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Invited review

The effects of motor cortex rTMS on corticospinal descending activity

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex can produce long-lasting changes in the excitability of the motor cortex to single pulse transcranial magnetic stimulation (TMS). rTMS may increase or decrease motor cortical excitability depending critically on the characteristics of the stimulation protocol. However, it is still poorly defined which mechanisms and central motor circuits contribute to these rTMS induced long-lasting excitability changes. We have had the opportunity to perform a series of direct recordings of the corticospinal volley evoked by single pulse TMS from the epidural space of conscious patients with chronically implanted spinal electrodes before and after several protocols of rTMS that increase or decrease brain excitability. These recordings provided insight into the physiological basis of the effects of rTMS and the specific motor cortical circuits involved.

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1. Introduction

Transcranial magnetic stimulation (TMS) techniques can activate non-invasively the human brain evoking artificial activity in cortical neuronal networks (Hallett, 2007). Technical advances have offered the possibility of delivering repetitive TMS (rTMS) and it has been observed that rTMS may induce changes in brain excitability that outlast the stimulation period. The after-effects of rTMS might relate to activity-dependent changes in the effectiveness of synaptic connections between cortical neurons reflecting plasticity mechanisms of the brain (Hallett, 2007). Several

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protocols of rTMS have been introduced: (1) protocols with individual stimuli spaced apart by identical interstimulus intervals termed "simple" (or conventional) rTMS-protocols; (2) protocols with variable interstimulus intervals (e.g. triplets of 50 Hz repeated at 5 Hz), termed "patterned" protocols such as: theta-burst stimulation (TBS) and paired-pulse rTMS at I-wave periodicity (iTMS); (3) protocols of paired associative stimulation (PAS) consisting of low-frequency repetitive peripheral nerve stimulation combined with timed TMS over the contralateral motor cortex (Classen and Stefan, 2008; Fitzgerald et al., 2006; Thickbroom, 2007). All the above forms of rTMS may have excitatory or inhibitory effect on cortical output depending on: stimulus frequency, stimulus intensity, total number of stimuli, and interstimulus interval between the individual pulses of the train of stimuli. Low frequency rTMS (stimulus rates of 1 Hz or less) produces a lasting decrease in motor cortex excitability (Chen et al., 1997) while high frequency rTMS (stimulus rates of 5 Hz or more) (Berardelli et al., 1998; Maeda et al., 2000; Pascual-Leone et al., 1994; Peinemann et al., 2000) promotes a short term increase in cortical excitability. The PAS protocol is based on the Hebbian concept of spike-timing-dependent plasticity: two inputs, the first arising from electrical peripheral nerve stimulation and the second delivered over the motor cortex using TMS, are paired to activate brain networks at approximately the same time (Stefan et al., 2000). If the TMS pulse is applied at an interstimulus interval slightly longer (PAS+) or slightly shorter (PAS−) than the time needed for the afferent inputs, generated by median nerve stimulation, to reach the cerebral cortex and if a sufficient number of pairs of stimuli is delivered (Nitsche et al., 2007), the excitability of the sensory-motor cortex increases or decreases, respectively (Stefan et al., 2000). The TBS protocol (Huang et al., 2005), employs brief bursts of high frequency (50 Hz) low intensity stimuli. Different patterns of delivery of TBS (continuous versus intermittent) produce opposite effects on the excitability of the stimulated motor cortex (Huang et al., 2005). The paradigm named intermittent theta-burst stimulation (iTBS) produces a prolonged increase of motor cortex excitability while the paradigm named continuous theta-burst stimulation (cTBS) produces a prolonged decrease of motor cortex excitability (Huang et al., 2005). Thickbroom (2007) have described a novel method of increasing excitability in the corticospinal system based on repetitive paired TMS. This uses paired TMS stimuli of equal strength with a 1.5 ms interstimulus interval delivered for several minutes at a rate of 0.2 Hz. They showed that during paired-pulse rTMS, cortical excitability increases steadily and it is also increased for several minutes after the end of stimulation (Thickbroom et al., 2006; Thickbroom, 2007). More recently, quadripulse rTMS has been introduced, a protocol that may produce consistent LTP and LTD-like changes, depending on the interpulse interval (Hamada et al., 2007a, 2008).

Since spinal excitability as evaluated by H-reflex amplitude is unaffected, it is usually assumed that the after-effects of rTMS are due to changes in neural circuits within the cortex, perhaps involving long-term potentiation (LTP)- or long-term depression (LTD)-like phenomena at cortical synapses. However, the changes in the excitability of central motor circuits induced by rTMS were revealed indirectly by measuring motor evoked potentials as elicited by single pulse TMS by using surface electromyography. Thus, it is still unclear in many instances whether and to which extent the main after-effects of rTMS take place at cortical, subcortical or spinal level. Moreover, the exact mechanisms of the after-effects of rTMS are still poorly understood. It is still unclear, whether the mechanism of action of rTMS is a relatively non-specific disruption of the activity of several circuits in the brain with the consequence of a change in the balance between excitatory and inhibitory circuits, or whether rTMS acts more selectively by modulating the activity of specific circuits in the brain.

The most straightforward way to address these questions is to evaluate directly the activity of cortical circuits targeted by the stimulation before and after rTMS. This was performed in several conscious subjects who had cervical spinal electrodes implanted chronically for the control of medically refractory pain (Di Lazzaro et al., 2004).

2. Corticospinal output evoked by single and paired pulse TMS

The effects of rTMS were evaluated on the output evoked by single or paired pulse TMS. The details of the recording methods of epidural volleys are given in previous papers (Di Lazzaro et al., 2004) In brief, all the recordings were taken from patients who had spinal cord stimulators implanted for the treatment of intractable dorsolumbar pain. The electrode was implanted percutaneously in the epidural space at high cervical level. Recordings were made of descending activity 2–3 days after implantation during the trial screening period when the electrode connections are externalised and before connection to the final implanted stimulator. In almost all of the studies, the amplitude of the volleys was measured from onset to peak, where onset was defined either as the immediately preceding trough, or as the initial deflection from baseline. In one of the studies, the amplitude of the volleys was measured peak-to-peak between the negative peak to the following positive peak (Di Lazzaro et al., 2008c).

