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The basal ganglia are hyperactive during the discrimination of tactile stimuli in writer's cramp

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Writer's cramp is a focal hand dystonia that specifically affects handwriting. Though writer's cramp has been attributed to a dysfunction of the basal ganglia, the role of the basal ganglia in the pathogenesis of writer's cramp remains to be determined. Seventeen patients with writer's cramp (nine females; age range: 24–71 years) and 17 healthy individuals (six females; age range: 27–68 years) underwent functional MRI (fMRI) while they discriminated the orientation of gratings delivered to the tip of the right index finger. Statistical parametric mapping was used to analyse the fMRI data. The significance level was set at a corrected *P*-value of 0.05. Relative to healthy controls, patients with writer's cramp showed a widespread bilateral increase in task-related activity in the putamen, caudate nucleus, internal globus pallidus and lateral thalamus. In these areas, hyperactivity was more pronounced in patients who had recently developed writer's cramp. The enhanced response of the basal ganglia to tactile input from the affected hand is compatible with the concept of impaired centre–surround inhibition within the basal ganglia–thalamic circuit and may lead to an excessive activation of sensorimotor cortical areas during skilled movements affected by dystonia. Outside the basal ganglia, dystonic patients showed task-related overactivity in visual cortical areas, left anterior insula and right intraparietal sulcus, but not in the primary or secondary sensory cortex. In addition, task-related activity in the cerebellar nuclei, posterior vermis, right paramedian cerebellar hemisphere and dorsal pons was inversely related with the severity of hand dystonia. Regional activity in these areas may reflect secondary adaptive reorganization at the systems level to compensate for the dysfunction in the basal ganglia–thalamic loop.

Keywords: basal ganglia; focal hand dystonia; functional MRI; tactile discrimination; thalamus; writer's cramp

Abbreviations: ADDS = Arm Dystonia Disability Scale; BOLD = blood oxygen level-dependent; fMRI = functional MRI; SPM = statistical parametric map

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Introduction

Writer's cramp is a task-specific dystonia of the hand (Sheehy and Marsden, 1982). Affected patients show co-contractions of agonist and antagonist muscles and an overflow of muscular activity spreading to more proximal muscles during handwriting (Sheehy and Marsden, 1982). Like other focal dystonias, writer's cramp is commonly attributed to a dysfunction of the basal ganglia (Berardelli *et al.*, 1998). Evidence for a critical involvement of the basal ganglia–thalamic circuit in the pathogenesis of dystonia stems from clinicopathological studies in patients with symptomatic dystonia (Marsden *et al.*, 1985) and intracerebral recordings from the globus pallidus and thalamus in patients who received surgery to treat dystonia (Vitek, 1999; Zhuang *et al.*, 2004). Intraoperative recordings demonstrated an alteration of neuronal activity in the basal ganglia thalamocortical motor circuits, including changes in mean discharge rate, firing pattern and responsiveness to sensory stimuli (Vitek, 1999). PET of resting glucose metabolism disclosed an abnormal topographic metabolic profile characterized by co-varying increases in metabolic activity in the lentiform nucleus and

other components of the motor system in patients with idiopathic dystonia (Eidelberg *et al.*, 1995) and carriers of the DYT1 gene mutation (Eidelberg *et al.*, 1998). PET of regional cerebral blood flow demonstrated an increased modifiability of the cortico-basal ganglia–thalamocortical loops after low-frequency transcranial magnetic stimulation (TMS) over the dorsal premotor cortex (Siebner *et al.*, 2003).

A putative role of the cortico-basal ganglia–thalamocortical loops is to focus and tune the motor output to a specific group of muscles by opening the sensory channel for the expected sensory feedback afferents during movement (Kaji, 2001). This concept is supported by the functional neuroanatomy of the basal ganglia (Mink, 1996). The direct pathway in the basal ganglia reduces the inhibitory drive from the output structures of the basal ganglia onto the thalamic ventrolateral nuclei and, thus, facilitates the thalamocortical output to the motor cortex, whereas the indirect pathway exerts an inhibitory effect on the output structures of the basal ganglia, causing a disfacilitation of the thalamocortical output (Mink, 1996). Concurrent activation of both pathways provides an efficient centre (excitatory) and surround (inhibitory) mechanism for motor control. The direct pathway facilitates the recruitment of a population of cortical neurons that subserve the intended movement, while the indirect pathway inhibits neuronal populations that are related to unwanted movements (Mink, 1996). It has been proposed that the focusing function of the basal ganglia is faulty in patients with dystonia (Kaji, 2001). This concept has been corroborated by recent studies that applied TMS to the primary motor cortex and showed deficient centre excitation and surround inhibition during the performance (Sohn and Hallett, 2004) and imagery (Quartarone *et al.*, 2005) of simple finger movements in writer's cramp.

Another line of research has revealed that central sensory processing is altered in patients with writer's cramp. (Hallett, 1998; Tinazzi *et al.*, 2003). Quantitative testing of temporal (Bara-Jimenez *et al.*, 2000*b*; Sanger *et al.*, 2001; Fiorio *et al.*, 2003) and spatial (Bara-Jimenez *et al.*, 2000*a*; Sanger *et al.*, 2001; Molloy *et al.*, 2003) tactile discrimination as well as kinaesthetic perception (Grunewald *et al.*, 1997) revealed deficits in patients with writer's cramp relative to healthy age-matched controls. Spatial discrimination thresholds were significantly increased in both hands (Sanger *et al.*, 2001; Molloy *et al.*, 2003) but showed no correlation with the severity or duration of dystonic symptoms (Molloy *et al.*, 2003). These psychophysiological abnormalities are paralleled by dysfunctional processing of sensory inputs in writer's cramp, including deficient sensorimotor inhibition (Abbruzzese *et al.*, 2001; Tinazzi *et al.*, 2005), disturbances of sensory gating (Murase *et al.*, 2000) and abnormal integration of dual somatosensory input (Tinazzi *et al.*, 2000).

