1. **Dr. Angela Auriat** (Supervisor: Dr. Lara Boyd), ***University of British Columbia***

   Project Title: ***It is time to start listening to 'silent lesions': the impact of covert lesions on post-stroke recovery***

   Brief Project Description: This study will assess the impact that covert lesions (tiny difficult to see lesions that can accumulate) have on motor and cognitive recovery from severe stroke over time.

   Project Summary: Covert lesions are areas of brain damage that occur without noticeable symptoms. Covert lesions change over time, growing or shrinking. We do not fully understand why or how these changes occur but advanced neuroimaging suggests that early brain changes in white matter can identify areas at risk. Our previous CPSR funded research found that stroke patients with covert lesions have worse outcomes. It is critical that we build on this knowledge to create a better understanding of the interaction between covert lesions and stroke.

   In collaboration with our CPSR partners at Sunnybrook Research Institute, we recently developed expertise in the quantification of covert lesions. We found that covert lesions significantly impact cognitive and motor outcomes after stroke. However, these data are derived from individuals at least 6 months after stroke. Thus, we do not understand how covert lesions affect the timing of recovery. We expect they negatively impact outcome, specifically slowing the rate and decreasing the final level of recovery. Advancements in neuroimaging at UBC have allowed for detailed imaging of brain myelin, which is damaged in many covert lesions. With this sensitive imaging we will look at the structure in and around covert lesions and identify any changes occurring after stroke.

   We will utilize the Human Brain Imaging Analysis Pipeline, a highly valuable infrastructure platform available through CPSR, and myelin water imaging, to expand our understanding of the relationship between covert and overt stroke. We will study individuals throughout the first 6 months after stroke to understand how covert lesions affect recovery. **Aim 1:** To use advanced neuroimaging and extensive cognitive, motor, and psychosocial assessments to map the relationship between covert lesions and stroke recovery. **Aim 2:** To determine if covert lesions change after stroke, both in terms of size and structure, and relate these changes to recovery.

   This work will expand our understanding of how covert lesions impact the trajectory of recovery after stroke. Targeting covert lesions as a way to promote recovery after overt stroke is an under-explored area with great potential.

2. **Dr. Andrea Bandini** (Supervisors: Drs. Yana Yunusova, Petros Faloutsos, and Melanie Baljko), ***University Health Network – Toronto Rehabilitation Institute***

   Project Title: ***Markerless facial tracking for speech rehabilitation***

Brief Project Description: This project will develop, validate and pilot-test a novel facial tracking algorithm in conjunction with an exercise-based intervention to improve speaking in patients recovering from stroke.

Project Summary: Stroke results in debilitating changes in individuals' abilities to communicate through speech. Speech rehabilitation is often indicated post stroke, but not always effective, particularly in cases of severe and multiple deficits (e.g., coexisting language, cognitive, and/or sensory disorders). Novel rehabilitative approaches based on innovative technologies are needed to expand the repertoire of available therapeutic options. Since motor rehabilitation in general and speech motor rehabilitation in particular require intense treatment, which is too demanding to be fully supported by the current healthcare system, there is a particularly strong and urgent need for the development of technologies that can be used for home-based and remotely delivered therapy.

This study capitalizes on technological advances in tablet-device developments (e.g., iPad). Nowadays, tablet devices are equipped with high-quality cameras that can be adapted for high-resolution facial tracking. Facial tracking has been used to understand speech and oro-motor control of the jaw and lips and the conduct of emotional information, essential for communicative success. In this project we will develop a means of using facial tracking as a basis for providing augmented visual feedback while re-learning speech and oro-motor movements that have been affected by stroke.

The overall goal of this work is to develop and implement novel technology in speech rehabilitation. The specific objectives of this project include (1) development a suitable algorithm to track facial movements using a tablet camera, (2) validation of this algorithm against a well-established high-resolution facial tracking technology, and (3) pilot testing of the game-based treatment powered by the algorithm in an ongoing study of a novel augment feedback game-based intervention. Our overall hypothesis presumes that engaging and memorable games, based on visualizing facial/lips/jaw movements, will enhance learning of oral and speech movements, which will improve the overall quality of speech in those recovering from stroke.

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3. **Matthew Chilvers** (Supervisor: Dr. Sean Dukelow), ***University of Calgary***

Project Title: ***Brain stimulation and robotic therapy to promote sensory recovery after stroke***

Brief Project Description: This project will investigate robotic therapies in combination with Transcranial Direct Current Stimulation (TDCS) in an attempt to enhance recovery in chronic stroke patients.