The motor cortex was stimulated using a focal coil with a posterior to anterior (PA) induced current across the central sulcus in the brain. This form of transcranial stimulation activates several structures within the central motor circuits and, as observed in experimental studies, produces a repetitive discharge of corticospinal cells (Amassian et al., 1987). However, the threshold for the activation of the different structures is substantially different (Di Lazzaro et al., 2008d). At low intensity, PA TMS evokes a single descending wave that is thought to originate from the activation of monosynaptic cortico-cortical connections projecting onto corticospinal neurones (Fig. 1). This descending wave produced by indirect activation of cortico-spinal cells is termed I1-wave. At higher stimulus intensities later volleys appear, these are termed late I-waves and are thought to originate from a separate and more complex circuit composed of a chain of cortical interneurons with oscillatory properties whose activation produces a repetitive discharge of cortico-spinal cells (Di Lazzaro et al., 2008d) (Fig. 1). Experimental studies have shown that cooling the surface of the motor cortex abolished later I-waves more readily than early I-waves (Amassian et al., 1987). Accordingly, it has been proposed that late I-waves are produced by activation of superficial cortico-cortical connections (more vulnerable to surface cooling) (Amassian et al., 1987), A further increase of the stimulus intensity leads to a direct activation of the axons of the cortico-spinal cells evoking the so-called D-wave (Di Lazzaro et al., 2008d) (Fig. 1). The D-wave evoked by monophasic PA TMS has the same latency of the D-wave evoked by electrical anodal stimulation and it is not modified by changes in cortical excitability produced by voluntary contraction. Thus, it is believed to originate from activation of corticospinal axons in the subcortical white matter at some distance from the cell body (Di Lazzaro et al., 2004). When a biphasic magnetic pulse or a non-focal magnetic stimulation is used, the evoked D-wave has a slightly longer latency than the D-wave evoked by monophasic magnetic stimulation and this longer latency D-wave, called "proximal D-wave", is facilitated by voluntary contraction. These features suggest that it is initiated closer to the cell body of the corticospinal neurons than the conventional D-wave evoked by monophasic magnetic stimulation, perhaps at the initial segment rather than at some distance down the axon (Di Lazzaro et al., 2004).

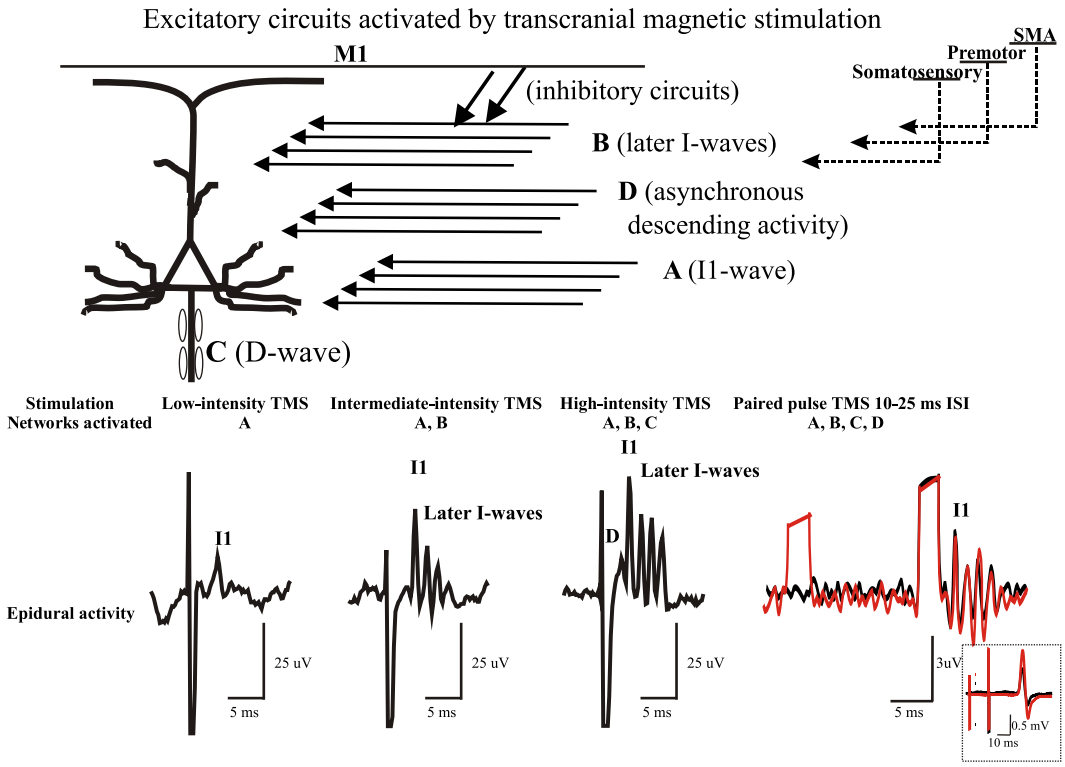

Fig. 1. Diagrammatic representation of possible sites and structures of central motor circuits activated by magnetic stimulation at different stimulus intensities and with paired pulse stimulation. The triangular neuron is a corticospinal cell and the arrows labeled with A, B and D indicate excitatory inputs to the corticospinal cells from excitatory interneurons. The epidural volleys evoked at different intensities are shown in the lower part of the figure, each trace is the average of 10 sweeps. At low intensity TMS evokes a single descending wave that is presumably produced by trans-synaptic activation of cortico-spinal cells by monosynaptic cortico-cortical projections (A), this indirect wave is called I1-wave; at intermediate intensity the I1-wave increases in amplitude and later I-waves are recruited, these waves presumably originate from complex cortico-cortical circuits represented by a chain of cortical interneurons (B) that might have oscillatory properties projecting upon the cortico-spinal cells; at higher intensities an earlier small potential appears that presumably originates from the direct activation of the corticospinal axons (C), this direct potential is termed D-wave. Using paired pulse TMS with a conditioning stimulus intensity below motor threshold at 10 ms interstimulus interval (ISI) the amplitude of motor evoked potential is increased (red trace in the lower right insert) when compared with the response evoked by single pulse stimulation (black trace) while the epidural activity evoked by paired pulse (red trace) is unmodified when compared with the epidural activity evoked by single pulse stimulation (black trace). This suggests that paired pulse stimulation probably evokes an asynchronous descending activity in addition to the highly synchronised I-wave activity evoked by single pulse stimulation, that presumably originate from a different population of cortico-cortical connections with different size and/or orientation (D).

The circuit generating the I1-wave and that generating the late I-waves have a different sensitivity to GABAA activity (Paulus et al., 2008) and also have different behaviour in several TMS protocols testing intracortical inhibition (Fig. 2) (Di Lazzaro et al., 2008d). Benzodiazepines, positive modulators of the GABAA receptor, produce a selective suppression of late I-waves with no effect on the I1-wave (Fig. 2) (Di Lazzaro et al., 2000). Similarly all the TMS inhibitory protocols such as the short interval (SICI) and the long interval (LICI) intracortical inhibition produced by paired pulse stimulation of the motor cortex, the short latency afferent inhibition (SAI) produced by conditioning electrical stimuli of peripheral nerves, and the transcallosal inhibition (TCI) produced by conditioning stimuli over the contralateral hemisphere, produce a selective inhibition of the late I-waves conceivably through the activation of inhibitory projections to the circuits generating late I-waves (Fig. 2) (Di Lazzaro et al., 2008d).

