Principal Investigator	Supervisors	Research Institution	Funding Program	Project Title	Abstract	Start date	Funding Keywords
Brais, Bernard	NULL	Centre hospitalier de l'Université de Montréal (CHUM)	Operating Grant	Cloning and characterization of the mutated gene responsible for a new form of French-Canadian recessive spastic ataxia	Recessive ataxias are a heterogeneous group of neurodegenerative diseases. We have identified a group of 25 cases belonging to 19 families that share clinical similarities that allowed us to described the new form of autosomal recessive spastic ataxia of Portneuf (ARSAP). The major clinical features are the presence of ataxia, dysarthria, spasticity and hyperreflexia. The more severe cases have severe spasticity from birth, scoliosis, dystonia and cognitive impairment and are often considered cases of cerebral palsy. A genome scan uncovered linkage of the ARSAP families to chromosome 2q33-q35 markers. Our objectives are to: 1) complete the clinical characterization of cases; 2) complete the fine mapping of the candidate region; 3) complete a genealogical study to establish who likely introduced the different mutations; 4) screen candidate genes for mutations; 5) develop diagnostic tests; 6) screen a large cohort of ataxic patients; 7) screen a large cohort of cerebral palsy cases; 8) complete in situ hybridization experiments in mice embryos and adults animals to establish the expression profile of the mutated gene; and 9) characterize the normal function of the protein. The identification of the mutated gene in ARSAP will help the genetic counseling for this disease in Quebec, in particular in the Portneuf region.	01-Oct-2005	ATAXIA; CEREBELLUM; FRENCH-CANADIAN; GENETICS; LEUKODYSTROPHY; SPASTICITY
Bulman, Dennis E	NULL	Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa	Operating Grant	Identification and characterization of genes responsible for inherited myoclonus dystonia	Our current understanding and treatment of most inherited disorders involving abnormal involuntary movements remains poor. Inherited myoclonus dystonia (IMD) is an autosomal dominant form of myolconus and dystonia and is characterized by rapid muscle contractions (myoclonus) and repetitive movements resulting in abnormal postures (dystonia). Symptoms normally begin in the first or second decades of life and classically have no other associated features with the possible exception of subtle psychiatric symptoms (obsessive-compulsive disorder). IMD is a genetically heterogeneous disorder with only two loci responsible for the disorder. The one known disease gene, e-sarcoglycan (SGCE) maps to 7q21. Approximately 40% of IMD patients demonstrate a mutation in SGCE. The second locus, DYT15 was identified in our laboratory and maps to 18p11. While we are in the process of identifying this gene and we are also making the first animal model of IMD by recapitulating a known human mutation of SGCE in a mouse.	01-Apr-2005	DISEASE GENE IDENTIFICATION; LINKAGE; MOVEMENT DISORDERS; MYOCLONUS DYSTONIA
Bulman, Dennis E	NULL	Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa	Operating Grant - Priority Announcement: Institute of Genetics (Bridge Funding)	Identification and characterization of genes responsible for inherited myoclonus dystonia	Our current understanding and treatment of most inherited disorders involving abnormal involuntary movements remains poor. Myoclonus dystonia (MD) is inherited as an autosomal dominant (50% of offspring are at risk of developing the disease) form of myoclonus and dystonia and is characterized by rapid muscle contractions (myoclonus) and repetitive movements resulting in abnormal postures (dystonia). Symptoms normally begin in the first or second decades of life and classically have no other associated features with the possible exception of subtle psychiatric symptoms (obsessive-compulsive disorder). MD is a genetically heterogeneous disorder with only two loci responsible for the disorder. The one known gene, e-sarcoglycan (SGCE) is on chromosome 7. Approximately 40% of IMD patients demonstrate a mutation in SGCE. The second locus, DYT15 was identified in our laboratory and is on chromosome 18. The research project is divided into three parts. Firstly, we are trying to determine the role played by SGCE in the brain. This includes identifying those proteins which interact with SGCE. Secondly, we are making a mouse model of myoclonus dystonia so that we can study the disorder and determine at a cellular level what is happening in the brain. Thirdly, we are characterizing a gene on chromosome 18 which we think also causes myoclonus dystonia. The results of this work will enable us to establish a genetic test for this disorder. It will also teach us about how this movement disorder occurs. We can then determine if pharmacological treatment will be possible.	01-Jan-2009	DISEASE GENE IDENTIFICATION; LINKAGE; MOVEMENT DISORDERS; MYOCLONUS DYSTONIA
Bulman, Dennis E	NULL	Children's Hospital of Eastern Ontario (Ottawa)/Centre hospitalier pour enfants de l'est de l'Ontario	Operating Grant	Mutations in a long non-coding RNA cause Myoclonus Dystonia	Myoclonus dystonia (MD) is a debilitating neurological disorder where patients have abnormal movements. The disorder can be broken down into myoclonus, rapid muscle contractions and dystonia, which is a sustained twisting movements resulting in abnormal postures. There is no effective treatment for this disorder and this may be due in part to the fact that we know very little as to its cause. The following hyper link connects to YouTube, where examples of the disorder can be seen: http://www.youtube.com/results?search_query=myoclonus+dystonia&oq=myoclonus+dystonia&gs_l=youtube.3..0.5196.11172.0.11978.18.11.0.7.7.0.197.1325.5j6.11.0...0.0...1ac.1.Xy21LH3KBVw Symptoms usually begin before the age of 20 and 40% of the cases are due to mutations in the gene epsilon sarcoglycan. With the help of a large family afflicted with myoclonus dystonia we were able to identify a new gene. This gene belongs to a new class of genes called the long non-coding RNAs. The gene itself is an evolutionary new gene as it only exists in primates; humans, great apes etc. The proposal aims to determine the role of this new gene in healthy individuals as this gene is completely uncharacterized. At the same time we will determine the effects of the mutated gene. The work will be performed using a variety of human neuronal cell lines. By understanding the mechanism by which the mutation causes myoclonus dystonia we hope to identify biological pathways which may be targeted for treatment.	01-Jul-2015	DISEASE; DYSTONIA; GENES; MYOCLONUS; NON CODING RNA; RARE DISEASE