Using magnetoencephalography (MEG) (Bara-Jimenez *et al.*, 1998; Elbert *et al.*, 1998; Meunier *et al.*, 2001; Braun *et al.*, 2003) or functional MRI (fMRI) (Butterworth *et al.*, 2003), several groups demonstrated distorted somatotopic representations of individual digits in the primary somatosensory cortex in patients with task-specific hand dystonia. These findings tie in with the dedifferentiation of cortical sensory maps in a non-human primate model of hand dystonia. In New World owl monkeys, prolonged training of rapid, repetitive, highly stereotypic movements led to a marked degradation of somatosensory cortical representations and the manifestation of hand dystonia (Byl *et al.*, 1996, 1997). A similar somatosensory dedifferentiation was demonstrated in the human thalamus with intraoperative recordings in dystonic patients who underwent thalamotomy (Lenz and Byl, 1999*a*; Lenz *et al.*, 1999*b*)

Here, we used blood oxygen level-dependent (BOLD) fMRI while participants had to discriminate the grating orientation of a plastic dome that was gently pressed on the tip of the right index finger. The study was designed to test the hypothesis that dysfunctional processing of tactile inputs from the affected hand would lead to an excessive activation of the basal ganglia and somatosensory cortex in writer's cramp relative to healthy controls. Since previous studies showed that patients with writer's cramp are significantly impaired on this task (Bara-Jimenez *et al.*, 2000*a*; Sanger *et al.*, 2001; Molloy *et al.*, 2003), we reasoned that this task would be particularly suited to reveal dysfunctional processing in the sensory cortex and basal ganglia. We further predicted that patients with writer's cramp would recruit additional cortical and subcortical areas such as occipitoparietal cortex and the cerebellum to compensate for impaired processing in the somatosensory system.

Material and methods

Participants

We studied 17 patients with writer's cramp (nine females; 50.6 ± 12.2 years; range: 24–71 years) and 17 healthy individuals (six females; age = 49.8 ± 13.8; range: 27–68 years). Participants were consistent right-handers according to the Edinburgh handedness inventory (Oldfield, 1971). Before participating in the experiment, subjects gave written informed consent according to the Declaration of Helsinki. The experimental protocol was approved by the local ethics committee.

In patients, the diagnosis of writer's cramp was based on medical history and standard clinical examination. The clinical course was compatible with primary dystonia, with no features to suggest secondary dystonia. Other inclusion criteria were (i) no cause for dystonia disclosed by investigation, including MRI and biochemical tests; (ii) no peripheral neuropathy of the right median or ulnar nerve as revealed by standard neurography; (iii) no history of neuroleptic medication; (iv) no history of other neurological or psychiatric disease; and (v) a tactile discrimination threshold of at least 3.0 mm (for details, *see* below).

We screened 22 patients with writer's cramp who had a history of at least 2 years of impaired handwriting. Five patients were excluded from the study because neurography revealed a carpal tunnel syndrome (n = 2) or tactile discrimination threshold was >3.0 mm (n = 3). The remaining 17 patients had a mean disease duration of 10.0 ± 7.3 years, ranging from 2 to 25 years. Writer's cramp was defined as simple if dystonia was present only during writing and as dystonic if dystonia was also present during other

manual motor tasks (Sheehy and Marsden, 1982). Five patients had simple writer's cramp, whereas 12 patients had dystonic writer's cramp. In the group presenting with dystonic writer's cramp, five patients reported additional difficulties only when using a PC-mouse. Seven patients noted dystonic symptoms during other manual tasks. No patient presented with dystonia at rest. Fourteen patients had been previously treated with botulinum toxin injections. Those patients were studied at least 3 months after the last injections, and any drug effect had fully worn off at the time of the experiment. None of the participants was taking medication known to modulate the function of the CNS, including anticholinergic drugs.

We used the Arm Dystonia Disability Scale (ADDS) according to Fahn to assess the functional impairment of manual activity in each patient (Fahn, 1989). A score of 100% indicated that arm dystonia did not affect motor function. At a score of 90%, manual motor activities were not affected, but the patient was socially affected by dystonia. Patients who reported any limitations of functional activities had to answer seven questions that referred to daily manual activities, using a score from 0 to 3. The total points scored were divided by the maximum possible points and multiplied by 90. The result was then subtracted from 90%. The final score presents the percentage of normal manual activity (i.e. the lower the ADDS score the more severe the functional impairment). The patients who participated in the fMRI study had a mean ADDS score of 58.1 ± 15.5% (range: 17.1–77.1%).

Psychophysiological measurements

Before the fMRI experiment, tactile spatial acuity was evaluated at the tip of the right and left index finger using a set of eight hemispheric plastic domes (Stoelting, Wood Dale, IL, USA). Testing was performed according to the procedure reported by Van Boven and Johnson (1994). Participants were seated comfortably in a chair with their eyes closed and the arm held in a supine position. These domes had gratings of different gap values (mm): 3.0, 2.0, 1.5, 1.2, 1.0, 0.75, 0.50 and 0.35. Domes were applied in decreasing order of gap values. During testing, a dome was gently pressed for ~1 s on the tip of the right index finger. For each gap value, a random sequence of horizontal and vertical grating orientations were applied and participants were required to identify the orientation. If participants were unsure, they were asked to guess in order to obtain an answer for all 20 applications. The grating discrimination threshold was defined as the gap value at which the participant identified 75% of the orientations correctly. Only individuals with a tactile discrimination threshold of at least 3.0 mm were included in the study.

Differences in mean grating discrimination threshold between groups were assessed using a two-sample *t*-test. Because the grating discrimination threshold increases with age (O'Dwyer *et al.*, 2005), simple linear regression was used to characterize the age-related decrease of sensory thresholds in both groups. Group data are presented as means ± 1-fold SD.

Experimental paradigm

We employed an epoch-related fMRI design to map regional changes in BOLD signal while participants discriminated the orientation of gratings delivered to the tip of the right index finger. In contrast to previous studies that mapped regional neuronal activity during tonic vibration (Tempel and Perlmutter, 1993; Butterworth *et al.*, 2003), we chose a tactile discrimination task because the task required active processing of the sensory stimuli.

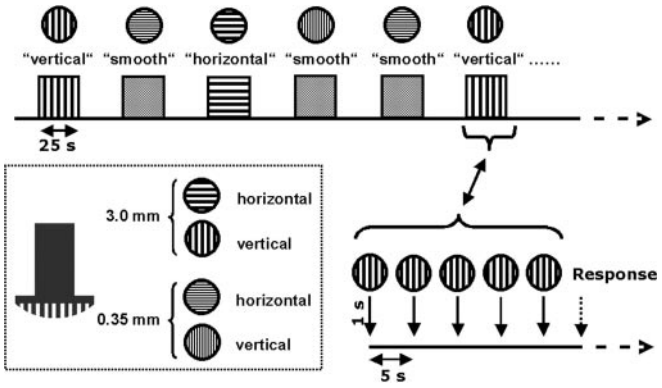

Fig. 1 Experimental design. Each fMRI session consisted of two alternating 25-s epochs with and without tactile stimulation. During the stimulation blocks an experimenter gently pressed a horizontally or vertically oriented plastic dome onto the pad of the participant's right index finger. In a single block, the same stimulus was repeatedly applied for 1 s every 5 s. After the fifth stimulus, participants were required to indicate the orientation of the gratings by pressing a button with the left index finger (smooth surface), middle finger (vertical orientation) or ring finger (horizontal orientation). We used two domes with a gap value of 0.35 mm and of 3.0 mm and two grating orientations for tactile stimulation (panel marked by the dotted line). Gratings with a gap value of 0.35 mm were below tactile discrimination threshold and perceived as smooth surface. Conversely, gratings with a gap of 3.0 mm were above the tactile discrimination threshold and the horizontal and vertical grating orientations were easily perceived by the participants.

