How Does Repetitive Transcranial Magnetic Stimulation Influence the Brain in Depressive Disorders? A Review of Neuroimaging Magnetic Resonance Imaging Studies

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Objective: Repetitive transcranial magnetic stimulation (rTMS) is a nonpharmacological technique used to stimulate the brain. It is a safe and proven alternative tool to treat resistant major depressive disorders (MDDs). Neuroimaging studies suggest a wide corticolimbic network is involved in MDDs. We researched observable changes in magnetic resonance imaging induced by rTMS to clarify the operational mechanism.

Methods: A systematic search of the international literature was performed using PubMed and Embase, using papers published up to January 1, 2017. The following MESH terms were used: (*depression* or *major depressive disorder*) and (*neuroimaging* or *MRI*) and (*rTMS* or *repetitive transcranial magnetic stimulation*). We searched the databases using a previously defined strategy to identify potentially eligible studies.

Results: Both structural and functional changes were observed on magnetic resonance imagings performed before and after rTMS. Various areas of the brain were impacted when rTMS was used. Although the results were very heterogeneous, a pattern that involved the anterior cingulate cortex and the prefrontal cortex emerged. These are known to be regions of interest in MDDs. However, the various parameters used in rTMS make any generalization difficult.

Conclusions: Repetitive transcranial magnetic stimulation helps to treat MDDs with good efficacy. Its effect on the brain, as observed in several neuroimaging studies, seems to impact on the structural and functional features of several networks and structures involved in major depressive disorders.

Key Words: major depressive disorder, MRI, neuroimaging, repetitive transcranial magnetic stimulation, psychiatry

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T ranscranial magnetic stimulation (TMS) is a nonpharmacological technique used to stimulate the brain, invented by Barker et al¹ in 1985. Further development led to the identification of repetitive TMS (rTMS) as an add-on therapy for major depressive disorders (MDDs).² It has been shown to be a safe³ alternative tool to treat MDDs⁴ with the US Food and Drugs Administration⁵ approval in clinical practice to treat MDDs.

According to a systematic meta-analysis performed by Gaynes et al⁶ in 2014, patients who receive rTMS are 5 times more likely to achieve remission than those who receive a placebo treatment. Repetitive TMS has been associated with a meaningful decrease in the Hamilton Depression Rating Scale.⁶

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The aim of this technique is to induce neuromodulation, activating or inhibiting brain areas, according to the frequency of the pulse applied to the area: that is, a 1-Hz rTMS frequency has an inhibitory effect whereas a more than 5-Hz frequency has an enhancing effect.7 Pascual-Leone et al8 described the enhancing effect of high frequency rTMS on the primary motor cortex in the early 1990s. More recently, the inhibiting effect of low-frequency rTMS was demonstrated when Chen et al9 found that the application of a 1-hour course of 1-Hz rTMS over the motor cortex produced a decrease of the motor evoked potential. However, these studies initially focused on the motor cortex and there is still no real consensus to decide if the results can be extrapolated to other brain areas, such as the prefrontal cortex (PFC).¹⁰ The use of TMS in major depressive disorders is based on several neuroimaging studies that have shown a hypoactivity of the left dorsolateral PFC¹¹ and a hyperactivity of the right PFC.¹² Thus, psychiatrists used the inhibiting or enhancing properties of rTMS to modulate dysfunctional brain areas. To induce this neuromodulation, a coil is placed over the cortex whose shape depends on the depth of the brain structure to be stimulated.

The most usual methods involve 2 different protocols that exist in clinical practice: low-frequency rTMS, applied to the right dorsolateral PFC,^{13,14} or high-frequency rTMS, applied to the left dorsolateral PFC.¹⁵ Both require 5 daily sessions per week, for 4 to 6 weeks in a row.

Major depressive disorders are common psychiatric disorders diagnosed by their clinical manifestations¹⁶: sadness, diminished interest in activities, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue, worthlessness or guilt, loss of concentration, or recurrent thoughts of death, for at least 2 consecutive weeks, with these symptoms significantly impairing the patient's quality of life. Because of the high prevalence¹⁷ and social cost of MDDs,^{18,19} they are a major focus of psychiatric research. However, the pathophysiological mechanisms of MDDs are still not fully understood.

