Published in final edited form as:

Somatosens Mot Res. 2002 ; 19(4): 347–357. doi:10.1080/0899022021000037827.

Sensory representation abnormalities that parallel focal hand dystonia in a primate model

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Abstract

In our hypothesis of focal dystonia, attended repetitive behaviors generate aberrant sensory representations. Those aberrant representations interfere with motor control. Abnormal motor control strengthens sensory abnormalities. The positive feedback loop reinforces the dystonic condition. Previous studies of primates with focal hand dystonia have demonstrated multi-digit or hairy-glabrous responses at single sites in area 3b, receptive fields that average ten times larger than normal, and high receptive field overlap as a function of horizontal distance. In this study, we strengthen and elaborate these findings. One animal was implanted with an array of micro-electrodes that spanned the border between the face and digits. After the animal developed hand dystonia, responses in the initial hand representation increasingly responded to low threshold stimulation of the face in a columnar substitution. The hand-face border that is normally sharp became patchy and smeared over one millimeter of cortex within six weeks. Two more trained animals developed a focal hand dystonia variable in severity across the hand. Receptive field size, presence of multi-digit or hairy-glabrous receptive fields, and columnar overlap covaried with the animal's ability to use specific digits. A fourth animal performed the same behaviors without developing dystonia. Many of its physiological measures were similar to the dystonic animals, but receptive field overlap functions were minimally abnormal, and no sites shared response properties that are normally segregated such as hairy-glabrous combined fields, or multi-digit fields. Thalamic mapping demonstrated proportionate levels of abnormality in thalamic representations as was found in cortical representations.

Keywords

cerebral cortex; focal dystonia; cortical representation; somatosensory; cortical column

Introduction

Our hypothesis on the genesis and remediation of focal hand dystonia has centered on the abnormal hand representation observed in owl monkeys, *Aotus nancymae*, which developed the disorder in the lab (Byl et al., 1996; Byl et al., 1997). Attended repetitive stereotypical behaviors cause simultaneous stimulation of large skin surfaces. This simultaneous activation

of receptor sheets in a learning context has been demonstrated to cause receptive field enlargement (Wang et al., 1995). As receptive fields enlarge and begin to occupy more than single phalanges, cortical sensory feedback for motor control becomes less independent, and even ambiguous. Animals, including humans, commonly compensate for difficulties in motor control by applying more repetition, attention, and stereotypy to the task performance. At some point the reduction in the dimensionality of the feedback crosses a stability point, and the result is a pathologic movement dysfunction called focal hand dystonia. Glabrous and hairy skin representations are not well differentiated in animals with focal hand dystonia, nor are responses restricted to single phalanges or single digits.

The exact pathway by which this abnormal feedback occurs is not known. The hand representation in primary somatosensory cortex, area 3b (Merzenich et al., 1978), is dominated by the inputs from low threshold mechanoreceptors (Mountcastle, 1977). Area 3b neurons project to posterior parietal somatosensory areas 1, 2, 5, and 7, along with proprioceptive afferent input from area 3a. These areas all project to the striatum which is one possible site of interference in motor control (Alexander et al., 1986; Tempel and Perlmuter, 1993). There are also projections directly from the somatosensory strip, primarily area 3a and area 2, to area 4, primary motor cortex (Jones et al., 1978). Any of these pathways, or some combination of them, may be responsible for carrying the abnormal sensory feedback cues in dystonia. Area 3b is necessary for hand functionality (Randolph and Semmes, 1974), whereas selective pharmacological lesions of area 2 cause specific motor control problems with similarities to dystonia (Hikosaka et al., 1985).

In prior studies (Byl et al., 1996; Byl et al., 1997), hand dystonia rendering the entire hand dysfunctional has been induced by operant behaviors. In one case (Byl et al., 1996), passive and rapid sequential hand opening and closing induced hand dystonias characterized by failure to achieve the stereotyped hand positioning required to initiate the task. In a second case (Byl et al., 1997), one animal developed dystonia in a palmar grasp task. In the current study, area 3b was physiologically monitored using implant recording throughout the development of focal hand dystonia. The changes in receptive field size and representational maps were monitored in the awake behaving monkey as they occurred. Later, thalamic maps of the implanted animal examined the representation in the ventral posterolateral cutaneous representation.

In new acute mapping physiological studies, the variability in sensory abnormalities was compared with the variability in individual motor use. Dystonia can variably degrade specific aspects of motor function, and the target task can usually be continued more slowly with alternative postures or motor strategies. Two of the animals induced to develop focal hand dystonia had large differences in degraded ability to use different digits at a target task. Some digits were functionally normal; the motor control of others was severely impaired. These behavioral changes were systematically compared to the sensory maps. A behavioral control animal performed all the dystonia inducing tasks, and shared some but not all representational abnormalities with the other dystonia animals.