In addition to the circuits generating highly synchronised I-wave activity, TMS might also activate different circuits of the cerebral cortex. The activation of these circuits may evoke additional descending activity. This is suggested by the facilitatory effects on MEPs produced by paired pulse TMS protocols with an interstimulus interval of 10–25 ms. This protocol is termed intracortical facilitation (ICF) and produces a clear facilitation of MEPs with no change in epidural activity (Di Lazzaro et al., 2006a) (Fig. 1). The facilitation of MEPs without concomitant change in I-waves suggests that paired pulse TMS evokes asynchronous descending activity in addition to the highly synchronised I-wave activity through the activation of excitatory connections different from those involved in I-wave generation (Fig. 1). This additional activation of corticospinal activity would lead to MEP facilitation but leave I-wave amplitude unaffected. The reason why these connections are preferentially activated by paired pulse TMS at 10–25 ms interstimulus interval is still unclear.

The existence of multiple networks that can be activated by TMS may explain why rTMS has a considerable potential for inducing LTP/LTD-like plasticity as a single stimulus evokes artificial activity at multiple levels which includes the possibility to induce associative forms of plasticity.

We evaluated whether the effects observed in individual subjects after the different rTMS protocols exceed those of spontaneous variability of epidural volleys over time, and compared the changes in epidural volleys produced by the different rTMS protocols. The limits of spontaneous variability were calculated in a previous study on 15 subjects with cervical epidural electrodes by evaluating the variation in size of repeated measurements of I-waves in the absence of rTMS or any other intervention (Di Lazzaro et al., 2008c). This study showed that a change greater than 16.1% of the amplitude of late I-waves (mean plus two standard deviations of the mean variation in the 15 subjects) and a change greater than of 14.4% of the amplitude of the I1-wave (mean plus two stan-

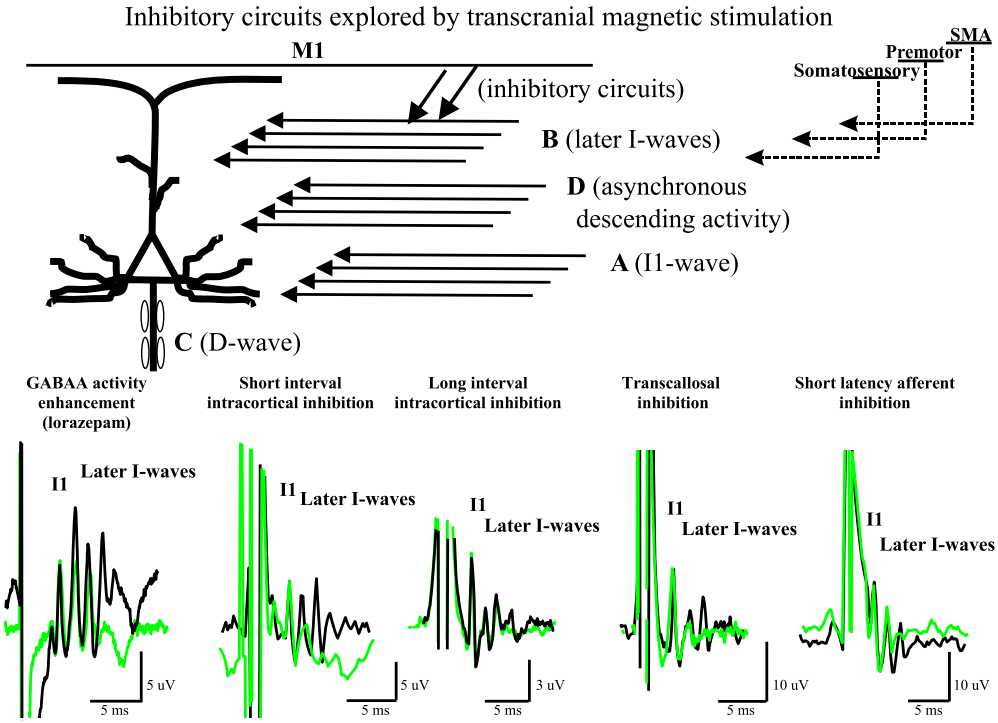

Fig. 2. Diagrammatic representation of the inhibitory circuits explored by transcranial magnetic stimulation. The corticospinal cell and excitatory interneurons are represented as in Fig. 1, input from inhibitory neurons is indicated by the downhead arrows. The effects produced by pharmacological or electrophysiological activation of inhibitory circuits on the epidural volleys are shown in the lower part of the figure, the control traces are shown in black while the conditioned epidural volleys are shown in green, each trace is the average of 10 sweeps. The enhancement of GABAA activity with lorazepam and the activation of the inhibitory connections using several conditioned transcranial magnetic stimulation protocols produce similar effects. The test stimulus evokes multiple descending waves, the later corticospinal volleys are suppressed after lorazepam administration, when test magnetic stimulus is preceded by a magnetic conditioning stimulus at short (short interval intracortical inhibition) and long (long interval intracortical inhibition) interstimulus intervals or by a conditioning stimulus to the contralateral hemisphere (transcallosal inhibition) or to a peripheral nerve (short latency afferent inhibition) the later I-waves are inhibited. Because only the later I-waves are suppressed with no effect on the I1-wave it is hypothesised that the inhibitory interneurons project selectively to the circuits generating the later I-waves (B).

Table 1
Studies evaluating the effects of different rTMS protocols on corticospinal descending activity.

Study	rTMS protocol	Number of stimuli	Intensity	Subjects studied	MEP	Epidural volleys
Di Lazzaro et al. (2002a)	5 Hz	20 (5 trains)	120% RMT	2	↑	D*↑, Late I-waves↑
Di Lazzaro et al. (2008b)	iTBS	600	80% AMT	3	↑	Late I-waves↑
Di Lazzaro et al. (2007)	iTMS	156 pulse pairs	Adjusted MEP-size 0.5 mV	1	↑	No change
Di Lazzaro et al. (2009b)	PAS+	90 pulse pairs	Adjusted MEP 1 mV	4	↑	Late I-waves↑
Di Lazzaro et al. (2008c)	1 Hz	900	110% RMT	5	↓	Late I-waves↓
Di Lazzaro et al. (2005)	cTBS	300	80% AMT	4	↓	I1-wave↓
Di Lazzaro et al. (2009)	PAS-	90 pulse pairs	Adjusted MEP 1 mV	2	↓	Late I-waves↓
Di Lazzaro et al. (2008b)	iTBS contralateral hemisphere	600	80%AMT	2	↓	Late I-waves↓

RMT, resting motor threshold; AMT, active motor threshold; MEP, motor evoked potentials.
* Proximal D-wave.

dard deviations of the mean variation in the 15 subjects) is outside the expected range of spontaneous variation (Di Lazzaro et al., 2008c).

3. rTMS protocols and corticospinal descending activity

The effects of rTMS on descending corticospinal activity were evaluated for four facilitatory protocols (5 Hz rTMS, PAS+, iTBS, iTMS) and for three inhibitory protocols (1 Hz rTMS, PAS−, cTBS). Because it has been shown that the facilitatory iTBS protocol has substantial inhibitory effects on the non-stimulated contralateral hemisphere (Suppa et al., 2008), the effects of this protocol on the corticospinal activity evoked by stimulation of the contralateral hemisphere were also evaluated. The results of these studies are summarized in Table 1.