Cash, Robin	Chen, Robert	Toronto Western Research Institute (Toronto)	Fellowship - Priority Announcement: Dystonia (SHOPP)	A novel brain stimulation intervention to investigate the pathophysiology and modulate plasticity in dystonia	Transcranial Magnetic Stimulation (TMS) is a technique for non-invasive stimulation of the human brain, and has been in use for approximately 20 years in clinical and research environments. It is safe and painless. Different areas of the body are mapped out in a stereotyped manner in the brain, such that different muscles can be targeted. TMS was initially used to investigate brain function, in particular in neurological disorders. The most exciting recent development in this field was the finding that targeted protocols (TMS interventions) could modulate plasticity (increase or decrease brain activity) for minutes to hours beyond the period of stimulation. This offers the potential for targeted, non-invasive treatment in neurological disorders, which could be used as an alternative to or in combination with conventional pharmaceutical and physical therapies. We have recently developed a novel TMS intervention which is able to increase or decrease brain activity, according to stimulation parameters. Such modulation of brain excitability would be desirable and is likely to be therapeutically beneficial in neurological disorders in which brain excitability is abnormal. One such condition is focal hand dystonia which is characterised by debilitating muscle contractions during repeated specific tasks such as writing. This is thought to arise from excessive excitability and plasticity in motor areas of the brain in genetically susceptible individuals. We therefore wish to apply this non-invasive intervention to the hand area of the motor cortex in dystonia patients in order to downregulate hyperexcitability. We hypothesise that this will lead to a reduction in brain excitability and dystonic symptoms. We will also apply this intervention in combination with another TMS intervention and expect that this will further improve the efficacy and therapeutic benefit of the intervention. These studies will also further our understanding of the mechanisms underlying dystonia.	01-Apr-2012	DYSTONIA; INTERVENTION; PARKINSON'S DISEASE; PATHOPHYSIOLOGY; PLASTICITY; TRANSCRANIAL MAGNETIC STIMULATION
Chen, Robert	NULL	University Health Network (Toronto)	CIHR/SME Collaborative Research Program - Investigator	Mechanisms of deep brain stimulation and relation to oscillations in the basal ganglia	Parkinson's disease (PD) is related to abnormal functioning of an area of the brain known as the basal ganglia. A model of how the basal ganglia works, known as the rate model, was proposed about 15 years ago has led to new surgical treatment for PD and other movement disorders. However, there is emerging evidence that the model is inadequate. A new model, known as the oscillation model of the basal ganglia, proposed that the frequencies of oscillations are important and PD is due to an imbalance of oscillations at beneficial and harmful frequencies. This research proposal is designed to test the oscillatory model by examining the effects of medications and movement on the frequency content of electrical activities recorded directly from the basal ganglia in patients who are undergoing surgery for deep brain stimulation. The clinical effects of deep brain stimulation at frequencies that are specific for each individual will be determined in a subsequent study. The results will lead to greater understanding of the functional organization of the basal ganglia and may help develop new treatment for PD and other movement disorders.	01-Jul-2007	BASAL GANGLIA; DEEP BRAIN STIMULATION; DYSTONIA; LOCAL FIELD POTENTIALS; OSCILLATION; PARKINSON'S DISEASE

Chen, Robert	NULL	Toronto Western Research Institute (Toronto)	Operating Grant	Pathophyisological mechanisms of dystonia: insights from deep brain stimulation and brain plasticity	Dystonia is a brain disorder associated with excessive contraction of muscles, leading to twisted positions of the arms and legs. It causes severe disability in the affected patients. How abnormalities in the brain causes dystonia is not known. A treatment that involve insertion of electrodes into the brain for electrical stimulation, know as deep brain stimulation (DBS), is an established treatment for patients with advanced dystonia. However, it has not been known how DBS works. Brain plasticity refers to how the brain changes and adapts in situations such as learning and memory, and in response to injury. Dystonia may be due to abnormal and excessive plasticity. The proposed research will study whether brain plasticity is abnormal in dystonia and whether DBS can correct the abnormal brain plasticity. We will also investigate whether differences among individuals in a gene that encodes a protein in the brain known as "glial-derived neurotrophic factor" influences brain plasticity and the response to DBS in dystonia patients. The results will improve our knowledge of how brain abnormalities lead to dystonia and provide better ways to predict the patients' response to DBS.	01-Oct-2012	BASAL GANGLIA; BRAIN PLASTICITY; DEEP BRAIN STIMULATION; DYSTONIA; HUMAN SUBJECTS; MOVEMENT DISORDERS; SINGLE NUCLEOTIDE POLYMORPHISM; TRANSCRANIAL MAGNETIC STIMULATION