Materials and Methods

Behavioral training

Four owl monkeys, *Aotus nancymae*, were used in this study. One animal developed dystonia on a repetitive operant task. This animal was implanted in cortical area 3 before behavioral training as described later in *Materials and Methods*. The task required the animal to position its right dominant hand in a hand mold and place its first and second digits on two metal contacts, each one millimeter in diameter and positioned under the natural conformation of the hand shown in Figure 1B. The animal was required to hold its hand in place for several hundred milliseconds before release could result in liquid reward. After focal dystonia developed, the

animal was trained on tasks that delivered 100–200 μm taps to its fingertips. This task was a cross-digit interval discrimination task. It was part of planned experiments not initially intended for studies of focal hand dystonia. The task used a limited hold reaction time paradigm. In this type of task, a trial begins with an orienting response, which was the animal placing its hand in a hand mold, and making electrical contact with the tips of two motors on its thumb and index fingers. Then, a series of stimuli began. In all cases each element of the series was a pair of taps separated by an interval. In the pair of taps, a tap to the index finger occurred before a tap on the thumb. A new pair of taps occurred after an onset to onset 500 millisecond interval. After at least two standard interval tap pairs, the series elements changed to the target, which differed from the standards only in inter-tap interval length. Initial standard interval lengths were 250 milliseconds, and shorter standards were used later in the task, as described in *Results*. The animal was rewarded with a few drops of Tang for releasing after the interval length changed to the target of 100 milliseconds, and time-outs followed releases at other times. After two months of performance at this task, the animal's performance dropped below 50% of its starting performance. The cortical implant was explanted and a mapping experiment was performed.

Two of the animals developed dystonia using an established experimental method (Byl et al., 1997) shown in Figure 1A. Each animal held two vertical rods with a palmar grasp in its dominant right hand and closed its grip. A light signaled adequate contact, and a 20 Hertz vibration began. The end of the vibration signaled the end of the hold period, and the animal was rewarded with food or liquid for releasing within reaction time limits. Each rod had to be independently pushed together, and the force between the rods was adjusted to challenge the animals' abilities. Animals typically performed several hundred to two thousand trials per day at a rate of approximately one trial per three seconds. Each dystonic animal's performance dropped to less than 50% of starting performance before the animals were mapped.

A fourth behavioral control animal used its dominant left hand to perform the first task, the palmar grasp task, for over a year without developing a dystonia. At that point it was trained to touch two small metal rods in a hand mold, as the implanted animal did before developing focal hand dystonia. The behavioral control performed the hand positioning task for more than six months without developing a dystonia. At that point it was mapped.

Diagnosis of focal hand dystonia

The clinical diagnosis of focal hand dystonia involves a confluence of a range of symptoms. For focal dystonia, the symptoms include intermittent arrhythmic, involuntary contractions of the muscles of the hand while performing a target task (Cohen et al., 1989; Lockwood, 1989; Marsden and Sheehy, 1990; Newmark and Hochberg, 1987; Rothwell et al., 1983; Sheehy and Marsden, 1982; Wilson, 1989), co-contraction of agonist and antagonist muscle groups along with inaccurate, inappropriately timed and sequenced movements between adjacent fingers and wrist during task performance (Chen et al., 1995), and poor hand posture outside task performance. We have documented decrements in performance levels in number of trials per minute, number of trials per day, and hit percentage. Co-contraction of antagonist muscle groups is difficult to document objectively without EMG recordings which were not performed. However, abnormal stiffness of the digits was noted in some animals. Each training session was videotaped, and video analysis was carried out during food retrieval from food tray (Byl et al., 1996).

Mapping experiments

High density microelectrode mapping experiments were performed at the end of each study under areflexic barbiturate anesthesia. A craniotomy contralateral to the affected hand exposed SI cortex and permitted thalamic recording access for mapping procedures. All mapping was

