Investigations of pathophysiology of Dystonia and Complex Regional Pain Syndrome

1. Introduction and Background
Complex Regional Pain Syndrome (CRPS) is a disabling condition which is usually preceded by minor to severe trauma or surgical procedure (1,3,5). Up to 25% of patients with CRPS suffer movement disorders (8). The movement disorders in CRPS have been variously described as loss of voluntary control or failure to initiate movement, weakness, bradykinesia, dystonia, myoclonus, spasm and tremor (2,3,7,8,9). The movement disorders have been reported to occur even early in the disease and may even precede the onset of the more typical symptoms of CRPS (3). A recent systematic review of literature of movement disorders preceded by a peripheral trauma described the characteristics and sub classified them as Peripherally induced movement disorders (PIMDs). The review demonstrated that the majority of the movement disorders post injury were fixed dystonias with characteristics very similar to CRPS dystonia. However, they demonstrated some similarities in the characteristics to Psychogenic movement disorders (PMDs). Of note the time interval between initial trauma and onset of symptoms was very variable. Besides a large proportion of these PIMD patients (36%) eventually developed CRPS and the movement disorders preceded the development of frank symptoms of CRPS (Rooijen, Jankovic, van Hilten et al) (44). Movement disorders associated with CRPS were initially classified to be psychogenic mainly due to no basal ganglia involvement and the fixed postures adapted by these patients were reported to be secondary to pain (17-28,31). However, the psychological profiles of these patients were found to be no different than the patients with organic dystonias (12,13,14,15,16).

Recent studies have demonstrated that the physiologic profiles of CRPS dystonias are similar to those demonstrated in organic dystonias (32,34). The similarities being demonstrated in abnormalities of short and long interval intracortical inhibition (SICI and LICI) and cortical silent period (cSP) (33-43). However, since the affected body parts were studied it was unclear whether the abnormalities demonstrated were primary or secondary to the chronic dystonic posturing. A study demonstrating similar abnormal physiologic profiles in the unaffected limbs in patients with CRPS dystonias was initially shown by Avanzino et al (33). A study demonstrating abnormal sensorimotor plasticity in addition to the physiologic abnormalities already demonstrated in previous studies was shown in organic but not in psychogenic dystonias (38). Hence movement disorders in CRPS are still considered under the spectrum of psychogenic movement disorders (PMDs) by many clinicians.

SPECT evaluation studies demonstrate differences in the thalamic perfusion early (<7 months) versus late (>7 months) in the course of CRPS. Hyperperfusion early in the course is considered reactive to pain whereas hypoperfusion later in the disease course represents an adaptive response to nociception (Fukumoto et al) (45). Functional MRI (fMRI) studies in CRPS dystonia have noted abnormalities in the inferior parietal and the adjacent sensory cortex implicating abnormalities in the interface between the pain-associated and the higher order motor control circuitry (56). However, it is unclear as to whether the fMRI abnormalities noted are inherent characteristics of dystonia or an epiphenomenon due to pain related afferent barrages associated
with CRPS. The comparative characteristics of dystonia using fMRI will help ascertain the differences in cortical activation under similar experimental conditions and provide further insight into dystonia pathophysiology.

Various physiologic abnormalities have been noted in organic dystonia implicating loss of motor inhibition, abnormalities in sensorimotor integration and alterations of synaptic plasticity (57). Using Transcranial Magnetic Stimulation (TMS) based techniques influences on motor cortical excitability of certain cortical regions have been probed using double pulse and now even triple pulse experimental paradigms (62,63). The studies involve providing a conditioning stimulus (CS) to an area of interest followed by stimulation of the primary motor cortex (M1) to note for the changes in motor evoked potentials (MEPs). The cortical areas of most interest, as implicated in dystonia pathophysiology, seem to be the premotor and parietal cortices.