Project Summary: About 50% of patients suffer from sensory loss after stroke. Sensory loss impairs one's ability to perform activities of daily living. However, sensory rehabilitation techniques are poorly studied and often not used. In part, this is because bedside clinical measures of sensory function tend to be insensitive and unreliable. Enhancement of sensory recovery through improved rehabilitation techniques may be the key to unlocking further improvements in overall recovery.

Our lab has developed valid, reliable and precise robotic tools to measure a particularly important aspect of sensation – proprioception. Proprioception is the sense of the position and movement of one's body parts without the use of vision. We have recently developed robotic therapies to help rehabilitate proprioceptive loss after stroke. We will study these therapies in combination with Transcranial Direct Current Stimulation (TDCS) in an attempt to enhance recovery. TDCS is a non-invasive brain stimulation technique that has been shown to improve motor recovery, swallowing and aphasia post-stroke. TDCS uses scalp electrodes to apply weak direct currents (1-2 mA) to induce changes in brain excitability.

We are planning a randomized controlled trial to evaluate robotic rehabilitation and TDCS after stroke. Chronic stroke survivors with confirmed proprioceptive deficits will be randomized to either: 1) Robotic rehabilitation plus TDCS or 2) Robotic rehabilitation plus sham TDCS. *We hypothesize that robotic rehabilitation plus anodal TDCS applied over affected somatosensory cortex will lead to the largest gains in proprioceptive function.*

We are uniquely positioned in the world to evaluate and rehabilitate sensory function following stroke. Enhancement of sensory recovery represents an area that is virtually untapped. The present proposal will serve as a catalyst for larger studies using novel technologies to improve sensory rehabilitation techniques.

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4. **Lucas Crosby** (Supervisor: Dr. Kara Patterson), ***Toronto Rehabilitation Institute – University Health Network***

   Project Title: ***Exploring how rhythmic abilities and self-perceptions shape gait symmetry post-stroke***

   Brief Project Description: This project will determine whether the ability to hear a rhythm positively influences the ability to respond to a treatment for walking asymmetry in stroke patients.

   Project Summary: After stroke, people walk slower, and spend unequal amounts of time standing on each leg within the walking pattern, known as temporal asymmetry. Treatments such as rhythmic stimulation (walking to match foot steps to a beat played by a metronome) are used to help people with stroke walk to a rhythm. This treatment helps improve walking speed and step length, but walking asymmetry does not improve as much. This could be because after stroke, people's ability to hear the beat in music and/or make movements in time to the beat in music is decreased, or that they are poor at evaluating their own walking asymmetry.

   The goal of this research is to determine if the ability to hear a rhythm affects the ability to respond to a rhythmic cue treatment for walking asymmetry. Thirty people with stroke will be tested on their ability to find the beat in music and their ability to tap accurately to the beat in music to be classified as strong-rhythm perceivers/producers or weak-rhythm perceivers/producers. Participant's walking asymmetry will be measured. Next, participants will walk to a rhythmic cue (metronome beat) with the tempo set to each person's normal walking pace. We will measure how well they match their steps to the cue, and how much their walking asymmetry changes. Comparisons between the strong- and weak- rhythm perceives/producers

on these measures will be made to determine if the ability to hear and produce a rhythm affects the ability to respond to cue. Finally, we will compare each participant's evaluation of their own walking symmetry to their ability to respond to cue. It is expected that people who are both strong-rhythm perceivers/producers and can more accurately estimate their own walking asymmetry will improve their walking pattern with stimulation more than people who are poor at these tasks.

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5. **Ayan Dey** (Supervisor: Dr. Brian Levine), ***Rotman Research Institute, Baycrest***

Project Title: ***Functional neuroimaging of Vascular Cognitive Impairment due to Cerebral Small Vessel Disease***

Brief Project Description: This project will investigate the impact of Cerebral Small Vessel Disease (a pathological condition of the brain's small blood vessels) on brain network function and cognitive decline in those with evidence of significant changes to the brain's white matter on MRI using a combination of behavioural testing and functional neuroimaging.

Project Summary: Cerebral Small Vessel Disease (CSVD) is a pathological condition of the brain's microvasculature that affects the small vessels supplying white matter and subcortical brain regions**.** CSVD is one of the most prevalent neurological disorders worldwide, the most common cause of Vascular Cognitive Impairment and a strong risk factor for Alzheimer's disease and other forms of dementia. It is believed that damage to white matter tracts and silent infarcts may be responsible for accelerating age-related cognitive decline through interruption of brain networks that support attention and other executive functions.