4. Facilitatory rTMS protocols

4.1. Five Hz rTMS

High frequency rTMS (5 Hz or higher frequencies) typically increases MEP amplitude (Berardelli et al., 1998; Pascual-Leone et al., 1994). The effects of 5 Hz rTMS were evaluated in two subjects by using direct epidural recording of the descending corticospinal volley (Di Lazzaro et al., 2002b). Suprathreshold 5 Hz rTMS of motor cortex was accompanied by a gradual increase in the size and number of descending corticospinal volleys evoked by TMS (Fig. 3) and this effect paralleled the increase in MEP amplitude (Di Lazzaro et al., 2002b). The analysis of the individual corticospinal volleys demonstrated an increase in amplitude of both late I-waves and of the D-wave, while the amplitude of the I1-wave

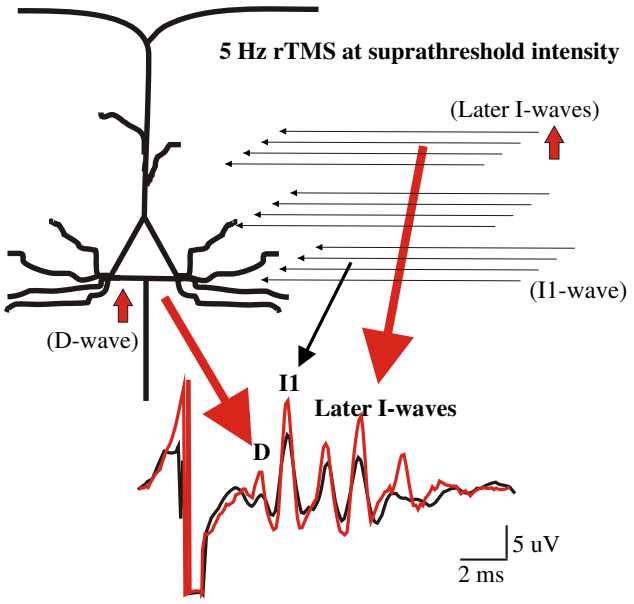

Fig. 3. Diagrammatic representation of the effects of 5 Hz rTMS on different circuits activated by transcranial magnetic stimulation. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after rTMS are shown in red, each trace is the average of 10 sweeps. After 5 Hz rTMS the amplitude of the D-wave is increased, the amplitude of the I3-wave is increased and a late I-wave (I4) appears. It is suggested that this protocol increases the excitability of the corticospinal axons and of the circuit generating late I-waves (see red arrows).

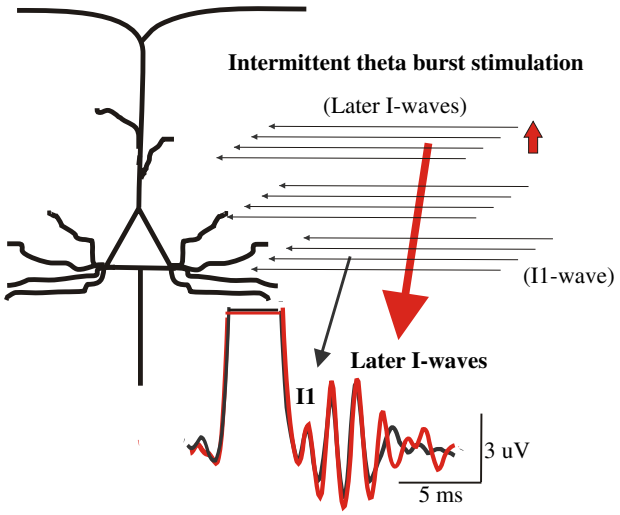

Fig. 5. Diagrammatic representation of the effects of iTBS on different circuits activated by transcranial magnetic stimulation. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after iTBS are shown in red, each trace is the average of 10 sweeps. After iTBS the amplitude of later I-waves is increased. It is suggested that this protocol increases the excitability of the circuit generating later I-waves.

was not modified (Fig. 3). This increase might be explained by an enhancement of the excitability of cortical connections generating late I-waves (Fig. 3). It should be noted that the increase in amplitude of late I-waves was larger than the spontaneous variability of the amplitude of these waves in only one of the studied subjects (Fig. 4a). At first sight it might seem surprising that there was a change in the amplitude of the D-wave since previous work suggests that the D-wave is produced by activation of corticospinal axons at some distance from the cell bodies (Di Lazzaro et al., 1999). However, as reported above, this is not the case for the D-wave produced by the biphasic repetitive stimulator that was used in the experiments evaluating the effects of 5 Hz rTMS. It was shown (Di Lazzaro et al., 2001) that a biphasic stimulus elicits a D-wave with a latency that is some 0.3–0.4 ms longer than that of the D-wave evoked by monophasic magnetic stimulation. Accordingly, it was proposed that the D-wave elicited by biphasic stimulation originates closer to the cell body of the pyramidal neurones where it is sensitive to changes in the level of neuronal excitability. Thus the increase in the amplitude of this D-wave after 5 Hz rTMS suggests that the excitability of pyramidal neurones is enhanced compared to their resting state.

4.2. Intermittent TBS

TBS employs bursts of high frequency stimulation (3 pulses at 50 Hz) repeated at intervals of 200 ms (i.e. 5 Hz, the theta rhythm

