Abnormal associative plasticity of the human motor cortex in writer’s cramp

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Summary
Low-frequency median nerve stimulation, paired with suprathreshold transcranial magnetic stimulation (TMS) over the optimal site for activation of the abductor pollicis brevis (APB) muscle induces a long-lasting increase in the excitability of corticospinal output neurons, if median nerve stimulation is given 25 ms before TMS. Here we employed this protocol of stimulation to assess associative plasticity of the primary motor hand area in 10 patients with writer’s cramp and 10 age-matched controls. Motor evoked potentials (MEPs) were recorded from right APB muscle and right first dorsal interosseus (FDI) muscle. Resting and active motor threshold, mean MEP amplitude at rest, short-latency intracortical inhibition (SICI) at an interstimulus interval of 2 ms and the duration of the cortical silent period (CSP) were assessed immediately before and after associative stimulation. In both groups, associative stimulation led to an increase in resting MEP amplitudes which was more pronounced in the right APB muscle. Compared with healthy controls, stimulation-induced facilitation of MEP amplitudes was stronger in patients with writer’s cramp. In addition, only patients showed a slight decrease of resting and active motor thresholds after conditioning stimulation. In both groups, associative stimulation induced a prolongation of CSP in the APB and FDI muscles, that was significant only in the APB muscle in healthy controls. Associative stimulation had no effects on SICI in patients and healthy controls. Taken together, in patients with writer’s cramp, the motor system exhibited an abnormal increase in corticospinal excitability and an attenuated reinforcement of intracortical inhibitory circuits that generate the CSP in response to associative stimulation. This altered pattern of sensorimotor plasticity may favour maladaptive plasticity during repetitive skilled hand movements and, thus, may be of relevance for the pathophysiology of writer’s cramp and other task-specific dystonias.

Keywords: writer’s cramp; plasticity; focal dystonia; TMS; associative stimulation

Abbreviations: AMT = active motor threshold; ANOVA = analyses of variance; APB = abductor pollicis brevis; CSP = cortical silent period; FDI = first dorsal interosseus; ISI = inter-stimulus interval; LTP = long-term potentiation; MEPs = motor evoked potentials; NMDA = N-methyl-D-aspartate; RMT = resting motor threshold; SEPs = somatosensory evoked potentials; SICI = short-latency intracortical inhibition; TMS = transcranial magnetic stimulation

Introduction
Repetitive peripheral sensory stimulation and movements induce plastic changes of the primary sensorimotor cortex in studies of learning and neuroplasticity (Wang et al., 1995; Spengler et al., 1997). Similarly, chronic alteration of afferent inputs in arm amputees can cause a reorganization of in the sensorimotor cortex (Flor et al., 1995). Ablation studies, conducted in monkeys, suggest that afferents from the somatosensory cortex play an important role in the acquisition of new motor skills (Pavlides et al., 1993). One important neural substrate of motor learning is long-term enhancement of synaptic efficacy in the primary motor cortex, caused by repetitive stimulation of somatosensory inputs to the primary motor area (Asanuma and Pavlides, 1997). Topographical specificity is the most peculiar feature of this form of stimulation-induced plasticity as a substantial part of the projections from the somatosensory cortex to the primary motor cortex is organized so that it exhibits high topographical specificity, by connecting homologous somatosensory and motor areas (Rosén and Asanuma, 1972; Caria et al., 1997). The intracortical horizontal fibres may be an ideal...
candidate for the site of such plastic synaptic changes because they play a pivotal role in the enhancement of synaptic efficacy in the primary motor cortex (Donoghue et al., 1996). This hypothesis was substantiated by experiments which demonstrated a strengthening of horizontal connections in cortical layers II and III during the acquisition of a new motor skill (Riout-Pedotti et al., 1998).

Long-term potentiation (LTP) is operationally defined as a long-lasting increase in synaptic efficacy in response to high-frequency stimulation of afferent fibres. The increase in synaptic efficacy persists from minutes to days, and is thus a robust example of a long-term increase in synaptic strength. LTP was first observed in the rabbit hippocampus (Bliss and Lomo, 1973), but has been observed also in numerous brain structures, including the cortex, brain stem and amygdala. LTP is not limited to the mammalian brain, but occurs in other vertebrates such as fish, frogs, birds and reptiles, as well as in some invertebrates (Murphy and Glanzman, 1997). The LTP is called associative, or Hebbian, if it occurs at an input to a post-synaptic cell, conditional on concomitant and synchronous activation of another input to the same cell (Buonomano and Merzenich, 1998).