Each fMRI session consisted of two alternating 25-s epochs of rest and task (Fig. 1). Participants kept their eyes open fixating a central cross presented on the screen. During the rest condition, subjects were instructed to look straight ahead and rest. During the grating orientation task, the examiner (H.R.S. or M.P.) repeatedly applied a horizontally or vertically oriented plastic dome (Johnson-Van Boven-Phillips domes, Stoelting, Wood Dale, IL, USA) to the tip of the participant's right index finger for ~1 s (Van Boven and Johnson, 1994). Tactile stimulation was repeated five times every 5 s with the same dome without changing the orientation (Fig. 1). The examiner wore fMRI-compatible headphones connected via a plastic tube to the room outside the magnet. An instruction alerted the examiner to the next trial. The onset and duration of sensory stimulation were indicated by a tone to standardize sensory stimulation across trials and sessions. Two seconds before tactile stimulation, a visual warning cue was presented to alert the participants to the first tactile stimulus. After the application of the fifth stimulus, participants were prompted by a visual cue to judge the orientation of the gratings by pressing a button with the left index finger (smooth surface), middle finger (vertical orientation) or ring finger (horizontal orientation). Participants were asked to make their responses during a 2 s period after the visual cue. Button presses were recorded using an fMRI-compatible response box.

Because sensory stimulation and response preparation were separated in time, it was possible to dissociate neuronal processes related to sensory processing from those implicated in response generation.

Since previous studies showed an increase in the discrimination threshold of grating orientation in patients with focal hand dystonia (Bara-Jimenez *et al.*, 2000*a*; Sanger *et al.*, 2001; Molloy *et al.*, 2003), we were concerned that differences in task-related changes in BOLD signal might be confounded by between-group differences in task difficulty or task performance. To avoid this confound, we designed a grating orientation task that could be easily performed by the patients. During fMRI, we applied domes with gap values of 3.0 and 0.35 mm. Each dome was gently pressed on to the tip of the right index finger using a horizontal or vertical grating orientation. The grating orientation of the dome with the large gap value (3.0 mm) could be easily perceived by all participants. Conversely, the gratings of the dome with the small gap value (0.35 mm) were clearly below the tactile perception threshold of all participants and consistently perceived as having a smooth surface. The grating orientation task was repeated 12 times per fMRI session. The four stimuli (0.35 mm gap/horizontal orientation; 0.35 mm gap/vertical orientation; 3.0 mm gap/horizontal orientation; 3.0 mm gap/vertical orientation) were presented three times per fMRI session in a pseudorandom order. It should be noted that we only included individuals with a tactile discrimination threshold of at least 3.0 mm. This selection criterion ensured that patients and controls could easily perform the task.

Functional magnetic resonance imaging

Structural and fMRI were conducted with an MR scanner at 3 T (Trio, Siemens, Erlangen) while participants performed a grating orientation task. A T_1-weighted FLASH 3D sequence was used for structural MRI of the whole brain [repetition time (TR) = 15 ms, echo time (TE) = 4.92 ms, flip angle = 25°, 192 slices, slice thickness = 1 mm, gap: 20%, matrix: 256 × 256 mm]. fMRI was performed using single-shot gradient-echo echo-planar imaging (TR = 2670 ms, TE = 25 ms, flip angle = 80°) to measure task-related changes in BOLD signal as an index of regional synaptic activity. fMRI measurements covered the whole brain (35 transverse slices, slice thickness = 3 mm, gap: 0%, matrix: 64 × 64 voxels, in-plane resolution = 3 × 3 mm). The position of the head was stabilized with foam to minimize head movements. The fMRI experiment consisted of a single session lasting ~13 min (300 brain volumes per session).

The Presentation software package (Neurobehavioural Systems, Inc., Albany, CA, USA) was used for presentation of the visual (participant) and auditory (examiner) instruction cues as well as synchronization of stimulus presentation, image pulse acquisition and recordings of motor responses during fMRI. Visual stimuli were projected with a video-projector on a screen that was positioned in the magnet's bore. Participants viewed the stimuli via a mirror that reflected the image displayed on the screen.

fMRI data were analysed using SPM2 (www.fil.ion.ucl.ac.uk/spm). The first three scans of each session were excluded from data analysis because of the non-equilibrium state of magnetization. The effect of head motion across time was corrected for by realigning all scans to the first scan of the first session. Realigned images were spatially normalized to a standard echo-planar imaging template and spatially smoothed using an isotropic Gaussian kernel at 8-mm full width at half-maximum.

For individual subject analysis (first level), a general linear model was specified using multiple regression analysis (Friston *et al.*, 1995). Task-related changes in BOLD signal were estimated at each voxel by modelling the onsets of each event (e.g. application of the dome) as delta functions convolved with a haemodynamic response function (HRF). For tactile stimulation, we specified two separate regressors that modelled the time of stimulus application for the dome with small and large gap value separately. Two additional regressors were included to model event-related BOLD signal changes induced by the visual warning cue and the motor response, respectively. Regression coefficients for all regressors were estimated using least squares within SPM2 (Friston *et al.*, 1995). Condition-specific effects were tested using the appropriate linear contrasts of the parameter estimates for the HRF regressors of all trial types, resulting in a *t*-statistic for each voxel. These *t*-statistics constitute a statistical parametric map (SPM). For each participant, we generated separate SPMs that estimated relative BOLD signal increases elicited by tactile stimulation with 3.0- and 0.35-mm gratings as well as relative differences in BOLD signal between the two types of tactile stimulation (stimulation with 3.0-mm gratings versus stimulation with 0.35-mm gratings).

At a group level (second level), random-effects models were used to test for between-group differences in task-related brain activations. For each contrast, the contrast images from the first level were entered into a second-level *t*-test, to create SPM_t. We used a one-sample *t*-test for within-group comparisons and a two-sample *t*-test for between-groups comparisons. In patients with writer's cramp, we additionally performed within-group regression analyses to identify areas in which task-related changes in BOLD signal showed a linear relationship with disease severity (as indexed by the ADDS score), disease duration or grating discrimination threshold. The individual age of each patient was entered in the statistical model as additional regressor of no interest to account for possible age effects.

