

# Disordered plasticity in the primary somatosensory cortex in focal hand dystonia

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**Interventional paired associative stimulation (PAS) can induce plasticity in the cortex, and this plasticity was previously shown to be disordered in the primary motor cortex in focal hand dystonia (FHD). This study aimed to test whether associative plasticity is abnormal in the primary somatosensory cortex (S1) in FHD and whether PAS modulates excitatory or inhibitory interneurons within the cortex. Ten FHD patients and 10 healthy volunteers were studied. We investigated the changes in single- and double-pulse somatosensory-evoked potentials before and after PAS, which consisted of peripheral electrical nerve stimulation and subsequent transcranial magnetic stimulation over S1. Four sessions of somatosensory-evoked potentials recordings were performed: before PAS, and immediately, 15 and 30 min after PAS. We compared the time course of the somatosensory-evoked potentials between the FHD and healthy groups. In the single-pulse condition, the P27 amplitudes were significantly higher in FHD immediately after PAS than before PAS, while no changes were observed in healthy subjects. In the double-pulse condition, significant differences in the suppression ratio of P27 were found immediately after and 15 min after PAS, while there were no significant differences in healthy subjects. The P27 suppression tended to normalize toward the level of the healthy volunteer group. In FHD, PAS transiently induced an abnormal increase in excitability in S1. In addition, intracortical inhibition in S1 was found to increase as well. This abnormal plasticity of the intracortical neurons in S1 may contribute to the pathophysiology of dystonia.**

**Keywords:** associative plasticity; paired associative stimulation; focal hand dystonia; somatosensory-evoked potential

**Abbreviations:** APB = abductor pollicis brevis; BA = Brodmann area; EEG = electroencephalogram; FHD = focal hand dystonia; ISI = interstimulus-interval; LTD = long-term depression; LTP = long-term potentiation; M1 = primary motor cortex; MD = musician's dystonia; PAS = paired associative stimulation; S1 = primary somatosensory cortex; SICI = short-latency intracortical inhibition; TMS = transcranial magnetic stimulation; WC = writer's cramp

## Introduction

Patients with focal hand dystonia (FHD) have task-specific uncontrolled muscle activity with simultaneous contractions of agonist and antagonist muscles. It is usually associated with the repetitive performance of certain hand tasks such as writing, typing or playing a musical instrument. The pathophysiology of this phenomenon has been partly explained by an animal model of dystonia, in which highly repetitive sensory inputs over a large region induced plasticity-based remodelling of the primary somatosensory cortex (S1), with enlarged and overlapping cortical receptive fields (Byl *et al.*, 1996).

It has been proposed that FHD has a genetic basis, and thus bears a hereditary predisposition, although the penetrance seems low (Meunier and Hallett, 2005; Breakefield *et al.*, 2008). Evidence has accumulated that there is a pre-existing abnormality in the sensory and motor systems in FHD. Bilateral abnormality of the sensory and motor systems, despite unilateral symptoms, is one of the characteristics in FHD, which was demonstrated in behavioural (Fiorio *et al.*, 2003; Molloy *et al.*, 2003), electroencephalogram (EEG)/MEG (Meunier *et al.*, 2001; Tamura *et al.*, 2008), PET (Tempel and Perlmutter, 1993), MRI (Garraux *et al.*, 2004) and transcranial magnetic stimulation (TMS) (Ridding *et al.*, 1995; Rona *et al.*, 1998) studies. These findings suggest that the dystonic symptoms manifest themselves when repetitive movements of the hand superimpose on the latent pathological condition in the sensorimotor systems. This maladaptive response of the brain to repetitive stimuli has been considered to be due to disordered homeostatic plasticity in sensorimotor structures (Quartarone *et al.*, 2006). Repetitive hand movement is an effective strategy to learn new skills, which may be associated with the reorganization of synaptic efficacy at the neuronal level. But when this is disordered, the reorganization of the synaptic efficacy may be directed out of the homeostatic range and this may result in overflow of the motor output.

