PAPER

An expanded cortical representation for hand movement after peripheral motor denervation

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Objectives: Functional reorganisation of the motor or sensory cortex has been demonstrated in animals after section of mixed peripheral nerves. Here functional changes in the motor cortex specifically after peripheral motor denervation in humans are investigated.
Methods: Functional MRI (fMRI) was used to study brain activation during a finger flexion-extension task in patients with a late onset, acquired pure motor neuropathy (n=6), contrasting results with those from patients with pure sensory neuropathies (n=4) or healthy controls (n=7).
Results: Increases in the extent of activation in the motor cortex both ipsilateral and contralateral to the hand moved were found in the patients with motor neuropathy. The neuroanatomical localisation of the mixed contralateral sensorimotor cortex activation volume was more posterior for the patients with motor neuropathy than for the healthy controls (mean difference, 12 mm, $p<0.05$). The pure sensory neuropathy group by contrast showed no change in the extent of activation relative to healthy controls and a trend for more anterior primary sensorimotor cortex activation ($p<0.06$). To test whether the increased activation volumes found in patients with motor neuropathy were a result simply of factors such as increased effort with movement rather than the motor denervation, patients with hand weakness from inclusion body myositis (n=4) were studied while making similar hand movements. No differences in either the numbers of significantly activated voxels or in their localisation were found relative to healthy controls (n=10).
Conclusions: These results provide a novel demonstration that peripheral denervation (as distinguished from factors related to weakness) leads to functional reorganisation of the sensorimotor cortex in the adult brain. This suggests that adaptive responses to motor denervation involve the central as well as the peripheral nervous system.

Animal models with peripheral nerve lesions have suggested that substantial cortical plasticity[1–8]is preserved even into adulthood. However, conclusions from studies of experimentally induced lesions in animals are difficult to extrapolate confidently to understanding cortical changes with human disease because human lesions may differ in chronicity, severity, or extent. The capacity of the human cortex for adaptive change may also be different from that of experimental animals. None the less, transcranial magnetic stimulation (TMS) studies with amputated limbs or peripheral deafferentation have suggested that there also is a significant capacity for reorganisation after peripheral nervous system injury in the adult human.[9 10]

The work to date reviewed briefly above has focused on assessing responses to whole nerve section or limb amputation. The former involve loss of both sensory and motor nerves. The latter involve both whole nerve section and loss of the affected limb segment. Little information is available regarding the effects of *selective* injury to peripheral motor nerves in humans. Such information would help to better interpret functional imaging studies that demonstrate both local[11] and more distant[12–15] changes in the patterns of activation of the motor cortex with movement after brain injury affecting central motor outflow tracts.

The normal contribution of sensory afferents to activation of the sensorimotor cortex as defined by functional imaging is not entirely clear from previous work, for example. One fMRI study showed that brain activation during a simple finger flexion movement task not involving finger contact did not differ substantially from that with touch,[16] suggesting that any changes in motor activation patterns with sensory nerve injury alone could be modest. Consistent with this, a study with TMS cortical mapping after selective somatosensory loss from anaesthesia showed only a small decrease in cortical representation for the affected area[10] and Weeks *et al* did not report reduced sensorimotor cortex activation using PET during hand movements by three patients with pure sensory neuropathies.[17] However, the finding that passive and active hand movements are associated with comparable volumes of sensorimotor cortex activation could be interpreted as evidence that brain activation during motor tasks may include a substantial component related directly to the processing of afferent sensory information.[18 19]

An observation from animal studies (such as those cited above) has been that nerve injury is associated with changes in the extent of cortical representations for movement. Here we have used functional MRI (fMRI) to study groups of patients with either pure motor or pure sensory neuropathies while they performed a simple finger flexion-extension task. We wished to test the hypothesis that selective motor nerve injury would alter the cortical representation for voluntary movement in humans. To ensure that any changes found in the motor neuropathy group were not a non-specific consequence of weakness (for example, related to the increased effort of movement) rather than nerve injury, patients with distal muscle weakness from inclusion body myositis were also studied.

