# *Neurobiological mechanisms of repetitive transcranial magnetic stimulation on the underlying neurocircuitry in unipolar depression*

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*For nearly two decades now, transcranial magnetic stimulation (TMS) has been available as a noninvasive clinical tool to treat patients suffering from major depression. In this period, a bulk of animal and human studies examined TMS parameters to improve clinical outcome. However, the neurobiological mechanisms underlying mood changes remain an important focus of research. In addition to having an effect on neuroendocrinological processes, neurotransmitter systems, and neurotrophic factors, TMS may not only affect the stimulated cortical regions, but also those connected to them. Therefore, we will review current human data on possible neurobiological mechanisms of repetitive (r) TMS implicated in the deregulated neurocircuitry present in unipolar depression. Furthermore, as the rTMS application can be considered as a "top-down" neuronal intervention, we will focus on the neuronal pathways linked with the stimulated area and we will present an integrative model of action.*

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Unipolar major depression is one of the most common mental diseases worldwide.[1,2] Unfortunately, not all patients respond to the available pharmacological treatment algorithms and refractory depression is not uncommon.[3] Furthermore, the underlying pathophysiological mechanisms of this affective disorder are still under debate.[4] In spite of these neurobiological uncertainties, we are in need of alternative treatment options.[5] Repetitive transcranial magnetic stimulation (rTMS; a type of TMS that occurs in a rhythmic and repetitive form) has been put forward as a new technique to treat this debilitating illness.[6] Current evidence suggests that rTMS applied to the dorsolateral prefrontal cortex (DLPFC) is a promising treatment strategy for depression, but not all patients show a positive outcome.[7,8] Current clinical outcome studies report rather modest superiority compared with placebo (sham).[9-11] To date, it remains unclear which TMS parameters, such as stimulation duration and intensity, can produce the most benefits.[6,8,9,12] Moreover, there is no consensus of the exact brain localization for individual coil placement.[13] To answer these important questions, it would be important to gain more insight in the underlying neurobiological working mechanisms of rTMS. To date, no clear theo-

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## Selected abbreviations and acronyms

| | |
|---|---|
| ***ACC*** | *anterior cingulate cortex* |
| ***BDNF*** | *brain-derived neurotrophic factor* |
| ***DLPFC*** | *dorsolateral prefrontal cortex* |
| ***HF*** | *high-frequency* |
| ***HPA*** | *hypothalamic-pituitary-adrenal* |
| ***LF*** | *low-frequency* |
| ***rTMS*** | *repetitive transcranial magnetic stimulation* |

retical framework has yet emerged as to why rTMS treatment could result in a "normalization" of mood in depressed patients.[14,15]

## rTMS, the dorsolateral prefrontal cortex, and unipolar depression

The majority of rTMS treatment studies target the DLPFC.[15,17] The (dorsolateral) prefrontal cortex is implicated in regulating affective states, providing cognitive control over stress and emotion responsiveness.[18] A variety of studies has shown that a series of daily sessions of high frequency (HF)-rTMS delivered to the left DLPFC or low frequency (LF)-rTMS applied to the right DLPFC are effective in reducing symptoms in clinically depressed populations.[10,11,15] rTMS can either activate or suppress motor, sensory, or cognitive functions, depending on the brain location and parameters of its delivery: LF-rTMS (≤1Hz) is considered to "inhibit" cortical regional activity, while HF-rTMS (>1Hz) "activates" cortical areas.[19,20] The stimulation effects not only affect neuronal activities in the stimulated regions primarily but also those connected to them secondarily.[21,22] The vast majority of rTMS studies in major depression target the left DLPFC with HF stimulation.[10]

The rationale to use the DLPFC as the rTMS target area originates from brain imaging research, where patients with unipolar depression show prefrontal abnormalities (predominantly on the left).[23,24] Decreased neuronal activities in the (dorsolateral) prefrontal regions, as well as in the rostral anterior cingulate cortex (ACC) areas, closely connected to the DLPFC, are often reported.[23] These frontal hypoactivities result in apathy, psychomotor slowness, and impaired executive functioning. Besides dysfunctional "frontocingulate networks," other neuronal pathways between the orbital and medial prefrontal cortex, the amygdala, and hippocampus are implicated in the pathophysiology of mood disorders.[24,25]

Endocrinological disturbances and hypothalamic-pituitary-adrenal (HPA) system deregulations are commonly found.[26,27] The most consistently described biological abnormality in chronic major depression is a failing negative feedback system resulting in hypercortisolism[28] *(Figure 1)*.

