | ▼ | Monte-Silva et al. (2011) |
| | | atDCS | ▼ | Nitsche et al. (2006) |
| | | ctDCS | ▼ | Nitsche et al. (2006) |
| | | PAS-LTP | – | Nitsche et al., 2009 |
| | | PAS-LTD | ▼ | Nitsche et al., 2009 |
| Haloperidol | D2R antagonist | PAS-LTP | ▼ | (Korchounov and Ziemann, 2011) |
| *5. The cholinergic system* | | | | |
| Rivastigmine | Cholinesterase inhibitor | atDCS | ▼ | Kuo et al. (2007) |
| | m/nAChR stimulation | ctDCS | ▼▲ | Kuo et al. (2007) |
| | | PAS-LTP | ▲ | Kuo et al. (2007) |
| | | PAS-LTD | ▲ | Kuo et al. (2007) |
| Tacrine | Cholinesterase inhibitor | PAS-LTP | – | Korchounov and Ziemann (2011) |
| | m/nAChR stimulation | PAS-LTD | – | Korchounov and Ziemann (2011) |
| Nicotine | nAChR agonist | atDCS | ▼ | Thirugnanasambandam et al. (2011a) |
| | | ctDCS | ▼ | Thirugnanasambandam et al. (2011a) |
| | | PAS-LTP | ▲ | Thirugnanasambandam et al. (2011a) |
| | | PAS-LTD | ▼ | Thirugnanasambandam et al. (2011a) |
| Biperiden | mAChR antagonist | PAS-LTP | ▼ | Korchounov and Ziemann (2011) |
| *6. The serotonergic system* | | | | |
| Citalopram | SSRI | atDCS | ▲ | Nitsche et al. (2009b) |
| | | ctDCS | ►LTP | Nitsche et al. (2009b) |

**Table 2** (*continued*)

| System/Drug | Mode of action | Protocol | Effect | Literature |
|---|---|---|---|---|
| | | PAS-LTP | ▲ | Batsikadze et al. (2013) |
| | | PAS-LTD | ▼ | Batsikadze et al. (2013) |
| *7. The adrenergic system* | | | | |
| Amphetamine | Monoamine reuptake inhibitor | atDCS | ▲ | Nitsche et al. (2004a) |
| | | ctDCS | ▼ | Nitsche et al. (2004a) |
| Methylphenidate | Indirect norepinephrine agonist | PAS-LTP | – | Korchounov and Ziemann (2011) |
| Prazosine | Alpha1-R antagonist | PAS-LTP | ▼ | Korchounov and Ziemann (2011) |
| Propanolol | Beta-adrenergic antagonist | atDCS | ▼ | Nitsche et al. (2004a) |

atDCS, anodal tDCS; $cTBS_{300}$, LTP-like plasticity inducing continuous TBS (300 pulses); $cTBS_{600}$, LTD-like plasticity inducing continuous TBS (600 pulses); ctDCS, cathodal tDCS; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; D3R, dopamine D3 receptor; GABAAR, GABA A receptor; GABABR, GABA B receptor; $iTBS_{600}$, LTP-like plasticity inducing intermittent TBS (600 pulses); laser-PAS, LTP-like plasticity inducing associative pairing of painful laser stimuli applied to the hand with focal TMS of contralateral primary motor cortex; mAChR; muscarinic acetylcholine receptor; nAChR; nicotinergic acetylcholine receptor; NMDAR, NMDA receptor; PAS, paired associative stimulation; PAS-LTD, LTD-like plasticity inducing PAS; PAS-LTP, LTP-like plasticity inducing PAS; SGRI, selective GABA reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TBS, theta-burst stimulation; tDCS, transcranial direct current stimulation; VGCC, voltage-gated calcium channel; VGSC, voltage-gated sodium channel.
▲, increase/facilitation; ▼, decrease/suppression; ►LTP, switch to LTP-like plasticity; ►LTD, switch to LTD-like plasticity; –, no effect on TMS measures of cortical plasticity.