In stroke patients, prevalence of white matter damage due to CSVD varies from 67-98%. CSVD is thought to exacerbate cognitive symptoms and predispose stroke survivors to earlier onset dementia. Despite the high prevalence of CSVD in stroke survivors and the general population, relatively little is understood regarding the mechanism through which it differentially affects individuals, as not all individuals with white matter changes have overt cognitive complaints. This disparity may be related to the limits of conventional clinical imaging, which provides an excellent means for identifying lesions, but does not permit assessment of how brain regions may be communicating with each other. Moreover few effective interventions exist for helping individuals overcome executive deficits commonly associated with vascular cognitive impairment.

Thus, this project aims to investigate the impact of CSVD on neural network function and cognitive decline in those with evidence of significant white matter changes on MRI. Specifically, using a combination of behavioural testing and functional neuroimaging we hope to investigate what differentiates individuals with symptomatic versus asymptomatic CSVD. Moreover, because this project takes place within the context of a randomized control trial for Goal Management Training (GMT), a 5-week intensive cognitive rehabilitation program, we hope that insights from this study will validate methods currently being used to assess the benefits of this program in stroke and TBI populations.

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6. **Dr. Jodi Edwards** (Supervisor: Dr. Sandra Black), ***Sunnybrook Research Institute***

Project Title: ***The effect of antihypertensive treatment on stroke severity and post-stroke functional outcome***

Brief Project Description: Using ten years' worth of data from the Ontario Stroke Registry, this study will investigate whether the type of high blood pressure medication stroke patients were on made a difference to their stroke severity and recovery.

Project Summary: In 2013, over 400,000 Canadians were living with stroke-related disability, with 40% suffering moderate or severe problems with the ability to function, either physically or cognitively. Identifying factors that might help improve function after stroke is an important step in planning therapies and facilities for stroke recovery. Having "silent" strokes in the brain might affect people's ability to recover function after stroke. A potential factor in the development of silent strokes is the buildup of a toxic protein called beta-amyloid. High blood pressure causes stroke and affects how much beta-amyloid is in the brain. Medications, including angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly prescribed for high blood pressure, but an important difference is that ARBs help the brain clear away beta-amyloid while ACEIs cause the brain to build up more beta-amyloid, which may affect function after stroke.

This study will test whether those using ARB medications have less severe strokes and recover function better than those using ACEI medications. We will identify individuals who had a stroke between 2003 and 2013 from the Ontario Stroke Registry, a provincial database of all patients with stroke at major hospitals. We will determine what blood pressure medications these individuals were using before their stroke and use statistical modeling to compare 1) how severe the stroke was when they were admitted, using a clinical scale (NIHSS) and 2) what their ability to function was when leaving the hospital, using a function test called the Modified Rankin, in those taking ACEI and ARB medications. This study will have an immediate effect on what medications are prescribed to treat high blood pressure and will also increase our understanding of how beta-amyloid in the brain affects both the number of silent strokes and people's ability to recover function after a stroke.

7. **Annette Gower** (Supervisor: Dr. Mario Tiberi), ***Ottawa Hospital Research Institute***

Project Title: ***Effect of specific activation of D1-class dopamine receptors and exercise in an asynchronous therapy paradigm on stroke recovery***

Brief Project Description: This project will test whether drugs that specifically target a subgroup of dopamine receptors in the brain improve functional recovery of movement skills, when combined with physical training in a mouse stroke model.

Project Summary: Studies suggest that post-stroke recovery can be augmented by a combined approach relying on physical activity and pharmacological interventions, with drugs such as amphetamines and levodopa. Because of inconclusive clinical studies using physical

therapy paired with these drugs, the jury remains somewhat undecided about the added benefits of pharmacotherapy in post-stroke recovery. However, two reasons may explain why some clinical studies have failed to show any significant benefits in post-stroke recovery using combined physical exercise with these drugs.

First, amphetamine-like drugs and levodopa can act on multiple components and chemicals of the brain. Amphetamine-like drugs and levodopa change the level of dopamine, a brain chemical, which attaches on the cell surface of brain cells to five different proteins known as dopamine receptors (D1, D2, D3, D4 and D5). These multiple actions could lead to either positive benefits in some stroke patients or ineffective improvement in other afflicted individuals. Refining the pharmacotherapy by using drugs acting on a specific subgroup of dopamine receptors may prove to be more beneficial in post-stroke recovery when combined with physical activity. Secondly, the success of post-stroke recovery for movement skills critically depends on the timing and sequence of applied pharmacotherapy and physical training.