Chen, Robert	NULL	Toronto Western Research Institute (Toronto)	China-Canada Joint Health Research Initiative	Role of the basal ganglia in inhibiting and promoting voluntary movements	Deep brain stimulation (DBS) or causing a injury to specific parts of the brain know as the basal ganglia nuclei are accepted treatments for movement disorders such as Parkinson's disease (PD), and dystonia. Impulse control disorder (ICD) such excessive gambling, eating, shopping or sexual activities occurs in a significant proportion of PD patients and is a source of severe disability. The basal ganglia play an important role in producing and stopping movements. Very few studies examined how the basal ganglia stop movement although it is an important everyday function and relates to ICD. The proposed study is a new collaborative effort between Xuanwu Hospital of Capital Medical University (XHCMU) and the Toronto Western Hospital (TWH). Both hospitals are centers of excellence in brain surgery for movement disorders. Patients with PD or dystonia scheduled to undergo brain surgery will be recruited. The team at XHCMU will perform recordings of single brain cell activities during surgery and the team at TWH will record brain signals that reflect activities of a large group of brain cells at 1-5 days after surgery. The subjects will perform the same "conditional stop-signal paradigm" to allow researchers to examine activities of different parts of the basal ganglia that are associated with movement and stopping of movement. The studies at the two sites nicely complement each other as the recordings at each site obtain different information. The study will address a fundamental question in neuroscience of the role of the basal ganglia in mediating wanted movements and stopping of unwanted movements. It may lead to a new way of treating PD patients with ICD and other movement disorders using DBS.	01-Jan-2014	BASAL GANGLIA; DEEP BRAIN STIMULATION; DYSTONIA; LOCAL FIELD POTENTIALS; MOVEMENT INHIBITION; PARKINSON'S DISEASE; STOP SIGNAL; VOLUNTARY MOVEMENTS
Cheyne, Douglas O	NULL	Hospital for Sick Children (Toronto)	Operating Grant	Neural Correlates of Movement Disorders Resulting From Childhood Stroke	In childhood, the potential for learning to induce changes in the brain, a phenomenon known as neuroplasticity, is greater than at any other time in our lifespan. For example, recovery from brain damage due to a stroke is three times better in comparison to adults. On the other hand, development of movement disorders is about 100 times more common in children and is thought to be a result of maladaptive plasticity, with negative consequences and lifelong impact. The most common of these movement disorders is dystonia, which is the presence of uncontrollable twisting and repetitive movements and abnormal postures, or both. Children with dystonia have a remarkable ability to adjust their muscle activity with the aid of visual biofeedback, often within a short time. This is thought to be a result of visual feedback compensating for a lack of normal sensations of touch in these children. Similarly, delivering repetitive sensory pulses to the hand can enhance sensations in very short therapy sessions. The primary aim of the proposed studies is to measure brain activity during biofeedback learning and sensory retraining, combined and alone, in children following a stroke with and without dystonia. We will directly observe changes in brain activity during each therapy using a novel technique of measuring small magnetic fields to image electrical activity of different brain areas (magnetoencephalography). We will test if 1) the same brain areas and types of brain activity would support both types of learning in both groups of children, 2) if brain activity tends to be stronger with visual biofeedback learning or sensory training, and 3) if sensory training can improve biofeedback learning. This work will help establish the most effective therapeutic approach and provide the basis for future studies on how to predict if dystonia will occur in stroke patients and how best to treat individual patients, with benefit to Canadians of all ages impacted by stroke.	01-Apr-2014	BIOFEEDBACK; BRAIN INJURY; CHILDHOOD STROKE; DYSTONIA; FUNCTIONAL NEUROIMAGING; LEARNING; MEG; REHABILITATION; REPETITIVE SENSORY STIMULATION; STROKE
Elahi, Behzad	Chen, Robert	Toronto Western Research Institute (Toronto)	Fellowship - Priority Announcement: Dystonia (SHOPP)	Regulatory effect of intra cortical inhibition on Paired Associative Stimulation(PAS) induced sensory-dependent, motor cortex plasticity	Long-term goal of this study is to understand mechanisms by which inhibitory intra cortical circuits are able to adapt to sensory inputs from the peripheral nerves, and to maintain their balance with the cortical excitatory circuits in sensory/motor cortex. Trans-cranial magnetic stimulation (TMS) is a powerful none invasive tool to investigate human brain function. The aim of the following experiments is to evaluate the brain dynamics during temporary changes in synaptic strengths. Paired Associative trans-cranial magnetic stimulation (PAS-TMS), simultaneous electroencephalography (EEG) and electromyography (EMG), will be used to analyze the brain responses to the long term temporary changes in the brain. In this study new implementation of the above techniques will be used to understand plasticity and cortical excitation. We believe that inhibitory intra cortical networks play a significant role in this phenomenon and we would like to assess these changes through spectral EEG and EMG analysis of motor evoked potentials, and delicately designed paired pulse stimulations to target different intra cortical networks. The results of the study will provide important and basic knowledge on brain activity and sensory induced cortical plasticity and its physiology. The findings will have implications in neurology and rehabilitation, especially in disorders with defective motor skills, such as stroke and Parkinson's disease, and Dystonia.	01-May-2009	BRAIN DYNAMICS; ELECTROMYOGRAPHY (EMG); LONG TERM POTENTIATION (LTP); MOTOR CORTEX; NEUROELECTROPHYSIOLOGY; PAIRED ASSOCIATIVE STIMULATION (PAS); PLASTICITY; SPECTRAL ELECTROENCEPHALOGRAPHY (EEG); TRANS CRANIAL MAGNETIC STIMULATION (TMS)
