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REVIEW ARTICLE

Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review

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Depression is one of the most prevalent mental illnesses worldwide and a leading cause of disability, especially in the setting of treatment resistance. In recent years, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising alternative strategy for treatment-resistant depression and its clinical efficacy has been investigated intensively across the world. However, the underlying neurobiological mechanisms of the antidepressant effect of rTMS are still not fully understood. This review aims to systematically synthesize the literature on the neurobiological mechanisms of treatment response to rTMS in patients with depression. Medline (1996–2014), Embase (1980–2014) and PsycINFO (1806–2014) were searched under set terms. Three authors reviewed each article and came to consensus on the inclusion and exclusion criteria. All eligible studies were reviewed, duplicates were removed, and data were extracted individually. Of 1647 articles identified, 66 studies met both inclusion and exclusion criteria. rTMS affects various biological factors that can be measured by current biological techniques. Although a number of studies have explored the neurobiological mechanisms of rTMS, a large variety of rTMS protocols and parameters limits the ability to synthesize these findings into a coherent understanding. However, a convergence of findings suggest that rTMS exerts its therapeutic effects by altering levels of various neurochemicals, electrophysiology as well as blood flow and activity in the brain in a frequency-dependent manner. More research is needed to delineate the neurobiological mechanisms of the antidepressant effect of rTMS. The incorporation of biological assessments into future rTMS clinical trials will help in this regard.

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Introduction

Upwards of 120 million people globally have depression, with 10–15% enduring a lifelong prevalence (Lepine & Briley, 2011). An estimated 15–35% of depressed patients have treatment-resistant depression (TRD), failing to reach remission (Nemeroff, 2007). TRD is associated with significant economic and medical burden: medical costs are six times more for patients with TRD compared with patients with non-TRD ($42 344 *v.* $6512) (Crown *et al.* 2002).

Repetitive transcranial magnetic stimulation (rTMS) has emerged as an effective brain stimulation treatment for depression and TRD specifically (O'Reardon *et al.* 2007; Connolly *et al.* 2012). Several large-scale studies have established the efficacy of this treatment (O'Reardon *et al.* 2007; Schutter, 2009; Fitzgerald *et al.* 2011; George *et al.* 2013). rTMS was approved as a treatment for TRD by the US Food and Drug Administration in 2008, and, since then, it has been used successfully for the treatment of depression in clinical practice, with response and remission rates of 53.4 and 31.5% (Connolly *et al.* 2012), as compared with those of 13.7 and 16.8% for additional sequential

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trials of pharmacotherapy after two failed medication trials (Rush *et al.* 2006).

rTMS uses an electromagnetic coil placed on the scalp to create brief magnetic field pulses. The conventional approach for the treatment of depression directs the magnetic field pulses over the left dorsolateral prefrontal cortex (DLPFC) or the right DLPFC, or both in a sequential pattern. These magnetic fields penetrate the cortex unimpeded and induce an electrical current in the underlying cortex, altering the brain's activity (George *et al.* 2013). Studies have investigated the effect of rTMS on neural circuits by investigating molecular, genetic, electrophysiological and imaging measures of brain function. Despite the large number of clinical trials that have been conducted on the efficacy of rTMS, there is a gap in the understanding of how rTMS exerts its antidepressant action and a summary of biological findings is lacking. Thus, the goal of this systematic review is to summarize and synthesize the literature on the neurobiological mechanisms of action of rTMS over the DLPFC in depressed patients.

Method

Search strategy

We searched three electronic databases: Medline, EMBASE and PsycINFO. Medline was searched from 1996 to March week 4 2015, EMBASE from 1980 to 2015 week 10, and PsycINFO from 1986 to March week 4 2015. The databases were searched using keywords and medical subject headings (MeSH). The search terms that were used to identify potentially relevant articles differed in the Medline, EMBASE and PsycINFO search and focused on terms related to rTMS, neurophysiology and neurobiology. The specific terms used in the search of the Medline database are presented in online Supplementary Table S1. The preliminary database search was conducted by one author (W.K.S.) and three authors (Y.N., W.K.S. and D.M.B.) independently extracted the data from all studies. Bibliographies of articles and review articles were manually searched to identify primary articles that may have been missed in the initial search. Only published, peer-reviewed articles of primary human studies available in English were considered for this review. These publications were identified in the initial stage of the search process, and articles with abstracts indicating relevance, which met the predetermined eligibility criteria, were retrieved to review for inclusion criteria.

Criteria for study selection

Inclusion criteria

We included studies evaluating any neurobiological mechanisms of rTMS in human subjects with depression. Only studies that utilized an rTMS protocol where the stimulation site was the DLPFC were included as this is the predominant target area for the treatment of depression. Studies of any design were included (i.e. experimental and observational) even when there was no comparison group of individuals who did not receive rTMS (i.e. sham rTMS). Studies had to include a neurobiological measure before and after a course of treatment.

Exclusion criteria

We excluded studies evaluating only the cognitive effects of rTMS. Studies with animal, healthy subjects and subjects with other disorders were also excluded. Clinical treatment studies without a concomitant investigation of neurobiological effects were also excluded. Conference abstracts, narrative reviews and editorials were excluded.

Data analysis

A meta-analysis on the effect of rTMS on the various neurobiological functions was planned. However, we were unable to do so as there were an insufficient number of studies per biological factor to effectively analyse the data quantitatively. Additionally, the large degree of heterogeneity in rTMS treatment protocols and the measures used to quantify the neurobiological factors prohibited a quantitative meta-analysis.

Quality assessment

The methodological quality of each study was assessed by first examining the sample size of the study. Those studies with 20 subjects or more were classified as being 'strong' studies, based on expert opinion that this is the minimum sample size needed for a study of biological mechanisms (Schoenfeld, 1980; Birkett & Day, 1994; Julious, 2005; Moore *et al.* 2011). To further classify the quality of the findings, those studies with a control condition of individuals who were not exposed to rTMS were considered stronger than studies without. A four-tiered classification system of strength was thus developed, whereby a score of 1, the strongest-quality study, had 20 or more subjects and control subjects, a score of 2 had 20 or more subjects without a control condition, a score of 3 had fewer than 20 subjects with a control condition, and a score of 4, the weakest-quality study, had fewer than 20 subjects without a control condition.