SPMs were interpreted by referring to the probabilistic behaviour of Gaussian random fields. A statistical threshold of $P < 0.05$ was applied for all analyses. *P*-values were corrected for multiple non-independent comparisons across the entire brain volume. Correction for multiple testing was performed at a cluster level using the family-wise-error method and an extent threshold of $P < 0.01$. For each cluster, stereotactic coordinates (*x*, *y*, *z* in millimetres) refer to local maxima and Z_{max}, to the corresponding *Z*-score. The areas showing significant changes in BOLD signal were characterized in terms of cluster size (number of voxels per cluster) and the voxel showing peak difference (*Z*-score and stereotactic coordinates).

Results

All participants found the discrimination task easy to perform. Two patients and two controls made a single false response; the remaining participants committed no errors during the fMRI session. The examiner who was continuously present in the MR suite to apply the plastic domes to the right index finger did not notice movements of the right hand or dystonic symptoms in any of the participants.

Grating orientation discrimination

Between-group comparison revealed no differences in grating discrimination threshold between patients and controls who participated in the fMRI study ($P > 0.4$). In patients, the mean discrimination threshold was 1.60 ± 0.70 and 1.74 ± 0.68 mm for the right or left index finger. Healthy controls showed comparable thresholds of 1.68 ± 0.74 and

1.38 ± 0.84 mm for the right or left index finger. While healthy controls showed a linear increase of the discrimination threshold with age (r^2 = 0.57; β = 0.775; P < 0.001), patients only showed a trend towards a linear increase in discrimination threshold with age (r^2 = 0.11; β = 0.407; P = 0.105).

BOLD responses to tactile stimulation common to both groups

In patients and controls, tactile stimulation of the right index finger activated a widespread set of cortical and subcortical sensorimotor areas relative to rest baseline (Fig. 2). Regional increases in BOLD signal were found in a large bilateral cluster covering lateral and mesial areas of the frontoparietal cortex, including the primary and secondary somatosensory cortices, parietal opercular cortex, intraparietal sulcus, angular and supramarginal gyri, caudal SMA, anterior cingulate cortex, lateral prefrontal cortex, and dorsal and ventral premotor cortices (Fig. 2). Additional bilateral activations were observed in the anterior insular cortex and superior temporal gyrus. While we found some task-related activation in the left primary motor cortex, the right primary motor cortex was relatively spared (Fig. 2). Only patients with writer's cramp showed a consistent activation of occipital visual areas. Subcortical increases in BOLD signal comprised the upper part of the cerebellar hemispheres, putamen, internal globus pallidus, the body of the caudate nucleus, thalamus, substantia nigra and the subthalamic region bilaterally (Fig. 2).

Only gratings with a groove width of 3.0 mm resulted in the perception of grating orientation, whereas gratings with a small groove width of 0.35 mm were perceived as smooth surface. Considering both groups together, we compared the activation patterns elicited by the two types of domes (Fig. 3 and Table 1). Tactile stimulation with a groove width of 3.0 mm (i.e. being perceived as oriented gratings) led to bilateral increases in BOLD signal in the intraparietal sulcus and frontal eye fields relative to tactile stimulation with a groove width of 0.35 mm (i.e. being perceived as a smooth surface). The parietal cluster spanned the entire intraparietal sulcus (Fig. 3). At the interhemispheric surface, the percept of a grating orientation elicited greater activation in the rostral cingulate motor area and rostral supplementary motor area (Fig. 3; Table 1). No brain region showed a relative increase in BOLD signal during tactile stimulation with a groove width of 0.35 mm relative to tactile stimulation with a groove width of 3.0 mm.

Differences in task-related BOLD responses between patients and controls

In patients with writer's cramp, tactile stimulation of the right index finger produced stronger increases in BOLD signal in the basal ganglia and thalamus relative to healthy controls (Table 2). Focal increases in task-related activity were located in the left posterior putamen, right and left anterior putamen, the body of caudate nucleus and lateral thalamus (Fig. 4). Significant increases in BOLD signal were also found in posterior visual areas, left frontal opercular cortex, left anterior

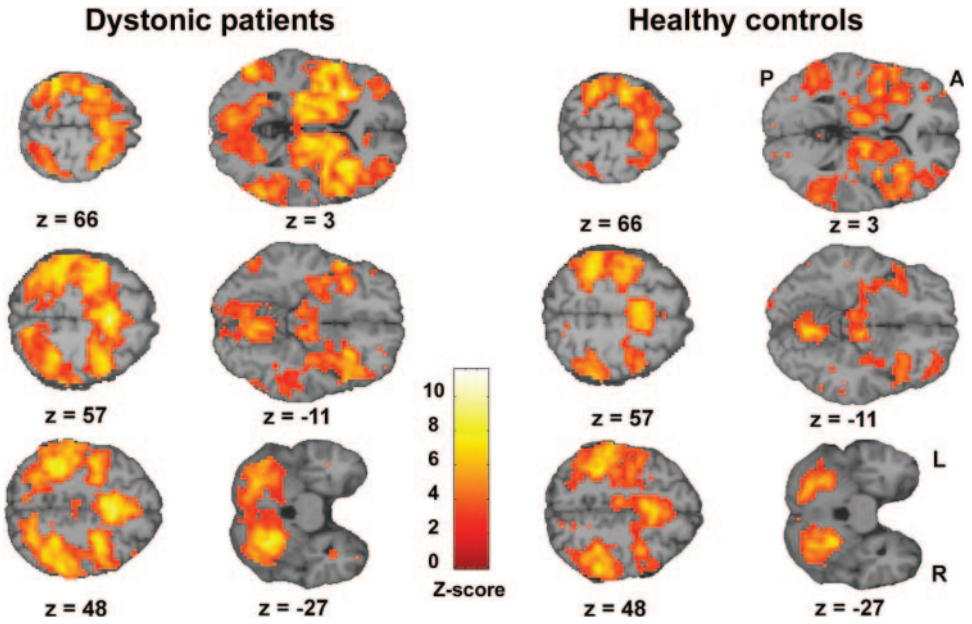

Fig. 2 Regional increases in BOLD signal during grating orientation discrimination in patients with writer's cramp and healthy controls. The sagittal, coronal and axial *Z*-score maps show brain regions with increased activity during tactile stimulation regardless of the gap width of the domes (extent threshold: P < 0.01, uncorrected). *Z*-score maps are superimposed on the T_1-weighted MRI template implemented in SPM2. The corresponding stereotactic coordinate (z-value in millimetres) is given for each axial slice. L = left; R = right.

