Title
Task Specific Focal Hand Dystonia: Temporal and Spatial Abnormalities in Sensory and Motor Processing in the Contralateral and Ipsilateral Hemispheres

Author
Dolberg, Rebecca

Publication Date
2009

Peer reviewed|Thesis/dissertation

Task Specific Focal Hand Dystonia: Temporal and Spatial Abnormalities in Sensory and Motor Processing in the Contralateral and Ipsilateral Hemispheres

by

Rebecca Dolberg

MANUSCRIPT

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHYSICAL THERAPY SCIENCE

in the

GRADUATE DIVISIONS

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

and

SAN FRANCISCO STATE UNIVERSITY

Acknowledgements:
This work was supported by NIH grants RO1DC4855 and RO1DC6435 and grants from the Dana Foundation and Dystonia Foundation.

ABSTRACT

Introduction: Task-specific focal hand dystonia (FhDtsp) is a debilitating, recalcitrant involuntary movement disorder characterized by end-range postures resulting from involuntary co-contractions of agonists and antagonists when performing a common repetitive task. **Purpose:** This study used magnetoencephalography (MEG) to elaborate the differences in contralateral and ipsilateral temporal and spatial processing in the primary somatosensory cortex (S1), secondary somatosensory cortex and parietal ventral area (S2/PV), primary motor cortex (MI) and premotor motor cortex (PMC) between healthy controls and patients with FhDtsp. **Subjects:** Thirteen with FhDtsp and 13 age- and sex-matched healthy controls. **Procedures:** Whole head MEG was used to investigate the spatiotemporal integration of novel, low and high rate sensory stimulation in S1 and S2/PV and self-paced finger movement responses in M1 and PMC. Clinical measures of function, sensation, motor speed, strength, and motor control were integrated into regression equations to predict aberrant neurophysiological processing. **Results:** Compared to controls, subjects with FhDtsp had: 1) increased peak amplitude in contralateral and ipsilateral S2/PV in response to high rate and novel stimuli; 2) increased latency in contralateral S1 in response to novel stimuli and in ipsilateral S1 and ipsilateral S2/PV in response to high rate stimuli; 3) early activation with maintenance of firing in contralateral M1 and ipsilateral PMC associated with finger movement and 4) impaired sensation, motor speed and intrinsic muscle strength with sensation predictive of aberrant somatosensory processing (latency). **Conclusions:** Given the simultaneous increases in amplitude in contralateral and ipsilateral S2/PV related to novel and high rate stimulation in patients with FhDtsp, bilateral sensory retraining targeting higher levels of sensory discrimination may be needed to reduce the heightened sensory response. Additionally, bilateral, simultaneous biofeedback technology may

be able to increase patient awareness as well as assist in retraining to better balance ipsilateral firing to aid inhibition while decreasing excessive contralateral MI excitation.

List of Tables and Figures

INTRODUCTION

Task-specific focal hand dystonia (FhDtsp) is an idiopathic, debilitating movement disorder. It is characterized by abnormal, involuntary co-contractions of agonist and antagonist muscles of the hand and forearm. Excessive muscle activation leads to end range twisting postures of the fingers and wrist (43) during specific hand activities such as playing a musical instrument, writing or typing (14). Diagnosis is made by a physician based primarily on clinical presentation: clear signs of involuntary movements associated with a target task, self-reported sensory tricks to decrease abnormal movements, history of overuse or stress, normal neurological examination (e.g. no signs of neurological disease or injury, no spasticity, rigidity, resting tremor, or hyperactive stretch reflexes, no radicular sensory loss or weakness, and normal light touch). Currently no treatment leads to a long term cure (50) thus intervention strategies currently focus on prevention and management rather than a cure. These strategies include drugs (eg. botulinum toxin), exercise (eg. neurological retraining), splinting, magnetic stimulation, or surgery (eg. deep brain stimulators) (43, 72). As a consequence, although the incidence and prevalence of FhDtsp is low (93), the condition can bring an abrupt halt to a successful career that requires coordinated fine motor control of the hand.

While the etiology of focal hand dystonia is considered idiopathic, most researchers and clinicians agree focal dystonia is a multifactorial disorder developing from an interaction of intrinsic factors [genetics (45, 47, 74), musculoskeletal limitations (25), an imbalance of inhibition and excitation (1, 106, 110, 119), sensory dysfunction (17, 23, 24, 85, 83), aberrant homeostatic plasticity (99)] and extrinsic factors [trauma, perseveration or injury to the upper extremity (64), neuropathy (30), personal stress (62), perfectionism (62), poor ergonomics and excessive repetitive overuse (18)]. The cause–effect relationship between intrinsic

pathophysiology and extrinsic influences is a current subject of debate. It is not clear whether abnormal intrinsic factors predispose one to developing FhDtsp or whether the intrinsic features measured in patients with FhDtsp represent the consequences of the disease.

The effect of extrinsic, behavioral factors on the development of focal hand dystonia has been studied in longitudinal animal models (5, 21, 26, 118). These animal studies report the development of task-related movement dysfunction following extended periods of high rate, moderate force repetitions of the hand (5, 21, 26). However, not all of the trained animals develop the dystonia, suggesting there may an underlying predisposition in those animals that develop symptoms. The effects of intrinsic factors have been investigated using human longitudinal genetic studies of family members with and without dystonia. Members from these families are followed over time to determine who develops the condition (47, 74, 75). Several genes of low penetrance for focal dystonia have been identified on chromosome 9. All family members with dystonia have the gene, but all family members with the gene do not develop dystonia. It is not uncommon that stress, increased work load, and/or trauma precede the onset of clinical dystonia. This suggests the importance of clearly defining the underlying intrinsic factors associated with FhDtsp including aberrant neurophysiological processing. If clinicians understood the neurophysiological idiosyncrasies it would help the treatment team better direct prevention and intervention (4, 86, 119).

Background: Aberrant Neurophysiology and Clinical Performance in Focal Hand Dystonia

Degradation in Somatosensory Topography in Patients with FhDtsp

The early electrophysiological studies on the pathogenesis of focal dystonia focused on the changes in topography of the digit representation in animals (5, 21, 26) and in patients with focal hand dystonia (4, 28, 41). Following moderate rate sensory stimulation, these studies demonstrate degradation in the differentiation of digit representations in contralateral primary somatosensory cortex (S1) for both affected and unaffected hand (9, 18). The hand was essentially mapped inferior to superior in the same location, but the area of receptive fields corresponding to the representation of the dystonic fingers and fingers adjacent to the dystonic fingers were enlarged and overlapped with adjacent finger segments, adjacent fingers and dorsal and palmar surfaces. These findings were reported in both the animal studies driving the onset of dystonia as well as the human subjects with the condition.

Aberrant Amplitude and Latency of Cortical Somatosensory Processing in FhDtsp

In recent years, neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), and spectroscopy have been utilized to highlight aberrant neurophysiology in humans with hand dystonia in order to further elucidate the pathophysiology of the disorder (1, 4, 13, 17, 18, 23, 33, 38, 41, 46, 75, 81, 83, 92, 95, 98, 113, 115). Using these techniques, it has been possible to evaluate the timing and amplitude of sensory and motor responses in the primary somatosensory cortex (S1), the secondary somatosensory cortex and parietal ventral area (S2/PV) as well as the primary motor (M1) and premotor (PMC) cortices .

The focus of research has been on the amplitude and latency in the contralateral primary somatosensory cortex (S1) in response to a moderately paced stimulus with conflicting results. One MEG study reported decreased peak amplitude in contralateral S1 for the affected hand of subjects with FhDtsp but increased amplitude for the unaffected hand (81) compared to healthy controls. In addition one MEG study reported the latency at this peak amplitude occurred earlier for the affected hand of subjects with FhDtsp compared with healthy controls (24). However in another MEG study including more severely affected patients with FhDtsp no significant differences were reported in either the amplitude or latency of the response in contralateral S1 compared to controls (23). None of the studies on latency and amplitude for patients with FhDtsp have recorded ipsilateral responses in SI following moderate stimulation. It has been proposed that contralateral and ipsilateral responses are linked because of the interhemispheric connections via the corpus collosum (10, 60, 61, 62) and that the ipsilateral hemisphere serves an inhibitory function (83). It would be helpful to know if this ipsilateral S1 response specifically is affected in subjects with FhDtsp.

In addition to parallel processing in S1 there is also serial activation from S1 to S2/PV in response to a non-painful somatosensory stimulus (10, 79). The secondary somatosensory cortex and parietal ventral area also receive input from contralateral S1 (10). In healthy subjects there is usually a well-defined late (70-130 milliseconds) response observable in MEG signals that corresponds to *bilateral* S2/PV activity associated with a unilateral tactile stimulus (51, 52, 55). The secondary somatosensory cortex and parietal ventral area are associated with somatomotor integration and may involve object discrimination (8). Interestingly, sensory discrimination is impaired clinically in patients with FhDtsp**.** One study by Butterworth and colleagues reported decreased activity in contralateral S2/PV in response to a tactile stimulus of

the affected hands of subjects with FhDtsp compared with healthy controls (17). It is unknown if the latency or the amplitude was affected in the ipsilateral hemisphere.

Aberrant Processing in the Motor Cortices

There is growing evidence of abnormal processing in the motor cortex in patients with FhDtsp. Self-initiated movements involve motor planning and activation followed by sensory feedback to make error corrections. The primary motor cortex (M1) is involved in the initiation and execution of movement while the premotor cortex (PMC) is involved in the planning of movement and using sensory feedback to refine movement and movement selection. There are direct connections from PMC to M1. In individuals with FhDtsp, PET and fMRI studies report increased activity in contralateral M1 and decreased activity in contralateral PMC (28, 58, 75, 98) associated with voluntary finger and wrist movements of the affected hand. However it is not known if the timing of activation in contralateral M1 and contralateral PMC are also affected.

In addition to serial processing from PMC to M1 there is parallel processing via interhemispheric connections in both the primary motor cortex and premotor cortex (32). The ipsilateral motor cortices may be involved in inhibiting unwanted movements. Transcranial magnetic stimulation (TMS) studies reveal decreased intracortical inhibition in the primary motor cortex (M1) and premotor cortex (69) in subjects with FhDtsp. This may be suggestive of an abnormal interaction between the two hemispheres (7, 110). It is also not known if spatial and temporal processing is abnormal in ipsilateral M1 and ipsilateral PMC which may be related to the decreases observed in intracortical inhibition.

In healthy individuals neural activity in the cortex oscillates at certain frequencies due to large populations of firing neurons. From EEG and MEG studies (36, 37) it is known that this activity occurs in the beta (12-30 Hz) and high gamma (65-100 Hz) frequency bands in the motor cortices. Decreased power in the beta frequency band in contralateral M1 associated with a self-paced finger movement occurs around -250 to 250 milliseconds relative to the movement (36). This decrease in beta power is associated with an increase in high gamma power in contralateral M1 of healthy individuals (35, 114). The amplitude and timing of cortical activity within these frequency bands in the motor cortex are unknown in patients with FhDtsp. We can use our understanding of the normal physiology of these neural oscillations related to movement to better understand the dynamics of the sensorimotor system in patients with FhDtsp.

Clinical Performance and Neuroimaging Measures

Subjects with FhDtsp demonstrate clinical deficits in sensory measures of stereognosis and graphesthesia (19, 23, 81), reduced muscle strength with a lower ratio of intrinsic to extrinsic muscle strength in the hand, and reduced quality of performance at the target task (23, 24, 81, 82). Fine motor speed may not be affected in patients with FhDtsp unless related to the target task. In a previous study by McKenzie and colleagues (81), clinical measures were correlated with the latency and amplitude of the response to a moderately paced stimulus in contralateral S1. A longer latency was associated with slower fine motor speed for both affected and unaffected hands of subjects with FhDtsp. A lower amplitude was associated with faster motor speed and better motor control at target task for both the affected and unaffected hands of subjects with FhDtsp. Interestingly no significant correlations were found between clinical sensory measures (graphesthesia, stereognosis, kinesthesia, and localization) and amplitude or

latency of the response in contralateral S1 (81). It is unknown if clinical measures correlate with cortical activity in ipsilateral S1, contralateral and ipsilateral S2/PV or contralateral and ipsilateral motor and premotor cortices.

PURPOSE AND HYPOTHESES OF STUDY

The overall goal of this study was to close the gaps in research relative to amplitude and latency in contralateral and ipsilateral sensory and motor cortices and their correlation with clinical performance in patients with FhDtsp compared to healthy controls. As the somatosensory system has previously been investigated using moderately paced stimuli we chose to study somatosensory activity using high rate and novel stimuli (tactile inputs that are implicated in the development of the disorder such as playing a musical instrument or typing). Since temporal processing has not been studied to date in the motor system in subjects with FhDtsp we chose a simple, self-paced finger movement to investigate oscillatory fluctuations in motor and premotor cortices. A secondary purpose of the study was to determine if clinical parameters of function, sensory discrimination, fine motor speed and strength could be used to predict aberrant cortical sensory or motor processing.

We hypothesized that subjects with FhDtsp would show significant differences in *somatosensory response* amplitudes and latencies for high rate and novel stimuli in: a) primary and secondary somatosensory cortices; b) ipsilateral and contralateral hemispheres; c) affected and unaffected hands. We also hypothesized subjects with FhDtsp would show significant differences in *motor response* amplitudes and latencies in: a) ipsilateral and contralateral hemispheres; and b)

affected and unaffected hands. Finally we tested the hypotheses that clinical measures of function, sensation, motor speed, and strength would predict aberrant somatosensory (S1 and S2/PV) and motor (M1 and PMC) abnormalities in patients with FhDtsp.

SUBJECTS

Fifteen subjects with FhDtsp were recruited to participate in the study. All subjects with focal hand dystonia had to be diagnosed by a physician. Subjects were clinically evaluated for severity using the Burke-Fahn-Mardsen dystonia movement scale (15). Inclusion criteria included: ages 21-75 years, clear dystonic movements related to the performance of a target task, no specific neurological disorder that would explain the signs and symptoms, and no Botox injections within the three months prior to participation in the study. Exclusion criteria included: systemic or neurologic disease associated with a known movement disorder, medical instability, electromagnetically activated medical equipment or devices which might cause damage to the sensitive detection circuits. All subjects with focal hand dystonia were recruited from the UCSF Faculty Practice in Physical Therapy and the Movement Disorders Clinic at UCSF. One subject was excluded because a structural MRI could not be obtained. A second subject was also excluded due to the presence of a pre-existing neurological disorder (eg. seizure disorder).

