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Nonlinear Sensory Cortex Response to Simultaneous Tactile Stimuli in Writer's Cramp

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Abstract: Writer's cramp is a task-specific dystonia that leads to involuntary hand postures during writing. Abnormalities of sensory processing may play a pathophysiological role in this disorder. Electrophysiology studies in a monkey model of focal dystonia have revealed de-differentiation of sensory maps and the existence of single cells in hand regions of area 3b with enlarged receptive fields that extend to the surfaces of more than one digit. These changes may lead to abnormal processing of simultaneous sensory inputs. To study abnormal processing of simultaneous sensory information in adult humans with writer's cramp, we used functional magnetic resonance imaging to compare the response in primary sensory cortex with simultaneous tactile stimulation of the index and middle finger, with the response to stimulation of each finger alone. We tested five patients with writer's cramp and seven unaffected (normal) subjects. In the normal subjects, a linear combination of the activation patterns for individual finger stimulation predicts the pattern of activity for combined stimulation with 12% error. In writer's cramp patients, the linear combination predicted the combined stimulation pattern with 30% error. Results indicate a nonlinear interaction between the sensory cortical response to individual finger stimulation in writer's cramp. This altered interaction may contribute to the motor abnormalities. © 2001 Movement Disorder Society

Key words: writer's cramp; sensory cortex; functional magnetic resonance imaging; dystonia; receptive fields; nonlinearity

Although the primary manifestations of dystonia are abnormalities of motor function, there is increasing evidence of a dysfunction of sensory processing that may be an associated or contributing factor.[1–6] It has been suggested that de-differentiation of the normally independent sensory representations of multiple digits may be an element in the cause of dystonia.[7] This claim is supported by electrophysiological studies in monkeys with experimentally induced hand dystonia, which found disorganization of somatotopic maps of the hand in area 3b, as well as cells with enlarged, overlapping, or multiple-digit receptive fields.[8–10] Multiple-digit receptive fields are never found in normal monkeys, and there is normally a well-defined somatotopic representation of the digit surfaces.[8] Disorganization of sensory representations could lead to confusion of sensory inputs arising from different fingers and, thereby, poorly differentiated control of fine movements.

In humans with writer's cramp, the possibility of disorganized sensory somatotopic maps is suggested by the finding of decreased distance between the centers of activation in response to stimulation of different digits by using somatosensory evoked potentials (SEPs),[11] magnetoencephalography (MEG),[12] and functional magnetic resonance imaging (fMRI).[13] Although these studies suggest alterations in the spatial properties of the sensory activation map, interactions between processing at multiple fingers were not tested. In 10 patients with either focal or generalized dystonia, the somatosensory evoked potential amplitude elicited by combined electrical

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stimulation of the median and ulnar nerves was increased compared with stimulation of each alone,[14] but the effect on the somatotopic map was not tested. It is not known whether these abnormalities lead to confusion of sensory inputs.

We hypothesize that in writer's cramp there is an abnormal interaction between sensory signals arising from adjacent fingers. We investigated this hypothesis by examining the complete spatial activation pattern in primary sensory cortex resulting from simultaneous stimulation of two adjacent fingers. We compare the spatial pattern of blood oxygenation level dependent (BOLD) activity resulting from simultaneous or individual stimulation of the index and middle finger. The experimental design is conceptually similar to the interaction in electrical response tested by Tinazzi and colleagues.[14] The quantitative value of the BOLD response at each pixel is compared between the single-finger and double-finger stimulation conditions, and a standard test of linearity is used to determine whether the double-finger response can be represented as a linear combination of the two single-finger responses.