## Brain imaging studies and rTMS

Brain imaging results suggest that antidepressant response to rTMS might vary as a function of stimulation frequency[29,30] and may depend on pretreatment prefrontal brain metabolism.[31,32] For instance, the stimula-

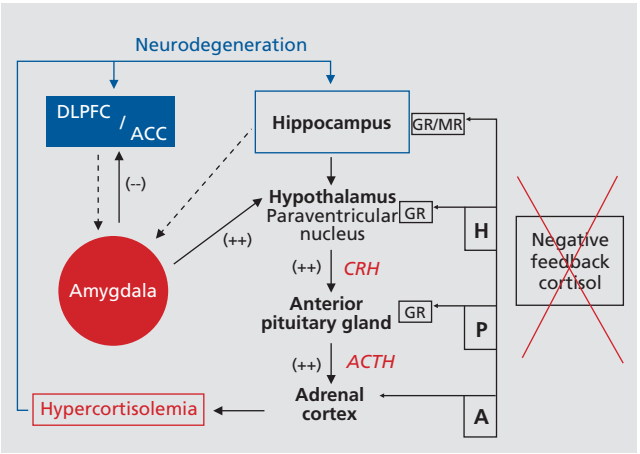


**Figure 1.** Theoretical framework of deregulated cortico-thalamic-limbic pathways in unipolar major depression. In major depression there is a pronounced shift in the homeostasis with diminished activity in the prefrontal cortex (DLPFC and dorsal ACC - blue), enhanced activity in the amygdala (red) and activation of the core stress system. Hyperactivity in limbic areas results in higher neural activities at the hypothalamic level, evoking higher corticotrophin-releasing hormone (CRH) secretions, resulting in elevations of cortisol levels. Hippocampal dysfunction may also result in reduction of the inhibitory regulation of the HPA axis, which could then lead to hypercortisolemia.[18] The failing negative feedback system results in chronic hypercortisolemia. In long-term depressive episodes, chronically elevated levels of cortisol contribute to hippocampal and cortical atrophy[27] and reducing hippocampal ability to inhibit amygdala hyperactivity.[76] Abnormal modulation of cortical-hippocampal-amygdala pathways may contribute to chronically hypersensitive stress responses, mediating features of anxiety, anhedonia, and affective dyscontrol.[76] Additionally, the dysfunctional ACC fails to serve its inhibitory role in emotional regulation on the amygdala, resulting in further motivational and affective disruption.[77] DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; ACTH, adenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal

tion of prefrontal regions with lower metabolic activity with HF-rTMS may significantly improve clinical outcome.[29] However, opposite results, where higher baseline metabolic activities in the DLPFC bilaterally were associated with better clinical outcome, have been reported as well.[32-35] Additionally, higher baseline activities in the ACC are not only predictive for treatment outcome in pharmacological antidepressant trials, electrophysiological imaging studies, and sleep deprivation studies,[23,36,37] but high pretreatment ACC activities were also a positive clinical predictor in HF-rTMS treatment protocols.[32,38]

Concerning the neurobiological effects, rTMS seems to influence metabolic activity of the ACC.[39] Whereas right-sided LF-rTMS showed metabolic ACC decreases,[40] left-sided HF-rTMS treatment resulted in higher ACC metabolic activity,[41,42] especially in those subdivisions of the ACC which are strongly interconnected with DLPFC areas.[17,32] However, in some reports successful HF-rTMS treatment did not result in significant ACC metabolic increases.[43] Furthermore, Luborzewski et al[44] failed to demonstrate neurochemical ACC alterations post HF-rTMS, and Loo et al[45] demonstrated that one session of LF-rTMS seemed rather to deactivate the ACC than to activate it. Altogether, the majority of successful rTMS treatment studies correspond with pathophysiological models of major depression that are based on dysfunctions within fronto-cingulate networks,[23-25] although the direction of the changes is not consistent over studies.

## Neuroendocrinology and rTMS

An important aspect of the physiology of rTMS could be related to the endocrinological response of the HPA axis.[46,47] Keck[48] proposed that rTMS influences occur at the hypothalamic level, suggesting that the (dorsolateral) prefrontal cortex participates in the rTMS-induced blunted response of HPA activity. HF-rTMS would inhibit cortisol-releasing hormone synthesis and release *(Figure 2)*. Some studies have examined this hypothesis in depressed patients.[47] For instance, in a sample of severely depressed patients, salivary cortisol concentrations decreased immediately after one active left DLPFC HF-rTMS session and not after sham rTMS.[48] Pridmore[50] observed normalization of the dexamethasone suppression test in a small sample of medicated depressed subjects after multiple sessions of HF-rTMS.