In this project, we test if drugs specifically targeting the dopamine D1-class receptors (D1 and D5) improve functional recovery of movement skills, when combined with different physical training protocols, using a mouse stroke model. Stroke mice will be evaluated with different motor behavior tests. Mouse brains will be also examined with biochemical and microscopy techniques to assess the functional state of D1 and D5 receptors. We trust that these studies will shed light into the scientific basis of rehabilitation exercise training paired with dopamine receptor-specific pharmacotherapy in functional movement recovery after stroke. It is also hoped that our studies will provide new avenues for the development of novel combined pharmacotherapy and rehabilitative physical training for stroke survivors.

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8. **Dr. Olinda Habib-Perez** (Supervisor: Dr. William McIlroy), ***Sunnybrook Research Institute***

Project Title: ***The effects of bimanual light touch contact on bipedal inter-limb synchronization after stroke***

Brief Project Description: The current study will assess whether simultaneous light touch on both sides of the body can improve balance control in individuals with chronic stroke.

Project Summary: Weight-bearing asymmetry in individuals post-stroke leads to increased balance instability and a greater risk of falls. In addition to impaired balance stability there is a decreased between-limb synchrony, which has been shown to be an important index of balance control in individuals post-stroke. Between-limb synchrony, a reflection of bipedal coordination, illustrates a temporally locked in-phase motion of the movements applied from both limbs in healthy individuals. Though individuals post-stroke have difficulty maintaining in-phase coordination patterns, in-phase coordination is a highly stable movement pattern in healthy individuals.

As coordination requiring two limbs is impaired after stroke, impaired between-limb synchrony may benefit from augmented sensory information to improve control. It is hypothesized that providing feedback for both sides of the body to augment control of balance via bilateral haptic inputs may serve to influence inter-limb coupling and serve as a novel approach to retrain balance control. Light touch contact, contact that provides no physical support by the fingertip,

from either the affected or less affected hand has been shown to improve balance control in individuals post-stroke. Additionally, there is a relationship between the forces produced by light touch contact and the ground reaction forces, with the former leading the latter; however that phase relationship is unknown after stroke.

The current study will assess the effects of bimanual light touch contact on bipedal between-limb synchrony during balance control in individuals with chronic stroke. Additionally, the timing at which bimanual light touch contact is provided will be analyzed to understand whether stroke patients require bimanual in-phase information to produce bipedal in-phase between-limb synchrony. The findings of this study will help understand how to improve a critical aspect of balance control in individuals post-stroke, in order to reduce their risk of falls and in turn be applied to rehabilitation interventions.

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9. **Dr. Andrew Huntley** (Supervisor: Dr. Avril Mansfield), ***Toronto Rehabilitation Institute – University Health Network***

Project Title: ***Optimizing clinical assessment of reactive balance control post-stroke***

Brief Project Description: The goal of the proposed project is to determine the combination of conditions and instructions that optimize the "lean and release test" to inform clinical practice and fall risk after stroke.

Project Summary: People with stroke have an increased risk of falling. Current clinical tests do not properly assess fall risk. The ability to react to an unexpected slip, trip, push, pull or fall in the clinic or laboratory is related to the risk of falling in daily life. Researchers and clinicians at the Toronto Rehabilitation Institute have developed a simple method designed to test balance reactions and falls risk in the clinic. We call this the 'lean and release test'; the participant leans forward in a harness attached to a cable, and at an unexpected time the cable is released causing the participant to start to fall forward. The participant must take a quick step to stop from falling down. We have used this test with over 500 people admitted to in-patient stroke rehabilitation at Toronto Rehab.

Our current protocol includes: 5 trials of 'usual response' (no constraints on stepping), 1 trial of 'dual task' (where the participant completes a distracting task while waiting for the cable to release), and 5 trials of 'encouraged use (where we block the preferred limb and try to encourage the participant to step with the non-preferred limb). We would like to optimize this protocol for informing clinical practice and fall risk.

The goal of the proposed project is to determine the combination of conditions and instructions that optimize the lean and release test. We expect that this work will lead to a standardized test that can be used in other clinical and research settings to assess balance reactions and fall risk after stroke.

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10. **Dr. Timal Kannangara** (Supervisors: Drs. Diane Lagace and Jean-Claude Béïque), ***University of Ottawa***

    Project Title: ***Optogenetic activation of newly-generated astrocytes to improve stroke recovery***

    Brief Project Description: This project will use optogenetics to increase the electrical activity of new brain cells (astrocytes) to assess if this alters behavioral recovery after stroke in a transgenic mouse model.

    Project Summary: A stroke interrupts blood flow and oxygen supply to the brain causing neurons within regions of the brain to die. The impact of this cell death is devastating for the 62,000 Canadians every year that have a stroke; this is especially destructive due to the dearth of available treatments that can reverse the stroke-induced motor and cognitive deficits. However, there is hope that treatments can be developed to allow the brain to regenerate – to help the brain repair the injured region *itself*.

