Modulatory effects of low- and high-frequency repetitive transcranial magnetic stimulation on visual cortex of healthy subjects undergoing light deprivation

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The aim of the present study was to explore further the effects of light deprivation (LD) on visual cortex excitability. Healthy subjects reporting reliable induction of phosphenes by occipital transcranial magnetic stimulation (TMS) underwent 60 min of complete LD. Phosphene threshold (PT) was measured before (T_0), after 45 min (T_1) and 60 min (T_2) of LD, and then every 10 min after light re-exposure until recovery to T_0 values. Repetitive TMS (rTMS) (at 1 or 10 Hz) was applied in separate sessions during the last 15 min of LD. PTs significantly decreased after 45 min of LD. rTMS differentially modified the effects of 60 min LD on PTs depending on stimulation frequency. One hertz rTMS did not change the decreasing of PT values as observed in baseline condition, but significantly prolonged the time to recover T_0 PT values after light re-exposure. By contrast, 10 Hz rTMS significantly increased PT and the time to recover T_0 PT values after light re-exposure was shortened. The results of this study show that the modulatory effects of different rTMS frequencies on visual cortex critically depend on the pre-existing excitability state of inhibitory and facilitatory circuits, and provide novel insights into the neurophysiological changes that take place in the visual cortex following functional visual deafferentation.

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Transcranial magnetic stimulation (TMS) has proven to be a safe and valuable tool to investigate cortical excitability (Pascual-Leone *et al.* 1998). In particular, TMS delivered to the occipital cortex can evoke the perception of flashes or spots of light (phosphenes) in the absence of visual stimuli. The phosphene threshold (PT), i.e. the minimum intensity required to evoke phosphenes, provides a measure of visual cortex excitability in normal subjects and in patients affected by migraine (Afra *et al.* 1998; Aurora *et al.* 1998).

Repetitive TMS (rTMS) can modulate cortical excitability beyond the duration of the train itself. Depending on stimulation frequency, rTMS can exert facilitatory or suppressive effects on the stimulated cortex. In healthy subjects, low-frequency rTMS (1 Hz) has been demonstrated to generally induce a lasting decrease in motor (Chen *et al.* 1997) and visual (Boroojerdi *et al.* 2000*a*) cortical excitability, while high-frequency stimulation has been observed to generally increase excitability of the motor cortex (Pascual-Leone *et al.* 1994) Such rTMS-induced changes in cortical excitability are probably dependent on the pre-existing level of excitability. For example, 1 Hz rTMS delivered to the visual cortex of migraineurs with aura has a paradoxical facilitatory effect (Brighina *et al.* 2002) (decreased PT that can last for about 30 min). This has been related to the interictal hyperexcitability state of the visual cortex in migraine with aura due to a failure of inhibitory circuits, which are unable to be upregulated by low-frequency TMS. Similar paradoxical effects were found in motor cortex by Ziemann *et al.* (1998*a*) who showed that low-frequency (0.1 Hz) rTMS can induce a strong facilitatory influence when delivered in conditions of increased cortical excitability following transient forearm deafferentation.

Deafferentation, i.e. transient or irreversible deprivation of peripheral stimuli, leads to prominent changes in the organization and excitability of the corresponding cortical area (Pettet & Gilbert, 1992; Merzenich & Jenkins, 1993; Ziemann *et al.* 1998*a*,*b*; Werhahn *et al.* 2002). In blind individuals, visual hallucinations have been interpreted as

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due to the hyperexcitability of cortical circuits following sensory deprivation (Fernandez *et al.* 1997; Merabet *et al.* 2004). Suppression of visual hallucinations in a partially blind subject by means of occipital rTMS, presumably through modulation of cortical excitability, has been recently reported (Merabet *et al.* 2003). Transient light deprivation (LD) results in physiological and functional changes in the human visual cortex. They consist in a rapid increase of cortical excitability, expressed as a reduction of PT and enhanced activation to incoming visual input on functional magnetic resonance imaging (Boroojerdi *et al.* 2000*b*). The aim of the present study was to explore how low- and high-frequency rTMS modulate visual cortical excitability when applied to light-deprived visual cortex, in order to enhance our understanding on the impact of input deprivation on cortical excitability in the adult human brain.