Results

Characteristics of included studies

Our search terms yielded an initial 1647 articles. Reference lists of relative articles and 11 relevant

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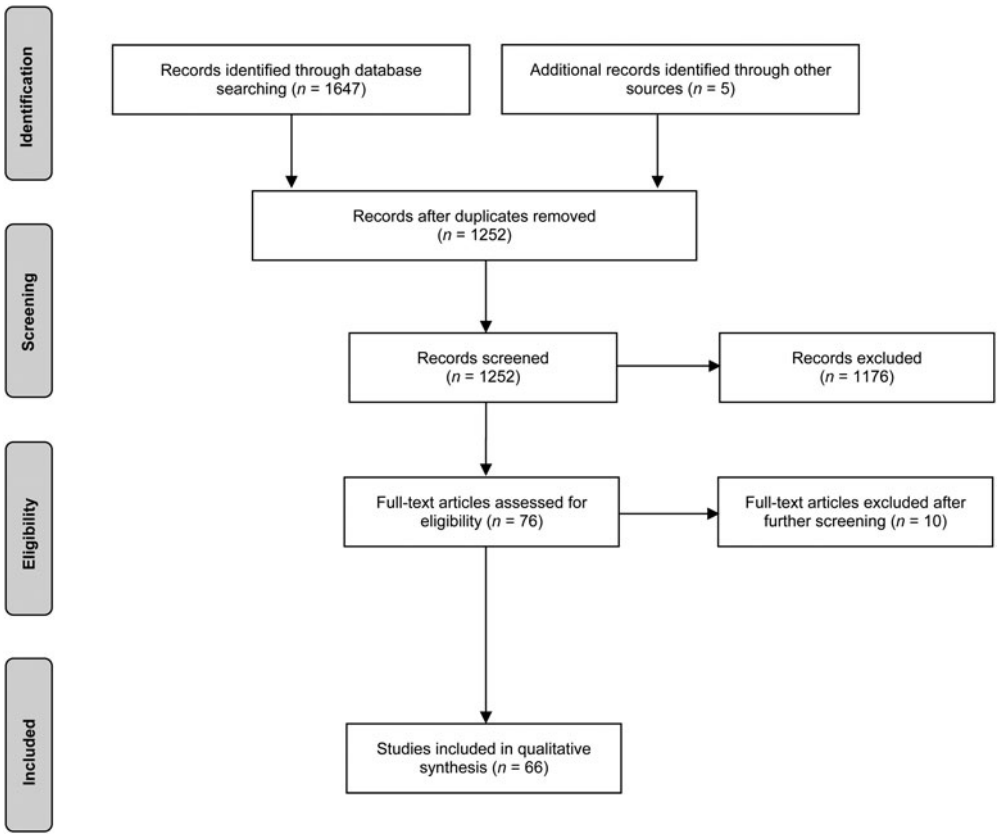

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Moher *et al.* 2009).

reviews were examined and five additional articles meeting inclusion criteria were identified. A total of 1252 were screened for eligibility with 76 full-text articles retrieved and reviewed. After further review, a total of 66 met the full inclusion criteria (Fig. 1). Of these, 14 studies included a control condition and 52 did not. Five studies investigated only the effects of low-frequency right-sided (LFR) rTMS, and 11 studies investigated the effects of LFR and high-frequency left-sided (HFL) rTMS combined. The remaining 50 studies examined the effects of HFL-rTMS alone. Data are presented qualitatively in Table 1 (for detailed information, see online Supplementary Tables S2–S4), and main findings are described in the text.

Effects of rTMS on molecular mechanisms

Neurotransmitters

The neurotransmitter hypothesis of depression postulates that the deficit of certain neurotransmitters such as serotonin, dopamine and/or norepinephrine in the synaptic clefts throughout the brain is responsible for the corresponding features of depression. In this context, the rTMS effect of dopamine is disputed; some studies found that HFL-rTMS did not induce dopamine level changes as measured with magnetic resonance spectroscopy (MRS), positron emission tomography (PET) scans or biochemical examinations (Miniussi *et al*. 2005; Yukimasa *et al*. 2006; Kuroda *et al*. 2006, 2010), whereas other single photon emission computed tomography studies found increased dopamine levels (Pogarell *et al*. 2006, 2007). HFL-rTMS increased norepinephrine measured with biochemical examination (Yukimasa *et al.* 2006), glutamate (Luborzewski *et al.* 2007), choline (Luborzewski *et al.* 2007) and myo-inositol (Zheng *et al.* 2010) levels measured with MRS. Specifically, one study showed a relative increase in glutamate levels (11%) in the left DLPFC in responders after HFL-rTMS (Yang *et al.* 2014). Another MRS study reported that the choline:creatine ratio increased post-HFL-rTMS (Zheng *et al.* 2010). Last, there were no significant differences in the levels of serotonin and 5-hydroxyindoleacetic acid measured with biochemical examination after bilateral rTMS, compared with sham-treated patients (Miniussi *et al.* 2005).

Brain-derived neurotrophic factor (BDNF)

BDNF is a critical neurotrophic factor involved in neuronal homeostasis and neuroplasticity that is decreased in depressed patients (Lee & Kim, 2010). Measures of

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Table 1. *Summary of findings of the various studies, according to the biological function being examined*[a]

Function	Authors	Strength	rTMS protocol	Effect
Genetics				
c-Fos	Teyssier *et al.* (2013)	4	LFR DLPFC	c-Fos expression in leucocytes significantly reduced by 60%
DUSP1				DUSP1 expression in leucocytes significantly reduced by 48.6%
Neurochemical				
3*α*,5*α*-THP	Padberg *et al.* (2002)	2	HFL DLPFC	No change in neuroactive steroid after rTMS compared with baseline
3*α*,5*β*-THP				No change in neuroactive steroid after rTMS compared with baseline
3*β*,5*α*-THP				No change in neuroactive steroid after rTMS compared with baseline
ACTH	Mingli *et al.* (2009)	1	Sleep EEG-modulated/ conventional-rTMS	Plasma ACTH is significantly reduced after rTMS
BDNF	Gedge *et al.* (2012)	4	HFL DLPFC	No change
	Lang *et al.* (2006)	4	HFL DLFPC	No change
	Yukimasa *et al.* (2006)	2	HFL DLPFC	Increased BDNF
	Zanardini *et al.* (2006)	4	LFR DLPFC or HFL DLPFC	Increase BDNF
Choline:creatine ratio	Zheng *et al.* (2010)	3	HFL DLPFC, active or sham	Elevation of choline:creatine ratios after treatment response
Choline	Luborzewski *et al.* (2007)	4	HFL DLPFC	Total choline concentration in the DLPFC increased significantly in responders
Cortisol	Baeken *et al.* (2009*a*)	2	HFL DLPFC, sham-controlled, crossover design	Salivary cortisol concentrations decreased significantly immediately and 30 min after active HF-rTMS
	Mingli *et al.* (2009)	1	SEM/conventional-rTMS	Plasma cortisol is significantly reduced after rTMS
	Reid & Pridmore (1999)	4	HFL DLPFC	Cortisol levels decreased after rTMS
	Zwanzger *et al.* (2003)	2	HFL DLPFC	Decrease not significant
DHEA	Padberg *et al.* (2002)	2	HFL DLPFC	No change in neuroactive steroid after rTMS compared with baseline
Dopamine	Kuroda *et al.* (2006)	3	HFL DLPFC	No significant difference between [^{11}C] raclopride binding potential before and after rTMS in the right ($p = 0.217$) and left caudate nucleus ($p = 0.873$), and the right ($p = 0.938$) and left putamen ($p = 0.607$), and so dopamine levels probably do not change
	Kuroda *et al.* (2010)	4	HFL DLPFC	There was no significant interactions between time and regions with regard to dopamine synthesis rate for L-[*β*-^{11}C]DOPA
	Miniussi *et al.* (2005)	1	17 Hz or 1 Hz left DLPFC, open-label, or double-blind, sham-controlled, crossover design	No significant differences between active and sham rTMS
	Pogarell *et al.* (2006)	4	HFL DLPFC	Left and right striatal iodobenzamide binding to striatal D2 dopamine receptors showed a significant decrease after rTMS, which reflects an increase in binding of endogenous dopamine, and this is probably due to an increased dopamine concentration in the vicinity of the receptors
	Pogarell *et al.* (2007)	4	HFL DLPFC	rTMS caused a decrease in mean specific-to-non-specific iodobenzamide binding, which is probably due to an increase in binding of endogenous dopamine due to an increased concentration of dopamine in the vicinity of the receptors
	Yukimasa *et al.* (2006)	2	HFL DLPFC	No significant change in plasma levels of homovanillic acid
Glutamate	Luborzewski *et al.* (2007)	4	HFL DLPFC	Increase in responders and decrease in non-responders in the DLPFC