Eubanks, James H	NULL	University Health Network (Toronto)	Dissemination Events - Priority Announcement: Musculoskeletal Health, Arthritis, Skin and Oral Health	Raising Awareness for Rett Syndrome: Connecting Scientists, Clinicians, and Parents	Rett syndrome is a neurodevelopmental disorder affecting primarily females that arises from mutations of the MECP2 gene. Rett syndrome occurs with a frequency of about one in every 10,000 female births, making it one of the top genetic causes of severe mental impairment in girls worldwide. Rett syndrome has only been recognized as a specific condition since about 1983, and to this day it remains under-recognized, and is often confused with the completely unrelated condition of Tourette syndrome. Girls with Rett syndrome do not display "ticks", but rather suffer from co-morbidities such as epilepsy, Parkinson-like dystonia, brittle bones, breathing apnea, severe gastrointestinal reflux, curvature of the spine, and they often display bouts of anxiety and depression. It is difficult to care for, or clinically manage, a Rett syndrome patient also, as Rett syndrome girls are not able to speak and have minimal if any meaningful communicative use of their hands. There is hope for Rett syndrome patients, however, as recent scientific studies in mouse models of Rett syndrome strongly suggest that the condition can be corrected - but more research in this direction is needed. One of the goals of the conference we propose is to bring together the leading Canadian researchers in this field to foster collaborations to address these needed issues. In addition, though, ongoing clinical trials and new rehabilitative treatment options are now showing promise for better treating and managing girls with this condition. And recent technological advances in eye-gaze based computer systems offers the possibility of opening communication with these girls for the first time. But, surprisingly few parents and caregivers, general practitioners, or policy makers know much about these advances. Thus, a second goal of our meeting is to provide information to members from these groups so it can be distributed to others within their geographical and professional areas.	01-Nov-2013	AUTISM-SPECTRUM DISORDER; BETTER TREATMENT OPTIONS; BRAIN AND BEHAVIOR; GASTROINTESTINAL IMPAIRMENTS; KNOWLEDGE TRANSFER; ORTHOPEDIC INTERVENTIONS; RETT SYNDROME; SEIZURES; SOCIAL WELFARE AND CONDITION MANAGEMENT; TRANSLATIONAL RESEARCH

Isayama, Reina	Chen, Robert	Toronto Western Research Institute (Toronto)	Fellowship - Priority Announcement: Dystonia (SHOPP)	Exploring the Premotor and the Parietal Connectivity with Primary Motor Cortex during the Rubber Hand Illusion in Focal Hand Dystonia	Focal hand dystonia (FHD) is a neurological disorder which is characterized by sustained arm muscle contractions and abnormal postures. These muscle movements are involuntary and may interfere with the patient's performance on tasks everyday life. The exact cause and the mechanism of dystonia is not yet fully understood but recent studies have revealed that abnormalities exist not only in the motor cortex, which is a cortical region of the brain involved in the execution of voluntary movement, but also in the sensory cortex, which is another cortical region related to touch, temperature and body position sense. A key mechanism of dystonia lies within the process called sensorimotor integration in which these sensory inputs are processed by the central nervous system and interact with the motor system. The abnormalities in the sensorimotor integration may be indicated by a clinical phenomenon known as a 'sensory trick' which is a temporal suppression of the abnormal muscles contractions induced by just touching the affected or adjacent part of the body. The aim of this research is to throw some light on the mechanism of the abnormal sensory connection with motor function using a technique known as transcranial magnetic stimulation (TMS). TMS is a non-invasive technique for stimulation of the human brain and can be used to study the interaction between the two brain areas. In this research, the sensorimotor integration process in the healthy controls and the patients with dystonia will be explored by TMS stimulus over the motor cortex and the sensory cortex while the sensory inputs are being processed in the brain. This study will help us to understand the pathophysiology of dystonia and the result will contribute to designing a 'sensory training based treatment' for dystonia.	01-May-2013	CORTICAL PLASTICITY; FOCAL HAND DYSTONIA; RUBBER HAND ILLUSION; SENSORIMOTOR INTEGRATION; TRANSCRANIAL MAGNETIC STIMULATION
Jog, Mandar S	NULL	London Health Sciences Centre Res. Inc. (Ont.)	Proof of Principle Program - Phase II	Multi-channel Electrode for Application in Neurosurgery and treatment of severe motor dysfunction	NULL	01-Jan-2004	DYSTONIA; ELECTRODE; ESSENTIAL TREMOR; FIBEROPTIC DEVICE; FUNCTIONAL NEURISURGERY; MICROMACHINING; PARKINSON'S DISEASE; PRECISION MACHINING; STIMULATION
Jog, Mandar S	NULL	University Hospital (London, Ontario)	Proof of Principle Program - Phase I	Multi-channel electrode for application in neurosurgery and treatment of severe motor dysfunction.	NULL	01-Nov-2002	DYSTONIA; ELECTRODE; ESSENTIAL TREMOR; FIBEROPTIC DEVICE; FUNCTIONAL NEUROSURGERY; LASER MATERIAL REMOVAL; MICROMACHINING; NEUROPHYSIOLOGY; PARKINSON'S DISEASE; PRECISION MACHINING; STIMULATION
Kiss, Zelma T	NULL	University of Calgary	CIHR Clinician Scientist - Phase 2	Mechanisms of therapeutic deep brain stimulation	The most exciting new treatment for movement disorders (Parkinson's disease, tremor, dystonia) is that of surgically implanting fine electrodes into the brain and connecting them to a type of pacemaker. These deep brain stimulators (DBS) can reduce patients' tremors, stiffness, slowness of movement and reduce their reliance on medication. Whereas the benefits of DBS in patients are well recognized, the way it achieves these effects is unknown. My research AIM is to understand the mechanism of action of DBS directly at the level of individual brain cells and the brain circuits within which these cells exist. This will be performed by means of parallel studies in patients who already have the stimulators in place and in rat brain slices in a recording chamber to learn what happens inside the cells that are located close to the DBS electrodes. Because we believe that DBS works by modulating the activity of cells near the electrode tip, this therapy can alter brain function focally and specifically, instead of a drug which has broad effects on all parts of the brain. DBS has the potential to significantly advance the management of neurological and psychiatric illness. It is only by understanding its mechanisms at the most fundamental level that it can be appropriately applied to these conditions.	01-Sep-2007	BASAL GANGLIA; DYSTONIA; ELECTRICAL STIMULATION; ELECTROPHYSIOLOGY; EPILEPSY; INTRACELLULAR RECORDING OR PATCH CLAMP
