Defective cerebellar control of cortical plasticity in writer’s cramp

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A large body of evidence points to a role of basal ganglia dysfunction in the pathophysiology of dystonia, but recent studies indicate that cerebellar dysfunction may also be involved. The cerebellum influences sensorimotor adaptation by modulating sensorimotor plasticity of the primary motor cortex. Motor cortex sensorimotor plasticity is maladaptive in patients with writer’s cramp. Here we examined whether putative cerebellar dysfunction in dystonia is linked to these patients’ maladaptive plasticity. To that end we compared the performances of patients and healthy control subjects in a reaching task involving a visuomotor conflict generated by imposing a random deviation (–40° to 40°) on the direction of movement of the mouse/cursor. Such a task is known to involve the cerebellum. We also compared, between patients and healthy control subjects, how the cerebellum modulates the extent and duration of an ongoing sensorimotor plasticity in the motor cortex. The cerebellar cortex was excited or inhibited by means of repeated transcranial magnetic stimulation before artificial sensorimotor plasticity was induced in the motor cortex by paired associative stimulation. Patients with writer’s cramp were slower than the healthy control subjects to reach the target and, after having repeatedly adapted their trajectories to the deviations, they were less efficient than the healthy control subjects to perform reaching movement without imposed deviation. It was interpreted as impaired washing-out abilities. In healthy subjects, cerebellar cortex excitation prevented the paired associative stimulation to induce a sensorimotor plasticity in the primary motor cortex, whereas cerebellar cortex inhibition led the paired associative stimulation to be more efficient in inducing the plasticity. In patients with writer’s cramp, cerebellar cortex excitation and inhibition were both ineffective in modulating sensorimotor plasticity. In patients with writer’s cramp, but not in healthy subjects, behavioural parameters reflecting their capacity for adapting to the rotation and for washing-out of an earlier adaptation predicted the efficacy of inhibitory cerebellar conditioning to influence sensorimotor plasticity: the better the online adaptation, the smaller the influence of cerebellar inhibitory stimulation on motor cortex plasticity. Altered cerebellar encoding of incoming afferent volleys may result in decoupling the motor component from the afferent information flow,
and also in maladjusted sensorimotor calibration. The loss of cerebellar control over sensorimotor plasticity might also lead to building up an incorrect motor program to specific adaptation tasks such as writing.

Keywords: cerebellum; dystonia; plasticity; transcranial magnetic stimulation; sensorimotor adaptation

Abbreviations: AN = angle of the trajectory 250 ms after movement onset; PAS = paired-associative stimulation; MEP = motor evoked potential; RT = reaction time; TC = time to curvature; TMS = transcranial magnetic stimulation; TT = target time; WCIS = Writer’s Cramp Impairment Scale

Introduction

The classical view that basal ganglia dysfunction is responsible for the abnormal sensory processing (Tinazzi et al., 2009) and disturbed sensorimotor integration associated with dystonia (Abbruzzese et al., 2001; Tamburin et al., 2002; Tecchio et al., 2008) has been challenged by new evidence of cerebellar dysfunction in both focal and generalized dystonia (Sadnica et al., 2011; Raike et al., 2012). Like the lemniscal pathway, the cerebellum relays sensory afferent inputs to the motor cortex (M1) (Butler et al., 1992) and processes proprioceptive information for both temporal and spatial discrimination of sensory signals (Restuccia et al., 2001; Pastor et al., 2004). Cerebellar dysfunction might therefore affect sensory processing in patients with dystonia.

Numerous studies have demonstrated that the cerebellum is involved in sensorimotor adaptation (Wolpert and Miall, 1996; Wolpert and Kawato, 1998; Doya, 1999; Paulin, 2005; Shadmehr and Krakauer, 2008; Izawa and Shadmehr, 2011; Izawa et al., 2012), and cerebellar dysfunction in dystonia might therefore affect sensorimotor adaptation. Indeed, eye blink conditioning is altered in patients with various forms of focal dystonia (Teo et al., 2009), and saccadic adaptation is impaired in patients with myoclonus-dystonia (Hubsch et al., 2011).

The cerebellum is defective in dystonia associated with structural (Delmaire et al., 2007) and functional abnormalities: abnormally increased cerebellar activity is consistently observed in neuroimaging studies of dystonias, including focal dystonia (Galardi et al., 1996; Odergren et al., 1998; Hutchinson et al., 2000; Preibisch et al., 2001; Hu et al., 2006). Altered functional connectivity between the cerebellum and thalamus has been shown in DYT1 dystonia (Argyelan et al., 2009) but not yet in focal dystonia. However, in patients with occupational dystonia, transcranial magnetic stimulation (TMS) experiments point to defective connectivity between the cerebellum and motor cortex both ipsilateral and contralateral to the dystonic upper limb (Brighina et al., 2009).

The pathophysiology of dystonia also involves maladaptive sensorimotor plasticity (Hallett, 2006; Breakefield et al., 2008). Aberrant plasticity in patients with focal dystonia, shown by the enhanced response of their motor cortex to plasticity-inducing TMS interventions such as paired-associative stimulation (PAS) (Quartarone et al., 2003), is more likely to be directly related to the cause of dystonic movements than to be a simple consequence (Tisch et al., 2007). Indeed, intensive repetition of highly trained activity is a risk factor for developing writer’s cramp or other task-specific dystonia of the upper limb (Roze et al., 2009; Le Floch et al., 2010), and this could be mediated through aberrant M1 plasticity, although it is unclear which defect leads to this aberrant plasticity. Excitation or inhibition of the cerebellar cortex exerts a powerful priming effect on the development and extent of M1 sensorimotor plasticity by processing the sensory afferent volley at a subcortical level, either in the cerebellum itself or upstream of the cerebellum in the olivary nucleus (Popa et al., 2013). This is compatible with the role of the cerebellum in filtering or encoding sensory inputs (Dean and Porrill, 2010).