In a recent paper, Stefan and co-workers (Stefan et al., 2000) reported that they could induce a long-lasting increase in the excitability of cortical output circuits using associative stimulation. The paradigm of stimulation was similar to protocols that were capable of inducing associative (Hebbian) LTP in previous studies on animals and cortical slices. In brief, low-frequency electrical stimulation of the right median nerve was paired with single-pulse transcranial magnetic stimulation (TMS) of the left primary motor hand area. TMS was given to the cranial site that was optimal for stimulating the relaxed abductor pollicis brevis (APB) muscle. When median nerve stimulation preceded the TMS pulse, this associative protocol induced an increase in the amplitudes of the motor evoked potentials (MEPs) in the relaxed APB muscle, as well as a prolongation of the silent period measured in the pre-contraction APB muscle. Excitability changes induced by associative stimulation evolved rapidly (within 30 min) and lasted at least for 30–60 min. Changes in excitability were also topographically specific as excitability changes were restricted to the APB muscle. Moreover, the induction of changes in MEP amplitude strictly followed a temporal Hebbian rule (Wolters et al., 2003) and could be blocked by the N-methyl-D-aspartate (NMDA) receptor antagonist dexamethorphan (Stefan et al., 2002). Based on these findings, Stefan et al. (2000, 2002) proposed that LTP-like mechanisms in the stimulated motor cortex underlie cortical plasticity induced by associative stimulation.

Writer’s cramp forms part of a group of focal task-specific dystonias affecting fine manual skills and is characterized by excessive muscular activation during writing (Marsden and Sheehy, 1990). Focal task-specific dystonias of the hand usually occur in people working under conditions of repetitive skilled movements (e.g. musicians), which are highly demanding in terms of sensorimotor integration (Lim et al., 2001). Although the primary manifestations of task-specific hand dystonia are abnormalities of motor function, there is an increasing evidence of a dysfunction of central sensory processing in writer’s cramp (Tempel and Perlmutter, 1990; Odergren et al., 1996; Tinazzi et al., 2000; Abbruzzese et al., 2001; Sanger et al., 2002; Tamburin et al., 2002). Based on these findings, it has been suggested that abnormal sensorimotor integration might significantly contribute to the pathogenesis of dystonia (Hallett, 1995, 1998; Berardelli et al., 1998; Lim et al., 2001).

Here, we employed the associative stimulation protocol introduced by Stefan et al. (2000) to investigate acute sensorimotor reorganization in patients with writer’s cramp. Using a conditioning-test paradigm, Abbruzzese et al. (2001) found that electric nerve stimulation resulted in an abnormal increase in corticospinal excitability in patients with focal dystonia. Based on this finding, we hypothesized that, in patients with writer’s cramp, the abnormal facilitation caused by sensory stimulation will enhance the response of corticospinal motor circuits to associative stimulation. If so, the altered pattern of plasticity might provide relevant new insights into the pathophysiology of task-specific hand dystonia.

Material and methods

Participants

Ten patients with simple writer’s cramp (five men, five women, age range 25–58 years, mean age 45 years) and 10 healthy subjects (five men, five women, age range 23–57 years, mean age 40 years) were enrolled in the present study. All participants were consistent right-handers according to the Edinburgh handedness inventory (Oldfield, 1971). No patient had a family history of degenerative disorder nor a personal history of cerebrovascular disease. All patients underwent extensive neurological examination, including detailed clinical testing of tactile sensation and position sense of the right hand. The clinical data of dystonic patients are summarized in Table 1.

All participants gave written informed consent according to the declaration of Helsinki. The experimental protocol was approved by the local ethics committee.

Study design

In patients with writer’s cramp and healthy subjects, we stimulated the right median nerve and the left primary motor hand area. The protocol used for associative stimulation was identical to the paradigm published by Stefan et al. (2000). Associative stimulation consisted of suprathreshold electrical stimulation of the right median nerve combined with a suprathreshold magnetic pulse applied over the left primary motor hand area 25 ms after peripheral nerve stimulation. Ninety pairs of stimuli were given every 20 s.
Cortical excitability of the primary motor hand area was probed with single and paired pulse TMS before (referred to as baseline) and after associative stimulation. Motor responses to TMS were recorded from the right APB and first dorsal interosseus (FDI) muscles to explore whether the conditioning effects of associative stimulation were topographically specific. Therefore, our study had a $2 \times 2 \times 2$ factorial study design with the factors: time (before associative stimulation versus after associative stimulation), group (patients versus controls), and muscle (APB muscle versus FDI muscle). All measurements were performed in a single session and the experiment lasted for ~90 min.