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
	Yang *et al.* (2014)	4	HFL DLPFC	After rTMS, responders showed a relative increase of glutamate levels (11%) in the left DLPFC, which corresponded to an improvement in depressive symptom severity. Non-responders had elevated baseline glutamate levels in the same region, compared with responders, which decreased with rTMS (−10%)
Myo-inositol	Zheng *et al.* (2010)	3	HFL DLPFC, active or sham	Increase in myo-inositol in ipsilateral DLPFC
Norepinephrine	Yukimasa *et al.* (2006)	2	HFL DLPFC	3-Methoxy-4-hydroxyphenylglycol (norepinephrine metabolite) was significantly reduced 2 weeks after rTMS
Progesterone	Padberg *et al.* (2002)	2	HFL DLPFC	No change in neuroactive steroid after rTMS compared with baseline
Serotonin and 5-HIAA	Miniussi *et al.* (2005)	1	17 Hz or 1 Hz left DLPFC, open-label, double-blind, sham-controlled, crossover design	No difference between active and sham rTMS
Electrophysiology				
RMT	Bajbouj *et al.* (2005*b*)	4	HFL DLPFC	No significant effect
	Shajahan *et al.* (2002)	4	5 Hz, 10 Hz, or 20 Hz left DLPFC	Motor threshold increases for each frequency
	Triggs *et al.* (1999)	4	HFL DLPFC	Decrease in motor-evoked potential threshold
	Zarkowski *et al.* (2009)	1	HFL DLPFC	On average, the within-subject change from visit 1 to visit 4 was −1.39 units motor threshold (decrease by 2.45% from visit 1)
CSP	Bajbouj *et al.* (2005*b*)	4	HFL DLPFC	No change in CSP
	Bajbouj *et al.* (2005*a*)	2	HFL DLPFC	CSP increases in responder
ICF	Bajbouj *et al.* (2005*b*)	4	HFL DLPFC	No change in ICF
	Bajbouj *et al.* (2005*a*)	2	HFL DLPFC	No change in ICF
ICI	Bajbouj *et al.* (2005*b*)	4	HFL DLPFC	ICI increases
	Bajbouj *et al.* (2005*a*)	2	HFL DLPFC	ICI is significantly enhanced after 10 sessions of rTMS
Auditory threshold	Loo *et al.* (2001)	3	HFL DLPFC	Audiology results did not differ between real- and sham treatment groups over the first 2 weeks. No significant changes were detected after the first 4 weeks of rTMS (for real and sham groups analysed together)
ERP – N1 amplitude	Spronk *et al.* (2008)	4	HFL DLPFC	In left hemisphere, the N1 amplitude after rTMS was smaller compared with pre-rTMS. In the right hemisphere, there was no difference between N1 pre- and post-rTMS
ERP – N2 amplitude	Spronk *et al.* (2008)	4	HFL DLPFC	In the left hemisphere, N2, pre-rTMS were more negative compared with after rTMS, and in the right hemisphere, N2 amplitude was comparable pre- and post-rTMS
	Choi *et al.* (2014)	4	HFL DLPFC	In ERP auditory oddball task, P200 amplitudes showed a main effect of time and increased after 3 weeks of rTMS treatment. Standardized low-resolution brain electromagnetic tomography showed significant activation in the left middle frontal gyrus by 3 weeks of rTMS treatment
ERP – P2 amplitude	Spronk *et al.* (2008)	4	HFL DLPFC	In the left hemisphere, P2 was larger post-rTMS than pre-rTMS, whereas there were no significant differences pre- and post-, in the right hemisphere
ERP – P3 amplitude	Spronk *et al.* (2008)	4	HFL DLPFC	P3 was larger in the left hemisphere post-rTMS, and P3's amplitude was about the same in the right hemisphere, pre- and post-treatment

