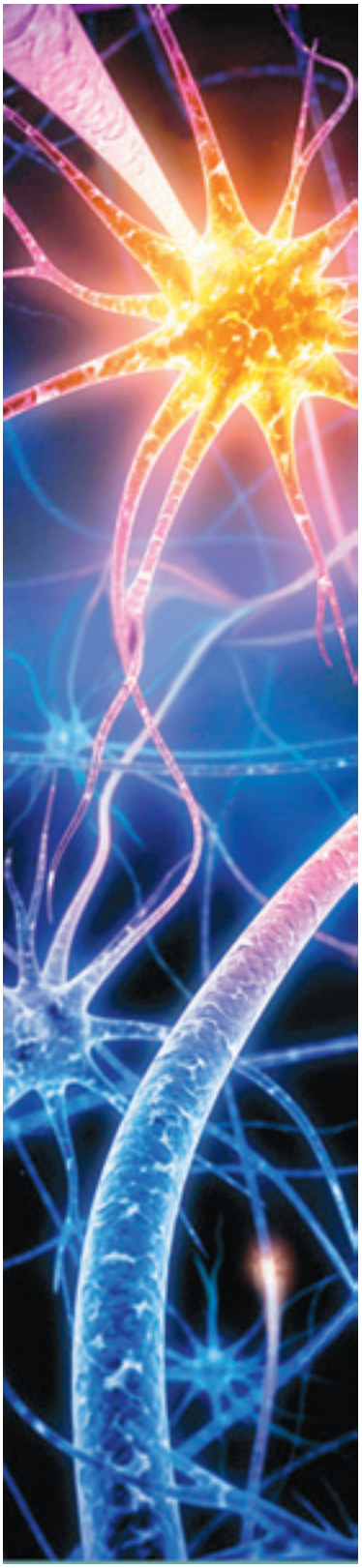

THE NEUROMODULATION UNIT AT THE MUHC.
— DEVELOPMENT PLAN —

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McGill University Health Centre

THE NEUROMODULATION UNIT AT THE MUHC: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

We are proud to announce that the **MUHC** is now offering **Transcranial Magnetic Stimulation** ***(rTMS)*** treatment for our patients. This procedure is an important advancement in the treatment of many neurological and psychiatric conditions, and has been endorsed by **CANMAT**, the ***Canadian Network for Mood and Anxiety Treatments***, as an effective treatment for depression, and other neurological and psychiatric disorders.

rTMS is now an insured treatment offered by **Medicare** ***(RAMQ)***.

There are two avenues for access to it:

1. Clinical research trials in which we are trying to better understand the application of **rTMS** for different illnesses. Patients who fulfill the criteria for entry into a clinical research trial may be recruited into our studies and would have access to treatment at no cost.

2. We are also offering it to patients who suffer from disorders for which **rTMS** is a recognized 2nd and 3rd line treatment. The cost is covered by **RAMQ**.

On behalf of the team that has developed the **MUHC Modulation Unit**, we are confident that, in Quebec, the **MUHC** will take a leadership role in further developing **rTMS** and other neurostimulation treatment options for our patients .

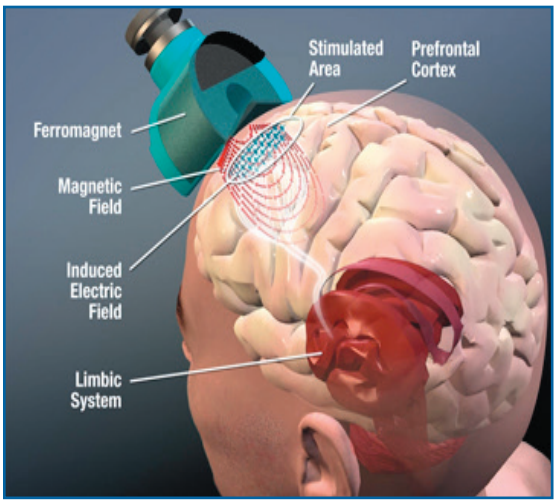
Our Center is located in a beautifully renovated historical building at 835 Pine Avenue W.

Sincerely,

Nadia Szkrumelak,
Psychiatrist-in-Chief
Associate Professor of Psychiatry
McGill University

Alain Ptito, PhD
Director, Department of Psychology
Professor, Neurology/Neurosurgery
McGill University

What is Neuromodulation?