Kiss, Zelma T	NULL	University of Calgary	Operating Grant	Mechanisms of therapeutic deep brain stimulation (DBS) for dystonia	The most exciting new treatment for movement disorders (Parkinson's disease, tremor, dystonia) is that of surgically implanting fine electrodes into the brain and connecting them to a type of pacemaker. These deep brain stimulators (DBS) can reduce patients' tremors, stiffness, slowness of movement and reduce their reliance on medication. Whereas the benefits of DBS in patients are well recognized, the way it achieves these effects is unknown. My research AIM is to understand the mechanism of action of DBS directly at the level of individual brain cells and the brain circuits within which these cells exist. This will be performed by means of parallel studies in patients who already have the stimulators in place and in rat brain slices in a recording chamber to learn what happens inside the cells that are located close to the DBS electrodes. Because we believe that DBS works by modulating the activity of cells near the electrode tip, this therapy can alter brain function focally and specifically, instead of a drug which has broad effects on all parts of the brain. DBS has the potential to significantly advance the management of neurological and psychiatric illness. It is only by understanding its mechanisms at the most fundamental level that it can be appropriately applied to these conditions.	01-Apr-2007	BASAL GANGLIA; DYSTONIA; ELECTRICAL STIMULATION; ELECTROPHYSIOLOGY; EPILEPSY; INTRACELLULAR RECORDING OR PATCH CLAMP
Kothary, Rashmi K	NULL	Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa	Operating Grant	Dystonin/bpag1 - a versatile linker protein	Several neuromuscular disorders involve cytoskeletal protein abnormalities. Our long-term goal is to understand the role of a novel class of cytoskeletal and nucleoskeletal linker proteins that function to ensure cellular integrity by crosslinking actin microfilaments, intermediate filaments, and microtubules. More specifically, we have identified and are characterizing dystonin/Bpag1, a prototype member of this family. We have shown that mutations in dystonin are responsible for the mouse neuromuscular disorder dystonia musculorum (dt). Mutations in dystonin lead to a multi-system disorder affecting sensory neurons, Schwann cells, and skeletal muscle. This proposal is based on the hypothesis that dystonin isoforms have distinct roles in the maintenance of a nuclear to plasma membrane link. The results from these experiments will yield novel insights into an important component of cell biology. This knowledge will contribute to our understanding of the etiology of neuromuscular disorders that implicate the cytoskeleton and the nucleoskeleton.		CYTOSKELETON; GENE STRUCTURE; LINKER PROTEINS; MOUSE MODELS; MUSCULAR DYSTROPHY; NEURODEGENERATION; NUCLEAR ENVELOPE

Kothary, Rashmi K	NULL	Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa	CIHR Research Resource Grant Program	Establishment of a centralized mouse modeling facility	N/A	01-Apr-2006	BRACHDACTYLY; CARDIAC DISEASE; CHROMATIN REMODELLING; CNS DEVELOPMENT; CYTOSKELETON; MYOCLONUS DYSTONIA; MYOGENESIS; RETINAL DEVELOPMENT; SPINAL MUSCULAR ATROPHY; STEM CELLS; X-LINKED MENTAL RETARDATION
Lee, JungRyun	Kiss, Zelma T	Hotchkiss Brain Institute (University of Calgary)	Fellowship - Priority Announcement: Dystonia (SHOPP)	Pallidal deep brain stimulation for dystonia: neuronal activity, stimulus parameters, and motor output	The most exciting new treatment for movement disorders such as Parkinson's disease (PD), tremor, and dystonia is deep brain stimulation (DBS), which refers to high-frequency electrical stimulation delivered through surgically implanted fine electrodes into specific brain regions. DBS can markedly reduce patients' tremors, stiffness, slowness, and abnormal muscle contractions. Whereas the benefits of DBS in patients are well recognized, the way it achieves these benefits is unknown. My research AIM is to understand how DBS works at the level of brain cells and the brain circuits where DBS electrodes are implanted. I am specifically concentrating on how it works for dystonia, a debilitating movement disorder. Dystonia produces involuntary muscle contractions and writhing movements that limit mobility, often with pain and can make sufferers completely unable to function. While DBS for dystonia is very effective in most cases, it requires more variable parameters of electrical stimulation to yield clinical benefits and it takes from weeks to months to become effective after surgery, unlike DBS for other movement disorders such as PD and tremor. Furthermore, it requires more battery power to maintain stimulation, causing discomfort and potential complications due to battery replacement surgery. Therefore, we need toclarify how such variable electrical stimulation affects activities of brain cells and dystonic muscles. During DBS electrode implantation surgery for dystonia patients, we are able to access brain cells by lowering a microelectrode into target brain area. Using this technique, we will examine the electrical activity of brain cells in the DBS target site and abnormal muscle activity in dystonia patients in response to a variety of DBSparameters. This will allow us to determine how DBS affects target brain cells as well as muscle output. These studies will help us develop the optimial stimulation paradigms to maximize the clinical benefit of DBS for dystonia.		BASAL GANGLIA; DEEP BRAIN STIMULATION; DYSTONIA; ELECTROPHYSIOLOGY; MOVEMENT DISORDER