In healthy humans the influence of premotor cortex is notably site as well as task specific. The Ventral Premotor area (PMv), implicated in fine motor control tasks like pincer grasp, has an inhibitory influence on M1 at rest whereas the Dorsal Premotor area (PMd), associated with gross motor movements like whole hand grasp, has a facilitatory influence on M1. Of note the inhibitory influence of PMv on M1 is lost in focal hand dystonia (FHD). The premotor and motor cortices have been further shown to be regulated by the parietal cortex, specifically the Inferior Parietal Lobule (IPL). The anterior Inferior Parietal Lobule (aIPL) having an inhibitory influence on M1 and dorsal Inferior Parietal Lobule (dIPL) having a facilitatory influence on M1 at rest. The aIPL especially has been noted to be connected to PMv via the superior longitudinal fasciculus. These connections have been well defined using both anatomical and functional techniques. The influence of aIPL on M1 via the PMv is important especially for fine motor control as noted for pincer grasp wherein there is activation of a finite set of muscles and inhibition of the unwanted muscle activity (58-61). A common physiologic abnormality noted especially in task specific FHD is the loss of this inhibitory tone leading to aberrant activation of unwanted muscles. A similar aberrant activation has also been noted in healthy volunteers via inhibition of aIPL using continuous Theta Burst Stimulation (cTBS) further implicating a potential critical role of this region in the pathophysiology of dystonia (58). We anticipate that baseline differences exist in PMv-M1 and IPL-M1 interactions in organic FHD and CRPS dystonia compared to HVs. As noted in previous studies, aIPL has an inhibitory influence on M1 which seems to be via PMv. The influence of IPL on motor cortex excitability becomes more facilitatory as we move more dorsally within the IPL. It is plausible that this differential gradient of influence is due to the effects of the conditioning stimulus within the IPL itself. We would like to study this differential influence by inhibition of dIPL using cTBS. We would like to explore if inhibition of dIPL using cTBS may lead to partial restoration of the normal inhibitory influences on M1 as may be indicated by increased inhibitory influence of aIPL on M1 and partial restoration of the PMv-M1 inhibitory influence, which is known to be lost in dystonia. Since loss of inhibition seems to be a major pathology in dystonia, the information obtained from these exploratory experiments may provide further insights into the pathophysiology of dystonia and help design potential treatment strategies to restore the normal inhibitory influences. We propose that differences exist with regards the mechanism of dystonia associated with CRPS, compared to FHD. We anticipate a more predominant parietal motor influence in CRPS dystonia compared to FHD, where the prominent physiologic abnormality noted previously has been the loss of
premotor inhibition. Exploring these differences would have potential therapeutic and future research implications.

Another physiologic abnormality noted in dystonia is loss of Surround inhibition (SI). SI in the sensory system has been known for several decades (64). It is a physiological phenomenon wherein the central signals are facilitated and eccentric signals are inhibited thus enhancing the contrast between them. It was only recently that SI was demonstrated in the human motor system. It is believed that SI in the motor system is necessary for the performance of skilled fine motor tasks by selective execution of desired movements and inhibiting unwanted ones (64-67). Thus, understanding the neurophysiological mechanism underlying motor SI is likely to shed light on the physiology of fine motor control and also the pathophysiology of FHD. SI has only been shown to be present in the involved limb in FHD and the presence of SI in the uninvolved limbs is unknown in FHD. No abnormalities in SI have been noted in the uninvolved limbs in patients with cervical dystonia (68). The presence or absence of SI in the uninvolved hand in FHD will help ascertain whether loss of SI is an endophenotypic trait in FHD or an epiphenomenon which evolves as a result of development of aberrant plasticity. Besides we will also explore the influence of inhibition of dIPL using cTBS on the phenomenon of SI.

Abnormalities in somatosensory temporal and spatial discrimination thresholds (TDT and SDT) have been reported in patients with dystonia, in the involved and uninvolved limbs. Similar abnormalities have also been noted in the unaffected carrier of DYT-1 related genetic dystonia. The presence of these sensory abnormalities have been suggested to be endophenotypic traits of dystonia. The characteristics of these sensory abnormalities in FHD in comparison to CRPS dystonia are not known. Exploring these differences would further advance our understanding regarding the development of these dystonia (69-73).

2. Study Objectives

This protocol will investigate in detail the differences in the pathophysiology of dystonia associated with CRPS compared to organic FHD. We anticipate that there might be a predominant influence of the parietal sensorimotor integration area, specifically the Inferior parietal lobule (IPL), in CRPS more than FHD on motor cortex excitability. Additionally we will explore whether inhibition of the dIPL using TBS in organic FHD will lead to partial restoration of the inhibitory influence of premotor cortex on motor cortical excitability as measured by post TBS SI and PMv-M1 interactions. We intend to show these differences using a combination of neuroimaging and neurophysiologic testing. Additionally we will explore the presence of surround inhibition in the uninvolved limb in organic focal hand dystonias and CRPS dystonias. Pending results of these explorations, hypotheses will be developed that could be evaluated in
future research. Since all the planned experiments are exploratory in nature we will list all the study objectives as below without any specific primary/secondary objectives.