Neuromodulation involves the delivery of a physical intervention using a magnetic field ***(repetitive transcranial stimulation; rTMS)*** either to generalized brain regions or to selected cerebral areas. **rTMS** received the **Food and Drug Administration's** ***(FDA)*** approval in 2008. **rTMS** relies on electromagnetic induction to generate a superficial current to specific cerebral brain regions, particularly the dorsolateral prefrontal cortex ***(DLPFC)***. The stimulation may be of high or low intensity and no adverse effects on cognition have been reported, especially when used in the treatment of major depressive disorder ***(MDD)***.

During the past decade, a large amount of work on **rTMS** has been performed, including the development of new paradigms of stimulation and the coupling of **rTMS** techniques with electroencephalography and/or neuroimaging. Recently, a group of French experts conducted a comprehensive review of the literature on **TMS** and reported a therapeutic indication of **rTMS** for the treatment of chronic neuropathic pain, major depressive episodes, and auditory hallucinations. The number of therapeutic indications of **rTMS** is expected to increase in coming years, in parallel with the optimisation of stimulation parameters. **rTMS** has also been endorsed by **CANMAT**, the **Canadian Network for Mood and Anxiety Treatments**, as an effective treatment for depression and other neurological and psychiatric disorders.

In addition to studies utilizing low and high frequency stimulation, a newly developed **theta-burst stimulation** ***(TBS)*** protocol, also known as 'patterned **TMS'** has been developed. This technique has shown promise for the treatment of conditions such as epilepsy, depression and **Parkinson's disease** ***(Paulus, 2005)***. **TBS** usually involves short bursts of 50 Hz **rTMS** applied at a rate of 5Hz ***(hence the name theta burst stimulation)*** and it can be applied as either a continuous ***(cTBS)***, or intermittent ***(iTBS)*** train of stimulation.

Reference:

Recommandations françaises sur l'utilisation de la stimulation magnétique transcrânienne répétitive (rTMS) : Règles de sécurité et indications thérapeutiques. *— J.-P. Lefaucheur, N. André-Obadia, E. Poulet, H. Devanne — Travail de consensus réalisé sous l'égide de la* ***Société de neurophysiologie clinique de langue française****, de l'****Association française de psychiatrie biologique et neuropsychopharmacologique****, de la* ***Société française de neurologie****, de la* ***Société française d'ORL*** *et de la* ***Ligue française contre l'épilepsie****. © 2011 Elsevier Masson SAS. [****French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications****].*

History Of the Unit for 2012 & 2013

The Neuromodulation unit started operation in January 2012.The project has been initiated by **Dr Alain Ptito**, **Dr Warren Steiner**, **Dr Theo Kolivakis** supported by **Marcel Mazaltarim** and **Philippe Mazaltarim** as operational staff. It was established thanks to the generous support for the infrastructure of the **Allan Fainman Morris & Bella Fainman Foundation** *(2010)*. It required complete renovation of the **Gate house**, including the landscaping, fiber optics, furniture and treatment equipment (2010 &2011).

Marcel and **Philippe Mazaltarim** also generously donated countless hours of work to the development of the Unit.

The first patients treated were within a research protocol involving two groups:
Unipolar depression patients resistant to a least 2 pharmacological treatments and a second group comprised of patients **that had suffered a mild traumatic brain injury *(mTBI)*** resulting in **long term post-concussive symptoms *(PCS)***, including depression.

In the latter group, functional magnetic resonance imaging studies, supported by a grant from **CIHR** to **Drs Ptito**, **Kolivakis** and **Koski**, revealed a lack of activation in **DLPFC**, suggesting that transcranial magnetic stimulation of this region may lead to an improvement of **PCS**. Since the positive outcome of **rTMS** in **unipolar depression** is well documented, this group was chosen as controls.

So far, 38 patients have been tested at the Unit within the context of this study and we expect to recruit another 20.

Preliminary data have shown very encouraging results suggesting potential benefits from **rTMS** treatment for the **mTBI** population. The neuromodulation unit has also treated six patients on a pay for service basis. More than a thousand sessions have been delivered with no negative issues. Labour costs were covered by research funds (technicians and administrator) and revenues from paying patients. One piece of equipment purchased with donor funds is in place and another is in the process of being purchased.