METHODS

All experimental procedures were approved by the Beth Israel Deaconess Medical Center institutional review board. Five patients with writer's cramp (mean age, 53 years; S.D., 12) were recruited from the Movement Disorders Center, and seven normal control subjects (mean age, 45 years; S.D., 16) were recruited through public advertising. Patients were on no neurological medications at the time of the study, and if receiving botulinus toxin injections for their dystonia, the most recent injection was given at least 3 months before the study. None of the subjects had any other clinically significant neurological abnormalities. Patients' symptoms were scored with a standard dystonia rating scale.[15] One of the writer's cramp subjects was left-handed, but all other patients and controls were strongly right-handed as tested by the Edinburgh handedness inventory.[16]

MRI studies were performed with echoplanar imaging hardware, using a standard head coil (1.5 Tesla Siemens Vision scanner; Siemens Medical Systems, Erlagen, Germany). Anatomic MPRAGE images were initially acquired with 1-mm isotropic resolution, and then a sequence of BOLD functional images was acquired. A total of 270 three-dimensional BOLD images were acquired at 3-second intervals for each subject. An additional pause of 7 seconds occurred between each block of 15 image volumes. Each three-dimensional BOLD image consisted of 18 nonoverlapping adjacent slices of 4 mm thickness acquired in the axial plane with a 64 × 64 square matrix of voxels covering a 256-mm field of view to yield an in-plane (isotropic) resolution of 4 mm between voxels. BOLD acquisition parameters were adjusted for T2* sensitivity, with echo time (TE) 64 msec, slice-to-slice acquisition time of 125 msec, and repetition time (TR) between the same slice in subsequent volumes of 3 seconds.

Patients lay supine in the scanner with eyes closed and dominant hand resting palm-upward on a cushioned support. The experiment consisted of four stimulation conditions: rest, digit 2 (D2), digit 3 (D3), and simultaneous stimulation of digits 2 and 3 (D23). In each case, stimulation was performed by rubbing the palmar surface of the distal phalanx of either the index, the middle, or both fingers simultaneously on the dominant hand with medium-bristle adult toothbrushes, with oscillations along the axis of the finger at approximately 2 Hz. When two fingers were stimulated, two identical toothbrushes were fixed together by using adjustable Velcro strips so that equivalent regions on the two fingertips were contacted. Stimulation was performed by the same experimenter in all cases, and the subject was monitored visually to ensure that there was no active movement of the hand or arm. Six stimulation conditions were performed in the following order: rest, D2, rest, D3, rest, D23. A block of 15 BOLD volume images was acquired during each of the six conditions before proceeding to the next condition. This complete cycle was repeated three times for a total of 18 blocks of 15 volumes each.

Analysis and display of the anatomic and functional images were performed using *AFNI v. 2.2* software.[17,18] The first 3 volumes of each block of 15 BOLD volumes were discarded to eliminate T1 saturation effects and to achieve steady state of the spin system and the initial hemodynamic response. The remaining images were corrected for motion artifacts by using AFNI's built-in three-dimensional rotation and translation operations. Adjacent pairs of conditions (rest, D2), (rest, D3), or (rest, D23) were collected yielding 6 blocks of 12 volumes each for a total of 72 volumes per condition comparison (i.e., from the original 18 blocks, D2 vs. rest was measured in blocks 1, 2, 7, 8, 13, 14; D3 vs. rest in blocks 3, 4, 9, 10, 15, 16; and D4 vs. rest in blocks 5, 6, 11, 12, 17, 18). For each voxel, the time series of activation was subjected to a three-point median filter to remove spike artifacts and activation values were spatially blurred by using a spherical Gaussian filter with full width at half maximum (fwhm) of 8 mm. The time series was then compared with a reference time series to generate the scaled covariance and correlation coefficient at each voxel indicating the task-related component of the BOLD signal, according to the usual method[17,18]:

$$D(x,y,z) = \frac{\langle b(x,y,z,t) \cdot r(t) \rangle}{\langle r(t)^2 \rangle}$$

$$corr(x,y,z) = \frac{\langle b(x,y,z,t) \cdot r(t) \rangle}{\sqrt{\langle b(x,y,z,t)^2 \rangle \langle r(t)^2 \rangle}}$$

where $b(x,y,z,t)$ is the zero-mean BOLD signal at each voxel and each point in time, $r(t)$ is the zero-mean reference time series, angle brackets indicate calculation of the mean value of the argument, $D(x,y,z)$ is the scaled covariance value at each voxel, and $corr(x,y,z)$ is the correlation coefficient at each voxel. Note that $\langle r(t)^2 \rangle$ is a constant.