Methods

Subjects

Twelve healthy subjects (eight male, four female; aged 41 ± 10.5 years) were enrolled, but only six with reliable phosphenes participated in the study. None of the subjects had a history of migraine, or any visual abnormalities on neuro-ophthalmological examination. All had normal visual acuity and none were taking any drugs. All were naïve to the experimental purposes. Subjects were instructed on experimental conditions and techniques, and gave their informed consent prior to entering the study, which had been approved by the local ethics committee.

Test–retest reliability of phosphene perception was assessed in a preliminary investigation. Only subjects perceiving phosphenes with high reproducibility participated in the study. The subjects underwent three sessions of complete LD for 60 min on three different days. On one of the days, they received low (1 Hz)-frequency rTMS in the last 15 min of LD. On another day they received high (10 Hz)-frequency rTMS in the last 15 min of LD. On the third day, they were not exposed to any rTMS. The order of these three sessions was randomized and counterbalanced across subjects using a Latin square design. Changes of visual cortex excitability were serially assessed by means of PT.

Magnetic stimulation

PT assessment. All experiments were conducted in a darkened room and the subjects were blindfolded to accomplish total darkness (they did not report any light perception). To avoid nonspecific effect of drowsiness, during LD the examiner monitored subjects' alertness by frequently requesting that the subjects report their sensations. Subjects wore a tight-fitting plastic swimmer's cap marked with a grid of 3×3 points, with each point 2 cm apart, centred over Oz (international 10/20 system). A Cadwell high-frequency magnetic stimulator equipped with a 9 cm water-cooled figure-of-eight coil delivering magnetic stimuli with monophasic configuration (pulse width of 200 μs) was used. The coil was placed, with its handle pointing upward, so as to induce a current flowing in a craniocaudal direction. The starting position of the coil was in the midline 2 cm above the inion, and subsequently it was shifted laterally to both sides until the optimum point for induction of phosphenes was found. This point was marked on the swimmer's cap in order to maintain a constant coil position during the experiment. The correct position was monitored by using a small flash light. Paired stimuli with 50 ms interstimulus intervals were used to induce phosphenes. This double pulse stimulation was chosen on the basis of previous experiments (Boroojerdi *et al.* 2001; Brighina *et al.* 2002). Magnetic stimulation was started at an intensity of 30% of the maximum stimulator output, and then increased in 2% steps until phosphenes could be elicited, or until a maximum of 100% intensity of stimulation was reached. PT was defined as the minimum intensity required for evoking phosphenes in three of five trials. Average of between six and seven trials were needed for each PT assessment. The intertrial interval was not fixed, but it was not less than 10 s.

rTMS (1 and 10 Hz). rTMS was applied to the optimal scalp position for induction of phosphenes after 45 min LD, at a PT intensity as assessed before LD. One hertz rTMS (900 stimuli) was delivered continuously for 15 min, and 10 Hz rTMS (900 stimuli) was delivered in trains of 50 stimuli separated by 45 s intervals (15 min).

Phosphene reliability

Only subjects with reliable phosphenes limited to exposure to real TMS were eligible for the study. Phosphenes had to be experienced in the visual field contralateral to the stimulated hemisphere at least 80% of the time upon repeated TMS of the same point. Sham TMS, tilting the coil 90% degree with respect to the scalp, had to fail to induce phosphenes.

Main experiment

Subjects that met the phosphene reliability criteria (four males, two females; mean age: 38 ± 9 years) participated in the experiment. They underwent five experimental sessions with at least 1 day interval between sessions.

Sessions 1–3. Subjects underwent 60 min LD. In session 1, no rTMS was applied (baseline condition). In the other

two sessions, rTMS was applied after 45 min LD at low frequency or high frequency.

In all sessions PT was measured before LD (T_0), after 45 min (T_1) and 60 min of LD (T_2), and then every 10 min after light re-exposure until PT came back to baseline value (T_0). The time to recover baseline PT (recovery time) was also recorded. Each PT assessment took no more than a few minutes. A time schedule of the overall experiment is summarized in Fig. 1.

Sessions 4–5. Subjects underwent two further control experiments without LD but with exposure to low-frequency (session 4) or high-frequency (session 5) rTMS. The order of sessions 4 and 5 was also counterbalanced across subjects. PT was measured just before and after rTMS. Time to recover baseline PT values after rTMS was recorded by measuring PT at 10 min intervals.

The order of the two groups of sessions (1–3; 4–5) was counterbalanced across subjects.

Statistical analysis

Repeated measures ANOVA was used to compare PT values at different times and between different experimental sessions. Intraindividual variability (reproducibility) of PT measures at T_0 and T_1 in the different sessions was analysed by means of test–retest reliability (Cronbach alpha coefficient).