METHODS

Imaging Paradigms

MEG data was acquired with a 275-channel CTF Omega 2000 whole-head MEG system from VSM MedTech (Coquitlam, BC, Canada) with a 1200 Hz sampling rate. Head position relative to the MEG sensors was determined with three small coils placed at fiducial sites (nasion, right and left preauricular points) in order to detect head motion and for co-registration with structural MR images. Structural MR images were obtained for each subject using a 1.5T MRI scanner (GE Medical System, Milwaukee, WI) to acquire a 3D structural image and to determine the anatomic location of cortical activation (flip angle = 40°, TR/TE = 27/6 msecs, FOV = 240 x 240 mm, 1.5 mm slice thickness, 256 x 256 x 124 pixels).

Somatosensory paradigm

Somatosensory stimuli were presented in three separate blocks: low rate (0.5 Hz ISI), high rate (3 Hz ISI), and an oddball paradigm where novel stimuli were interspersed with more frequent stimuli (3 Hz ISI, 10 msec jitter) to an adjacent digit (Figure 1). Standard and deviant stimuli were presented at probabilities of 0.83 and 0.17 respectively. Standard stimuli served as the background noise while the deviant stimuli served as the test stimuli. The three blocks were tested on both hands. For FhDtsp subjects the most affected digit was selected for the deviant stimulus and the adjacent unaffected or less affected digit was selected for the standard. The most affected digit was also selected for the high rate and low rate blocks in subjects with FhDtsp. For healthy control subjects digit two (D2) was used as the deviant and digit three (D3) as the standard. The tactile stimuli were delivered by pneumatically driven pulses (~140 msecs duration) to the tips of the hand with a balloon diaphragm. The intensity of the stimuli was set

at 17psi (pounds per square inch) and was detectable by all subjects. This somatosensory paradigm was similar to that employed by Zhu et al. (121) in healthy individuals but has not to date been tested in patients with FhDtsp.

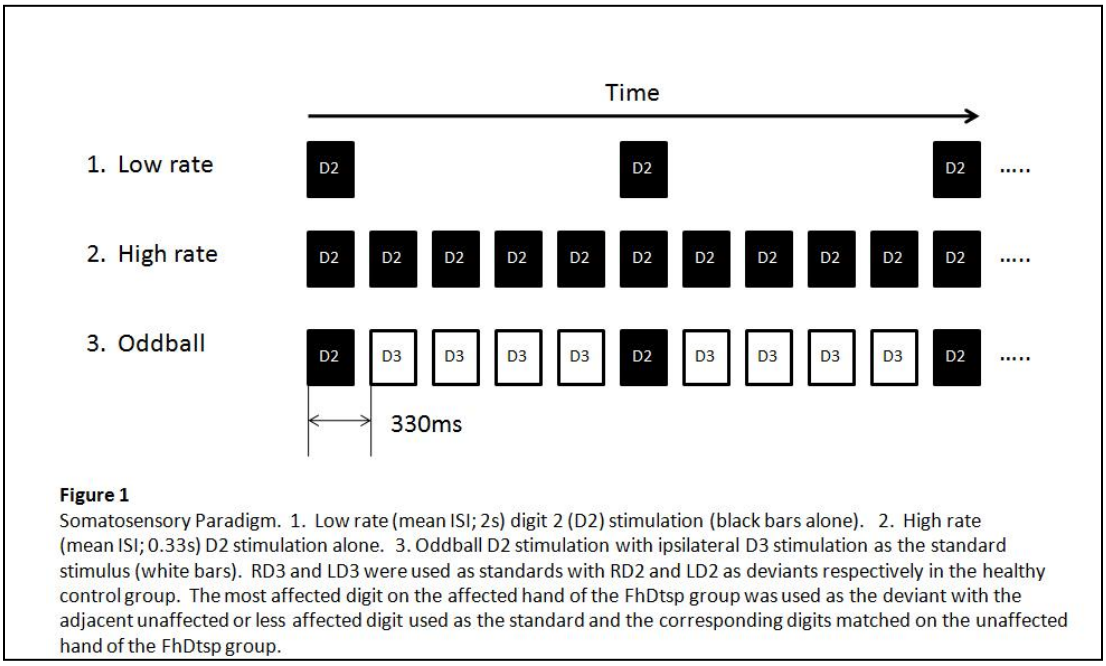

Figure 1
Somatosensory Paradigm. 1. Low rate (mean ISI; 2s) digit 2 (D2) stimulation (black bars alone). 2. High rate (mean ISI; 0.33s) D2 stimulation alone. 3. Oddball D2 stimulation with ipsilateral D3 stimulation as the standard stimulus (white bars). RD3 and LD3 were used as standards with RD2 and LD2 as deviants respectively in the healthy control group. The most affected digit on the affected hand of the FhDtsp group was used as the deviant with the adjacent unaffected or less affected digit used as the standard and the corresponding digits matched on the unaffected hand of the FhDtsp group.

Motor paradigm

A self-paced button press protocol was used to investigate a self-initiated movement of a digit using a procedure identical to previous studies (36, 89). We selected a simple finger movement since the the temporal dynamics associated with movement of a digit is unknown in subjects with FhDtsp. The digit being tested was placed on a button pad adapted for use in the MEG scanner (35). Subjects were instructed to depress the button approximately once every 3 seconds at a self-paced interval for approximately 100 events. The most affected digit was

selected for the subjects with focal hand dystonia as well as the corresponding digit on the unaffected hand. Digit two of the right and left hand was selected for healthy volunteers.

Clinical Performance Measures

All subjects with focal hand dystonia were evaluated using a battery of clinical measures for function, sensation, motor speed, strength, and motor control to determine the relationship between clinical presentation and cortical activation measured with MEG (19, 20, 81). Clinical measures included activities of daily living (Café 40) to determine overall level of function; sensation (graphesthesia and stereognosis) to assess higher levels of sensory processing; motor speed (digital reaction time and tapping speed) to quantify motor deficits associated with focal hand dystonia; strength (grip strength, 3 jaw chuck pinch, lateral pinch, and lumbrical strength) to investigate weakness associated with the muscles of the hand; and motor control (video analysis of performance) to quantify abnormal movements associated with the target task.

Function was assessed using the Café 40 (40); a questionnaire to assess the level of independence or assistance needed for carrying out activities of daily living. Items are rated on a scale from 1 (least independent) to 7 (most independent). There are 234 points possible. The average healthy adult scores 83% on this tool.

Sensation was assessed using graphesthesia (a modified subtest from the Jean Ayers Sensory Integration Praxis Test) and stereognosis (Byl-Cheney-Boczai Sensory Discriminator) (22). Graphesthesia consisted of the examiner drawing symbols on the palmar side of the distal segment of each digit with the subject's eyes closed. The subject was asked to replicate the

symbol by using the end of an open paperclip to draw on the same finger where it was delivered. Performance was graded for accuracy, size, and orientation. Two symbols were drawn, one at a time, on each of the distal segments of each finger on each hand. The scores were then converted to indicate the percentage of correct answers given. This was a subtest of the Jean Ayers Integration Praxis Test (3). In the test of stereognosis subjects were asked to run a finger over a plastic cube that included nine metal stimuli creating different shapes. The subject was asked to keep the eyes closed. The examiner moved the distal pad across the stimulus twice, at a rate of approximately one second. The subject then opened the eyes and had to identify the shape from an assortment of 20 shapes represented in graphical form on a sheet of paper. Ten shapes were tested on both hands, targeting digits two and four on each hand. The scores were then converted to indicate the percentage of correct answers given. A sum sensory discrimination score was then calculated by adding the percent correct scores from both tests (81).

Motor speed and accuracy was assessed using a stopwatch and a finger tapper. The stopwatch measured digital reaction time as the speed at which the subject could start and stop a stopwatch (12). The time was recorded to the millisecond. Each digit was tested three times and the average of those three trials was recorded. A total average of the five digits was then calculated for each hand. This average was subtracted from the mean reaction time of healthy adults to determine a normative score. Tapping speed was measured by the amount of times a subject could depress a tapper (PAR Psychological Assessment) in a 10 second period of time (40). Each digit was tested and an overall average was calculated for each hand. A sum motor speed score was then calculated by summing the normative score of the digital reaction time test with the average score from the tapping speed test.

Grip strength was measured with a handheld Jamar dynamometer with the shoulder adducted, the elbow flexed to 90 degrees and the forearm in midrange supination and pronation (96). An average of three trials per hand was then calculated. The 3 jaw chuck pinch strength and lateral pinch strength were measured with a pinch dynamometer and an average of three trials was calculated for each hand (80, 96). Lumbrical strength was measured with a MicroFet dynamometer with the hand positioned in metacarpalphalangeal joint flexion and interphalangeal joint extension (96). Pressure was applied to the dorsal surface of the middle and distal phalanges in the direction of flexion. An average of three trials per hand was calculated. A sum score was then calculated for strength by summing the averages for each of the strength measures.

Motor control was assessed using video analysis developed by Byl, NN. Subjects were asked to perform the target task and graded on an ordinal scale for posture, movement patterns, and control of movement. A percent score of the total possible points was then calculated.

All clinical measures were previously pilot-tested and good interrater and intrarater reliability (19, 20) and prior factor analysis was conducted for all tests revealing that all clinical measures were considered an independent family (81).

DATA RECORDING AND ANALYSIS

Somatosensory Data Analysis

For somatosensory trials the data was bandpass filtered at 2-40 Hz. Events with excessive noise or artifact were manually removed from each trial. Approximately 100 stimuli were averaged separately in each of the three blocks (low rate, high rate, and deviant stimuli in the oddball condition). Averaged data were then analyzed using an equivalent current dipole (ECD) model to localize the cortical activity (51). SEFs (somatosensory evoked fields) arising from the primary and secondary somatosensory cortices in the time window up to 150 milliseconds following the stimulus onset were analyzed. The early response (30-70 msecs) was analyzed for activation in the primary somatosensory cortex and the late response (70-130msecs) was analyzed for activation in secondary somatosensory cortex/parietal ventral area (61, 84, 121).

Sensor recordings from the hemisphere contralateral to the digit stimulated were chosen to determine the ECD of the strongest source. The position and orientation of the ECD corresponding to the early response was first found and then fixed. Another dipole corresponding to the late response was then added with the early one fixed. Dipoles corresponding to the ipsilateral early and late responses were then fitted and fixed successively. Only sources with high goodness of fit (>85%) were accepted. The response latencies and amplitudes (room-mean-square value, RMS), the dipole moments (Q value) for all four dipole locations (ipsilateral S1, contralateral S1, ipsilateral S2, contralateral S2***)*** were estimated for the three different stimulus conditions based on the peaks within the early and late time periods in each hemisphere.

Statistical analysis of the somatosensory data was performed using SPSS version 16 (SPSS, Chicago, IL). ANOVAs were used to assess the statistical significance of the peak amplitudes, dipole source strengths, and latencies at peak amplitudes in S1 and S2/PV with factors: group (FhDtsp affected hand, FhDtsp unaffected hand, healthy controls), condition (low rate, high rate, oddball), and hemisphere (contralateral, ipsilateral). Post hoc t-tests with a Bonferroni correction for multiple comparisons were then performed with a significance threshold of $p \leq 0.05$.

Motor Data Analysis

For the button press task, MEG data was reconstructed in source-space using an adaptive spatial filtering technique identical to those described in previous studies (24, 123). Events with excessive noise or artifact were manually removed from each trial. From the MEG sensor data, changes in oscillatory power were estimated in several overlapping temporal windows with a step size of 50 milliseconds for the alpha (4-12Hz), beta (12-30 Hz), gamma (30-55Hz), high gamma (65-90 Hz) and ultra-high gamma (90-115Hz) frequency bands. At each time window, source power was estimated using a pseudo-F statistic by comparing the specified window to an inter-trial baseline period. A space-time-frequency power map was then assembled for each subject using a spherical head model based on each subject's head shape and relative sensor position.

Cortical activation in the beta frequency band associated with activity in the primary motor cortex that peaked between -250 and 250 msecs relative to the button press was analyzed (36). The peak response amplitude (f) and latency at peak amplitude were recorded for the contralateral and ipsilateral hemispheres. A laterality index score was calculated to determine

the contribution of the ipsilateral hemisphere to the primary motor cortex response (contralateral M1 activation – ipsilateral M1 activation/contralateral M1 activation + ipsilateral M1 activation).

Statistical analysis of the motor data was also performed using SPSS version 16 (SPSS, Chicago, IL). ANOVAs were used to assess the statistical significance of the peak amplitudes and latencies of the test digit with factors: group (FhDtsp affected hand, FhDtsp unaffected hand, healthy controls) and hemisphere (contralateral, ipsilateral). ANOVA was also used to assess the statistical significance of the laterality index score with factor: group (FhDtsp affected hand, FhDtsp unaffected hand, healthy controls). Post hoc t-tests with a Bonferroni correction for multiple comparisons were then performed with a significance threshold of $p \leq 0.05$.

A within group analysis of both FhDtsp and control subjects was conducted to determine those areas of significant cortical activation. All subjects with FhDtsp had the right hand affected. The groups included: FhDtsp affected right hand, FhDtsp unaffected left hand, healthy control right hand, and healthy control left hand. T-tests with a Bonferroni correction were used with a significance threshold of $p<0.05$. Subsequently the following contrasts were done to compare motor cortex activation between subjects with FhDtsp and healthy controls: FhDtsp affected right hand versus healthy control right hand, FhDtsp unaffected left hand versus healthy control left hand. A t-test was performed with significance set at $p \leq 0.05$.

