



## DEPARTMENT OF CLINICAL NEUROSCIENCES

- I. **TITLE:** Clinical heterogeneity and progression of adult-onset idiopathic dystonia: A multidisciplinary study.

**SHORT TITLE:** Multidisciplinary study of adult-onset idiopathic dystonia

- II. **SPONSORS:** Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary; Hotchkiss Brain Institute; Tourmaline Oil Chair in Parkinson's Disease

III. **PRINCIPAL  
INVESTIGATOR:**

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This consent form is only part of the process of informed consent. It will give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Please take the time to read the following pages carefully. You will receive a copy of this form.

#### **IV. BACKGROUND:**

We are asking you to participate in this study because you have been diagnosed with adult-onset idiopathic dystonia.

This is an observational study. Complete participation in the study comprises 3 visits over a period of 8 weeks. If you are interested in taking part but cannot commit to all 3 visits, we would ask you to consider participating in the first two visits only.

As part of this study, we will ask you to undergo two clinical assessments involving physical examination, questionnaires and rating scales, one MRI scan of your head, one transcranial magnetic stimulation (TMS) session, and a one-time blood sample collection. The clinical assessment is repeated two times (before and after your routinely scheduled treatment with botulinum toxin injections) in order to see whether the severity of psychiatric symptoms improves after botulinum toxin alongside your dystonia.

**You are completely free to choose whether or not to participate in this research study. If you decide to participate, you can change your mind and withdraw from the research study at any time; you are not required to give any reasons for your decision. Deciding not to participate will not affect your current or future clinical care in any way.**

#### **V. WHAT IS THE PURPOSE OF THE STUDY?**

This research study has two main purposes:

1. The first purpose is to get a better understanding of how brain circuits are wired and how they function in patients with adult-onset idiopathic dystonia compared to other patients who do not have this same condition. Also, we want to understand in what way brain circuits and functions differ between patients with adult-onset idiopathic dystonia who have only one body region affected and those in whom dystonia has spread to affect more than one body region. Additionally, we want to explore what genes are affected in patients with adult-onset idiopathic dystonia. We aim to study this using clinical examinations and questionnaires, Transcranial Magnetic Stimulation (TMS), Magnetic Resonance Imaging (MRI), and DNA testing.

TMS is a technology that tests in a non-invasive fashion the basic electrical properties of the brain circuits controlling movements. In particular, we will test how the brain circuits that send out signals to arm/hand muscles (motor output) are influenced by sensory experiences perceived in the same

body region (sensory input). This part of the study could help understanding how patients with adult-onset idiopathic dystonia differ from patients without this condition in the basic electrical properties of these brain circuits.

MRI is a type of brain scan that looks at how brain circuits are wired and how they function. This part of the study could help understanding how patients with adult-onset idiopathic dystonia differ from patients without this condition in the organization of these brain circuits. Moreover, it may help understanding if the same circuits are organized and function differently in patients who have dystonia in several body regions compared to those who have dystonia only in one body region. Eventually, these findings might help us to understand if patients with different forms of dystonia should receive different types of treatment.

DNA testing involves the analysis of genetic material extracted from blood samples in order to explore the differences in genes, and consequent proteins, in patients with and without adult-onset idiopathic dystonia. This analysis may help with the identification of genetic mutations and maladaptive proteins, which might be contributing to adult-onset idiopathic dystonia.

2. The second purpose of this research study is to understand emotional and behavioral problems associated with adult-onset idiopathic dystonia, in particular their nature and how common they are. This is important because co-existing emotional and behavioral problems, especially anxiety and depression, may not always be recognized by physicians in these patients, and therefore may not receive adequate treatment. This will be done using clinical questionnaires and rating scales. This part of the study might eventually guide towards an improvement in their management.

## **VI. WHAT WOULD I HAVE TO DO?**

If you decide to participate in this study and the study team finds that you are eligible to participate, you will have to sign this consent form. You will be asked to complete three in-person visits over 8 weeks throughout this study.

### **VISITS AND PROCEDURES:**

#### **Visit 1      1 week before or same week as botulinum toxin injection (3 hours):**

- Informed consent procedure.
- Blood sample collection.
- Assess the presence and severity of co-existing emotional and behavioral problems and the degree of emotional stress. This involves answering some questionnaires online.
- Assess dystonia symptoms using the Global Dystonia Rating Scale and another scale related to your specific form of dystonia.
- Assess quality of life using two specific quality of life questionnaires online.
- MRI scan.

**Visit 2**      *Same week as visit 1 (2<sup>1</sup>/<sub>2</sub> hours):*

- TMS session

**Visit 3**      *Between 4 and 6 weeks after botulinum toxin injection (1<sup>1</sup>/<sub>2</sub> hours):*

- Assess the presence and severity of co-existing emotional and behavioral problems and the degree of emotional stress. This involves answering some questionnaires online.
- Assess dystonia symptoms using the Global Dystonia Rating Scale and another scale related to your specific form of dystonia.
- Assess quality of life using two specific quality of life questionnaires online.