**Objectives**

1. To identify differences in the fMRI pattern of cortical activation in CRPS patients with hand dystonia compared to CRPS patients without dystonia, FHD and HVs. The evaluation using fMRI will be performed under 3 conditions; 1. Rest 2. Voluntary activity 3. Motor imagery task.
2. To identify differential influences of PMv and IPL on motor cortical excitability at baseline using paired pulse TMS in patients with CPRS dystonia compared to FHD. We further aim to identify changes in these differential influences after inhibition of the dIPL using cTBS (inhibitory theta burst stimulation) in patients with CPRS dystonia compared to FHD and HVs.
3. To identify abnormalities in the temporal and spatial discrimination sensory thresholds in CRPS dystonia and organic dystonias compared to HVs.
4. To identify the presence of surround inhibition in the un-involved upper limb in patients with CRPS and FHD.
5. To identify the presence and abnormalities in the cortical silent period (cSP) between the groups and the influence of cTBS on the cSP.
6. To explore the influence of inhibition of dIPL on the physiology of Surround Inhibition (SI) in FHD.

**3. Study overview**

This study includes patients with FHD, CRPS dystonia involving at least one upper limb, CRPS patients without dystonia and healthy volunteers. The initial screening visit and the subsequent study visits can be either planned on consecutive days if the subject satisfies the study criteria or can be conducted on separate visits. Of note there will be a mandatory gap between cTBS and sham TBS studies of at least one day. No stopping of any medications will be needed for the initial screening visits. The study will involve 2 arms; 1. Imaging studies (which includes obtaining initial screening scan if needed, followed by research MRI scan); 2. Physiologic evaluation arm which will be conducted on up to 3 separate visits after obtaining the baseline clinical imaging studies. If the fMRI cannot be performed after or with the clinical MRI prior to TMS studies, we will allow for 1 week time to make sure there is no influence of TMS on the fMRI. Session 1 will involve baseline spatial and temporal discrimination thresholds. Session 2 will include TMS based studies evaluating for surround inhibition, cSP and differential influences of PMv and IPL (both anterior and dorsal) on M1 at baseline followed by cTBS vs sham TBS. Session 3 will be scheduled at least one day after the initial cTBS/ sham TBS; the order of which will be randomized across the subjects. Note: Surround inhibition in FHD will be evaluated in both the involved and the uninvolved hand at baseline and the influence of cTBS on SI will be noted in the involved limb. SI will only be measured in the uninvolved upper limb in CRPS dystonia at baseline, since the presence of tonic contracture as noted in CRPS dystonia abolishes the SI phenomenon. In case of dystonia in both upper limbs in CRPS patients, we will not perform SI measurements in those patients.

**4. Outcome Measures**

- **fMRI based outcomes:**
  - We will explore the differences in BOLD signal in the parietal lobe, (which is the primary defined ROI) in CRPS dystonia compared to FHD, in the different conditions noted. We will look for changes in the BOLD signal in the defined
ROI, which is the parietal sensorimotor integration area, from baseline resting state.
- We will further explore the differential activation in CRPS dystonia vs CRPS without dystonia to identify any specific features inherent to patients with CRPS dystonia compared to CRPS related pain.

**TMS outcomes:**
- We will note for the baseline differential influences of PMv and IPL on motor cortical excitability and to note for the changes after cTBS of dIPL.
- We will explore the presence of baseline SI measures in FHD in the involved and uninvolved limbs.
- Changes noted in the SI measures post TBS in FHD.
- Baseline cSP to be noted in the involved and uninvolved limb in FHD and CRPS dystonia and to note for the influence of cTBS on cSP between the groups in the involved limb.

**TDT/SDT outcomes:**
- We will note for the TDTs/SDTs in both the involved and uninvolved limbs in FHD and CRPS dystonia compared to HVs.

**References**
27 Parsons AM, Honda CN, Jiay P, et al. Spinal NK1 receptors contribute to the increased excitability of the nociceptive flexor reflex during persistent peripheral inflammation. Brain Res 1996;739:263–75.
41 Kessler KR, Ruge D, Ilic TV, Ziemann U. Short latency afferent inhibition a...


60. T Bäumer ; S Schippling ; A Münchau. Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest—a bifocal TMS study. 2009. Clinical Neurophysiology. 120(9) 1724-31