Recovery times were compared by means of one-way ANOVA.

Results

Phosphene perception and reliability

Eight out of 12 subjects (66%) participating in the study reported phosphenes induced by TMS. Phosphenes met reliability criteria (see above) in six subjects, who went on to complete the experiment.

Main experiment

Experimental sessions 1–3. rTMS was well tolerated and no subjects reported phosphene perception during the trains.

Repeated measures ANOVA with times (T_0, T_1 and T_2) and conditions (baseline, 1 Hz and 10 Hz rTMS) as within subject factors showed a significant interaction main effect ($F_{4,2} = 7.70$; $P < 0.0006$). *Post-hoc* analysis (Duncan) revealed that PT was significantly reduced after 45 min LD (T_1 *versus* T_0) in sessions 1–3 (baseline: $P < 0.001$; 1 Hz and 10 Hz rTMS: $P < 0.01$). Further significant reduction of PT values was observed after 60 min LD (T_2 *versus* T_1) in the baseline ($P < 0.01$) and 1 Hz rTMS conditions ($P < 0.005$); however, 1 Hz rTMS did not change PT level with respect to baseline. Opposite changes were induced by 10 Hz rTMS that significantly increased PT values (T_2 *versus* T_1: $P < 0.01$) (Fig. 2*A*). Figure 2*B* displays the individual values. Repeated PTs at T_0 and T_1 showed high test–retest reliability related to the three measurements for each subject (T_0: alpha coefficient = 0.966; T_1: alpha coefficient = 0.990). Mean time to recover T_0 PT values after light re-exposure was about 30 min in the baseline condition. One-way ANOVA for recovery time in the experimental sessions 1–3 (baseline, 1 Hz and 10 Hz rTMS) showed a significant main effect: $F_{2,8} = 39.24$; $P < 0.0001$. Duncan *post-hoc* analysis demonstrated significant opposite effects by the different rTMS frequencies: as compared with the baseline condition, recovery time was increased by 1 Hz ($P < 0.01$) and decreased by 10 Hz rTMS ($P < 0.001$) (Fig. 3). Overall PT changes at different times during LD and light re-exposure are displayed in Fig. 4.

Control sessions 4–5. In control sessions 4 and 5, repeated measures ANOVA with rTMS frequency (1 Hz and 10 Hz) and times (before and after TMS) as within subject factors showed a significant main effect of the interaction: $F_{2,10} = 12.45$ $P < 0.005$. As shown by Duncan *post-hoc* analysis, PT values were significantly increased by 1 Hz ($P < 0.05$) and decreased by 10 Hz rTMS ($P < 0.05$) (Fig. 5). Mean PT recovery time was 30 min for 1 Hz and 15 min for 10 Hz rTMS.

Discussion

Our results reproduce those of Boroojerdi *et al.* (2000*b*) regarding changes in visual cortical excitability with relatively short-lasting light deprivation. Furthermore, we

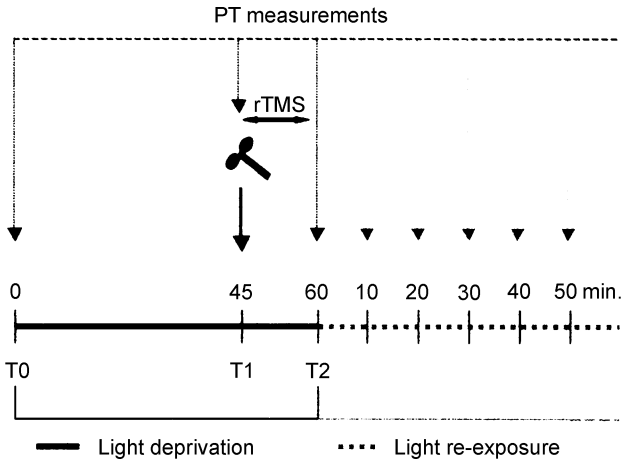

Figure 1. Time schedule of the experiments including phosphene threshold (PT) measures and repetitive transcranial magnetic stimulation (rTMS)

provide novel insights demonstrating that the altered excitability of the visual cortex following LD in normal subjects can be differentially modulated by different rTMS frequencies. The usual effect of 1 Hz rTMS is to decrease cortical excitability while, though to a lesser extent, 10 Hz increases cortical excitability. In our study, opposite modulatory effects of low- and high-frequency rTMS were observed. Following light-deprivation, 1 Hz rTMS sustains the increased sensitivity of visual cortex, prolonging the induced changes in PT. Conversely, 10 Hz frequency rTMS decreases sensitivity of visual cortex, significantly increasing PT values during LD and shortening recovery of baseline excitability soon after light re-exposure.