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
	Moller *et al.* (2006)	3	HFL DLPFC, double-blind, sham-controlled, crossover design	P300 amplitude increased significantly, but latency did not change
Alpha band power of the EEG	García-Anaya *et al.* (2011)	2	LFR DLPFC	rTMS causes changes mainly over the frontal, central and temporal regions, but the effect was not as great as for beta
			HFL DLPFC	rTMS caused particularly significant changes in the frontal, central regions
	Loo *et al.* (2001)	3	HFL DLPFC	No change
	Noda *et al.* (2013)	2	HFL DLPFC	Alpha band power significantly increases at seven prefrontal electrode sites
	Pellicciari *et al.* (2013)	4	Sequential bilateral rTMS; LFR and HFL DLPFC	Significant decrease of alpha power over the left-DLPFC during rapid eye movement sleep
	Spronk *et al.* (2008)	4	HFL DLPFC	Alpha band powers do not change significantly during eyes open after rTMS treatment
	Valiulis *et al.* (2012)	2	HFL DLPFC	Alpha power increased in the right hemisphere and central and parietal regions post-HFL-10 Hz-rTMS
			LFR DLPFC	Frontal alpha power asymmetry increased towards the right hemisphere post-LFR-1 Hz-rTMS
Beta band power of the EEG	García-Anaya *et al.* (2011)	2	LFR DLPFC	rTMS caused changes in the frontal, central and temporal regions, but the effect was not as large as with alpha
			HFL DLPFC	rTMS elicited changes mainly over the frontal and temporal regions
	Loo *et al.* (2001)	3	HFL DLPFC	No change
	Spronk *et al.* (2008)	4	HFL DLPFC	No significant differences seen – this is with eyes open
Delta band power of the EEG	Loo *et al.* (2001)	3	HFL DLPFC	No change
	Noda *et al.* (2013)	2	HFL DLPFC	Delta band power significantly increased at seven prefrontal electrode sites
	Saeki *et al.* (2013)	4	HFL DLPFC	Local significant increase in delta band power (i.e. slow wave activity) at F3 during stage II–IV sleep periods
	Spronk *et al.* (2008)	4	HFL DLPFC	Delta band power increased in the right hemisphere, but no significant change
	Valiulis *et al.* (2012)	2	HFL DLPFC	Delta band power increased in the central and parietal regions, as well as in the left hemisphere
Theta band power of the EEG	Loo *et al.* (2001)	3	HFL DLPFC	No change
	Noda *et al.* (2013)	2	HFL DLPFC	Theta band power significantly increases at seven prefrontal electrode sites
	Spronk *et al.* (2008)	4	HFL DLPFC	No significant effect in theta power after rTMS sessions
	Valiulis *et al.* (2012)	2	HFL DLPFC	Theta power was increased in the central, parietal and occipital regions, as well as across the whole brain
Sigma band power	Saeki *et al.* (2013)	4	HFL DLPFC	No significant changes in sigma band power
Cordance in delta and theta band power	Ozekes *et al.* (2014)	2	HFL DLPFC	After HFL-rTMS, cordance, which is related to absolute and relative spectral powers derived from the resting EEG, increased in both delta and theta bands at all right, except for F8, and left frontal electrodes in responders, whereas it decreased in left frontal and right prefrontal regions in non-responders
Functional connectivity in gamma band	Kito *et al.* (2014)	4	HFL DLPFC	In sLORETA, resting EEG functional connectivity anti-correlation between the left DLPFC and precuneus in gamma band was

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
				significantly modulated by HFL-rTMS treatment in patients with depression
Psychomotor inhibition	Crevits *et al.* (2005)	4	HFL DLPFC	The latency of the antisaccade after rTMS was significantly shorter than before rTMS, and the better suppression of unwanted saccade behavior paralleled a decrease in psychomotor inhibition
Sympatho-vagal balance	Udupa *et al.* (2007)	2	HFL DLPFC	rTMS reduced the sympathovagal balance by causing an increase in PNS activity and a decrease in SNS activity
Neuroimaging				
Global blood flow	Mottaghy *et al.* (2002)	4	HFL DLPFC	After rTMS, right–left asymmetry favored the left hemisphere, whereas before rTMS it favored the right side
Glucose metabolism	Baeken *et al.* (2009*b*)	2	HFL DLPFC	Significant increase of baseline prefrontal brain glucose metabolism (cerebral metabolic rate of glucose) in the left BA32, right BA32 and right BA24. Significantly decreased in the left fusiform gyrus and left middle temporal cortex. Significant increases in the middle cingulum, bilateral somatosensory areas, and precuneus
	Li *et al.* (2010)	2	HFL DLPFC	Significant decreases of rCBF in the left fusiform gyrus and left middle temporal cortex, and significant increases of rCBF in the middle cingulum, bilateral somatosensory areas and precuneus with HFL-rTMS
Blood–brain barrier	Li *et al.* (2003)	3	LFL DLPFC	No significant difference in diffusion MRI was found between pre-rTMS scans and post-rTMS scans, and so rTMS does not appear to result in pathological changes or leakage of the blood–brain barrier in patients with depression
Frontal lobe	Nahas *et al.* (2001)	3	20 Hz, 5 Hz, or sham left DLPFC, double-blind sham-controlled design	Active rTMS ($n = 14$) showed relatively increased rCBF in the right medial frontal lobe and left middle frontal gyrus compared with baseline
Frontal white matter	Kozel *et al.* (2011)	3	HFL DLPFC, sham-controlled design	There was a mean increase that was found for the left prefrontal white matter (ipsilateral side). Post-FA values were higher for active rTMS than for sham
	Peng *et al.* (2012)	3	HFL DLPFC, randomized double-blind, sham-controlled design	The reduced FA in the left frontal gyrus was significantly improved and increased after active rTMS treatment compared with sham rTMS
	Kito *et al.* (2011*b*)	2	LFR DLPFC	rCBF in the right frontal cortex was significantly decreased after rTMS, and therapeutic efficacy of rTMS was correlated with decreased rCBF in bilateral frontal white matter
PFC	Catafau *et al.* (2001)	4	HFL DLPFC	Significant increase of rCBF in the left lateral PFC with HFL-rTMS at endpoint compared with baseline and during the rTMS activation
	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the bilateral medial prefrontal cortex after rTMS
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the right prefrontal cortex during LFL-rTMS

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
	Nahas *et al.* (2000)	3	20 Hz, 5 Hz, or sham left DLPFC, randomized double-blind, sham-controlled design	No significant changes in the ratio of total volume of left prefrontal cortex and the intracranial volume after active rTMS
	Speer *et al.* (2000)	3	HF, LF, or sham left DLPFC, randomized cross-over design	rCBF significantly increased with 20 Hz rTMS in left PFC (left > right), and it decreased with 1 Hz rTMS in right PFC
Middle frontal gyrus (BA9)	Fitzgerald *et al.* (2007)	2	LFR or HFL DLPFC, double-blind, randomized design	Significant decrease of activation in the bilateral middle frontal gyrus with LFR-rTMS in responders
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz, or sham left DLPFC, double-blind sham-controlled design	Significant increase of rCBF in the left middle frontal gyrus from baseline with active rTMS
Medial frontal gyrus	Fitzgerald *et al.* (2007)	2	LFR or HFL DLPFC, double-blind, randomized design	Significant increase of activation in the left medial frontal gyrus with HFL-rTMS in responders
DLPFC	Kito *et al.* (2008*a*)	4	HFL DLPFC	Significant increase of rCBF in the left DLPFC after HFL-rTMS and significant clinical correlation was observed between the rCBF increase and HAM-D improvement
	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the bilateral DLPFC after rTMS
	Kito *et al.* (2011*a*)	2	LFR DLPFC	rCBF in the right DLPFC was significantly decreased after rTMS, and therapeutic efficacy of rTMS was correlated with decreased rCBF in the right DLPFC
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase in %BOLD signal change in the bilateral DLPFC during LFL-rTMS
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz, or sham left DLPFC, double-blind sham-controlled design	Subjects with HFL-rTMS showed relatively increased rCBF in the left DLPFC with fast 20 Hz rTMS, as compared with slow 5 Hz rTMS
Dorsomedial frontal cortex	Loo *et al.* (2003)	3	HFL DLPFC	Significant increase of rCBF in the right dorsomedial frontal cortex with HFL-rTMS
Ventrolateral prefontal cortex	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significant decrease of rCBF in the right VLPFC after rTMS
Ventromedial prefrontal cortex	Li *et al.* (2004)	4	LFL DLPFC	Significant decrease of %BOLD signal change in the right ventromedial prefrontal cortex during LFL-rTMS
Inferior frontal lobe	Fitzgerald *et al.* (2007)	2	LFR or HFL DLPFC, double-blind, randomized design	Significant increase of activation in the right inferior frontal gyrus with HFL-rTMS in responders
	Loo *et al.* (2003)	3	HFL DLPFC	Significant increase of rCBF in the bilateral inferior frontal cortices (left > right) with HFL-rTMS
	Teneback *et al.* (1999)	3	20 Hz, 5 Hz, or sham left DLPFC	Significant increase of rCBF in the bilateral inferior frontal lobe in responders with HFL-rTMS compared with non-responders
Orbitofrontal cortex	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the bilateral orbitofrontal cortex after rTMS
	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significant decrease of rCBF in the right orbitofrontal cortex after LFR-rTMS, and therapeutic efficacy of LFR-rTMS was correlated with decreased rCBF in the bilateral orbitofrontal cortex
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the right orbitofrontal cortex during LFL-rTMS
	Nadeau *et al.* (2002)	4	HFL or LFR DLPFC	Large decrements of rCBF in orbitofrontal cortex in association with improvement (responders)