In patients with writer’s cramp, defective sensory encoding by the cerebellum could affect sensorimotor plasticity in M1, possibly leading to abnormal sensorimotor adaptation.

To test for abnormal sensorimotor adaptation in writer’s cramp, we compared the performance of patients with writer’s cramp and healthy control subjects in a reaching task that included a visuo-motor conflict. To test the effect of putative, abnormal cerebellar sensory encoding on M1 plasticity development, we modulated the excitability of the cerebellar cortex and examined how this influenced the M1 plasticity induced by PAS.

Materials and methods

Subjects

Twenty-one patients with writer’s cramp (mean age 42.9 ± 14.3 years; seven from France, 12 from India, two from Italy) participated in the study (Table 1). They were recruited through the Movement Disorders clinics of the three participating centres (Table 1), namely Pitie`-Salpêtriere Hospital (Paris, France), Sree Chitra Tirunal Institute for Medical Sciences and Technology (Trivandrum, India), and Clinica Neurologica II of Policlinico Universitario (Messina, Italy). They were compared with 25 age-matched healthy volunteers (mean age: 41.7 ± 16.6 years; nine from France, 13 from India, three from Italy; 15 females, 10 males). The patients experienced dystonia only when writing, with the exception of two patients, one of whom also had laryngeal dystonia. None of the participants had a history of neurological disorders (other than dystonia in the patients) or psychiatric illness, or were taking drugs acting on the CNS at the time of the study. Medical treatment (Table 1) was stopped at least 3 weeks before the study and was withheld until study completion. Twelve patients had never received botulinum toxin injections, and the remaining nine patients had not received botulinum toxin injections for at least 3 months before the study (Table 1). All the subjects were right-handed.

The experimental procedures were approved by the local ethics committees of the participating centres and conformed to the Declaration of Helsinki. All the subjects gave their written informed consent before participating in the experiments.
Video recording

Dystonia severity in the affected limb was assessed from videos recorded at the beginning of the first session. The video protocol was designed to score the Writer’s Cramp Impairment Scale (WCIS) and was used by all three centres. The WCIS scale, developed at HMCS, NINDS, NIH (Bethesda, USA), is awaiting validation. The WCIS scale assesses the speed of writing, the number of breaks during writing, the occurrence and intensity of involuntary (pathological) postures/abnormal movements (while writing, while performing repetitive wrist movements), the degree of tremor that occurs while performing repetitive spiral movements, and the presence of mirror movements. All videos from the three centres were rated offline by the same movement disorders specialist (R.E.), who was blinded to the electrophysiological data.

Experiment 1

All the subjects (healthy volunteers = 25, writer’s cramp = 21) were invited to attend three sessions. In all three sessions, 5 Hz PAS (Quartarone et al., 2006) was used to induce plasticity in the dominant (left) M1. PAS was preceded by right cerebellar stimulation consisting of the following three randomized interventions: cortical cerebellar cortex excitation [cerebellar-intermittent theta burst stimulation (CB-iTBS)], cerebellar cortex inhibition [cerebellar-continuous theta burst stimulation (CB-cTBS)], or sham stimulation of the cerebellum (CB-sham). The three sessions were separated by intervals of at least 1 week. PAS (5 Hz) was applied 5 min after the end of cerebellar conditioning.

Electromyography recordings

The subjects were seated comfortably in an armchair, with the two hands resting symmetrically on a pillow placed on their lap. They were asked to fix their vision on a point 1 m in front of them during the procedure. Motor evoked potentials (MEPs) were recorded from the right Abductor pollicis brevis (the target muscle) and Abductor digitii minimi (the control surround muscle) through disposable Ag/AgCl surface electrodes in a muscle belly–tendon montage. The cortical representations of the Abductor pollicis brevis and Abductor digitii minimi are close enough for consistent measurable MEPs to be evoked simultaneously in the two muscles (Weise et al., 2006, 2011; Quartarone et al., 2008).

Responses were amplified (×1000) and filtered (100–3000 Hz) with a Digitimer D360 amplifier (Digitimer Ltd), then digitally transformed at a sampling rate of 10 000 Hz (CED Power 1401 MkII, CED Ltd), and stored offline for analysis (Signal 4.02, CED Ltd).

Transcranial magnetic stimulation sessions

Evaluation of cortico-spinal excitability

TMS pulses were applied over the left M1 by using a 70-mm figure-of-eight coil connected to two MAGSTIM 200 stimulators via a Bistim unit (The Magstim Company). The coil was held at ~45° from the midline for optimal trans-synaptic activation of the motor cortex (Werhahn et al., 1994; Kaneko et al., 1996). The direction of the induced current was posterior to anterior.

The motor ‘hot spot’ of the right Abductor pollicis brevis was first marked on a default image in a MRI-based neuronavigation system (eXimia 2.2.0, Nexstim Ltd in the Paris and Messina labs; Brainsight 2, Rogue Resolutions in the Indian lab). This allowed the same position to be maintained over the ‘hot spot’ across the different sessions. The resting motor threshold (RMTbistim) was then calculated for Abductor pollicis brevis by using the standard procedure (Rossini et al., 1994; Rothwell, 1997).