We hypothesize that the paradoxical effects of rTMS in our study must be related to the LD-induced changes in cortical excitability prior to the exposure to rTMS.

It has been suggested that under normal cicumstances the glutamatergic system is tonically inhibited by GABA (Schroeder *et al.* 1997). In this condition, low-frequency rTMS generally exerts inhibitory effects, probably upregulating inhibitory circuits (Boroojerdi *et al.* 2000*a*), whereas high-frequency rTMS has facilitatory effects likely to be acting on excitatory circuits. The mechanisms underlying plasticity induced by deprivation of sensory inputs are still unclear, but they seem to include the unbalance of cortical inhibition and excitation involving several neurotransmitter circuits such as GABA, NMDA and muscarinic pathways (Ziemann *et al.* 1998*b*; Boroojerdi *et al.* 2001; Philpot *et al.* 2001). A central role appears to be played by GABA: GABA levels and GAD (glutamic acid decarboxylase, the key enzyme in the synthesis of GABA) are reduced in the deafferentated cortex (Jones, 1993), as are $GABA_A$ receptors and synapse efficacy (Kilman *et al.* 2002). Additionally, synaptic plasticity in the visual cortex requires activation of NMDA receptors and is favoured by reduced GABAergic inhibition (Artola & Singer, 1987).

Pharmacological evidence supports the hypothesis of GABA involvement, together with other neurotransmitters, in plastic changes induced by functional deafferentation in humans. In particular, drugs which enhance GABA function inhibit the effects of sensory deprivation in visual (Boroojerdi *et al.* 2001) and motor cortex (Ziemann *et al.* 1998*b*), while blockade of GABA receptors, enhances plastic changes in deafferentated cortex (Jacobs & Donoghue, 1991; Chowdhury & Rasmusson, 2002, 2003).

Taken together, these findings suggest that the involvement of GABAergic inhibition, NMDA receptor activation and cholinergic transmission are operating in