dose of L-Dopa (100 mg) turned anodal tDCS-induced LTP-like plasticity into LTD-like plasticity (Monte-Silva et al., 2010), but prolonged the duration of PAS-induced LTP-like plasticity (Thirugnanasambandam et al., 2011b). These effects of a medium L-Dopa dose may depend on the balance of D1R- and D2R-stimulation as selective stimulation of either receptor produces different effects (Fresnoza et al., 2014; Monte-Silva et al., 2009). In addition, data suggested that the modulatory effects of dopamine depend on the NIBS protocol applied. This may be explained by the different underlying physiology of the induced plasticity effects (i.e., spike-timing dependent plasticity-like effects after PAS vs. membrane polarization effects after tDCS).

Similarly, for LTD-like plasticity a dose-dependent U-shape-like effect of dopamine was shown. Low and high doses of L-Dopa suppressed both cathodal tDCS- (Monte-Silva et al., 2010) and PAS-induced LTD-like plasticity (Thirugnanasambandam et al., 2011b). In contrast, a medium dose of L-Dopa had no effect on cathodal tDCS-induced LTD-like plasticity (Monte-Silva et al., 2010) but enhanced PAS-induced LTD-like plasticity (Thirugnanasambandam et al., 2011b). For cathodal tDCS-, but not for PAS-induced LTD-like plasticity, these effects were largely reproduced by selective stimulation of D1Rs and D2Rs (Fresnoza et al., 2014; Monte-Silva et al., 2009). In addition, data from studies blocking D2R activity by sulpiride or haloperidol showed a consistent suppression of tDCS-, PAS-, and TBS-induced plasticity (Korchounov and Ziemann, 2011; Monte-Silva et al., 2011; Nitsche et al., 2006). Thus, a certain amount of background dopamine activity seems necessary for induction of plasticity. In line with the cellular studies reviewed above further enhancement of dopaminergic activity results in complex non-linear effects on plasticity, which depend on drug concentration, the balance between D1R and D2R activation, and the plasticity induction protocol.

#### 6.4.5. The cholinergic system

Global cholinergic activation (i.e., activation of both muscarinic [mAChR] and nicotinergic [nAChR] acetylcholine receptors) by the cholinesterase inhibitor rivastigmine enhanced and prolonged LTP- and LTD-like plasticity induced by PAS, whereas it abolished LTP-like plasticity induced by anodal tDCS (Kuo et al., 2007). In contrast, tacrine, another cholinesterase inhibitor, had no effect on PAS-induced plasticity (Korchounov and Ziemann, 2011). The reason for these conflicting results might have been a dose-dependent effect of cholinergic activation on plasticity, which has not yet been explored. With regard to the contribution of mAChRs vs. nAChRs, nicotine abolished anodal tDCS-induced, but prolonged PAS-induced LTP-like plasticity, while it abolished LTD-like plasticity in both stimulation protocols (Thirugnanasambandam et al., 2011a). Finally, the mAChR antagonist biperiden reduced LTP-like plasticity induced by PAS (Korchounov and Ziemann, 2011). In summary, cholinergic activity seems to exert important modulatory effects on NIBS-induced plasticity, but the knowledge about receptor- and dose-dependent effects is still limited.

#### 6.4.6. The serotonergic system

The impact of serotonin on NIBS-induced plasticity in humans has been studied in both the tDCS- and PAS-model of cortical plasticity. A single dose of the selective serotonin reuptake inhibitor citalopram enhanced and prolonged LTP-like plasticity induced by anodal tDCS, while it converted LTD-like plasticity induced by cathodal tDCS into LTP-like plasticity (Nitsche et al., 2009). Likewise, citalopram showed a trend towards enhanced PAS-induced LTP-like plasticity, whilst PAS-induced LTD-like plasticity was abolished (Batsikadze et al., 2013). Taken together, these findings show that serotonin has prominent effects on human cortical plasticity, which seem to facilitate LTP-like M1 plasticity.