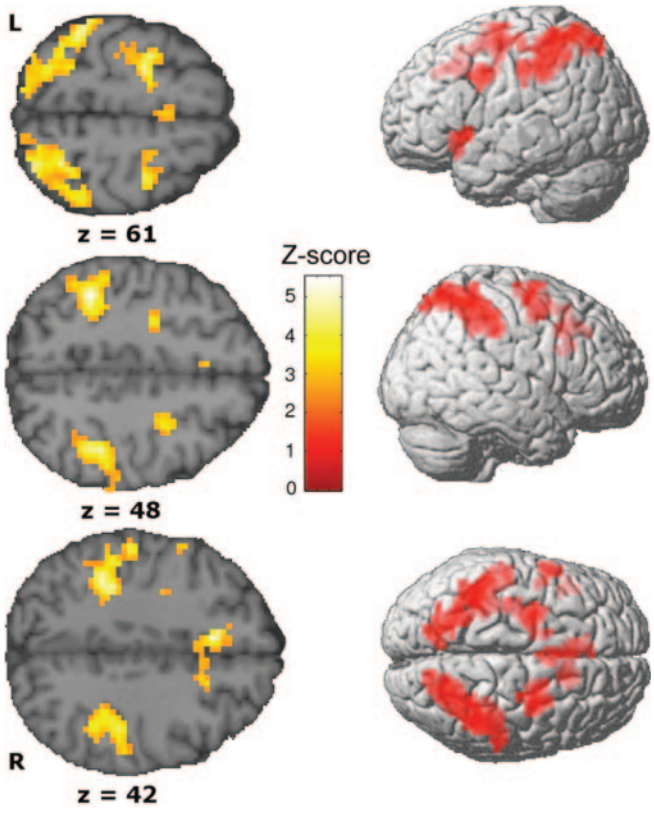

Fig. 3 Regional increases in BOLD signal evoked by the perception of grating orientation in dystonic patients and controls. The sagittal, coronal and axial *Z*-score maps highlight cortical increases in BOLD signal during tactile stimulation with 3.0-mm domes relative to tactile stimulation with 0.35-mm domes (extent threshold: $P < 0.01$, uncorrected). In this comparison, dystonic patients and controls were pooled together. Only gratings with a gap value of 3.0 mm induced a percept of grating orientation, whereas gratings with a gap value of 0.35 mm were perceived as smooth surface. *Z*-score maps are superimposed on the T_1-weighted MRI template implemented in SPM2. The corresponding stereotactic coordinate (z-value in millimetres) is given for each axial slice. L = left; R = right.

insula and right anterior parietal cortex (Table 2), but there were no differences in the post-central gyrus or parietal opercular cortex even when using a liberal statistical threshold (i.e. $P < 0.01$, uncorrected). In healthy controls, no brain region showed a stronger BOLD response to tactile discrimination relative to patients with writer's cramp.

Analysis of regional BOLD signal changes revealed no interaction between group (i.e. patients versus controls) and the groove width of the domes (gap value of 0.35 mm versus 3.0 mm). Taken together, a distinct set of subcortical and cortical areas showed greater responsiveness to tactile stimulation with dome-shaped plastic gratings in patients with writer's cramp relative to healthy controls. However, the overactivity elicited by tactile stimulation was independent of the groove width and thus was not related to the percept of grating orientation.

Table 1 Main effect of the grating orientation task

Anatomical location	Side	Cluster extent	Peak difference in BOLD signal			
			MNI coordinates			*Z*-value
			x	*y*	*z*	
Post-central sulcus	L	495	−45	−42	63	4.59
Anterior intraparietal sulcus			−39	−42	48	4.49
Superior parietal lobule			−27	−57	63	4.29
Superior parietal lobule	L	489	21	−63	66	4.09
Anterior intraparietal sulcus			42	−36	48	4.09
Superior parietal lobule			24	−54	57	4.06
Frontal eye field	R	124	33	0	51	4.39
Dorsal premotor cortex			33	−9	60	3.66
Dorsal premotor cortex	L	144	−27	−9	57	4.21
Dorsal premotor cortex			−33	−24	57	3.57
Anterior cingulate motor area	L	153	−6	21	42	4.41
	R		15	15	39	3.69
Anterior insular cortex	L	42	−45	15	−3	4.49
Ventral premotor cortex	L	41	−57	6	33	3.38*

The table lists brain regions that showed task-related increases in BOLD signal during the perception of grating orientation ($P < 0.05$, corrected at the cluster level); dystonic patients and controls are considered together; R = right; L = left; M = mesial; asterisk marks a cluster that showed a trend activation ($P < 0.001$, uncorrected) but failed to survive correction for multiple comparisons.

Within-group regression analyses in patients with writer's cramp

In patients with writer's cramp, we performed an additional regression analysis to examine whether task-related increases in BOLD signal were influenced by disease severity or duration. Since the age of the patients was included in the analysis as a separate regressor of no interest, these results cannot be attributed to simple age effects. There was no brain area where the BOLD signal increase during tactile stimulation co-varied positively with disease duration. However, several brain regions showed an inverse linear relation between regional neuronal activity and disease duration. In the right posterior putamen and caudate nucleus, disease duration was associated with a gradual decrease in BOLD signal during tactile discrimination (Fig. 5; Table 3). A similar trend was found in the left posterior putamen (Fig. 5; Table 3). This finding indicates that the enhanced responsiveness of the basal ganglia to tactile stimulation gradually tapers off with disease duration. Within the cerebral cortex, only the frontal opercular cortex showed a bilateral trend towards an inverse relation between the regional BOLD signal and the duration of dystonia (Fig. 5; Table 3).

A large bilateral cluster in the cerebellum and pons showed a positive linear relation between the BOLD response to tactile stimulation and the ADDS score (Table 3). As outlined above, the lower the ADDS score the more severely the hand

Table 2 Between-groups difference in activation during the grating orientation task

Anatomical location	Side	Cluster extent	Peak difference in BOLD signal			
			MNI coordinates			*Z*-value
			x	*y*	*z*	
Posterior putamen	L	249	−33	−12	0	3.84
Anterior putamen			−27	9	6	3.74
Caudate nucleus (body)			−12	6	6	3.68
Lateral thalamus			−21	−21	6	3.32
Anterior putamen	R	115	30	3	6	3.86
Lateral thalamus			18	−18	9	3.70
Globus pallidus			18	−6	6	3.33
Lingual gyrus	R	148	15	−51	−3	4.57
Calcarine sulcus			15	−69	12	3.13
Lingual gyrus	L	302	−15	−42	−3	3.96
			−24	−57	3	3.52
Anterior insular cortex	L	118	−48	15	−6	3.90
Anterior insular cortex			−48	6	−9	3.30
Intraparietal sulcus	R	106	24	−63	48	3.57
Post-central gyrus			24	−45	54	3.11
Temporo-occipital junction	L	32	−51	−69	3	3.83*
Pregenual cingulate cortex	M	31	9	36	3	3.70*
Lateral cerebellum (crus 1)	L	39	−45	−63	−33	3.65*
Anterior insular cortex	R	36	54	0	0	3.66*
Anterior cingulate motor area	M	66	−3	6	39	3.62*
			0	33	30	3.07*
Precuneus	L	44	−12	−48	57	3.52*
Dorsolateral prefrontal cortex	R	47	33	24	30	3.38*

The table lists brain regions in which patients with writer's cramp showed greater task-related activation than healthy controls (both groups; $P < 0.05$, corrected at the cluster level); R = right; L = left; M = mesial; asterisks mark clusters that showed a trend to activation ($P < 0.001$, uncorrected) but failed to survive correction for multiple comparisons.

