

## Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex

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1. Intracortical inhibition (ICI) and facilitation (ICF) of the human motor cortex can be induced by paired transcranial magnetic stimulation (TMS). Although demonstrated in experimental animals, the existence of intracortical inhibitory and excitatory circuits in parietal sensory cortex has not been documented in humans. The aim of this study was to investigate the effects of paired TMS of the parietal cortex on contralateral tactile perception.
2. Fifteen healthy subjects were involved in a task of discrimination of electrical stimuli delivered at near-threshold intensity of sensory perception over the left thumb. Paired TMS was delivered with a focal coil on the right posterior parietal lobe after various delays from the presentation of finger stimuli. The effects of different interstimulus intervals (ISI: 1, 3, 5, 7, 10 and 15 ms) between the conditioning and the test TMS stimulus on tactile perception were studied. The conditioning stimulus intensity was set at 70% of motor threshold, while test TMS intensity was 130% of motor threshold.
3. Single pulse suprathreshold TMS interfered with the perception of finger stimuli, while subthreshold stimuli such as the 'conditioning' stimuli had no effect on sensory perception. Paired TMS differentially influenced the performance depending on the ISI. At an ISI of 1 ms, paired TMS stimuli induced a significant worsening of the performance compared with single pulse TMS; at an ISI of 5 ms, paired TMS stimuli induced a significant facilitation of the performance compared with single pulse TMS, restoring baseline performance levels.
4. These results suggest that paired TMS can reveal a selective pattern of ICI and ICF in the human parietal cortex.

Since its first description (Kujirai *et al.* 1993), paired transcranial magnetic stimulation (TMS), with a conditioning–test protocol, has been applied over the motor cortex, where it provides an indication of the excitability of the neuronal circuits underlying intracortical inhibition and facilitation. In particular, paired TMS has been used to study motor intracortical circuits in normal humans performing different tasks (Liepert *et al.* 1998), as well as in patients with various neurological disorders (Ridding *et al.* 1995*a,b*; Brown *et al.* 1996; Cohen *et al.* 1998; Ziemann *et al.* 1998*a*; Rossini & Rossi, 1998 (review); Liepert *et al.* 2000).

In normal subjects, the test motor potential (motor evoked potential; MEP) evoked in the intrinsic hand muscles is inhibited by a conditioning subthreshold stimulus at short interstimulus intervals (ISI) of between 1 and 5 ms (intracortical inhibition, ICI), while with longer ISIs of

8–15 ms, the test responses are facilitated (intracortical facilitation, ICF) (Kujirai *et al.* 1993; Ridding *et al.* 1995*a,b*; Ziemann *et al.* 1996; Shimizu *et al.* 1999). The inhibition has been assumed to reflect the activity of a subset of intracortical GABAergic interneurons (Ridding *et al.* 1995*a,b*; Ziemann *et al.* 1996), while less is known of the mechanisms underlying the MEP facilitation, which is also likely to be at least partly cortical in origin (Ziemann *et al.* 1996; Nakamura *et al.* 1997; Liepert *et al.* 1997).

Anatomical studies in experimental animals indirectly suggest that this pattern of intracortical connections could extend outside the motor areas to the level of parietal sensory cortex (Huntsman *et al.* 1995; Salin & Prince, 1996). On the other hand, there are no TMS studies directly documenting the existence of inhibitory, as well as excitatory, interactions within the parietal cortex itself in

normal humans. A possible way to address this question, at least in part, could be to investigate the effects of paired *vs.* single pulse TMS of the parietal cortex on the perception of contralateral finger stimuli. In fact, it has been reported that single pulse TMS of the sensorimotor cortex can reduce the perception of a threshold cutaneous stimulus from the fingers of the contralateral hand (Cohen *et al.* 1991; Seyal *et al.* 1992; Oliveri *et al.* 1999). Although the physiological basis of this action is not yet fully understood, it has been hypothesised that the induced current could act by adding a random 'noise' and disrupting activity in the context of the targeted cortical region involved in the perceptual task (Oliveri *et al.* 1999). This means that the stimulus-linked tactile deficits do not imply cortical inhibition *per se* (Pascual-Leone *et al.* 1999). In this scenario, paired TMS protocols could represent a useful tool for combining this interfering mechanism of action (as induced by the single test stimulus) with distinct facilitatory or inhibitory effects on tactile detection (as determined by the preceding conditioning stimulation applied at various ISIs), provided that they could work at the parietal level in the same fashion as in the motor cortex.