Correlation and Regression Analysis of Imaging Data with Clinical Performance Measures

The relationship between somatosensory and motor MEG measures and clinical performance measures in the focal hand dystonia group was analyzed using the Pearson product-moment

correlation coefficient with significance set at $p \leq 0.05$. Additionally a feedforward stepwise linear regression analysis was performed to determine if clinical parameters could predict aberrant somatosensory and/or motor processing variables for latency and amplitude on the contralateral and ipsilateral sides of the affected and unaffected hand. Statistical analyses were performed using SPSS version 16. The affected hand and unaffected hand of subjects with focal hand dystonia were analyzed separately. Clinical performance measures included scores for function, sensation, motor speed, and strength. MEG measures for the somatosensory paradigm (sensor analysis) included amplitude (RMS), dipole moment (Q), and latency at peak amplitude. MEG measures for the motor paradigm (source-space analysis) included amplitude and latency, as well as the laterality index score. Only those MEG values of FhDtsp subjects that differed significantly from healthy controls were analyzed.

RESULTS

Subjects

Thirteen subjects with idiopathic focal hand dystonia (9 males, 4 females; mean age ± SD, 45.0 ± 10.4 years; 8 with severe dystonia, 5 with moderate dystonia) participated in the somatosensory paradigm and a battery of clinical measures. Characteristics of the subjects are summarized in Table 1. All subjects had the right hand affected. Eleven subjects were right handed and two subjects were left handed. Seven subjects had writer's cramp, four subjects had musician's dystonia and two subjects had dystonia related to typing. All thirteen subjects with focal hand dystonia participated in the motor paradigm. However, the data from eleven subjects with focal hand dystonia was used (8 males, 3 females; mean age ± SD, 42.0 ± 8.1 years; 7 with severe

dystonia, 4 with moderate dystonia). The data from the two left handed subjects was excluded since handedness may affect the motor paradigm (68).

Thirteen volunteers (9 males, 4 females; mean age ± SD, 38.0 ± 10.0 years) served as healthy controls for the somatosensory paradigm. Eight subjects were right handed and five subjects were left handed. Right and left handed subjects were included since no effect of handedness has been shown using this somatosensory paradigm (121). A different set of eleven healthy volunteers (8 males, 3 females; mean age ± SD, 38 ± 14.6 years) served as healthy controls for the motor paradigm. All subjects were right handed. All healthy controls were age- and sex-matched to the FhDtsp group. Age did not differ significantly across groups. All subjects with focal hand dystonia and healthy volunteers gave written consent for the study as approved by the Committee on Human Research of the University of California, San Francisco.

Table 1 Description of subjects with focal hand dystonia

Patient	Affected Hand	Dominant Hand	Target Task	Gender (M/F)	Age (years)	Most Affected Digit	Severity
1*	Right	Left	Writing/Typing	M	63	D3	Severe
2	Right	Right	Writing	M	53	D3	Severe
3	Right	Right	Writing	M	41	D2	Severe
4	Right	Right	Guitar	M	48	D3	Severe
5	Right	Right	Typing	M	43	D2	Severe
6	Right	Right	Writing	F	46	D2	Moderate
7	Right	Right	Writing/Typing	M	27	D2	Moderate
8*	Right	Left	Piano	F	60	D4	Moderate
9	Right	Right	Drums	M	53	D2	Severe
10	Right	Right	Writing/Typing	M	36	D2	Moderate
11	Right	Right	Writing	F	40	D2	Severe
12	Right	Right	Guitar	M	32	D2	Severe
13	Right	Right	Writing	F	43	D2	Moderate
Sensory Controls	N/A	8 R/5 L	N/A	9M/4F	24-66	N/A	
Motor Controls	N/A	11 R	N/A	8M/3F	24-66	N/A	

*Excluded from button press motor paradigm

Somatosensory Dipole Localizations

Dipole localization using co-registration of MEG data with structural MRI scans verified activation in the primary somatosensory cortex for the early response (30-70msecs) and secondary somatosensory cortex/parietal ventral area for the late response (70-130msecs). Figure 2 demonstrates the averaged RMS (root mean square) responses over time beginning at the onset of the stimulus (0msecs) and including the early (S1) and late (S2/PV) responses through 1500msecs for the oddball condition. Similar characteristic waveforms were generated for the low rate and high rate conditions. Figures 2A and 2B show the affected hand and unaffected hand of FhDtsp subjects compared with healthy controls for the contralateral and ipsilateral hemispheres respectively. Amplitude differences and latency shifts can be visualized in the early and late responses in both hemispheres.

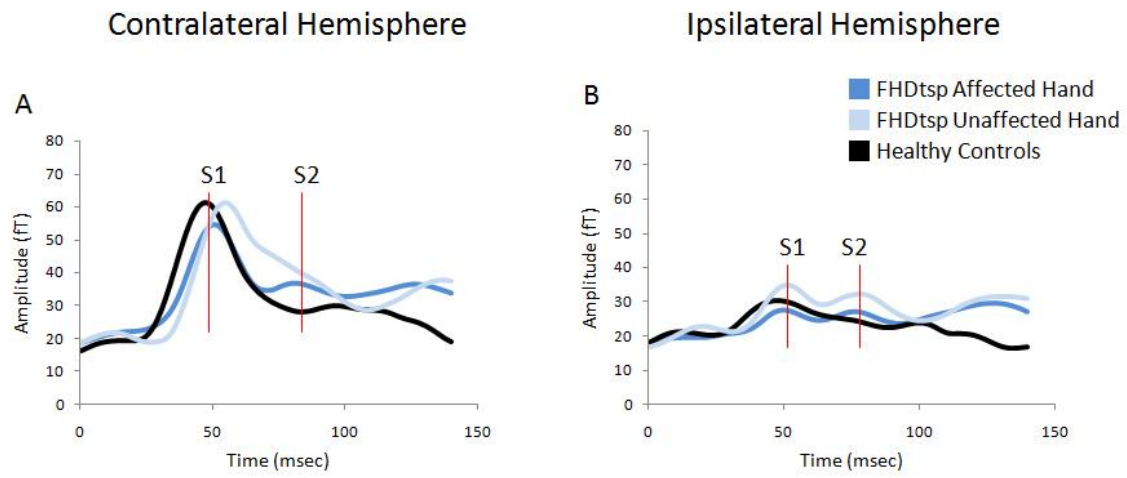

Figure 2
Average amplitude (RMS) over time: Oddball condition. Average of the peak sensor amplitude (RMS: root mean square) from the time of the somatosensory stimulus at 0 msecs to 150 msecs after the stimulus for the ipsilateral (A) and contralateral hemispheres (B) is represented for the affected hands of subjects with FhDtsp, the unaffected hands of subjects with FhDtsp, and the right and left hands of healthy volunteers. The approximate early (S1) and late (S2/PV) peaks are marked (red lines). Similar waveforms occur for both the low rate and high rate conditions.

Activation Levels in Primary Somatosensory Cortex (S1)

Mean RMS values and standard errors for contralateral and ipsilateral S1 are shown in Figures 3A and B respectively for FhDtsp affected hand, FhDtsp unaffected hand and the average of right and left hands for healthy controls. Mean dipole moment (Q) values and standard errors for contralateral and ipsilateral S1 are shown in Figures 3E and F respectively for FhDtsp affected hand, FhDtsp unaffected hand and the average of right and left hands for healthy controls.

ANOVA revealed no significant differences in the amplitude (RMS) or dipole moment strength (Q) between groups for either contralateral or ipsilateral S1 (Figures 3A,B,E,F).

Activation Levels in Secondary Somatosensory Cortex and Parietal Ventral Area (S2/PV)

Mean RMS values and standard errors for contralateral and ipsilateral S2/PV are shown in Figures 3C and D respectively for FhDtsp affected hand, FhDtsp unaffected hand and the average of right and left hands for healthy controls. ANOVAs revealed a significant effect of group (p=0.001), condition (p=0.001), and hemisphere (p=0.001) and significant interaction between group and hemisphere (p= 0.040) and hemisphere and condition (p=0.001).

Mean dipole moment strength (Q) values and standard errors for contralateral and ipsilateral S2/PV are shown in Figures 3G and H respectively for FhDtsp affected hand, FhDtsp unaffected hand and the average of right and left hands for healthy controls. ANOVAs revealed a significant effect of group (p=0.001), condition (p=0.001) and hemisphere (p=0.050).

Post-hoc analyses revealed greater amplitude (RMS) and dipole moment strength (Q) in both contralateral and ipsilateral S2/PV for the affected hands of subjects with FhDtsp compared with

healthy controls for the high rate condition ($p \leq 0.05$ after Bonferroni correction) (Figures 3C,D,G,H). Post-hoc analyses also revealed greater amplitude (RMS) and dipole moment strength (Q) for the unaffected hands of subjects with FhDtsp compared with healthy controls for the high rate condition in contralateral S2/PV ($p \leq 0.05$ after Bonferroni correction) (Figures 3C, G) but not in ipsilateral S2/PV (Figures 3D,H). Additionally the amplitude (RMS) was greater in both the affected and unaffected hands of subjects with FhDtsp compared with healthy controls for the oddball condition in ipsilateral S2/PV ($p \leq 0.05$ after Bonferroni correction) (Figure 3D) although no significant difference in dipole moment strength (Q) was observed. Again there was no significant difference between groups for the low rate condition in contralateral and ipsilateral S2/PV.

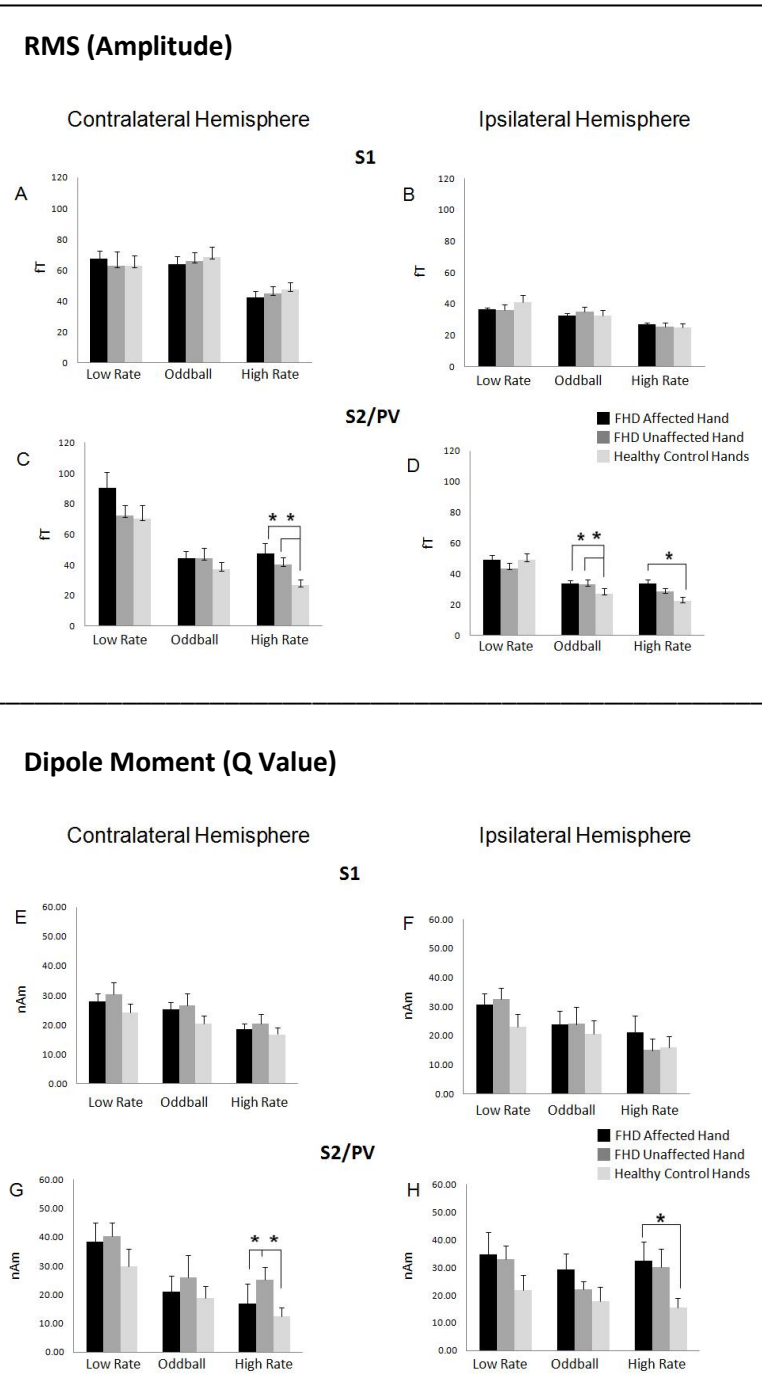

Figure 3

Amplitude (RMS) and Dipole Moment (Q) in S1 and S2/PV. Average of the peak sensor amplitude (RMS) and dipole moment (Q) for the ipsilateral and contralateral early S1 (30-70msecs) and late S2/PV (70-1300 msecs) responses under the three experimental conditions is compared between the affected hands of subjects with FhDtsp, the unaffected hands of subjects with FhDtsp, and the right and left hands of healthy volunteers. The three experimental conditions include the deviant stimuli at low rate (condition 1 in Figure 1, means ISI: 2 secs), the deviant plus the standard stimuli or oddball condition (condition 3 in Figure 1, mean ISI: 0.33 secs), the deviant at high rate (condition 2 in Figure 1, mean ISI: 0.33 secs). Asterisks indicate the responses that are significantly different ($p<.05$) from others that are connected by lines. A and E) Average RMS and Q of contralateral S1 to the hand stimulated. B and F) Average RMS and Q of ipsilateral S1 to the hand stimulated. C and G) Average RMS and Q of contralateral S2/PV to the hand stimulated. D and H) Average RMS and Q of ipsilateral S2/PV to the hand stimulated.