One form of plasticity in the nervous system is associative plasticity, which was suggested as a mechanism representing the physiological basis of human memory and learning (Hebb, 1949; Iriki *et al.*, 1989; Rioult-Pedotti *et al.*, 1998; Antonov *et al.*, 2003). The human *in vivo* analogue of this associative plasticity was developed by employing a particular stimulation protocol termed paired associative stimulation (PAS): a peripheral nerve stimulation paired with TMS after a certain time interval, which can lead to increased cortical excitability. The change in cortical excitability was demonstrated in both the primary motor cortex (M1) (Stefan *et al.*, 2000) and S1 in normal humans (Wolters *et al.*, 2005; Litvak *et al.*, 2007). In FHD, this associative plasticity was pathologically enhanced when PAS was applied to M1, which may partly explain the overflow phenomenon in this condition (Quartarone *et al.*, 2003).

One question addressed herein is whether the associative plasticity is abnormal in S1 in FHD. It has been proposed that dystonia might be a sensory disorder (Hallett, 1995) and several studies showed impaired somatosensory capabilities (Tinazzi *et al.*, 1999; Bara-Jimenez *et al.*, 2000a, b; Fiorio *et al.*, 2003; Molloy *et al.*, 2003) and impaired sensory-motor integration (Murase *et al.*, 2000; Abbruzzese *et al.*, 2001; Tamburin *et al.*, 2002) in dystonia

patients. Therefore, it is conceivable that cortical S1 plasticity is disordered as well in FHD. In addition, we studied whether PAS leads to enhanced excitatory or inhibitory neural circuits within S1. It was suggested that excessive movement in dystonia is attributable to loss of inhibition, given that the central nervous system operates through a balance between excitation and inhibition (Hallett, 2004). We recently demonstrated that intracortical inhibitory function in S1 was impaired in FHD, showing the reduced suppression of an SEP component at a short (5 ms) interstimulus-interval (ISI) in a paired-pulse paradigm (Tamura *et al.*, 2008). This specific physiologic function significantly correlated with somesthetic discrimination capability in both FHD patients and healthy volunteers, and therefore, the SEP suppression presumably induced by intracortical inhibitory interneurons in S1 can be regarded as an electrophysiological correlate of somesthetic temporal discrimination. We investigated whether PAS of S1 could induce cortical plasticity and whether the plasticity was guided toward the excitatory or inhibitory direction by recording single-pulse and double-pulse SEPs.

## Subjects and methods

### Subjects

We studied 10 patients with idiopathic FHD (one female and nine males; mean age  $\pm$  SD,  $51.2 \pm 8.4$  years). All patients were right-handed according to the Edinburgh handedness inventory. Five patients had writer's cramp (WC) and five had musician's cramp. At the time of the study: (i) all patients had symptoms only in the dominant right hand; (ii) none had switched to using the non-dominant left hand in daily life activities; (iii) none had any abnormality of elemental somatosensory function (e.g. tactile, pain and position sensation tested by bedside clinical examination); (iv) none had botulinum toxin injection for at least 3 months prior to the examination and (v) none had chronic exposure to neuroleptic drugs. Dystonia disability score was evaluated in all patients (Fahn, 1989). Characteristics of the patients are summarized in Table 1. Ten healthy right-handed volunteers (two females and eight males; mean age  $\pm$  SD,  $48.2 \pm 9.8$  years) served as controls. All patients and healthy volunteers gave written consent for this study protocol, which was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board.

All patients and healthy volunteers underwent both EEG recording and PAS intervention. During both examinations, subjects were seated in an armchair in a quiet room, the temperature of which was kept constant  $\sim 26^\circ\text{C}$ . They were asked to keep their eyes open, and to gaze at the fixation point placed  $\sim 1.5\text{ m}$  ahead of them.