Structural and functional neuroimaging studies suggest that many networks and brain regions are involved in the pathophysiology of MDDs, which form a wide corticolimbic network. These regions include the amygdala²⁰; the dorsolateral PFC,^{21,22} ventrolateral PFC,^{23,24} and ventromedial PFC²¹; the hippocampus^{25,26}; the anterior cingulate cortex (ACC)^{27,28}; the inferior frontal cortex²⁹; and the basal ganglia.³⁰ These impairments exist in the resting state as well as during emotional and cognitive work.³¹ Furthermore, molecular changes have also been reported.

A growing body of evidence shows that these different structures may be involved in the clinical disturbances observed in patients suffering from MDD. Some studies have shown the impact of treating these potential areas. Although rTMS has been demonstrated to be a good adjuvant treatment for patients suffering from MDDs, the way it works and improves a patient's health has not been clearly established. In this review, we aim to clarify how

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TABLE 1. Main Results	of the Studies Included in the Review			
Article	Patients Features	TMS Feature	MRI Features	Results
Baeken et al ³³ (2014)	Controlled cross-over trial 20 Patients with stage 3 treatment-resistant unipolar depressed patients (7 males; mean age, 48.80 y old; mean HDRS, 25.65; all right-handed) after a 2 wk (3 with fluoxetine) wash-out for treatment	MRI neuronavigation Group A: 1 wk high-frequency rTMS over left DLPFC followed by 1 wk sham TMS Group B: 1 wk sham TMS followed by 1 wk high-frequency rTMS over left DLPFC 5 Sessions per day, 4 days in a wk 110% of motor threshold, 20 Hz	3 T Functional MRI: resting-state	Augmentation of resting state functional correlation between subgenual anterior cingulate cortex and perigenual PFC (perigenual anterior cingulate cortex and superior medial frontal gyrus)
Liston et al ³⁴ (2014)	Controlled trial 17 Patients (3 males; mean, 42.3 y) DSM-IV-TR resistant depressive episode in major depressive disorder or bipolar disorder (22 medications during 8 wk) 35 Healthy control subjects (12 males; mean age, 36 y)	High-frequency Left DLPFC 10 Hz frequency 5-wk course, 5 days per wk	3 T Functional MRI: resting-state Seed regions of interest: left DLPFC and sgACC on the DMN and the CEN	TMS effects on connectivity DMN: decreased connectivity in ventromedial PFC, pregenual ACC and precuneus TMS effects on connectivity between the CEN and DMN: – DMN: increased connectivity between DLPFC and right parahippocampal area, expanding to ventromedial PFC and posterior circulate correct
Salomons et al ³⁵ (2014)	25 Patients (10 males; mean, 42.6 y) 21 Resistant major depressive disorder (≥2 medications during 6 wk) or with medication intolerance 3 Unipolar or bipolar disorder Mean HDRS score, 21.3	MRI neuronavigation Bilateral stimulation of left then right hemisphere 120% resting motor threshold 10 Hz frequency 4-wk course	3 T Functional MRI: resting-state Seed regions of interest: dm-PFC and sgACC	 dm-PFC: dm-PFC: decreased connectivity with bilateral insula (best response marker) and parahippocampal gyrus/amygdala increased connectivity with bilateral thalamus (medial dorsal nuclei and pulvinar) sg-ACC: decreased connectivity with ventral striation. candate dm-PFC
Furtado et al ³⁶ (2013)	29 Patients (11 males; mean, 43.97 y; 23 right-handed) DSM-IV-TR resistant major depressive disorder (≥2 medications during 6 wk) HDRS > 20 (mean, 25.34)	No neuronavigation Left DLPFC 10 Hz or Sequential bilateral DLPFC (15 min 1 Hz rTMS on right DLPFC and 15 min 10 Hz rTMS on left DLPFC) 120% resting motor threshold 6-wk course, 5 days per wk	1.5 T Structural MRI 6 wk interval	No significant interaction between treatment response outcome and type of rTMS treatment (unilateral or sequential) Left annygdala volume increased in responders Prevention of left hippocampus volumetric loss