Temporal Processing in Primary Somatosensory Cortex (S1)

Mean latency values at peak amplitudes and standard errors for contralateral and ipsilateral S1 are shown in Figures 4A and B for FhDtsp affected hand, FhDtsp unaffected hand and the average of right and left hands for healthy controls. ANOVAs revealed a significant effect of group ($p=0.001$) and hemisphere ($p=0.050$). Post-hoc analyses revealed significantly later latencies at peak amplitude in contralateral S1 for the unaffected hands of subjects with FhDtsp compared with healthy controls for the low rate condition and for the affected hands of subjects with FhDtsp compared with healthy controls and the unaffected hands of subjects with FhDtsp compared with healthy controls for the oddball condition ($p\leq0.05$ after Bonferroni correction) (Figure 4A). Although the latencies were also later in FhDtsp subjects for the high rate condition in contralateral S1 the differences between groups were not significant. However post-hoc analyses did reveal a significantly later latency at peak amplitude in ipsilateral S1for the high rate condition for the affected hand of subjects with FhDtsp compared with healthy controls ($p\leq0.05$ after Bonferroni correction) (Figure 4B). There were no significant differences in the latencies between groups for the low rate and oddball conditions in ipsilateral S1.

Temporal Processing in Secondary Somatosensory Cortex and Parietal Ventral Area (S2/PV)

Mean latency values at peak amplitudes and standard errors for contralateral and ipsilateral S2/PV are shown in Figures 4C and D for FhDtsp affected hand, FhDtsp unaffected hand and the average of right and left hands for healthy controls. ANOVAs revealed a significant effect of group ($p=0.050$) and condition ($p=0.050$). Post-hoc analyses revealed no significant differences in latencies in contralateral S2/PV between groups. Post-hoc analyses showed a significantly later latency in ipsilateral S2/PV for the affected hand of subjects with FhDtsp compared with healthy controls for the high rate condition while the latency for the low rate condition in the

affected hands of subjects with FhDtsp was significantly earlier than healthy controls ($p \leq 0.05$ after Bonferroni correction) (Figure 4D). There were no significant differences in the latency between groups for the oddball condition in ipsilateral S2/PV.

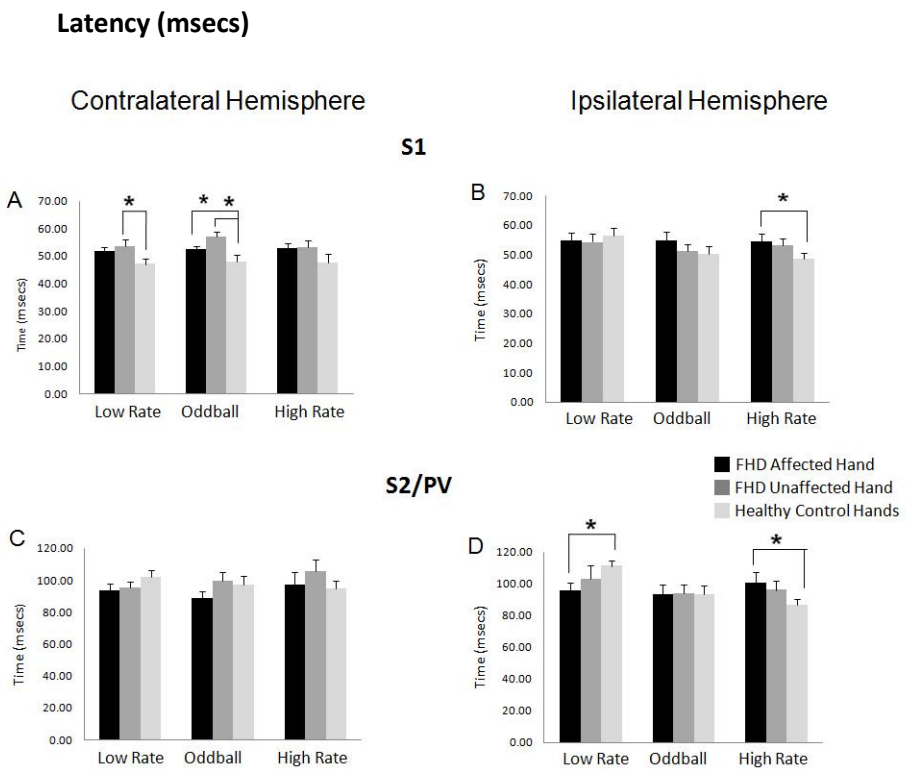

Figure 4

Latency of S1 and S2/PV responses. Average latency at the peak sensor amplitude (RMS) for the ipsilateral and contralateral early S1 (30-70msecs) and late S2/PV (70-1300 msecs) responses under the three experimental conditions is compared between the affected hands of subjects with FhDtsp, the unaffected hands of subjects with FhDtsp, and the right and left hands of healthy volunteers. The three experimental conditions include the deviant stimuli at low rate (condition 1 in Figure 1, means ISI: 2 secs), the deviant plus the standard stimuli or oddball condition (condition 3 in Figure 1, mean ISI: 0.33 secs), the deviant at high rate (condition 2 in Figure 1, mean ISI: 0.33 secs). Asterisks indicate the responses that are significantly different ($p<.05$) from others that are connected by lines. A) Average latency in contralateral S1 to the hand stimulated. B) Average latency in ipsilateral S1 to the hand stimulated. C) Average latency in contralateral S2/PV to the hand stimulated. D) Average latency in ipsilateral S2/PV to the hand stimulated.

Activation in Primary Motor Cortex

The means and standard errors of the peak M1 amplitude within the -250 to 250msec time window in the beta frequency band are shown in Figure 5A and B. ANOVA revealed no significant differences in amplitude in either contralateral or ipsilateral M1 between groups at

the time of the button press. Additionally there were no significant differences in laterality index score between groups.

The means and standard errors of the latency at peak M1 amplitude within the -250 to 250msec time window of the beta frequency band are shown in Figure 5C and D. ANOVA revealed a significant effect of group ($p=0.038$). Post-hoc analysis revealed a significantly earlier latency at the peak amplitude in contralateral M1 for the affected hand of subjects with FhDtsp compared with both the unaffected hands of subjects with FhDtsp and healthy controls ($p \leq 0.05$ after Bonferroni correction) (Figure 5C). A similar finding occurred in ipsilateral M1 although no significant differences were observed between groups (Figure 5D)

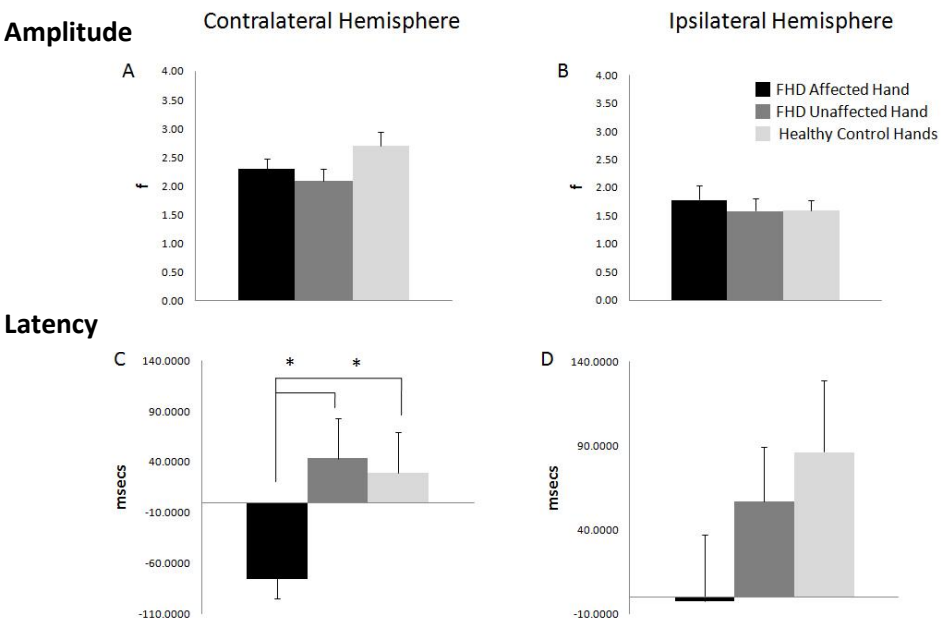

Figure 5
Amplitude and latency of primary motor cortex activation at time of button press. Average peak primary motor cortex (M1) latency at peak amplitude and amplitude in the beta frequency band (15-30 Hz) for the contralateral and ipsilateral hemispheres are compared between the affected digits of subjects with FhDtsp, the unaffected digits of subjects with FHdtsp, and the right and left digits of healthy controls. Average latency at peak amplitude and peak response amplitude occurring between -250 and 250 msecs associated with the self-paced button press are represented. Asterisks indicate responses that are significantly different ($p<.05$) from others that are connected by lines. A) Average latency at peak amplitude in the hemisphere contralateral to the test digit. B) Average latency at peak amplitude in the hemisphere ipsilateral to the test digit. C) Average peak amplitude in the hemisphere contrlateral to the test digit. D) Average peak amplitude in the hemisphere ipsilateral to the test digit.

Whole Brain Analyses of Motor Activity

We conducted a time-frequency analysis of whole brain activation during the motor task using recently developed advanced source localization techniques (35). For both subjects with FhDtsp and healthy controls we observed consistent beta band power decreases bilaterally in the primary motor cortex that reached statistical significance across subjects. One sample t-tests with Bonferroni correction thresholded at $p \leq 0.05$ for the affected right hand, unaffected left hand, and the right and left hands of normal controls revealed significant activation within groups for both ipsilateral and contralateral primary motor cortex associated with the button

press (see figure 6). However healthy control subjects appear to have more focal bilateral activation prior to movement. We also observe similar time-frequency activation overall with some subtle differences between groups. Group comparisons (FhDtsp affected right hand – healthy control right hand, FhDtsp unaffected left hand – healthy control left hand) however did not reveal any significant differences between groups in the beta band in the primary motor cortex at the time of the button press.

However across group analyses did reveal a significant increase in amplitude in the high gamma band of contralateral M1 for the affected right hands of FhDtsp subjects compared with the right hands of healthy controls prior to (-475 msecs, MNI coordinates: -45.5, -15.0, 55.5) and following (525 msecs, MNI coordinates: -39.7, -15.0, 58.1) the button press (see Figure 7). Figure 7 also shows additional areas of increased activation for the affected hands of subjects with FhDtsp compared with healthy controls which included cingulate gyrus (BA 24) prior to the button press (-475 msecs, MNI coordinates: 6.3, 11.4, 34.2) and contralateral middle frontal gyrus (BA 10) following the button press (525 msecs, MNI coordinates: -37.3, 49.2, 16.1). No differences between groups were observed in ipsilateral M1. Additionally there were no significant differences between the unaffected left hand of subjects with FhDtsp and the left hand of healthy controls in the high gamma band.

Additionally across group analyses revealed a significant increase in amplitude in the beta band of ipsilateral premotor cortex for the affected right hands of FhDtsp subjects compared with healthy controls prior to (-575 msecs, MNI coordinates: 48.3, -1.0, 35.9) and following (625 msecs, MNI coordinates: 48.3, -1.0, 34.2) the button press (see Figure 7). There was an additional area of activation in the superior frontal gyrus (BA8) following the button press (625

msecs, MNI coordinates: 25.3, 44.2, 44.1). No differences between groups were seen in contralateral premotor cortex.

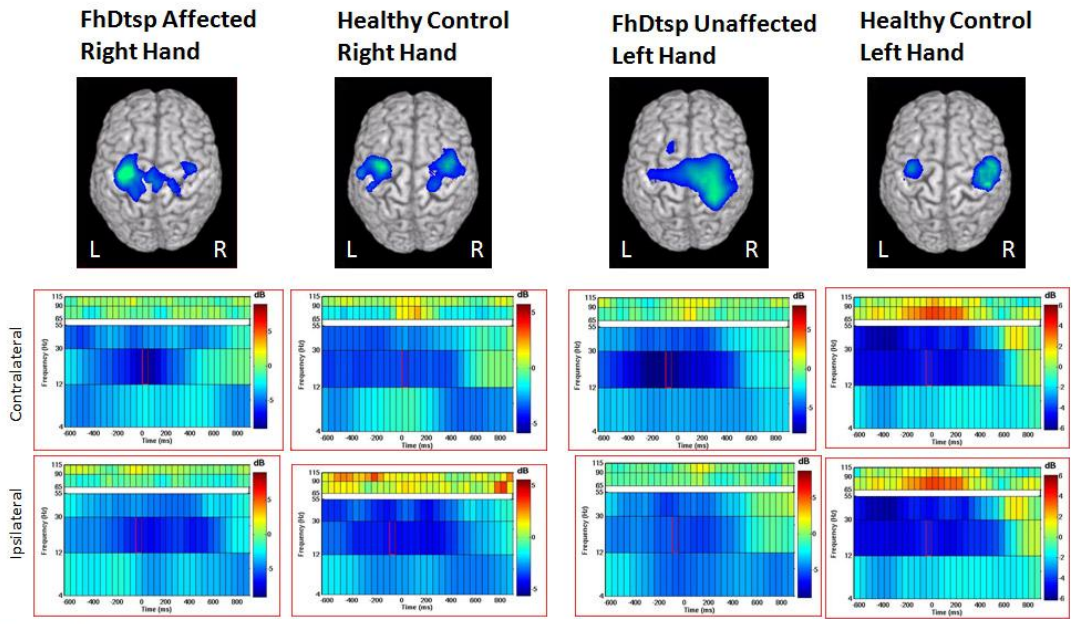

Figure 6

Time-frequency analysis of M1 beta band activity. Shown above are the average reconstruction results for the self-paced button press superimposed on MNI template brains. The functional maps are thresholded at $p<0.05$ with Bonferonni correction. The time-frequency spectrum displays 600 msecs prior to the self-paced button press (time 0) through 1000 msecs after the button press. Frequency bands including the beta-band (12-30Hz) associated with motor activity are represented along the y axis. The peak activation in the contralateral and ipsilateral primary motor cortex is shown with the corresponding spectrograms below.