Lynch-Godrei, Anisha	NULL	University of Ottawa/Université d'Ottawa	Master's Award: Frederick Banting and Charles Best Canada Graduate Scholarships	The role of neuronal dystonin in the autophagic process	In 2012, a study by Edvardson and colleagues described a new disease in four infants, which they termed hereditary sensory and autonomic neuropathy type 6 (HSAN6). The disease presented with joint contractures, difficulty breathing and eating, poor movement coordination, and autonomic irregularities, ultimately leading to death before the age of two. The underlying cause of this disease was found to be a mutation in the dystonin gene. This gene is responsible for creating a very large protein. The dystonin protein helps to link up different parts of the cellular scaffolding (known as the cytoskeleton) in order to allow the cell to maintain its shape as well as permit efficient movement of cellular cargo. It is predicted that without dystonin, the scaffolding that holds the cell together would fall apart, which would in turn disrupt many processes within the cell. One such process that is likely to suffer from the defective cytoskeleton is autophagy. Autophagy is the process of degrading and recycling old cellular material, to allow for newer and more efficient materials to be made from their remains. This process is crucial for maintaining balance within the cell, especially in neurons, which are non-replaceable cells. Works previously done by our laboratory have discovered abnormalities in autophagy within the neurons of a mouse model of HSAN6. The research proposed here aims to investigate how the dystonin protein is involved in autophagy, which could help us to better understand this protein and could even help identify potential treatments for HSAN6.	01-Sep-2014	AUTOPHAGY; BPAG1; CYTOSKELETON; DYSTONIA MUSCULORUM; DYSTONIN; HSAN-VI; MICROTUBULES; NEURODEGENERATION
Mcdougall, Laura M	Welsh, Timothy N	University of Calgary	Master's Award: Frederick Banting and Charles Best Canada Graduate Scholarships	Cortical activation during action observation in patients with dystonia: A transcranial magnetic stimulation study	Not Applicable.	01-Sep-2008	DYSTONIA; MIRROR NEURON SYSTEM (MNS); MOTOR CONTROL; OBSERVATION; TMS; WRITER'S CRAMP
Nelson, Aimee J	Chen, Robert	Toronto Western Research Institute (Toronto)	CIHR Fellowship	Somatosensory Processing in Cortical and Sub-cortical loci in dystonia patients	I will investigate the processing of touch in cortical and sub-cortical loci in focal and generalized dystonia patients. This research capitalizes on known principles to promote cortical reorganization and is hypothesized to improve motor and perceptual behaviour in dystonia patients. In the primary somatosensory cortex (SI) of focal hand dystonia patients, the somatotopic organization of hand digits is typically abnormal. The first proposed project will attempt to re-organize digit representation in SI. Patients will participate in a tactile training regime paired with or without repetitive transcranial magnetic stimulation (rTMS) to premotor cortex. Variables quantified pre and post training include: 1) Somatotopy (the representation of adjacent digit surfaces in SI) using functional magnetic resonance imaging and magnetoencephalography, 2) Neurophysiology (the modulation of somatosensory evoked potentials and motor evoked potentials) using median nerve stimulation and TMS 3) Tactile perception (temporal & spatial discrimination, tacitle motion perception). Project 2 investigates touch propcessing in the basal ganglia of generalized dystonia patients. Patterns of neuronal activity will be quantified from the internal segment of the globus pallidus (GPi) during surgery for deep brain stimulation implants. Recordings will be made from single neurons during passive states, tactile stimulation, and also active and passive limb movement. Local field potentials will be recorded from GPi during identical task conditions in the days following surgery. Cortical and sub-cortical studies will utilize multiple acquisition tools to improve localization and quantification of population activity and compare with single-unit activity. Characterizing neural responses at multiple levels (single-unit, population response) and foci (SI, GPi) is imperative to understanding the pathophysiology of dystonia.	01-Sep-2005	CORTICAL DIGIT REPRESENTATION; CORTICAL RE-ORGANIZATION; ELECTROPHYSIOLOGY; FOCAL & GENERALIZED DYSTONIA; FUNCTIONAL MAGNETIC IMAGING; GLOBUS PALLIDUS INTERNAL SEGMENT; LFPS; MEG; REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION; SOMATOSENSORY PROCESSING

Overduin, Simon A	Carmena, Jose M	University of California (Berkeley)	CIHR Fellowship	Evidence for postural primitives in the convergence of behavioral, muscular, and neural patterns	For the nervous system to control movements of the body requires the coordination of a large number of muscles. How this "motor control" is accomplished remains a subject of intense study. Both our understanding of the signals communicated through the motor system and our techniques for probing these signals are frequently subject to revision as more studies are performed. In this investigation we will use a uniquely comprehensive set of data acquired from monkeys performing a simple video game, in which they use a joystick to reach to targets following visual cues. The data illustrate this behavior at the level of the brain, the muscles, and the movements of the arm. We will correlate these recordings across levels in order to better understand what movement variables are actually being coded by the brain. In addition to these recordings, the data will be complemented by electrical microstimulation. This painless technique uniquely allows brain function to be probed in a causal way, as it evokes complex movements resembling those naturally performed by the animal. Each site stimulated in the brain tends to drive the body to a particular posture regardless of its initial configuration. This suggests that the brain may plan movements according to a map of possible end postures. We will examine these evoked movements to validate both this technique and the idea of postural planning in voluntary movement. This research has important clinical implications. For instance, insofar as dystonia can be described as a malfunction of the brain's postural control system, our use of microstimulation to evoke different postures may be useful in simulating this disorder. Also, neuroprosthetic devices may be able to rehabilitate patients with spinal cord injury, stroke and other causes of paralysis, so long as these devices are able to download movement intentions from the brain. Our analyses may show that the current translation of these signals into movement is flawed.	01-Mar-2010	ARM; BRAIN-MACHINE INTERFACE; CORTEX; MONKEY; MOTOR; MOVEMENT; MUSCLE; NEURON; REACHING; STROKE