Abbreviations: fMRIB, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation; IBM, inclusion body myositis; BOLD, blood oxygenation level dependent; SMA, supplementary motor area; CMC, contralateral primary motor cortex; IMC, ipsilateral primary motor cortex; ALS, amyotrophic lateral sclerosis;

METHODS

Subjects

Six patients with adult onset multifocal motor neuropathy with conduction block,[20] four patients with adult onset idiopathic pure sensory neuropathy,[21] and four patients with inclusion body myositis[22] were studied (table 1). The ranges of ages in the three groups were similar. All patients had developed their neurological dysfunction as adults. None of the patients with motor neuropathy and only two of four of the patients with sensory neuropathy (patients 8 and 10) had symptoms or signs of autonomic neuropathy. All were right handed and able to perform the motor task for the fMRI studies at a constant rate for the required periods of time. The patients with sensory neuropathy had no difficulty performing this at a rate identical to the healthy controls. Despite weakness, the maximum rate of finger movement (against no resistance) was reduced for only three of the patients with motor neuropathy relative to healthy controls (see below) (table 1).

Separate groups of right handed healthy controls (ages 22–30 years old) were studied for contrasts with the patients with neuropathy (n=7) and with the patients with inclusion body myositis (n=10). Precise age matching of the healthy controls was not considered essential both because the sensory neuropathy and inclusion body myositis groups (which had similar age ranges to the patients with motor neuropathy) were used as disease controls for interpretation of changes in the motor neuropathy group. Previous studies in this laboratory also have not identified consistent differences in activation changes with this form of hand movement between younger (n=10, 22–38 years old) and older (n=10, 56–83 years old) healthy controls. We have not appreciated and are not aware of results suggesting significant sex linked differences in motor cortex activation with hand movements (unpublished data).

All patients consented to the study, which was approved by the Central Oxford Research Ethics Committee.

Task

Hand movement tasks used for testing the patients with neuropathy and those with inclusion body myositis both were performed with the right hands. Patients with neuropathy (and healthy controls) performed repetitive flexion-extension (a tapping movement) at the metacarpal-phalangeal joints with the pronated hand resting on a wooden support. The support had a plastic bar to standardise the amplitude of movements. The patients also wore wrist splints to restrict movements to the fingers.

Movements were performed at both 10% and 75% of each patient's mean maximum rate as measured before scanning over three 30 second trial periods (although data at one of the two rates was unavailable for two patients). For the patients with neuropathy we chose to scale task performances to individual maximum rates in an effort to make the task similarly difficult for patients and controls. A consequence of this was that patients 1, 2, and 6, with motor neuropathy, performed the task more slowly than any of the controls. However, if the differences in movement rates between patients and controls were to bias results, then they would be expected to lead to *less* activation associated signal change in the patient group, as the magnitude of the BOLD (blood oxygenation level dependent) signal change *decreases* with the slower hand movement.[23] Previous data obtained by us for the same movement showed an average 16% decrease in activation volume per Hz decrease in rate between 3.3–0.3 Hz.[24]

All subjects wore prism glasses that allowed them to see both visual cues for the movements presented on a back projection screen and the hand movements themselves. Subjects were pretrained in the movements outside the scanner. Lack of recruitment of more proximal muscles was confirmed by palpation of the proximal muscles during hand movements and by visual inspection during this training phase. These clinical impressions were confirmed for the most severely affected patient (patient 1) using surface EMG. Subjects were monitored visually while in the scanner to ensure that the task was performed correctly.

A different hand movement using the same muscle groups was performed by patients with inclusion body myositis and the larger group of healthy controls. Subjects were given a palm sized rubber bulb to hold with the supinated right hand resting on a pillow resting on the scanner patient tray. They were asked to compress it fully by similar flexion-extension at the metacarpal-phalangeal joints at a rate of 1 Hz. The rubber bulb was used for this part of the study as it had a constant resistance and allowed monitoring of the movement without the need for direct visualisation of the hand movements. Before scanning, it was confirmed that the task could be performed by both patients and controls without recruitment of more proximal arm muscles (determined by observation of patients and surface EMG performed outside of the magnet; data not shown). All subjects were trained in the task before scanning and wore prism glasses throughout the experiment that allowed them to be cued visually for their movements.

For both movement tasks subjects alternated 30 second periods of rest and movement over 5 minutes in each trial.

Imaging

Images were acquired using a Siemens/Varian 3T MRI scanner with a custom made head radio frequency transmitter-receiver coil (E Barberi, University of Western Ontario). Multishot echo planar images were obtained continuously in a transverse orientation using the following acquisition parameters: TR=3.0 seconds, TE=30 ms, 6 mm slice thickness, 21 slices, FOV=256×256mm, 64×64 matrix.