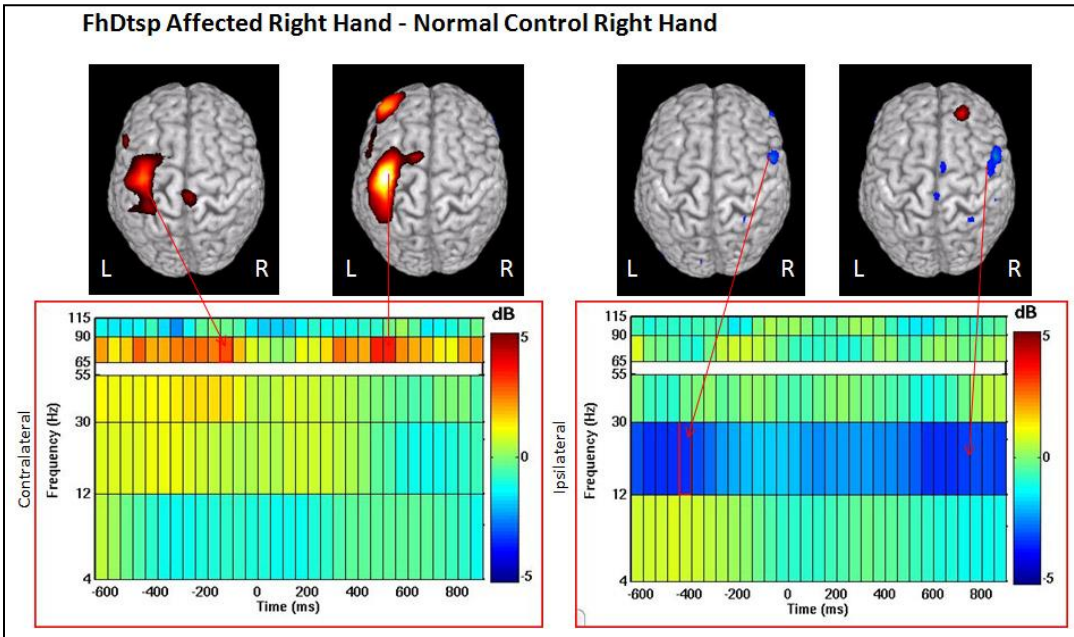

Figure 7

Whole brain contrasts. Shown above are the subtraction (FHD affected right digits – healthy control right digits) reconstruction results for the self-paced button press superimposed on MNI template brains. The functional maps are thresholded at $p<0.05$. The peak activation in the high gamma band (65-90 Hz) of the contralateral primary motor cortex is shown on the left with the corresponding spectrogram below. The peak activation in the beta band (15-30 Hz) of the ipsilateral premotor cortex is shown on the right with the corresponding spectrogram below.

Correlation and Linear Regression Analyses

The average scores for each of the clinical measures in the subjects with FhDtsp are displayed with average scores of healthy controls from historical normative data in Figure 8. Significant differences between groups were calculated using the standard error of the mean to account for differences in sample sizes.

The correlations made between the behavioral performance measures and the MEG measures that differed significantly between FhDtsp subjects and healthy controls are summarized in Table 2. There were no significant correlations between the behavioral performance measures

and the latency at the peak amplitude in the beta frequency band in the primary motor cortex in FhDtsp subjects. The significant Pearson correlations are shown in Figure 9.

Sensory Measures

There was a significant correlation between the sensory score (sum of percent correct answers for graphesthesia and stereognosis) for the affected hand and the latency in ipsilateral S1 for the high rate condition (Figure 9A). A higher sensory score is associated with a longer latency at peak amplitude. There were no other significant correlations between clinical sensory measures and MEG measures. The sensory score was also a significant predictor of the latency in ipsilateral S1 of the affected hand for the high rate condition using the stepwise linear regression model (Beta=0.6, $p<0.05$).

Motor Speed Measures

There was a significant correlation between motor speed score (average sum of tapper and digital reaction) for the affected hand and the latency in ipsilateral S2/PV for the low rate condition (Figure 9B). Faster motor speed is associated with increased latency in the affected hand. There were no other significant correlations between clinical motor speed measures and MEG measures. Motor speed was not a significant predictor of the sensory and motor MEG measures.

Strength Measures

There was a significant correlation between the strength (average sum of grip, 3 jaw chuck pinch, lateral pinch, and lumbrical strength) of the affected hand and the latency in ipsilateral S2/PV for the low rate condition (see Figure 9C). Stronger grip, pinch, and

lumbricals were associated with increased latency. There were no other significant correlations between strength and MEG measures. Strength was not a significant predictor of the sensory and motor MEG measures.

Quality of Life Measure

There were no significant correlations between the Café 40 and MEG measures. The Café 40 was not a significant predictor of the sensory and motor MEG measures.

Motor Control Measure

There were no significant correlations between motor control at the target task and MEG measures. Motor control was not a significant predictor of the sensory and motor MEG measures.

Figure 8
Clinical Performance Measures. Average clinical measures for FhDtsp affected hand, FhDtsp unaffected hand, and normative data from healthy controls.

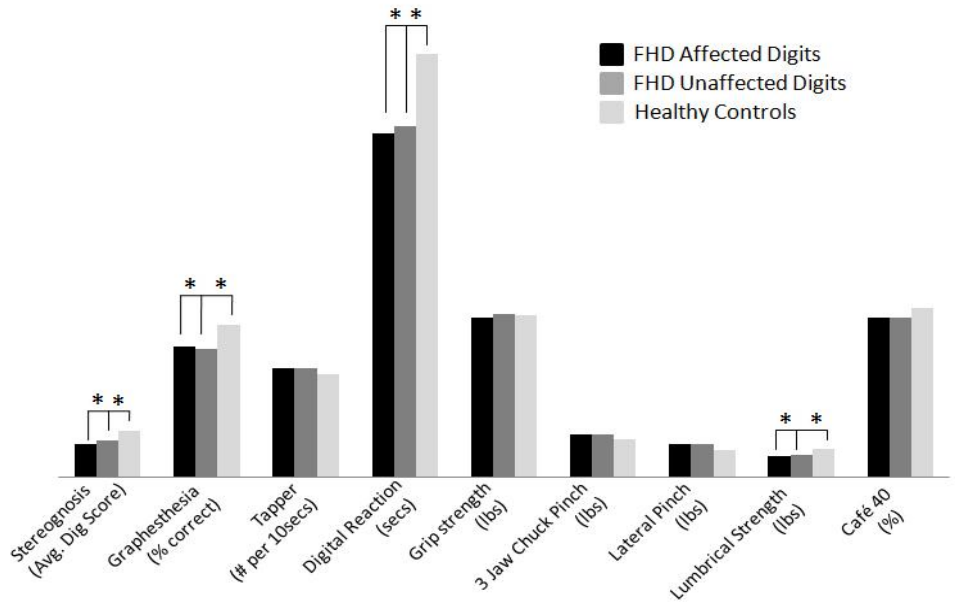

Table 2

Pearson's Correlation coefficients for the affected hands and unaffected hands of subjects with FhDtsp for the conditions found to be significantly different than healthy controls in the Somatosensory paradigm(RMS, Q, and Latency) and the Motor paradigm (Latency). Asterisks indicate the correlations that are significant (p<.05).

	Sensory Score	Motor Score	Strength	Function	Motor Performance
Mismatch Somatosensory RMS					
High rate condition, contralateral hemisphere, late response, affected digits	-.17	.12	.15	.33	.49
High rate condition, contralateral hemisphere, late response, unaffected digits	.25	-.24	-.29	.33	na
High rate condition, ipsilateral hemisphere, late response, affected digits	-.27	.26	.20	.33	.54
Oddball condition, ipsilateral hemisphere, late response, affected digits	-.15	-.02	.37	.30	.19
Oddball condition, ipsilateral hemisphere, late response, unaffected digits	-.10	-.11	.06	.40	na
Mismatch Somatosensory Q					
High rate condition, contralateral hemisphere, late response, affected digits	-.33	-.19	.02	.23	.48
High rate condition, contralateral hemisphere, late response, unaffected digits	-.47	-.25	.25	-.03	na
High rate condition, ipsilateral hemisphere, late response, affected digits	-.56	-.26	-.02	-.09	.55
Mismatch Somatosensory Latency					
Low rate condition, contralateral hemisphere, early response, unaffected digits	-.04	.39	.13	.14	na
Oddball condition, contralateral hemisphere, early response, affected digits	-.49	-.26	-.04	-.17	.45
Oddball condition, contralateral hemisphere, early response, unaffected digits	.04	.12	.13	-.35	na
High rate condition, ipsilateral hemisphere, early response, affected digits	.59*	.17	.30	.05	-.24
Low rate condition, ipsilateral hemisphere, late response, affected digits	-.03	.58*	.56*	.53	.47
High rate condition, ipsilateral hemisphere, late response, affected digits	.09	.14	.17	.28	.51
Primary Motor Cortex Latency					
Contralateral hemisphere, affected digits	-.24	-.18	.60	-.04	-.09

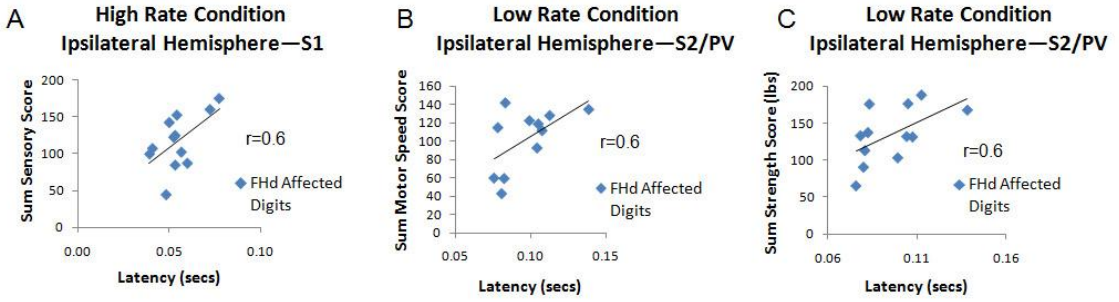

Figure 9

Scatter plots of the significant correlations (p<.05) between MEG measures and clinical performance measures.

A) Correlation between the sensory score (sum of the percentage correct answers for the measures of graphesthesia and stereognosis) and the latency at the peak amplitude in ipsilateral S1 of the hand stimulated for the high rate condition in the affected hands of subjects with FhDtsp. B) Correlation between the motor score (sum of the average scores of the finger tapper and stopwatch) and the latency at the peak amplitude in ipsilateral S2/PV of the hand stimulated for the low rate condition in the affected hands of subjects with FhDtsp C) Correlation between the sum strength score (grip, 3 jaw chuck pinch, lateral pinch , and lumbricals) and the latency at the peak amplitude in ipsilateral S2/PV of the hand stimulated for the low rate condition in the affected hands of subjects with FhDtsp..

DISCUSSION

The present study used MEG to provide unique information about the spatial and temporal properties of cortical somatosensory and motor processing in both contralateral and ipsilateral hemispheres in subjects with task-specific focal hand dystonia. The current study demonstrates that there are clear problems in the timing of activation and the amplitude of excitation in S1, S2/PV, M1 and PMC in subjects with FhDtsp. These findings provide evidence to accept our hypotheses. Subjects with FhDtsp show significant increases in the latency of both the S1 and S2/PV responses compared with healthy controls in contralateral S1 for the low rate and oddball conditions, in ipsilateral S1 for the high rate condition, and in ipsilateral S2/PV for the high rate condition. The hypothesis of significant differences in amplitude in S2/PV for high rate and novel stimuli must be accepted. There were increases in activation in the contralateral and ipsilateral hemispheres for the affected and unaffected hands. Subjects with FhDtsp also had significant increases in contralateral M1 activation and ipsilateral premotor cortex activation for the affected digits that occurred earlier and remained on later. Aberrant somatosensory (S1) responses for the high rate condition in patients with FhDtsp predicted sensory performance outcomes.

A seminal study reported in 1996, raised increased attention to extrinsic factors that might influence the development of hand dystonia. Byl et al, 1996 reported repetitive, rapid, and attended movements could result in maladaptive changes in the sensory and motor cortices of the brain (21). In patients who had developed focal hand dystonia, electrophysiological studies reveal dedifferentiation of the normal topography of the hand in the primary somatosensory cortex on both the contralateral sides of the trained and untrained hand (23). The learning

based sensorimotor hypothesis was proposed as one etiology of hand dystonia: excessive, near simultaneous individuated movements of the fingers can de-differentiate the representation of the hand and interfere with normal motor control at a practiced, target task. Several additional research studies contributed evidence in support of this hypothesis (5, 9, 118) in monkeys and rats.

Abnormal amplitude of activation in the somatosensory cortices of subjects with FhDtsp

We did not find any significant differences in the amplitude of the response in S1 between subjects with FhDtsp and healthy controls for low rate, high rate, or novel stimuli (see Table 3). This suggests altered spatial representations do not necessarily have an effect on the amplitude of cortical activity in S1. This is consistent with a study by Byl et al. (23) who found no difference in the amplitude of response in contralateral S1 to a moderately paced stimulus (rate≈0.5secs). However in a subsequent study, in response to a moderately paced stimulus, these researchers reported a decrease in amplitude in contralateral S1 for the affected hands of FhDtsp subjects and an increase in contralateral S1 for the unaffected hands compared with controls (81). These differences in results may be accounted for by a larger proportion of severely affected subjects in the first study which more closely resembles the subjects in the present study. These findings raise some question about whether the severity of dystonia impacts amplitude responses in S1.

Since somatosensory information is processed serially from S1 to S2/PV (10, 79), one could hypothesize that the amplitude of the response in S2/PV should be consistent with the lack of amplitude changes in S1. However increased amplitude (RMS and Q) for high rate stimulation was observed in contralateral S2/PV for both affected and unaffected hands of subjects with FhDtsp (see Table 3). This finding is in contrast to an fMRI study by Butterworth et al (17).

These researchers reported decreased activation in contralateral S2/PV during vibratory tactile stimulation which activates Pacinian corpuscles. The stimuli in the current study primarily activated Meissner's corpuscles which may account for the conflicting findings. Sensory information from the periphery is also processed through the posterior nuclei of the thalamus to S1 and S2/PV. It is possible abnormal processing occurs between the thalamus and S2/PV via direct connections. When subjects with dystonia undergo thalamotomy for treatment of the disorder, increased receptive field sizes are reported in the sensory thalamus (73). These findings have been replicated in a non-human primate model of task-specific focal hand dystonia (9).