#### 6.4.7. The noradrenergic system

The monoamine reuptake inhibitor amphetamine enhanced the duration of the LTP-like after-effects induced by anodal tDCS (Nitsche et al., 2004a). In contrast, methylphenidate had no effect on PAS-induced LTP-like plasticity (Korchounov and Ziemann, 2011). In line with the notion that adrenergic activity plays a role in NMDAR-dependent LTP-like cortical plasticity, anodal tDCS-induced after-effects were reduced by the ß-adrenergic receptor antagonist propranolol (Nitsche et al., 2004a), and PAS-induced LTP-like plasticity was abolished by the α1-receptor antagonist prazosine (Korchounov and Ziemann, 2011).

### 6.5. Summary and conclusions

NIBS-plasticity models provide an excellent tool to investigate the effect of CNS active drugs on cortical plasticity in humans non-invasively. These studies closely link knowledge on mechanisms and pharmacological modulation of synaptic plasticity as derived from animal studies to mechanisms and pharmacological modulation of NIBS-induced cortical plasticity in humans.

## 7. Effects of CNS active drugs on TMS-EMG measures of motor cortical excitability in epilepsy

The TMS studies concerned with the effects of CNS active drugs on measures of cortical excitability reviewed in the previous sections were all performed on healthy subjects to whom drugs were administered. Therefore, none of the observed drug effects can be

ascribed to brain pathology. In those studies, cortical excitability was measured immediately before the administration of a single dose of the study drug (baseline). Thereafter, repeat measurements were performed at delays adjusted to the pharmacokinetics of this drug. The basic concept behind these experiments is that drugs with different modes of action will produce different patterns of effects on the various TMS measures of motor cortical excitability. In this section, we review the effect of chronic administration of CNS active drugs on patients with epilepsy. We chose this particular disorder because it is one of the most studied in the pharmaco-TMS field and is likely to be representative of the interaction between these drugs and "abnormal brain circuits".

Epilepsy is a complex group of syndromes characterized by episodic brain dysfunction manifesting as the occurrence of recurrent seizures (Fisher et al., 2005). Epilepsy syndromes can be broadly classified into two main types: generalized and focal with diverse etiologies for each type (Berkovic et al., 2006). Regardless of the type or cause, the proposed underlying mechanism for the epileptic process (based on animal and experimental data) is that it is mediated by a disturbance in the neuronal excitatory/inhibitory balance leading to the formation of hyper-excitable seizure networks (McCormick and Contreras, 2001). From that perspective, TMS studies in epilepsy have been very helpful. While findings vary somewhat between studies, and likely reflect subject and methodology differences predominantly caused by medication and timing of studies, overall, cortical hyper-excitability resulting from defective inhibitory mechanisms seems to be a common feature in most types of epilepsy (Badawy et al., 2014). It also seems that the alterations occurring within intracortical inhibitory circuits depend on the type of epilepsy, the underlying etiology and site of epileptic focus. Despite the considerable advances made in cellular and molecular biology, the mechanisms via which different anti-epileptic drugs achieve seizure freedom are still unclear. The hypothesized mechanisms inferred from *in vitro* and animal studies suggest that most of the available anti-epileptic drugs (AEDs) eventually lead to decreased excitability with multiple potential modes of action for many of the available drugs, although actions on ion channels are a common general mechanism (Rogawski and Löscher, 2004). Whether these hypotheses are applicable to humans and whether the interaction between AEDs and the normal versus epileptic brain is different remains to be determined.