done using MAP (Peterson and Merzenich, 1995), and penetrations were introduced into the area 3b hand representation at a sampling density of approximately 20 per mm². For each cortical penetration, the electrode signal was amplified, filtered between 300 and 10,000 Hz, and played on headphones. Receptive field boundaries on hairy or glabrous skin were drawn on photographs of the digits in MAP. Criteria for inclusion of a skin surface in a receptive field was sensitivity equal to that found in the low threshold region of a peripheral mechanoreceptive or hairy afferent, or consistent responses to just-visible skin indentations with 1–2 mm diameter tip glass probes. Thalamic procedures began with dorso-ventral penetrations at interaural +5.0mm, lateral 5.0 mm, at depths of 12 to 17 mm. A 250 μ m volumetric grid of penetrations was made to include all areas of ventral posterolateral nucleus (VPL), and the reticular thalamus, spanning from interaural 6.25 mm to interaural 4.25 mm. Only VPL responses were included for analysis based on location of the electrode and evoked response characteristics (Mountcastle and Henneman, 1952; Poggio and Mountcastle, 1963; Kaas et al., 1984). By these criteria, recording in the deepest 300 μ m of these penetrations in which cutaneous response properties were noted that had extraordinarily large receptive fields were categorized as reticular thalamus recordings.

In all animals, the cortical hemisphere contralateral to the dystonic or behaviorally relevant hand was mapped. In animal om311, the ipsilateral cortical hemisphere was also mapped. In animals om624 and omt592 the thalamic representation of the behaviorally relevant hand was mapped.

Awake animal mapping

One animal was implanted with a dense microelectrode array in the left hemisphere cortical area 3b shortly before focal hand dystonia developed in the right hand. The techniques for implantation have been previously described in detail (deCharms et al., 1999). Briefly, 49 parylene-iridium microelectrodes were implanted into a 2 by 2 mm cortical area. The animal was engaged in behavior for juice rewards in a standard primate chair.

All procedures conformed to animal use protocols approved by the UCSF Committee on Animal Research.

Results

Diagnosis of focal hand dystonia

Animal t592 had a sudden onset of focal hand dystonia first indicated by a physiologic tremor of the forearm when it attempted to position digits one and two on contacts under the natural position of the fingers in abduction. The tremor began as the animal's hand approached the hand mold. The animal would often abort the attempt to initiate a trial by pulling its right trembling arm back into the primate chair with its left arm. In parallel, the hand posture became abnormal, with marked thumb adduction. This condition progressively worsened over the subsequent four month period. The posture of digits three, four, and five also became abnormal over time, marked by extension at metacarpophalangeal joints accompanied by flexion at proximal interphalangeal joints. These fingers, not involved in the task, involuntarily curled when the animal attempted to initiate trials.

After the onset of focal hand dystonia, the animal was engaged in a behavioral study in which pairs of 100 μ m taps were delivered to the distal fingerpads of digits one and two with stimulus onset asynchronies greater than 100 milliseconds. The task required a discrimination based on cross-digit tap intervals; more detail on this task is provided later in *Results* in the description of the receptive field changes in omt592. The animal performed this task at better than chance behavior if false positive trials meeting the following criteria were excluded: the animal

released contact at a time too early to be rewarded under any conditions. These early releases are included in table 1 to indicate the animal's increasing tendency to release early as the focal hand dystonia progressed.

Animal 311 developed abnormal posturing of digit four during and to some extent outside of the palmar flexion training task. During the task, digit four remained extended while the animal performed palmar flexion with digits two, three, and five. Its rate of successful completion of trials fell to below 50% of its starting performance rate within four months. The behavioral summary for om311 is shown in table 2. The bias towards the extension of digit four persisted throughout the mapping procedure, ie: even while the animal was under areflexic barbiturate anesthetics, digit four remained extended and stiff. Post-mortem examination of the hand revealed that the digital flexor profundus tendon on digit four inserted to the middle phalanx instead of its normal insertion on the distal phalanx. However, the fourth digit was capable of flexing normally outside the task, and occasionally at the task. For example, om311 could flex digit four normally while grasping fruit from a food tray. The abnormal tendon insertion was also found in the nondominant hand on the third digit, without a corresponding postural abnormality.

In om574, focal hand dystonia at the palmar grasp task was characterized by abnormal use of digits one, two, and five. Digits three and four grasped the rod and closed for task performance. As those digits flexed, digits two and five were extended at the metacarpo-phalangeal joint, flexed at the interphalangeal joints, and incapable of grasping the rods. The thumb was flexed under the rods and was useless in the task. Om574 had normal performance with its dominant hand in retrieving fruit from a food tray (Byl et al., 1996).

Postural changes in the hand in om574 were slow to develop. After six months of using the behavioral apparatus, this animal began to try to use its other hand to perform the task. This practice was disallowed. Postural difficulties became marked after eight months, and in parallel, performance at the task dropped substantially. A behavioral statistical summary is shown in Table 3.

