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# rTMS, antidepressant effect and synaptic plasticity in rodents

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Depressive disorders have been with man since the beginning of recorded history. In the Bible, King David, as well as Job, suffered from this affliction. Hippocrates referred to depression as melancholia, which literally means black bile. Black bile, along with blood, phlegm, and yellow bile were the four humors (fluids) that accounted for the basic medical physiology of that time. Depression has been portrayed in literature and the arts for hundreds of years, but what do we mean today when we refer to a depressive disorder? In the 19th century, depression was seen as an inherited weakness of temperament. In the first half of the 20th century, Freud linked the development of depression to guilt and conflict. John Cheever, the author and a modern sufferer of depressive disorder, wrote of conflict and experiences with his parents as influencing his development of depression. In the 1950s and 60s, depression was divided into two types, endogenous and neurotic. Endogenous means that the depression comes from within the body, perhaps of genetic origin, or comes out of nowhere. Neurotic or reactive depression has a clear environmental precipitating factor, such as the death of a spouse, or other significant loss, such as the loss of a job. In the 1970s and 80s, the focus of attention shifted from the cause of depression to its effects on the afflicted people. Currently, researchers are focusing their effort in understanding the biological causes of this condition in order to develop new treatments.

Depressive disorders are a huge public health problem. Depression costs the United States huge amounts of direct costs, which are the treatment costs, and

indirect costs, such as lost productivity and absenteeism. In a major medical study, depression caused significant problems in the functioning of those affected more often than did arthritis, hypertension, chronic lung disease, and diabetes, and in two categories of problems, as often as coronary artery disease. Depression can increase the risks for developing coronary artery disease, HIV, asthma, and some other medical illnesses. Furthermore, it can increase the morbidity (illness) and mortality (death) from these conditions. Depression is usually first identified in a primary-care setting, not in a mental health practitioner's office. Moreover, it often assumes various disguises, which causes depression to be frequently under-diagnosed. In spite of clear research evidence and clinical guidelines regarding therapy, depression is often under-treated. Hopefully, this situation can change for the better. For full recovery from a mood disorder, regardless of whether there is a precipitating factor or it seems to come out of the blue, treatments with medications and/or brain stimulation therapy and psychotherapy are necessary.

**What are the causes of depression?**

Some types of depression run in families, indicating that a biological vulnerability to depression can be inherited. This seems to be the case especially with bipolar disorder. Studies have been done of families in which members of each generation develop bipolar disorder. The investigators found that those with the illness have a somewhat different genetic makeup than those who do not

become ill. Apparently, additional factors, possibly a stressful environment, are involved in its onset.

An external event often seems to initiate an episode of depression. Thus, a serious loss, chronic illness, difficult relationship, financial problem, or any unwelcome change in life patterns can trigger a depressive episode. Very often, a combination of genetic, psychological, and environmental factors is involved in the onset of a depressive disorder.

Nothing in the universe is as complex and fascinating as the human brain. The over 100 chemicals that circulate in the brain are known as neurochemicals or neurotransmitters. Much of our research and knowledge, however, has focused on four of these neurochemical systems: norepinephrine, serotonin, dopamine, and acetylcholine. After new discoveries are made, it is possible that these four neurochemicals will be viewed as the "black bile, yellow bile, phlegm, and blood" of the 20th century.

Different neuropsychiatric illnesses seem to be associated with an overabundance or a lack of some of these neurochemicals in certain parts of the brain. The depressive disorders appear to be associated with altered brain serotonin and norepinephrine systems. Both of these neurochemicals are lower in depressed people. Please note that I specified, "associated with" instead of, "caused by." I made this distinction because we really don't know whether low levels of neurochemicals in the brain cause depression or whether depression causes low levels of neurochemicals in the brain.