Image processing and statistical analysis were carried out using MEDx v3.0 (Sensor Systems Inc, VA, USA). Motion correction (Automated Image Registration, AIR, developed by R Woods, UCLA) and spatial smoothing (gaussian smoothing with full width at half maximum (FWHM)=5 mm) were applied before statistical analysis. The MEDx software was modified inhouse (courtesy of S Smith, D Flitney, and M Jenkinson, FMRIB Centre, Oxford) for automation of sequential steps and to allow temporal filtering (matched bandpass filter with σ=2.8 seconds and the highpass frequency cut off set to four times the task block length). Activation Z maps initially were calculated based on the block design paradigm using an unpaired Student's *t* test. Cluster detection was performed on all voxels above Z=2.3 to determine those significantly activated ($p<0.01$). This method relies on information concerning both signal intensity changes in the voxel of interest and in adjacent voxels to determine the significance of changes and correcting for multiple comparisons.[25] The cluster detection output was registered with the structural image using FLIRT (www.fmrib.ox.ac.uk/fsl/), a locally developed linear registration tool (12 parameter fit). To determine cluster localisation in a standard brain space, FLIRT was used to register the functional image with the structural image and the structural image with the Montreal Neurological Institute 305 brain (MNI305).[26] The combined transforms (fMRI→structural, structural→305 brain) were used to register the individual functional images in the standard space and the geometric centre of activation for each cluster calculated.

Centres of activation for the sensorimotor cortex activation are reported as coordinates (x, y, and z) in the MNI305 standard brain space. They were measured for the entire sensorimotor cortex activation cluster (which included confluent activation of voxels including sensory, motor, and premotor cortex). No attempt was made to neuroanatomically segment this cluster into separate functional regions as any subsequent measurement of geometric centres for segmented regions of interest would be determined as much by the assumptions used for the segmentation as by the patterns of activation.

Table 1 Clinical descriptions of patients

Patients	Age (y)	Duration of disease (y)	Clinical features	Electrophysiology	Other laboratory features	Diagnosis
Motor neuropathy:						
1	47	13	Asymmetric muscle wasting and weakness. Good response to IVIg Max FT=1 Hz	Normal SNAPs Motor conduction block	Anti GM1 negative	Multifocal motor neuropathy with conduction block
2	46	17	Asymmetric leg then progressive distal arm weakness and wasting. Good response to IVIg Max FT=2 Hz	Normal SNAPs EMG: asymmetric denervation NCV: asymmetric motor nerve slowing.	Anti GM1 positive	Multifocal motor neuropathy with conduction block
3	66	16	Progressive leg weakness and wasting. Good response to IVIg Max FT=4 Hz	Normal SNAPs EMG: chronic partial denervation NCV: Motor slowing	CSF protein 1.85 g/l Anti GM1 negative	Symmetric pure motor demyelinating neuropathy
4	44	8	Progressive asymmetric arm and leg weakness and wasting. Good response to IVIg Max FT=4 Hz	Normal SNAPs NCV: focal condution block	Anti GM1 negative	Multifocal motor neuropathy with conduction block
5	60	5	Progressive asymmetric arm and leg weakness. Good response to IVIg Max FT=4 Hz	Normal SNAPs NCV: Focal conduction block	Anti GM1 negative	Multifocal motor neuropathy with conduction block
6	78	9	Progressive asymmetric arm and leg weakness. Good response to IVIg Max FT=3 Hz	Normal SNAPs NCV: focal conduction block	Anti GM1 negative Biopsy: axonal neuropathy	Multifocal motor neuropathy with conduction block
Sensory neuropathy:						
7	59	4	Ascending sensory loss with relative presentation of pinprick sensation. Steroid responsive	SNAPs decreased or absent EMG normal NCV: no motor slowing	Anti GQl_b negative Anti GMl negative	Idiopathic pure sensory neuropathy
8	61	11	Progressive asymmetric numbness of upper limbs. Myotonic pupils without sicca syndrome	SNAPs decreased or absent Motor NCV normal	Anti Hu negative	Sensory ganglionitis
9	62	8	Asymmetric ascending numbness	SNAPs absent	IgM λ peak Anti $GQ1_b$ positive	Idiopathic pure sensory neuropathy
10	51	18	Ascending numbness. autonomic impairment. IVIg responsive	SNAPs absent Motor NVC normal	Anti $GQ1_b$ positive	Idiopathic pure sensory neuropathy
Inclusion body myositis:						
11	74	12	Profound symmetric weakness finger flexors and quadriceps	NA	CK 510 IU/l Muscle biopsy consistent with IBM	IBM
12	62	7	Mild symmetric weakness of finger flexors and marked weakness of quadriceps	NA	CK 650 IU/L Muscle biopsy consistent with IBM	IBM
13	50	6	Mild asymmetric weakness of elbow and finger flexion. Moderate symmetric quadriceps weakness	NA	CK 600 IU/l Muscle biopsy consistent with IBM	IBM
14	66	9	Mild symmetric weakness to finger flexion. Moderate symmetric weakness to hip flexion and knee extension. Dysphagia	Normal SNAPs EMG: myopathic changes and denervation	CK 319 IU/l Muscle biopsy consistent with IBM	IBM

Max FT, maximum finger-thumb opposition rate; IVIg, intravenous immunoglobulin; SNAP, sensory nerve action potential; EMG, electromyography; NCV, nerve conduction velocity; CSF, cerebrospinal fluid; ND, not done; NA, not available (another hospital).