Following this theoretical framework, we aimed to study the recovery cycle to paired TMS of the right posterior parietal cortex in a group of healthy subjects involved in a contralateral tactile discrimination task. According to our working hypothesis, paired TMS with ISIs supposed to enhance the effects of the single disrupting magnetic pulse should be associated with a decrease in tactile perception; in contrast, double TMS pulses with ISIs supposed to attenuate (or even abolish) the effects of the single disrupting magnetic pulse should facilitate, or at least leave unchanged, the pattern of contralateral tactile detection.

## METHODS

### Subjects

Fifteen healthy subjects, five males and ten females, aged 22–34 years, participated in the experiments after providing written, informed consent. All subjects were right-handed, according to the Edinburgh Inventory (Oldfield, 1971). The experimental protocol was approved by the local ethical committee and the experiments were performed according to the Declaration of Helsinki.

### Tactile stimulation

Subjects sat comfortably in an armchair, with their hands supinated and their eye/gaze directed straight ahead.

Electrical tactile stimuli were delivered with pairs of surface electrodes applied around the left thumb (cathode on the first phalanx, anode on the second phalanx). Square-wave pulses, 0.3 ms in duration, were delivered by an electrical stimulator connected via a trigger cable to the magnetic stimulator. Starting with suprathreshold stimuli, the stimulus intensity of the current pulse was gradually decreased until the percentage of stimuli correctly identified by the subject was ranged at about 60–70% of the delivered stimuli. This intensity was then kept constant throughout the experiments.

### Transcranial magnetic stimulation

TMS was performed with two Novamatrix MagStim 200 magnetic stimulators, connected to the same stimulating coil through a BiStim module (The Magstim Company, Dyfed, UK), using a figure-of-eight coil, 70 mm in diameter. The coil was placed tangential to the skull, over a right parietal scalp site corresponding to the P4 position of the 10–20 EEG system, with the handle pointing backwards parallel to the midline, so as to induce a current flowing in a posterior–anterior direction in the underlying brain. This selection of the stimulation sites, according to the EEG scalp electrode co-ordinates, shows some interindividual variability with regard to their correlation with specific brain structures. On the other hand, the anatomical localisation of these positions on brain magnetic resonance imaging scans and a 3-D brain reconstruction, performed in previous studies (Oliveri *et al.* 1999), showed a rough correspondence of the parietal site to the intra-parietal sulcus in the posterior parietal lobe.

The intensity of stimulation was determined relative to the resting motor excitability threshold (ET), defined according to international standards (Rossini *et al.* 1994). The protocol of stimulation was similar to that used by Kujirai *et al.* (1993), with a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS). The CS was set at 70% of the resting ET, while the TS intensity was 130% of ET. Moreover, the TMS threshold for disruption of tactile perception – defined as the minimal TMS intensity able to suppress tactile detection in at least 50% of a sequence of 10 trials – was determined.

### Experimental tasks

The electrical stimulator triggered the Bistim module after various delays (*D*), controlled by a timer, and defined as the time between the onset of the electrical stimulus on the thumb and the onset of the magnetic test stimulation on the brain (TS).

**Experiment 1: effects of the CS alone on contralateral tactile stimulus detection.** In this experiment (see Fig. 1A) the subject's performance during the application of the CS alone over the right parietal cortex (60 trials), was compared with that during a corresponding number of randomly intermingled baseline trials: this was done in order to exclude the possibility that the transcranial conditioning stimulus (including the effects of noise and local – i.e. scalp cutaneous – effects) could be interfering, either *per se* or by influencing the attentional level, with the perception of the finger stimulus. A fixed *D* of 40 ms between tactile stimulation and TMS was used. All of the subjects participated in this experiment.

**Experiment 2: effects of paired parietal TMS at different ISIs on contralateral tactile stimulus detection.** This experiment (see Fig. 1B) was performed in six blocks of 30 trials each, corresponding to six ISIs between the conditioning and the test TMS (1, 3, 5, 7, 10 and 15 ms), with 10 single TS stimuli (130% of ET), 10 paired stimuli and 10 baseline trials randomly intermingled within each block. The order of the blocks was randomised across subjects. A fixed *D* of 40 ms was used. This interval was selected, on the basis of previous experiments (Oliveri *et al.* 1999), as the most effective one for single pulse parietal TMS to disrupt contralateral finger stimuli perception. In fact, it allows the time for impulse arrival to primary somatosensory cortex (about 20–25 ms, as known from the somatosensory evoked potential latency, Rossini *et al.* 1987) and the following evolution of intracortical processing. All of the subjects participated in this experiment.