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Peng et al^{37} (2012)	30 Young treatment-resistant unipolar depression patients (19 males and 11 females) Double-blind, randomized study: 17 patients were treated with real stimulation, and 13 were treated with sham stimulation. Group control : 25 age- and gender-matched subjects	High-frequency (15 Hz) rTMS treatment 20 sessions of stimulation over a 4-wk period, from Monday to Friday, at 110% stimulation intensity	3 T DTI White-matter (FA) was evaluated using VBA of FA maps derived from DTI before and after treatment	The reduced FA was significantly improved after active rTMS treatment, but not sham stimulation. FA increases were correlated with decreased depressive symptoms.
Fox et al ³⁸ (2012)	Reproductability study between 2 data sets analysis: healthy subjects a and major depressive disorder patients 98 Healthy subjects (48 males; mean age, 22 y old; right-handed) without MDD without MDD 13 DSM-IV-TR MDD patients (3 males; mean age, 40.2 y old; mean HAM-D, 23.8; right-handed)	With and without neuronavigation depending on the target aimed for brain stimulation: EEG F3, average of 5 cm, BA9 center, Rusjan target, Paus/Cho target, Fitzgerald target and BA46 center High-frequency left DLPFC	3 T Functional MRI: resting-state Seed regions of interest: sgACC and multiple targets depending on the stimulation site	Healthy subjects: all stimulation sites led to an anticorrelation between DLPFC and sgACC MDD patients: similar results, with best improvements for patients when aiming for a strongly anticorrelated stimulation targets (eg, BA46 center)
Fitzgerald et al ³⁹ (2007)	26 Right-handed patients (13 males) DSM-IV-TR resistant major depressive disorder (≥2 medication during 6 wk) MADRS > 20	No neuronavigation LFR-TMS on PFC 1 Hz or HFL-TMS on PFC 10 Hz 110% resting motor threshold 4-wk course, 5 days per wk	1.5 T Functional MRI (3-condition block sequences: planning, counting and rest)	LFR-TMS: decreased activity in bilateral middle frontal gyrus and left precuneus for responders only HFL-TMS: increased activation of left precuneus and for responders increased activation in right inferior frontal gyrus, left precentral gyrus and left medial frontal gyrus
Li et al ⁴⁰ (2004)	14 MDD patients	Low frequency rTMS (1 Hz): left PFC Intensity: 100% motor threshold	1.5 T Functional MRI: resting state: BOLD/ROI	Increased activity at the site of stimulation as well as in connected limbic regions: bilateral middle PFC, right orbital frontal cortex, left hippocampus, mediodorsal nucleus of the thalamus, bilateral putamen, pulvinar, and insula ($P < .001$). Significant deactivation was found in the right ventromedial frontal cortex.
BA, Brodmann areas; E Fourth Edition, Text Revis high-frequency left-sided T	OLD, blood-oxygen level dependent; CEN, C ion; HDRS, Hamilton Depression Rating Sc MS.	ntral Executive Network; DLPFC, dorsolateral ale; dm-PFC, dorsomedial PFC; sgACC, subg	prefrontal cortex; DSM-IV-TR, <i>Diagn</i> enual anterior cingulate cortex; VBA	ostic and Statistical Manual of Mental Disorders, , voxel-based analysis, LFR-TMS, ; HFL-TMS

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rTMS induces functional and structural changes in the brain, when used to treat MDDs.

MATERIALS AND METHODS

We performed a systematic search of the international literature using bibliographic search engines (PubMed, Cochrane, Medline, Embase) and a Boolean combination of the following MESH terms: (*depression* or *major depressive disorder*) and (*neuroimaging* or *MRI*) and (*rTMS* or *repetitive transcranial magnetic stimulation*). We included articles published in English up to January 1, 2017. We focused on prospective studies, in which a magnetic resonance imaging (MRI) was performed before and after rTMS treatment.

We searched the databases using a previously defined strategy to identify potentially eligible studies. We first independently, and then jointly, selected studies based on their abstracts. All online abstracts were reviewed, and the full-text papers were retrieved if relevant. This search procedure followed the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).³²

RESULTS

We identified 8 studies (Table 1) that dealt with structural MRI, diffusion tensor imaging (DTI), and functional MRI (fMRI). In these reports, MRIs showed both structural and functional changes after rTMS therapy.