There is no universally accepted basis for choosing the reference time series. Because there is a 7-second delay between task conditions and the first three BOLD volume images of each condition (occurring over 9 seconds) are discarded, there is a 16-second delay between the last volume of one condition and the fourth volume of the next one. Therefore, we expect that any measured change in cortical activity between the two conditions will be reflected in an abrupt change in BOLD signal between these two volume images. In preliminary tests, we found that many subjects did not maintain changes in the BOLD signal in postcentral gyrus for more than a few seconds in the active state. We also found that, in some cases, the change in BOLD signal was due to artifact, when a random increase in the time-varying signal (perhaps due to respiration) occurred either preceding or after the change in stimulus condition. Thus, we selected a reference function that emphasized the importance of a change in signal at exactly the time of a change in stimulation condition but decreased the emphasis on sustained BOLD activity. The reference function for an off-on cycle of 24 volumes was (−1, −1, −1, −1, −1 , −1, −2, −2, −4, −4, −8, −8, 8, 8, 4, 4, 2, 2, 1, 1, 1, 1, 1, 1). Figure 1 shows a typical single-voxel time series for an active voxel with the reference function plotted above it. Preliminary testing on normal subjects demonstrated that this time series generated more robust activation in postcentral gyrus in response to finger stimulation, whereas the more commonly used "boxcar" time series yielded spurious correlation values in unrelated cortical areas both at rest and during stimulation.

The postcentral gyrus from the vertex to the superior margin of the lateral ventricles contralateral to the dominant hand was outlined manually on the anatomic MPRAGE images separately for each subject. The outline was used to select a set of voxels in a region of interest (ROI). The set of BOLD voxels with greater than 25% of their volume contained within the ROI were used

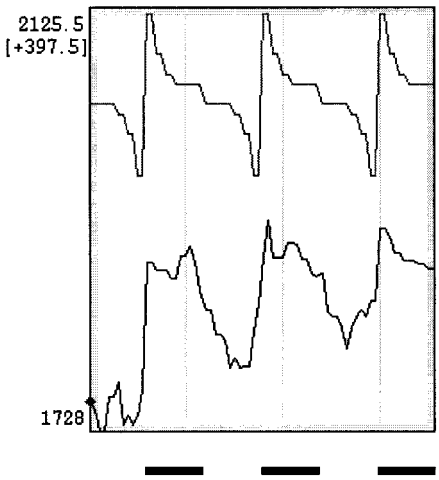

FIG. 1. A: Reference time series used for functional magnetic resonance imaging analysis. **B:** Sample time series of blood oxygenation level dependent signal intensity from a single voxel in postcentral gyrus. Black bars below the figure indicate the duration of fingertip stimulation.

for further analysis. The covariance with the reference function at each voxel defines a covariance image within the ROI, and three covariance images were thus available for each subject, corresponding to the rest versus D2, rest versus D3, and rest versus D23 conditions. Each image contains both positive and negative covariance values.

