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## CHANGING THE PICTURE IN DEPRESSION: TRANSCRANIAL MAGNETIC STIMULATION (TMS) THERAPY

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In the past two decades, we have seen amazing pictures tying various clinical syndromes to certain operational patterns in the brain's networks. Alas, we had no tools to improve these pictures directly by making a particular circuitry more or less active without tampering with other subsystems of the brain. That is, we could not photoshop these pictures in order to selectively correct specific patterns of dysfunction in the substrates of mood, cognition and behavior. But at last, and almost unbelievably, I have found myself doing just that: Correcting the picture in depression in a targeted way using an effective and fine-enough brush. My brush is the Transcranial Magnetic Stimulation (TMS) device and the bristles of the brush are provided in the form of rhythmically pulsed, MRI-strength magnetic fields. The paint is the minute electrical currents induced in and around cortical neurons, just enough to alter their firing patterns and underlying biology, without involving run-away electrical currents that seize the whole brain.

This historical development is coinciding with a relative saturation in other treatment paradigms. For example, the pharmaceutical industry has been struggling lately to find truly novel drugs. The low-hanging fruit, it turns out, is long gone. Moreover, any differences in efficacy between alternative treatments have remained minor. For example, older and newer types of antidepressants, antipsychotics, anxiolytics, antiepileptics, and mood-stabilizers are, on the whole, equipotent. Surely, there is still more room for refinements within psychopharmacology. For example, now the focus is mostly on finding allosteric modulators of target biomolecules, rather than head-on inhibitors or stimulators (agonists). The hope is to have more nuanced effects, perhaps reducing the side effect problem. However, this approach is yet to be translated to clinical use (with the exception of benzodiazepines), and nobody is suggesting that the problem of adverse effects will be fully overcome with this approach. Pharmacotherapy paradigm bears inherent constraints, insurmountable for as long as we are inside this treatment box, limiting its efficacy and tolerability. One of these limitations stems from our long and messy evolutionary history. The human body has evolved to use a relatively limited set of biochemical molecules for numerous purposes in multiple tissues. As we attempt to manipulate one of these molecules some where in the body for a specific clinical purpose, we also end up affecting other processes that we rather would not meddle with. Psychopharmacological treatment is *spatially non-selective*. Any drug that crosses the blood brain barrier has already reached all other organs and tissues, and it will roam everywhere in the brain, not just specific cerebral subsystems we would like to target. For example, serotonin is an ancient intercellular communicator used by all animals, plants and fungi for a myriad of purposes. As central nervous systems developed, serotonin also acquired behavioral functions. However, most of what it does have nothing to do with mood or behavior. More than 80% of serotonin in the human body is made in the gut and some of this is ferried by platelets to other target tissues to be taken up by the serotonin transporter (yes, the same one interfered with by SSRIs) into various types of cells, such as osteoblasts and osteocytes in the bone. Too high intercellular concentrations of serotonin outside the bone cells (e.g., due to lurking SSRI molecules) preferentially

stimulate osteoclasts, which degrade bone. Thus, patients on SSRIs and SNRIs are at increased risk for fractures, and women have double the incidence of osteoporosis. Serotonin is involved in numerous processes, including platelet aggregation, GI motility, liver repair, reproduction, endothelial function, fibrocyte stimulation (especially in the pulmonary vasculature, heart valves and the retroperitoneum), plus fetal and childhood CNS development. SRIs that perturb these processes are capable of causing clinically significant adverse outcomes. At least as importantly, serotonin-modulated processes are involved in a diverse array of brain subsystems and networks subserving numerous, and sometimes antithetical, functions. It is not possible to pick and choose the ones we want to affect among these subsystems as long as the tool is a diffusing chemical. No matter how selective a drug is for its molecular targets, as long as those targets are widely distributed in the brain and the body, it is unavoidable that all of those targets will be affected. This not only leads to untoward effects but also constrains efficacy. For example, SSRIs interact with serotonin transporters in therapeutically untargeted parts of the brain leading to phenomena like reduced drive and enthusiasm, and emotional detachment or apathy, particularly in a subset of patients. In fact, such inadvertent psychological effects may be common, at least in lesser degrees. As these iatrogenic aberrations are counter-therapeutic, the bottom-line efficacy of SSRIs and SNRIs suffers.

Thus, TMS, as a spatially-selective biomedical treatment alternative, represents a significant advancement. None of our previous therapies could fulfill this role. ECT, for example, is diffuse (spatially non-selective) in the brain. In contrast, TMS does not seize the whole brain, sparing subsystems or circuitry that are not relevant to depression, and thus avoiding neurobehavioral toxicities, such as memory loss.