Chronic administration of carbamazepine and lamotrigine over five weeks in healthy volunteers increased motor threshold which then decreased following subsequent withdrawal of medication (Lee et al., 2005). Carbamazepine also resulted in a progressive increase in MT until the serum levels reached a steady state but did not alter MEP amplitudes or CSP duration in stroke patients with partial seizures (Turazzini et al., 2004). Similarly, lamotrigine also increased MT in patients with epilepsy while MEP amplitude and CSP duration remained unchanged (Manganotti et al., 1999). Chronic administration of valproate (multiple mechanisms of action) elevated RMT in patients with idiopathic generalized epilepsy (Kazis et al., 2006; Reutens et al., 1993) and benign childhood epilepsy with centro-temporal spikes (Nezu et al., 1997). Another study reported an increase in motor threshold following valproate in patients with focal epilepsy but not idiopathic generalized epilepsy (Cantello et al., 2006), but the numbers in each group were small, which hinders reliable comparison. That study also reported normalization of the increased ICF observed in patients with idiopathic generalized epilepsy prior to starting treatment, while changes in SICI failed to reach significance in either idiopathic generalized epilepsy or focal epilepsy after medication. Valproate also reduced MEP and CSP recruitment curves in patients with epilepsy (Kazis et al., 2006). No comment was made on the whether the patients were seizure free on medication or not in any of those studies.

Reversal of cortical hyper-excitability (seen as increased MT, SICI and LICI) after initiation of AEDs in drug naïve patients was suggested in an early study which reported an increase of motor threshold with valproate use in patients with new onset idiopathic generalized epilepsy (Reutens et al., 1993). This phenomenon was recently systematically investigated in patients with idiopathic generalized epilepsy and focal epilepsy (Badawy et al., 2010). The investigators found that treatment with AEDs reduced cortical excitability to normal or near normal values (pre-treatment reduced MT, SICI and LICI) only in patients who became seizure free but not those who continued to have seizures (Fig. 3). This occurred irrespective of clinical factors such as seizure type or fre-