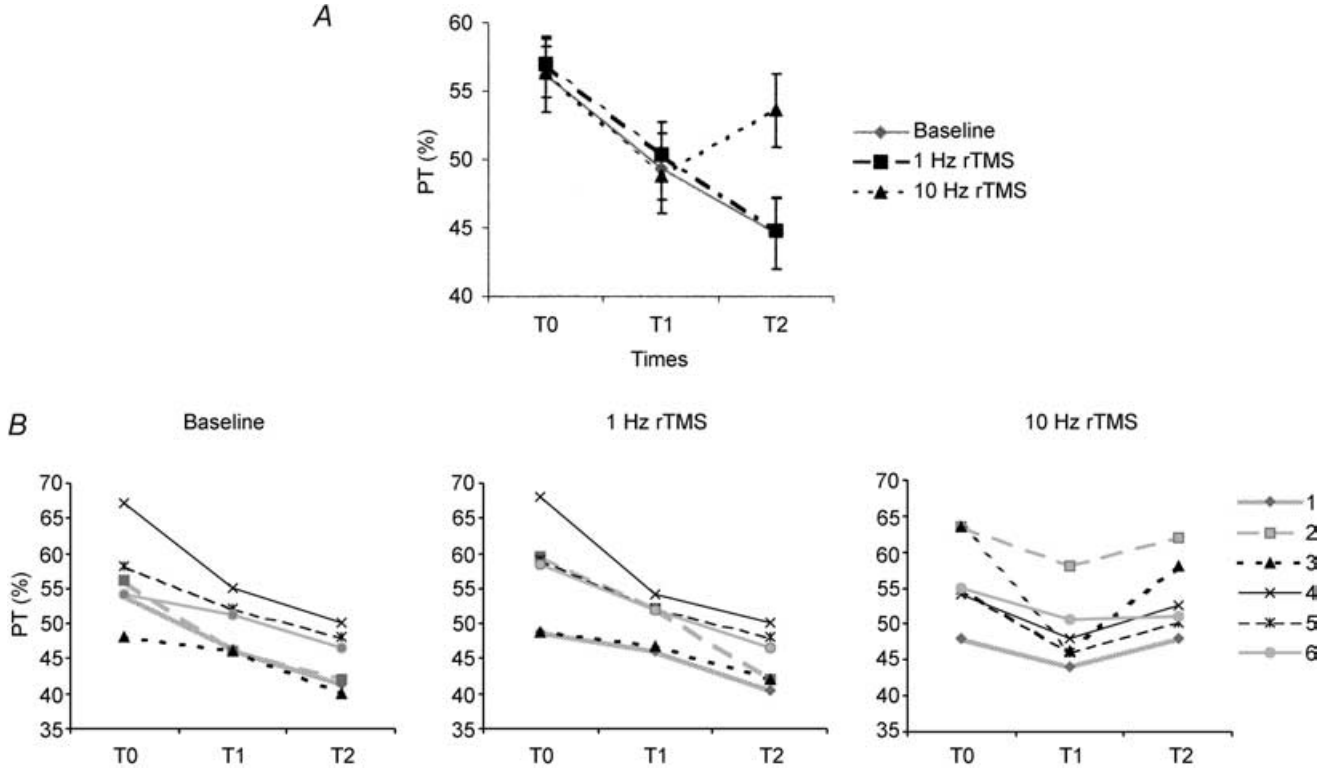

Figure 2. PT changes during LD in baseline and after rTMS
A, mean PT (±S.E.M.) changes during light deprivation (LD) in baseline and after 1 and 10 Hz rTMS (T_1 *versus* T_0: baseline $P < 0.001$; 1 Hz and 10 Hz: $P < 0.01$. T_2 *versus* T_1: baseline $P < 0.01$; 1 Hz $P < 0.005$; 10 Hz $P < 0.01$). *B*, individual PT values (six subjects) in the same experimental conditions. Overall PT values are expressed as percentages of maximal stimulator output.

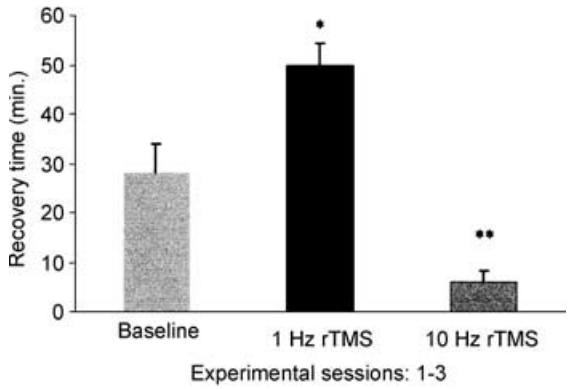

Figure 3. PT recovery times after light re-exposure
Mean recovery times (±S.E.M.) after light re-exposure in baseline, and after 1 and 10 Hz rTMS (*$P < 0.01$, **$P < 0.001$ *versus* baseline).

rapid, experience-dependent plasticity in the human visual cortex. These effects are interpreted as secondary to the unmasking of pre-existent excitatory connections, which normally are supposed to be blocked by local inhibitory circuits.

When a failure of inhibitory circuits occurs, i.e. after functional deafferentation, the slight depolarization of postsynaptic membrane, removing Mg^{2+} ions from NMDA receptors, is able to prime the LTP phenomenon. In this condition, the loss of balance between facilitatory and inhibitory circuits might invert the stimulation frequency-dependent effects of rTMS on cortical excitability. In particular, the functional suppression of inhibitory circuits in the light-deprived visual cortex could allow a facilitatory effect even when low-frequency rTMS is applied. This is in agreement with the effects of rTMS on deafferentated motor cortex (Ziemann *et al.* 1998*a*), and seems to further support the hypothesis that the TMS findings in migraineurs with aura may be due to the reduction in interictal inhibition in their visual cortex (Brighina *et al.* 2002). More recently, Siebner *et al.* (2004) demonstrated that preconditioning corticospinal excitability with transcranial direct current stimulation over the M1 can modulate the direction of plasticity induced by subsequent administration of 1 Hz rTMS. The authors concluded that the plastic changes induced by 1 Hz rTMS critically depend on the functional state of the stimulated cortex before and at the time of rTMS conditioning.