Increased amplitude (RMS and Q) of response for high rate stimulation was observed in ipsilateral S2/PV for affected hands only (see Table 3). These increases in activation in both contralateral and ipsilateral S2/PV for high rate stimulation may suggest abnormal parallel processing between contralateral and ipsilateral S2/PV for the affected hand (see Figure 10). The abnormal activity in ipsilateral S2/PV may not yet be evident in the unaffected hand when presented with high rate stimuli to the digits. Similarly significantly increased amplitude (RMS) was evident in ipsilateral S2/PV and contralateral S2/PV (although not significant) for both affected and unaffected hands of subjects with FhDtsp in response to novel stimulation. However no differences in amplitude were seen in either contralateral or ipsilateral S2/PV in response to low rate stimulation. These results indicate that somatosensory processing appears to be normal in response to non-task specific low rate stimulation, but may become abnormal in response to high rate stimulation (as shown in Figure 10) or novel stimulation for the affected and unaffected hands of subjects with FhDtsp. These increases in cortical activity in ipsilateral

S2/PV may be related to abnormalities in intracortical inhibition in the somatosensory system (123).

Table 3 Summary of Somatosensory Results

Cortical Area		Contralateral Hemisphere			Ipsilateral Hemisphere		
		Low Rate Stim	High Rate Stim	Oddball Stim	Low Rate Stim	High Rate Stim	Oddball Stim
S1	Latency	**↑ Unaffected Hand**	*No sig. effect*	**↑ Affected Hand** **↑ Unaffected Hand**	*No sig. effect*	**↑ Affected Hand**	*No sig. effect*
	Amplitude (RMS)	*No sig. effect*	*No sig. effect*	*No sig. effect*	*No sig. effect*	*No sig. effect*	*No sig. effect*
	Dipole Moment	*No sig. effect*	*No sig. effect*	*No sig. effect*	*No sig. effect*	*No sig. effect*	*No sig. effect*
S2/PV	Latency	*No sig. effect*	*No sig. effect*	*No sig. effect*	**↓ Affected Hand**	**↑ Affected Hand**	*No sig. effect*
	Amplitude (RMS)	*No sig. effect*	**↑ Affected Hand** **↑ Unaffected Hand**	*No sig. effect*	*No sig. effect*	**↑ Affected Hand**	**↑ Affected Hand** **↑ Unaffected Hand**
	Dipole Moment	*No sig. effect*	**↑ Affected Hand** **↑ Unaffected Hand**	*No sig. effect*	*No sig. effect*	**↑ Affected Hand**	*No sig. effect*

Note: Bold indicates significant effect ($p<0.05$)

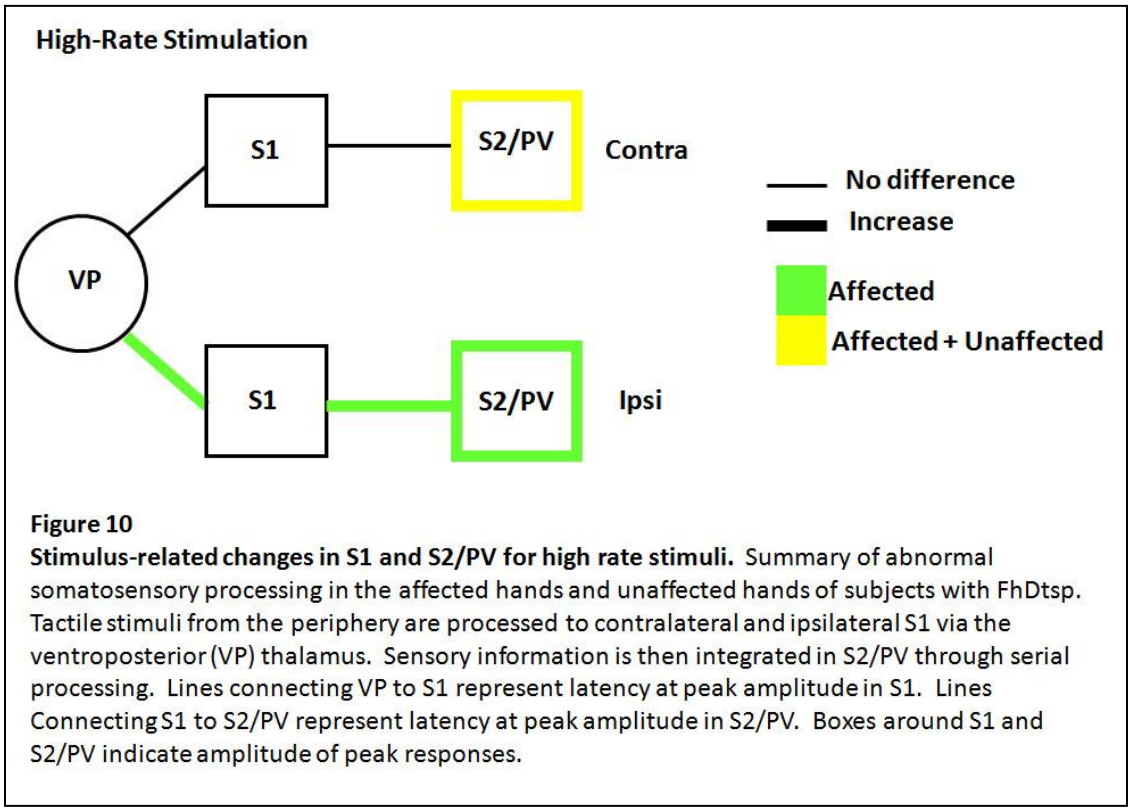

Figure 10

Stimulus-related changes in S1 and S2/PV for high rate stimuli. Summary of abnormal somatosensory processing in the affected hands and unaffected hands of subjects with FhDtsp. Tactile stimuli from the periphery are processed to contralateral and ipsilateral S1 via the ventroposterior (VP) thalamus. Sensory information is then integrated in S2/PV through serial processing. Lines connecting VP to S1 represent latency at peak amplitude in S1. Lines Connecting S1 to S2/PV represent latency at peak amplitude in S2/PV. Boxes around S1 and S2/PV indicate amplitude of peak responses.

Abnormal latency of activation in the somatosensory cortices of subjects with FhDtsp

Although we only observed increased amplitudes in S2/PV there were significant differences in the latency of peak responses in both S1 and S2/PV (see Table 3). There was longer processing time in the contralateral hemisphere for all three somatosensory conditions (especially significant for low rate and novel stimuli). This may be a result of the altered topography that has previously been reported for contralateral S1 for affected and unaffected hands and thus may contribute to the increased processing time for tactile input. Byl et al. (23) also reported increased latencies in contralateral S1 (although not significantly different from healthy controls) while in a case series of three subjects with FhDtsp earlier latencies were observed in response to a moderately paced stimulus (rate≈0.5 secs) (24). The inconsistent findings between this study and the current study may be due to the small sample size in the case series and the difference in stimulus rates employed.

Despite the increased processing time in contralateral S1 latencies in contralateral S2/PV were not significantly different between subjects with FhDtsp and healthy controls for low rate, high rate, or novel stimulation suggesting that serial processing between contralateral S1 and contralateral S2/PV remains intact. On the other hand serial processing from ipsilateral S1 to ipsilateral S2/PV may be affected as there were significantly later latencies in ipsilateral S2/PV for the high rate condition in the affected hands of subjects with FhDtsp.

Additionally somatosensory processing speed from S1 to S2/PV may be faster in subjects with FhDtsp when the tactile stimulus is not associated with the target task, indicative of normal plasticity. There were earlier latencies in ipsilateral S1 (although not significant) and significantly earlier latencies in ipsilateral S2/PV for low rate stimulation for the affected hands

of subjects with FhDtsp. However faster processing time in the ipsilateral hemisphere may not be beneficial as we found that faster motor speed and higher strength were associated with an increase or normalization of latency in ipsilateral S2/PV for low rate stimulation.

In the present study, participants had clear deficits in spatial and temporal processing at different cortical sites (e.g. contralateral and ipsilateral) for S1 and S2/PV. However it is not clear which neural pathways are responsible for the changes. They may be related to abnormal intracortical inhibition, possible changes in thalamic connections or topography or potential changes in the topography of S2/PV in subjects with FhDtsp. Nevertheless the increases in amplitude and latency may result in increased or abnormal feedback to the motor cortex and result in increased motor output. This increase in motor output would be consistent with the Sanger-Merzenich model of FhDtsp which postulates abnormal topography in S1 leads to increased gain in the somatosensory system which in turn leads to increased gain in the motor system and aberrant muscle contractions (103).

Abnormal spatiotemporal processing in the primary motor cortex of subjects with FhDtsp

In addition to amplitude changes in S2/PV we also saw increased amplitudes in the motor cortices in subjects with FhDtsp compared with healthy controls. Although we found no differences in the amplitude of M1 activity at the time of the button press in either the beta (12-30Hz) or high-gamma ranges (65-90Hz) in FhDtsp subjects compared with healthy controls we did find that in the high gamma band subjects with FhDtsp activated contralateral M1 earlier and maintained that activation longer than healthy controls when using their affected hands (see Table 4).

These findings may be consistent with the fMRI and PET studies (71, 96) that reported increased activation in M1 during a motor task. Due to the low temporal resolution of both fMRI and PET the increased activity reported may be reflective of an earlier onset and longer duration of activity during the motor task, and not necessarily increased activity per se. Additionally activation in fMRI and PET studies may be confounded by contribution of the somatosensory cortex due to the low temporal resolution in these methods while in the present study we are able to investigate motor cortex activity prior to the movement on the millisecond timescale without somatosensory interference. Although it could be posited that our finding of increased activity following the button press may have been a result of FhDtsp subjects depressing the button for a longer period of time, we found no significant difference in the duration of the button press between subjects with FhDtsp and healthy control hands. These neurophysiological findings are consistent with the clinical presentation that patients with FhDtsp activate muscles inappropriately and have difficulty turning off muscle activity.

Table 4 Summary of Motor Results

Cortical Area		Contralateral Hemisphere		Ipsilateral Hemisphere	
		Beta Freq Band	High Gamma Band	Beta Freq Band	High Gamma Band
Premotor	Latency	*No sig. effect*	*No sig. effect*	**Affected Digits--Early and Prolonged**	*No sig. effect*
	Amplitude	*No sig. effect*	*No sig. effect*	**Affected Digits--Early and Prolonged**	*No sig. effect*
Primary Motor	Latency	**Affected Digits--Early (at time of movement)**	**Affected Digits--Early and Prolonged**	*No sig. effect*	*No sig. effect*
	Amplitude	*No sig. effect*	**Affected Digits--Early and Prolonged**	*No sig. effect*	*No sig. effect*

Note: Bold indicates significant effect ($p<0.05$)

Abnormal spatiotemporal processing in the premotor cortex of subjects with FhDtsp

There was a similar response in the beta band over ipsilateral premotor cortex in the affected hand of subjects with FhDtsp. An increase in activity occurred earlier and remained longer than

in healthy controls (see Table 4). These findings may be consistent with increased activation in the premotor cortex which has been reported during a writing task using fMRI (119). However Pujol et al. (96) and Oga et al. (92) demonstrated decreased premotor activity while simulating guitar playing or maintaining a tonic wrist contraction respectively. These studies involved more complex muscle contractions than the current study and may account for the inconsistent findings observed in the premotor cortex.

Premotor cortex (PMC) is involved in the planning of voluntary movement. Although contralateral PMC has direct projections to M1 of the same hemisphere, it is not clear how ipsilateral premotor cortex contributes to contralateral primary motor cortex for the execution of movement. The ipsilateral premotor cortex may be involved in inhibiting unwanted movements. This may be reflected in the decrease in intracortical inhibition seen in premotor cortex (87). The early activation of PMC found in this study may result in early activation of the primary motor cortex or may be related to the extended activation seen in contralateral M1 (see Figure 11). Additionally subjects with FhDtsp may have a general problem with turning off cortical activity appropriately. In a study by Blood et al. (11) activity in some structures of the motor system, such as the basal ganglia, persisted following completion of a tapping task in subjects with FhDtsp compared with healthy controls. This is consistent with our findings in maintained activity in contralateral M1 and ipsilateral premotor cortex.

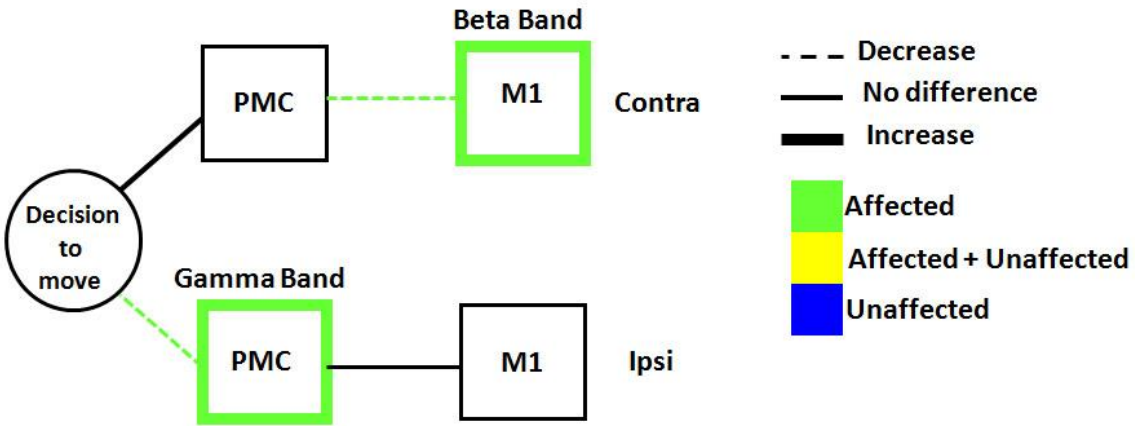

Figure 11
Abnormal cortical motor processing associated with a button press. Summary of abnormal motor processing occurring in the affected hands only of subjects with FhDtsp. A decision is made to move the digit and the movement occurs due to processing in the premotor cortex (PMC) to the primary motor cortex (M1). Abnormal processing occurs in the high gamma frequency band of M1 and the beta frequency band of PMC. Connecting lines represent latency at peak amplitude. Boxes around PMC and M1 indicate amplitude of peak responses.