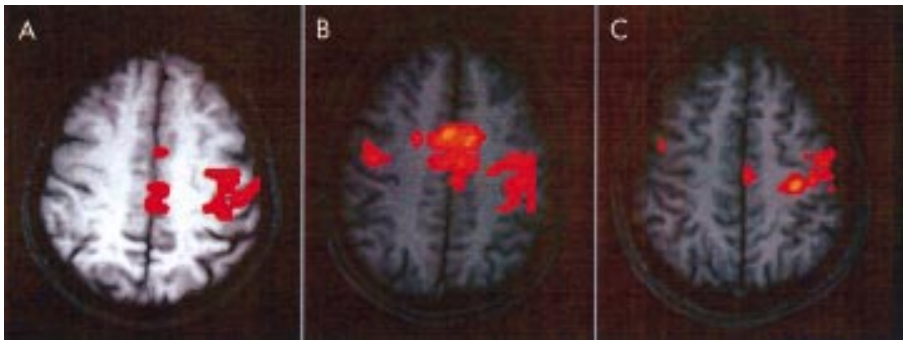

Figure 1 Activation of contralateral, ipsilateral, and supplementary motor areas during the fast (75% of maximum rate) hand tapping task for (A) typical patients with sensory neuropathy, (B) patients with motor neuropathy, and (C) a normal control. Significantly activated clusters ($p<0.01$) are superimposed on a high resolution structural image.

For measurement of relative numbers of significantly activated voxels in specific neuroanatomical regions, region of interest masks first were drawn manually onto the individual structural scans to define the motor cortical areas using anatomical landmarks, transformed into functional space as described above and applied to the activation map. The extent of activation within these areas is reported in numbers of voxels in clusters that exceed threshold ($p<0.01$).

Quantititative analysis of the extent of activation was limited to brain regions showing the greatest difference between the patient groups: the contralateral and ipsilateral primary motor cortex and the supplementary motor area (SMA). The region of interest defined as the primary motor cortex (contralateral, CMC; ipsilateral, IMC) included the voxels in the upper 30 mm of the brain around the hand region[27] and within a volume lateral to the interhemispheric fissure and approximately 15 mm anterior to the central sulcus. The SMA was defined to include cortex of the medial half of the superior frontal gyrus above the cingulate sulcus and anterior to the paracentral lobule as far as the genu of the corpus callosum. This therefore includes both the SMA and the pre-SMA.

We did not attempt to further segment the primary motor from lateral premotor cortex, as precise localisation of the two functional regions are overlapping and variable between subjects.[28] With these tasks we generally did not appreciate separable clusters of activation that could correspond to distinct motor or premotor activation volumes in individual subjects. Thus, the measured numbers of significantly activated voxels in the two regions if separately segmented likely would reflect any assumptions used for the segmentation more than the "true" functionally relevant activation volumes.

Results are reported with respect to a single activation threshold ($p<0.01$). A limitation of this approach is that the absolute extent of activation changes with use of different thresholds. The results therefore were checked at multiple thresholds to confirm that a greater extent of activation was found in the patients with motor neuropathy relative to healthy controls regardless of the precise threshold (ranging from $p=0.05$–0.001) used for analysis and that the patients with sensory neuropathy did not show significant differences from controls at any threshold (data not shown).

The relative activation in the ipsilateral and contralateral motor cortex was expressed as a motor activation lateralisation index, where the lateralisation index=(C-I)/(C+I) where C=the number of significantly activated voxels in the CMC and I=the number of significantly activated voxels in the IMC.

Group differences were tested using a two tailed, unpaired Student's *t* test with a significance threshold of $p<0.05$.

RESULTS

Patterns of movement associated BOLD signal increase

Flexion-extension hand movements were consistently associated with significant task associated BOLD signal intensity increases in the contralateral and ipsilateral sensorimotor cortex, supplementary motor area (SMA), and cerebellar activation in all subjects (fig 1). As the imaging volume did not include the full cerebellum, cerebellar activations are not further characterised in this report.