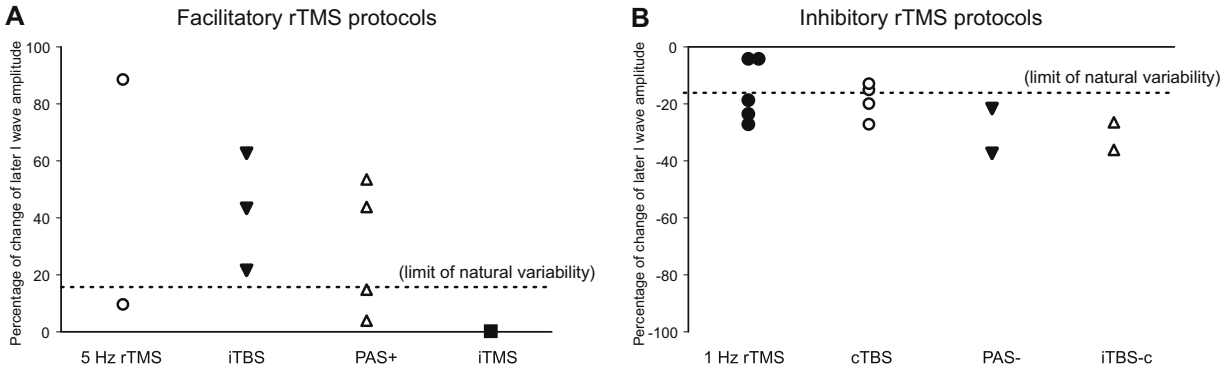

Fig. 4. (A) Scatterplot showing the percentage change in late I-wave amplitude in individual subjects after different protocols of rTMS enhancing cortical excitability. Dotted line represents the limit of natural variation of later I-wave amplitude calculated in 15 subjects. Five Hz rTMS (O open circles: $n = 2$) produced a change in late I-wave amplitude larger than the natural variability in one of the subjects; PAS+ (Δ open triangles: $n = 4$) produced a change in late I-wave amplitude larger than the natural variability in two of the subjects; Intermittent TBS (▼ filled downhead triangles: $n = 3$) produced a change in later I-wave amplitude larger than the natural variability in all studied subjects; iTMS (■ filled squares: $n = 1$) produced no change in late I-wave amplitude though the motor evoked potential was largely facilitated. (B) Scatterplot showing the percentage change in later I-wave amplitude in individual subjects after different protocols of rTMS suppressing cortical excitability. Dotted line represents the limit of natural variation of later I-wave amplitude calculated in 15 subjects. One Hz rTMS (● filled circles: $n = 5$) produced a change in late I-wave amplitude larger than the natural variability in three of the subjects; PAS− (▼ filled downhead triangles: $n = 2$) produced a change in later I-wave amplitude larger than the natural variability in both studied subjects; Continuous TBS (○ open circles: $n = 4$) produced a change in later I-wave amplitude larger than the natural variability in two of the subjects; facilitatory iTBS of the contralateral hemisphere (Δ open triangles: $n = 2$) produced a change in later I-wave amplitude larger than the natural variability in both studied subjects.

in the EEG nomenclature). Different patterns of TBS have opposite effects on excitability of the stimulated motor cortex (Huang et al., 2005). The protocol termed intermittent theta-burst stimulation (iTBS) produces a persisting increase in the amplitude of motor evoked potentials evoked by TMS. The corticospinal volleys evoked by single pulse TMS of the motor cortex before and after iTBS were recorded in three conscious patients with a cervical epidural electrode (Di Lazzaro et al., 2008b). iTBS increased MEPs, and this was accompanied by a significant increase in the amplitude of late I-waves, but not the I1-wave (Fig. 5). The increase in late I-wave amplitude ranged from 22% to 65% and was above the spontaneous variability of late I-wave amplitude in all subjects (Fig. 4a). The results of this study demonstrate that rTMS given as iTBS leads to a pronounced increase in the excitability of cortical circuits generating the late I-waves, whilst the earliest I-wave is unaffected (Fig. 5).

4.3. rTMS at I-wave periodicity

Thickbroom and colleagues (Thickbroom et al., 2006) described a novel method of increasing excitability in the corticospinal system based on repetitive paired TMS at I-wave periodicity (iTMS). This protocol employed paired TMS stimuli of equal strength with a 1.5 ms interstimulus interval delivered for several minutes at a rate of 0.2 Hz. Those authors showed that paired pulse MEP amplitude increases steadily during iTMS and that single-pulse MEP amplitude is increased for several minutes after the end of stimulation (Thickbroom et al., 2006; Thickbroom, 2007). The effects of iTMS were evaluated in a single patient with direct epidural recordings (Di Lazzaro et al., 2007). In that patient, there was a pronounced enhancement of MEP amplitude after iTMS; with an increase of amplitude of more than 200%. However, the marked increase in MEP after iTMS was paralleled by only a slight and non-significant change in epidural volley amplitude (Figs. 4a and 6). Because MEPs evoked by cervicomedullary junction stimulation are not modified by iTMS (Hamada et al., 2007b), thus confirming that the increase in MEP amplitude takes place at supraspinal level, it was suggested (similar to the arguments explaining the dissociation between the facilitatory effect of ICF on MEP amplitude but not I-waves, see above) that iTMS produces an increase in excitability of circuits different from those generating the I1- and late I-waves (Di Lazzaro et al., 2007). It was hypothesised that the epidural volleys do not represent all the descending activity evoked by TMS and that there may be additional activity that is less synchronous and therefore, not evident in the epidural recordings (Di Lazzaro et al., 2007). If this asynchronous descending corticospinal activity is increased by iTMS, then the MEP would be larger while the increase in the I-wave activity may remain non-significant (Fig. 6). However, because only a single patient was studied, this interpretation should be considered with caution and further data are required to confirm the above hypothesis.

4.4. Paired associative stimulation

rTMS protocols that resemble models of associative stimulation in animal studies have been introduced. The most widely used protocol is paired associative stimulation (PAS) with two inputs to motor cortex, one arising from electrical peripheral nerve stimulation and the other delivered over the motor cortex using TMS (Stefan et al., 2000). If the TMS pulse is applied at an interstimulus interval slightly longer than the time needed for the afferent inputs, generated by median nerve stimulation, to reach the cerebral cortex (PAS+) and if a sufficient number of pairs of stimuli are delivered, then the amplitude of MEPs increases (Nitsche et al., 2007; Stefan et al., 2000, 2002; Wolters et al., 2003; Ziemann et al., 2004). The effects of the PAS+ protocol have been evaluated in four subjects with the epidural electrode (Di Lazzaro et al., 2009b). Mean MEP amplitude was increased after PAS+ and this was paralleled by an increase of the mean amplitude of late I-waves by 50% (Fig. 7). The mean amplitude of I1-wave remained unchanged. However, there was a substantial variation in the size of the effects produced by PAS + in individual subjects: an increase of later I-waves clearly above the spontaneous variability was observed in two subjects, an increase close to the limits of spontaneous variability was observed in one subject and no substantial change in the remaining subject (Fig. 4a). Thus, the results of this study suggest that PAS+ may increase the excitability of cortico-cortical connections of the motor cortex that generate late I-waves (Fig. 7).

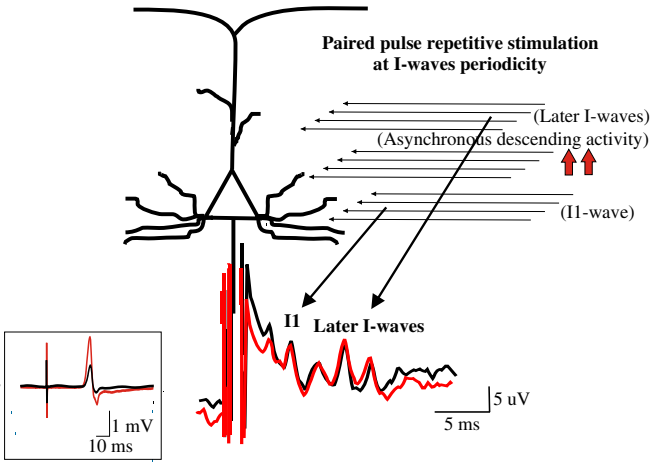

Fig. 6. Diagrammatic representation of the effects of iTMS on different circuits activated by transcranial magnetic stimulation and on motor evoked potentials. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after iTMS are shown in red, each trace is the average of 5 sweeps. After iTMS the amplitude of motor evoked potential is increased (lower left insert) while the amplitude of I-waves is not modified. This suggests that this protocol probably enhances the excitability of a population of cortico-cortical connections different from those generating the I-waves that evokes an asynchronous descending activity in addition to the highly synchronised I-wave activity evoked by single pulse stimulation.