Repetitive transcranial magnetic stimulation

Repetitive TMS stimulation was delivered through a 70-mm figure-of-eight cooled coil connected to a SuperRapid2 magnetic stimulator (Magstim Company). The magnetic stimulus had a biphasic waveform

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Table 1 Clinical features of the patients

<table>
<thead>
<tr>
<th>Centre</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Disorder</th>
<th>Symptoms duration (years)</th>
<th>Total WCIS score</th>
<th>Treatment</th>
<th>Time from the last injection (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>23</td>
<td>WC</td>
<td>3</td>
<td></td>
<td>46</td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>1 M</td>
<td>54</td>
<td>WC</td>
<td>11</td>
<td></td>
<td>41</td>
<td>BT</td>
<td></td>
</tr>
<tr>
<td>1 F</td>
<td>40</td>
<td>WC</td>
<td>17</td>
<td></td>
<td>66</td>
<td>BT</td>
<td></td>
</tr>
<tr>
<td>1 F</td>
<td>68</td>
<td>WC</td>
<td>16</td>
<td></td>
<td>16</td>
<td>BT</td>
<td>4</td>
</tr>
<tr>
<td>1 F</td>
<td>68</td>
<td>WC</td>
<td>7</td>
<td></td>
<td>19</td>
<td>BT</td>
<td></td>
</tr>
<tr>
<td>1 M</td>
<td>58</td>
<td>WC</td>
<td>11</td>
<td></td>
<td>39</td>
<td>BT</td>
<td></td>
</tr>
<tr>
<td>1 F</td>
<td>44</td>
<td>WC, LD</td>
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<td></td>
<td>31</td>
<td>BT (vocal cords)</td>
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<td>WC</td>
<td>2</td>
<td></td>
<td>26</td>
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</tr>
<tr>
<td>2 M</td>
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<td>11</td>
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</tr>
<tr>
<td>2 F</td>
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<td>WC</td>
<td>5</td>
<td></td>
<td>25</td>
<td>BT</td>
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<td>WC</td>
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<td></td>
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<td>WC</td>
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<td></td>
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<td>BT</td>
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</tr>
<tr>
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<td>36</td>
<td>WC, MC</td>
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<td>24</td>
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<tr>
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<td>WC</td>
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<td>46</td>
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<td>3.5</td>
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<tr>
<td>2 F</td>
<td>53</td>
<td>WC</td>
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<td>15</td>
<td>Atenolol</td>
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<tr>
<td>2 F</td>
<td>41</td>
<td>WC</td>
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<td>47</td>
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<tr>
<td>2 F</td>
<td>18</td>
<td>WC</td>
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<td>54</td>
<td>MD</td>
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<tr>
<td>3 M</td>
<td>63</td>
<td>WC</td>
<td>20</td>
<td></td>
<td>19</td>
<td>MD</td>
<td></td>
</tr>
<tr>
<td>3 M</td>
<td>35</td>
<td>WC</td>
<td>12</td>
<td></td>
<td>19</td>
<td>MD</td>
<td></td>
</tr>
</tbody>
</table>

1 = Paris, France; 2 = Trivandrum, India; 3 = Messina, Italy. M = male; F = female; WC = writer’s cramp; MC = musician cramp; LD = laryngeal dystonia; BT = botulinum toxin.
with a pulse width of 0.3 ms. The RMT\textsubscript{rapidstim} and active motor threshold (AMT\textsubscript{rapidstim}) for the right Abductor pollicis brevis were assessed first, using the standard procedure (Rossini et al., 1994; Rothwell, 1997).

**Paired associative stimulation of M1**

The 5 Hz PAS protocol (Quartarone et al., 2006) was applied to the left M1. Electric pulses (Digitimer D 180 stimulator Digitimer) were delivered over the right median nerve at the wrist at 2.5 times the perceptual threshold and always below the electromyographically measured motor threshold. Each pulse was followed 25 ms later by a magnetic pulse delivered over the ‘hot spot’ of the right Abductor pollicis brevis at 90% AMT\textsubscript{rapidstim}. Six hundred pairs of stimuli were delivered at 5 Hz.

Twenty MEPs were averaged just before the intervention (cerebellar stimulation followed by PAS), and at 10 (T10), 20 (T20) and 30 (T30) min after the end of the intervention, using the same intensity of stimulation followed by PAS), and at 10 (T10), 20 (T20) and 30 (T30) min.

Short- and long-interval intracortical inhibitions, intracortical facilitation, and short- and long-latency afferent inhibitions were measured before and at 15 and 25 min after the intervention.

**Evaluation of intracortical inhibition and facilitation**

The pre-PAS test stimulation was set at 1.3 × RMT\textsubscript{rapidstim} and was then adjusted at the 15-min (T15) and 25-min (T25) test points to maintain the test MEP amplitude at the same level as before the intervention (Sanger et al., 2001). The conditioning TMS stimulus was set at 0.7 × RMT\textsubscript{rapidstim} to measure short interval intracortical inhibition and intracortical facilitation. The inter-stimulus interval was 2.5 ms for short interval intracortical inhibition (Fisher et al., 2002) and 15 ms for intracortical facilitation (Kujirai et al., 1993). The conditioning stimulus was set at 1.2 × RMT\textsubscript{rapidstim} and the interstimulus interval at 100 ms when measuring long-interval intracortical inhibitions. To measure short and long-latency afferent inhibitions, an electrical conditioning stimulus (200 μs pulse width) was delivered to the median nerve at an intensity three times the perception threshold, using a Digitimer DS7A Constant Current Stimulator. The interstimulus interval was 20 ms for short-latency afferent inhibition and 200 ms for long-latency afferent inhibition (Di Lazzaro et al., 2005). Fifteen trials of test stimulation alone and 15 trials of conditioning plus test stimulation were delivered in random order.

Short-interval intracortical inhibition, long-interval intracortical inhibition, intracortical facilitation, short-latency afferent inhibition, long-latency afferent inhibition, and intracortical facilitation were expressed...
as the ratio (percentage) of the mean amplitude of the conditioned MEP to the mean amplitude of the test MEPs.