### Electromyographic recordings
EMG activity of the right APB and FDI muscles was recorded with Ag–AgCl surface electrodes using a belly-tendon montage. EMG signals were amplified and filtered using a time constant of 3 ms and a high pass filter set at 3 kHz (Neurolog System, Digitimer Ltd, Welwyn Garden City, Herts, UK). Signals were acquired at a rate of 5 kHz (CED 1401 laboratory interface, Cambridge Electronic Design, Cambridge, UK) on a personal computer for off-line analysis.

### Stimulation techniques
All subjects were seated in a comfortable reclining chair. During the experiments EMG activity was continuously monitored with visual (oscilloscope) and auditory (speakers) feedback to ensure either complete relaxation at rest or a constant level of EMG activity during tonic contraction.

Focal TMS of the left primary motor hand area was performed with a High Power Magstim 200 stimulator using an eight-shaped coil with mean loop diameters of 9 cm (Magstim, Whitland, Dyfed, UK). The magnetic stimulus had a nearly monophasic pulse configuration with a rise time of ~100 μs, decaying back to zero over ~0.8 ms. The coil was held tangentially to the skull with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane. Thus, the electrical current induced in the brain was approximately perpendicular to the central sulcus. This orientation of the induced electrical field is thought to produce predominantly a trans-synaptic activation of the corticospinal neurons (Rothwell et al., 1999). The site at which stimuli of slightly suprathreshold intensity consistently produced the largest MEPs in the relaxed right APB muscle was marked with a pen as the ‘motor hot spot’ and used for TMS of the motor cortex.

### Intervention
Associative stimulation consisted of a single electrical stimulus given to the right median nerve at 300% of the perceptual threshold, followed by a single pulse of suprathreshold TMS given to the motor hot spot of the right APB muscle. The inter-stimulus interval (ISI) between peripheral median nerve stimulation and TMS of the primary motor hand area was set at 25 ms because this ISI has been shown to be optimal for inducing a sustained increase in motor cortex excitability (Wolters et al., 2003). The intensity of TMS was adjusted to evoke a peak-to-peak amplitude of ~1 mV in the relaxed APB muscle, as determined at the beginning of the experiment. Associative stimulation was given with the target muscle at complete rest, as monitored by audiovisual feedback. The conditioning protocol consisted of 90 pairs of stimuli which were delivered at 0.05 Hz over 30 min.

### TMS measurements of motor cortex excitability
Several parameters of corticospinal excitability—resting and active motor threshold (RMT, AMT), peak-to-peak MEP amplitude at rest, cortical silent period (CSP) and short-interval intra-cortical inhibition (SICI)—were tested before and after conditioning associative stimulation in the right APB and FDI muscle. Coil position and orientation during

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<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of disease (years)</th>
<th>Dystonic pattern</th>
<th>Last treatment with botulinum toxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>Female</td>
<td>5</td>
<td>Wrist flexion with ulnar deviation</td>
<td>No treatment</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>Female</td>
<td>7</td>
<td>Wrist flexion with ulnar deviation, pronation</td>
<td>4 months</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>Male</td>
<td>3</td>
<td>Finger extension with ulnar deviation</td>
<td>No treatment</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>Male</td>
<td>14</td>
<td>Wrist flexion with ulnar deviation, supination</td>
<td>1 year</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>Male</td>
<td>8</td>
<td>Finger extension, supination</td>
<td>7 months</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>Female</td>
<td>7</td>
<td>Wrist flexion, pronation</td>
<td>4 months</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>Male</td>
<td>11</td>
<td>Wrist flexion and thumb extension</td>
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</tr>
<tr>
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<tr>
<td>9</td>
<td>48</td>
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<td>5</td>
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<td>No treatment</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>Female</td>
<td>9</td>
<td>Wrist flexion with ulnar deviation, supination</td>
<td>4 months</td>
</tr>
</tbody>
</table>
Table 2. Mean group data (± SEM) of the various measures of corticospinal excitability and intracortical inhibition before and after associative stimulation