To determine whether there is a nonlinear interaction between the sensory signals arising from the two fingers, we tested in each subject whether the rest versus D23 covariance image was a linear combination of the rest versus D2 and rest versus D3 images. We performed a linear least-square error estimate (LLSE) of the D23 field as a combination of the D2 and D3 fields. If $D_2(x,y,z)$, $D_3(x,y,z)$, and $D_{23}(x,y,z)$ are the unthresholded zero-mean covariance values for each task condition as a function of voxel center coordinates (x,y,z), then the linear estimate can be written as

$$D_{23}(x,y,z) = \alpha D_2(x,y,z) + \beta D_3(x,y,z) + D_{error}(x,y,z)$$

where the least-square error estimate is $D_{approx}(x,y,z) = \alpha D_2(x,y,z) + \beta D_3(x,y,z)$ and $D_{error}(x,y,z)$ represents the error component of each voxel that is not estimated by the linear combination. We can estimate the optimal coefficients α and β by using standard linear techniques.[19] Note that α and β are the same for all voxels, so that it is the entire pattern of positive and negative activation that must be predicted. Also note that $D_{error}(x,y,z)$ will have both positive and negative values and that a property of the best linear approximation is that the average value over all the pixels of $D_{error}(x,y,z)$ will be zero. We

can then calculate the fraction of the total variance that is accounted for and the residual error by using

$$\text{var} = \frac{\langle(\alpha D_2(x,y,z) + \beta D_3(x,y,z))^2\rangle}{\langle D_{23}(x,y,z)^2\rangle} = \frac{\langle D_{approx}(x,y,z)^2\rangle}{\langle D_{23}(x,y,z)^2\rangle}$$

$$err = 1 - \text{var} = \frac{\langle D_{error}(x,y,z)^2\rangle}{\langle D_{23}(x,y,z)^2\rangle}$$

where the angle brackets take the mean of the argument over all voxels *x,y,z*. The procedure is summarized in Figure 2. A larger value of the residual error (err) or a smaller value of the variance accounted for (var) indicates a poorer linear approximation and, therefore, a greater degree of nonlinear interaction occurring during simultaneous finger activation. Note that no threshold is applied to the correlation values because it is not needed for the linear analysis and would introduce an artifactual nonlinearity into the data.

Statistical comparisons between subject groups were performed by using the analysis of variance module of *SPSS v. 9* (SPSS, Chicago, IL), and the threshold for significance was taken at $P = 0.05$.

RESULTS

Figure 3 shows representative examples of D2, D3, D23, D_{approx}, and D_{error} overlaid on the MPRAGE anatomic image for two different horizontal slices of a control subject and patient. The pattern of activation was frequently distributed over a large region of the postcentral gyrus, occasionally with more than one locus of activity.

In normal subjects, the response to simultaneous stimulation of digits D2 and D3 was well approximated by a linear superposition of the individual finger responses. The mean-squared approximation error was only 12% (S.D., 5.6%) of the total image variance in the ROI. In writer's cramp subjects, the mean error was 29% (S.D., 12%), indicating increased nonlinear interaction between the finger representations. This difference in the means was significant ($P = 0.008$; $F = 11.0$). The error percentage is plotted against subject age in Figure 4. There was no significant difference between groups in