**Experiment 2**

Subjects who were willing to participate in a fourth session (writer’s cramp = 16, healthy volunteers = 10) performed a visuomotor adaptation task. This task derived from the task design used by Tseng et al. (2007).

All subjects who participated in Experiment 2 had also participated in Experiment 1. The subjects were instructed to move a computer mouse with their right hand in order to make the cursor touch five different targets on a computer screen. The mouse position was sampled at 30 Hz by using a custom Matlab program that controlled a black circular cursor on a white screen. The target was displayed in one of five positions arrayed radially at −90°, −45°, 0°, 45° and 90° in a half circle (Fig. 2). The subjects were asked to move the cursor straight to the target and then to return it to the starting position. The targets were randomly presented one by one. A visuomotor conflict was generated during the task by imposing a random deviation (−40°, −20°, −10°, 0°, 10°, 20°, 40°) on the direction of movement of the mouse/cursor.

**Data analysis**

Different strategies were used to evaluate data from different methods used. The analytical method for each section will be described at the beginning of the section.

**Correlations**

Correlations between the severity of dystonia (WCIS scale) and baseline physiological parameters were sought, as well as correlations between performance in the visuomotor task (reaction time, time to curvature/time to reach the target, and angle of the trajectory 250 ms after movement onset) and baseline physiological parameters, and correlations between task performance and the degree of PAS-induced plasticity. Values were considered significant at $P < 0.05$.

Stat View software (SAS Institute Inc) was used for all statistical analyses.

**Results**

None of the subjects reported any adverse effects. None of the interventions resulted in a visible change in the severity of dystonia or in the appearance of any sign of overt cerebellar dysfunction.

**Clinical scores**

The patients’ mean score on the WCIS scale was $28.8 \pm 18.1$ (range 0–180).

**Physiological parameters**

Physiological parameters (RMTbistim, AMT rapidstim, test MEP mean amplitude, short-interval intracortical inhibition, intracortical facilitation, short-latency afferent inhibition, long-latency afferent inhibition, long-interval intracortical inhibition) were measured at baseline in each of the three sessions. It was first verified that all the parameters were stable across the three sessions by using a repeated-measures ANOVA in which the three measures formed the repeats. As the parameters were stable across time, their mean value was used in subsequent analyses and compared between the patients with writer’s cramp and healthy volunteers using unpaired $t$-tests.

RMTbistim and AMT rapidstim were not different between the healthy volunteers and patient groups (RMTbistim: healthy volunteers: $46.7 \pm 7.4\%$, writer’s cramp: $48.4 \pm 9.0\%$; $P = 0.1$; AMT rapidstim: healthy volunteers: $39.8 \pm 6.3\%$, writer’s cramp: $40.6 \pm 8.3\%$; $P = 0.3$).

At baseline, long-latency afferent inhibition was significantly lower in the patients than in the healthy volunteers (Table 2) (healthy volunteers: $−40.6 \pm 3.2\%$, writer’s cramp: $−23.2 \pm 7.6\%$; $P < 0.03$). None of the other parameters measured for Abductor pollicis brevis were different between the healthy volunteers and patients (Table 2).

None of the baseline parameters measured for Abductor digitii minimi were different between the healthy volunteers and patients.

**Paired-associative stimulation-induced plasticity in healthy subjects and in patients with writer’s cramp**

PAS-induced plasticity preceded by sham cerebellar stimulation served as the control condition; it was compared between the healthy volunteers and patients with writer’s cramp and between the Abductor pollicis brevis and Abductor digitii minimi muscles by using repeated-measures ANOVA, in which the three values of the normalized MEPs (MEP$_{110}$/MEP$_{0}$, MEP$_{120}$/MEP$_{0}$, MEP$_{130}$/MEP$_{0}$) formed the repeats.

PAS-induced plasticity differed according to the muscle tested (muscle: Abductor pollicis brevis target muscle or Abductor digitii minimi control surrounding muscle) and the group to which the subjects belonged (group: healthy volunteers or patients with writer’s cramp) [Group: $F(1,86) = 0.9$, $P = 0.3$;...
The effects of cerebellar cortex conditioning on M1 plasticity were compared between the healthy volunteers and patients with writer’s cramp (‘Group’ factor) and/or between the cerebellar cortex excitation, cerebellar cortex inhibition and sham stimulation of the cerebellum interventions (‘Intervention’ factor) by using repeated ANOVA in which the nine normalized values of the MEPs formed the repeats (MEPT10/MEPT0, MEPT20/MEPT0, MEPT30/MEPT0 after cerebellar cortex excitation, cerebellar cortex inhibition and sham stimulation of the cerebellum). Bonferroni’s post hoc test was used to characterize the time course of the parameters after each type of intervention.

### Effect of cerebellar cortex conditioning on paired-associative stimulation-induced plasticity

The effects of cerebellar cortex conditioning on M1 plasticity were compared between the healthy volunteers and patients with writer’s cramp (‘Group’ factor) and/or between the cerebellar cortex excitation, cerebellar cortex inhibition and sham stimulation of the cerebellum interventions (‘Intervention’ factor) by using repeated ANOVA in which the nine normalized values of the MEPs formed the repeats (MEPT10/MEPT0, MEPT20/MEPT0, MEPT30/MEPT0 after cerebellar cortex excitation, cerebellar cortex inhibition and sham stimulation of the cerebellum). Bonferroni’s post hoc test was used to characterize the time course of the parameters after each type of intervention.