Animal 624 was trained on the palmar grasp task for over a year without developing focal hand dystonia. The task was changed to the hand positioning task that was performed by the implanted animal. Animal 624 performed this task for over six months without slowing its behavioral trial rate or developing dystonia. The animal maintained a performance rate of approximately 20 trials per minute throughout both tasks.

Time course of receptive field enlargement in omt592

In omt592, a dense-array cortical implant was positioned in area 3b for several weeks before focal hand dystonia onset. Each behavioral trial in the operant training conditions that led to dystonia consisted of the animal placing its hand so that the tips of digit one and digit two contacted the tips of two displacement motors. After the dystonia developed, the animal would reach its hand out of the primate chair, and on many trials, involuntary tremor of magnitude sufficient to make the trial impossible began. The animal controlled the tremor by using its other arm to pull the operant arm back into the primate chair. If the animal established hand contact in the task before the tremor movements aborted the trial, the tremor usually quieted, and that allowed the animal to finish the trial normally. Also, the interference of the tremor with trial initiation was strongest at the start of a training session.

Two weeks after focal hand dystonia onset, the animal was engaged in operant behaviors in which 100 μ m taps were delivered to the distal fingerpads of digit one and two. Each stimulus consisted of a pair of taps, with the tap on digit two delivered before the tap to digit one. After one to three standard stimuli in which the stimulus onset asynchrony (SOA) was longer than

100 milliseconds, the target SOA of 100 milliseconds was presented. The standard was readily discriminable from the target through week five, as a standard of 250 milliseconds was used weeks one and two, and a 180 millisecond standard was used weeks three through five. At week six, the task used stimuli close to threshold. Three standards were used in each session in randomized trials: 120, 140, and 160 milliseconds. The animal performed the task consistently better than behavior from week four onward. At week six, the animal only performed above chance for interval lengths of 140 and 160 milliseconds for the first two days. After two days of training with exposure to 120 millisecond intervals, the animal performed equally well, and consistently better than chance behavior, for all interval lengths. Note that trials in which the animal released too early to ever be rewarded were excluded from analyses used to determine if the animal performed better than chance.

Daily receptive field mapping began the third week after the animal showed initial signs of focal dystonia onset. The development of focal dystonia in this animal was unanticipated. As can be inferred from the use of the implant device, electrodes were not moved during the experiment, and receptive field mapping throughout the experiment was conducted on the same electrodes. As shown in Figure 2, the beginning of the tapping behavior was not associated with a change in mean digital receptive field values. The mean receptive field size was close to 30 mm² for the first three weeks of the behavior. During the next week, the standard stimuli in the behavior were more similar to target stimuli, so the behavior required a more difficult discrimination. Over a two week period, receptive fields enlarged threefold. After the first three weeks of the behavior, all receptive fields on digits one and two were co-localized on the fingertips at the points the fingers contacted the motor tips. After another two weeks of near-threshold behavior, many receptive fields included entire glabrous digits; some included two entire glabrous digits.

Another way of viewing these changes in hand surface representations in area 3b is by reconstructing maps throughout the period of development of focal dystonia. In Figure 3, a map showing the receptive fields defined two months before focal dystonia onset is shown. The next map, in the center in Figure 3, shows the representation two weeks after focal dystonia, and the next shows it six weeks later. The blue circles indicate recording locations that had receptive fields on the head or neck; gray circles indicate locations that shared head/neck and hand responses. Within two weeks after dystonia onset, the most medial positions recording face responses were one millimeter from the most medial face response before the dystonia onset. This expansion of the face into the hand representation continued six weeks after the focal dystonia onset. Additionally, there were a number of sites from which evoked spiking responses could be derived from both the glabrous skin of the hand and hairy skin of the lower face. At some sites, isolated single units responded to mechanical stimulation of both the hand and face.

One of the observed mechanisms by which response properties changed in cortex involved a process of response substitution. In this cortical columnar substitution, receptive fields from one electrode were very similar over a series of successive recording sessions receptive fields. A period then followed in which there were no mapped responses from the electrode, although spontaneous spiking could still be recorded. In subsequent days, responses emerged at a new locus that was disjoint from the previous cutaneous receptive field locus. We observed this phenomena five times during one month of almost daily implant recordings. One example of a substitution between hand and face properties is shown in Figure 4. In this case, the face response appeared in a cortical zone surrounded by hand responses, so that it was highly improbable that electrode movement could have been responsible for the receptive field shift. We term this cortical columnar substitution because it is observed focally over a region of cortex comparable in size to a cortical column (Powell and Mountcastle, 1959).