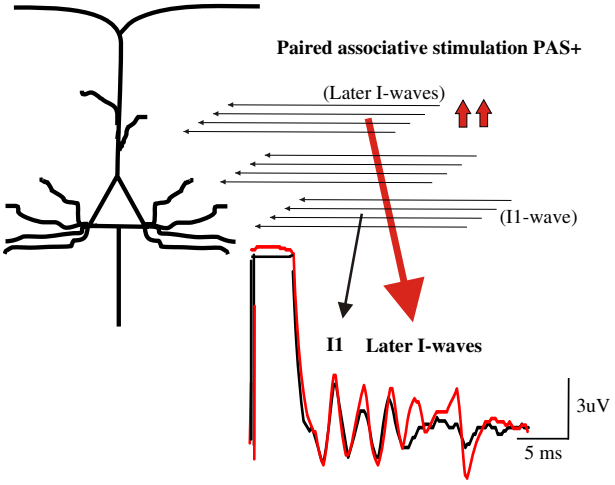

Fig. 7. Diagrammatic representation of the effects of PAS+ on different circuits activated by transcranial magnetic stimulation. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after PAS+ are shown in red, each trace is the average of 10 sweeps. After PAS+ the amplitude of later I-waves is increased. It is suggested that this protocol increases the excitability of the circuit generating later I-waves.

5. Inhibitory rTMS protocols

5.1. One Hz rTMS

One of the first and still commonly used protocols is low frequency (around 1 Hz) rTMS. Chen and colleagues (Chen et al., 1997) found that corticospinal excitability was reduced for about 15 min after applying 0.9 Hz rTMS for 15 min. They speculated that this was due to long-term depression of synapses in motor cortex.

The effects of 1 Hz rTMS were evaluated in five patients with direct epidural recording of the descending corticospinal volley (Di Lazzaro et al., 2008c). Suprathreshold 1 Hz rTMS of motor cortex produced a decrease in the size of the late I-waves (Di Lazzaro et al., 2008c). In contrast, the I1-wave amplitude remained unchanged (Fig. 8). The suppression of the late I-waves was paralleled by a suppression of MEPs and there was a significant linear correlation between changes in late I-wave and MEP amplitudes. However, there was a substantial variation in the size of the effect produced by rTMS in individual subjects. In only two of the subjects the reduction of late I-waves was clearly larger than the spontaneous variability of the amplitude of these waves (Fig. 4b).

In summary, 1 Hz rTMS, at least in some subjects, suppresses the excitability of circuits generating the late I-waves (Fig. 8).

5.2. Continuous TBS

The cTBS protocol produces a consistent inhibitory effect of MEPs (Huang et al., 2005). The effects of cTBS on the epidurally recorded corticospinal volleys were evaluated in four patients (Di Lazzaro et al., 2005). The recordings in these subjects showed a significant inhibition on the I1-wave, with a less pronounced effect on late I-waves. The maximal effect of on the I1-wave amplitude occurred 7–8 min after the end of cTBS. At this delay the amplitude of the I1-wave decreased by more than 50% (Fig. 10). The suppression of the I1-wave was paralleled by a suppression of MEPs, these were reduced to about 60% of their pre-cTBS size 7–8 min after the end of cTBS (Di Lazzaro et al., 2005). In two of the subjects the effects of cTBS on the amplitude of the D-wave were also evaluated, but this wave was not substantially modified by cTBS. Thus, cTBS represents the unique rTMS protocol capable of modulating the excitability of the circuits generating the I1-wave (Fig. 9). The analysis of the individual data showed that the reduction in amplitude of the I1-wave ranged from 71% to 23% which is beyond the spontaneous variability of this wave (e.g. >14.4%) in all studied subjects (Fig. 4b).

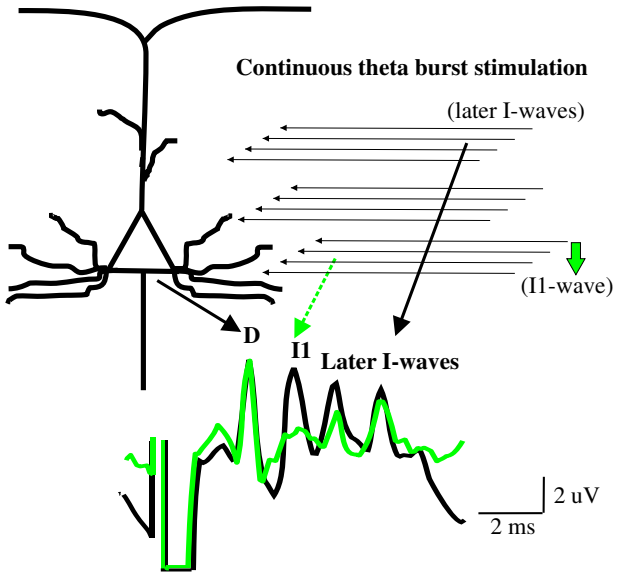

Fig. 9. Diagrammatic representation of the effects of cTBS on different circuits activated by transcranial magnetic stimulation. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after cTBS are shown in green, each trace is the average of 10 sweeps. After cTBS the amplitude of the I1-wave is suppressed with no change of the D-wave. It is suggested that this protocol decreases the excitability of the circuit generating the I1-wave.

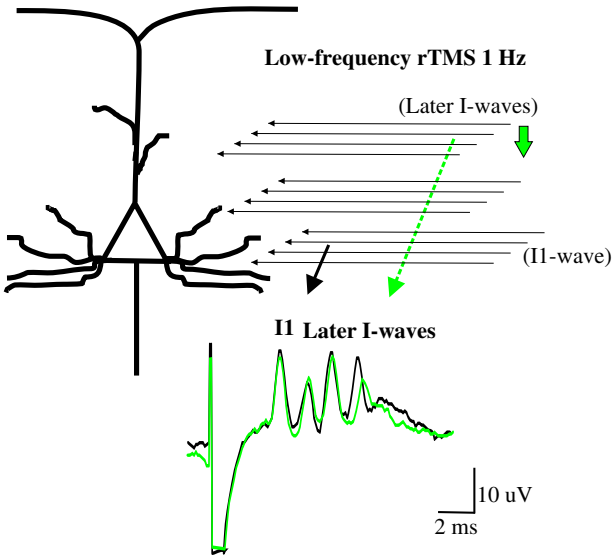

Fig. 8. Diagrammatic representation of the effects of 1 Hz rTMS on different circuits activated by transcranial magnetic stimulation. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after rTMS are shown in green, each trace is the average of 10 sweeps. After 1 Hz rTMS the amplitude of the later I-wave is reduced. It is suggested that this protocol decrease the excitability of the circuit generating later I-waves.