Patients with motor neuropathy show an increased extent of activation with movement

Patients with neuropathy and healthy controls performed the hand flexion-extension task at 10% of their individual maximum finger tapping rates. This individualisation of rate helped to balance effort, although four of six of the patients with motor neuropathy and all of the patients with sensory neuropathy performed the task at the same rate as control subjects. The extents of activation (numbers of voxels) in the contralateral primary motor cortex (CMC) were similar for the sensory neuropathy and healthy control groups, but was increased in the pure motor neuropathy group ($p<0.003$, table 2). None the less, the magnitude of BOLD signal changes did not differ between the patients and healthy controls (for example, the maximum Z scores in the primary motor cortex were 13.2 (SD 0.2) for healthy controls and 13.2 (SD 1.8) for patients with motor neuropathy). The motor neuropathy group showed an even larger relative increase in the extent of IMC activation ($p<0.005$). There also was a substantial relative increase in the extent of SMA activation in patients with motor neuropathy ($p<0.02$, table 2).

Each of the individual patients with motor neuropathy showed an increase in activation extent relative to controls. This was found even for patients 1 and 2, despite their slower absolute rates of hand flexion-extension (table 2). Previous work with healthy controls has shown that activation decreases with lower rates of movement.[23 24] There was no correlation between activation extent and the maximum rate of finger flexion-extension.

No significant differences were found in the extent of CMC, IMC, or SMA activation in the sensory neuropathy group relative to the normal controls at any threshold tested.

The relatively increased extent of activation with movement in patients with motor neuropathy is not simply a consequence of differences in movement rate

To test directly whether any activation differences between the controls and the patients might arise simply from differences in the rates with which the task was performed, the finger flexion-extension task also was performed at 75% of the individual maximum rates for both patients and controls (mean rate, 2.4 Hz for patients with motor neuropathy and 3.3 Hz for healthy controls). As expected from previous work,[23 24] increasing the rate of finger movements generally was associated with a larger extent of activation for both patients and controls (table 2). Thus, the somewhat slower mean absolute rate of task performance by the patients with motor neuropathy cannot account for the greater number of voxels activated above threshold.

Table 2 Extents of activation with hand movements. Numbers of voxels with activation above threshold in neuroanatomically defined volumes of cortex during slow (10% of maximum rate) or fast (75% of maximum rate) hand flexion-extension for individual patients with motor or sensory neuropathies and for normal controls.

	Activation extent										
	Slow hand movements (voxels)				Fast hand movements (voxels)				Relative increase in activation extent (slow to fast)		
	CMC	IMC	SMA	LI	CMC	IMC	SMA	LI	CMC	IMC	SMA
Motor neuropathy (n=6):											
1	148	62	86	0.41	196	169	152	0.07	1.3	2.7	1.8
2	–	–	–	–	63	27	64	0.40	–	–	–
3	100	84	55	0.09	–	–	–	–	–	–	–
4	134	97	187	0.16	170	83	100	0.34	1.3	0.9	0.5
5	54	38	92	0.17	200	132	117	0.20	3.7	3.5	1.3
6	150	71	200	0.36	155	92	159	0.26	1.0	1.3	0.8
Mean	117***	70**	124*	0.24**	157*	101	118**	0.26**	1.8	2.1	1.1
SD	41	22	65	0.14	56	54	39	0.13			
Sensory neuropathy (n=4):											
7	19	3	11	0.73	35	8	11	0.63	1.8	2.7	1.0
8	8	3	3	0.45	60	53	71	0.06	7.5	17.7	23.7
9	39	19	9	0.34	52	30	44	0.27	1.3	1.6	4.9
10	44	11	55	0.60	62	2	0	0.94	1.4	0.2	0.0
Mean	28	9	20	0.53	52	23	32	0.47	3.0	5.5	7.4
SD	17	8	24	0.17	12	23	32	0.39			
Normal controls (n=7):											
Mean	15	2	5	0.73	52	14	22	0.66	1.6	1.3	1.1
SD	9	3	6	0.23	31	14	27	0.21			

*p<0.02; **p<0.005; ***p<0.003.
CMC, contralateral sensorimotor cortex; IMC, ipsilateral sensorimotor cotex; SMA, supplementary motor cortex; LI, lateralisation ratio (see methods); . A hyphen indicates that the data was not collected due to a technical fault. Standard deviations for the ration of the relative increase in activation extent are not given. Values for the patients are listed in numerical order (see table 1) from the top down for the right hand (except where no data were obtained). The ratios of activation extent for fast relative to slow movements arealso given (mean values only for the healthy controls). Note that the mean increases in activation are similar for all three groups for CMC. The sensory SN group shows a higher mean for IMC and SMC changes, but this seems to be determined by results from a single subject (subject 8).