Over the last few decades, various types of studies documented a common pattern in depression involving two types of asymmetries: (1) Between hypoactive dorsolateral prefrontal (DLPF) cortex and hyperactive paralimbic and limbic regions; and (2) between right versus left DLPF cortex (right being relatively more functionally active in depression compared to the left.) TMS can increase or decrease neuronal firing patterns, depending on the stimulation parameters, principally the pulse frequency. High frequencies (3-20 Hz) lead to increased activity in the cortical neurons beneath the treatment coil (through a depolarizing influence), whereas low frequencies (1 Hz or less) lead to the opposite. It is therefore possible to alter functioning patterns of a selected neural network in different ways. Brain imaging reveals that these effects right under the treatment coil are selectively carried over to certain other regions of the brain *trans-synaptically following relevant anatomical and functional circuitry*, not in an indiscriminate and diffuse way. In this way, as I apply TMS to a patient's DLPF cortex, I am not only aiming for a direct functional enhancement there, but also for a trans-synaptically mediated amelioration of overactivity in deeper regions, thus correcting the principle functional asymmetry in the neurobiology of depression. TMS achieves this feat in a top-down fashion and completely noninvasively, as opposed to deep brain stimulation via surgically implanted electrodes which electrically suppress this overactivity in deeper regions. As a plus, TMS is also capable of improving the right over left DLPF cortex bias in depressed affective states by using high frequency TMS to the left DLPF cortex (as in the currently FDA-approved version) or low frequency TMS to the right DLPF cortex.

Using isolated magnetic pulses, we can use TMS to induce either positive or negative neuropsychological phenomena, and this capability has been harvested by researchers, neurologists and neurosurgeons for brain mapping purposes. For example, we can make a person perceive either “phosphenes” (slowly flashing lights) or scotomas in a specific sector of either the right or left visual field by applying either high frequency or low frequency TMS directed to the corresponding regions of the primary visual cortex. During some of these studies, transient mood changes were also observed. Today, we aim for enduring positive changes in the mood states and inherent cognitive biases involved in depression by applying TMS *repetitively* within a session and for 20-30 sessions in a course of 4-6 weeks. This manner of application of repetitive TMS (rTMS) has been shown to possess the hallmarks of other effective biological treatments for depression, including induction of genes involved in neuron and synapse formation and maintenance, normalization of abnormal stress hormone responses, increases in brain monoamine turnover, adaptive changes in certain serotonin and norepinephrine receptors, normalization of regional cerebral blood flow and glucose utilization in the mood circuitry of the brain, and efficacy in animal behavioral models of depression. Several clinical studies in recent years, including the ones submitted to the FDA conducted in 23 premium research sites in a randomized, triple-blinded, sham-controlled fashion, demonstrated the efficacy and safety of TMS for depression. These studies indicate that we can expect to see clinical response in at least half of patients and complete remission in about one out of three patients even though they have already failed one antidepressant medication at therapeutic dosage and long enough in the current episode. These studies have confirmed the lack of any CNS or systemic side effects that are associated with pharmaceuticals or ECT. There have been no inadvertent seizures, drug-device interactions, treatment-emergent suicidal ideation, or cognitive impairments. Of interest, studies hint at cognitive improvements with TMS going beyond what is expected from lifting of depression alone. The main side effects are limited to discomfort or pain in the scalp or skin under the treatment coil and tension-type headaches in a subset of patients. These are typically mild to moderate and manageable, largely dissipating after the first 5 sessions. Less than 5% of patients discontinued due to side effects in an FDA-submitted study. In a maintenance study, about 50 % of responders maintained their level of response for 6 months without need for any repeat sessions. The other half of patients received repeat sessions as they began to show break-through symptoms (but before they actually relapsed). Those who needed repeat treatments almost invariably responded again. All patients were placed on one antidepressant for maintenance purposes, mostly at lowest therapeutic dosages. With this strategy, less than 10% of patients relapsed at the end of 6 months. This statistic compares favorably with ECT, which does not have a good track record when it comes to maintenance of efficacy in 6-month studies. The effect size with TMS in patients who failed one adequate antidepressant trial in the current episode was 0.52, which compares favorably with the effect size observed with medications, 0.31.

In conclusion, this is an exciting time for our profession, and for a large group of our depressed patients. TMS is a unique biomedical treatment option, either alone or in conjunction with medications, for patients who continue to suffer due to tolerability and/or efficacy limitations of pharmacotherapy. With this novel option comes a good potential to move many patients out of their unending misery or off the track toward riskier options, such as ECT. I know from numerous phone calls as well as electronic communications I am receiving through my website that a lot of colleagues share this excitement.

When a patient or a colleague contacts me directly regarding TMS therapy at my practice, often there are numerous important questions to address and issues to discuss. I have included a good amount of TMS-related information on my website ([www.brain2mind.com](http://www.brain2mind.com)) in order to facilitate this process, however I would like to encourage all colleagues interested in referring a patient to contact me directly to address all of the specific questions involved. I am committed to make this treatment option work for everybody in the best way that I can. For that, however, I need your feedback and suggestions in order to help me help you and your patients tap into the potential of TMS in the most optimal way that we can.