Only 1 study³⁶ focused on morphological changes, using volumetric MRI. Another³⁷ observed microstructural changes using DTI. Finally, 6 of the studies^{33–35,38–40} used functional MRI. Table 1 summarizes the methodological aspects of the studies, including rTMS and MRI features.

Structural MRI

Furtado et al³⁶ compared the effect of unilateral high-frequency rTMS applied over the left PFC with sequential bilateral prefrontal stimulation (1 Hz over the right PFC and 10 Hz over the left PFC). They failed to find a significant interaction between the outcome of the treatment and the type of rTMS treatment (unilateral left dorsolateral PFC 10-Hz or sequential), but an increase in the volume of the left amygdala in responders was reported.

Functional MRI

Six studies^{33–35,38–40} focused on functional evaluations before and after rTMS therapy, of which 5 used resting-state paradigms^{33–35,38,40} and the last a task realization protocol.³⁹

Resting-State fMRI

The use of high frequency rTMS to treat depression led to broad network modifications observable using resting-state fMRI. The most frequent findings were an increased functional connectivity between subgenual ACC and dorsolateral PFC,^{33,34} and a decreased functional connectivity between dorsolateral PFC and pregenual ACC.^{34,38} One study found a positive correlation between subgenual ACC and the perigenual ACC.³³ Finally, decreased functional connectivity was found between the dorsolateral PFC and both ventromedial PFC and precuneus.³⁴

Low-frequency rTMS on the left PFC showed an increased activity both right under and away from the stimulation site, in various limbic areas including bilateral middle PFC, right orbitofrontal cortex, left hippocampus, the putamen, the pulvinar, and the insula. It also demonstrated a deactivation of the right ventromedial PFC.⁴⁰ Finally, Salomons et al³⁵ focused on the effects of bilateral

Finally, Salomons et al⁵⁵ focused on the effects of bilateral rTMS. They showed decreased connectivity with the bilateral insula (best response marker) and the parahippocampal gyrus/ amygdala associated with the dorsomedial PFC. They also found increased connectivity of the bilateral insula with the bilateral thalamus (medial dorsal nuclei and pulvinar). Regarding the subgenual ACC, there was decreased connectivity with the ventral striatum and the caudate dorsomedial PFC.

Task-Performing fMRI

Fitzgerald et al³⁹ compared the effect of high-frequency rTMS over the left PFC and low-frequency rTMS over the right PFC during a multiple task-performing fMRI. Low-frequency right-sided TMS on the PFC led to decreased activity of the bilateral middle frontal gyrus and the left precuneus in responders only, whereas high-frequency left-sided TMS provoked an activation of the left precuneus but also highlighted an enhancement in the right inferior frontal gyrus, left precentral gyrus, and left medial frontal gyrus.

Diffusion Tensor Imaging

A single study, conducted in 2012 by Peng et al,³⁷ focused on diffusion tensor imaging. They revealed significantly reduced fractional anisotropy (FA) in the left middle frontal gyrus in treatment-resistant patients. This reduced FA was significantly improved after active rTMS treatment, but not placebo stimulation. Moreover, FA increases were correlated with the decrease in depressive symptoms.

DISCUSSION

General Results

The studies we reviewed showed significant results in a range of brain structures and networks, such as the subgenual ACC, ^{33,40} the perigenual ACC, ^{33,40} the superior medial frontal gyrus, ³³ the dorsolateral PFC, ^{34,38,40} the dorsomedial PFC, ^{35,40} the bilateral middle frontal gyri, ³⁹ the left precuneus, ³⁹ the hippocampus, ⁴⁰ the thalami, ⁴⁰ the putamen, ⁴⁰ the parietal lobes, ⁴⁰ the insula, ⁴⁰ the right orbitofrontal cortex, ⁴⁰ and the middle temporal cortex. ⁴⁰ One study demonstrates microstructural changes after treatment with rTMS.³⁷

The structures and cerebral networks involved in rTMS treatment correspond to a number of those implicated in depression (for example, these regions include the dorsolateral $PFC^{21,22}$; the hippocampus^{25,26}; the ACC^{27,28}; the inferior frontal cortex²⁹; and the basal ganglia³⁰).