<table>
<thead>
<tr>
<th>Measures of cortical excitability</th>
<th>Patients with writer’s cramp</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before stimulation</td>
<td>After stimulation</td>
</tr>
<tr>
<td>Right APB muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMT (%)*</td>
<td>46.3 ± 2.7</td>
<td>44.2 ± 2.7</td>
</tr>
<tr>
<td>AMT (%)*</td>
<td>41.0 ± 3.1</td>
<td>39.4 ± 3.1</td>
</tr>
<tr>
<td>SICI (%)†</td>
<td>71 ± 7.6</td>
<td>72 ± 6.0</td>
</tr>
<tr>
<td>MEP (mV)</td>
<td>0.64 ± 0.12</td>
<td>2.11 ± 0.29</td>
</tr>
<tr>
<td>CSP (ms)</td>
<td>109 ± 7</td>
<td>115 ± 8</td>
</tr>
<tr>
<td>Right FDI muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMT (%)*</td>
<td>44.8 ± 2.8</td>
<td>43.6 ± 2.8</td>
</tr>
<tr>
<td>AMT (%)*</td>
<td>39.3 ± 2.7</td>
<td>38.3 ± 3.1</td>
</tr>
<tr>
<td>SICI (%)†</td>
<td>74.3 ± 7.6</td>
<td>78.9 ± 7.0</td>
</tr>
<tr>
<td>MEP (mV)</td>
<td>1.11 ± 0.16</td>
<td>2.37 ± 0.20</td>
</tr>
<tr>
<td>CSP (ms)</td>
<td>102 ± 6</td>
<td>111 ± 6</td>
</tr>
</tbody>
</table>

P-values refer to a post hoc two-tailed t-test comparing mean values before and after associative stimulation. RMT = resting motor threshold; AMT = active motor threshold; SICI = short-latency intracortical inhibition; CSP = cortical silent period; n.s. = non-significant (P > 0.05). *Motor thresholds are given as percentage of maximum stimulator output. †The magnitude of short-latency intracortical inhibition is expressed as a percentage of the size of the unconditioned motor evoked response.

TMS measurements of motor cortex excitability matched the coil position and orientation used for TMS during associative stimulation. This ensured that we measured excitability in the same set of neurons that were conditioned by associative stimulation. A total number of ~250 magnetic stimuli were applied during the entire experiment, including stimuli given during associative stimulation.

RMT was determined according to the recommendation of the IFCN Committee (Rossini et al., 1994; Rothwell et al., 1999) and was defined as the intensity of stimulation which elicits at least five MEPs of 50 μV in 10 consecutive trials. AMT was defined as the lowest stimulus intensity at which at least five MEPs of 150 μV amplitude were elicited in 10 consecutive trials in the contracted APB muscle.

To assess mean peak-to-peak MEP amplitudes at rest, 20 monophasic magnetic stimuli were given to the motor hot spot of the APB muscle at a rate of 0.1 Hz. Stimulus intensity was set at a stimulator output that induced MEPs of ~1 mV in the right APB muscle. This intensity was defined prior to baseline measurements and was kept constant throughout the experiment.

For measurements of the CSP, EMG traces were rectified but not averaged. The mean length of the CSP was determined on the basis of measurements from each individual trial and defined as the interval between the onset of the MEP and the recovery of continuous EMG activity after the period of EMG suppression. The CSP was evoked with single-pulse TMS during continuous isometric contraction of the target muscle. Stimulus intensity was set at 130% of RMT. Participants were asked to produce an isometric contraction at ~15% of maximal voluntary contraction.

Visual feedback was provided through an oscilloscope placed in front of the subject to ensure a constant force level. Measurements of SICI were carried out using the conditioning-test paradigm published by Kujirai et al. (1993). The intensity of the conditioning stimulus was set at 90% AMT. The intensity of the test stimulus was readjusted after associative stimulation in order to match the size of test MEPs after associative stimulation to the size of test MEPs evoked before the intervention. The interval between the conditioning and test stimulus was 2 ms. Fifteen conditioned and unconditioned MEPs were recorded in a pseudorandom order. The relative strength of SICI at an ISI of 2 ms is reported as a percentage of the unconditioned response.

**Statistical analysis**

The effects of associative stimulation on motor thresholds, peak-to-peak MEP amplitude, duration of CSP and SICI were evaluated by separate repeated-measures analyses of variance (ANOVA). For each dependent variable, we computed a three-way repeated-measures ANOVA with time (before intervention versus after intervention) and muscle (APB muscle versus FDI muscle) as within-subject factors and group (patients versus controls) as between-subjects factor. The Greenhouse–Geisser method was used if necessary to correct for non-sphericity. Conditional on a significant F-value, post hoc paired-samples t-tests were performed to explore the strength of main effects and the patterns of interaction between experimental factors. A P-value of <0.05 was considered significant. All data are given as mean ± SEM.
Results
Subjects did not report any adverse side-effects during the course of the study. In both, patients and controls, associative stimulation increased corticospinal excitability. For each measure of cortical excitability, Table 2 gives the averaged group values (mean ± SEM) before and after associative stimulation.