Thalamic data

Thalamic volume was the same in the two animals for which dense thalamic penetrations were made. In omt592 and om624, thalamic dorso-ventral penetrations were made over a 250 μm horizontal grid. Receptive fields were recorded each 125 μms in depth in omt592. Because receptive field change was relatively small relative to 125 μm steps, in om624 receptive field samples were determined every 250 μms in depth. The reconstruction of one interaural plane is shown in Figure 5. Each penetration was assigned a thalamic volume inversely proportional to the sampling density. The thalamic volume in om624 was 0.98 mm^3 , and in omt592, 0.99 mm^3 .

Mean digital receptive field areas were 11.9 mm^2 in om624, and 37.08 mm^2 in omt592. This compares to mean cortical digital receptive field areas of 16.72 mm^2 and 87.69 mm^2 respectively. As shown in Figure 5, there were a number of penetration sites in omt592 that contained receptive fields with either multidigit receptive fields, or hairy and glabrous response properties. These combination receptive fields were not found in the VPL of om624, or in the normal primate VPL (Mountcastle and Henneman, 1952; Poggio and Mountcastle, 1963; Kaas et al., 1984).

Mapping results

Maps of the animals om574 and om311 were disorganized relative to normal owl monkeys (Merzenich et al., 1978) and to animal om624, as shown in Figure 6. The two animals with dystonia showed more disorganization, had emergent areas combining hairy and glabrous response properties, and areas combining responses stimulated from more than one digit. There was a somewhat small somatosensory hand representation of the animal that did not develop focal dystonia. The normal range of variability in the size of the hand representation in area 3b makes it difficult to assess statistical significance of this effect (Merzenich et al., 1987). The animal without focal hand dystonia had no penetrations with mixed representations of hairy and glabrous skin surfaces, and the only penetration with multiple digit response properties was found on the proximal phalanges, where such responses are reasonably common.

The portions of the hand that showed greater motor dysfunction could also be readily identified from the hand maps. In om574, the large continuous representations of digits 3 and 4 corresponded to the digits used in the task. The other digit representations in that animal had substantial areas with combined hairy-glabrous, or multi-digit response properties, and were dysfunctional in the trained behavior. In om311, the area representing distal digit four showed similar mixing of response properties, and corresponded to the digit that remained hyperextended in the task. Om624's map, in contrast, had large, continuous glabrous cutaneous representations of all five digits.

The explantation procedure prevented a detailed exploration of the area 3b map in omt592. However, enough penetrations could be made to assess average receptive field size and gross topography in this dystonic animal.

Confirmation of enlarged receptive fields

All animals that developed a focal hand dystonia showed digital receptive field sizes in area 3b well beyond the distribution of receptive field areas recorded in normal animals. For our normal reference we used 8 mm^2 with a standard deviation of 3 mm^2 (Stryker et al., 1987). This normative data was collected in animals never trained in the laboratory using the same methods used in the present study. Omt592 developed receptive fields averaging 87.68 mm^2 at the time of mapping; the receptive fields on d1 and d2 measured in this awake animal shortly after hand dystonia onset were 101.41 mm^2 , as shown in Figure 2.

Om574 had a dystonia prominent on digits 1,2, and 5. A plot of mean receptive field area per digit is shown in Figure 7. Receptive fields on digits 1,2, and 5 averaged greater than 100 mm², where those on digits 3 and 4 had an average area of 42 mm², significantly smaller ($p < 0.001$ two tailed t test). A selection of receptive fields on digits 4 and 1/2 from om574 are shown in Figure 8 to demonstrate this size difference. Receptive fields were pooled across digits 1 and 2 in om574 because a substantial fraction of the penetrations into the representations of these digits had two digit receptive fields.

Om311 had a focal hand dystonia with an enduring extension of d4. The mean digital rf area was 18.9 mm² across all digits, as shown in Figure 7. Digit 4, the digit that was dysfunctional in the behavior, had an average area of 21.3 mm², significantly greater than digits 1, 2, and 5 (two tailed t-test, $P < 0.05$). The mean digital receptive field size in the ipsilateral SI hemisphere was 20.30 mm².

Om624 did not develop focal hand dystonia. Mean rf size was 16.72 mm², significantly larger than normal (Stryker et al., 1987) ($p < 0.0001$ one tailed t test), which has been true for all animals engaged in behavioral training in studies of focal hand dystonia in our lab (Byl et al., 1996; Byl et al., 1997).