**MRI SCAN:**

Magnetic resonance imaging (MRI) will be performed on you using the 3 Tesla (3T) MR imaging machine housed in the Seaman Family Magnetic Resonance Research Centre at the Foothills Hospital.

This MR imaging procedure is being done for research purposes and is in no way a substitute for a clinical imaging study that may be requested by your physician. You should also be aware that the images that are obtained may use experimental methods and will not be reviewed by a physician. In the unlikely event that a researcher observes a suspected abnormality, it will be brought to the attention of a radiologist who will determine the potential significance of this finding to your health. If considered to be a finding of potential clinical significance, it is a policy of the MR Centre to inform you through your family doctor.

**TMS:**

TMS is a non-invasive method used to stimulate the outer regions of the brain. During each TMS session, you will be seated in a comfortable chair wearing a headband or glasses that hold a tracker so that the coils can be placed accurately over the area of the head to be stimulated. During the TMS procedure, two "coils" will be placed over your head. The coils are connected to a stimulator that delivers electrical current to the coils. By that, the coils apply a magnetic field to the regions of the brain immediately beneath them. This produces small electrical currents in those brain regions. When this happens, the coils produce a click and you may experience a slight superficial skin sensation in the region of the scalp where the coil is placed. We will also place a small sensor of electrical current (called electrode) on the skin of one hand, just above a muscle belly. When this muscle receives the signal coming from the brain, you will experience a small muscle twitch, and the electrode will pick up the electrical current coming from that muscle.

During one part of the TMS session, the electrical current applied to the brain will be preceded by a brief electrical current applied to a nerve at the level of your wrist. Using this method, we can test how the electrical properties of the two brain regions upon which we will apply the two coils are linked, and how this influences the signal that the brain is sending to the hand muscle.

Each TMS session will be done in Dr. Monchi's lab and will last between 2.5 to 3 hours.

## **VII. WHAT ARE THE RISKS?**

### **Risks associated with clinical assessments:**

All clinical assessments will be performed under the supervision of neurologists, nurses, psychologists, and psychiatrists. There are no known risks associated with clinical assessments. In the course of doing questionnaires or tests you may feel tired and/or irritable. If this happens, please tell a member of the research staff and ask them to allow you time to rest.

### **Risks associated with MRI procedures:**

Risks associated with having an MRI brain scan are minimal. There are no known risks from exposure to the magnetic field used for these tests. Participants with metallic objects in their bodies will not be eligible for the study because the strong magnetic field in the scanner could cause these objects to change position and may cause injury.

The MRI machine is loud when turned on and the noise may cause some discomfort. Therefore, you will be given earplugs that must be worn. The space inside the MRI machine is limited, so some people may feel claustrophobic. There is an intercom system that allows communication with the researcher even during the scan and you will be given an emergency squeeze-ball, so that the testing can be stopped at any time if you become too uncomfortable or too anxious.

### **Risks associated with TMS procedures:**

The TMS procedure is usually well tolerated. Minor local discomfort, skin irritation and dysesthesia (unpleasant, abnormal sense of touch) may occur. In some cases, participants experience some pain in the lateral facial muscles. In order to avoid this sensation, the researcher will start the stimulation at a low intensity, increasing the intensity in slow steps with constant feedback from you. If at any point pain occurs, the intensity will be scaled back to an acceptable level that does not cause any pain. Additionally, the stimulating coil can be moved to a region on the head that does not induce any pain. During one part of the TMS session, the electrical current applied to your brain will be preceded by a brief electrical current applied to a peripheral nerve at the level of your wrist. Mild wrist pain may be experienced when this current is applied, which becomes rapidly tolerated by the majority of people.

In rare cases, for example in people with craniotomy defects or history of epilepsy, participants have been reported to develop seizures. For this assessment, any participants who might be susceptible to seizures or might have any metal or electronic devices in their body will be excluded. If you have any craniotomy defects, brain electrodes or have a history of epilepsy, you will not be eligible for this study.

As an additional safety measure, any nonmagnetic metal in the body (that has not been mentioned to the investigator before the TMS or the MRI sessions), would be triggered during the initial low intensities TMS stimulations, and would be detected immediately allowing an appropriate response to be taken (either

removal of the non-magnetic device, assessment of the potential danger for you, or canceling the TMS procedure).

**Risks associated with blood sample collection:**

Collection of blood samples by venipuncture from healthy, non-pregnant adults who weigh at least 50 kilograms poses minimal risk. The general risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

**Risks associated with genetic testing:**

Results of genetic testing can identify genetic disorders or risk factors that have implications for your insurability. It is also possible that other clinically relevant incidental genetic findings (not directly relevant to the research study) are discovered. In all situations, minimization of risk is achieved by confidentiality and advance counselling and planning regarding the risk of incidental findings. If you consent to having disclosure of incidental findings, such information will be provided only in the appropriate clinical setting by in-person discussion with the appropriate clinician (e.g. physician and/or genetic counsellor). Information concerning genetic results will be provided only to you, and only if you consent to such disclosure.