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
	Loo *et al.* (2003)	3	HFL DLPFC	Significant decrease of rCBF in the right orbital cortex for HFL-rTMS
Premotor area	Kito *et al.* (2008*a*)	4	HFL DLPFC	Significant increase of rCBF in the premotor area after HFL-rTMS
	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the bilateral premotor area after LFR-rTMS
Precentral gyrus	Fitzgerald *et al.* (2007)	2	LFR or HFL DLPFC, double-blind, randomized design	Significant increase of activation in the left precentral gyrus with HFL-rTMS in responders
Somato-sensory regions	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the left somatosensory region after rTMS
	Loo *et al.* (2003)	3	LFL DLPFC	Significant increase of rCBF in the left somatosensory cortex for LFL-rTMS
Temporal lobe	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the left middle temporal cortex during LFL-rTMS
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	Significant decrease of rCBF in the left middle temporal gyrus with active rTMS compared with the sham rTMS
	Speer *et al.* (2000)	3	LFL DLPFC	Significant decrease of rCBF in the left medial temporal lobe after LFL-rTMS
	Teneback *et al.* (1999)	3	20 Hz, 5 Hz, or sham left DLPFC	Significant decrease of rCBF in the right medial temporal lobe in responders compared with non-responders after HFL-rTMS
Parietal region	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the left inferior parietal region after LFR-rTMS
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the bilateral parietal lobes during LFL-rTMS
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	Significant decrease of rCBF in the bilateral parietal lobe with active rTMS compared with sham rTMS
Insula	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the bilateral anterior insula after LFR-rTMS
	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significantly decreased rCBF in the right anterior and posterior insula after LFR-rTMS, and therapeutic efficacy of rTMS was correlated with decreased rCBF in the anterior cortex
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the bilateral insula during LFL-rTMS
	Loo *et al.* (2003)	3	LFL DLPFC	Significant increase of rCBF in the left and right insula with LFL-rTMS
	Nadeau *et al.* (2002)	4	HFL or LFR DLPFC	Reductions of rCBF in bilateral insula in responders
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	Significant decrease of rCBF in the left insula from baseline with active rTMS
	Speer *et al.* (2000)	3	HFL DLPFC	Significant increase of rCBF in the bilateral insula with HFL-rTMS
Amygdala	Furtado *et al.* (2013)	2	HFL DLPFC or sequential bilateral HFL + LFR DLPFC	Left amygdala volume non-significantly increases in responders with HFL-rTMS
	Nadeau *et al.* (2002)	4	HFL or LFR DLPFC	Reduction of rCBF in the right amygdala in responders
	Speer *et al.* (2000)	3	HFL DLPFC	rCBF significantly increases in the left amygdala with HFL 20 Hz rTMS while it significantly decreases in the left amygdala with LFL 1 Hz rTMS.
Cingulate cortex	Loo *et al.* (2003)	3	HFL DLPFC	Significant increase of rCBF in the right posterior cingulate with HFL-rTMS

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	rCBF in the left cingulate significantly decreased from baseline with active rTMS, and it relatively increased in the left mid-cingulate with fast 20 Hz as compared with slow 5 Hz
	Speer *et al.* (2000)	3	HFL DLPFC	rCBF in the cingulate gyrus (left>>right) significantly increased with HFL 20 Hz rTMS
	Teneback *et al.* (1999)	3	20 Hz, 5 Hz, or sham left DLPFC	Significant increase of rCBF in the cingulate from baseline within responders after HFL-rTMS
ACC (BA 24, 32, 33)	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the left anterior cingulate after rTMS
	Li *et al.* (2004)	4	LFL DLPFC	Significant decrease of %BOLD signal change in the anterior cingulate cortex during LFL-rTMS
	Loo *et al.* (2003)	3	LFL DLPFC	Significant increase of rCBF in the right dorsal anterior cingulate with LFL-rTMS
	Nadeau *et al.* (2002)	4	HFL or LFR DLPFC	Large decrements of rCBF in anterior cingulate in association with improvement (responders)
	Shajahan *et al.* (2002)	4	5 Hz, 10 Hz, or 20 Hz left DLPFC	Rostral anterior cingulate cortex was significantly activated with HFL-rTMS
	Zheng (2000)	4	HFL DLPFC, double-blind, sham-controlled, cross-over design	Significant increase of rCBF in the left anterior cingulate cortex with HFL-rTMS
Subgenual cingulate (BA 25, 32)	Kito *et al.* (2008*b*)	4	LFR DLPFC	Significant decrease of rCBF in the right subgenual cingulate after LFR-rTMS
	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significant decrease of rCBF in the right subgenual cingulate after LFR-rTMS and therapeutic efficacy of rTMS was also correlated with decreased rCBF in the same region
Subgenual ACC/Cg25 (BA 24 anteriorly and 25 posteriorly)	Takahashi *et al.* (2013)	4	HFL DLPFC	rCBF in the Cg25 decreases after HFL-rTMS in responders
	Baeken *et al.* (2014)	1	HFL DLPFC, five sessions/day, spread over 4 days, randomized, single-blind, sham-controlled crossover experimental design	At baseline, responders showed strong anti-correlation between the subgenual ACC and parts of the left superior medial prefrontal cortex, while non-responders showed a slightly positive correlation. After HFL-rTMS treatment, the roles were inverted: the anti-correlation became slightly positive in responders while the correlation become slightly negative, although not significant, in non-responders
Precuneus	Dumas *et al.* (2012)	4	LFR DLPFC	Clinical correlation was observed between improvement of health-related quality of life scores and decrease of rCBF in the precuneus
	Fitzgerald *et al.* (2007)	2	LFR or HFL DLPFC, double-blind, randomized design	Significant decrease of activation in the left precuneus with LFR-rTMS in responders, and significant increase of activation in the left precuneus with HFL-rTMS in all subjects
	Loo *et al.* (2003)	3	LFL DLPFC	Significant increase of rCBF in the right precuneus with LFL-rTMS
Perirhinal cortex	Richieri *et al.* (2012)	2	HFL or LFR DLPFC	Responders presented significant rCBF decrease in the left perirhinal cortex compared with non-responders (BA35, BA36) after rTMS in the whole group of patients (patients with either left or right stimulation)
Uncus	Loo *et al.* (2003)	3	HFL DLPFC	Significant decrease of rCBF in the left uncus with HFL-rTMS