### SEP recordings

The single-pulse SEP and double-pulse SEP with 5-ms ISI were measured. Transcutaneous electrical stimulation was applied with an electrical stimulator (DS7A, Digitimer Ltd., Welwyn Garden City, UK), the timing of which was controlled by Stim2 software (Neuroscan, El Paso, TX, USA). Electrical pulses were given to the trunk of the right median nerve at the wrist through a conventional bar electrode with cathode proximal. The electrical pulse was a constant current square-wave pulse of 0.2 ms duration; intensity of each stimulus was adjusted to 1.2 times motor threshold for the right abductor pollicis brevis (APB) muscle. None of the patients complained of any discomfort or pain at

**Table 1** Clinical characteristics of patients with focal hand dystonia

Patient	Type (Writer/Musician)	Age (years)	Gender (M/F)	Duration (years)	Dystonia with	Disability score (%)	Treatment (months from last injection)
1	Musician	55	M	3	Several actions	30	None
2	Musician	44	M	13	One specific action	30	Botulinum toxin (6)
3	Musician	39	M	6	One specific action	0	None
4	Writer	55	F	17	Several actions	27.4	None
5	Writer	57	M	4	Several actions	43.0	Botulinum toxin (7)
6	Musician	37	M	3	One specific action	0	Botulinum toxin (4)
7	Writer	61	M	36	Several actions	18.9	None
8	Writer	57	M	16	One specific action	0	Botulinum toxin (7)
9	Writer	50	M	7	Several actions	33.8	Botulinum toxin (4)
10	Musician	57	M	17	Several actions	32.7	Botulinum toxin (8)
Healthy volunteers	(NA)	31–61	8/2	(NA)	(NA)	(NA)	(NA)

this stimulus intensity. One session consisted of recording the responses to single electrical pulse and the responses to double pulses with an ISI of 5 ms. In one session, 800 epochs were collected for a single stimulus and 800 epochs for double stimuli with digital event marking. The interval between the beginnings of each epoch was 333 ms. The order of the stimulus conditions was pseudo-randomized within one session. During the recording, to keep the subjects' attention on the stimulated hand consistently and to standardize the level of attention among the subjects, we asked them to perform a task in which 2000 ms gaps were inserted pseudo-randomly in the series of electrical stimuli. Subjects were asked to count the number of gaps mentally and then report the answer at the end of each session (no cognitive manipulation such as calculation was required). EEG was recorded with a 64-channel surface electrode cap (Electro-Cap International, Eaton, OH, USA) with reference to left ear-lobe (A2). Each electrode of the cap was made detachable in order to place the TMS coil tightly onto the scalp. EEG signals were recorded from the following four electrodes, F3, F4, C3P, C4P, according to the International 10–20 System. In addition, the signals from Fz and Oz were monitored to ensure that the recordings were appropriate. An electrooculogram was monitored with a pair of electrodes placed 1 cm below the lateral canthus of the right eye and 1 cm above the upper edge of the right orbit. The ground electrode was placed on the volar forearm of the right hand. Impedance between electrodes was kept <5 k $\Omega$ . Signals from all channels were amplified (Neuroscan, El Paso, TX, USA), filtered (0.05–2 kHz), digitized (sampling frequency, 10 kHz) and stored for offline analysis.

## Paired associative stimulation

An interventional PAS was performed using a similar paradigm employed previously (Wolters *et al.*, 2005). PAS consists of applying a peripheral electrical nerve stimulation and a subsequent TMS. Median nerve trunk at the wrist was stimulated at the intensity of 1.2 times motor threshold for the right APB muscle. Magnetic stimulation was produced with a 7-cm figure-of-eight-shaped coil connected to a Magstim200 stimulator (The Magstim, Dyfed, UK). Prior to the PAS procedure, the 'motor hot spot' was determined as the location where the best motor responses were obtained for the right APB muscle. In the present study, our interest involved plasticity of S1, and therefore, during the PAS, magnetic stimulation was delivered over the position 2 cm posterior to the 'motor hot spot'. This position was believed to overlie S1 (Okamoto *et al.*, 2004). With this targeting

excitability changes were induced in S1, whereas M1 stimulation failed to yield the effect in the same experiment (Wolters *et al.*, 2005). The coil was held tangentially to the skull with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane; stimulus intensity was 1.5 times the resting motor threshold. The interval between preceding median nerve stimulation and magnetic stimulation over S1 was adjusted to the individual N20 peak latency. One hundred and eighty pairs were administered at 0.1 Hz over 30 min. During the PAS the subjects were instructed to perform a task that demanded attention to the stimulated hand, because attention accentuates the PAS effect maximally (Stefan *et al.*, 2004). A single electrical pulse (without any following magnetic stimulation) was delivered periodically in a pseudo-random manner. With this procedure each subject could differentiate single peripheral stimulation (without magnetic stimulation) from the paired stimuli (Ueki *et al.*, 2006). Each subject was asked to count the number of single median nerve pulse to keep their attention on the target hand.