In the present study, PT values were significantly decreased after 60 min of LD and were not modified by 1 Hz rTMS. This stimulation frequency, however, induced a significant prolongation of the cortical hyperexcitability state induced by the LD as indexed by the longer time needed to recover the baseline PT after light re-exposure. This effect is interpreted as an rTMS-induced potentiation of the impact of LD on cortical excitability and may be due to a strengthening of the excitatory synapses. However, further suppression of inhibitory circuits cannot be excluded. The ability of high-frequency rTMS to restore normal excitability of the visual cortex following LD seems harder to explain. In the setting of LD-induced enhanced excitability, high-frequency rTMS seems to act preferentially by upregulating inhibition. In this respect, it seems worth noting that the effects of 10 Hz rTMS during LD are similar to those induced by light re-exposure. In both conditions, a rapid recovery of GABA function could play a role in restoring PT baseline levels.

The effect of high-frequency rTMS on the silent period (SP), a measure of intracortical inhibition (Berardelli *et al.* 1999), also supports upregulation of inhibitory circuits. During muscle contraction (a condition of

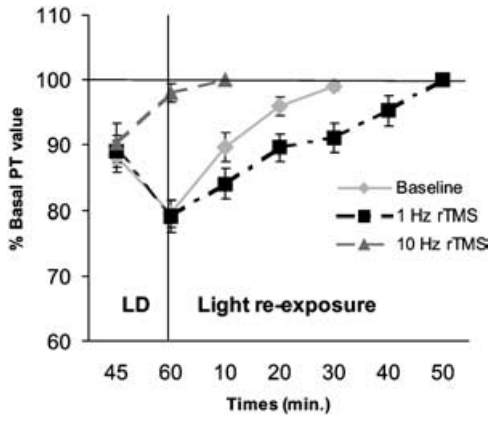

Figure 4. Overall PT changes during LD and light re-exposure
Mean PT changes(±S.E.M.) as percentages of T_0 values during LD and after light re-exposure in sessions 1–3 (baseline, 1 and 10 Hz rTMS conditions). PT values are expressed as percentages of maximal stimulator output.

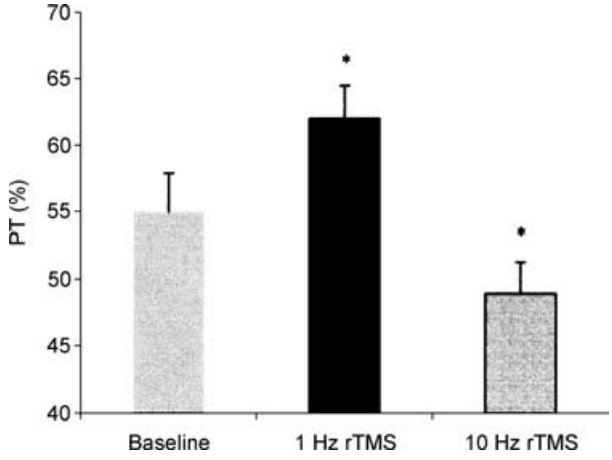

Figure 5. PT changes in control experiments
Mean PT (±S.E.M.) values in control conditions, i.e. without LD (sessions 4 and 5) before and after 1 and 10 Hz rTMS (*$P < 0.05$ *versus* baseline). PT values are expressed as percentages of maximal stimulator output.

increased motor cortex excitability), high-frequency rTMS potentiates inhibitory circuits, increasing SP duration. A possible explanation is that in a condition of hyperexcitability, when excitatory circuits reach a ceiling of activation and cannot be further upregulated, high-frequency rTMS may paradoxically potentiate inhibitory circuits. Other suggestions of upregulation of inhibitory circuits by high-frequency rTMS in pathological conditions might come from studies in Parkinson's disease (Siebner *et al.* 2000; Gilio *et al.* 2002), where a reduced cortical inhibition has been repeatedly reported, along with a reduced cortical activation (Cantello *et al.* 2002). Here, SP duration is increased during (Gilio *et al.* 2002) or after (Siebner *et al.* 2000) 5 Hz rTMS trains arguing in favour of a facilitatory effect of high-frequency rTMS also on intracortical inhibition.

The relationship between TMS-evoked phosphenes and visual function is not fully understood. Indeed we do not know exactly which neuronal elements or mechanisms are involved in phosphene perception. Pascual-Leone & Walsh (2001) suggested that feedback–feedforward loops between secondary and primary visual areas have to be sufficiently activated to generate phosphene perception.

However, we know that after low-frequency rTMS of the occipital cortex, visual evoked potentials are modulated (Thut *et al.* 2003; Schutter & van Honk, 2003) in a manner similar to the changes induced in PT (Boroojerdi *et al.* 2000*a*). Therefore, even though insufficiently studied, the modulatory effects of rTMS on visual cortex excitability may follow similar rules than those that apply to motor cortex rTMS.