In addition, in a sham-controlled left prefrontal HF-rTMS trial, Szuba et al[51] found acute mood and serum thyroid-stimulating hormone elevations in drug-free depressed patients after each active stimulation session. Mood improvement was only observed after active HF-rTMS. These observations could imply that the clinical effects of rTMS act in a similar way to pharmacological interventions: clinical improvement after antidepressant treatment has been associated with a normalization of HPA system function and different antidepressants may act in the same way in attenuating the HPA axis.[52,53] However, it has to be noted that in depressed patients HPA system abnormalities are not consistently observed.[47]

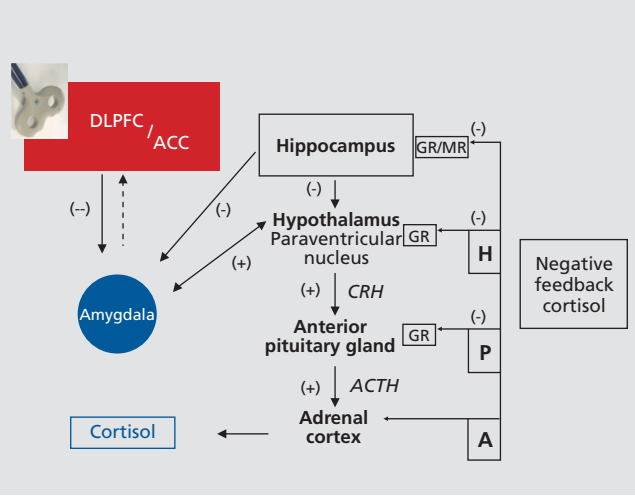


**Figure 2.** Visualization of a theoretical working mechanism of HF-rTMS applied to the DLPFC on the HPA-system in unipolar major depression. In the left hand corner a figure-of-eight shaped repetitive transcranial magnetic stimulation (rTMS) coil is depicted. rTMS treatment results in increased neuronal activity in the (dorsolateral) prefrontal cortex, which through cortico-subcortical trans-synaptic connections (presumably through frontocingulate networks)[32] suppresses hypothalamic and/or indirectly amygdala overactivity, resulting in CRH decreases and ultimately in decreased salivary cortisol concentrations. In line with successful pharmacological interventions, successful rTMS treatment results in normalization of the negative feedback system.[46] The areas in red represent an elevated neuronal activity. The blue areas represent the reverse, a diminished level of neuronal activity. ACTH, adenocorticotropic hormone DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; GR, glucocorticoid receptors; MR, mineral-corticoid receptor; CRH, corticotrophin-releasing hormone; ACTH: adenocorticotrope hormone; H, Hypothalamus; P, Pituitary gland; A, Adrenal cortex; (-), inhibitory; (+) ,excitatory

## Neurotransmitter systems and rTMS

Only a few studies have examined the rTMS effects on neurotransmitter systems in major depression. Because rTMS treatment resulted in psychomotor symptom improvement, such as a reduction in motor slowness in bodily movement and speech, increased voice volume, and facial inexpressivity, some authors suggested that a possible working mechanism of action could be by activating the dopaminergic system.[54,55] Indeed, several brain imaging studies using dopaminergic ligands point to an rTMS-related release in endogenous dopamine when stimulating prefrontal cortical areas,[56,57] although others found no impact on the dopaminergic system at all.[58,59] In major depression, the serotonergic system has been extensively investigated, and serotonin (5-HT) is an important excitatory transmitter involved in HPA-system regulation.[60] In a severely depressed medication-resistant sample, successful clinical outcome after HF-rTMS treatment was associated with DLPFC 5-$HT_{2A}$ receptor upregulation and hippocampal 5-$HT_{2A}$ receptor downregulation, measured with 123I-5-I-R91150 SPECT.[61] Interestingly, this prefrontal increase of this type of postsynaptic receptor agrees with treatment response findings after treatment with selective serotonin uptake inhibitors (SSRIs) and electroconvulsive therapy (ECT).[62,63] As clinical recovery is reported to be associated with increased brain-derived neurotrophic factor (BDNF) expression in the hippocampus,[64] it was suggested that the observed 5-$HT_{2A}$ receptor downregulation in the hippocampus would be associated with BDNF increases in this area comparable to the effects of most pharmacological antidepressant agents.[65] However, as rTMS responders seem to be resistant to acute mood changes after trypthophan depletion,[66] it may be possible that the neurobiological influence of rTMS does not only depend on the central availability of serotonin to exert antidepressant effects. In short, whether the rTMS effects are attributed to the modulation of only the serotonergic system remains unclear. A beneficial treatment outcome has been related to glutaminergic increases under the stimulated area (left DLPFC) in depressed patients.[44] From an electrophysiological point of view, stimulation of the DLPFC might influence 5-$HT_{2A}$ receptors in the hippocampus via (glutaminergic) pyramidal neurons.[67] Furthermore, research on the chronic effects of TMS on hippocampal evoked potentials demonstrates that TMS is accompanied by changes in the local hippocampal inhibitory circuits (γ-aminobutyric acid, GABA).[68] The implication of glutaminergic/GABAergic deficits in major depression has been proposed, but to date the influence of rTMS on the glutaminergic/GABA system has only been demonstrated in healthy individuals.[69,70] A single active HF-rTMS session increased glutamate/glutamine levels in the prefrontal cortices, suggesting that this application may act via the stimulation of the glutaminergic prefrontal neurons.[69] Concerning the inhibitory effects, active rTMS resulted in increases in cortical inhibition; however, in this study only the left motor cortex was stimulated.[70]