## Experimental design

We investigated the changes in both single- and double-pulse SEPs before and after PAS. Four sessions of SEP recordings were performed: before PAS, and immediately after PAS, 15 and 30 min after PAS. Individual N20 peak latency was used as an interval between the nerve and magnetic stimulation during PAS, which was elucidated in the first SEP recording (prior to the PAS).

## Data analysis

SEP waveforms in the single- and double-pulse conditions were obtained time-locked to the stimulus onset of the single-control pulse and to the onset of the first stimulus in the double-pulse condition. The duration of one epoch was 100 ms including a prestimulus period of 30 ms. For each epoch, the baseline was adjusted based on EEG potentials during the prestimulus period (–30 to –5 ms). Epochs with electric artifacts exceeding 150  $\mu$ V in peak-to-peak amplitude, such as those from blinking or ocular movements, were automatically excluded from analyses. To isolate the SEP to the second stimulus in the double stimuli, the averaged waveforms to the single control stimulus were subtracted from those to the double stimuli. We identified N20 and P27 in the centroparietal region (C3P). Amplitudes of these components were measured from the preceding peak to avoid the effects of baseline shift. Amplitudes of SEP components in response

to the second stimulus were compared as a ratio to the amplitudes of single control SEP response.

For the statistics, we compared the time course of each of the single-pulse and double-pulse SEPs between the FHD patients and healthy volunteers. We performed two-way repeated-measures analyses of variance (ANOVA) with time (before PAS, immediately, 15 min, 30 min after PAS) as a within-subject variable and group (FHD patients and healthy volunteers) as a between-group variable for each component and each stimulus condition independently. For the single-pulse SEP, amplitude values were compared, whereas for the double-pulse condition, SEP ratios of the second stimuli to the first were compared. *Post hoc* analyses were performed with correction for multiple comparisons where appropriate. A  $P$ -value  $< 0.05$  was considered significant in each statistical analysis.

## Results

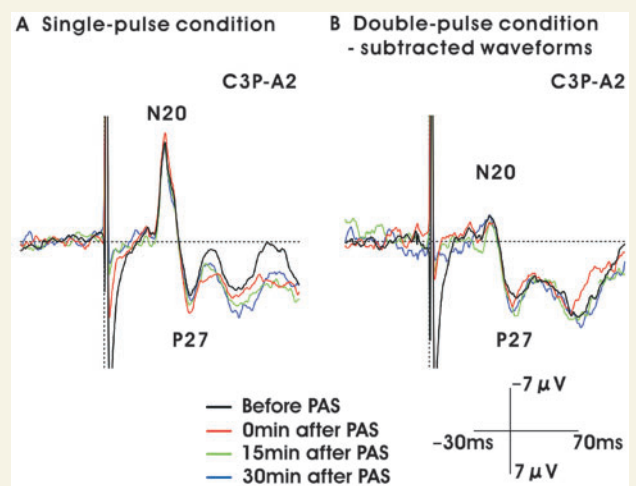
None of the subjects experienced any adverse events during the examination. No patients showed abnormal dystonic posturing with the stimulation. Both N20 and P27 components were found in all subjects at the C3P electrode referenced to A2. Waveforms in the single-pulse condition and subtracted waveforms in the double-pulse condition in a representative FHD patient are shown in Fig. 1.

Mean values and standard deviations of the N20 and P27 components in the single-pulse condition are shown in Fig. 2A. For the N20 amplitude, the repeated-measures ANOVA failed to reveal either significant effect of group ( $P = 0.755$ ), time ( $P = 0.673$ ), or their significant interaction ( $P = 0.932$ ). On the other hand, for the P27 amplitude, there was significant effect of time ( $P = 0.030$ ), while no significant effect was found in group ( $P = 0.399$ ). Their interaction was also significant ( $P = 0.049$ ). *Post hoc* analysis showed a significant difference in P27 amplitude immediately after PAS ( $P < 0.05$ , after Bonferroni correction): P27 amplitudes were significantly higher in FHD immediately after PAS than before PAS. No significant differences were found at any other sampling points.