At this higher relative finger flexion-extension rate differences between patients with motor neuropathy and controls were less marked (only a threefold increase in CMC in patients with motor neuropathy relative to healthy controls ($p<0.02$), for example) than with the slower movements, but the extents of activation in both the CMC and SMA still were greater for patients with motor neuropathy than for the controls (table 2). As with the slower movements, there were no significant differences in the activation extent at 75% of maximum rate for the patients with sensory neuropathy relative to the healthy controls.

There is decreased lateralisation of motor cortex activation in patients with motor neuropathy

Because of the larger relative extent of IMC relative to CMC activation in the pure motor neuropathy group, the hemispheric lateralisation index for motor cortex activation for the patients with motor neuropathy was lower than for either the healthy controls ($p<0.003$) or the pure sensory neuropathy ($p<0.05$) groups. The lateralisation index did not change significantly with an increased rate of movement for any of the three groups studied (table 2).

Patients with neuropathy show shifts in the neuroanatomical localisations of centres of primary sensorimotor cortex activation clusters

The coordinates of the geometric centre of an activation cluster provide a precise summary measure of its neuroanatomical localisation. The geometric centres of the sensorimotor cortex activation clusters were determined in a standard brain space to test whether patients with chronic sensory or motor denervation show any consistent changes in relative localisation of this functional region relative to healthy controls (table 3). There was a trend for the centre of primary sensorimotor cortex activation contralateral to the hand moved to be more anterior in the sensory neuropathy than in the healthy control group (mean y axis shift, 8 mm, $p<0.06$). The centre clearly was more posterior in the motor neuropathy than in the sensory neuropathy group (mean y axis shift −19 mm, $p=0.005$) group. The patients with motor neuropathy also showed a more posterior centre of contralateral primary sensorimotor cortex activation relative to the healthy controls (mean shift −11 mm, $p<0.03$). There was no apparent correlation between the extent of motor impairment (assessed from the maximum rate of hand flexion-extension) and the coordinates of the

Table 3 Geometric centres of activation. Talaraich coordinates (x, y, z) for the means (SD) of fMRI geometric centres of activation in the primary sensorimotor cortex contralateral to the hand being moved (CMC) for the neuropathy patients and healthy controls during hand flexion-extension and for inclusion body myositis (IBM) patients and healthy controls during bulb squeezing

	x	y	z
Motor neuropathy (n=6):			
Mean	−30.6	−33.2*	53.9
SD	4	6.3	14.4
Sensory neuropathy (n=4):			
Mean	−34.5	−14	63.5
SD	1.9	6.2	4.1
Healthy controls (for contrast with neuropathy patients) (n=7):			
Mean	−39.3	−21.8	58
SD	3.2	5.5	4.5
Inclusion body myositis (n=4):			
Mean	−38.8	−21.6	54.0
SD	7.3	8.1	12.2
Healthy controls (for contrast with IBM patients) (n=10):			
Mean	−37.9	−20.0	53.8
SD	5.8	7.9	3.2

*p<0.05 relative to controls (different healthy control groups were used for comparisons with neuropathy and IBM patients).

Table 4 Extents of activation for IBM patients and healthy controls. Activation in neuroanatomically defined volumes of cortex during bulb squeezing with the right hand for individual patients with inclusion body myositis and for healthy controls are shown. Values for the patients are listed in numerical order (see table 1) from the top down for the right hand.

	Numbers of voxels			
	CMC	IMC	SMA	LI
IBM patients (n=4):				
11	61	10	41	0.73
12	138	26	69	0.68
13	104	2	47	0.94
14	113	3	25	0.96
Mean	104	10	45	0.8
SD	32	11	18	0.1
Controls (n=10):				
Mean	105	13	26	0.8
SD	46	10	19	0.1

CMC, contralateral sensorimotor cortex; IMC, ipsilateral sensorimotor cortex; SMA, supplementary motor cortex; LI, lateralisation ratio. There were no significant differences between the patients and the healthy controls.

CMC activation cluster centre for the patients with motor neuropathy.