**Experiment 3: effects of paired parietal TMS at different  $D$  on contralateral tactile stimulus detection.** Eight of the subjects participated in this experiment, performed in order to test the effects of paired parietal TMS as a function of different  $D$  between tactile stimuli and TS. Two ISIs of 1 and 5 ms were tested (Fig. 1C). The experiment consisted of three blocks of 80 trials each (one block for each  $D$ : 10, 20 and 30 ms). Within each block, 10 single TS (130% of ET), 10 single CS (70% of motor threshold), 10 paired stimuli and 10 baseline trials were delivered in random order for each ISI (1 and 5 ms). The order of the blocks was randomised across subjects.

The sequence of the different experimental conditions was performed according to two blocked, computer-based randomisation procedures. The first randomisation was made on the order of the three  $D$  values; the second, executed within each  $D$  block, was run on the eight stimulation conditions, namely baseline, single TS, single CS and paired TMS trials at the two ISIs.

In all experiments, after the presentation of each single or paired stimuli (finger stimulus followed by magnetic pulse(s)), the subject had to indicate whether he/she perceived the tactile stimulus or not.

#### Data analysis

The mean percentage of correct responses was evaluated separately for baseline trials and for those 'conditioned' by single pulse or paired TMS.

In the first experiment, correct response rates in baseline trials were compared with those in trials with the CS alone by means of Student's paired  $t$  test.

In the second experiment, the number of correct responses in the various experimental conditions was analysed with repeated measures ANOVA, with block (ISI: 6 levels) and condition (3 levels: baseline *vs.* single pulse *vs.* paired TMS) as within-subject factors.

In the third experiment, a repeated measures ANOVA was performed on the number of correct responses, with  $D$  (3 levels: 10, 20 and 30 ms), ISI (2 levels: 1 and 5 ms) and condition (4 levels: baseline, single TS, single CS and paired TMS) as within-subject factors. Planned comparisons were applied to test the significance between single factors. In all the statistical tests, the level of significance was set at  $P < 0.05$ .

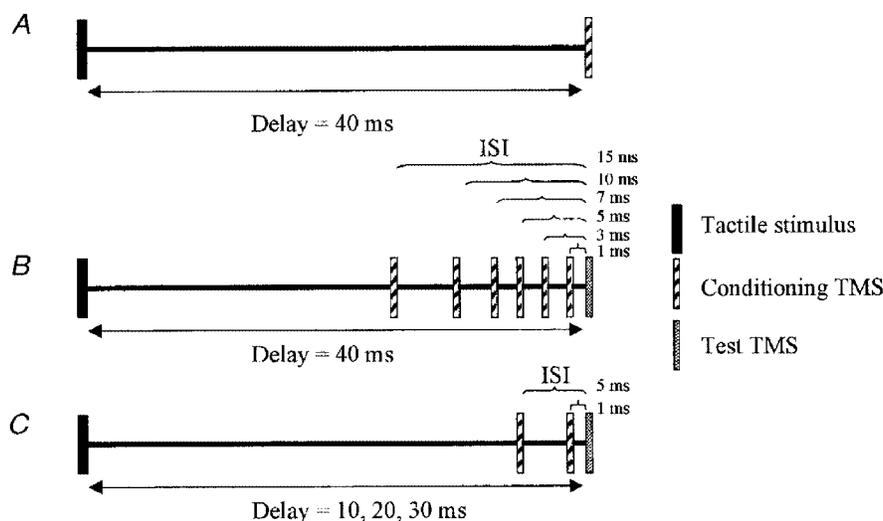
## RESULTS

In all experiments, mean conditioned stimulus intensity was  $38.3 \pm 5.9\%$  and mean test stimulus intensity was  $72.6 \pm 10.3\%$  of the maximal stimulator output. In none of the cases was the applied TMS able to elicit motor twitches or sensory paraesthesias in hand or forearm.