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	Relative decrease of rCBF in the left uncus with active rTMS
	Speer *et al.* (2000)	3	HFL DLPFC	Significant increase of rCBF in the bilateral uncus with HFL 20 Hz rTMS
Subcallosal gyrus	Loo *et al.* (2003)	3	HFL DLPFC	Significant decrease of rCBF in the right subcallosal gyrus with HFL-rTMS
Hippocampus	Furtado *et al.* (2013)	2	HFL DLPFC or sequential bilateral HFL + LFR DLPFC	Overall significant group reduction in the left hippocampal volume in non-responders with HFL-rTMS
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in ipsilateral hippocampus with LFL-rTMS
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	Significant decrease of rCBF in the left hippocampus with fast 20 Hz rTMS in comparison with those receiving slow 5 Hz rTMS
	Speer *et al.* (2000)	3	HFL DLPFC	Significant increase of rCBF in the bilateral hippocampus with HFL 20 Hz rTMS
Para-hippocampus	Loo *et al.* (2003)	3	HFL DLPFC	Significant increase of rCBF in the right parahippocampus with HFL-rTMS
	Speer *et al.* (2000)	3	HFL DLPFC	Significant increase of rCBF in the bilateral parahippocampus with HFL 20 Hz rTMS
Basal ganglia	Speer *et al.* (2000)	3	HFL or LFL DLPFC	rCBF significantly increased in the bilateral basal ganglia with 20 Hz rTMS while it significantly decreased in the left basal ganglia with LFL 1 Hz rTMS
Globus pallidus	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significant decrease of rCBF in the right globus pallidus with LFR-rTMS
Putamen	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the bilateral putamen after LFL-rTMS
Cerebellum	Loo *et al.* (2003)	3	LFL DLPFC	Significant increase of rCBF in the left cerebellum (vermis, intermediate zone) with LFL-rTMS
	Speer *et al.* (2000)	3	HFL DLPFC	Significant increase of rCBF in the bilateral cerebellum with HFL 20 Hz rTMS
Thalamus	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significant decrease of rCBF in the right thalamus with LFR-rTMS
	Li *et al.* (2004)	4	LFL DLPFC	Significant increase of %BOLD signal change in the bilateral thalamus (ipsilateral mediodorsal, bilateral pulvinar, anterior nucleus) with LFL-rTMS
	Nahas *et al.* (2001)	3	20 Hz, 5 Hz or sham left DLPFC, double-blind sham-controlled design	Significant decrease of rCBF in the right thalamus with active rTMS compared with sham rTMS
	Speer *et al.* (2000)	3	HFL DLPFC	Significant increase of rCBF in the bilateral thalamus with 20 Hz rTMS
Midbrain	Kito *et al.* (2011*a*)	2	LFR DLPFC	Significant decrease of rCBF in the right midbrain with LFR-rTMS
DLPFC circuit	Shajahan *et al.* (2002)	4	5 Hz, 10 Hz, or 20 Hz left DLPFC	Connectivity of DLPFC to caudate as well as caudate to globus pallidus increase in the left, but no significant changes were seen in the right hemisphere
Limbic circuit	Shajahan *et al.* (2002)	4	5 Hz, 10 Hz, or 20 Hz left DLPFC	Connectivity of medial orbitofrontal cortex to ventral striatum connectivity and amygdala to ventral striatum increase in the left. Connectivity of medial orbitofrontal cortex to ventral striatum, and thalamus to medial orbitofrontal cortex increased, but that of ventral striatum to globus pallidus decreased
Default mode network	Liston *et al.* (2014)	3	HFL DLPFC	HFL-rTMS selectively modulates functional connectivity both within and between the

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Table 1 (*cont.*)

Function	Authors	Strength	rTMS protocol	Effect
and central executive network				central executive network and default mode network. Modulation of subgenual cingulate connectivity may play an important mechanistic role in alleviating depression

rTMS, Repetitive transcranial magnetic stimulation; LFR, low-frequency right-sided; DLPFC, dorsolateral prefrontal cortex; THP, tetrahydroprogesterone; HFL, high-frequency left-sided; ACTH, adrenocorticotropic hormone; EEG, electroencephalography; BDNF, brain-derived neurotrophic factor; SEM, sleep electroencephalogram modulated; DHEA, dehydroepi-androsterone; 5-HIAA, 5-hydroxyindoleacetic acid; RMT, resting motor threshold; CSP, cortical silent period; ICF, intracortical facilitation; ICI, intracortical inhibition; ERP, event-related potential; sLORETA, low-resolution brain electromagnetic tomography; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; BA, Brodmann area; FA, fractional anisotropy; rCBF, regional cerebral blood flow; PFC, prefrontal cortex; BOLD, blood oxygen level-dependent; LFL, low-frequency left-sided; HAM-D, Hamilton Depression Rating Scale; ACC, anterior cingulate cortex.

[a] Findings were categorized by neurobiological function in three tables; each table contained the neurobiological factors of molecular factors, genetic polymorphisms or gene expression, electrophysiology, and neuroimaging changes induced by rTMS treatment (see Supplementary Tables S2–S4). For each function, the effect of rTMS on the function was summarized. The authors' names, number of subjects, study design (e.g. experimental, observational), rTMS protocol, the neurobiological parameter under study, and the findings were extracted from each included study. Studies were then categorized by the biological measure examined: molecular factors, genetic polymorphisms or gene expression, electrophysiology, and neuroimaging.

BDNF using the enzyme-linked immunosorbent assay (ELISA) method before and after rTMS treatment have shown some conflicting results; some studies found that HFL-rTMS causes BDNF levels not to change (Lang *et al.* 2006; Gedge *et al.* 2012), whereas others found it to increase (Yukimasa *et al.* 2006; Zanardini *et al.* 2006). However, it should be noted that brain regions stimulated by rTMS could potentially show localized and important changes in BDNF activity that are not detectable in peripheral blood samples.