With respect to the double-pulse condition, mean values and standard deviations of the ratios of the amplitude suppression are shown in Fig. 2B. For the N20, there was no significant effect of group ( $P = 0.473$ ), time ( $P = 0.619$ ), or their interaction ( $P = 0.126$ ). As to the P27, we found significant effects of both group ( $P = 0.048$ ), time ( $P = 0.009$ ) and their interaction ( $P = 0.018$ ). *Post hoc* analysis revealed that the suppression ratios immediately and 15 min after PAS were significantly less than before PAS ( $P < 0.05$ , after Bonferroni correction). On the other hand, there were no significant differences between the ratios before PAS and those obtained 30 min after PAS. P27 suppression tended to be normalized toward the level of the healthy volunteer group.

## Discussion

The present study explored associative plasticity in S1 in FHD. We found that cortical excitability as probed by single-pulse SEP was enhanced by PAS more in FHD patients than in healthy volunteers. In addition, the intracortical inhibitory function investigated by the

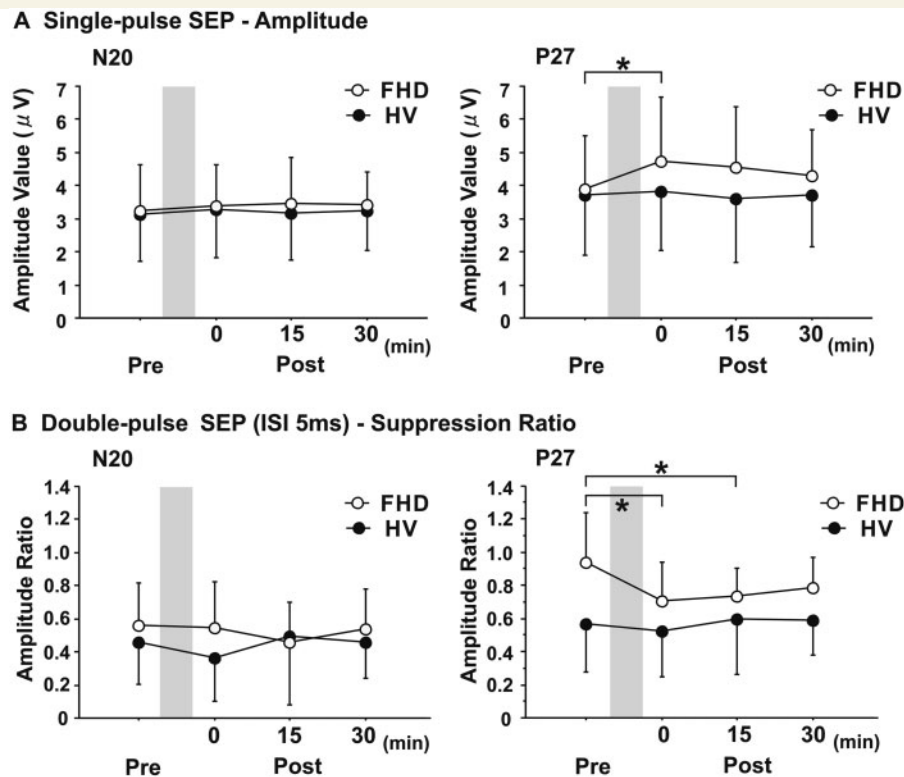


**Figure 1** Waveforms of somatosensory-evoked potentials (SEPs) in a representative FHD patient. (A) SEP responses to a single electrical pulse for each time point are superimposed. N20-P27 complexes are conspicuous in centroparietal region (C3P). PAS intervention yielded a transient increase in N20-P27 amplitude. (B) SEP responses to the second stimuli were isolated by subtracting the waveforms in the single-pulse condition from those in the double-pulse condition. N20-P27 complexes remained unchanged after PAS.

paired-pulse paradigm was affected by PAS: the suppression ratio tended to normalize toward the level of the healthy volunteer group. These changes were shown in the P27 component and not in the N20 component.