What we do know is certain medications that alter the levels of norepinephrine or serotonin can alleviate the symptoms of depression. Some medicines that affect both of these neurochemical systems appear to perform even better or faster. Other medications that treat depression primarily affect the other neurochemical systems. The most powerful treatment for depression, electroconvulsive therapy (ECT), is certainly not specific to any particular neurotransmitter system. Rather, ECT, by causing a seizure, produces a generalized brain activity that probably releases massive amounts of all of the neurochemicals.

## Antidepressant Medications

**Selective serotonin reuptake inhibitors (SSRIs)** are medications that increase the amount of the neurochemical serotonin in the brain. (Remember that brain serotonin levels are low in depression.) As their name implies, the SSRIs work by selectively inhibiting (blocking) serotonin reuptake in the brain. This block occurs at the synapse, the place where brain cells (neurons) are connected to each other. Serotonin is one of the chemicals in the brain that carries messages across these connections (synapses) from one neuron to another. The SSRIs work by keeping the serotonin present in high concentrations in the synapses. These drugs do this by preventing the reuptake of serotonin back into the sending nerve cell. The reuptake of serotonin is responsible for turning off the production of new serotonin. Therefore, the serotonin message

keeps on coming through. This, in turn, helps arouse (activate) cells that have been deactivated by depression, and relieves the depressed person's symptoms. The most common side effects are nausea, diarrhea, agitation, insomnia, and headache. However, these side effects generally go away within the first month of SSRI use. Some patients experience sexual side effects, such as decreased sexual desire (decreased libido), delayed orgasm, or an inability to have an orgasm. Some patients experience tremors with SSRIs. The so-called serotonergic (meaning caused by serotonin) syndrome is a serious neurologic condition associated with the use of SSRIs. It is characterized by high fevers, seizures, and heart rhythm disturbances. This condition is very rare and has been reported only in very ill psychiatric patients taking multiple psychiatric medications.

**Tricyclic antidepressants (TCAs)** were developed in the 1950s and 60s to treat depression. They are called tricyclic antidepressants because their chemical structures consist of three chemical rings. TCAs work mainly by increasing the level of norepinephrine in the brain synapses, although they also may affect serotonin levels. Doctors often use TCAs to treat moderate to severe depression. TCAs are safe and generally well tolerated when properly prescribed and administered. However, TCAs can cause life-threatening heart rhythm disturbances. Thus, some TCAs can produce dry mouth, constipation, and dizziness upon standing. The dizziness results from low blood pressure that occurs upon standing (orthostatic hypotension). Anticholinergic side effects can

also aggravate narrow angle glaucoma, urinary obstruction due to benign prostate hypertrophy, and cause delirium in the elderly.

### Electroconvulsive therapy (ECT)

In the ECT procedure, an electric current is passed through the brain to produce controlled convulsions (seizures). ECT is useful for certain patients, particularly for those who cannot take or are not responding to antidepressants, have severe depression, or are at a high risk for suicide. ECT often is effective in cases where antidepressant medications do not provide sufficient relief of symptoms. This procedure probably works, as previously mentioned, by a massive neurochemical release in the brain due to the controlled seizure. Highly effective, ECT relieves depression within one to two weeks after beginning treatments. After ECT, some patients will continue to have maintenance ECT, while others will return to antidepressant medications.

In recent years, the technique of ECT has been much improved. The treatment is given in the hospital under anesthesia so that people receiving ECT do not feel pain. Most patients undergo six to 10 treatments. An electrical current is passed through the brain to cause a controlled seizure, which typically lasts for 20 to 90 seconds. The patient is awake in five to 10 minutes. The most common side effect is short-term memory loss, which resolves quickly. After the initial course of treatment, ECT can be safely done as an outpatient procedure.

## A new potential

One very promising avenue for influencing the living brain has emerged in the last decade, based on the use of pulsed magnetic fields. The skull is a good insulator, and past efforts to alter the electrical activity happening inside it have required high voltages, with little opportunity for fine control or focus of the effects. Consider instead how easily a magnet under a wooden tabletop can move a pin on the surface - magnetic fields pass almost unaffected through insulators, including the skull.