Genetic testing may also disclose non-paternity. For purposes of this study we will not disclose such information to participants and will not offer participants the option to receive information regarding paternity via this study. Any risks regarding this issue are mitigated by strict maintenance of privacy.

The privacy, psychological, physical, and legal risks are extremely small and every effort will be made to minimize these risks. At all times your safety will be prioritized and any incidental findings with a direct impact on your health will immediately be brought to the attention of your personal physician for appropriate medical care.

**VIII. WILL I BENEFIT IF I TAKE PART?**

You will not receive a direct health benefit from participating in this study. However, your participation will contribute to our understanding of the mechanisms of body spread and co-existing emotional and behavioral problems of dystonia, and may help future patients with dystonia.

**IX. DO I HAVE TO PARTICIPATE?**

You do not have to participate in this study. Choosing not to participate will not affect your current or future medical care at the University of Calgary.

**X. WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?**

You will receive payment for participating in this study to cover your parking and possible lunch or snack expenses. Payment will be \$90 for participation to three visits and \$60 for participation to two visits. You will not have to pay anything to participate in this research study.

**XI. IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?**

In the event, that you suffer an injury as a result of participating in this research, no compensation will be provided to you by the University of Calgary, Alberta Health Services, or the researchers. You still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

**XII. WILL MY RECORDS BE KEPT PRIVATE?**

We will not put your name, address or any other information that could directly identify you on the clinical, neuroimaging, and electrophysiological information you allow us to collect from you. Only the site research staff will be aware of your identity and will be able to link the information collected during your study visits to you. All information collected for the study will be stored securely on password protected computers and in locked filing cabinets in locked offices.

Because this is a research study, you will not be told the results of any of the tests performed. Should the researchers discover any incidental findings of potential significance to your health, you will be told about the findings. The principal investigator will contact your family doctor who will then follow up with you and give you information on appropriate referrals if necessary.

While we will make every effort to keep information we learn about you private, this cannot be guaranteed. Authorized representatives from the University of Calgary and the Conjoint Health Research Ethics Board may look at your identifiable medical/clinical study records for quality assurance purposes. All information from this research study will be contained in a separate research file at the University of Calgary, Cumming School of Medicine, Department of Clinical Neurosciences, Hotchkiss Brain Institute.

The study physician and/or study coordinator will need to access your personal health records for health information such as past medical history (to look into past surgeries to determine if there are any clips etc.) to ensure your eligibility if you decide to participate in the study.

Results of the research may be presented at meetings or in publications, but your name or any other identifying information will not be used. For the purposes of this study, your data will be identified through the use of a coded number only.

**XIII. VOLUNTARY PARTICIPATION:**

Your participation in this research study is completely voluntary. You are free to not participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would

otherwise expect to receive. In the event that you do withdraw from this research study, you will be asked to choose between these two options: the information you have already provided should not be used in the research and destroyed; the information you have already provided can be stored, used, and disclosed in the manner described in this form.

**XIV. CONTACT PERSONS:**

For more information concerning this research or if you believe that you have suffered a research related injury, please contact:

The Principal Investigator:	Dr. Davide Martino	403-210-8726	davide.martino@ucalgary.ca
The Study Coordinator:	Yamile Jasoui	403-220-4992	yjasauic@ucalgary.ca

**XV. SIGNATURES:**

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate. In no way does this waive your legal rights nor release the investigators, or involved institutions from their legal and professional responsibilities. You are free to withdraw from this study at any time without jeopardizing your health care. Should you have any further questions concerning matters related to this research, please contact the Principal Investigator Dr. Davide Martino or the study coordinator Yamile Jasoui.

If you have any questions concerning your rights as a participant in this research, please contact The Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

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Participant's Signature	Printed Name	Date
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Investigator/Delegate's Signature	Printed Name	Date
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The University of Calgary Conjoint Health Research Ethics Board has approved this research study. A signed copy of this consent form has been given to you to keep for your records and reference.



## Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain.



During a TMS session, an insulated coil is placed over the scalp, over the area to be stimulated. The coil generates brief magnetic pulses, which pass easily and painlessly through the skull and into the brain. These pulses are of the same type and strength as those generated by MRI machines.

TMS allows us to test the basic electrical properties of the brain circuits controlling movements. In this study, we will test how the brain circuits that send out signals to arm/hand muscles (motor output) are influenced by sensory experiences perceived in the same body region (sensory input).

The TMS procedure is usually well tolerated and adverse side effects tend to be mild, short-term, and limited to headaches, scalp pain, or discomfort at the stimulation site.