## Neurotrophic factors and rTMS

Brain and endocrinological data indirectly suggest that a clinical beneficial rTMS outcome affects neurotrophic factors in the brain.[71] Animal studies already demonstrated increases in the expression of BDNF in the rat hippocampus after the application of long-term HF-rTMS similar to antidepressant drug treatment and ECT.[72] In a sample of drug-resistant depressed patients, Zanardini et al[73] reported on a normalizing rTMS effect of initially decreased serum BDNF. Yukimisa et al[74] demonstrated that changes in serum BDNF correlated positively ($r_s$=0.34) with changes on the 17-item Hamilton Depression Rating Scale in all depressed patients treated with HF-rTMS. These trend-like correlations were found to be significant when comparing responders with nonresponders; an increase of BDNF levels was only observed in those patients who clinically responded to the HF-rTMS treatment.

## Conclusions

In unipolar depressed patients, beneficial rTMS treatment has immediate and prolonged neurobiological effects. Neurobiological data support the choice of the left DLPFC as a valid rTMS target site to intervene with the neuronal pathways deregulated in major depression. The observed changes in a depression-related neurocircuitry seem to agree with other successful treatment modalities, such as pharmacological antidepressant treatment and ECT. Although further research is required, biological data indicate that depressed patients with some kind of "preserved" cortico-subcortical neurocircuitries could be susceptible to

rTMS treatment. Displaying a metabolically more active fronto-cingulate network at baseline indicates a possible better clinical outcome. This observation is consistent with the hypothesis that the synchronized modulation of "dysfunctional fronto-cingulate pathways" is critical for illness remission.[23] In short, successful rTMS treatment seems to result in a cascade of neurobiological changes in brain areas linked with the stimulated area, supporting the integrative model of action depicted in *Figures 1 and 2*. Whether the rTMS effects are modulated by NT systems or neurotrophic factors remains to be clarified. ❑

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# Brief report

## *Mecanismos neurobiológicos de la estimulación magnética transcraneal repetitiva sobre los neurocircuitos subyacentes a la depresión unipolar*

*Desde hace casi dos décadas se dispone de la estimulación magnética transcraneal (EMT) como una herramienta clínica no invasora para tratar a los pacientes con depresión mayor. En este período se han examinado numerosos estudios clínicos y en animales acerca de los parámetros de la EMT para mejorar sus resultados clínicos. Sin embargo, los mecanismos neurobiológicos a la base de los cambios del ánimo siguen constituyendo un importante foco de investigación. Además de tener un efecto sobre los procesos neuroendocrinos, los sistemas de neurotransmisión y los factores neurotróficos, la EMT no solo puede afectar las regiones corticales estimuladas, sino también las que están conectadas con ellas. Por lo tanto, se revisarán los datos actuales en humanos acerca de los posibles mecanismos neurobiológicos de la EMT repetitiva que participan en los neurocircuitos disregulados de la depresión unipolar. Además, ya que la aplicación de la EMT repetitiva se puede considerar como una intervención neuronal "desde arriba hacia abajo", la revisión se centrará en las vías neuronales relacionadas con el área estimulada y se presentará un modelo de acción integrador.*

## *Mécanismes neurobiologiques de la stimulation magnétique transcrânienne répétée (rTMS) sur le circuit neuronal sous-jacent dans la dépression unipolaire*

*Depuis presque 20 ans, la stimulation magnétique transcrânienne (TMS) constitue un outil clinique non invasif pour traiter les patients souffrant de dépression majeure. Pendant ce temps, un grand nombre d'études humaines et animales ont examiné les paramètres de la TMS afin d'en améliorer les résultats cliniques. Cependant, les mécanismes neurobiologiques sous-tendant les modifications de l'humeur restent un important sujet de recherche. Outre l'effet sur les processus neuroendocriniens, sur les systèmes de neurotransmission et les facteurs neurotrophiques, la TMS toucherait non seulement les régions corticales stimulées mais aussi celles qui lui sont connectées. Nous allons donc analyser les données humaines actuelles sur les mécanismes neurobiologiques possibles de la rTMS impliqués dans le dysfonctionnement des circuits neuronaux dans la dépression unipolaire. De plus, la rTMS pouvant être considérée comme une technique neuronale « descendante », nous nous consacrerons aux voies neuronales liées aux aires stimulées et nous présenterons un modèle d'action intégratif.*

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