Ryan, Scott D	Kothary, Rashmi K	Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa	Fellowship - Priority Announcement: Dystonia (SHOPP)	Dystonin/Bpag1 - Cytoskeletal linker proteins mediate organelle function in neurons	The cause of many diseases often relates to hereditary factors passed on over generations and how those factors respond to environmental influences. When comparing the many genetic and environmental factors that contribute to the onset of neuromuscular or degenerative diseases, one commonality resurfaces continuously; failure of cells to send and receive signals vital to function and survival. In deed, multiple diseases of the nervous and muscle systems have at their core a break down in subcellular communication. While this break down is paramount to disease pathology, restoring cellular communication may lead to the development of novel therapeutic approaches. This proposal focuses on one group of proteins that function as a link between micro-structures of the cell called "organelles" and the scaffold that holds them in place. This protein family, known as "plakins," anchors the organelles responsible for housing DNA, synthesizing proteins and storing proteins until needed. The impairment of plakin protein linkages causes stress on these systems resulting in a complete breakdown in cellular function. This proposal will evaluate the contribution of these linker proteins to neuromuscular disease and determine whether restoring communication between the various organelles can alleviate disease symptoms. This proposal aims to identify novel gene products responsible for linking and maintaining organelle communication in neuromuscular and degenerative diseases. The work proposed herein will add to our understanding of disease by exploring the effect of cellular communication on cell function, evaluate novel therapeutics through functional recovery assessment and identify new protein and gene targets for therapeutic intervention.	01-Mar-2011	APOPTOSIS; CELL CULTURE; DYSTONIA; ER-STRESS; MICROSCOPY; NEURODEGENERATION; NEUROMUSCULAR DISEASE; PROTEOMICS; SECOND MESSENGERS; TRANSGENIC ANIMALS
Smith, Amanda	Bulman, Dennis E	Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa	Fellowship - Priority Announcement: Dystonia (SHOPP)	Investigation into the cause of Myoclonus Dystonia	Myoclonus dystonia (MD) is a neurological disorder characterized by rapid muscle contractions (myoclonus) and sustained twisting movements resulting in abnormal postures (dystonia). Symptoms begin in the 1st or 2nd decades of life and are associated with subtle psychiatric symptoms (obsessive-compulsive disorder). MD can range from mild to severe, even in the same family. Most patients have a drastic reduction of myoclonus in response to alcohol ingestion, however, as the alcohol level in their system lowers, their symptoms become worse than before. This temporary and severe rebound affect makes alcoholism a significant problem. Forty percent of MD patients have mutations in the gene e-sarcoglycan (SGCE), which is a member of the sarcoglycan (SG) family. To date, 6 sarcoglycan genes (a,b, e,g,d,and z) have been identified. Mutations in a, b, g and d sarcoglycan are responsible for recessive (both parents must be carriers) limb-girdle muscular dystrophy. The sarcoglycans are members of the dystrophin-dystroglycan complex (DGC) in muscle. Mutations in other members of the complex are also responsible for other forms of muscular dystrophies. Interestingly, SGCE is expressed in more tissues than the other family members. Its expression within the brain explains how a mutation in the gene encoding SGCE causes the movement disorder, MD. To date, evidence of its role or interacting partners within the brain are unknown. The aim of my project is to identify the components of the SGCE complex in the brain using a method called, Tandem affinity purification-mass spectrometry. My goal is to identify the SG-complex in the brain including new members not seen in the complex found in muscle. By determining the proteins which interact with SGCE we will determine the reason mutations in this gene cause MD. Furthermore, the interacting proteins will be candidates for other similar movement disorders, just as the binding partners in muscle cause other forms of muscular dystrophy		EPSILON SARCOGLYCAN; HUMAN GENETICS; MASS SPECTROMETRY; MOVEMENT DISORDER; MYOCLONUS DYSTONIA; NEURONAL CELLS; SARCOGLYCAN COMPLEX; TANDEM AFFINITY PURIFICATION
Soman, Teesta B	NULL	Hospital for Sick Children (Toronto)	New Investigator Research Grants in Child and Youth Health	Globus pallidus deep brain stimulation in children with dystonia.	NULL	01-Aug-2008	NULL
Udupa, Kaviraja	Chen, Robert	Toronto Western Research Institute (Toronto)	Fellowship - Priority Announcement: Dystonia (SHOPP)	Prediction of clinical improvement by deep brain stimulation surgery in primary generalized dystonia using clinical, genetics and neurophysiologic measures	Dystonia is a common movement disorder characterized by excessive muscle contraction and severe refractory cases can be effectively treated with deep brain stimulation (DBS) of one of the deeper brain structure viz., globus pallidus internus. Previous studies found that dystonia is associated with abnormal motor cortical functions as measured by plasticity and DBS corrects this abnormality through basal ganglia-motor cortical connections. However, the effects of DBS on motor cortex have not been investigated before and after the surgery to assess the changes in motor cortical plasticity. In this study, we plan to investigate the effects of DBS on motor cortex before and at different time points after the surgery. We also plan to study the single nucleotide polymorphisms of brain derived neurotrophic factor (genetic factor associated with changes in cortical plasticity) and clinical dystonia scores. Based on these neurophysiologic measures coupled with genetic and clinical profile, we propose to derive the prediction of improvement following DBS surgery in patients with dystonia.	01-Apr-2011	CORTICAL PLASTICITY; DEEP BRAIN STIMULATION; INTRACORTICAL CIRCUITS; LONG TERM POTENTIATION; PAIRED ASSOCIATIVE STIMULATION; PAIRED PULSE PARADIGMS; PRIMARY GENERALISED DYSTONIA; TRANSCRANIAL MAGNETIC STIMULATION