Cortisol and other neurohormones

Hypothalamic–pituitary–adrenocortical dysregulation is a pathophysiological mechanism involved in depression. In three out of four studies that used a dexamethasone–corticotrophin-releasing hormone test, cortisol levels decreased significantly among subjects after HFL-rTMS (Reid & Pridmore, 1999; Baeken *et al.* 2009*a*; Mingli *et al.* 2009). In the fourth study, cortisol levels decreased only among subjects who did respond to HFL-rTMS treatment (Zwanzger *et al.* 2003). However, one strong study showed significantly lower plasma adrenocorticotropic hormone and cortisol concentrations post-rTMS (Mingli *et al.* 2009). In another study, no changes in the quantity of dehydroepi-androsterone (DHEA), progesterone, allopregnanolones [3β,5α-tetrahydroprogesterone (THP), 3α,5β-THP and 3α,5α-THP] were detected following HFL-rTMS (Padberg *et al.* 2002).

Gene expression

Leucocyte expression of c-FOS and DUSP1 is recognized as unique peripheral biomarker (Le-Niculescu *et al.* 2011) of anxiety and psychological stress. The expression of c-FOS and DUSP1 decreased in leucocytes post-LFR-rTMS (Teyssier *et al.* 2013), which suggests a down-regulation in the expression of stress response genes.

Effects of rTMS on electrophysiological mechanisms

Electroencephalography (EEG) studies

Alpha band. HFL-rTMS causes significant changes in frontal regions of the alpha (about 8–13 Hz) and beta (about 14–30 Hz) bands of the EEG, where the effect is greater in the alpha band (García–Anaya *et al.* 2011). Specifically, HFL-rTMS was shown to increase alpha band power in the central and parietal regions (Valiulis *et al.* 2012). In addition, HFL-rTMS increased the alpha 2 (high-alpha) power when eyes are open (Spronk *et al.* 2008). Alpha power increases in the right hemisphere post-HFL-rTMS (Valiulis *et al.* 2012) have been shown, whereas others found increases without electrode specificity in the prefrontal region after HFL-rTMS (Noda *et al.* 2013). Post-HFL-rTMS, alpha power significantly decreased over the left-DLPFC during rapid eye movement sleep (Pellicciari *et al.* 2013). rTMS administered in the alpha frequency band synchronized to patient's individual alpha frequency (i.e. synchronized rTMS) promoted immediate event-related synchronization followed by

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event-related desynchronization in the alpha band (Leuchter *et al.* 2013).

Beta band. One study found that LFR-rTMS caused changes in the alpha (8–13 Hz) and beta (14–30 Hz) bands of the EEG, particularly over the frontal, central and temporal regions, where the effect was more pronounced in the beta band (García-Anaya *et al.* 2011).

Theta band. The theta (4–7 Hz) band of the EEG was found not to change post-HFL-rTMS in two out of four studies (Loo *et al.* 2001; Spronk *et al.* 2008). However, it was reported that theta power was lower post-HFL-rTMS when the subjects' eyes were closed (Spronk *et al.* 2008). Other studies demonstrated that theta power increased post-HFL-rTMS in the prefrontal (Noda *et al.* 2013), central, parietal and occipital regions, where the increase in power was seen across the whole brain (Valiulis *et al.* 2012).

Delta band. Some studies demonstrated delta (0.5–3 Hz) band activity increased post-HFL-rTMS (Spronk *et al.* 2008; Saeki *et al.* 2013; Noda *et al.* 2013), particularly in the central and parietal regions (Valiulis *et al.* 2012), which led to a subsequent theta power increase in the left hemisphere (Valiulis *et al.* 2012). One study showed delta power was significantly increased without specificity at prefrontal electrode sites (Noda *et al.* 2013).

Cordance in delta and theta band power. Cordance, which is related to absolute and relative spectral powers derived from the resting EEG, increased after HFL-rTMS in both delta and theta bands at left frontal and all right electrodes, except for the F8 electrode, in responders, whereas it decreased in left frontal and right prefrontal regions in non-responder (Ozekes *et al.* 2014).

Sigma band. HFL-rTMS also did not cause significant changes in the sigma band (i.e. 11–15 Hz; spindle at stage 2 in sleep EEG) power (Saeki *et al.* 2013).

Resting-state functional connectivity in gamma band. In a standardized low-resolution brain electromagnetic tomography (sLORETA) method, resting-state functional connectivity anti-correlation in the gamma band between the left DLPFC and precuneus was significantly modulated by HFL-rTMS (Kito *et al.* 2014).

Event-related potentials (ERPs)/rTMS-related potentials. rTMS also affects various different event-related potentials. Specifically, in the oddball ERP, the amplitude of P2 and P3 post-HFL-rTMS increased ipsilaterally, whereas the amplitude of N1 and N2 decreased ipsilaterally (Spronk *et al.* 2008). A more recent study has replicated the result that P2 amplitude was significantly increased in the left middle frontal gyrus after 3 weeks of HFL-rTMS (Choi *et al.* 2014). Also, LFR-rTMS was shown to increase frontal alpha power asymmetry towards the right hemisphere (Valiulis *et al.* 2012).

TMS neurophysiology studies in the motor cortex

There are conflicting findings as to what the effect of rTMS is on resting motor threshold (RMT); one study demonstrated that HFL-rTMS does not affect RMT (Bajbouj *et al.* 2005*b*) whereas other studies have shown that HFL-rTMS causes MT to decrease (Triggs *et al.* 1999; Zarkowski *et al.* 2009) or increase (Shajahan *et al.* 2002). HFL-rTMS causes P300 (Moller *et al.* 2006; Spronk *et al.* 2008) and intracortical inhibition (Bajbouj *et al.* 2005*a*, *b*) to increase, the latter suggesting that rTMS further activates the GABAergic system, whereas auditory threshold (Loo *et al.* 2001), and intracortical facilitation (Bajbouj *et al.* 2005*a*, *b*) remain unchanged. The effect of HFL-rTMS on the cortical silent period (CSP) is not clear; one study has found that it does not change (Bajbouj *et al.* 2005*b*) whereas another shows it does (Bajbouj *et al.* 2005*a*). In summary, these studies provide relatively inconclusive information on the neurobiological effects of rTMS in depression.

Other neurophysiology studies

Post-HFL-rTMS, sympathovagal balance was found to be reduced as it causes an increase in parasympathetic nervous system activity, and a decrease in sympathetic nervous system activity (Udupa *et al.* 2007). Last, HFL-rTMS suppressed unwanted saccade behavior, which is thought to represent decreased psychomotor inhibition (Crevits *et al.* 2005).