Motor threshold
For the ANOVA that used motor threshold as dependent variable, the factor state (rest versus contraction) was included as an additional factor into the ANOVA model. There was a strong main effect of the factor state on motor threshold \([F(1,18) = 138.2; P < 0.001]\) because RMT was always higher than AMT. Despite the fact that TMS was given to the motor hotspot of the APB muscle, motor thresholds of the FDI muscle were consistently lower than motor thresholds of the APB muscle [main effect for muscle: \(F(1,18) = 14.8; P = 0.002\)]. Associative stimulation had a group-dependent effect on motor thresholds in the APB and FDI muscle at rest and during tonic contraction [one-way interaction between time and group: \(F(1,18) = 6.2; P = 0.024\)]. This interaction was caused by a slight reduction in AMT and RMT in patients, whereas healthy controls showed a subtle increase in AMT and RMT after associative stimulation (Table 2).

Amplitude of motor evoked responses at rest
Figure 1 illustrates the time-dependent changes in mean MEP size for the APB and FDI muscle in patients and controls. Repeated measures ANOVA showed a significant main effect of time \([F(1,18) = 47.2; P < 0.001]\). This was caused by an overall increase in mean peak-to-peak MEP amplitudes after associative stimulation in both groups. In addition, there was also a time × group interaction \([F(1,18) = 12.4; P = 0.003]\) because associative stimulation induced a stronger increase in MEP size in patients with writer’s cramp compared with healthy controls (Fig. 1). There was also a significant time × muscle interaction \([F(1,18) = 7.2; P = 0.017]\). This was due to
the fact that the facilitatory effect of associative stimulation was more pronounced in the APB muscle compared with the FDI muscle. However, three-factorial ANOVA demonstrated no significant difference between groups regarding topographic specificity of stimulation induced plasticity because there was no time × group × muscle interaction [\(F(1,18) = 0.14; P = 0.71\)].

To explore within-group effects, we computed separate two-factorial ANOVA for each group with time (before intervention versus after intervention) and muscle (APB muscle versus FDI muscle) as within-subject factors. In patients, ANOVA revealed only a prominent main effect for the factor time [\(F(1,9) = 31.5; P < 0.001\)] but no significant time × muscle interaction [\(F(1,9) = 1.9; P = 0.20\)], whereas, in healthy controls, ANOVA demonstrated both, a main effect for the factor time [\(F(1,9) = 19.5; P = 0.002\)] and a time × muscle interaction [\(F(1,9) = 7.4; P = 0.026\)].

Post hoc t-tests revealed that, in both groups, the FDI muscle and the APB muscle showed a significant increase in MEP size at rest after associative stimulation. In healthy controls, associative stimulation led to a marked increase in mean MEP amplitude in right APB muscle [\(T(1,9) = 3.68; P = 0.006\)]. The relative increase in MEP size varied among subjects, ranging from +50% to +150% of the baseline value (Fig. 1A). Although the relative increase in MEP size was small in magnitude, associative stimulation also caused a consistent increase in mean MEP amplitudes of the right FDI muscle in healthy controls [\(T(1,9) = 3.68; P = 0.005\)]. In patients with dystonia, associative stimulation had a stronger facilitatory effect on mean MEP amplitude in both hand muscles (Fig. 1B). Compared with MEPs at baseline, the right APB muscle showed a relative increase in MEP amplitude of ~210%, ranging from 40 to 380% [\(T(1,9) = 4.86; P < 0.002\)]. MEP amplitudes of the right FDI muscle increased on average by ~95% [\(T(1,9) = 5.33; P = 0.001\)].

**Intracortical inhibition**

Changes in the duration of the CSP are summarized in Fig. 2. The duration of CSP was slightly shorter in patients, but this difference did not reach significance. There was a main effect of time [\(F(1,18) = 12.4; P = 0.003\)]. This was due to a slight overall prolongation of the CSP in both muscles and groups. In addition, ANOVA revealed a two-way time × muscle ×
group interaction \( [F(1,18) = 5.1; P = 0.04] \), indicating that associative stimulation exerted a muscle-specific effect on the duration of CSP that differed between groups. This interaction was caused by a stronger prolongation of CSP in the APB muscle that was specific for healthy controls (Fig. 2). Pairwise comparisons of measurements before and after associative stimulation revealed that a significant prolongation of the CSP after associative stimulation only occurred in the APB muscle in healthy controls \( [T(1,9) = 3.24; P = 0.01] \).