### Cerebellum and writer’s cramp

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### Table 2 Physiological parameters at baseline and after cerebellar cortex conditioning

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy volunteers</th>
<th>Writer’s cramp</th>
<th>Time</th>
<th>Test (mV)</th>
<th>F</th>
<th>P</th>
<th>Group</th>
<th>Test (mV)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST (mV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.01 (0.06)</td>
<td>0.93 (0.07)</td>
<td></td>
<td>2.9</td>
<td></td>
<td>0.003</td>
<td>Group</td>
<td>3.7</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Post sham</td>
<td>1.08 (0.09)</td>
<td>0.89 (0.09)</td>
<td></td>
<td>3.5</td>
<td></td>
<td>0.0002</td>
<td>Group</td>
<td>3.7</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Post iTBS</td>
<td>1.04 (0.06)</td>
<td>0.90 (0.08)</td>
<td></td>
<td>2.6</td>
<td></td>
<td>0.01</td>
<td>Group</td>
<td>3.7</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Post LAI</td>
<td>0.97 (0.07)</td>
<td>0.97 (0.09)</td>
<td></td>
<td>2.9</td>
<td></td>
<td>0.003</td>
<td>Group</td>
<td>3.7</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Post SICI</td>
<td>1.24 (0.06)</td>
<td>1.21 (0.06)</td>
<td></td>
<td>8.9</td>
<td></td>
<td>0.0001</td>
<td>Group</td>
<td>3.7</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Post SAI</td>
<td>1.20 (0.09)</td>
<td>1.22 (0.08)</td>
<td></td>
<td>4.6</td>
<td></td>
<td>0.0001</td>
<td>Group</td>
<td>3.7</td>
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<td>0.05</td>
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<tr>
<td>Post T20</td>
<td>1.12 (0.11)</td>
<td>1.12 (0.11)</td>
<td></td>
<td>3.5</td>
<td></td>
<td>0.0002</td>
<td>Group</td>
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ADM = abductor digiti minimi; APB = abductor pollicis brevis; ICF = intracortical facilitation; SICI = short interval intracortical inhibition; SAI = short latency afferent inhibition; LAI = long latency afferent inhibition; LICI = long interval intracortical inhibition; MEPc = conditioned MEP; MEPt = test MEP; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; SEM = standard error of the mean.

ICF, SICI, SAI, LAI, LICI are expressed as the size of the conditioned MEP normalized to the size of the test MEP. A value < 1 indicates an inhibition and smaller the value, larger the inhibition; a value > 1 indicates a facilitation and larger the value, larger the facilitation.

At T10 there was no effect of PAS in either group or muscle [Group: F(1,86) = 0.5, P = 0.5; Muscle: F(1,86) = 0.04, P = 0.8]. At T20, there was a bigger effect of PAS on Abductor pollicis brevis than on Abductor digiti minimi in both groups [Group: F(1,86) = 0.4, P = 0.6; Muscle: F(1,86) = 4.5, P < 0.03]. At T30, the effect of PAS was no longer detected in the healthy subjects, while in the patients, MEP was clearly facilitated in both Abductor pollicis brevis and Abductor digiti minimi [Group: F(1,86) = 9.5, P < 0.003; Muscle: F(1,86) = 3.5, P = 0.06] (Fig. 3).
PAS-induced plasticity of the abductor digiti minimi in healthy subjects, but not in patients (Fig. 3B). In contrast, in the healthy subjects, cerebellar cortex inhibition enhanced PAS-induced plasticity more than sham stimulation of the cerebellum or cerebellar cortex excitation [Intervention: F(2,38) = 0.7, P = 0.5; Time: F(2,38) = 0.08, P = 0.9]. In the patients, the effect did not differ across the interventions [Intervention: F(2,38) = 0.7, P = 0.5; Time: F(2,38) = 0.08, P = 0.9].

**Effects of cerebellar cortex conditioning on intracortical inhibition and facilitation**

The effects of 5 Hz PAS on MEPs in the control condition (preceded by sham stimulation of the cerebellum) were compared between the healthy volunteers and patients with writer’s cramp by using repeated ANOVA, in which the three values of the normalized MEPs (MEP_{T10}/MEP_{T0}, MEP_{T20}/MEP_{T0}, MEP_{T30}/MEP_{T0}) formed the repeats.

The test MEPs were of similar sizes before each intervention [Intervention: F(2,78) = 0.4, P = 0.7; Group: F(2,38) = 0.4, P = 0.7], suggesting that any effect of the intervention on short-interval intracortical inhibition, intracortical facilitation, short-latency afferent inhibition, long latency afferent inhibition, long-interval intracortical inhibition would not be due to a difference in test MEP sizes [Intervention: F(2,78) = 0.4, P = 0.7; Group: F(1,39) = 1.3, P = 0.2; Group × Intervention: F(2,78) = 0.6, P = 0.6].

Short-interval intracortical inhibition, intracortical facilitation, long-interval intracortical inhibition, and short-latency afferent inhibition were similar in the two groups at baseline and were not modified by any of the interventions. Long-latency afferent inhibition, which was smaller in the patients than in the healthy volunteers at baseline, remained at the same level after each intervention [long-latency afferent inhibition: Intervention F(3,105) = 0.4, P = 0.7; Group F(1,39) = 4.1, P < 0.05; Group × Intervention F(3,105) = 1.6, P = 0.2] (Fig. 4).

**Correlations between the extent of paired-associative stimulation-induced plasticity and physiological parameters or clinical scores**

Extent of PAS-induced plasticity was assessed in two ways: (i) the overall effect of PAS (mean MEP amplitude at T10, T20 and T30 normalized to MEP amplitude at T0 (MEP_{overall})); and (ii) the peak...
value of the MEP amplitude post-PAS (MEP_peak). Linear regression was used to assess correlations.