    This hope arose due to the discovery that the brain contains stem cells that can generate new cells even throughout adulthood. Amazingly, after a stroke, these new cells migrate to the stroke-afflicted brain region, and turn into special types of brain cells, called astrocytes. Astrocytes have many functions, but perhaps their primary role is to ensure that communication in the brain is working properly. As such, it is intriguing to think that the brain is making new astrocytes to help restore brain communication and aid recovery after injury. However, the exact function of these astrocytes in stroke recovery is unclear.

    My goal is to determine the function of the adult-generated astrocytes by activating them during recovery. I will use transgenic mouse models that allow us to visualize and alter cell activity in order to influence recovery after we induce a stroke. Specifically, I will use a method called optogenetics to increase the electrical activity of the new astrocytes for a sustained period of time after stroke or only when performing clinically-relevant stroke tasks, to assess if this alters behavioral recovery. Determining the function of activating the newly generated astrocytes during stroke recovery has important clinical implications for stimulation-based therapies and may act as a viable new option to improve the lives of stroke survivors.

11. **Liam Kelly** (Supervisors: Drs. Michelle Ploughman & Fabien Basset), ***Memorial University of Newfoundland***

    Project Title: ***In chronic stroke survivors, does high-intensity functional exercise training lead to similar improvements in peak aerobic capacity as traditional aerobic exercise training?***

    Brief Project Description: This study will assess whether high intensity task-oriented exercise training improves cardiorespiratory fitness in chronic stroke survivors.

Project Summary: Individuals recovering from stroke often have physical and cognitive impairments that limit their ability to perform activities of daily living and engage in structured physical activity. This can affect their quality of life and increase their risk for having another stroke along with developing comorbid conditions such as diabetes and cardiovascular disease. Accordingly, cardiorespiratory (CR) fitness is consistently reported at levels reflecting less than half of what is expected in age and gender matched populations. Although aerobic exercise training improves CR fitness and reduces cardiovascular risk factors in stroke survivors, current therapeutic strategies do not elicit adequate cardiovascular stress to induce a training effect. In addition, traditional endurance training modalities are not practical for many stroke survivors and novel interventions are needed.

The primary objective of the current research program is to determine the efficacy of high intensity task-oriented exercise training toward improving CR fitness in chronic stroke survivors. After successfully completing a medical examination, forty chronic stroke survivors (> 6 months) will be randomized to receive thirty sessions of either aerobic exercise training (AET) or functional exercise training (FET) over a ten week period. Briefly, AET involves 30-minutes of body-weight supported treadmill exercise at workloads corresponding to 65% of $\dot{V}O_2$ peak, while FET includes 30-minutes of multi-joint simple functional movements (i.e. sit- to-stand, lying-to-siting, kneeling-to-stand, etc.) performed in sequential order with minimal rest periods to achieve a mean heart rate 30-50 beats above resting. Participants perform maximal graded exercise tests and have anthropometrics recorded at baseline, immediately following the exercise interventions and again 3 months later. It is hypothesized that progressive high intensity FET will be well-tolerated in chronic stroke survivors and that FET will produce similar improvements in CR fitness as treadmill ergometry.

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12. **Dr. Hsing-Ching (Cherie) Kuo** (Supervisor: Dr. Adam Kirton), ***University of Calgary***

Project Title: ***Mapping motor cortex developmental plasticity following perinatal stroke with robotic transcranial magnetic stimulation***

Brief Project Description: This project will use exciting new technologies (robotic transcranial magnetic stimulation) to generate motor maps of brain organization in children with perinatal stroke, before and after an intervention, to better understand how the brain has changed to achieve better function.

Project Summary: Blockage of a brain artery near birth causes lifelong disability for thousands of Canadian children. Such perinatal strokes damage the brain's motor system, leading to weakness on the opposite side of the body (cerebral palsy). These large brain injuries early in life also provide a unique opportunity to understand how the brain develops and changes (plasticity) during development.

The motor cortex is the primary brain area that controls our movements. Understanding how and where the motor cortex has developed following perinatal stroke has immediate implications for therapy. In fact, our program has used such brain mapping to complete two clinical trials of non-invasive brain stimulation, showing that stimulating specific brain areas can enhance the effects of therapy and improve functional outcomes.

Our program is internationally recognized for our use of advanced technologies to explore the brain in children with perinatal stroke. Transcranial magnetic stimulation (TMS) applies gentle magnetic stimulations to the brain surface to map where the motor system is and how it is working in real patients. Our Alberta Children's Hospital Pediatric Non-invasive Brain Stimulation Laboratory, the first of its kind in Canada, has safely applied >3 million stimulations to nearly 300 children. Next month, we will be the 1st pediatric center in the world to install a TMS Robot, an advanced technology with enormous potential to better map the brain's motor system.