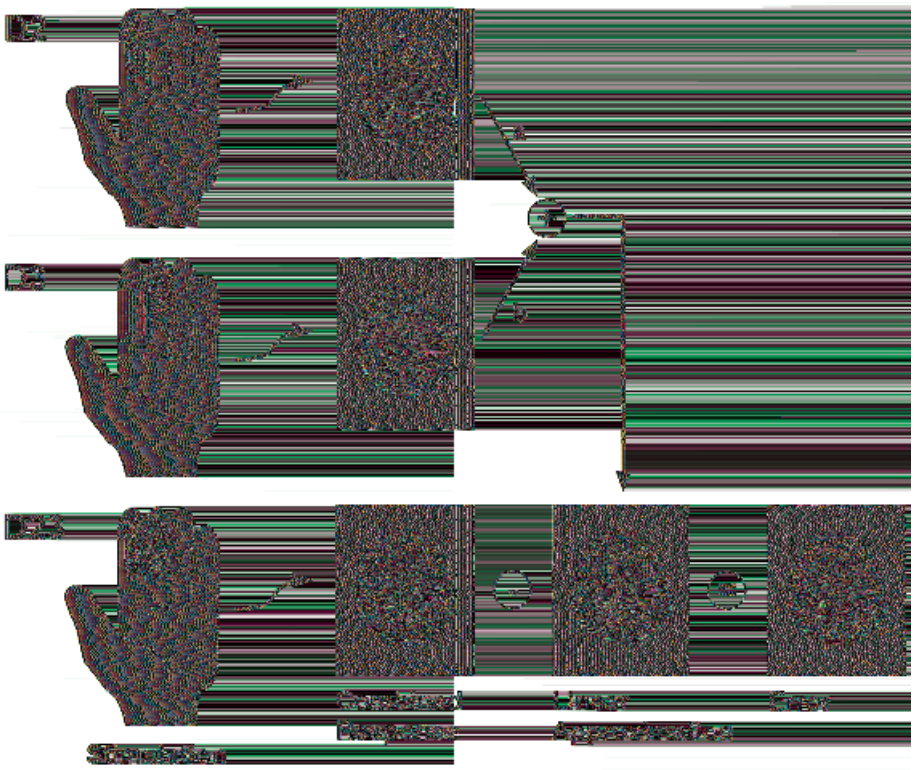

FIG. 2. Illustration of the analysis method. Three separate blood oxygenation level dependent covariance images are formed by comparing activation between the rest condition and either stimulation of each finger individually (**A** and **B**) or simultaneous stimulation of the two fingers (**C**). The covariance images for the individual fingers are combined linearly pixel-by-pixel to produce the best approximation to the simultaneous stimulation image. The difference produces an error image, and the mean-squared error as a fraction of the combined stimulation image variance is an indication of the degree of nonlinear interaction.