WCIS scores did not correlate with physiological parameters (RMT_bistim, AMT_rapidstim, short-latency afferent inhibition, long latency afferent inhibition, short-interval intracortical inhibition, intracortical facilitation, long-interval intracortical inhibition) or with the degree of PAS-induced plasticity in the abductor pollicis brevis, irrespective of the type of cerebellar cortex conditioning.

At baseline, short-interval intracortical inhibition, intracortical facilitation, long-interval intracortical inhibition, short-latency afferent inhibition and long-latency afferent inhibition did not correlate with the extent of PAS-induced plasticity, regardless of the type of cerebellar conditioning.

**Visuomotor adaptation task**

Task performance was assessed in terms of (i) the reaction time, i.e. the time between the ‘go’ signal and the onset of the movement (RT); (ii) the total time taken to reach the target (TT); and (iii) the time taken to correct the initial trajectory towards the correct trajectory when an artificial error was introduced (TC). The trajectories had a parabolic shape and were fitted by polygons; the time corresponding to the maximum of the curve was assumed to be the time taken by the subject to begin correcting the trajectory. We also calculated TC/TT in order to compare the time taken to adjust the trajectory to the ideal trajectory, independently of the speed of movement; and (iv) the angle between the actual trajectory and the ideal one (trajectory curve) measured 250 ms after the onset of movement (AN). These measures were evaluated for each angle of imposed error (0°, 10°, 20°, 40°), and for all the angles together. TC/TT and AN measured at imposed error angles of 10°, 20°, and 40°, reflect the capacity for online error correction, while those made at 0° reflect the capacity for washing out previous correction strategies, as the 0° trials were randomly interleaved with the other deviations (Fig. 2).

The performance of the patients and healthy volunteers was compared by using the non-parametric Mann Whitney U test.

**Comparative performance of healthy volunteers and patients with writer’s cramp**

The patients reacted with the same speed as the healthy volunteers (reaction time was similar in the two groups for all angles) but were slower than the healthy volunteers in reaching the target (target time was longer in the patients), irrespective of the imposed deviation (Mann Whitney U test: TT_all_angles: P < 0.03; TT_0°: P < 0.01; TT_10°: P < 0.03; TT_20°: P < 0.05; TT_40°: P = 0.09). As a group, the patients were able to adjust for the deviation
Correlations between behavioural parameters and the response to cerebellar stimulation

In the healthy volunteers, there was no correlation between the behavioural parameters [reaction time (RT), target time (TT), time to curvature (TC), time to curvature/target time (TT/TC), angle of deviation 250 ms after movement onset (AN)] and the effects of PAS (MEPoverall or MEPpeak) regardless of the type of cerebellar conditioning.

In the patients, there was no correlation between the behavioural parameters (RT, TT, TC/TT, AN) and the effects of PAS after sham stimulation. However, performance in the task was predictive of the effect of cerebellar cortex inhibition on M1 plasticity but not of the effect of cerebellar excitation: the poorer the task performance (larger TC/TT values or higher AN), the larger the enhancement of test MEP size after cerebellar inhibitory conditioning (Fig. 5) (MEPmax after CB-cTBS-PAS versus TT/TCall angles: P < 0.002, R² = 0.5; versus TT/TC10: P < 0.005, R² = 0.6; versus TT/TC20: P < 0.0004, R² = 0.6; versus TT/TC40: P = 0.01, R² = 0.4) (MEPmax after CB-cTBS-PAS versus ANall angles: P < 0.01, R² = 0.4; versus AN30: P < 0.03, R² = 0.3; versus AN40: P < 0.01, R² = 0.4; versus AN50: P < 0.02, R² = 0.3; versus AN60: P = 0.3). This correlation was also seen with the overall effect of PAS, assessed in terms of MEPoverall (MEPoverall after CB-cTBS-PAS versus TT/TCall angles: P < 0.001, R² = 0.5; versus TT/TC10: P < 0.01, R² = 0.4; versus TT/TC20: P < 0.003, R² = 0.5; versus TT/TC40: P < 0.02, R² = 0.3) (MEPoverall after CB-cTBS-PAS versus ANall angles: P < 0.02, R² = 0.3; versus AN30: P < 0.04, R² = 0.3; versus AN40: P < 0.02, R² = 0.35; versus AN50: P < 0.05, R² = 0.3, versus AN60: P = 0.3). Reaction time and target time did not correlate with PAS-induced plasticity following cerebellar cortex inhibition.

Correlation between task performance and baseline physiological measures

In the healthy volunteers, the larger the baseline long-latency afferent inhibition, the shorter the reaction time in the visuomotor task, for all angles of deviation (healthy volunteers: RTall angles: P < 0.02, R² = 0.6; RT10: P < 0.01, R² = 0.6; RT20: P < 0.007, R² = 0.75; RT40: P < 0.02, R² = 0.6; TR10: P < 0.04, R² = 0.5). A similar but weaker correlation was found in the patients (RTall angles: P = 0.3; RT10: P = 0.4; RT20: P < 0.02, R² = 0.3; RT40: P < 0.05, R² = 0.3).

Discussion

We report that patients with writer’s cramp exhibit a complete loss of both inhibitory and excitatory cerebellar priming of cortical sensorimotor plasticity. Online adaptive performance in a visuomotor task predicted the effect of cerebellar cortex conditioning on M1 plasticity. Patients with writer’s cramp were also less efficient than healthy subjects at washing out a previous adaptation strategy during task performance. These findings point to a dysfunction of cerebellar sensory adaptive encoding in patients with writer’s cramp, and to maladjusted sensorimotor calibration. These alterations might play a role in the pathophysiology of task-specific dystonias such as writer’s cramp.