For each group, we computed an additional two-factorial ANOVA with time (before intervention versus after intervention) and muscle (APB muscle versus FDI muscle) as within-subject factors. In patients, there was a prominent main effect for the factor time \( [F(1,9) = 26.1; P = 0.001] \) but no significant time \( \times \) muscle interaction \( [F(1,9) = 0.03; P = 0.87] \), whereas, in healthy controls, ANOVA revealed a main effect for the factor time \( [F(1,9) = 6.4; P = 0.03] \) and a time \( \times \) muscle interaction \( [F(1,9) = 9.4; P = 0.015] \).

At baseline, the relative strength of SICI at an ISI of 2 ms was reduced in patients compared with healthy controls. This was the case for the APB muscle \( [T(1,18) = 3.69; P = 0.002] \) and the FDI muscle \( [T(1,18) = 3.79; P = 0.003] \). Associative stimulation had no effect on the relative strength of SICI. ANOVA revealed neither a significant main effect for the factors time and muscle nor a significant interaction for the factors time, muscle and group.

**Discussion**

Using the stimulation protocol introduced by Stefan et al. (2000), we found that associative stimulation is capable of inducing a rapid functional reorganization within the corticospinal motor system in healthy subjects and patients with writer’s cramp. The pattern of stimulation-induced reorganization, however, differed between dystonic patients and healthy subjects. Compared with healthy controls, patients with writer’s cramp showed a stronger increase in corticospinal excitability along with an attenuated facilitation of intracortical inhibitory circuits that generate the CSP.

**Conditioning effects in healthy subjects**

In accordance with previous works by Stefan et al. (2000, 2002), associative stimulation at an ISI of 25 ms induced an increase in corticospinal excitability at rest (as indexed by an increase in MEP amplitude evoked by single-pulse TMS), as well as an increase in intracortical inhibition (as indexed by a prolongation in CSP) in healthy controls. Plastic changes were more pronounced in the APB muscle, but were also expressed to some extent in the FDI muscle. This finding extends previous TMS work on associative plasticity in healthy subjects, showing that topographic specificity of motor reorganization in response to associative stimulation is relative rather than absolute in nature. It is worth noting that, in the study by Stefan et al. (2000), the abductor digiti minimi muscle was used to demonstrate a somatotopic specificity of conditioning effects on the APB muscle. These muscles usually do not act together during skilled manipulative tasks. By contrast, we recorded motor responses from the APB muscle and FDI muscle. Although these muscles act on different fingers, both muscles cooperate during fine manipulative movements. Therefore, sensory input from the median nerve might also be somatotopically linked to some extent to the central motor representations of the FDI muscle. Moreover, cortical motor thresholds for activation of the APB muscle were lower than thresholds for activation of the FDI muscle in the present study, indicating that the corticospinal representations of both muscles were effectively stimulated by TMS. Therefore, it is not surprising that associative stimulation over the hot spot of the APB muscle led to a subtle, yet consistent increase in corticospinal excitability also in the FDI muscle.

**Conditioning effects on corticospinal excitability in patients**

Patients with writer’s cramp showed a larger increase in excitability of corticospinal output neurons after associative stimulation at an ISI of 25 ms. This was the case for the right APB and FDI muscle. The amount of facilitation of MEP amplitudes at rest exceeded the effect found in healthy controls. In addition, associative stimulation caused a subtle decrease in motor threshold in patients that was not observed in healthy controls. Since Stefan et al. (2000) have shown that plastic changes occur at the level of the motor cortex, our findings indicate an increased modifiability of the motor cortex in patients with writer’s cramp to reorganization driven by sensory input from the affected hand.

There was no significant muscle-specific difference between groups regarding the facilitatory effects of associative stimulation on corticospinal excitability. Within-group analyses, however, suggest that conditioning effects on MEP amplitudes were less focal in patients than in healthy subjects. In controls, the facilitatory effect of associative stimulation on the size of the MEP was significantly larger in the APB muscle compared with the FDI muscle. By contrast, the size of the facilitatory effect was equal for both muscles in patients with writer’s cramp.

The increased responsiveness of corticospinal output neurons to associative stimulation could be due to abnormal sensory processing. Several studies have provided converging evidence for defective perception (i.e., kinaesthesia, temporal and spatial discrimination) in focal task-specific dystonia (Grunewald et al., 1997; Bara-Jimenez et al., 2000; Sanger et al., 2002). Although the amplitudes of somatosensory evoked potentials (SEPs) are not consistently modified in resting conditions (Tinazzi et al., 2000), several SEP studies have revealed abnormal sensory-motor processing. For instance, the integration of afferent inputs from adjacent body parts is abnormal in idiopathic dystonia (Tinazzi et al., 2000) and SEP recordings demonstrate abnormal premove-
ment gating of somatosensory input in writer’s cramp (Murase et al., 2000). Abnormal central sensory processing has also been confirmed by functional imaging techniques: Tempel and Perlmutter (1993) demonstrated bilateral diminished regional blood flow response in the contralateral sensorimotor cortex in patients with writer’s cramp during vibrotactile stimulation. Magnetic source imaging revealed an abnormality of the finger representations in the primary somatosensory cortex in focal task-specific hand dystonia (Bara-Jimenez et al., 1998; Elbert et al., 1998; Meunier et al., 2001).