It was initially shown that S1 plasticity could be induced by PAS in healthy humans (Wolters *et al.*, 2005). This system-level plasticity was believed to represent the mechanisms observed in the reorganization of the synaptic connections called long-term potentiation (LTP) or long-term depression (LTD), which follow a spike-timing-dependent manner (Dan and Poo, 2004). In healthy humans, plasticity induced by PAS over S1 was demonstrated as a change in the cortical P25 component (P27 in the present study) and not in the N20 component (Wolters *et al.*, 2005). In our study, we showed P27 changes after PAS in FHD, but not in normal subjects. The mean value of P27 amplitude obtained immediately after PAS in the normal subjects was slightly higher than that obtained before PAS. Because the difference in P27 amplitude reported by Stefan and colleagues was somewhat small (but significantly different), our failure to show the difference is probably due to the statistical lack of power. However, the experimental design of the present study was only to show the difference between the two groups.

Although the precise localization of the generator of the SEP components is still debatable, it is highly likely that centroparietal N20 and P27 are generated within S1. An electrophysiological study on monkeys (Peterson *et al.*, 1995) showed that the earliest component, N10, reflected the depolarization of layer 4 cells in area 3, whereas the subsequent P20 component was recorded more superficially and included activities from multiple laminae including layer 2/3. Because most of the thalamocortical



**Figure 2** Time courses of the SEP amplitude in each condition. (A) Mean amplitude values ( $\pm$ SD) of N20 and P27 components in the single-pulse condition are shown for each sampling point (open circle, FHD; filled circle, healthy volunteers). With respect to N20 amplitude, a two-way repeated measures analysis of variance (ANOVA) failed to reveal significant effect of time, group or their interaction. For the P27, a significant effect was found only in group and the interaction between group and time was also significant. *Post hoc* analysis showed that P27 amplitude was significantly higher immediately after PAS than that before PAS ( $*P < 0.05$  after Bonferroni correction). (B) Mean amplitude values ( $\pm$ SD) of N20 and P27 suppression ratios in the double-pulse condition were shown. For N20, a two-way ANOVA revealed no significant effect of time or group. Their interaction was not significant either. For P27, significant effects were found both in group and time, and their interaction was significant. *Post hoc* analysis showed that the suppression ratio immediately after and 15 min after PAS were significantly less than that before PAS in FHD ( $*P < 0.05$  after Bonferroni correction).

projections terminate in layer 4 and the overlying part of layer 3 in area 3b (Jones, 1975; Jones and Burton, 1976), it is unlikely that changes in P27 suppression in the present finding reflect abnormal thalamocortical activity. Therefore, alteration of the P27 component is more attributable to functional changes of intracortical structures in S1 connecting between layers 4 and 2/3. A detailed source analysis of the SEP change was performed with 64-channel EEG recordings in healthy subjects (Litvak *et al.*, 2007). This study clearly demonstrated that the effect of S1 PAS was observed as an increased tangential activity while the radial component remained stable, suggesting that the structures modified by PAS were located in the upper cortical layers of Brodmann area (BA) 3b. Therefore, the increased plasticity in S1 in FHD should be attributable to the disorganized interneurons in upper cortical layers of the BA 3b.

Our results show that S1 plasticity is abnormal in FHD. Many studies have demonstrated that FHD patients have somesthetic discrimination abnormality, suggesting that excessive movement in FHD may be attributable to an abnormal somatosensory processing. It was demonstrated that spatial discrimination is impaired in FHD (Bara-Jimenez *et al.*, 2000a; Molloy *et al.*, 2003). Animal models of dystonia (Byl *et al.*, 1996) and concurrent human