Cerebellar priming of paired-associative stimulation-induced plasticity

Effects of cerebellar cortex conditioning on M1 plasticity are not exerted directly through a change in M1 excitability but rather upstream of M1, by processing the sensory afferent volley in PAS. Indeed, cerebellar cortex conditioning has been found to influence the subsequent M1 response to a 5 Hz PAS protocol (involving a sensory component) but not its response to a theta-burst protocol (not involving a sensory component) (Popa et al., 2013). As cerebellar cortex conditioning did not influence
somatosensory evoked potentials that travel through the lemniscal pathway via the thalamus to the somatosensory cortex, Popa et al. (2013) concluded that these latter two structures were unlikely to be the sites where the afferent volley was modified. Our findings support this hypothesis, as 5 Hz PAS, whether preceded by sham or real cerebellar cortex stimulation, did not modify the short-latency afferent inhibition (SAI10ms). The short-latency afferent inhibition has been suggested to reflect the modulation of M1 excitability by somatosensory afferent inputs (Classen et al., 2000; Tokimura et al., 2000; Tamburin et al., 2001; Sailer et al., 2002; Chen and Curra, 2004). With a 20 ms interval between median nerve stimulation and the TMS pulse, short-latency afferent inhibition can be mediated by direct projection of afferent inputs from the thalamus to M1 or, after a short relay, through the primary sensory cortex (Tokimura et al., 2000). The absence of change in the SAI10ms after 5 Hz PAS or cerebellar cortex inhibition-PAS, as observed here, confirms that the afferent volley was not modified along the relay of the lemniscal pathway. In contrast, when a 25 ms interstimulus interval was used for short latency afferent inhibition in a previous study (Quartarone et al., 2006), short-latency afferent inhibition was decreased after 5 Hz PAS, suggesting that short-latency afferent inhibition was modified by an additional subcortical relay.

Here, cerebellar cortex output modulation in healthy subjects influenced M1 sensorimotor plasticity. Cerebellar cortex inhibitory stimulation led to an enhancement of PAS-induced plasticity that involved both the target muscle and a control muscle with close cortical representation. In contrast, cerebellar cortex excitation prevented PAS-induced plasticity only in the target muscle. Given the spatio-temporal filtering properties of the cerebellum (Solinas et al., 2010), this spatially non-specific and prolonged enhancement of plasticity after cerebellar cortex inhibition in healthy subjects may be secondary to a lack of filtering and or to prolonged relay of the sensory afferent volley to M1. In contrast, the spatially specific decrease in plasticity after cerebellar excitation in healthy subjects may be secondary to exaggerated filtering of the afferent volley. Depending on cerebellar cortex excitability, the unexpected afferent input resulting from PAS could be modified by the cerebellum through its sensory filtering capability (Hamada et al., 2012; Popa et al., 2013). How non-invasive stimulation techniques influence excitability of the cerebellar cortex is not fully understood. According to their bidirectional effects on cerebellar brain inhibition (Galea et al., 2009) and on M1 plasticity (Popa et al., 2013) and the lack of concomitant changes of M1 excitability it is commonly thought that stimulations acts locally by changing the tonic excitability of Purkinje cells.

In this study, patients with writer’s cramp showed a complete loss of both the inhibitory and the excitatory cerebellar cortex conditioning effect on PAS-induced M1 plasticity in both the target and control muscles. The observed correlation between the effect of cerebellar inhibition and the impairment of behavioural parameters in the visuomotor task suggests that this loss of cerebellar priming of M1 plasticity may be due to: (i) a dysfunction that makes the cerebellum unable to control sensorimotor encoding or scaling; or (ii) a hyperactive cerebellum that is no longer able to be modulated by inhibitory thetaburst stimulation, owing to a ceiling effect. The latter hypothesis is supported by neuroimaging studies of dystonic patients that have consistently shown above-normal cerebellar activity (Neychev et al., 2011). Cerebellar hyperactivity might serve to compensate for deficient basal ganglia functioning (at a cost of some cerebellar functions) or play a role in the primary dysfunction associated with dystonia. The observed correlation between the effect of cerebellar inhibition and the impairment of behavioural parameters (Fig. 5), supports direct involvement of the cerebellum in the impaired motor function that results in writer’s cramp.

How might cerebellar dysfunction cause motor dysfunction in a limited territory and only during writing? One possible explanation comes from recent animal experiments in which the extent of cerebellar dysfunction was found to determine the topographical extent of abnormal movements (Raike et al., 2012). It is therefore conceivable that limited cerebellar impairment might produce abnormal movements only in an isolated anatomical region and/or in a particular task.

### Adaptation to a visuomotor perturbation in patients with writer’s cramp

Impaired sequence learning has been described in both non-manifesting (Ghilardi et al., 2003) and manifesting carriers of the DYT1 mutation, and was found to be associated with increased activation of the left lateral cerebellar cortex (Carbon et al., 2011). Patients with writer’s cramp have not been explored during sequence learning and are reported to have normal (Meunier et al., 2012) or impaired performance (Belvisi et al., 2013) when learning a simple motor task. Here we sought behavioural disturbances linked to a potential cerebellar dysfunction. We thus measured performance during adaptation to a visuomotor conflict in a reaching task. Indeed, the cerebellum is a key node of the neural network involved in adapting goal-directed arm movements. We chose a pointing task that allowed for online corrections and for abrupt perturbation, as subjects with cerebellar dysfunction are able to adapt to gradual but not to abrupt perturbation (Crisimagnag-Hemminge et al., 2010; Schlerf et al., 2012). The different degrees of perturbation were introduced randomly, in order to separate, as far as possible, online corrections from motor learning. Trials with no perturbation were also randomly introduced in order to test the subjects’ ability to wash out the adaptation process (forgetting). The patients with writer’s cramp showed longer movement times (increased target time) than the healthy volunteers in all movement conditions. Slowness of simple and sequential movements is a known characteristic of patients with dystonia (Agostino et al., 1992; Curra et al., 2000) and specifically of patients with writer’s cramp (Prodoehl et al., 2008), but it remains to be shown whether this is related to cerebellar or basal ganglia dysfunction.