Following the announcement of coverage by RAMQ, the demand for rTMS treatment has increased significantly as its cost was a dissuading factor for many patients. Physicians were also reticent to refer their patients because of the cost, but this is no longer the case. After a month of operation post RAMQ support for patient treatment, the unit is at its full capacity *(12 to 14 patients per day)*.

A typical treatment of rTMS consists of between 20 to 30 daily 30-minute sessions *(i.e. five times per week excluding week-ends)*. The complete course runs between 4 to 6 weeks. Maintenance sessions may be suggested by the treating psychiatrist, if deemed necessary.

THE TEAM

Theodore Kolivakis, MD, CM, FRCPC,

- Co-Director Neuromodulation Unit, McGill University Health Centre, Allan Memorial Institute
- Assistant Professor, McGill University
- Staff Psychiatrist, Royal Victoria Hospital and Montreal Neurological Institute.

Alain Ptito, PhD,

- Co-Director Neuromodulation Unit
- Director, Department of Psychology, McGill University Health Center
- Professor, Neurology/Neurosurgery, McGill University
- Neuropsychologist, Montreal Neurological Institute

Michaela Barbarosie, MD,Ph.D

- Co-Director Neuromodulation Unit, McGill University Health Centre, Allan Memorial Institute
- Staff Psychiatrist, Royal Victoria Hospital and Montreal General Hospital

Pablo Cervantes, MD, CM, FRCPC

- Clinical Director and Staff Psychiatrist, Mood Disorders Clinic, McGill University Health Centre
- Assistant Professor, McGill University

Lisa Koski, Ph.D.

- Clinical Psychologist & Medical Scientist, McGill University Health Centre
- Assistant Professor, McGill University

Marcel Mazaltarim, M.Sc

- Service Coordinator

Philippe Mazaltarim

- Neuromodulation Technician

OBJECTIVES

Our Goal is to build a world renowned Neuromodulation Unit. Other well recognized units exist elsewhere. They are:

- The **Berenson-Allen Center** for Noninvasive Brain Stimulation at **Harvard**
- The **Temerty Centre for Therapeutic Brain Intervention** in **Toronto**
- **UHN rTMS Clinic University Health Network Repetitive Transcranial Magnetic Stimulation Clinic** at **Toronto Western Hospital**

WE AIM TO FOCUS ON 3 MAIN AREAS:

1. CLINICAL ACTIVITIES

Neuromodulation has several clinical indications well documented in the scientific literature:

DEPRESSION :

Major depression is a common disorder with millions of sufferers around the world and a lifetime prevalence of about 13% in men and 21% in women ***(Blazer, Kessler, McGonagle & Swartz, 1994))***. The **World Health Organization** has predicted that depression will become the second largest burden of disease by 2020, following cardiovascular conditions ***(Murray & Lopez, 1997)***.

At the **Neuromodulation Unit** of the **MUHC**, we are accepting patients with unipolar depression having failed one trial antidepressant medication, or experiencing side effects/not tolerating/refusing the use of antidepressants. Treatment includes: 20 to 30 daily rTMS sessions (excluding week-ends) delivered in approximately 30 minutes. Exclusion criteria include: Psychosis, Bipolar Affective Disorder, Anxiety Disorder as primary diagnosis, Substance use Disorders, history of Seizures or Epilepsy. We also discourage the use of benzodiazepines for the duration of the treatment.

SHIZOPHRENIA :

Patients with auditory hallucinations and negative symptoms will be treated in the near future.

2. RESEARCH ACTIVITIES

The MUHC has a long history of world-leading research and treatment in the field of brain stimulation for neurological and psychiatric disorders.

TRAUMATIC BRAIN INJURY *(TBI)*

Primary investigators: Dr Alain Ptito, Dr Theo Kolivakis and **Dr Lisa Koski**

Traumatic brain injury *(TBI)* is a major public health concern because it can result in long-lasting impairment of physical, cognitive, and psychosocial functioning. Its prevalence is **over 1 million cases per year** in **North America**, the highest incidence being among young people *(15–24 years)* entering their most productive years.