Patients with hand weakness from inclusion body myositis show extents of movement associated BOLD activation similar to controls

To test whether the increased extent of activation with movement in patients with motor neuropathy is a consequence of hand weakness alone, movement associated activation changes in patients with myopathic hand weakness from inclusion body myositis were compared with healthy controls. Patients with inclusion body myositis and controls were asked to perform similar flexion-extension movements with the supinated hand. By compression of a rubber bulb (against no back pressure) the movements were recorded on line to ensure that patients did not slow movement rates with fatigue. By contrast with results for the weak patients with motor neuropathy, the mean extents of activation in the CMC, IMC, and SMA for patients with inclusion body myositis were not different from controls (table 4). The hemispheric lateralisation index for activation also was similar between patients with inclusion body myositis and healthy controls. There was no shift in the localisation of the geometric centre of the sensorimotor activation cluster in the hemisphere contralateral to the hand moved for the patients with inclusion body myositis relative to healthy controls (table 3).

DISCUSSION

There was a strikingly increased mean extent of activation during hand movements for the patients with motor neuropathy relative to either healthy controls or patients with sensory neuropathy in each of the three regions of interest (CMC, IMC, and SMA) studied. This was found even when an attempt was made to control for the relative performance of patients and controls by normalising to each subject's own maximum movement rate. The notion that these changes reflect functional reorganisation of the motor cortex is supported by results from our earlier study of a smaller group of patients with motor neuropathy who show increases in the extent of activation in motor cortex with passive, as well as active hand flexion-extension movements.[19]

The most obvious potential confounds in the experiment do not compromise interpretation of this observation. Contrast of activation extent with movements at 10% and 75% of maximum rates showed similar trends for increases at higher rates (table 2), so the slower rate of task performance by two of six patients with motor neuropathy cannot account for the difference between the motor neuropathy and control groups. There was no evidence for autonomic dysfunction that might alter the coupling of the haemodynamic response to neuronal activation in the motor neuropathy group and the increased extent of activation in the patients with motor neuropathy was not associated with any change in the magnitude of maximum signal changes.

To our knowledge, this and our previous report[19] are the first functional imaging studies of motor cortex activation in patients with peripheral motor neuropathies. An increased extent of motor cortex activation with movement was found previously in patients with amyotrophic lateral sclerosis.[29] However, interpretation of these results seems to us to have been uncertain, as motor neuron disease is associated with degeneration of both cortical and anterior horn cell motor neurons, damage to either of which could be associated with cortical functional activation changes. Identification of qualitatively similar functional changes in the brains of patients with amyotrophic lateral sclerosis and in the healthy brains of patients with motor neuropathy clearly argues that the functional changes need not be a primary consequence of excitotoxic degenerative mechanisms of amyotrophic lateral sclerosis, as the earlier study had been suggested. Instead, it suggests that they may arise from more general adaptive mechanisms of the normal brain in response to neuropathic weakness. The specificity of an association between an increased extent of activation and nerve injury (rather than weakness alone) was demonstrated in our study by the normal extent of activation in the weak patients with inclusion body myositis with the bulb squeezing task.

More than one mechanism may contribute to these chronic changes in cortical activation with motor denervation. Local disinhibition can "unmask" latent intracortical connections[30] and may contribute to cortical plasticity after nerve injury.[31] A longer latency for suppression of voluntary contraction has been found in patients with tetraplegia from spinal cord injury—for example, a phenomenon attributed to a "down regulation" of inhibitory connections normally activated by TMS.[32] Indirect evidence suggesting decreased cortical inhibition after nerve injury comes from observation of locally reduced cortical GABA staining.[33] Enlarged cortical representations for movement can be found with learning[34] or altered patterns of use,[35] but these seem to be much more modest than those described here for the patients with motor neuropathy. Longer term changes could arise as a consequence of reinnervation of muscle by surviving anterior horn motor neurons normally subserving more proximal muscles as has been suggested to occur after limb amputation.[36] Recruitment of these motor neurons in the normal brain would involve areas outside the normal hand area. It also is possible that the cortical changes simply reflect adaptive changes in subcortical nuclei that drive altered patterns of cortical recruitment.[37]

Ipsilateral as well as contralateral sensorimotor cortex activation was increased (both in absolute and relative terms) in the patients with motor neuropathy. Up to 8% of precentral neurons are involved in ipsilateral simple finger movements in monkeys.[38] Ipsilateral pathways seem to contribute to the control of hand movements in the normal adult[39–42] and seem to play a greater part with more demanding tasks.[23] Ipsilateral activation therefore also may adaptively facilitate motor unit recruitment with nervous system injury. Pathologically increased relative ipsilateral activation previously was found in patients with weakness secondary to strokes,[14 15 43] tumours,[44 45] or multiple sclerosis[11 46] using PET, fMRI, and electrophysiological techniques. In patients with multiple sclerosis, a direct correlation was found between the extent of ipsilateral motor cortex activation and measures of central axonal injury.[11 46]

Alternative explanations for the increased ipsilateral motor cortex activation (for example, simultaneous movements of both hands or use of accessory, more bilaterally represented proximal muscles) in the patients with motor neuropathy seem unlikely. Evidence for mirror movements was not found either by direct observation or using surface EMG recording with the weakest patient (patient 2; H Reddy, unpublished observations) and these movements are not characteristic of patients with motor neuropathy in general.