The structural and functional changes found were similar to those reported after electroconvulsive therapy (ECT),⁴¹ although few data are currently available on this topic. Indeed, this review shows similarities with data from the literature concerning morphological changes secondary to treatment with ECT.^{42,43} Subsequent to treatment by both techniques, an increase in the volume of the amygdale was found, predominantly on the left in the course of the rTMS.³⁶ Similarly, there appears to be an increase in hippocampus activity in resting-state fMRI in both ECT⁴⁴ and rTMS.⁴⁰ There are also similarities in the microstructural modifications in DTI, although the cerebral structures explored are different. Electroconvulsive therapy patients showed significant increases in FA in dorsal frontolimbic circuits encompassing the anterior cingulum, forceps minor, and left superior longitudinal fasciculus between baseline and transition to maintenance therapy,45 whereas rTMS increased FA in the left middle frontal gyrus in treatment resistant depression patients.³⁷ Moreover, current data from the literature make it difficult to compare the 2 therapeutic techniques with regards to their influences on the brain. However, there appears to be greater morphological changes after treatment with ECT (amygdala, hippocampi, anterior right cingulate gyrus, caudate nuclei)^{42,46–48} compared with rTMS therapy (left amygdala).³⁶ It

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seems more difficult to compare the data in fMRI. Indeed, although the structures and networks studied overlap, the study hypotheses are different for most of them, ^{33–35,44,49–51} compromising any comparison. However, regardless of the technique, there appears to be a decrease in the default mode network (DMN) activity, which is hyperactivated during MDDs.⁵² Liston et al³⁴ (rTMS), Mulders et al⁵³ (ECT), and Delaveau et al⁵² (antidepressants) show decreasing activity of the DMN at the end of the treatment. It may be interesting to compare the decrease in DMN activity according to the type of therapeutic technique for the same level of severity of the disease. In addition, a more meaningful comparison of the 2 techniques could be made by comparing the changes induced by both ECT and rTMS from the biological level (immunoinflammatory) to structural and functional changes (MRI). This would make it possible to include the hypotheses of the studies in resting-state MRI in a more global framework and maybe to allow an initial comparison.

Methodological Considerations

1. Parameters of rTMS

A serious limitation in the interpretation of rTMS effects on depressive disorders is the lack of consensus on the coil position for optimum stimulation. However, 1 of the studies reviewed³⁸ tried to compare this aspect. Fox et al³⁸ reported that the position of stimulation gave different results regarding the efficacy of rTMS used to treat depression, with this forming an inverse correlation between the subgenual ACC and the dorsolateral PFC. It was confirmed by Baeken et al,⁵⁴ using positron-emission tomography (PET), that the results differed according to the stimulation sites. Because of the difficulty in targeting some of the stimulation sites, this review emphasized the need for neuronavigation.⁵⁵

The number of rTMS sessions also varied considerably in the studies, from 20 to 30. The current recommendations suggest that patients with MDDs should have 4 to 6 weeks of treatment, corresponding to 20 to 30 sessions. The efficacy of the treatment seems directly linked to the number of sessions, however, accelerated rTMS (used in Baeken et al's⁵⁴ study) might have different effects to a more classical course of 30 sessions conducted over 6 weeks. These differences in protocols might limit the generalization of the results and the comparison between the studies.

The intensities of the magnetic pulses were homogeneous between each study and were systematically over the motor threshold (from 110% to 120%) in accordance with the current medical recommendation for MDDs. On the other hand, the frequencies of rTMS were either low (1 Hz) or high (10 Hz or more) depending on the site of stimulation. However, in 1 of the studies,⁴⁰ researchers performed lowfrequency rTMS over the left dorsolateral PFC, which is inconsistent with both neuroimaging data and medical recommendations. The improvement in the depression scores was statistically significant, and they succeeded in showing neuroimaging changes among brain areas right under or at a distance from the coil.