The mean TMS threshold for disruption of tactile perception was  $62 \pm 13\%$ , a value close to the motor threshold intensity ( $55.6 \pm 7.8\%$ ).

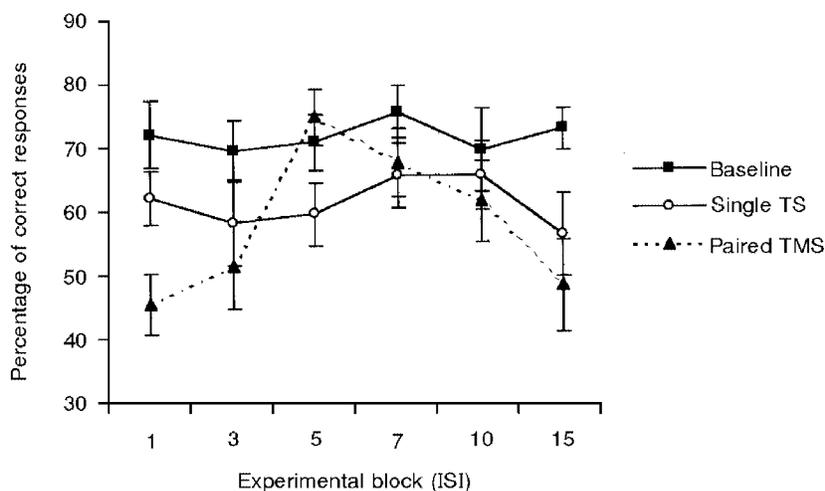
#### Effects of the CS alone on contralateral tactile stimulus detection

The subjects' performance during the application of the CS alone (correct response rate:  $70.5 \pm 17.6\%$ ) was not significantly different from that of the corresponding



**Figure 1. Experimental procedure**

*A*, experiment 1: a single CS was given after a single fixed delay of 40 ms from the tactile stimulus. Baseline trials were randomly intermingled with test trials. *B*, experiment 2: the TS was given after a single fixed delay of 40 ms from the tactile stimulus. The CS preceded the test stimulus at ISIs of 1, 3, 5, 7, 10 and 15 ms in different blocks of trials. Baseline, single TS and paired TMS trials were randomly intermingled within each block. *C*, experiment 3: the TS was given after delays of 10, 20 and 30 ms (in 3 different blocks of trials) from the tactile stimulus. The CS preceded the test stimulus at ISIs of 1 and 5 ms. For each ISI, paired TMS was randomly intermingled with baseline, single CS and single TS trials. In the case of paired TMS trials, the delay indicates the time interval between the onset of the tactile stimulus and the onset of the TS. In the case of single CS and TS trials, the delay indicates the time interval between the onset of the tactile stimulus and the onset of the TMS.



**Figure 2. Experiment 2: mean performance level in the different trials as a function of the experimental block**

Each point represents the mean ( $\pm 1$  s.e.m.) percentage of correct responses (contralateral tactile stimulus detection) during baseline, single pulse and paired TMS trials as a function of the experimental block.

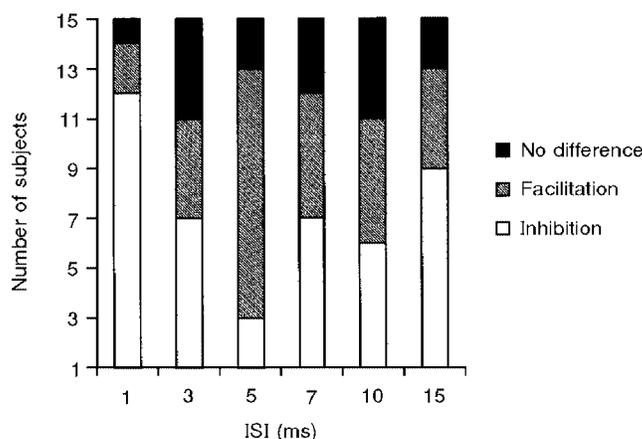
baseline trials (correct response rate:  $72.0 \pm 6.0\%$ ,  $P > 0.05$ , Student's paired  $t$  test).