Patients with writer’s cramp were slower than healthy volunteers to wash out the previous adaptation. This is in agreement with a previous report showing that patients with cerebellar disorders exhibited slower wash-out than healthy volunteers (Crisimagnag-Hemminge et al., 2010). Slowness of the movement per se could influence the adaptation capabilities. To disentangle the effect of slowness from that of an impairment of the...
online adaptation process we only kept in the analysis of adaptation, parameters that were hardly influenced by the distance covered, i.e. time to curvature/target time and angle of the trajectory 250 ms after movement onset. At the group level, no significant differences were found in our study between patients with writer’s cramp and healthy volunteers with respect to their capacity to adapt to the visuromotor perturbation (no difference in time to curvature/target time or angle of the trajectory 250 ms after movement onset). Yet, in the group with writer’s cramp, the parameters reflecting the capacity for online adjustment to the perturbation and for washing out an earlier adaptation (reflected in the trajectory curvature, AN, and the time to reverse the actual trajectory to the ideal one, TC/TT) were good predictors of the capacity of cerebellar inhibitory conditioning to influence sensorimotor plasticity. The better the online adaptation, the smaller the influence of cerebellar inhibitory stimulation on M1 plasticity (less enhancement of the plastic response) (Fig. 5). Performance did not correlate with sham stimulation of the cerebellum-PAS effects, indicating that cerebellar inhibition rather than PAS determined the correlation.

The lack of effect of cortical cerebellar conditioning in patients with good performance may reflect their adaptive capabilities. Two explanations may account for this observation: (i) the cerebellum may not be involved during the task; or (ii) the cerebellum is so overactivated that it is no longer susceptible to inhibition because of a ceiling effect. (i) Patients who adapt well would be able to ‘silence’ their dysfunctioning cerebellum and to use alternative circuits (perhaps the basal ganglia) to perform the task. When alternative compensatory circuits fail, the cerebellum returns to the adaptive network and cerebellar inhibition becomes efficient. (ii) A hyperactive cerebellum may compensate for the deficiency of another circuit, such as the basal ganglia. When the cerebellum is overactive, patients would perform as well as healthy volunteers, but when the illness worsens, the cerebellum would become less active and cerebellar inhibition would become effective.

**Paired-associative stimulation-induced motor cortex plasticity in patients with writer’s cramp: the effect of 5 Hz paired-associative stimulation**

In the patients with writer’s cramp, the extent of M1 plasticity induced by 5 Hz (‘high frequency, low intensity’) PAS differed from that in healthy volunteers only by the longer duration of the plastic response in the target muscle. Such a prolonged effect of a plastic intervention has already been observed in patients with cervical dystonia and in DYT 1 patients after cTBS of M1 (Edwards et al., 2006). In contrast, ‘low frequency/low-dose’ PAS does not induce exaggerated plasticity in patients with writer’s cramp (Kang et al., 2011; Meunier et al., 2012). A key feature of the enhanced effect of ‘low frequency/high-dose’ PAS plasticity in dystonic patients is its spread to surrounding muscles not receiving the sensory inputs of PAS, namely the first dorsal interrosseous muscle (Quartarone et al., 2003) or the Abductor digiti minimi (Weise et al., 2006) during PAS targeting the Abductor pollicis brevis. This was also the case of the Abductor pollicis brevis during PAS targeting the Abductor digiti minimi (Weise et al., 2006, 2011). No such spread of the PAS effect was found in our patients with writer’s cramp. The spatial selectivity of the ‘high frequency/low dose’ 5 Hz PAS effect was not different between the healthy volunteers and patients with writer’s cramp and was limited to weaker facilitation of the Abductor digiti minimi MEP at T20 compared to the Abductor pollicis brevis MEP.

In the original description of 5 Hz PAS in healthy subjects (Quartarone et al., 2006), the non-target muscle was not the Abductor digiti minimi but the first dorsal interrosseous muscle, which showed no facilitation. Such differences in the spatial diffusion of PAS effects in dystonic patients according to the PAS technique used (‘high-frequency/low-dose’ versus ‘low-frequency/high-dose’) may be due to qualitative differences in the re-organization of muscle representations in M1 when stimulated with different PAS techniques (Quartarone et al., 2006). Confirmation of this explanation will require further experiments that are outside the scope of the present study. Contrary to previous studies, the ‘control’ PAS intervention in this study was preceded by sham stimulation of the cerebellum. The sham stimulation at the location used in this study does not reproduce the effects of real cerebellar stimulation (Popa et al., 2010). Nevertheless, in most of the subjects, sham stimulation led to small head or shoulder movements that might activate the afferents from neck and shoulder muscles. By itself, stimulation of peripheral afferents from these muscles could reorganize the cortical motor maps of hand muscles (Thickbroom et al., 2003) and mask possible differences in the spatial selectivity of PAS-induced effects in healthy volunteers and patients.

**Conclusion**

This study shows that patients with writer’s cramp have lost the normal bidirectional cerebellar priming effect on M1 sensorimotor plasticity. We propose that this is due to defective cerebellar adaptive filtering or encoding of incoming afferent volleys. Impaired online adjustment to visuomotor conflict in this setting might be due to deficient cerebellar sensory encoding, resulting in a decoupling of the motor component from the afferent information flow generated by changes in the environment. Such maladjusted sensorimotor calibration and the resulting loss of cerebellar control of sensorimotor plasticity could also lead to the build-up and recall of an incorrect motor program during specific adaptation tasks (such as writing) and thus participate in dystonic movements.

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