neuroimaging studies (Elbert *et al.*, 1998; Meunier *et al.*, 2001; Candia *et al.*, 2003) explained this phenomenon, showing enlarged and distorted cortical receptive fields. This could be due to loss of surround inhibition in sensory processing. In addition, in the time domain, there also appears to be reduced surround inhibition (Tinazzi *et al.*, 1999; Bara-Jimenez *et al.*, 2000b), which may lead to blurring of the temporal separation between consecutive distinct perceptions and yield an overflow of somatosensory information. We previously demonstrated that the capability of somesthetic temporal discrimination is well correlated with suppression of the P27 component in a paired-pulse SEP paradigm (Tamura *et al.*, 2008). In the present study, such P27 suppression was less in FHD in the baseline condition, which agrees with our previous results. This P27 suppression at short ISI is likely to reflect intracortical inhibitory function in S1. There are many types of highly-specialized inhibitory interneurons in the cortex (Somogyi *et al.*, 1998), and this temporal inhibition at short ISI may be carried out by a particular class of such interneurons. We found that one particular class of inhibitory interneurons showed an increase in function by PAS, which is conceivable because the neuronal structures targeted by PAS of S1 should be intracortical interneurons. We also found increased S1 excitability in the

single-pulse paradigm, but the functional change in the inhibitory interneurons clearly does not explain the overall increased cortical excitability. Therefore, each of those changes needs to be explained by different mechanisms, which warrants further investigations. Although it is unclear whether this responsiveness of the inhibitory neurons contributes to the pathophysiology of dystonia, it is possible that normalization of the P27 suppression by PAS may lead to improved somesthetic temporal discrimination because the temporal discrimination capability correlated closely with the P27 suppression at short ISI (Tamura *et al.*, 2008).

It is of note that the S1 physiology in FHD bears considerable analogy to that of M1. In the first place, the temporal inhibition at very short ISI is impaired in FHD both in M1 and S1 (Ridding *et al.*, 1995; Tamura *et al.*, 2008). Furthermore, these impairments were observed in both hemispheres, even though the dystonic symptoms were unilateral. In terms of cortical plasticity, the motor cortical excitability was facilitated by PAS, and this facilitation was greater in FHD patients. On the other hand, PAS over M1 failed to affect intracortical inhibitory function as indexed by short-latency intracortical inhibition (SICI) in the paired-pulse 'motor' TMS paradigm (Quartarone *et al.*, 2003). As to the associative plasticity in S1 in the present study, cortical excitability was enhanced more in FHD; temporal inhibition in the somatosensory system was facilitated by PAS as well. There may well be similar mechanisms of cortical plasticity in motor and sensory cortices. Taken together, it is possible that aberrant plasticity in M1 is primarily driven by the increased plasticity in S1 because sensory afferent information plays a substantial role in the associative plasticity in M1 in the PAS protocol (Stefan *et al.*, 2000). It is yet to be determined if the disordered plasticity in M1 is solely a result from the maladaptive response in S1 or a property of M1 independent from S1, for which further studies seem warranted.

We here included WC and musician's dystonia (MD) in the same entity as FHD. However, it was proposed that these two might have different pathophysiology. This is based on the finding that these have different sensorimotor physiology (Rosenkranz *et al.*, 2005, 2008). In MD repetitive performance of a highly skilled task is always the case, whereas this is frequent but not constant in WC. Physiological differences shown in previous studies may reflect just the extent of the performance repetition or the difference of the latent pathological condition irrespective of symptom manifestation. The former is supported by the finding that MD and other types of FHD, such as WC, are seen in the same families (Schmidt *et al.*, 2006). In the present study, a *post hoc* analysis dividing the patients into WC and MD groups showed the changes of the P27 after PAS, in both single- and double-pulse conditions, to not differ significantly. Larger numbers of patients would be needed to prove this more definitively. This issue is further partly testable by investigating whether the unaffected hand differs in physiology (e.g. SICI, PAS-induced cortical plasticity) between WC and MD. That would also solve whether the physiological abnormality represents a primary pathological condition or an adaptation process secondary to symptom manifestation.

In conclusion, we showed that cortical plasticity in S1 is disordered in FHD. This could contribute to the maladaptive responsiveness in dystonia, as well as to the abnormal plasticity in M1.

These findings further support the notion that dystonia can be considered as a sensory system disorder as well as a motor disorder.

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