We applied rTMS at PT intensity as assessed before LD. Even if lower intensity is needed to elicit phosphenes with paired stimuli (as used for PT assessment) compared to single pulse, PT decreased after 45 min LD. Therefore it cannot be excluded that rTMS was at threshold or slightly suprathreshold to elicit phosphenes. However, subjects did not report any phosphene perception during rTMS, as could be expected in particular with 10 Hz frequency. The lack of the effect might depend on the rapid, paradoxical increasing of PT by high-frequency train during LD, likely to be dependent on upregulation of inhibitory circuits.

In any case, in our experiment, comparison of control sessions 4 and 5 with sessions 2 and 3 demonstrates that the same rTMS parameters can induce significantly different modulations in the face of functional deafferentation of the targeted cortical site of stimulation.

The modulatory effect of different frequencies of rTMS may be facilitatory or inhibitory depending on inter-individual variability, duration, intervals and intensity of train stimulation (Maeda *et al.* 2000*a*,*b*). Therefore, one could make the point that the observed facilitatory or inhibitory effects may be attributable to the interindividual variability or to the spurious variation in other parameters (e.g. duration, threshold intensity) rather than to a more fundamental mechanism. We believe that this is highly unlikely since each subject underwent all experimental sessions, and rTMS parameters (threshold intensity and duration of the trains) were kept constant across rTMS frequencies for each subject. In addition, it is worth noting that in our study subjects also exhibited a low intra-individual variability as documented by the very consistent effect of LD on PT across repeated sessions.

Nevertheless, it should be noted that we studied only half of the normal subjects screened, and the selected subjects, with highly reliable phosphenes induced by TMS, may not be representative of a larger population. However, to our knowledge, no peculiar physiological properties of the visual cortex distinguish subjects with reliable phosphenes from those who do not perceive phosphenes induced by TMS.

In conclusion, the present study suggests that the lasting effects of rTMS trains depend on the functional state of cortical inhibitory and facilitatory circuits. Physiological mechanisms underlying rTMS modulation of visual cortex remain at present purely speculative, and direct measures in suitable animal model or with combined application of rTMS and other brain imaging methods are needed. However, it seems that findings in motor cortex parallel our results in the visual cortex, and suggest a fundamental property that may not be limited to rTMS, but one which is applicable to other forms of neuromodulation across brain regions.

References

Afra J, Mascia A, Gerard P, Maertens de Noordhout A & Schoenen J (1998). Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. *Ann Neurol* **44**, 209–215.

Artola A & Singer W (1987). Long-term potentiation and NMDA receptors in rat visual cortex. *Nature* **330**, 649–652.

Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P & Ramadan MN (1998). Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. *Neurology* **50**, 1111–1114.

Berardelli A, Inghilleri M, Gilio F, Romeo S, Pedace F, Currà A *et al.* (1999). Effects of repetitive cortical stimulation on the silent period evoked by magnetic stimulation. *Exp Brain Res* **125**, 82–86.

Boroojerdi B, Battaglia F, Muellbacher W & Cohen LG (2001). Mechanisms underlying rapid experience-dependent plasticity in the human visual cortex. *Proc Natl Acad Sci U S A* **98**, 14698–14701.

Boroojerdi B, Bushara KO, Corwell B, Immisch I, Battaglia F, Muellbacher W *et al.* (2000*b*). Enhanced excitability of the human visual cortex induced by short-term light deprivation. *Cereb Cortex* **10**, 529–534.

Boroojerdi B, Prager A, Muellbacher W & Cohen LG (2000*a*). Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. *Neurology* **54**, 1529–1531.

Brighina F, Piazza A, Daniele O & Fierro B (2002). Modulation of visual cortex excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. *Exp Brain Res* **145**, 177–181.

Cantello R, Tarletti R & Civardi C (2002). Transcranial magnetic stimulation and Parkinson's disease. *Brain Res Rev* **38**, 309–327.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallet M *et al.* (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* **48**, 1398–1403.

Chowdhury SA & Rasmusson DD (2002). Comparison of receptive field expansion produced by $GABA_A$ and $GABA_B$ receptor antagonists in raccoon primary somatosensory cortex. *Exp Brain Res* **144**, 114–121.

Chowdhury SA & Rasmusson DD (2003). Corticortical inhibition of peripheral inputs within primary somatosensory cortex: the role of $GABA_A$ and $GABA_B$ receptors. *J Neurophysiol* **90**, 851–856.