Vanstone, Megan R	Bulman, Dennis E	University of Ottawa/Université d'Ottawa	Master's Award: Frederick Banting and Charles Best Canada Graduate Scholarships	To identify, validate and characterize the gene on 18p which is responsible for causing Myoclonus-Dystonia (MD)	Two genes have been associated with Myoclonus-Dystonia (MD), a locus on 18p11 (DYT15) and the SGCE gene (DYT11) on chromosome 7. One of the goals of the current proposal is to identify within the DYT15 locus, a novel gene causing MD. 36 families have been recruited to the study so far and mutation screening has been performed. In this project I plan to sequence the entire critical region for DYT15 using the sequence capture technology from NimbleGen followed by sequencing the captured DNA using a Roche 454. My major goals are to: (1) identify the causative mutation in our family responsible for MD; (2) demonstrate significant functional differences between the wild-type and the mutant alleles. My long-term goal will be to make an animal model by first expressing the wild-type gene.	01-Sep-2010	ANIMAL MODEL; GENETIC DISORDERS; GENETICS; MUTATION IDENTIFICATION; MUTATION SCREENING; MYOCLONUS-DYSTONIA; NERVOUS SYSTEM; NEXT-GENERATION SEQUENCING; SEQUENCE CAPTURE MICROARRAY; SEQUENCING CRITICAL REGION OF GENE
Yugeta, Akihiro	Chen, Robert; Hutchison, William D	University Health Network (Toronto)	Fellowship - Priority Announcement: Dystonia (SHOPP)	Saccade-related beta band activity in local field potentials recorded from human basal ganglia	Objective: The aim of the proposed research is to study the beta band (15-30 Hz) activity of the local field potentials (LFPs) in subthalamic nucleus (STN) of Parkinson's disease (PD) and globus pallidus interna (GPi) of dystonia during eye movement (saccades) toward and away from visual cues and toward memorized targets. The results of these studies may shed light on the mechanisms of initiation and inhibition of saccades in patients with movement disorders. Background: In PD there is impairment of voluntary movement. Increased beta band oscillations in the basal ganglia (BG) are believed to produce motor symptoms of the disease. Dystonia is a excessive movements and abnormal inhibition is believed to produce motor symptoms of the disease. Abnormalities of the BG have been implicated in both disorders. Effective therapy for PD involves targeting the STN with deep brain stimulation (DBS) whereas that for dystonia involves targeting the GPi. Oscillatory activities in STN and GPi are thought to correlate with both eye movement and limb movements. STN DBS improved saccade performance in PD patients, and a clinical case report has shown improvement in saccades with GPi DBS in a dystonic patient. Methods: Two to 5 days after DBS surgery, we will record electrical activities from DBS electrodes implanted in the STN and the GPi during saccades toward and away from visual cues and toward memorized targets, and volitional arm movements. We will analyze how the electrical activities change with eye and limb movements. We will determine if activities associated with different types of eye and limb movements comes from different parts of the STN and GPi. Significance: This study will provide important knowledge on role of beta oscillations in the starting and inhibiting movements in the human STN and GPi. The findings will have implications in understanding the how of beta oscillations are related to eye movement control.		BASAL GANGLIA; DEEP BRAIN STIMULATION; DYSTONIA; GLOBUS PALLIDUS INTERNA; LIMB MOVEMENT; LOCAL FIELD POTENTIAL; OSCILLATION; PARKINSON'S DISEASE; SACCADIC EYE MOVEMENT; SUBTHALAMIC NUCLEUS
Zhang, Ying	NULL	Dalhousie University (Nova Scotia)	Operating Grant	Control of Movement: Reticulospinal circuits	Perhaps the most fundamental thing we do is move - whether in speaking, in playing the piano or dancing, or lifting weights. Large parts of our central nervous systems are wired to ensure that we move appropriately for the task at hand. But how are we wired to move? There are multiple brain circuits involved. Some do the planning, make the decision, and select the appropriate movement. These circuits tell "command" neurons in the brain stem which movement to perform, and these neurons inform our organising circuits in the spinal cord that in turn tell our motor neurons how strongly to activate muscles. In this application, I propose to study command circuits - those between the brain stem and the spinal cord. These neurons live in a crowded place in the brain stem, the reticular formation. Some of these neurons are wired to prevent movement, whereas others are wired to cause movement. For example, prevention of movement is necessary when we dream, so reticular formation neurons that prevent movement are activated in REM sleep. Others are activated to initiate walking. I will use a variety of techniques (for example: genetic manipulations, electrical recordings, advanced microscopy of living tissue) to study the organisation of such "OFF" and "ON" systems, with the aim of better understanding how we move. As many neurologic diseases and injuries affect movement - for example, spinal cord injury, traumatic brain injury, multiple sclerosis, dystonia, stroke, movement disorders, and other neurodegenerative diseases - this work has broad implications. This research does not aim to cure any specific disorder, but rather to develop strategies to improve the quality of life of people with any neurological diseases or injuries that affect movement. At the end of the proposed 5 years, we will have enhanced understanding of the organisation of motor command neurons in the reticular formation, and of the relationship between moving and not moving.	01-Jul-2014	CALCIUM IMAGING; CONTROL OF MOVEMENT; ELECTROPHYSIOLOGY; LOCOMOTION; MICROCIRCUITS; MULTIPHOTON MICROSCOPY; PHOTOACTIVATION; RETICULOSPINAL; SPINAL CORD; TRANSGENIC MICE