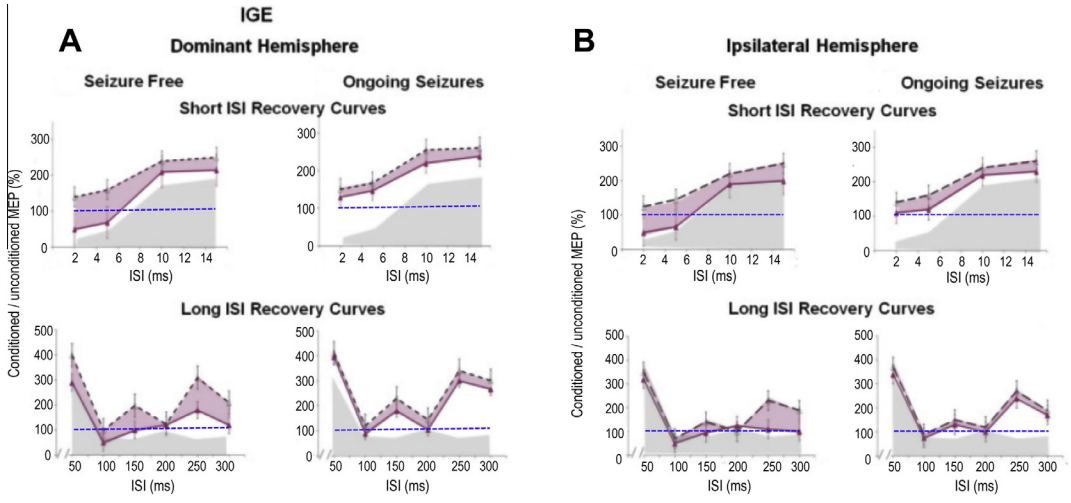


**Fig. 3.** Pre-medication and 4–16 weeks post-medication short and long interstimulus interval (ISI) recovery curves for seizure-free and ongoing seizure groups (as determined 1 year after start of medication) measured from the dominant hemisphere in idiopathic generalized epilepsy (IGE) **(A)** and from the epileptogenic (ipsilateral) hemisphere in focal epilepsy **(B)**. Ratios less than 100% (dashed blue lines) indicate inhibition, and ratios greater than 100% indicate facilitation. Purple shaded areas represent the difference between the pre-medication and post-medication measures; upper boundary of gray shaded areas represent the mean of healthy control subjects; dashed lines represent before medication; solid lines represent after medication. Note that normalization of intracortical excitability shortly after commencement of anti-epileptic drug treatment predicts seizure freedom after 1 year (modified from (Badawy et al., 2010), with permission). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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quency, age, or age of seizure onset. In particular, this effect was seen for a range of AEDs (carbamazepine, valproate, lamotrigine, levetiracetam and topiramate) with different mechanisms of action, and was not related to serum level. These results were then confirmed in different and larger cohorts (Badawy et al., 2013a,b,c). Of particular interest are the results of the recent longitudinal study performed by this group where patients with idiopathic generalized epilepsy and focal epilepsy were followed up for three years from onset (Badawy et al., 2013a). They were studied with TMS four times; the first was in the drug naïve state, and the second, third and fourth were respectively 2–6 months, 12–18 months and finally 30–36 months after commencement of AED treatment. At the end of this period the patients were grouped based on responsiveness to medication into seizure free on monotherapy (no seizures after starting the AED used), seizure free on dual therapy (initially uncontrolled but became seizure after starting the second AED) and refractory (ongoing seizures despite medication). In the refractory and seizure free on dual therapy groups, the only change that occurred 8–12 weeks after starting medication (study 2; 2–6 months from presentation) was observed in the contralateral hemisphere in patients with focal epilepsy. In this hemisphere, there was a paradoxical change as MT increased while LICI decreased at 250 and 300 ms interstimulus intervals resulting in loss of the inter-hemispheric difference initially observed in the drug naïve state.

When finally studied at 30–36 months, this loss of LICI in the refractory group had extended to involve all the long interstimulus intervals in both hemispheres of patients with refractory idiopathic generalized epilepsy and focal epilepsy. In the patients with refractory focal epilepsy, the contralateral hemisphere also became hyperexcitable at the short interstimulus intervals of 2 and 5 ms at 30–36 months (Badawy et al., 2013a). This did not occur in the groups who were uncontrolled initially and became seizure free after starting the second AED. In these patients, MT increased such that it was higher than in non-epilepsy controls and SICI and LICI gradually increased to assume normal or near normal values at most interstimulus intervals by the final study. Cortical excitability in the contralateral hemisphere, which had initially started to show evidence of hyperexcitability 2–6 months from presentation while the patients continued to have seizure (8–12 weeks after starting the first AED), returned to the drug naïve (normal range) values by 30–36 months at all interstimulus intervals (Badawy et al., 2013a). The seizure free on monotherapy group studied 2–6 months after presentation (8–12 weeks after medication), had reduced cortical excitability compared with the drug naive study, with an increase in MT and return of the measures of cortical inhibition at most interstimulus intervals in idiopathic generalized epilepsy and the ipsilateral hemisphere in focal epilepsy to values indistinguishable from controls. Cortical excitability in the contralateral hemisphere which was already the same as controls did not change after starting medication. No further changes were observed when these patients were studied again at 30–36 months.

The results suggest there is a close association between seizure freedom and normalization of cortical excitability with prolonged use of AEDs in patients with epilepsy (focal or generalized). It is not clear whether this effect is due to a change within the brain's predisposition to generate seizures, or simply attributable to the cessation of continued seizure activity. However, it seems that despite what is known about the mechanisms of action of each drug, whether it works on specific channels or receptors, a common effect of successful AED treatment is the restoration of normal responses to TMS, possibly occurring at the level of interactions amongst neurons in small cortical networks. Clearly, we cannot apply specific knowledge of the effect of AEDs on *in vitro* slices, animal models or presumably healthy brain circuits in people who do not have epilepsy to explain how this takes place, but it does appear that failure of this normalization process may be a general characteristic of refractory epilepsy.

## Conflict of interest

All authors state that they have no conflicts of interest. There was no external funding.

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