Fernandez A, Lichtstein G & Vieweg WV (1997). The Charles–Bonnett syndrome: a review. *J Nerv Ment Dis* **185**, 195–200.

Gilio F, Currà A, Inghilleri M, Lorenzano C, Manfredi M & Berardelli A (2002). Repetitive magnetic stimulation of cortical motor areas in Parkinson's disease: implications for the pathophysiology of cortical function. *Mov Disord* **17**, 467–473.

Jacobs KM & Donoghue JP (1991). Reshaping the cortical motor map by unmasking latent intracortical connections. *Science* **251**, 944–947.

Jones EG (1993). GABAergic neurons and their role in cortical plasticity in primates. *Cereb Cortex* **3**, 361–372.

Kilman V, van Rossum MCW & Turrigiano GC (2002). Activity deprivation reduces miniature IPSC amplitude by decreasing the number of postsynaptic $GABA_A$ receptors clustered at neocortical synapses. *J Neurosci* **22**, 1328–1337.

Maeda F, Keenan JP, Tormos JM, Topka H & Pascual-Leone A (2000*a*). Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortico-spinal excitability. *Exp Brain Res* **133**, 425–430.

Maeda F, Keenan JP, Tormos JM, Topka H & Pascual-Leone A (2000*b*). Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol* **111**, 800–805.

Merabet L, Kobayashi M, Barton J & Pascual-Leone A (2003). Suppression of complex visual allucinatory experiences by occipital transcranial magnetic stimulation: a case report. *Neurocase* **9**, 436–440.

Merabet L, Maguire D, Warde A, Altruescu K, Stickold R & Pascual-Leone A (2004). Visual hallucinations during prolonged blindfolding in sighted subjects. *J Neuroophthalmol* **24**, 109–113.

Merzenich MM & Jenkins WM (1993). Reorganization of cortical representation of the hand following alterations of skin inputs induced by nerve injury, skin island transfers, and experience. *J Hand Ther* **6**, 89–104.

Pascual-Leone A, Tormos JM, Keenan J & Catala MD (1998). Study and modulation of cortical excitability by repetitive transcranial magnetic stimulation. *J Clin Neurophysiol* **15**, 333–343.

Pascual-Leone A, Vall-Solé J, Wassermann EM & Hallet M (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* **117**, 847–858.

Pascual-Leone A & Walsh V (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* **292**, 510–512.

Pettet MW & Gilbert CD (1992). Dynamic changes in receptive-field size in cat primary visual cortex. *Proc Natl Acad Sci U S A* **89**, 8366–8370.

Philpot BD, Sekhar AK, Shouval HZ & Bear MF (2001). Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. *Neuron* **29**, 157–169.

Schroeder CE, Javitt DC, Steinschneider M, Mehta AD, Givre SJ, Vaughan HG *et al.* (1997). *N*-methyl-D-aspartate enhancement of plastic responses in primate neocortex. *Exp Brain Res* **114**, 271–278.

Schutter DJLG & van Honk J (2003). Reductions in CI amplitude after repetitive transcranial magnetic stimulation (rTMS) over striate cortex. *Brain Res Cogn Brain Res* **16**, 488–491.

Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN *et al.* (2004). Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci* **24**, 3379–3385.

Siebner HR, Mentschel C, Auer C, Lehner C & Conrad B (2000). Repetitive transcranial megnetic stimulation causes a short-term increase in the duration of the cortical silent period in patients with Parkinson's disease. *Neurosci Lett* **284**, 147–150.

Thut G, Theoret H, Pfenning A, Eves J, Kampmann F, Northoff G *et al.* (2003). Differential effects of low-frequency rTMS at the occipital pole on visual-induced alpha desynchronization and visual evoked potentials. *Neuroimage* **18**, 334–347.

Werhahn KJ, Mortensen J, Kaelin-Lang A, Boroojerdi B & Cohen LG (2002). Cortical excitability changes induced by deafferentation of the controlateral hemisphere. *Brain* **125**, 1402–1413.

Ziemann U, Corwell B & Cohen LG (1998*a*). Modulation of plasticity in human motor cortex after ischemic nerve block. *J Neurosci* **18**, 1115–1123.

Ziemann U, Hallet M & Cohen LG (1998*b*). Mechanisms of deafferentation-induced plasticity in human motor cortex. *J Neurosci* **18**, 7000–7007.