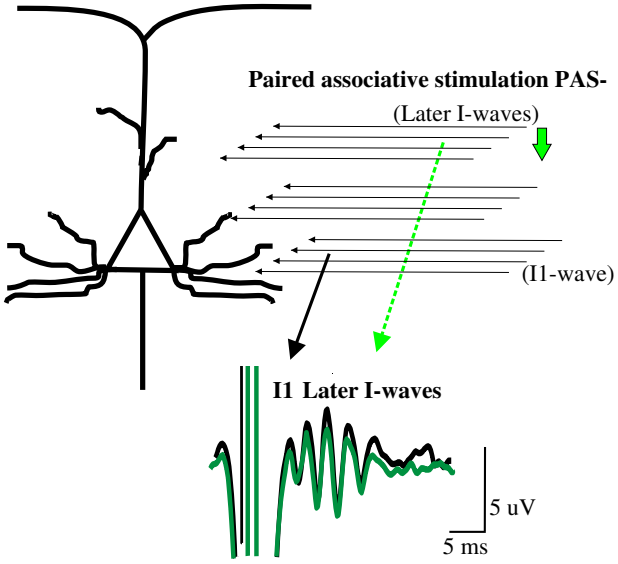

Fig. 10. Diagrammatic representation of the effects of PAS– on different circuits activated by transcranial magnetic stimulation. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after PAS– are shown in green, each trace is the average of 10 sweeps. After PAS– the amplitude of the later I-wave is reduced. It is suggested that this protocol decrease the excitability of the circuit generating later I-waves.

5.3. Paired associative stimulation

PAS with an interstimulus interval between the median nerve stimulation and cortical stimulation slightly shorter than the time needed by the peripheral afferent input to reach the cerebral cortex produces MEPs suppression (PAS−) (Muller et al., 2007; Wolters et al., 2003; Ziemann et al., 2004). The effects of the PAS− protocol on the descending corticospinal volley have been evaluated in two subjects (Di Lazzaro et al., 2009a). The recordings performed in one of the patients are shown in Fig. 10. In this subject PAS− produced a suppression of the late I-waves of about 40% (Fig. 10). In both subjects the reduction of the late I-waves was larger than the spontaneous variability of the amplitude of these waves (Fig. 4b). Thus, the results obtained in the two studied patients suggest that PAS− decreases the excitability of cortico-cortical connections of the motor cortex that generate the late I-waves (Fig. 10).

6. Effects of rTMS on the contralateral (non-stimulated hemisphere)

The conditioning effects of rTMS are not limited to the cortical area targeted by rTMS but may also occur at distant interconnected sites in the brain (Fitzgerald et al., 2006). An increase of MEP amplitudes elicited from the non-stimulated motor cortex has been reported after suppressive rTMS stimulation of the motor cortex of the other hemisphere (Plewnia et al., 2003) (Gilio et al., 2003; Schambra et al., 2003). Similarly, Di Lazzaro and colleagues (Di Lazzaro et al., 2008a) showed that the decrease of MEP amplitude in the hemisphere stimulated using the cTBS protocol was associated with a concomitant increase in MEP amplitude elicited from the motor cortex of the non-stimulated hemisphere. The reverse was observed using the facilitatory iTBS protocol: the increase of MEP amplitude in the hemisphere stimulated with iTBS was associated with a concomitant decrease of MEP amplitude elicited by stimulation of the contralateral hemisphere (Di Lazzaro et al., 2008a; Suppa et al., 2008). The effects of rTMS on the excitability of the non-stimulated hemisphere were evaluated in two patients by using the epidural recording technique using the facilitatory iTBS protocol (Di Lazzaro et al., 2008b). In these two patients the increase of the corticospinal volley and MEPs evoked from the hemisphere stimulated with iTBS was associated with a decrease in the amplitude of the late I-waves and of MEP amplitude elicited from the contralateral non-stimulated motor cortex. The I1-wave was not significantly modified while the mean amplitude of the late I-waves decreased by about 30% in both subjects (Fig. 11). In both subjects this reduction in amplitude of the late I-waves was larger than the upper limit of spontaneous variability of these waves (Fig. 4b).

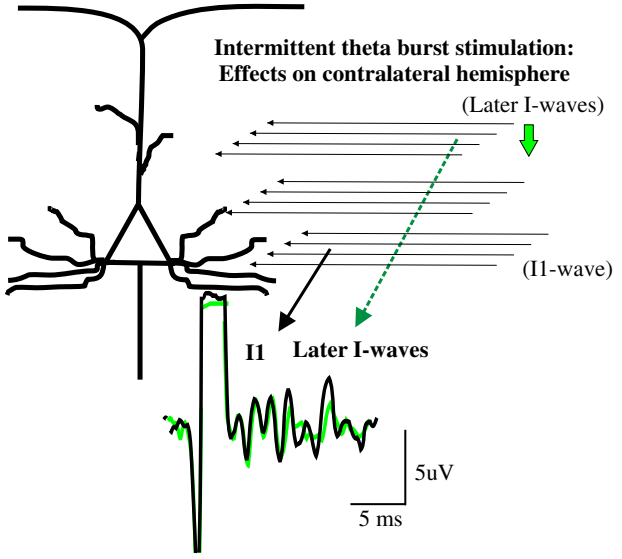

Fig. 11. Diagrammatic representation of the effects of iTBS on different circuits activated by transcranial magnetic stimulation of the contralateral hemisphere. The traces obtained in baseline conditions are shown in black while the epidural volleys recorded after rTMS are shown in green, each trace is the average of 10 sweeps. After iTBS the amplitude of the later I-wave evoked by stimulation of the contralateral hemisphere is reduced. It is suggested that these protocols decrease the excitability of the circuit generating later I-waves in the contralateral hemisphere.

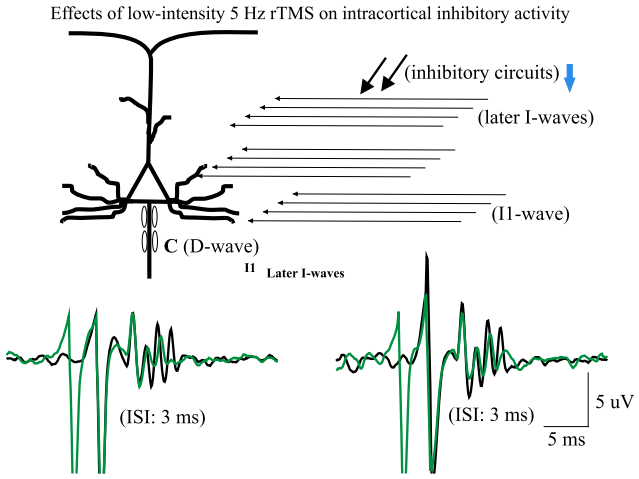

Fig. 12. Diagrammatic representation of the effects of low-intensity 5 Hz rTMS on intracortical inhibition produced by paired pulse magnetic stimulation at short interstimulus intervals. The effects produced by this protocol on the epidural volleys are shown in the lower part of the figure. Intracortical inhibition in baseline conditions is shown on the left: paired pulse stimulation at 3 ms interstimulus interval produces a suppression of the latest I-waves (green trace) when compared with the output evoked by single pulse stimulation (black trace), each trace is the average of 10 sweeps. Intracortical inhibition after rTMS is shown on the right: paired pulse stimulation at 3 ms interstimulus interval produces less inhibition of the latest I-wave (green trace), while the activity evoked by single pulse stimulation (black trace) is not modified. It is suggested that this protocol decreases the excitability of the inhibitory connections projecting over the circuit generating later I-waves.