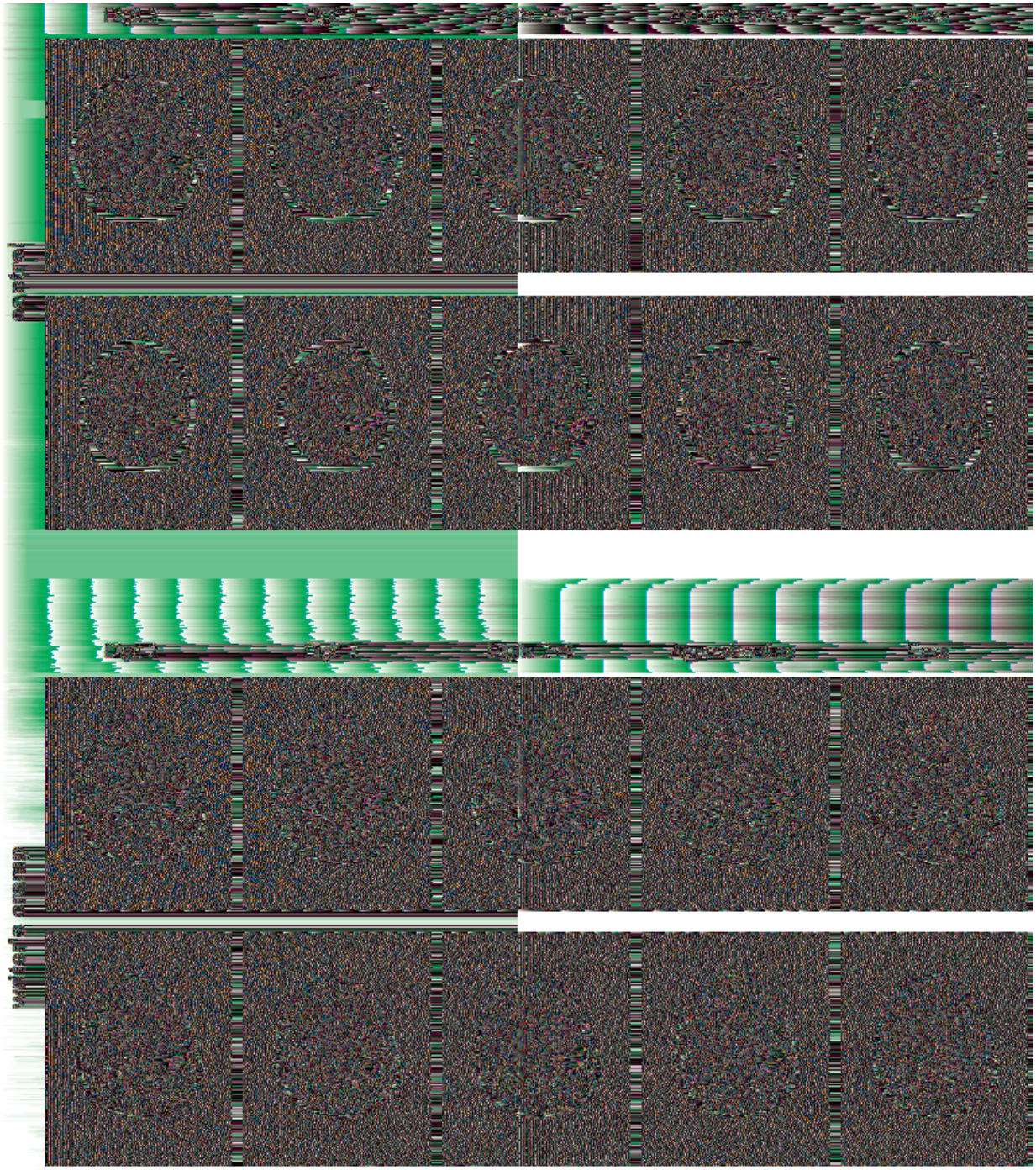

FIG. 3. Example of approximation of covariance images from one control subject (**A**) and one writer's cramp patient (**B**). Approximation results are given for two different slice levels with region of interest restricted to the left postcentral gyrus (on the right side of the image). Color indicates unthresholded covariance values within the region of interest (blue, negative; red and yellow, increasingly positive). Although the error images appear visually similar, the difference in error magnitude is statistically significant.

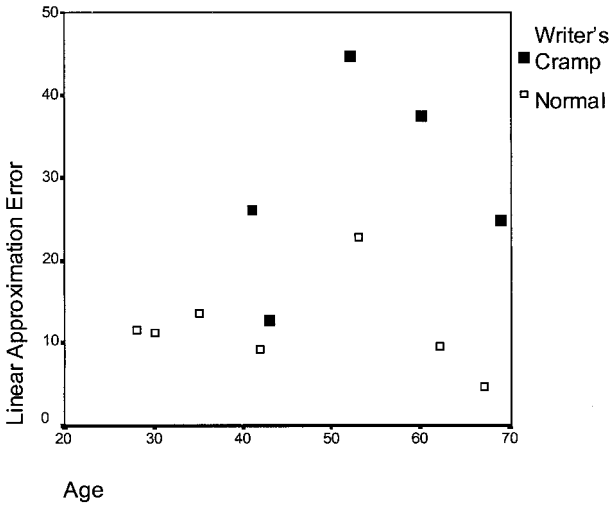

FIG. 4. Plot of the mean-squared approximation error versus subject age. Writer's cramp patients are shown with filled squares and normal subjects with open square.

either age or the number of voxels in the ROI. There was no significant correlation in patients between the approximation error and the dystonia severity score. There was no significant difference between subject groups in the distance separating the centroids of the thresholded responses to stimulation of the individual digits.