Receptive field overlap versus cortical distance

Receptive field overlap is the overlap ratio as a function of cortical horizontal distance. The overlap ratio is the intersectional area of two receptive fields divided by their union. We derived average receptive field overlap as a function of distance at 100 μ m intervals in all cortical maps, shown in Figure 9. All animals with focal hand dystonia had significantly larger receptive field overlap as a function of distance than did normal animals, or the trained non-dystonic animal. The graph shows that the first 17 data points for om624 are below corresponding data points for the dystonic animals (sign test, $p < 0.00001$). The hand representation ipsilateral to the dystonic hand in om311 also had more overlap than normals, or than the trained non-dystonic animal om624. Further, even the trained behavioral control animal had substantially more receptive field overlap than normal animals (Powell and Mountcastle, 1959; Sur et al., 1980).

To further test the hypothesis that abnormally large receptive field overlap was related to focal hand dystonia, maps of receptive field overlap were made for all hand maps. Such maps are displayed for the dystonic animal om311 and the non-dystonic animal om624 in Figure 10. These two animals had comparable mean digital receptive field sizes. The particularly high density area of receptive field overlap for om311 occurred over the cortical representation of digits 3 and 4. Hand dystonia in this animal manifested as hyperextension of digit 4 both in the palmar grasp task and at all other times. The cortical representation of om624 was noticeably smaller than that of om311, which can be viewed as a consequence of re-organization in an animal with larger than normal receptive fields, but without the magnitude of receptive field overlap found in animals with focal dystonia. The other dystonic animal for which such a map was derived, om574, displayed four prominent segregated areas of nearly equal and large receptive field overlap, in the representations of d1/2, d3, d4, and d5.

Discussion

Evaluation of hypothesis on physiology of the cause of focal dystonia

In this work, we confirmed several earlier findings on sensory representations in focal hand dystonia; receptive fields were up to 10 times larger than normal, abnormally large receptive field overlap was recorded at cortical distance up to two millimeters, and abnormal combinations of response properties were documented in microelectrode recordings. These findings are consistent with those from earlier work from our lab (Byl et al., 1996; Byl et al.,

1997), and are consistent with human imaging results (Bara-Jimenez et al., 1998; Byl et al., 2000; Elbert et al., 1998). Abnormal combinations of receptive fields and large sectors of the somatosensory thalamus with continuous representations were also found in human general dystonia patients (Lenz and Byl, 1999). Computational models have been developed to explain the phenomenology of focal dystonia through sensory feedback that is altered by normal plasticity mechanisms (Sanger and Merzenich, 2000). In addition, we have confirmed the finding (Byl et al., 1997) that abnormally large receptive fields were found ipsilateral to the focal hand dystonia, in the representation of the other untrained hand. In addition, receptive field overlap was abnormal ipsilaterally to the dystonia. Further, a non-dystonic animal trained in both dystonia-inducing behaviors also developed abnormally large receptive fields and abnormally large receptive field overlap, although not as large as any dystonic animal.

The hypothesis on the origins of focal hand dystonia has centered on the contributions of Hebb-like plasticity to receptive field enlargement in a sensory-motor task, and the possible disruption of motor function by altered receptive field structure and overlap. The sensory-motor behavior provides stimuli that are nearly coincidental to the hand. The normal response of the system is grouping inputs that occur nearly simultaneously in time. A central issue raised by our current study comes from an analysis of om624 and om311. Both had nearly the same mean digital receptive field size, and both had been trained on the same tasks. Yet one of the two developed focal hand dystonia. One of the two had a region of very high receptive field overlap centered on the representation of the most affected digit. The receptive field overlap was greater in the untrained hemisphere in om311 than it was in the trained hemisphere in om624. Only the dystonic animal had areas of cortex responsive to both hairy and glabrous skin, or to multiple distal digits. Receptive field size alone appears to be less important than the presence of abnormal overlap functions, and combined receptive fields.

The estimated cortical column size in the hand area in om311 and om574 was close to two millimeters, which translates to a ten-fold increase in columnar area or volume compared to untrained normals. Column size is defined as the longest distance across which receptive field overlap is observed. Previous extensions of the cortical column have been observed in animals that have been heavily trained on temporal tasks. The columnar enlargement occurred on the representation of the skin surface receiving inputs (Recanzone et al., 1992). In those cases columns enlarged up to a millimeter in size. These extended columns were the same size as the columns in the non-dystonic animal om624, which suggests that extension of receptive field overlap across distances greater up to one millimeter can occur without pathological consequences. However, we have not observed cortical columns two millimeters in size without pathology. Dystonia often follows a somatopic progression (Defazio et al., 1989; Greene et al., 1995) analogous to epilepsy, which suggests there may be some shared mechanisms between these two disorders.