In addition to altered sensory processing, several recent studies demonstrated abnormalities in sensorimotor integration in task-specific hand dystonia: Abbruzzese et al. (2001) studied changes of corticospinal excitability (as tested with TMS) in response to a conditioning electrical peripheral nerve stimulation in patients with focal hand dystonia and patients with cervical dystonia. In normal subjects and patients with cervical dystonia, electrical stimulation of the median nerve reduced the amplitude of MEPs recorded from the APB and FDI muscles with a maximum effect at an inter-stimulus interval of 200 ms. By contrast, patients with focal hand dystonia showed a significant increase in MEP size, indicating a deficient suppression of corticospinal excitability following peripheral electrical stimulation. Digital nerve stimulation produces an inhibitory effect on MEPs induced by TMS on intrinsic hand muscles in a somatotopic fashion, with the maximal inhibition observed in the muscle contiguous to the digit stimulated (Tamburin et al., 2002). In contrast in dystonic patients, the inhibitory effect of digital nerve stimulation was no longer restricted to the intrinsic hand muscle of the stimulated finger, suggesting an impairment of focusing the inhibitory effects of somatosensory afferents on the motor system (Tamburin et al., 2002). Since, in focal hand dystonia, a single electric stimulus induces an increased MEP facilitation (Abbruzzese, 2001) and/or less focal MEP inhibition (Tamburin et al., 2002) it is conceivable that median nerve stimulation caused a stronger and less focal activation of the motor cortex in the present study. This, in turn, may have (i) increased the efficacy of associative stimulation to induce a sustained increase in corticospinal excitability and (ii) reduced to some extent topographic specificity.

**Conditioning effects on intracortical inhibition in patients**

In contrast to increased facilitation of corticospinal excitability, the facilitatory effect of associative stimulation on intracortical inhibition was attenuated in patients with writer’s cramp. In healthy controls, the CSP recorded from the APB muscle was markedly prolonged after associative stimulation, whereas, in patients with writer’s cramp, there was only a subtle increase in the duration of the CSP. Since the duration of the CSP is thought to reflect the excitability of cortical (presumably GABA_B-ergic) interneurons (Siebner et al., 1998; Werhahn et al., 1999), this finding indicates that these intracortical inhibitory circuits were less responsive to the conditioning effects of associative stimulation in patients with writer’s cramp.

In contrast to the duration of CSP, associative stimulation had no lasting effects on the magnitude of SICI both in healthy controls and patients with dystonia. A recent study also found no effects on the strength of SICI in a group of healthy controls (Stefan et al., 2002). It has been shown that the strength of SICI is dependent on the excitability of GABA_A-ergic intracortical interneurons (Ziemann et al., 1996; Werhahn et al., 1999).

It is worth noting that mean AMT was increased in patients compared with controls in the present study. Since the intensity of the conditioning stimulus was adjusted to AMT, the mean intensity of the conditioning stimulus was higher than in the controls. This alone could have led to a reduced short-latency inhibition at baseline and might have contributed to rendering paired-pulse excitability insensitive to any changes induced by associative stimulation.

Taken together, associative stimulation protocol introduced by Stefan et al. (2000) induces a selective reinforcement of GABA_B-ergic intracortical circuits in healthy subjects and this ‘inhibitory’ after-effect is attenuated in patients with writer’s cramp. It is worth noting that, in a study by Siebner et al. (1999a), subthreshold 1 Hz repetitive TMS (rTMS) to the primary motor cortex was more effective in patients with writer’s cramp than in healthy controls to reinforce both GABA_A-ergic intracortical circuits (as indicated by an increase in SICI) and GABA_B-ergic intracortical circuits (as indicated by a prolongation of the CSP). Therefore, the attenuated responsiveness of inhibitory intracortical circuits in patients with writer’s cramp appears to be specific for associative stimulation that probes sensorimotor plasticity.