#### Effects of paired parietal TMS at different ISIs on contralateral tactile stimulus detection

Figure 2 shows the pattern of the correct responses during the different blocks of trials in experiment 2. As can be seen from the figure, the subjects' performance was relatively stable during both baseline and single pulse TMS trials across the six experimental blocks. On the other hand, there was a sharp modification of the performance as a function of experimental block (i.e. ISI) during paired TMS. The above observations were substantiated by ANOVA testing, showing a significant Block  $\times$  Condition interaction ( $F(10,140) = 2.90$ ;  $P = 0.002$ ). Specific effects showed a

significance of the paired TMS condition ( $F(5,70) = 5.76$ ;  $P = 0.0001$ ), whereas both baseline ( $F(5,70) = 0.32$ ;  $P = 0.89$ ) and single pulse TMS conditions ( $F(5,70) = 0.66$ ;  $P = 0.65$ ) were not significant.

In particular, paired TMS induced a significant worsening of the performance compared with single pulse TMS at ISI of 1 ms ( $45.3 \pm 18.8$  vs.  $62.0 \pm 16.5\%$ ;  $F(1,14) = 8.4$ ;  $P = 0.01$ ), while only a slight, non-significant inhibition was observed at an ISI of 3 ms ( $51.3 \pm 27.2$  vs.  $58.0 \pm 25.9\%$ ;  $P > 0.05$ ) and 15 ms ( $48.0 \pm 28.1$  vs.  $56.0 \pm 25.3\%$ ;  $P > 0.05$ ). In contrast, at an ISI of 5 ms, a sharp improvement in the performance level was induced by paired vs. single pulse TMS (correct response rate:  $74.6 \pm 16.8$  vs.  $59.3 \pm 19.1\%$ ;  $F(1,14) = 7.5$ ;  $P = 0.01$ ). For all the other tested ISIs, no significant differences in the



**Figure 3. Pattern of inhibition and facilitation of tactile stimulus detection induced by paired vs. single pulse TMS in experiment 2**

Each column represents the number of subjects (out of 15) in whom an inhibition or a facilitation in the performance was induced by paired vs. single pulse TMS at the various ISIs. 'No difference' indicates the cases of unchanged performance during paired vs. single pulse TMS.

mean percentage of correct responses during paired *vs.* single pulse TMS were observed.

In addition, there was a significant main effect of 'Condition' ( $F(2,28) = 7.30$ ;  $P = 0.003$ ), indicating a different pattern of performance during baseline, single pulse and paired TMS trials, regardless of the experimental block. In fact, the number of correct responses was significantly lower during both single pulse ( $61.0 \pm 21.2\%$ ;  $F(1,14) = 8.07$ ;  $P = 0.01$ ) and paired TMS ( $58.0 \pm 24.9\%$ ;  $F(1,14) = 9.2$ ;  $P = 0.009$ ), compared with baseline trials ( $71.5 \pm 18.2\%$ ). Conversely, there was no significant difference in the overall performance in the six blocks during single pulse *vs.* paired TMS ( $P > 0.05$ ).

The relative distribution of inhibition and facilitation of tactile stimulus detection induced by paired *vs.* single pulse TMS in the various subjects is shown in Fig. 3.

#### Effects of paired parietal TMS (ISIs of 1 and 5 ms) at different $D$ on contralateral tactile stimulus detection

Figure 4*A* and *B* shows the pattern of correct responses in the various experimental conditions of experiment 3, as a function of the time delays separating the presentation of finger stimuli from TMS. Figure 4 shows that, at  $D$  values of 20 and 30 ms, the disrupting effects of the TS were respectively enhanced or attenuated by a CS given at the ISI of 1 ms (Fig. 4*A*) and 5 ms (Fig. 4*B*), similar to that described for a fixed  $D$  of 40 ms. In contrast, at  $D$  of 10 ms, paired TMS was almost ineffective in modulating sensory perception at either ISI.

According to these observations, ANOVA showed a significant main effect of 'Condition' ( $F(3,21) = 13.6$ ;  $P = 0.00004$ ), a lack of significance of the 'Delay' effect ( $F(2,14) = 1.00$ ;  $P = 0.39$ ), and a significant triple interaction 'Delay'  $\times$  'ISI'  $\times$  'Condition' ( $F(6,42) = 5.14$ ;  $P = 0.0005$ ).