The posterior shift in the centre of the sensorimotor activation in the motor neuropathy group could reflect local cortical functional reorganisation as a consequence of the peripheral nerve injury, as has been found after brain injury.[11 44] In part, this could be a consequence of increased attention to movement by the patients as attention increases activation in the somatosensory cortex (although this effect should be modest).[47] This also seems less likely to explain our findings because the similarly weak patients with inclusion body myositis did not show a similar shift. Note that this study cannot rule out small mediolateral shifts (as reported in some studies of reorganisation[48]) because the relatively thick (6 mm) axial slices reduced relative spatial resolution along the z axis.

There were almost identical extents of activation in the control and sensory neuropathy groups. Consistent with the findings of Weeks *et al*,[17] we did not find a change in the extent of primary motor cortex or SMA activation with chronic sensory denervation. As suggested from studies of normal subjects, this argues that sensory afferents do not account for a large, independent proportion of the activation found in motor cortex during this type of simple finger movement.[16] None the less, there was a trend for an anterior shift in the geometric centre of the sensorimotor cortex activation in the patients with sensory neuropathy. This is to be expected if there is a small, relatively more posterior contribution that comes uniquely from sensory afferents in the total sensorimotor activation cluster.

There are two points that should be noted in comparison of these results with earlier work. Firstly, the apparent changes in motor representation of a muscle after acute sensory deafferentation noted by Rossi *et al*[10] using TMS may have arisen from differences in local stimulation thresholds rather than functional activity. Alternatively, the results may highlight a fundamental distinction between responses to acute and chronic sensory deafferentation. Secondly, we did not map the somatosensory cortex directly in this experiment and thus cannot rule out expansion of sensory representations of the more proximal limb in the patients with sensory neuropathy, as might be predicted from previous work.[7] It is useful to review some technical issues for assessment of the significance of our results. Firstly, although force generation was not controlled explicitly for the patients with motor neuropathy, all subjects in the initial experiments generated force only to raise the grouped fingers, the sizes (and therefore weights) of which were not consistently different between groups. Secondly, as we were interested in demonstrating dynamic changes in the cortical map's representation of movements we concentrated on measurement of changes in the extent of activation. Although this is a less precise measure than the magnitude of signal change,[49] it is an appropriate measure to address this question and the "effect" sizes were sufficiently large to detect changes in the motor neuropathy group. A cluster detection method was used as it enhances sensitivity and minimises false positives by taking into account spatially contiguous changes.[25] When the activation extent is expected to be large relative to voxel size (as in this case), this provides a powerful approach. As measurements were made within regions of interest defined in a standard brain space, comparisons of relative activation extents between subjects is a meaningful measure of differences in relative extents of activation. Finally, although the patients with inclusion body myositis squeezed a bulb and the patients with motor neuropathy did not, the basic flexion-extension movements were identical. Although for both controls and patients the mean absolute numbers of voxels above threshold was greater than for controls in the bulb squeezing than in the hand tapping protocol, in this and other work we have found that the same regions of motor cortex are activated by the two tasks (data not shown), a finding that is not unexpected if activation of the motor cortex is responsible primarily for encoding vectors of movement.[50] The key issue is that the bulb squeezing task, which was chosen for the final control experiment as it provided better control over movement force and easily adapted itself to giving recordable feedback of the movements, did not demonstrate any significant differences in extent of activation between the weak patients with inclusion body myositis and the healthy controls.

Our study again emphasises that changes in the location and extent of motor cortex activation do not arise solely in response to brain pathology. Our findings in patients with peripheral neuropathy demonstrate (along with—for example, studies of motor learning[51] or use dependent alterations[35]) that even large adaptive changes in motor cortex recruitment are part of the repertoire of the normal human brain. Cortical representations for movement are dynamic and capable of extensive reorganisation. Understanding the mechanisms responsible for this process could allow targeted interventions to enhance motor learning and also promise new strategies for improving outcomes after brain injury. An important question is whether the substantial changes reported here for simple hand movements are generalisable to more natural, specifically targeted movements, the control mechanisms for which may be different.

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