The proposed study will take these advances to the next level. The trainee will lead novel projects using the TMS robot to generate motor maps of brain organization in children with perinatal stroke. This will allow more specific mapping and targeting, both before interventions and again afterwards to understand how the brain has changed to achieve better function. This promises to bring personalized medicine to advanced stroke rehabilitation and improve the lives of affected children and their families.

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13. **Riley Louie** (Supervisor: Dr. Janice Eng), ***University of British Columbia***

Project Title: ***Use of a robotic exoskeleton to promote walking recovery after stroke***

Brief Project Description: The purpose of this study will be to evaluate the effectiveness of a powered robotic exoskeleton on walking ability in patients early after stroke.

Project Summary: The most sought after goal by patients with stroke in rehabilitation is improved walking ability. Individuals who do not regain walking ability are more likely to go to nursing homes and have a greater chance of death. However, there are insufficient resources to ensure that all patients, especially those who require more physical assistance, have the opportunity for walking early after stroke when the greatest recovery of the brain occurs.

A possible novel solution is the use of a powered robotic exoskeleton which can enable walking soon after stroke. This device straps to the legs and controls the motion of the hip and knee joints to assist the limbs in a normal walking pattern. The purpose of this study will be to evaluate the preliminary efficacy of a powered exoskeleton on walking ability in patients early after stroke. In addition, we will explore the perceptions of clinicians and patients towards the device. Newly admitted patients to stroke rehabilitation who need assistance from two people to walk will be randomly assigned to the Exoskeleton Group or the Usual Care Group. The Usual Care Group will receive daily one hour physical therapy which typically has approximately 45 minutes of walking-related activities. This will include muscle strengthening and standing activities for patients who are not yet walking. The Exoskeleton Group will receive the same care, except that the 45 minute walking-related activities will take place while wearing an exoskeleton which will allow walking from the first session.

Exoskeletons offer the potential to provide treatment to patients with severe stroke who are not yet walking. Walking immediately after rehabilitation admission may harness the brain recovery known to occur early after stroke. The results from this study will provide guidance to clinicians to help their patients receive the most benefits from this new technology.

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14. **Dr. Matthew McDonald** (Supervisors: Drs. Dale Corbett and Baptiste Lacoste), ***University of Ottawa*** ****Top ranked application for a post-doctoral fellow & winner of the Martin Rothstein Post-Doctoral Fellowship Award****

    Project Title: ***Engaging vascular plasticity to promote hindlimb functional recovery in a rat model of ischemic stroke***

    Brief Project Description: This study will assess whether the benefits of exercise can be augmented when combined with metformin, an FDA-approved anti-diabetic drug that produces changes in muscles similar to exercise in an animal model.

    Project Summary: Many stroke survivors have reduced ability to move their limbs, thereby greatly limiting their activities of daily living. Researchers are testing new approaches to improve recovery, including combining rehabilitation with other interventions. A promising intervention shown to improve stroke recovery in animal and human studies is exercise. However, a major barrier to widespread implementation of exercise into stroke rehabilitation is the rapid deterioration in cardiovascular fitness and muscle strength following stroke, superimposed on an interactive lifestyle prior to the stroke. This makes it difficult for individuals to exercise at intensities sufficient to restore and improve physical fitness levels.

    To address this problem, we will use an exercise program (similar to that used in humans) in rats that have stroke-induced hindlimb deficits reducing (but not preventing) their ability to walk and climb. Exercise will be preceded by dosing with metformin (MET), an FDA-approved anti-diabetic drug that produces changes in muscles similar to exercise and hence considered an "exercise mimetic". Exercise with and without MET will be used to determine if impairments in hindlimb function (assessed by sensitive behavioural tests) can be reduced. The impact of the exercise and/or MET treatments on the fitness level of the rats will be measured in the same way as human fitness levels (maximal oxygen consumption), to facilitate translation of our findings to the clinic. Finally, in organs important for stroke recovery (muscle and brain) we will investigate changes in the density of blood vessels and in different molecular pathways that affect vascular remodeling and inflammation. The proposed experimental approach has a high translational potential to significantly increase both the rate and level of motor recovery in stroke patients.

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15. **Fares Ould-Brahim** (Supervisor: Dr. Jing Wang), ***Ottawa Hospital Research Institute*** ****Top ranked application for a graduate student & winner of the Luc Vanneste Graduate Studentship Award****

    Project Title: ***Preconditioning of human neural stem cells with metformin to promote post-stroke recovery***

    Brief Project Description: This study will investigate whether metformin, an FDA-approved anti-diabetic drug that produces changes in muscles similar to exercise, can enhance neural stem cell survival, proliferation and maturation to promote stroke recovery.