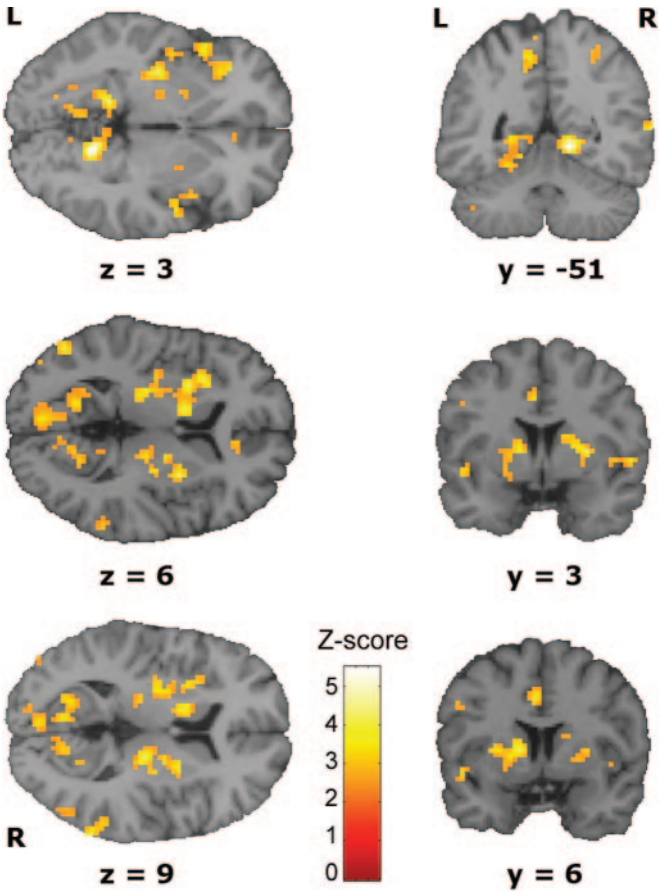

Fig. 4 Relative overactivity during the grating orientation task in patients with writer's cramp. The colour-coded *Z*-score maps delineate voxels showing stronger increases in BOLD signal in the basal ganglia and lateral thalamus during sensory processing of tactile stimuli in patients relative to healthy volunteers (extent threshold: $P < 0.01$, uncorrected). Sagittal, coronal and axial *Z*-score maps are superimposed on the T_1-weighted MRI template implemented in SPM2, and the corresponding stereotactic coordinate (in millimetres) is given for each slice. L = left; R = right.

function was affected by dystonia. Therefore, the gradual increase in regional BOLD signal with the ADDS score indicates that tactile stimulation elicited stronger activation in patients who were less affected by dystonia. The pontocerebellar cluster included the tegmentum pontis, the cerebellar nuclei and the middle part of the vermis, and extended into the right cerebellar hemisphere (Fig. 5). No cluster in the brain exhibited a negative linear relation between the BOLD response to tactile stimulation and the ADDS score (i.e. a gradual increase in activation depending on disease severity). No brain region showed a linear increase or decrease in task-related BOLD signal change depending on the grating discrimination threshold.

Discussion

To our knowledge, this is the first study to demonstrate that the discrimination of tactile input from the affected limb is associated with a widespread overactivation of the basal ganglia and lateral thalamus in patients with writer's cramp. Increased activity in the basal ganglia was not specifically linked to the perception of grating orientation and was less prominent in patients who had long-standing writer's cramp. Task-related activity was also found to be altered in other brain regions. At a cortical level, tactile processing was associated with a relative overactivity in posterior visual areas, left anterior insula and right intraparietal sulcus but not in the primary or secondary sensory cortex. A bilateral pontocerebellar cluster showed a linear decrease in task-related activity with increasing severity of dystonia. We discuss the implications of these results in terms of our understanding of the pathophysiology of focal task-specific hand dystonia.