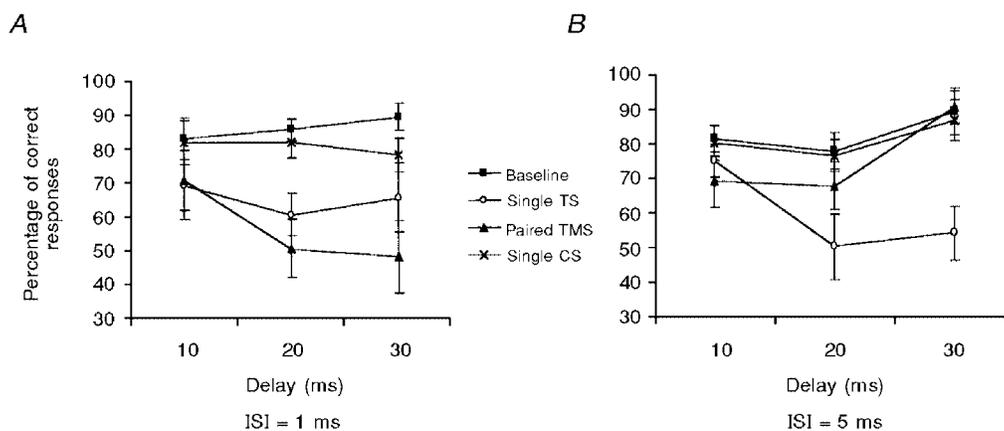
*Post hoc* comparisons revealed that single pulse TMS significantly reduced tactile detection rate *vs.* baseline at  $D$  of 20 ms ( $F(1,7) = 11.4$ ;  $P = 0.01$ ) and 30 ms ( $F(1,7) = 12.8$ ;  $P = 0.009$ ), but not at  $D$  of 10 ms ( $P > 0.05$ ).

In addition, at  $D = 10$  ms, no significant differences of tactile detection were induced by paired *vs.* single pulse TMS, at either ISI ( $P > 0.05$ ). On the other hand, at  $D = 30$  ms, paired TMS with 5 ms ISI significantly improved ( $F(1,7) = 17.6$ ;  $P = 0.004$ ), and paired TMS with 1 ms ISI significantly reduced the performance level ( $F(1,7) = 14.9$ ;  $P = 0.006$ ), compared with single pulse TMS. At  $D = 20$  ms, these effects were reduced: in fact, paired TMS with 5 ms ISI still improved the performance ( $F(1,7) = 5.8$ ;  $P = 0.04$ ), whereas paired TMS with 1 ms ISI failed to significantly alter it ( $P > 0.05$ ).

When considering the overall effects of paired *vs.* single pulse TMS on contralateral tactile detection as a function of  $D$ , there was a significant difference between the delays of 10 and 30 ms, both for the ISI of 1 ms ( $F(1,7) = 28.6$ ;  $P = 0.001$ ) and 5 ms ( $F(1,7) = 12.4$ ;  $P = 0.009$ ). A less significant difference was found between the delays of 10 and 20 ms, at ISI of 1 ms ( $F(1,7) = 3.8$ ;  $P = 0.09$ ) and 5 ms ( $F(1,7) = 5.4$ ;  $P = 0.05$ ). No significant differences were instead observed between the delays of 20 and 30 ms, for either ISI. Finally, the conditioning TMS shocks failed to significantly alter sensory perception at either delay.

## DISCUSSION

The main results of the present study show that paired TMS of the posterior parietal cortex can selectively modulate the perception of tactile stimuli, compared with single pulse TMS, depending on the ISI between the CS and the TS. In particular, a marked inhibition of peripheral sensory detection is observed at an ISI of 1 ms; in contrast, at an



**Figure 4.** Experiment 3: mean performance level in the different trials as a function of the peripheral delay (10, 20 and 30 ms)

Each point represents the mean ( $\pm 1$  s.e.m.) percentage of correct responses during baseline, single CS, single TS and paired TMS trials as a function of the delay between the tactile and the TMS stimuli. *A*, pattern of correct responses in experimental blocks with paired TMS at ISI = 1 ms; *B*, pattern of responses in experimental blocks with paired TMS at ISI = 5 ms.

ISI of 5 ms, paired TMS stimuli induce a transient recovery of the baseline level in tactile stimulus detection rate, which overwhelms the disrupting effect of the single pulse TMS alone.