Project Summary: The generation of human induced pluripotent stem cells (hiPSCs) from human somatic cells has revolutionized cell therapy by providing a source of one's own cells for transplantation to repair damaged tissues. Several studies have demonstrated that transplantation of hiPSC-derived neural stem cells (hiPSC-NSCs) increases regeneration and recovery following stroke, supporting their therapeutic potential. However, major concerns for translating hiPSC transplantation therapy to the clinic are efficacy and safety. Therefore, there is demand to develop an optimal strategy to enhance the engraftment and regenerative capacity of transplanted NSCs.

Recent publications from our lab showed that metformin, an FDA approved drug, represents an optimal candidate as a neuro-regenerative agent. Metformin is capable of not only expanding the NSC population but also subsequently driving them towards neuronal maturation. In this regard, we hypothesize that preconditioning of hiPSC-NSCs with metformin before transplantation into the stroke-damaged brain will improve engraftment and regenerative capabilities of hiPSC-NSCs, ultimately enhancing post-stroke functional recovery.

We will first test the ability of metformin to enhance cell survival, proliferation and maturation of hiPSC-NSCs in culture. Then, we will determine whether metformin preconditioning improves cell survival, proliferation, maturation, and functional recovery following transplantation of hiPSC-NSCs in a rat stroke model. To this end, we have successfully generated hiPSC-NSCs and have preliminary results that reveal metformin's capability to enhance proliferation and differentiation in culture. These studies represent a vital step in the optimization of hiPSC-based replacement therapy to enhance recovery following stroke.

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16. **Tijana Simic** (Supervisor: Dr. Elizabeth Rochon), ***Toronto Rehabilitation Institute – University Health Network***

Project Title: ***Executive control as a predictor of post-stroke aphasia therapy gains and generalization***

Brief Project Description: This project aims to examine whether executive control is an important predictor of how well individuals with post-stroke aphasia recover during and after treatment.

Project Summary: In Canada, one individual suffers a stroke every nine minutes, which amounts to approximately 62,000 strokes per year. Of those who survive, roughly 38% will have aphasia, a difficulty communicating with or understanding others. One of the most frustrating aspects of aphasia is the inability to say the names of common objects, familiar people and places. While therapy for this type of problem is helpful, some of the factors that make it so are still unclear. One factor that is often discussed is that of cognitive control.

Cognitive control, which is also known as executive control, can be thought of as a person's ability to perform tasks successfully by doing such things as: paying attention, ignoring distracting information, revising existing knowledge as new information is learned, and shifting their attention between multiple tasks at the same time. Research has shown that these executive control skills are important indicators of how well individuals will recover from stroke in general; however, there are very few studies examining how executive control may impact language recovery in particular.

This project aims to examine whether executive control is an important predictor of how well individuals with post-stroke aphasia recover during and after treatment. The first part of this project has already found evidence for a relationship between executive control and success in language therapy. In fact, it appears that executive control, rather than the degree of language impairment, might be a stronger predictor of how well an individual with aphasia will recover their language ability after a stroke. Continued research on this topic could provide important information about the role of executive control in language processing and language treatment, and could ultimately change the way in which stroke survivors with communication difficulties are assessed and treated in hospitals and clinics across Canada.

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17. **Faryn Starrs** (Supervisor: Dr. Joyce Chen), ***Sunnybrook Research Institute***

Project Title: ***Individualized transcranial direct current stimulation for stroke motor recovery***

Brief Project Description: The goal of the current project is to determine whether the amount of brain damage to regions that control movements predicts which type of brain stimulation is more effective in improving arm movements.

Project Summary: Advances in stroke care save the lives of many Canadians. However, up to 60% of stroke survivors still have significant difficulty performing simple activities such as feeding and dressing, months to years after the stroke. This affects their ability to live independently and is a personal and socioeconomic burden. Therefore, the optimization of effective rehabilitation approaches to maximize the recovery of movements remains a priority.

One promising approach that can help a stroke survivor improve their movements is transcranial direct current stimulation (tDCS). tDCS directs small electric currents through the scalp to the brain and is a non-invasive, safe, well-tolerated, painless, and portable technology. When we apply tDCS to regions of the brain that control movements at the same time stroke survivors perform exercises for the arm, there are more improvements in arm function, compared to when exercises are performed alone. However, not everyone benefits from tDCS and we think it may be because current research applies a ‘one-size-fits-all’ approach. Each person receives the same type of tDCS despite the stroke affecting each person in a different way. We believe a better understanding of how the stroke uniquely affects a person’s brain will help us know which is the correct type of tDCS to apply for that person.