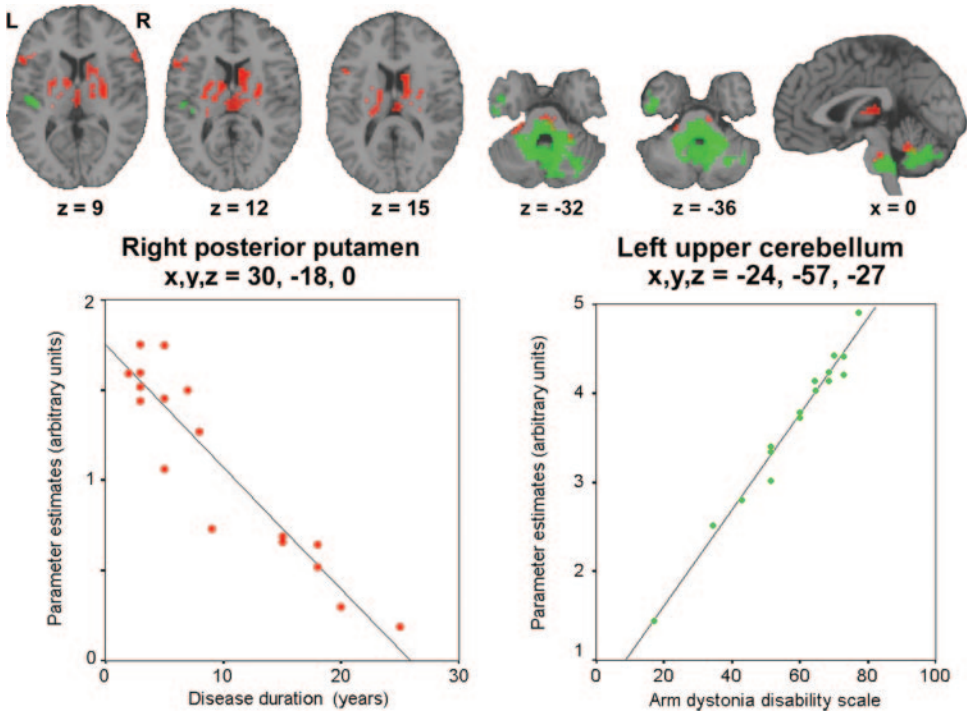

Fig. 5 Relationship between clinical features and phenotype and increases in BOLD signal during tactile discrimination. Upper panel: The voxels coded in red represent voxels that showed an inverse linear relationship between task-related increases in BOLD signal and disease duration, whereas the voxels coded in green denote voxels that showed an inverse linear relationship between task-related increases in BOLD signal and disease severity (extent threshold: $P < 0.01$, uncorrected). Sagittal and axial *Z*-score maps are superimposed on the T_1-weighted MRI template implemented in SPM2, and the corresponding stereotactic coordinate (in mm) is given for each slice. L = left; R = right. Lower left panel: The graph plots the individual effect size of task-related neuronal activity (*y*-axis) against disease duration (*x*-axis) for the voxel in the right putamen showing the strongest linear decrease in regional task-related activity with disease duration. Lower right panel: The graph plots the individual effect size of task-related neuronal activity (*y*-axis) against the individual scores of the ADDS (*x*-axis) for the cerebellar voxel that showed the strongest linear increase in regional task-related activity with the ADDS score. Note that the lower the ADDS score the more severe is the functional impairment. In both scatter plots, the line indicates the estimated linear relationship between the clinical measure and the task-related change in regional BOLD signal.

Basal ganglia

The majority of neuroimaging studies in focal hand dystonia reported changes in activation at the cortical level without concurrent functional alterations in the basal ganglia (Ceballos-Baumann *et al.*, 1997; Odergren *et al.*, 1998; Ibanez *et al.*, 1999; Pujol *et al.*, 2000; Oga *et al.*, 2002; Butterworth *et al.*, 2003; Lerner *et al.*, 2004). Extending these findings, two recent fMRI studies also disclosed abnormal movement-related activity in the basal ganglia. Patients with task-specific hand dystonia showed a distorted somatotopic representation of finger, toe or lip movements in the putamen, which may contribute to the loss of functional selectivity of muscle activity in dystonia (Delmaire *et al.*, 2005). Another fMRI study reported an abnormal persistence of neuronal activity of the basal ganglia after the end of a finger-tapping task in patients with focal hand dystonia (Blood *et al.*, 2004). This was interpreted as a functional correlate of faulty inhibitory control of the basal ganglia in focal hand dystonia (Blood *et al.*, 2004).

We found excessive activation of the basal ganglia and lateral thalamus during discrimination of tactile input from the affected hand. Dystonic patients displayed task-related overactivity not only in the left posterior putamen but also in the anterior putamen and the rostral body of the caudate nucleus, that is, increased activity in the basal ganglia was not restricted to the sensorimotor cortico-basal ganglia–thalamocortical loop (i.e. posterior putamen) but involved additional cognitive or limbic loops that support sensorimotor control in these patients (Alexander *et al.*, 1986; Parent and Hazrati, 1995).

The overactivity in the basal ganglia and thalamus cannot be explained by differences in task difficulty or task performance between groups because we used a grating discrimination task that patients could easily perform. For tactile stimulation, we used domes with a groove width that was clearly below or above individual discrimination threshold and thus caused an unequivocal perception of a smooth (i.e. groove width of 0.35 mm) or grooved surface (i.e. groove width of 3.00 mm) in all participants. Therefore, we attribute the hyperactivity in the basal ganglia to excessive neuronal processing of tactile input from the affected limb. Increased responsiveness of the basal ganglia to tactile stimuli may reflect the failure of the basal ganglia to efficiently process the incoming sensory information and may contribute to an

Table 3 Within-group regression analyses in patients

Anatomical location	Side	Cluster extent	Linear changes in BOLD signal			
			MNI coordinates			*Z*-value
			x	*y*	*z*	
Linear decreases in BOLD signal with disease duration						
Posterior putamen	R	213	30	−18	0	3.67
Caudate nucleus (head)	R		12	9	12	3.57
Posterior putamen	L	40	−27	−12	12	3.60*
Frontal opercular cortex	L	25	−54	21	9	3.40*
Frontal opercular cortex	R	36	60	24	6	3.32*
Linear increases in BOLD signal with the ADDS score						
Paramedian cerebellar cortex (Lobulus VI); dentate nucleus	L	1199	−24	−57	−27	4.11
Tegmentum pontis	R		6	−33	−39	3.99
Dentate nucleus; paramedian cerebellar cortex (Lobulus VI)	R		18	−54	−36	3.88
Inferior temporal gyrus	L	90	−45	−3	−39	3.79*

The table lists brain regions where task-related increases in BOLD signal showed a linear relation with clinical features of dystonia ($P < 0.05$, corrected at the cluster level); R = right; L = left; asterisks mark clusters that showed a trend activation ($P < 0.001$, uncorrected) but failed to survive correction for multiple comparisons.

abnormal activity pattern in the basal ganglia during motor tasks (Blood *et al.*, 2004).

The enhanced responsiveness of the basal ganglia may constitute an abnormal neuronal signal resulting in excessive reinforcement learning in the basal ganglia–thalamocortical loops during repetitive manual skills (Bar-Gad *et al.*, 2003). This may result in excessive reinforcement learning and contribute to maladaptive plastic changes such as the formation of excessive sensorimotor associations and progressive degradation of sensorimotor representations. In line with this hypothesis, several conditioning protocols that used transcranial cortex stimulation revealed an excessive modifiability of the sensorimotor system in patients with writer's cramp (Quartarone *et al.*, 2003; Siebner *et al.*, 2003; Quartarone *et al.*, 2006). According to a recent computational model, the basal ganglia conduct a dimensionality reduction that takes input from multiple sensory, motor, affective and cognitive cortical areas and relays a compressed encoding of this information into areas of the brain involved in the execution, planning and selection of actions (Bar-Gad *et al.*, 2003). Within this framework, the overactivity of the basal ganglia and lateral thalamus during tactile processing may indicate an inefficient 'compression' of the relevant information conveyed by the tactile stimulus within the basal ganglia, resulting in an impaired 'funneling' function of the basal ganglia. The increased responsiveness of the basal ganglia and lateral thalamus also supports the concept of impaired centre–surround inhibition within the cortico-striato-thalamocortical loops in focal dystonia (Sohn and Hallett, 2004). Defective centre–surround inhibition of sensory input within the basal ganglia may lead to an excessive activation of motor cortical areas, ultimately resulting in muscular overflow and co-contractions during handwriting.

In patients and healthy controls, tactile discrimination led to a bilateral activation in the anterior and posterior putamen as well as the caudate nucleus. While the posterior putamen receives major corticostriatal inputs from sensorimotor cortical areas, premotor and prefrontal areas project onto the anterior putamen and caudate nucleus (Parent and Hazrati, 1995). This pattern of activation indicates that tactile discrimination caused a concurrent activation of cortico-basal ganglia–thalamocortical loops involved in sensorimotor and cognitive evaluation of the tactile input (Alexander *et al.*, 1986). The bilateral overactivity of the basal ganglia after unilateral tactile stimulation also suggests a more generalized problem in tactile processing involving both hemispheres.