### Comparisons with paired TMS studies at motor cortical level

Paired TMS techniques have been extensively applied to investigate intracortical inhibition and facilitation in the human motor cortex, in physiological, as well as in pathological conditions (Ridding *et al.* 1995*a,b*; Brown *et al.* 1996; Chen *et al.* 1998; Cohen *et al.* 1998; Ziemann *et al.* 1998*a,b*; Liepert *et al.* 2000). In the present study, in order to verify whether similar physiological principles can be visualised and examined in the parietal cortex, we studied the effects of paired TMS on a psychophysical measure, defined as the subjects' perception of threshold tactile stimuli. It has been previously demonstrated that single pulse TMS over the sensory cortex can suppress both contralateral and ipsilateral tactile finger stimuli perception (Seyal *et al.* 1992; Cohen *et al.* 1998; Oliveri *et al.* 1999). A problem intrinsic to the application of paired TMS in such protocols is therefore to choose a 'conditioning' stimulus intensity adjusted with respect to the level of the TMS threshold for inducing finger stimulus suppression. In this context, it is worth noting that our 'conditioning' stimulus was subthreshold, not only for the motor but also for the sensory cortex, as it did not suppress the perception of contralateral stimuli at all. On the other hand, the 'test' stimulus intensity was well above the threshold both for inducing motor responses and for suppressing tactile perception.

Another aspect to consider in this protocol is the definition and the meaning of 'facilitation'. In fact, differently from what happens at the motor cortical level, a single magnetic shock has a disrupting action on the parietal cortex. This implies that any facilitative effect of the conditioning stimulus on sensory perception could be partly masked by the still present disruption induced by the test stimulus alone. Therefore, the term 'facilitation' should refer to a baseline condition represented by the disrupting effect of single pulse TMS, in addition to the real baseline performance without TMS interference.

Comparing the effects of paired TMS protocols over the parietal cortex with those over the motor area reported in the literature, we showed that the effects of test magnetic shocks were enhanced by conditioning stimuli given at 1 ms ISI, as opposed to the inhibitory interaction reported at motor cortical level with this ISI (Kujirai *et al.* 1993; Ziemann *et al.* 1996; Nakamura *et al.* 1997; Abbruzzese *et al.* 1999). Conversely, the ISI of 5 ms, mostly inhibitory for motor cortex functionality, appears to be the only interval in which the effects of the test shocks are attenuated by conditioning stimuli at the level of the posterior parietal cortex. For this purpose, we excluded the possibility of an order effect of ISI influencing the subjects' performance, by

randomly varying the sequence of the ISIs across subjects. Moreover, during both the baseline and single pulse TMS trials, the subjects' performance did not change across the experimental blocks, thus ruling out any bias due to unspecific modification of performance (i.e. due to attentional level fluctuations) in one block with respect to another.

### Supposed mechanisms of the inhibition and facilitation

Regarding the physiological mechanism of modulation of sensory perception by paired TMS, at present this remains speculative and relies on a comparison with the effects of paired TMS on the motor cortex. At this level, it is known that GABA and dopamine-mediated mechanisms are involved in determining intracortical facilitation and inhibition during paired TMS. GABA cortical neurones are aspiny non-pyramidal neurones, with limited horizontal connections (White, 1989; Jones, 1993). In the motor cortex (area 4), layer II has the highest concentration of GABAergic neurones that largely project to cortical pyramidal cells (Jones, 1993). It has been suggested that paired TMS shocks with short ISIs do not activate GABAergic neurones directly, but instead trigger cortico-cortical pyramidal cells or their collateral axons (Ziemann *et al.* 1996; Liepert *et al.* 1997; Nakamura *et al.* 1997) which, from layer V, project to GABAergic neurones in layer II (White, 1989; Keller, 1993). In contrast, ICF seems to be due to direct activation of corticocortical pyramidal cells and their axons, which extend over wide cortical areas (Huntley & Jones, 1991; Keller, 1993).

Studies on experimental animals suggest that a similar pattern of intracortical circuits and neurotransmitter systems operates at the level of the parietal cortex. In particular, in the rat somatosensory cortex, all anatomically identified pyramidal neurones of layers II–V are able to generate evoked inhibitory, GABA-mediated, postsynaptic currents after intracortical stimulation (Salin & Prince, 1996). This suggests the possibility of selectively activating intracortical GABAergic circuits within parietal areas, which could play a pivotal role in the cortical processing of sensory information.