2. Characteristics of the population

Among the reports included in the review, the populations studied were very heterogeneous, with variations in age, diagnosis (MDDs, bipolar depression, late-life depression, etc), add-on treatments, etc. These differences make it difficult to generalize the results.

First, the patient's age may be a confounding factor. Bashir et al⁵⁶ reported on the stimulation of the motor cortex in 2 groups (a "young" and an "elderly" cohort) that there was a

trend towards a lack of cortical plasticity and interhemispheric communication in the unstimulated hemisphere of older patients. This result could be of great interest because of the impaired interhemispheric balance seen in depressed patients.⁵ Whereas this result remains controversial,⁵⁸ previous randomized clinical trials showed that rTMS was less effective when used in elderly subjects than in a younger population.59 Several factors influencing the efficacy of rTMS in elderly subjects have been described, including brain atrophy, intensity and number of pulses, and the clinical profile of the patients. The cortical atrophy hypothesis for the lack of efficacy of rTMS in older patients has been supported in the past by a computer-based human brain model⁶⁰: classical spotting using anatomical markers might be impaired because of sulcus width and skull-brain distance, which is enhanced in older subjects. Adapting rTMS protocols for elderly patients may be a useful approach in further studies.

Another discussion point about the patients' characteristics included the level of resistance to the antidepressant treatments. Indeed, almost all the studies included in the review (except Fox et al³⁸ and Li et al⁴⁰) focused on treatmentresistant MDDs. Previously published studies raised the issue that refractory MDDs might imply, for example, glutamate receptors, glial cells,61 or subcallosal cingulated cortex white matter abnormalities.⁶² Thus, although presenting a common phenotype, the underlying mechanisms of classical and treatment-resistant MDDs might differ. Therefore, one might ask whether rTMS has a different mechanism of action when used on resistant MDDs. To answer this question, we propose 2 hypotheses. First is that rTMS increases the permeability of the blood-brain barrier, thus enhancing the concentration of the antidepressant treatment in the synapse. This first hypothesis is supported by one study by Alagona et al⁶³ showing increased blood lactate levels after rTMS sessions among patients. Although they interpreted this enhancement as proof of the opening of the blood-brain barrier, these results remain controversial and, to our knowledge, no study has tried to replicate them. However, this seems to be an interesting lead to explain rTMS mechanisms in resistant-MDDs. In a second hypothesis, rTMS and antidepressant medications may have a synergistic effect on each other, acting on different targets implied in the pathophysiology of MDDs, as previously stated. These theories remain unanswered, and further studies will be needed to elucidate the action mechanisms of rTMS on treatmentresistant MDDs.

Finally, in a more pragmatic way, interpreting the neuroimaging results of some studies is made difficult because of the joint presence of 2 treatments: rTMS and medications. Indeed, antidepressants induce structural and functional changes observable with MRI.⁶⁴ It is thus difficult to affirm that the structural and functional changes observed in MRI in the studies included in this review are only relevant to the effect of rTMS instead of a potential synergistic effect of the 2 treatments.

3. MRI features and connectivity changes in the brain

Functional MRI is now a popular area of research. However, most studies^{33–35,38–40} that have used this technique report different results depending on the design of the study. The pathophysiology of depression has been explored using functional MRI and resting-state connectivity. A recent review by Mulders et al⁶⁵ described several alterations in depressed patients during resting-state connectivity, such as increased connectivity within the anterior DMN, increased connectivity between the salience network and

the anterior default-mode network, changed connectivity between the anterior and posterior default-mode network, and decreased connectivity between the posterior default-mode network and the central executive network. This network is now known to be part of a social-affective network.⁶⁶ For example, the anterior cingulate and the subgenual cortices are known to be part of a subgroup that is associated with motivation, reward, and cognitive modulation. Another example would be the dorsomedial PFC, which is thought to be involved in mental and self-reference processes.

Four studies^{33–35,38} have focused on resting connectivity across the brain and the modifications caused by rTMS in depressed patients. These studies have observed modifications to the default-mode network of these structures, which seem to be very similar to the clinical features observed when patients have improved symptomatology.