It is easy in principle to get a magnetic field to produce electrical effects: simply change the field over time, and any charge-carriers (like the ions in the cells of the brain) will be influenced to flow, creating an induced current. However, affecting neurons inside the head requires a lot of magnetic force to be changed very quickly, and the technology to do this has only been around for about a decade. The first *trans-cranial magnetic stimulation* (TMS) machines, capable of delivering a pulse every three seconds, were developed as diagnostic aids for neurologists. For instance, the motor part of the brain can be stimulated, inducing a twitch of the thumb, which tells a neurologist that the intervening nerve pathways are intact. Machines are now available which can give up to 100 stimuli per second (rapid-rate TMS, or rTMS) and their effects are more interesting. Among a wide range of possibilities, it is believed that rTMS may have a place in the treatment of some mental illnesses. It is a non-invasive technique, apparently

free of serious side-effects, capable of modifying the activity of specific brain areas.

**How it works**

The magnetic fields used in TMS are produced by passing current through a hand-held coil, whose shape determines the properties and size of the field. The coil is driven by a machine which switches the large current necessary in a very precise and controlled way, at rates up to 50 cycles per second in rTMS. The coil is held on the scalp - no actual contact is necessary - and the magnetic field passes through the skull and into the brain. Small induced currents can then make brain areas below the coil more or less active, depending on the settings used.

In practice, TMS and rTMS are able to influence many brain functions, including movement, visual perception, memory, reaction time, speech and mood. The effects produced are genuine but temporary, lasting only a short time after actual stimulation has stopped.

**Safety issues**

Generally, TMS appears to be free from harmful effects. Research using animals and human volunteers has showed little effect on the body in general as a result of stimulation, and examination of brain tissue submitted to thousands of TMS pulses has shown no detectable structural changes. It is possible in unusual circumstances to trigger a seizure in normal patients, but a set of guidelines

which virtually eliminate this risk are available. Research continues, but TMS is certainly free of obvious side-effects like those of electro-convulsive therapy (ECT), which still makes quite an impact on patients despite refinements in technique.

**TMS / rTMS in the treatment of mental illness**

Many mental illnesses can be demonstrated to stem from the abnormal behaviour of particular brain regions. It is believed that some mental disorders are the result of nerve cells being over- or under-excitable (in other words, it is too easy or too difficult for them to "fire" and work properly). In this context, successful psychiatric treatment is achieved by modifying these cells behaviour. The range of effects produced by TMS are a clear indication of its potential to work in this way.

Of course, TMS could only be used to treat diseases whose functional causes are understood. Recent progress in understanding the mechanisms behind depression, obsessive-compulsive disorder, and neurological diseases like Parkinson's and Huntington's, offers some hope in these areas. It must be stressed that most of the excitement about TMS is based on potential rather than proven effectiveness, but research is being conducted around the world. For instance, there is reason to believe that rTMS could replace some ECT treatments currently used for severely depressed patients. Groups in Germany, the United States and Israel have reported positive results from using TMS and rTMS to treat depressed patients. The prospect of replacing ECT with a near-

painless treatment, which does not require anaesthesia, would change these people's lives remarkably.

## Ever-happy Mice

To investigate the mechanisms of action of rTMS we gave TMS to mice for five days, then we analysed their brains for evidence of plasticity and cell proliferation. We showed that rTMS enhanced Long term potentiation (LTP), a leading molecular model of plasticity in all areas of the brain tested, by modifying key glutamate receptors so that they stayed active for longer. We saw large increases in the proliferation of stem cells in the dentate gyrus hippocampus. These cells divide throughout life and are now believed to play a crucial role in memory and mood regulation.

Thus, is our study we highlighted the mechanism of action of rTMS.

Our results will help researchers to design more effective brain stimulation treatments for drug-resistant refractory depression.