DISCUSSION

These results show that in writer's cramp there is a significant decrease in the ability of a linear approximation of the D2 and D3 activity patterns to predict the combined activity pattern when both digits are stimulated simultaneously. This suggests altered processing of simultaneous sensory inputs, and it may reflect a nonlinear interaction between the sensory representations. It is consistent with the hypothesis that in writer's cramp there exist populations of cells in postcentral gyrus that respond abnormally to tactile stimulation of two fingertips. In particular, if cells with multifinger receptive fields exist, then we would expect nonlinear interactions when these cells are activated. Conversely, if no such cells exist, then simultaneous stimulation of two fingers should simply activate both of the two distinct cell populations activated by each finger alone. This would produce a linear combination of the measured activity under single-finger stimulation. These results, therefore, suggest the possibility of an enlargement and de-differentiation of tactile sensory receptive fields as predicted by animal models.[8,9,20] Such de-differentiation could lead to reduced discrimination of cutaneous stimuli arising from different fingers.

Although the receptive field changes may represent cortical reorganization responding to abnormal patterns of usage of the hand, it is also possible that confusion of the sensory representations of adjacent digits could lead to disorganized motor representations for these digits. Disorganization of the motor representation might then lead to poor differentiation of finger movements and decreased inhibition of unwanted movements or antagonist muscle activation. These results do not allow determination of the location of the abnormality, and the nonlinearity could occur at the thalamic or spinal level.

The processing of simultaneous sensory information has been previously studied by using electrical and tactile stimulation. Although the early components of the somatosensory evoked potential (SEP) respond linearly to combinations of right and left median nerve electrical stimulation[21] and very weak tactile or electrical stimulation of adjacent fingers on the same side,[22] there is a nonlinear interaction on the same side at higher intensities.[21,22] The location of this nonlinear interaction is debated, and it may be either subcortical[21] or primarily thalamic and cortical.[23] The nonlinear interaction of the SEP in normal subjects to electrical stimulation of median and ulnar nerves was confirmed by Tinazzi and colleagues,[14], but they showed that in writer's cramp there is a relative increase of the response to combined stimulation. The change in degree of linearity is consistent with our results, but the nonlinearity in the SEP response may be a property specific to the SEP and not seen in the spatial patterns of activation that we have studied. In particular, it is important to note that the fMRI BOLD signal is expected to increase with both excitatory and inhibitory neural activity, so that the fMRI signal may not be sensitive to the suppressive effect of cortical inhibitory interneurons. If these interneurons are responsible for the nonlinearity in the normal SEP,[23] then this would not be detected by fMRI, although a nonlinear interaction occurring within or before the excitatory and inhibitory neurons would be detected.

Prior functional imaging studies have investigated whether there is a general increase or decrease in cortical activity in dystonia. Positron emission tomography (PET) studies have shown an increase in prefrontal activation with a decrease in primary motor cortical activation during movement in idiopathic torsion dystonia.[24,25] However, a recent fMRI study suggested exactly the opposite pattern of activation in musician's cramp.[26] A PET study in response to a vibration stimulus showed decreased cortical response in patients with focal dystonia and writer's cramp.[2,27] A study with transcranial magnetic stimulation showed that the motor cortical region projecting to the hand and forearm was distorted and enlarged in writer's cramp.[28] Our results do not ad-

dress the issue of either increased or decreased sensory cortical activity. We investigated only the effect of interaction between adjacent fingers, and our technique does not provide a direct comparison of overall regional cortical activity.

We were not able to show a significant decrease in separation of the centroids of activation in writer's cramp, as had been found in a previous study.[13] This may be due to an insufficient number of patients to reach statistical significance for this test. Another possible reason is the use of two adjacent digits in our study, rather than D2 and D5, as well as the use of an MRI scanner with lower magnetic flux. It was not possible to have stimulation performed by a blinded experimenter, but it is unlikely that a consistent pattern of stimulus changes could have been introduced that would bias the data.

In conclusion, fMRI data demonstrated that in writer's cramp the cortical sensory response to simultaneous stimuli has increased nonlinearity compared with controls. This provides further evidence that disordered sensory cortical representations may be an important feature in writer's cramp.

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