Compared to the rate of other common neurological disorders *(e.g. **Parkinson's disease**: 20/100,000; **multiple sclerosis**: 3/100,000)*, **the incidence rate of close to 600/100,000 individuals is of epidemic proportion.**

Prompt treatment of **TBI** and early detection of problems can reduce morbidity. Most studies agree that of all the **TBI** cases, 80% to 90% fall within the category of **mild TBI** *(mTBI)*. This is the reason our interventions focus on this group. While some patients with **mTBI** recover within days, many display persistent **post-concussive symptoms** *(PCS)* including depressed mood and problems with attention and concentration that may suggest brain damage, despite the absence of findings on routine clinical imaging *(i.e. CT scan or MRI)*. The cognitive, emotional, behavioural and physical impairments experienced by **MTBI** survivors produce substantial disability and costs.

Currently there are few standards for treatment and management of **MTBI** and limited studies concerning treatment interventions exist. These consist of pharmacotherapy, cognitive rehabilitation and patient education. We are currently investigating whether **rTMS** has the potential to accelerate symptom resolution *(including depression)* and facilitate return to normal instrumental activities of daily living. During **rTMS**

sessions, we will target the **left DLPFC**, one of the cortical regions where we have observed with functional neuroimaging a significant reduction in brain activation after **mTBI**.

rTMS is known to produce localized changes in cortical activity through an increase in local prefrontal cortical excitability. In addition, recent evidence has shown that **rTMS** can modulate distal brain regions and potentially strengthen connections between brain regions.
Our preliminary results show very positive effects on patients.

This project is funded by the Canadian Institute of Health Research.

rTMS FOR BIPOLAR DISORDER

Primary investigators: Dr Pablo Cervantes and **Theo Kolivakis**
There is some scientific evidence that supports the use of **rTMS** for the treatment of bipolar depression as complementary treatment to mood stabilizers. The treatment consists of a magnetic coil used to stimulate a specific area of the brain, which is believed to result in improvement of depression symptoms.
No anesthesia is required for this procedure.

*"The three arms involved in the proposed study will be administering mood stabilizers(**epival a/o Lithium**) with or without **Novel Antipsycotics**.*
*Two of these tracks will be exposed to **repetitive Transcranial Magnetic Stimulation** (rTMS) while the latter will be exposed to **Wellbutrin** only. Only one of the two arms exposed to **rTMS** will also be exposed to **Wellbutrin**, while the latter will be exposed to **placebo**. This will not only allow us to assess the efficacy of **rTMS** in the management of patients with bipolar disorder in the depressive phase in contrast to **Wellbutrin**, but it will also enable us to determine the possibility of a **manic/hypomanic** switch in those treated with **Wellbutrin** versus **rTMS**, thus allowing us to appraise the overall value of **Wellbutrin** adjacent to **rTMS**.*

*This will certainly grant us the ability to fully assess and comprehend the true adequacy of **rTMS** as an adjunctive treatment to mood stabilizers with or without **Wellbutrin** in the treatment of bipolar depression, a topic to which the literature has failed to provide a diligent discernment"*

rTMS FOR MULTIPLE SCLEROSIS

Primary investigator: Dr Lisa Kosky
Neural excitability in multiple sclerosis – The goal of this study is to measure differences between the brains of healthy individuals and the brains of patients with **multiple sclerosis** *(MS)* to better understand the effects of brain lesions. The project involves studying neural compensation in people living with **MS** by using **rTMS** in order to measure differences in cortical silent period and cortical inhibition between **MS** patients and healthy individual.

This project is funded by the Canadian Institute of Health Research.

OTHER AREAS OF INTEREST FOR FUTURE STUDIES

PREGNANCY AND POST PARTUM DEPRESSION AND WOMEN'S MENTAL HEALTH

Perinatal depression occurs in about 13% of the general population.
This rate approaches 25% or higher in women with a history of mood disorder. Risks for both the mother and child of untreated depression during pregnancy include low birth weight, preterm birth. In addition, mothers who are depressed during pregnancy are more likely to adopt unhealthy habits (smoking, alcohol, drug use for example).
The benefits of using **rTMS** to treat major depression during pregnancy involve a minimal side effect profile, good tolerability while avoiding fetal exposure to medication side effects and toxicity. A similar argument is made for women during the postpartum period who are concerned about exposing their newborn infant to medication side effects through breastfeeding.
The **MUHC Neuromodulation Unit** is working toward improving women's mental health while alleviating concerns regarding medication side effects and improving access to psychiatric treatment.