Several recent studies on patients with writer’s cramp have accumulated evidence for a deficiency of intracortical inhibition in the primary motor hand area. The excitability of intracortical circuits that generate the CSP is reduced in patients with writer’s cramp (Filipovic et al., 1997; Mavroudakis et al., 1997; Niehaus et al., 2001). Filipovic et al. (1997) found a task-specific shortening of the CSP during writing as opposed to an isometric contraction in patients with writer’s cramp. In addition, Mavroudakis et al. (1997) reported a reduced increase in the duration of the CSP with increasing stimulus intensity. In the present study, the duration of CSP was slightly shorter in patients than in healthy controls, but this difference did not reach significance. It has also been shown that the strength of SICI is reduced in patients with writer’s cramp (Ridding et al., 1995; Siebner et al., 1999a). In agreement with previous studies, we found a reduced SICI and a non-significant shortening of the CSP in writer’s cramp patients. Therefore, it is conceivable that highly synchronized sensory inputs (evoked by median nerve stimulation) were abnormally processed in the primary
motor cortex due to a deficient inhibition. If the role of cortical inhibition is to ‘focus’ the motor command within the motor cortex so that the correct muscles are activated by the appropriate amount in every task, a deficiency of this system could account for the excessive motor overflow observed in dystonia. This notion was supported by the fact that reinforcement of intracortical inhibition produced by sub-threshold rTMS over the primary motor hand area in writer’s cramp patients was associated with some clinical improvement (Siebner et al., 1999a, b).

Pathophysiology of writer’s cramp
The present results add some new insight into the pathophysiology of task-specific hand dystonia. It has been shown that sensory input from the affected hand can trigger dystonic symptoms in writer’s cramp patients (Kaji et al., 1995). Frequent use of a body part or a disease in the peripheral nervous system often precede the manifestation of dystonia (Quartarone et al., 1998; Girlanda et al., 2000). Moreover, observations in monkeys indicate that rapid, repetitive, stereotypical movements in a learning context can actively degrade the cortical representations of sensory information that guide fine hand movements (Byl et al., 1996). Therefore, it has been proposed that a sensory mechanism can trigger dystonia, and de-differentiation of sensory feedback information plays an important role in the pathophysiology of task-specific hand dystonia (Hallett, 1995; Pascual-Leone, 2001). Although we did not assess dystonic symptoms before and after associative stimulation, the patterns of excitability changes found in the present study suggest that repetitive peripheral sensory stimulation of the affected hand can trigger abnormal plasticity in the primary motor hand area in task-specific hand dystonia. Therefore, it can be postulated that repetitive peripheral sensory stimulation during the execution of skilled manual tasks might lead to maladaptive sensorimotor plasticity in susceptible individuals via an enhanced and less focal facilitatory effect of sensory inputs on the motor output system.

The exact mechanisms that mediate this abnormal sensorimotor plasticity remain to be clarified. The primary cause of dystonia has been attributed to an abnormal pattern of GABA-ergic activity in pallidothalamic projections (Lozano et al., 1997; Berardelli et al., 1998; Vitek, 2002). The direct and indirect pathways in the basal ganglia provide a facilitatory and inhibitory influence on the motor cortex. This dual system gives a centre (excitatory) surround (inhibitory) mechanism that may account for the firing of a selected cortical neuronal population, focusing in this way the motor output to a restricted group of muscles (Kaji, 2001). The notion of an impaired ‘focusing’ function of the basal ganglia in patients with task-specific dystonia can account for a decrease of intracortical inhibition and an abnormally enhanced facilitatory effect of repetitive sensory inputs which might ultimately drive maladaptive plasticity.

The work by Stefan et al. (2000) has shown that the conditioning effects of associative stimulation last at least 30–60 min. Since only one block of measurements was carried out after associative stimulation, the present study provides no information about differences in the duration of after-effects between dystonic patients and controls. Furthermore, it remains to be clarified whether a similar abnormal pattern of sensorimotor plasticity can also be produced if associative stimulation is given to the non-affected limb and the corresponding representation of the motor cortex.

Taken together, associative stimulation revealed an altered modifiability of the corticospinal motor system in writer’s cramp patients with an increased tendency towards a facilitation of corticospinal output neurons and an attenuated facilitation of intracortical inhibitory circuits. In addition, stimulation-induced plasticity was less focused on the corticospinal output to the APB muscle that was targeted by TMS involving also to a great extent FDI muscle. This abnormal modifiability may be an important prerequisite for the development of maladaptive use-dependent plasticity during repetitive skilled hand movements and, therefore, may play an important role in the pathophysiology of task-specific arm dystonia.

References


Pascual-Leone A. The brain that plays music and is changed by it. Ann NY Acad Sci 2001; 930: 315–29.

Pavlidis C, Miyashita E, Asanuma H. Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. J Neurophysiol 1993; 70: 733–41.