We also lacked data regarding the morphological impact of rTMS in depressed patients who received MRI. There are several published studies that have reported on functional MRI and PET, but only 1 study has focused on the morphological aspects and one other on diffusion-tensor imagery. This lack of data is indicative of the importance placed on functional studies nowadays. We believe that an emphasis on the use of morphometric features could improve our understanding of how rTMS acts to treat depressive disorders.

Magnetic resonance spectroscopy appears to be a reliable tool to evaluate biochemical in vivo compounds of the brain.⁶⁷ Previous studies showed a downregulation of glutamate in MDDs patients, specifically in the ACC but also in other regions of interest (dorsolateral PFC, dorsomedial PFC, hippocampus).68 An inappropriate regulation of this compound leads to neurotoxicity and deleterious effects on neurotransmission.⁶⁹ The use of high-frequency rTMS over the left PFC showed a significant increase in the glutamate/ glutamine concentrations both under the stimulation site and in remote brain areas (right dorsolateral PFC and left ACC) in healthy volunteers.⁷⁰ One open-label study showed an increase in glutamate after rTMS treatment in young adults with MDDs.⁷¹ GABAergic levels also tend to be significantly lower in depressed patients compared with healthy volunteers⁷² but returns to normal after treatments.⁷³ Changes among N-acetylaspartate and myo-inositol have also been reported in the past when MDDs were treated with TMS.^{74,75} Every magnetic resonance spectroscopy study detailed previously showed a significant effect on neurotransmitters in regions of interest as we described previously in Results section. The changes observed in neuroimaging studies might be linked to changes in biochemical in vivo compounds in the brains of MDDs patients.

None of the studies reported the impact of 1 rTMS session on both brain structure and function. Currently, the exact mechanism of action of rTMS in depression remains unclear. In a few studies, the DTI imaging sequences were missing. These data would more precisely determine the connectivity that exists after rTMS treatment. Just as in studies on Parkinson's disease, multimodal MRI has increased our knowledge of rTMS. Indeed, the DTI sequences taken with anatomical and functional sequences would furnish simultaneously information on the microstuctural, morphological, volumetric, and functional changes. Another potential MRI technique is the quantification of mineral levels in the brain. Magnetic resonance imaging relaxometry is a sensitive method that evaluates the brain's iron content in vivo. Iron accumulation has been involved in the pathogenesis of many neurodegenerative diseases.^{76–78}

The pathophysiology of depressive disorders is a fast-moving field of research, and recent findings suggest that neuroinflammation may be involved. For example, microglial activation has been shown in PET in patients with MDDs. Indeed, the density of translocator protein, measured by distribution volume, is increased in activated microglia. This is an important aspect of neuroinflammation.⁷⁹ It is also now known that anti-inflammatory treatments impact on mood disorders,⁸⁰ and several previous studies highlighted inflammatory effects of the glutamate downregulation in the brain in MDDs.⁸¹ Thus, it seems legitimate to query the impact of anti-inflammatory rTMS therapy on depressive disorders. We could query whether rTMS has a role in the neuroinflammatory aspects of mood disorders or if it improves the passage of medications across the blood-brain barrier. Li et al⁸² studied the effect of rTMS on the blood-brain barrier when applied to the PFC at 1 Hz. These authors were unable to determine whether the blood-brain barrier changed: thus, it may be that rTMS only aids the passage of medication to the brain. We found no published study on the role of anti-inflammatories with rTMS: consequently, this would seem to be a very promising area of future research. It would be of particular interest to determine whether translocator protein, measured by distribution volume, is decreased in the PFC, ACC, and insula of patients who have undergone rTMS treatment for a MDDs.

Repetitive TMS is one of the many possibilities used to treat MDDs and shows good efficacy. Its effects on the brain, observed in several neuroimaging studies, affect both structural and functional features. It seems to modify some structures in the brain, such as the default-mode network. However, the underlying mechanism of these brain modifications remains unclear. It also appears that the efficacy of this therapy is linked to the site of brain stimulation. However, because of numerous heterogeneities in the recruitment of subjects and variations in stimulation sites, the studies included in our review are not clearly comparable. Future research should evaluate the effect of rTMS on the brain, especially concerning morphological MRIs.

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