REDUCING SYMPTOMS OF STROKE USING NON-INVASIVE NEUROMODULATION

Depression has a significant impact on poststroke recovery and mortality. There are a proportion of patients with poststroke depression (PSD) who do not respond to antidepressants. rTMS may be a safe and effective alternative in these refractory cases. Early-performed rTMS may become a valuable prognostic tool for motor recovery from stroke and may preserve motor evoked potentials (MEP) amplitude shortly after stroke as a better prognostic factor than normal central motor conduction time.

Dr. Theodore Kolivakis & Phillipe Mazaltarim
Applying rTMS in this CTV Video

THE EFFECT OF NEUROMODULATION ON AUTISM SPECTRUM

Autism is a developmental disorder characterized by abnormalities in speech and communication, impaired social functioning, and repetitive behaviors and interests. The term "**Autism spectrum disorders**" or **ASD** is often used to include autistic disorder, **Asperger syndrome** and **pervasive developmental disorder-not otherwise specified** *(PDD-NOS)*.

Epidemiological research suggests that **ASDs** affect at least 60 per 10,000 youth, with estimates as high as 120 per 10,000. The pathophysiology of autism has been studied extensively in the last decade. Abnormal neuronal connectivity has been implicated in a growing body of research. In addition, areas of over and/or under neuronal activation have been detected on functional **MRI** *(Magnetic Resonance Imaging)*. **rTMS** has been used in individuals with high functioning autism and found to help reduce repetitive behaviors and improve social functioning.

REDUCING SYMPTOMS OF PARKINSON USING NON-INVASIVE NEUROMODULATION

rTMS can be used to modify activity of targeted cortical areas. In patients with **Parkinson's disease** *(PD)* encouraging effects resulting from plastic changes in motor cortical networks have been obtained by stimulating different cortical regions with **rTMS** at inhibitory *(low)* or excitatory *(high)* frequency. Stimulation of the motor cortex could impact regions within the cortico-basal ganglio-thalamo-cortical loops that are involved in motor control, providing alleviation of Parkinsonian symptoms. The stimulation may also improve motor performance or other symptoms associated with **PD**, like **depression**.

3. TEACHING ACTIVITIES

- **Train residents, interns and students to become future rTMS clinicians**
- **Organise conferences on Neuromodulation**

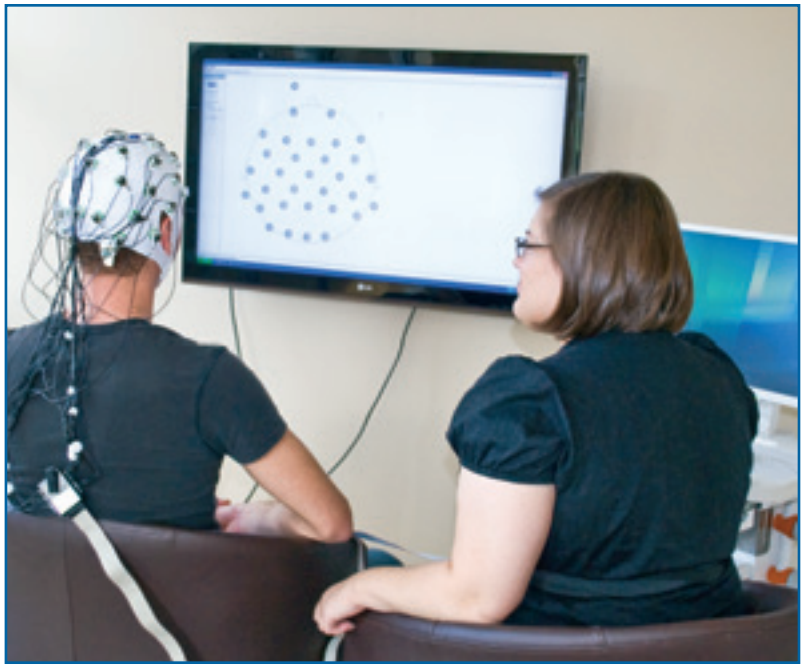
FUTURE DEVELOPMENTS & FINANCIAL NEEDS

Our goal is to develop further the technological aspect of the Unit and to expand new clinical treatment protocols with support from research protocols.

The other modalities of neurostimulation we wish to include at present are:

• QEEG GUIDED NEUROMODULATION:

Electroencephalography *(EEG)* is a well-known and widely used technique for the visualization of the brain's electrical activity. It has been suggested that power spectrum analysis *(?)* may be used as a tool for assessing the effects of a specific stimulation protocol as well as for evaluating the physiological outcome of the stimulation.