Our results provide indirect evidence in support of this view. We have in fact observed that some form of inhibitory interaction between CS and TS is occurring in the posterior parietal cortex. At this level, a subthreshold CS could selectively target somatosensory GABAergic intracortical circuits with a time constant of 5 ms, and this inhibitory current flow could attenuate – or even abolish – the disrupting action on sensory perception of the following TS. On the other hand, it cannot be excluded that the conditioning shocks, even if unable to affect task performance when given alone, could have a subliminal effect on sensory perception such that, when followed at short intervals (i.e. 1 ms) by a test stimulus, there would be facilitation between them. This mechanism could explain the significant suppression of tactile perception observed at 1 ms ISI. Paired TMS pulses at all the other tested

interstimulus intervals are probably outside the time window for GABAergic activation and the time constant of the relative circuitry, and seem mostly ineffective in modulating the excitability of parietal neurones. It is also conceivable that neuronal encoding strategies, such as a mean firing rate or temporal patterns of ensemble firing, are shorter during cortical processing of a single and weak tactile stimulus, compared with corresponding firing parameters of motor cortical neurones: this would also contribute to the different pattern of inhibition/facilitation observed in the parietal *vs.* motor cortex.

Several previous reports about paired TMS effects on motor cortical functionality (Kujirai *et al.* 1993; Ziemann *et al.* 1996; Chen *et al.* 1998; Di Lazzaro *et al.* 1998; Ashby *et al.* 1999) support the idea that, even in the parietal brain areas, the inhibitory/excitatory interactions between CS and TS could occur at the cortical level rather than at the spinal cord. Nevertheless, besides intracortical inhibition and facilitation, it is not possible to exclude corticofugal 'gating' mechanisms such as presynaptic effects on the stretch reflex circuitry or postsynaptic effects on propriospinal interneurons, possibly mediated by antidromic activation of sensory fibres from the primary somatosensory cortex (SI). However, the intensity of the CS adopted in the present study was lower than the threshold for propagating corticospinal volleys along pyramidal neurones from the primary motor cortex (M1); therefore, provided that the fibres from SI share the same electrophysiological properties as those arising from M1, the effects of the CS on the parietal areas should remain at a mainly cortical level.

### Effects of different delays between tactile stimuli and TMS

It could be hypothesised that, by using a single delay between the tactile stimulus and the TS, in individual subjects the strong magnetic pulse is acting at a different period of the parietal cortical processing time. This time window could be different from one individual to another, across a limited range of delays. Therefore, when using a single delay, the timing of enhancing or attenuating effects between CS and TS could be influenced by a superimposition of different response curves with respect to the peripheral stimulus. This issue was addressed by experiment 3, showing a comparable pattern of enhancing/attenuating effects of CS on TS – at the two critical ISIs of 1 and 5 ms – across a range of delays compatible with parietal cortical processing time; on the other hand, no significant effects were observed when paired TMS was given before the presumed time of sensory processing (i.e. at 10 ms). In addition, this experiment confirmed the lack of detectable effects of the CS alone on contralateral tactile detection at all the tested delays.

### Applications of paired TMS studies outside motor areas

To our knowledge, this is the first study attempting to test the effects of paired TMS protocols on the parietal sensory

cortex. Paired TMS could be useful in complementing repetitive TMS (rTMS) as a technique able to modulate cortical excitability in different brain areas (Pascual-Leone *et al.* 1998; Paus *et al.* 1998). In fact, a problem involved in studies employing trains of TMS is the poor temporal and spatial resolution of the induced effects. Paired TMS could provide the advantage of being applied with a more definite time window and a more focal spatial extent. This aspect could also make such experimental protocols useful for investigating mechanisms of rapid synaptic plasticity. Decreased inhibition or increased synaptic efficacy of neural circuits, leading to the unmasking of existing but functionally silent connections, is considered a possible mechanism for the rapid plastic modulation of motor or sensory areas in the context of skill acquisition (Ziemann *et al.* 1998a). It can be hypothesised that this kind of rapid cortical plasticity ought to result in changes in intracortical excitability that might be demonstrable using the paired-pulse TMS technique in many cortical regions.

### Conclusions

Paired TMS shocks can demonstrate a selective pattern of inhibition, interrupted by 'relative' facilitation, at the level of the parietal cortex of normal humans. Further studies, employing different experimental protocols and a larger number of ISIs would better elucidate the physiological basis of such findings.

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