Thalamic findings; implications for sites of plasticity

Another new finding from this work is that thalamic representation appears abnormal with de-differentiation by training paralleling that recorded in the cortical representation. Thalamic receptive fields contained enlarged receptive fields that were proportional to the cortical receptive field size expansion. Thalamic receptive fields contained the abnormal convergence of hairy and glabrous response properties. Cortex and thalamus are heavily interconnected with reciprocal specificity (Jones, 1985). Although the predominate view is that thalamo-cortical projections dominate receptive field structure in cortex, evidence is mounting that cortico-thalamic projections can have potent effects on thalamic representation (Ergenzinger et al., 1998). Physiological columnar architecture appears to be purely a cortical phenomena with a basis in the distribution of thalamic efferents (Rausell and Jones, 1995), and the magnitude of breakdown of columnar architecture noted in this and previous studies of focal hand dystonia

(Byl et al., 1996) has not been found in other normal or behaviorally trained primates in our or other laboratories. However, sensory representational abnormalities have been described in human dystonia patients (Lenz et al., 1999; Lenz and Byl, 1999). The finding of mixing of hand and face responses in cortical representations argues strongly that at least part of the representational remodelling is cortical in origin, as the inputs to the hand and face are segregated in the VPL and VPM..

Role of sensory representation in motor dysfunction

Inputs from mechanoreceptors are required to perform many simple manipulative tasks in feedback modes for which proprioceptive afferents are not adequately sensitive (Srinivasan and LaMotte, 1995; Macefield and Johansson, 1996; Macefield et al., 1996). The combined digital representations of skin surfaces normally excited in flexion, ventral glabrous skin, and surfaces stimulated by touch in extension, dorsal hairy surfaces, reduces the independence of these representations that could be used for feedback in such movements. Multi-digit representations are analogously a loss of independence in signals potentially used for feedback in adjacent finger movements. If such combined receptive fields mean necessary losses in control of finger movements that are normally antagonistic, or independent, then focal dystonia should be accompanied by an eroded ability to use sensory signals as feedback for movements. In fact, sensory modulated grip forces in people with writer's cramps are abnormal. During normal grip, subjects use more force than is necessary to avoid slip, and signals from low threshold mechanoreceptors are used for feedback to increase grip force (Johansson and Westling, 1987). People with writer's cramp use more force than normals (Odergren et al., 1996) and thus have a larger safety margin during lift than normals. Put another way, they have reduced their need for sensory feedback during lifting. With inadequate separation of the cortical representations of hairy and glabrous skin surfaces, or of unique digits, motor feedback is substantially limited. The sensory cortical role in providing feedback for motor commands may require segregating skin surfaces in area 3b that provide feedback for different or opposing motor commands to facilitate independence of motor control.

Treatment based on physiological findings

If large receptive fields and excessive receptive field overlap across the cortex are critical risk factors in focal dystonia, then sensory retraining should remove risk factors and allow normal cortical segregation to occur. A heavily attended sensory signal that is presented to a limited skin surface should be a signal that leads to redifferentiating the hand representation in primary sensory cortex. Examples of such tasks which depend on slowly adapting type I afferents include roughness estimation (Blake et al., 1997), reading Braille or embossed letters (Johnson and Lamb, 1981), or performing grating orientation discrimination (Phillips and Johnson, 1981). Examples of tasks that involve primarily rapidly adapting afferents include flutter discrimination (Mountcastle et al., 1969) and recognition of small surface asperities (LaMotte and Whitehouse, 1986). Use of the two mechanoreceptor systems that have small receptive fields and low mechanical thresholds to judge stimuli across a limited skin surface is essential for redifferentiating the sensory map. These psychophysical tasks must be presented in a task that is heavily attended in order to drive the coincident delivery of neuromodulators with a neural signal about which the cortex can reorganize. The tasks should only involve a limited skin surface within a training session so that the other process, the process leading to segregation, has cues only from a limited portion of the skin surface at one time. The tasks should be heavily practiced prior to reengaging a patient tasks that involve any level of motor training, and then should be applied concurrently as the patient begins the motor tasks that led to the dystonia.

Acknowledgments

David Moorman made critical commentary on the manuscript in addition to providing technical assistance. We would like to thank the following people for technical assistance: Jack Chase, Samir Sur, Earl Fitzhugh. This work supported by NIH grants 1F32NS10154, NS10414, and P01 NS34835.

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Figure 1.

Apparatus for tasks. A. In the palmar grasp task, the animal pulls the two rods together with a palmar grasp. Once the rods are closed, a 20 Hz vibration occurs. Upon cessation of vibration, the animal releases the rods within reaction time limits. B. In the hand positioning task, the animal contacts the tips of two probes with the distal phalanges of digits one and two. Contact detectors on the probe tips detect contact, and an LED turns on when contact is established. The animal must hold the hand position for one second. In a more advanced version of the task, the animal releases its hand after detecting a temporal pattern of taps delivered by the motors.