An important question is whether the overactivity of the basal ganglia can also be evoked by tactile stimulation of unaffected body parts. Since we only studied central processing of tactile stimuli from the clinically affected hand, this issue remains to be addressed in a future study. However, several lines of evidence suggest that the abnormal activation of the basal ganglia can also be elicited by tactile stimulation of non-affected body parts. Patients with focal hand dystonia show abnormalities of temporal (Fiorio *et al.*, 2003) and spatial (Sanger *et al.*, 2001; Molloy *et al.*, 2003) tactile discrimination of the unaffected side. Patients with writer's cramp also showed a bilateral reduction in kinaesthetic perception when they were asked to match the arm flexion induced by tonic vibration of the biceps tendons with their contralateral non-stimulated arm (Grunewald *et al.*, 1997). Meunier *et al.* (2001) used MEG to demonstrate severe somatotopic disorganization in the sensory cortex coding the representations of the non-dystonic upper limb (Meunier *et al.*, 2001).

The amount of overactivity within the basal ganglia did not correlate with the severity of dystonic symptoms or

individual discrimination thresholds. Hence, enhanced sensory processing in the basal ganglia may represent an endophenotypic trait that predisposes to focal task-specific hand dystonia. Interestingly, the increased neuronal response to tactile stimuli in the basal ganglia was most pronounced in patients who had a relatively short history of writer's cramp. If the relative overactivity of the basal ganglia represents a sensory dysfunction, this finding may indicate a long-term compensatory reorganization within the basal ganglia leading to a gradual attenuation of the overactivity in the basal ganglia. Alternatively, the initial overactivity in the basal ganglia may represent a compensatory effort that exists in the beginning of the disease but wears off with persisting disease.

Cerebellum

Previous neuroimaging studies reported an overactivation of the cerebellum during handwriting in patients with focal hand dystonia (Odergren *et al.*, 1998; Preibisch *et al.*, 2001), spasmodic torticollis (Galardi *et al.*, 1996) and essential blepharospasm (Hutchinson *et al.*, 2000). The cerebellar hemisphere showed a trend towards an increase in movement-related activity during freely selected movements as well as an increased responsiveness to premotor TMS conditioning in patients with focal hand dystonia (Siebner *et al.*, 2003). Finally, treatment with botulinum toxin injections was found to reduce activation in the upper part of the ipsilateral cerebellar hemisphere and the vermis during handwriting in patients with writer's cramp (Ceballos-Baumann *et al.*, 1997). Though these studies have shown functional reorganization of the cerebellum in focal dystonia, the pathophysiological significance of such reorganization is unclear. These findings may indicate a functional impairment of the cerebellum or constitute a neuronal substrate for functional compensation.

In this study, a cluster in the left lateral cerebellum showed a trend towards increased activity during tactile discrimination in patients. More importantly, patients who were clinically less affected showed greater bilateral activation of the dorsal pons and cerebellum during tactile discrimination. Since the age of the patients was modelled as separate regressor, the inverse relation between pontocerebellar activation and the severity of dystonia cannot be accounted for by the age of the patients. The areas showing a linear decrease in task-related activity with increasing disease severity included the dorsal pontine nuclei, cerebellar nuclei, posterior vermis and the intermediate part of the right cerebellar hemisphere. The dorsolateral pontine nuclei serve as an integrative interface between the various sensory signals required for performing intentional behaviours (Kobayashi *et al.*, 2002, 2004) and represent an important input channel to the cerebellar cortex and nuclei (Stein and Glickstein, 1992; Cicirata *et al.*, 2005). The cerebellar nuclei represent in turn the main output channel of the cerebellum to the thalamus and receive inhibitory input from the cerebellar cortex via Purkinje cells (Middleton and Strick, 1997). We therefore hypothesize that loops linking the dorsal pontine nuclei with the cerebellar cortex and cerebellar nuclei were recruited to compensate for dysfunctional processing in the cortico-basal ganglia–thalamocortical loop. However, this hypothesis needs to be confirmed in future studies.

Thalamocortical processing

In agreement with previous neuroimaging studies (Zangaladze *et al.*, 1999; Van Boven *et al.*, 2005; Zhang *et al.*, 2005), a bilateral set of dorsal frontoparietal areas was activated when dystonic patients and controls perceived a grating orientation relative to the perception of a smooth surface. This network comprised the post-central gyrus, intraparietal sulcus, parietal operculum, dorsal premotor cortex/frontal eye field and the anterior cingulate cortex.

In contrast to our prediction, the perception of a grating orientation produced a comparable activation of the primary and secondary sensory cortices in dystonic patients and healthy controls. However, patients did show a hyperactivity of the lateral thalamus, indicating that sensory processing was abnormal at the thalamic but not at the cortical level. In patients with generalized dystonia or hemidystonia who underwent thalamotomy, intraoperative recordings of neuronal responses to innocuous cutaneous stimuli revealed a sensory disorganization of thalamic receptive fields (Lenz and Byl, 1999*a*). This raises the possibility that the increased thalamic BOLD response to tactile stimulation was due to a degradation of thalamic cutaneous representations of the index finger in patients with writer's cramp.

Regardless of the groove width of the dome, tactile discrimination was associated with increased activity in the left anterior insula and right intraparietal sulcus in patients with writer's cramp relative to healthy controls. Several other cortical areas showed a trend towards increased activity in patients, including the right anterior insula, anterior cingulate areas, left precuneus and right dorsolateral prefrontal cortex. This regional overactivity suggests increased attentional monitoring of the tactile input in patients with writer's cramp.

Finally, patients with writer's cramp showed increased activation of posterior visual areas during grating discrimination. Since visual imagery has been shown to be implicated in tactile discrimination of object properties (Sathian and Zangaladze, 2001; Sathian and Zangaladze, 2002; Zhang *et al.*, 2004), our finding suggests that patients relied more strongly on visual imagery during tactile discrimination. The increased recruitment of visual areas may thus constitute another adaptive mechanism at the systems level to compensate for impaired sensory processing within cortico-basal ganglia–thalamocortical sensorimotor loops.

In conclusion, this is the first demonstration of a widespread overactivity of the basal ganglia and lateral thalamus during active processing of tactile input from the affected hand in focal dystonia. The excessive responsiveness

of the basal ganglia to tactile stimulation may contribute to motor dysfunction in affected patients. Sensory overactivity of the basal ganglia input may also constitute a predisposing factor for maladaptive sensorimotor plasticity in focal task-specific dystonia (Quartarone *et al.*, 2006).

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