Therefore, the goal of our project is to determine whether the amount of brain damage to regions that control movements predicts which type of tDCS is more effective in improving arm movements. If we are successful, we can personalize tDCS application so that everyone who receives this therapy will maximally benefit. The results of our research will thus optimize the rehabilitation of arm movements and improve quality of life for many Canadians.

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18. **Faranak Vahid-Ansari** (Supervisor: Dr. Paul Albert), ***Ottawa Hospital Research Institute***

Project Title: ***Optogenetic modulation to enhance recovery from post-stroke depression (PSD)***

Brief Project Description: This project aims to identify the changes in cellular activity associated with post-stroke depression and changes that occur upon successful treatment using optogenetics.

Project Summary: Post-stroke depression (PSD), a common disorder following stroke, limits recovery and increases mortality in stroke patients. PSD involves disruption to brain networks (i.e., prefrontal cortical-limbic-monoaminergic pathways) implicated in mood and emotion. While drugs like serotonin reuptake inhibitors (SSRIs) are the first-line clinical treatment for PSD, they produce remission in only 30% of patients.

My project aims to identify the changes in cellular activity associated with PSD and changes that occur upon successful treatment. First, I established a specific and reproducible mouse model of PSD by focally lesioning the left medial prefrontal cortex (mPFC). The PSD mice display a persistent depression and anxiety phenotypes associated with imbalance excitation/inhibition activity between lesion and contralateral side over time. Next, I showed that chronic treatment of either fluoxetine (SSRI) alone or in combination with voluntary exercise reverses both behavioral phenotypes and the imbalanced excitation/inhibition activity between lesion and contralateral side, using FosB/GAD67/VGLUTs/CamKII as markers. Successful treatment activated cells in mPFC, nucleus accumbens, septum, basolateral amygdala and serotonin neurons of the dorsal raphe.

These preliminary results led me to hypothesize that targeting selective activated brain areas identified by FosB expression is highly associated with effective PSD treatment. In order to target activated neurons, we will use the ArcCreERT2 mice to express optogenetic proteins (ChR2 or Arch) in stroke or SSRI activated cells. These cells will be then either inhibited (Arch) or stimulated (ChR2), respectively, and the behavioural outcome in PSD mice will be examined using standard behavioural tests. To our knowledge, these findings will provide the first insight into the neuroanatomical and cellular substrates of depression in a preclinical model of PSD, which could provide new insights for pharmacological and brain stimulation approaches to treating clinical PSD.

19. **Aaron Yurkewich** (Supervisor: Dr. Alex Mihailidis), ***Toronto Rehabilitation Institute – University Health Network***

Project Title: ***The effect of a robotic orthosis in improving the independence and recovery of stroke survivors with hand and wrist disability***

Brief Project Description: In this project, a robotic hand and wrist orthosis will be developed and its usability in providing intensified in-home exercise and assistance in daily activities will be assessed.

Project Summary: Worldwide, 15 million individuals experience a stroke each year with 62,000 of these cases occurring in Canada. Approximately two-thirds of these individuals will suffer neurological deficit, and half will never fully recover fine hand and wrist function, diminishing their independence in daily living. For maximal recovery of hand and wrist control, strength and range of motion, stroke survivors need to perform rehabilitation exercises daily with high intensity and proper form. In addition, their affected hand needs to be continually incorporated into daily activities to transfer these rehabilitative gains into functional abilities. Such intensive and time-consuming therapy cannot be afforded by governmental health care without advancing technology that gives stroke survivors the ability to complete their therapy independently, and in their home.

Robotic hand and wrist orthoses intensify therapy by applying assistive and resistive forces at multiple joints as the stroke survivor performs their exercises. These orthoses can also provide sensitive and accurate assessment of clinical measures such as spasticity and range of motion. Currently, robotic orthoses can only be used in therapy clinics with a therapist present, due to limitations in portability, usability, cost, sensing, and automatic intensity tuning, leaving many open questions regarding their efficacy in homes.

In this project a robotic hand and wrist orthosis will be developed from suggestions and feedback given by chronic stroke survivor outpatients, as well as researchers, therapists, and industry partners. The usability of the orthosis in providing intensified in-home exercise and assistance in daily activities will be assessed, followed by a randomized control trial to analyze its effect on recovery. Through collaboration within the Canadian Partnership in Stroke Recovery, the clinical efficacy of combining robotic orthotics with functional electrical stimulation will be tested and neurophysiological changes can be studied to further our understanding of the mechanisms of recovery impacted by therapy.