The present study employed high rate and novel somatosensory stimuli to the hand as a model for the development of the disorder in which the target task requires rapid sensory processing. However it might be crucial to investigate the spatial and temporal properties of motor processing with an experimental design utilizing etiologically relevant movements. We may have found more significant differences in the motor cortex if we had employed a similar paradigm to one the one we used for somatosensory processing: low rate, high rate, and novel movement.

The differences we found in sensory and motor processing in this study may be independent phenomenon since we investigated the two domains of cortical processing separately. However

consistent with the Sanger-Merzenich model of dystonia the changes we observed in the motor cortex could be a result of the maladaptive responses in latency and amplitude in S1 and S2/PV. Although we see differences in somatosensory processing associated with both affected and unaffected hands we only observed differences in motor processing associated with the affected hand. Thus changes in somatosensory processing may precede changes in the motor cortex or may result in abnormal processing in only the contralateral motor cortex to the affected hand. Sophisticated neuroimaging studies are needed to further investigate the relationship between S1, S2/PV, and the motor cortex as well as the relationship between the ipsilateral premotor areas and the primary motor cortex.

Relationship between clinical measures and MEG sensory and motor measures

Clinically our subjects displayed similar impairments in performance measures as reported in previous studies (23, 24, 81, 82): impaired graphesthesia and stereognosis, longer digital reaction time, and decreased lumbrical strength in the presence of normal grip strength representing an imbalance between the strength of the intrinsic and extrinsic muscles of the hand and forearm compared with healthy controls. These measures of sensation, motor speed, and strength were those clinical measures that correlated with MEG measures. In contrast to the Mckenzie study (81) where no correlations were found between clinical measures of sensation we found that increased latency in ipsilateral S1 for the high rate condition was correlated with higher sensory function. McKenzie and colleagues also found that increased latency in contralateral S1 was associated with slower motor speed while we found that increased latency in ipsilateral S2/PV was actually correlated with faster motor speed as well as higher strength. Additionally we found that clinical measures of stereognosis and graphesthesia were predictors for longer latencies in ipsilateral S1 for the high rate condition. Perhaps the

increased processing time in ipsilateral S1 and ipsilateral S2/PV are compensatory mechanisms associated with more normal processing to S2/PV and premotor cortex respectively and result in better sensory discrimination and sensory feedback to the motor system. Alternatively increased latency in ipsilateral S1 and S2/PV may indicate improved intracortical inhibition leading to normalized sensorimotor processing. Clearly these neuroimaging findings must be studied relevant to successful clinical intervention strategies.

Although not statistically significant we found several other correlations of clinical significance ($r>0.5$, explaining 25% of the variance). Again we found that increased latency in ipsilateral S2/PV for the high rate condition in the affected hands of subjects with FhDtsp correlated with higher scores on the Café 40 questionnaire and better motor performance at the target task further suggesting that increased processing time in the ipsilateral hemisphere is associated with better clinical performance. Additionally we found that higher amplitude (RMS and Q) in *ipsilateral* S2/PV for the high rate condition was associated with better motor performance at the target task suggesting that perhaps the increased activity in ipsilateral S2/PV results in enhanced intracortical inhibition and more effective motor control. In the motor cortex increased latency (normalized processing time) in contralateral primary motor cortex for the affected hands of subjects with FhDtsp was associated with higher strength. Although clinically significant we found no statistically significant correlations between clinical measures and motor MEG measures. It may be that abnormal cortical sensory processing is the primary predictor of clinical presentation. It is also possible that with a more specific motor paradigm modeling specific tasks we might find more significant correlations with clinical data.

Clinical Implications

Although sensory and motor retraining paradigms have been used clinically to restore function in patients with FhDtsp, these approaches have only been partially effective in remapping abnormal topography in contralateral S1 as well as modifying latency and amplitude differences in contralateral S1 (24, 28, 120). This current imaging study suggests that the aberrant neurophysiology extends well beyond the contralateral hemisphere of S1. The abnormalities in amplitude and/or latency were found in S2/PV, MI and premotor cortices, within both contralateral and ipsilateral hemispheres for both affected and unaffected hands. These findings suggest retraining may need to be bilateral and include the domains of sensory processing (e.g. light touch), cortical sensory processing (e.g. graphesthesia and stereognosis), motor planning and action selection as well as motor execution. Although these domains have been included by Byl and McKenzie and other colleagues (27, 82) the training has not been deliberately bilateral.

The increased latencies in contralateral S1 for all three conditions (significant for low rate and novel stimuli) suggest that sensory retraining begin with simple sensory input to the digits. The increased processing time may be reflective of disordered topography in contralateral S1 clearly demonstrated in prior studies (9, 19, 28, 41). Thus sensory retraining should be targeted at appropriately remapping the digits in the primary somatosensory cortex (24, 28).

The increases in amplitude in both contralateral and ipsilateral S2/PV for both affected and unaffected hands suggests that particular emphasis should be placed on sensory retraining involving higher levels of sensory processing that target S2/PV such as object discrimination and Braille reading. Perhaps the excessive excitation in S2/PV might be quieted or more focused by

improving the accuracy of sensory discrimination bilaterally. Normalized responses in S2/PV may then provide more appropriate sensory feedback to the motor system for targeted motor output.

The early and extended activation of ipsilateral PMC and contralateral M1 for the affected hands along with the high amplitude and persistent firing in contralateral and ipsilateral S2/PV for affected and unaffected hands suggest biofeedback may be a successful component of retraining for patients with FhDtsp. Biofeedback provides the necessary information for subjects with FhDtsp to possibly "turn off" prolonged muscle contractions or decrease high amplitude cortical sensory processing. Biofeedback by itself has been used successfully in the treatment of patients with hemiparetic limbs after stroke (2, 55, 78) and has been reported as effective in retraining patients with writer's cramp (7). Using biofeedback with target-specific training for patients with FhDtsp may be able to effect change in the spatial and temporal dynamics of cortical activity, potentially enhancing more controlled, appropriate motor performance of the target task.

The ipsilateral, aberrant firing patterns are of particular interest. Longer latencies in ipsilateral S1 and S2/PV are associated with better clinical performance in sensory discrimination, motor speed, and motor performance at the target task. If these pathways involve forms of inhibition and selectivity in both the sensory (S1 and S2/PV) as well as the motor domain (M1 and PMC) then it could be of value to activate these ipsilateral pathways to turn off the antagonists at the initiation of desired, voluntary movements (e.g. ipsilateral premotor cortex). However it is not clear how to specifically activate and retrain the ipsilateral pathways. It is not clear if bilateral practice would help activate the ipsilateral pathways to increase inhibition. In patients after

stroke, bilateral repetitive transcranial magnetic stimulation improved motor performance of the affected hemiparetic hand (115). However changes to the ipsilateral hemisphere (of the affected hand) by training the unaffected hand may not translate into normalized activity when employing the affected hand in subjects with FhDtsp.

Limitations of the study

Clinical studies including patients with hand dystonia are cross sectional studies. A cross sectional analysis is a one-time report on the signs and symptoms and neuroimaging responses that exist at that time. In these studies, it is difficult to relate cause and effect factors or speak to change over time. It is also difficult to explain the findings of abnormal cortical processing in the contralateral and ipsilateral hemispheres of not only the affected and but the unaffected hand.

This study included a small number of subjects (13 subjects). Although we found significant differences between subjects with FhDtsp compared with controls other differences may have been missed. Unfortunately, given the low prevalence of this disorder, it is difficult to enroll a larger number of subjects in a study from one local area. Where possible, collaborations are encouraged at multiple sites to strengthen the power of finding differences.

Differences in digit selection may also account for differences observed between FhDtsp subjects and healthy controls. Digit two was used for healthy controls for both somatosensory and motor MEG paradigms while the most affected digit was selected for FhDtsp subjects (digit two, three, or four). However the effect seen may actually be reduced as it has been shown that the spatial acuity of digit two is greater than the adjacent hand (116).

Although clinically significant there were no statistically significant correlations between the MEG measures and function as assessed with the Café 40 questionnaire. This may be a result of a ceiling effect of the Café 40 in this group of subjects. All of the patients were functioning at a level similar to healthy adults. A more sensitive measure of motor performance should be used to highlight the differences in the ability to perform specialized tasks in these relatively high-functioning individuals. Additionally it is difficult to objectively assess the severity of the disorder especially in a heterogenous population that includes musicians, writers, typists, etc. The current measurement tools may not be sensitive or specific enough to accurately describe the severity of symptoms (113).

Lastly this study did not address the effects of rehabilitation specifically on temporal and spatial sensorimotor processing. Therefore, further studies are needed to investigate the specific effects of sensorimotor retraining and other treatment modalities on processing in S1 and S2/PV as well as in M1 and the premotor cortex.

CONCLUSION

Cortical somatosensory amplitude was increased in S2/PV and latencies were longer in S1 and S2/PV in response to high rate and novel stimuli in contralateral and ipsilateral hemispheres in patients with FhDtsp. Increased amplitude in PMC and M1 occurred earlier and remained active longer in subjects with FhDtsp compared to age- and sex-matched healthy controls. Behavioral performance measures of sensation, motor speed and strength correlated with increased latency of the somatosensory response in the ipsilateral hemisphere. Bilateral sensory retraining in addition to self guided biofeedback technology may increase patient awareness of

abnormal sensory and motor responses. Learning-based sensory and motor training could potentially contribute to normalizing spatial-temporal processing as well as improve motor program selection and integration of sensory feedback to fine tune motor control. In addition, bilateral, simultaneous biofeedback technology may increase patient awareness in order to balance ipsilateral firing and aid inhibition while decreasing excessive contralateral MI excitation.

References

1. Abbruzzese G, et al. Abnormalities of sensorimotor integration in focal dystonia. *Brain* 2001; 124(3): 537-545.
2. Aeillo E, et al. Visual EMG biofeedback to improve ankle function in hemiparetic gait. *Conf Proc IEEE Eng Med Biol Soc* 2005; 7: 7703-06.
3. Ayres AF. Sensory Integration and Praxis Test (SIPT) Manual. Los Angeles, Western Psychological Services, 1989.
4. Bara-Jimenez W, et al. Sensory discrimination capabilities in patients with focal hand dystonia. *Ann Neurol* 2000; 47: 377-380.
5. Barbe MF et al. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. *J Orthop Res* 2003; 21(1): 167-76.
6. Barr AE et al. Work-related musculoskeletal disorders of the hand and wrist: epidemiology, pathophysiology, and sensorimotor changes. *J Orthop Sports Phys Ther* 2004: 34(10): 610-627.
7. Baur B, et al. Auditory grip force feedback in the treatment of writer's cramp. *J Hand Ther* 2009: 163-171.
8. Binkofski F et al. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI study. *Eur J Neurosci* 1999; 11(9): 3276-86.
9. Blake DT, et al. Sensory representation abnormalities that parallel focal hand dystonia in a primate model. *Somatosensory and Motor Research* 2002; 19(4): 347-357.
10. Blatow M et al. fMRI reflects functional connectivity of human somatosensory cortex. *Neuroimage* 2007; 37: 927-936.

11. Blood et al. Basal ganglia activity remains elevated after movement in focal hand dystonia. *Ann Neurol* 2004; 55: 744-748.
12. Bohannon RW. Stopwatch for measuring thumb movement time. *Percept Mot Skills* 1995; 81: 123-126.
13. Braun C, et al. Task-specific plasticity of somatosensory cortex in patients with writer's cramp. *Neuroimage* 2003; 20: 1329-1338.
14. Bressman SB. Dystonia update. *Clin Neuropharmacol* 2000; 23: 239-251.
15. Burke RE, Fahn S, Marsden CD, et al. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985;35:73–77.
16. Butefisch CM, et al. Task-dependent intracortical inhibition is impaired in focal hand dystonia. *Movement Disorders* 2005; 20(5): 545-551.
17. Butterworth S, et al. Abnormal cortical sensory activation in dystonia: an fMRI study. *Movement Disorders* 2003; 186: 673-682.
18. Butz M, et al. Oscillatory coupling in writing and writer's cramp. *J of Physiol* 2006; 99: 14-20.
19. Byl N et al. Sensory dysfunction associated with repetitive strain injuries of tendinitis and focal hand dystonia: A comparative study. *J Orthop Sports Phys Ther* 1996; 23: 234-44.
20. Byl N et al. The sensory consequences of repetitive strain injury in musicians: Focal dystonia of the hand. *JBack Musculoskeletal Rehabil* 1996; 7:27-39.
21. Byl NN, et al. A primate genesis model of focal hand dystonia and repetitive strain injury: 1. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. *Neurology* 1996; 47(2): 508-520.

22. Byl et al. The Byl-Cheney-Boczai Sensory Discriminator: Reliability, validity, and responsiveness for testing stereognosis. *J of Hand Therapy* 2002; 315-330.
23. Byl N et al. Correlation of clinical neuromusculoskeletal and central somatosensory performance: variability in controls and patients with severe and mild focal hand dystonia. *Neural Plasticity* 2002; 9: 177-203.
24. Byl NN, et al. Effect of sensory discrimination training on structure and function in patients with focal hand dystonia: A case series. *Arch Phys Med Rehabil* 2003; 84: 1505-1514.
25. Byl NN. Aberrant learning in individuals who perform repetitive skilled hand movements: Focal hand dystonia—Part 2. *J of Bodywork and Movement Therapies* 2006; 10(4): 261265.
26. Byl NN et al. A primate model for studying focal dystonia and repetitive strain injury: effects on the primary somatosensory cortex. *Phys Ther* 2007: 77(3): 269-284.
27. Byl NN et al. Focal hand dystonia: effectiveness of a home program of fitness and learning-based sensorimotor and memory training. *J Hand Ther* 2009; 22(2): 183-197.
28. Candia V, et al. Effective behavioral treatment of focal hand dystonia in musicians alters somatosensory cortical organization. *PNAS* 2003; 100(13): 7942-7946.
29. Candia V, et al. Changing the brain through therapy for musicians' hand dystonia. *Ann NY Acad Sci* 2005; 1060: 335-342.
30. Charness ME, et al. Ulnar neuropathy and dystonic flexion of the fourth and fifth hand: clinical correlation in musicians. *Muscle and Nerve* 1996; 19: 431-437.
31. Cheyne D et al. Self-paced movements induce high-frequency gamma oscillations in primary motor cortex. *Neuroimage* 2008; 42(1): 332-342.