Figure 2.

Mean digital receptive field area as a function of time. The digital receptive fields becomes rapidly localized on the points of stimulation in the first two weeks of behavior, without enlarging. The digital receptive fields enlarged substantially after threshold behavior. Receptive fields are four times larger than normal at week two, and more than ten times normal size at week seven.

Figure 3.

Cortical surface maps in area 3 at different times after focal hand dystonia onset. A. Two months before focal dystonia. B. Two weeks after focal dystonia. C. Six weeks after focal dystonia. Note that receptive fields representing the face region invaded territory that previously represented the hand. Abbreviations: lowlip: lower lip, lip-L: lateral lips, PR: proprioceptive, fhead: forehead, orbit: skin surrounding the eye, d1: digit one, d1p: proximal phalange digit one.

Receptive fields four
days before substitution

Receptive fields three
days after substitution

Figure 4.

Receptive fields on four consecutive recording sessions shown superimposed on the hand on the left. In the fifth recording session, the electrical activity on the electrode sounded similar to the first four days, but no receptive field could be drawn. On the sixth day, the receptive fields reappeared on the lower lip. The following day a single unit receptive field was mapped on the whiskers just superior to the lateral mouth. The eighth day the receptive field was on the lower lip and whiskers just inferior to the lower lip. Recording sessions three through seven occurred at 24 hour intervals; two day gaps separated these from other recordings.

Figure 5.

One representative plane of thalamic penetrations in omt592. Electrode penetrations were vertical in a 250 μm horizontal grid. Receptive field samples were derived each 125 μm . Different colors indicate each digit's responses. Abbreviations: d1, digit one; d2, digit two; d1d, digit one, distal phalange; H, hairy skin response; G, glabrous skin response; w, whole. All responses were evoked by glabrous skin stimulation unless otherwise indicated.

Figure 6.

Area 3b maps from om574, om311 and om624. The incidence of multi-digit and hairy/glabrous mixed responses is prominent in the animals with focal dystonia. The control animal, om624, had only one penetration with either hairy/glabrous mixed responses or multi-digit receptive fields. Anterior is left, medial is up. The right hemisphere map of om624 is left-right reflected, for direct comparison with the other left hemisphere maps.

Figure 7.

om311 and om574 receptive field areas by digit. om311 developed a focal dystonia prominent only on digit 4. om574 developed a focal dystonia primarily affecting digits 1,2, and 5.

Figure 8.

A collection of receptive fields for d1/2 and d4 for om574. After focal dystonia onset, the animal principally used digits 3 and 4 in the task. Receptive field sizes parallel the spatial distribution of dystonia as d4 receptive fields are smaller than d1/2 receptive fields. Note also that some d1/2 receptive fields are multidigit, or combine hairy and glabrous skin surfaces in the same receptive field. Each color represents one receptive field.

Figure 9.

Receptive field overlap as a function of cortical distance. The animal without focal dystonia, om624, has less receptive field overlap than the three animals with focal dystonia, and less than a hand representation ipsilateral to the focal dystonia in om311 (see OM311R in figure).

Figure 10.

Receptive field overlap maps for dystonic animal om311 and control animal om624. Each square marks the position of a microelectrode penetration. For each pair of receptive fields for which the shared receptive field area was at least 5 % of the union of the two areas, a line was drawn between the squares for the two penetrations. Line width is proportional to receptive field overlap. Both animals have mean digital receptive fields close to 20 mm², approximately 2.5 times larger than normal. Both animals trained on the palmar grasp task. Om624 went on to train on the precision hand positioning task. Om311 developed a focal hand dystonia prominent on d4. The right hemisphere map of om624 is left-right reflected to allow direct comparison with the left hemisphere map of om311.

Table 1

Behavioral data versus time for omt592

OMt592		
Week since onset	Trials/min	Percent correct
3	19	21
4	14	23
5	14	22
6	6	13
7	9	16

Table 2

Behavioral data versus time for om311

OM311		
Month of training	Trials/min	Percent correct
1	15	98
2	12	93
3	10	63
4	7	39.6
Mapped		

Table 3

Behavioral data versus time for om574

OM574		
Month of training	Trials/min	Percent correct
1	22	65
2	36	90
3	44	90
4	50	90
5	20	80
6	29	60
7	30	65
8	20	62
9	13	70
10	13	30
Mapped		