7. Effects of rTMS on inhibitory cortical circuits

Several authors investigated the effects of rTMS protocol on intracortical inhibitory activity as evaluated with paired pulse TMS at short interstimulus intervals (SICI) (Fitzgerald et al., 2006). It was shown that 5 Hz rTMS may reduce SICI (Peinemann et al., 2000; Quartarone et al., 2005; Wu et al., 2000). The effects of 5 Hz rTMS on intracortical inhibitory activity was evaluated by epidural recording in two patients (Di Lazzaro et al., 2002a). Because the threshold for activating intracortical inhibitory circuits is lower than the MEP-threshold (Kujirai et al., 1993), in the study by Di Lazzaro and co-workers (Di Lazzaro et al., 2002a) a very low-intensity rTMS was used. This was done in order to evaluate whether a low-intensity rTMS protocol at 5 Hz might have effects limited to intracortical inhibitory circuits. The study showed that subthreshold 5 Hz rTMS (total of 50 stimuli was given at an intensity of active motor threshold) has no effect on MEP amplitude but reduces SICI (Di Lazzaro et al., 2002a) suggesting that low-intensity rTMS at 5 Hz can selectively modify the excitability of GABAergic inhibitory networks in the motor cortex (Fig. 12). Because only two patients were studied and only a single rTMS protocol was investigated, further studies exploring the effects of rTMS on the

epidural activity recorded using the short interval intracortical inhibition and facilitation protocols are required.

8. Effects of rTMS in patients with brain lesions

The information about the effects of rTMS provided by direct epidural recordings of the descending corticospinal volley in patients with neurological disorders is limited and it is still unknown, whether the effects of rTMS applied to patients with brain diseases are the same or different to those observed in normal subjects. The effects of rTMS on epidural volleys were evaluated in a single patient with chronic stroke, with a lacunar lesion located in the posterior limb of internal capsula (Di Lazzaro et al., 2006b). The patient presented a complete motor deficit of the right upper limb and a severe right lower limb motor deficit (Di Lazzaro et al., 2006b). In this patient, iTBS of the affected motor cortex produced an increase of the corticospinal activity of about 80%. The increase in the excitability of the affected motor cortex produced by iTBS of this hemisphere was associated with a suppression of the amplitude of the descending corticospinal volley evoked by TMS of the contralateral motor cortex by about 40%. The preliminary results of this single case study suggest that the effects of rTMS in patients with brain lesions might be comparable to those obtained in normal subjects.

9. Information provided by invasive recordings

Before considering the significance of these findings in greater detail it would be circumspect to describe the limitations of our data set of recordings:

(a) Only a small number of individuals were tested. This renders it still difficult to assess inter-individual variations in the responsiveness to the various interventions.
(b) The contribution of circuits generating the proposed asynchronous descending activity cannot be clearly evaluated.
(c) Epidural recordings do not reveal the exact site of action of different rTMS protocols and it is possible that some of the effects are not due to changes in synaptic efficacy directly induced in cortico-cortical projections generating the I-waves, but they might take origin up-stream of these circuits even from the modulation of projections originating from cortical areas surrounding the motor cortex, in particular the premotor and supplementary motor areas and the somatosensory cortex, or from remote subcortical structures. Interestingly, it has been shown that TMS can modulate oscillatory activity in remote structures capable of influencing cortical excitability such as the subthalamic nucleus (Gaynor et al., 2008). Thus, it is possible that some of the observed changes are indirectly produced at cortical level trough the modulation of remote structures projecting to the motor cortex.
(d) It is difficult to judge the consistency of post-interventional changes of the descending volleys because in most of the studies only the pre-interventional and post-interventional averages of the descending volleys were evaluated without analysing the variability (noisiness) of individual recordings.
(e) The recordings lack muscle-specific information.

Even with the above provisors in mind, the recording of the epidural activity provided a relevant contribution to the knowledge of the physiological basis of rTMS effects.

Cumulatively, the recordings obtained from the epidural space of the spinal cord have confirmed many of the conclusions about the effects of different rTMS protocols that had been proposed on the basis of indirect measurements of MEPs. However, the invasive recordings have also revealed a number of additional and unexpected findings which expanded the knowledge of the physiological basis of rTMS effects.

Epidural recordings confirmed that the main changes produced by rTMS take place at the cortical level and that:

(1) rTMS delivered as 5 Hz (suprathreshold stimulation intensity), iTBS, and PAS+ can increase the excitability of central motor circuits.
(2) rTMS delivered as 1 Hz (suprathreshold stimulation intensity), cTBS, PAS− and iTBS of the contralateral hemisphere can decrease the excitability of central motor circuits.
(3) Similar to rTMS effects on MEP amplitude there is a high inter-individual variability of the effects of rTMS protocols on the amplitude of the descending corticospinal waves.

In addition, epidural recordings of the corticospinal volley provided the following new findings:

(1) rTMS does not simply disrupt the ongoing activity of the cerebral cortex but modulates the excitability of specific circuits of the human brain.
(2) As observed using paired pulse stimulation protocols, the cortical circuits generating the I1- and late I-waves can be modulated independently.
(3) For the first time it is suggested that rTMS can enhance the excitability of circuits independent from those generating the late I-waves and thus suggesting that there are segregated structures of the human cerebral cortex that can be modulated independently using rTMS. This was observed using iTMS stimulation.
(4) Though the changes produced by facilitatory rTMS protocols as evaluated with MEP recording are apparently similar, the effects may involve different structures within the central motor circuits: while iTBS and PAS+ modulate selectively cortico-cortical circuits generating the late I-waves, 5 Hz rTMS seems also to produce a direct modulation of the corticospinal cell excitability, and iTMS seems to involve completely different cortical mechanisms.
(5) The same is true for protocols of repetitive stimulation suppressing cortical excitability: while most of the protocols suppress the cortico-cortical circuits generating the late I-waves, cTBS seems to have a different mechanism by suppressing selectively the monosynaptic cortical circuit generating the I1-wave.

Though it is still unknown whether the different central motor circuits that can be recruited and modulated using TMS have different physiological roles, it is likely that the as exact as possible knowledge of the mechanisms of action of the different rTMS protocols will prove useful for the design of future studies aiming at evaluating the potential therapeutic role of rTMS. For instance, protocols acting at different levels of the central nervous system might be combined in order to boost the effect of individual protocols or, alternatively, protocols suppressing specific circuits might be coupled with protocols enhancing the excitability of different circuits in order to obtain a more focused action of rTMS.

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