32. Chouinard PA, Paus T. The Primary motor and premotor areas of the human cerebral cortex. *The Neuroscientist* 2006; 12(2); 143-152.
33. Cramer SC et al. Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *J Neurophysiol* 1999; 81(1): 383-387
34. Dalal SS, et al. NUTMEG: a neuromagnetic source reconstruction tool box. *Neruol Clin Neurophysiol* 2004; 52.
35. Dalal SS et al. Spatial localization of cortical time-frequency dynamics. *Conf Proc IEEE Eng Med Biol Soc*. 2007; 4941-4.
36. Dalal SS et al. Five-dimensional neuroimaging: localization of the time-frequency dynamics of cortical activity. *Neuroimage* 2008; 40(4): 1686-1700.
37. Darvas F et al. High gamma mapping using EEG. *Neuroimage* 2009; ahead of print.
38. Delmaire C, et al. Disorganized somatotopy in the putamen of patients with focal hand dystonia. *Neurology* 2005; 64(8): 1391-1396.
39. Deuschl G, et al. Movement-related cortical potentials in writer's cramp. *Ann Neurol* 1995; 38: 862-868.
40. Dilks L et al. Validity study of the Western Psychological Services finger tapping test. *Am J of Psychol Res* 2006; 2: 8-13.
41. Duquette M et al. Ipsilateral cortical representation of tactile and painful information in acallosal and callosotomized subjects. *Neuropsychologia* 2008; 46: 2274-2279.
42. Elbert T et al. Alteration of digital representations in somatosensory cortex in focal hand dystonia. *NeuroReport* 1998; 9: 3571-3575.
43. Fahn S et al. Classification of dystonia. *Adv Neurol* 1998; 78: 1-10.
44. Fiorio M, et al. Temporal processing of visuotactile and tactile stimuli in writer's cramp. *Ann Neurol* 2003; 53: 630-635.

45. Fiorio M, et al. Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia? *Brain* 2007; 130: 134-142.
46. Forss N et al. Interaction between afferent input from fingers in human somatosensory cortex. *Brain Res* 1995; 685(1-2): 68-76.
47. Gasser T et al. Phenotypic expression of the DYT1 mutation: a family with writer's cramp of juvenile onset. *Ann Neurol* 1998; 44(1): 126-128.
48. Guggisberg AG, et al. High-frequency oscillations in distributed neural networks reveal the dynamics of human decision making. *Front Hum Neurosci* 2007; 1 (14).
49. Hallett M. The neurophysiology of dystonia. *Arch Neurol* 1998; 55: 601-603.
50. Hallet M. Pathophysiology of writer's cramp. *Hum Mov Sci* 2006; 25: 454-463.
51. Hämäläinin H et al. Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P50 and P100 components. *Electroencephalography and clinical Neurophysiology* 1990; 75: 13-21.
52. Hammond G. Correlates of human handedness in primary motor cortex: a review and hypothesis. *Neuroscience and Biobehavioral Reviews* 2002; 26: 285-292.
53. Hari R, et al. Magnetoencephalography in the study of human somatosensory cortical processing. *Lond B Biol Sci* 1999; 354(1387): 1145-1154.
54. Hayashi MJ et al. Hemispheric Asymmetry of Frequency-Dependent Suppression in the Ipsilateral Primary Motor Cortex During Finger Movement**:** A Functional Magnetic Resonance Imaging Study. *Cerebral Cortex* 2008; 18(12): 2932-2940.
55. Hemmen B et al. Effects of movement imagery and electromyography-triggered feedback on arm hand function in stroke patients in the subacute phase. *Clin Rehabil* 2007; 21(7); 587-594.

56. Hinkley LB et al. Sensorimotor Integration in SP, PV, and Parietal rostroventral areas of the human sylvian fissure. *J Neurophysiol* 2007; 97: 1288-1297.

57. Hoechstetter K et al. Interaction of tactile input in the human primary and secondary somatosensory cortex—A magnetoenchephalographic study. *Neuoimage* 2001; 14: 759-767.

58. Hutchison WD, et al. Pallidal neuronal activity: Implications for models of dystonia. *Ann Neurol* 2003; 53: 480-488.

59. Ibanez V, et al. Deficient activation of the motor cortical network in patients with writer's cramp. *Neurology* 1999; 53(1): 96-105.

60. Iwamura et al. Bilateral hand representation in the postcentral somatosensory cortex. *Nature* 1994; 369: 554-556.

61. Iwamura Y. Bilateral receptive field neurons and colossal connections in the somatosensory cortex. *Philos Trans R Soc Lond B Biol Sci* 2000; 355: 267-273.

62. Iwamura et al. Processing of tactile and kinesthetic signals from bilateral sides of the body in the postcentral gyrus of awake monkeys. *Behav Brain Res* 2002; 135: 185-190.

63. Jabusch HC, et al. Anxiety in musicians with focal dystonia and those with chronic pain. *Movement Disorders* 2004; 19: 1169-1175.

64. Jankovic J. Can Peripheral Trauma Induce Dystonia and Other Movement disorders? Yes! *Movement Disorders* 2001; 16: 7-12.

65. Jurkiewicz MT et al. Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. *Neuroimage* 2006; 32: 1281-1289.

66. Kakigi R et al. The somatosensory evoked magnetic fields. *Progress in Neurobiology* 2000; 495-523.

67. Kekoni J, et al. Rate effect and mismatch responses in the somatosensory system: ERP-recordings in humans. *Biol Psychol* 1997; 46(2): 125-142.

68. Klöppel S et al. The effect of handedness on cortical motor activation during simple bilateral movements. *Neuroimage* 2007; 34: 274-280.

69. Koch G et al. Altered dorsal premotor-motor interhemispheric pathway activity in focal arm dystonia. *Mov Disor* 2008; 23(5): 660-668.

70. Kupsch A, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med* 2006; 355(19): 1978-1990.

71. Lerner A, et al. Regional cerebral blood flow correlates of the severity of writer's cramp symptoms. *Neuroimage* 2004; 21: 904-913.

72. Lenz FA et al. Pallidal activity during dystonia: somatosensory reorganization and changes with severity. *J Neurol Neurosurg Psychiatry* 1998; 65(5): 767-70.

73. Lenz FA, Byl NN. Reorganization in the cutaneous core of the human thalamic principal somatic sensory nucleus (ventral caudal) in patients with dystonia. *J Neurophysiol* 1999; 82:3204-3212.

74. Leube B et al. Frequency of familial inheritance among 488 index patients with idiopathic focal dystonia and clinical variability in a large family. *Mov Disord* 1997; 12(6): 1000-1006.

75. Leube B et al. Phenotypic variability of the DYT1 mutation in German dystonia patients. *Acta Neurol Scand* 1999; 99(4): 248-251.

76. Lin PT, Shamim EA, Hallett M. Focal hand dystonia. *Practical Neurology* 2006; 6: 278-287.

77. Lin PT and Hallett M. The pathophysiology of focal hand dystonia. *J Hand Ther* 2009; 22(2): 109-113.

78. Lourenção et al. Effect of biofeedback accompanying occupational therapy and functional electric stimulation in hemiplegic patients. *Int J Rehabil Res* 2008; 31(1): 33-41.

79. Manzoni T et al. The colossal connections of the primary somatosensory cortex and the neural basis of midline fusion. *Exp Brain Res* 1989; 76: 251-266.

80. Mathiowetz V et al. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985; 66(2): 69-74.

81. McKenzie A, et al. Somatosensory representation of the hand in clinical performance in patients with focal hand dystonia. *American J of Physical Med and Rehab* 2003; 82(10): 737-749.

82. McKenzie A et al. Differences in physical characteristics and response to rehabilitation for patients with hand dystonia: musician's cramp compared to writer's cramp. *J of Hand Ther* 2009; 22(12): 172-181.

83. Meunier S, et al. Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. *Ann Neurol* 2001; 50: 521-527.

84. Mertens M et al. Efficient neuromagnetic determination of landmarks in the somatosensory cortex. *Clin Neurophysiol* 2000; 111(8): 1478-1487.

85. Mima T et al. Brain structures related to active and passive finger movements in man. *Brain 1999;* 122(10): 1989-1997.

86. Molloy FM, et al. Abnormalities of spatial discrimination in focal and generalized dystonia. *Brain* 2003; 126: 2175-2182.

87. Murase N, et al. Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. *Brain* 2005; 128: 104-115.

88. Nagarajan SS et al. Practice-related improvements in somatosensory interval discrimination are temporarily specific but generalize across skin location, hemisphere, and modality. *J Neurosci* 1998; 15(18): 1559-70.
89. Nagarajan S et al. Preoperative localization of hand motor cortex by adaptive spatial filtering of magnetoencephalography data. *J Neurosurg* 2008; 109(2): 228-37.
90. Nordstrom MA and Butler SL. Reduced intracortical inhibition and facilitation of corticospinal neurons in musicians. *Exp Brain Res* 2002; 144: 336-342.
91. Nutt JG et al. Epidemiology of focal and generalized dystonia in Rochester, Minnesota. *Movement Disorders* 2004; 3(3): 188-194.
92. Oga T, et al. Abnormal cortical mechanisms of voluntary muscle relaxation in patients with writer's cramp: an fMRI study. *Brain* 2002; 125(4): 895-903.
93. Opavsky R, et al. Cortical Plasticity and its implications for focal hand dystonia. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2006; 150(2): 223-226.
94. Pantev C, et al. Representational cortex in musicians' plastic alterations in response to musical practice. *Ann NY Acad Sci* 2001; 930: 300-314.
95. Peller M, et al. The basal ganglia are hyperactive during the discrimination of tactile stimuli in writer's cramp. *Brain* 2006; 129: 2697-2708.
96. Peolsson A et al. Intra- and inter-tester reliability and reference values for hand strength. *J Rehab Med* 2001; 33: 36-41.
97. Priori A, et al. Limb immobilization for the treatment of focal occupational dystonia. *Neurology* 2001; 57: 405-409.
98. Pujol J, et al. Brain cortical activation during guitar-induced hand dystonia studied by functional MRI. *Neuroimage* 2000; 12: 257-267.

99. Quartarone A, et al. Homeostatic-like plasticity of the primary motor hand area is impaired in focal hand dystonia. *Brain* 2005; 128: 1943-1950.

100. Quartarone A, et al. Corticospinal excitability during motor imagery of a simple tonic finger movement in patients with writer's cramp. *Mov Disord* 2005; 22(11): 1488-1495.

101. Quartarone A, et al. Task-specific hand dystonia: Can too much plasticity by bad for you? *Trends Neurosci* 2006; 29(4): 192-199.

102. Ridding MC, et al. Changes in the balance between motor cortical excitation and inhibition in focal, task-specific dystonia. *J Neurol Neurosurg Psychiatry* 1995; 59(5): 493-498.

103. Sanger TD, et al. Computational model of the role of sensory disorganization in focal task-specific dystonia. *J Neurophysiol* 2000; 84(5): 2458-2464.

104. Sanger TD, Pascual-Leone A, Tarsy D, Schlaug G. 2002. Nonlinear sensory cortex response to simultaneous tactile stimuli in writer's cramp. *Movement Disorders* 2002; 17(1): 105-111.

105. Schreuders TA et al. Strength measurements of the lumbrical muscles. *J Hand Therapy* 1996; 9(4): 303-305.

106. Simonetta-Moreau M, et al. Lack of inhibitory interaction between somatosensory afferent inputs and intracortical inhibitory interneurons in focal hand dystonia. *Movement Disorders* 2006; 21(6): 824-834.

107. Sohn YH and Hallett M. Disturbed surround inhibition in focal hand dystonia. *Ann Neurol* 2004; 56: 595-599.

108. Sommer M, et al. Intracortical excitability in the hand motor representation in hand dystonia and blepharospasm. *Movement Disorders* 2002; 17(5): 1017-1025.

109. Spector JT and Branforbrener AG. Methods of evaluation of musician's dystonia: critique of measurement tools. *Mov Disord* 2007; 15;22(3): 309-312.

110. Stinear CM and Byblow WD. Impaired modulation of corticospinal excitability following subthreshold rTMS in focal hand dystonia. *Hum Mov Sci* 2004; 23: 527-538.

111. Takeuchi N et al. Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. *J Rehabil Med* 2009; 41(13): 1049-1054.

112. Tamura Y et al. Disordered plasticity in the primary somatosensory cortex in focal hand dystonia. *Brain* 2009; 132; 749-755.

113. Tecchio F et al. Sensorimotor integration in focal task-specific hand dystonia: A magnetoencephalagraphic assessment. *Neuroscience* 2008; 154(2): 563-571.

114. Tecchio F, et al. High-gamma band activity of primary hand cortical areas: A sensorimotor feedback efficiency index. *Neuroimage* 2008; 40(1): 256-264.

115. Toro C, Deuschl G, Hallett M. Movement-related electroencephalographic desynchronization in patients with hand cramps: Evidence for motor cortical involvement in focal dystonia. *Ann Neurol* 2000; 47: 456-461.

116. Vega-Bermudez F, et al. Differences in spatial acuity between digits. *Neurology* 2001; 56(10): 1389-1391.

117. Vitek JL, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann Neurol* 1999; 46: 22-35.

118. Xerri C, Coq Jo et al. Experience-induced plasticity of cutaneous maps in the primary somatosensory cortex of adult monkeys and rats. *J Physiol Paris* 1996; 90(3-4): 277-287.

119. Xing-yue H, et al. Functional magnetic resonance imaging study of writer's cramp. *Chin Med J* 2006; 119(15): 1263-1271.

120. Zeuner KE, et al. Motor training as treatment in focal hand dystonia. *Mov Disord* 2005; 20(3): 335-341.

121. Zhu Z, et al. Spatiotemporal integration of tactile information in human somatosensory cortex. *BMC Neuroscience* 2007; 8:21

122. Zhuang P and Hallet M. Neuronal activity in the basal ganglia and thalamus in patients with dystonia. *Clin Neurophysiology* 2004; 115: 2542-2557.

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis, dissertation,or manuscript to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.

Rebecca Webster — 11/22/09

Author Signature — Date