Recently, *Daskalakis et al. (2008)* were the first to report the potential predictive value of an **EEG biomarker** initially developed for prediction of treatment response to antidepressant medication. This biomarker *(labeled antidepressant treatment response (ATR) index)* is measured from frontal electrode positions and is based on the proportion of relative and absolute **Theta power**.

Within this context, **rTMS** can be administered: *(1)* when synchronized to a patient's individual alpha frequency *(IAF)*, or **synchronized rTMS** *(sTMS)*; *(2)* as a low magnetic field strength sinusoidal waveform; and, *(3)* broadly to multiple brain areas simultaneously. These modifications and combinations could enhance the therapeutic effectiveness of **rTMS** for the treatment of **MDD**.

• **NEURONAVIGATION ASSISTED RTMS:**

In traditional **TMS** studies, the coil is positioned over the head using external landmarks and measurements or by trial and error until the desired response *(finger twitch)* is generated.

In recent years, navigated **TMS** or **NeuroNavigation** has become possible allowing the **TMS** coil to be positioned over a specified target location based upon an individuals **MRI** image or **MRI generated 3D curvilinear reconstruction of the brain**.

Targets for stimulation can then be identified in numerous ways: manually by selecting and highlighting the desired structure / locations within the brain, or by combining anatomical **MRI** images with areas of activity highlighted with **fMRI**, **EEG** or near infra-red spectroscopy *(NIRS)*.

Navigated TMS allows precise targeting

• **TDCS (TRANSCRANIAL DIRECT CURRENT STIMULATION):**

Transcranial direct current stimulation *(tDCS)* involves applying weak electrical currents to the head in order to generate an electromagnetic field which modulates the activity of brain neurons. **tDCS** is known to selectively modulate neuronal excitability and can be used in conjunction with **fMRI**, **transcranial magnetic stimulation** *(TMS)* or centrally acting drugs. It is being investigated as a treatment for a variety of conditions such as stroke recovery, depression and migraine.

• Complex neurorehabilitation of subjects after brain damage *(including polytrauma, TBI, stroke, concussions)*.

• **DEEP TMS:**

Standard TMS coils are limited to activation of only cortical brain regions, up to a depth of about 1.5 cm. Hence when treating depression with a standard **TMS** system, the limbic system, which is related to mood regulation and is generally deeper than 1.5 cm, is only indirectly affected, through secondary processes involving cortical structures, which are directly activated by **TMS** and then affect the deeper limbic system structures.

Deep **TMS** uses a unique, patented coil design to produce directed electromagnetic fields that can induce excitation or inhibition of neurons deep inside the brain.

DEEP TMS: The H coil developed by Israel-based **Brainsway Ltd**

SOURCES FOR FINANCING:

- **MUHC**
- **MUHC Department of Psychiatry Practice Plan**
- **Private donors** and **foundations** through the **MGH**, **Montreal Neurological Institute** and **RVH foundations**
- Funding from **Government agencies**
- Potential revenues from **private affiliated clinics** at the **QEHC**
- Pay for service patients from out of the country

TESTIMONIALS

“ Thank you for allowing me to be a part of your research. You are a great team and it was nice to see you everyday for this last month ”

— Jimmy —

“ Thanks to the TMS treatment I received at the MUHC Neuromodulation Unit I am a new person or, at least back to the way I was before I encountered the 18 months of falling/depression which is, in my opinion, a very happy person. ”

— Monroe —

“ Thank you for all your help in improving my brain’s functioning feel much better. ”

— Lisa —

“ In just a short 4 weeks, the improvement for me was noticeable. With the treatment for both depression and then anxiety, I gained back my quality of life. I no longer experience “brain-fog”. I can think clearly and sharply. The confidence and strength have returned to start projects and even complete them! The energy level has risen and yes, probably the most significant: I can finally fall asleep without Ativan. Thank you to the staff and Doctors for the care and patience and even the laughter. ”

— Anonymous —

“ Yes it is a miracle for me. I experienced a complete transformation from night to day. I am happy now. If rTMS had not work, it was my last alternative. I was going to commit suicide with an arm in a hotel. ”

— Anonymous —

CONTACT US

Should you require further information about rTMS, please contact us:

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