Effects of rTMS on cerebral activity, blood flow, volume and functional connectivity as measured by neuroimaging

Global brain function

HFL-rTMS does not appear to affect the integrity of the blood–brain barrier (Li *et al.* 2003). LFR-rTMS decreased global blood flow, but HFL-rTMS also caused blood flow to increase ipsilaterally (Mottaghy *et al.* 2002; Kito *et al.* 2011*a*). HFL-rTMS caused glucose metabolism to decrease in the left fusiform gyrus and left middle temporal cortex (Baeken *et al.* 2009*b*; Li *et al.* 2010) and increase in the middle cingulum, bilateral somatosensory areas, precuneus, bilateral Brodmann area (BA) 32, and right BA24 (Baeken *et al.* 2009*b*; Li *et al.* 2010). White matter fractional anisotropy (FA) in the left prefrontal and middle frontal gyrus increased post-HFL-rTMS (Kozel *et al.* 2011; Peng *et al.* 2012).

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Cerebral cortex

Prefrontal cortex. HFL-rTMS caused regional cerebral blood flow (rCBF) to increase in most studies (Speer *et al.* 2000; Catafau *et al.* 2001; Li *et al.* 2004), although in one study it did not cause any rCBF change (Nahas *et al.* 2000) in the prefrontal cortex. In the DLPFC, HFL-rTMS increased rCBF (Nahas *et al.* 2001) and LFR-rTMS decreased it (Fitzgerald *et al.* 2007). Other studies have also found that HFL-rTMS increased rCBF (Nahas *et al.* 2001; Li *et al.* 2004; Kito *et al.* 2008*a*) and LFR decreased rCBF in the DLPFC (Kito *et al.* 2008*b*, 2011*a*). HFL-rTMS also caused blood flow and activity to increase in the dorsomedial frontal cortex (Loo *et al.* 2003; Fitzgerald *et al.* 2007). HFL-rTMS also caused blood flow and activity to consistently increase across several studies in the inferior frontal lobe (Teneback *et al.* 1999; Loo *et al.* 2003; Fitzgerald *et al.* 2007). In the orbitofrontal cortex, low-frequency left-sided rTMS increased rCBF in one study (Li *et al.* 2004), and decreased it in others (Nadeau *et al.* 2002; Loo *et al.* 2003), whereas LFR-rTMS only decreased rCBF (Kito *et al.* 2008*b*, 2011*a*). In the ventrolateral prefrontal cortex, activity and rCBF decreased post-LFR-rTMS (Kito *et al.* 2011*a*), while in the ventromedial prefrontal cortex, post-HFL-rTMS, activity and rCBF decreased (Li *et al.* 2004). In frontal white matter, activity and rCBF decreased post-LFR-rTMS (Kito *et al.* 2011*a*). White matter FA in the left prefrontal cortex and middle frontal gyrus increased post-HFL-rTMS (Kozel *et al.* 2011; Peng *et al.* 2012).

Primary motor and somatosensory cortex. HFL-rTMS increased rCBF (Kito *et al.* 2008*a*) and LFR-rTMS decreased rCBF in the premotor (Kito *et al.* 2008*b*) and somatosensory regions (Loo *et al.* 2003; Kito *et al.* 2008*b*). HFL and bilateral rTMS caused blood flow and activity to be consistently increased in the precentral gyrus (Fitzgerald *et al.* 2007; Takahashi *et al.* 2013).

Parietal, temporal, and occipital lobes. In the parietal lobe, HFL-rTMS caused rCBF to either increase (Li *et al.* 2004) or decrease (Nahas *et al.* 2001), whereas LFR-rTMS decreased rCBF (Kito *et al.* 2008*b*) and bilateral rTMS increased it in the parietal region (Takahashi *et al.* 2013). Bilateral rTMS consistently increased rCBF in the angular gyrus (Takahashi *et al.* 2013). Bilateral rTMS consistently increased rCBF in the bilateral anterior gyrus (Takahashi *et al.* 2013). HFL-rTMS increased rCBF (Loo *et al.* 2003) and LFR-rTMS decreased rCBF in the precuneus (Fitzgerald *et al.* 2007; Dumas *et al.* 2012). In the temporal lobe, in one study, HFL-rTMS increased rCBF (Li *et al.* 2004), whereas in other studies, HFL-rTMS caused rCBF to decrease (Teneback *et al.* 1999; Speer *et al.* 2000; Nahas *et al.* 2001). Bilateral rTMS also caused rCBF to decrease in the temporal lobe (Takahashi *et al.* 2013). In the uncus, HFL-rTMS increased rCBF (Speer *et al.* 2000) in certain studies, and it decreased it in others (Nahas *et al.* 2001; Loo *et al.* 2003). HFL-rTMS caused glucose metabolism to decrease in the left fusiform gyrus and left middle temporal cortex (Loo *et al.* 2001). Responders presented with significant decreases in activity and rCBF post-bilateral rTMS, as compared with non-responders, in the perirhinal cortex (Richieri *et al.* 2012). In the occipital lobe, activity and rCBF decreased post-bilateral rTMS (Takahashi *et al.* 2013).

Limbic cortex

Cingulate gyrus and insula. In the cingulate cortex, HFL-rTMS has demonstrated conflicting results regarding increased (Zheng, 2000; Shajahan *et al.* 2002; Loo *et al.* 2003) and decreased rCBF (Nadeau *et al.* 2002; Li *et al.* 2004). In the subgenual cingulate cortex, activity and rCBF was decreased post-bilateral-rTMS (Takahashi *et al.* 2013) and post-HFL-rTMS (Loo *et al.* 2003); LFR-rTMS decreased rCBF in the subgenual cingulate in some studies (Kito *et al.* 2008*b*, 2011*a*), but increased it in another (Kito *et al.* 2011*b*). In the insula, HFL-rTMS increased rCBF in some studies (Speer *et al.* 2000; Loo *et al.* 2003; Li *et al.* 2004), and decreased it in others (Nahas *et al.* 2001; Nadeau *et al.* 2002). LFR-rTMS decreased rCBF in the insula (Kito *et al.* 2008*b*, 2011*a*).

Amygdala. HFL-rTMS increased blood flow in one study (Speer *et al.* 2000), but in another study it decreased (Nadeau *et al.* 2002). HFL-rTMS caused a near-significant increase in amygdala volume in responders to rTMS (Furtado *et al.* 2013).

Hippocampus. HFL-rTMS increased rCBF and activation (Speer *et al.* 2000; Li *et al.* 2004); one study showed a decrease in rCBF post-HFL-rTMS (Nahas *et al.* 2001). Bilateral rTMS decreased blood flow in the hippocampus (Takahashi *et al.* 2013). HFL-rTMS caused a decrease in hippocampal non-responders (Furtado *et al.* 2013). HFL-rTMS caused blood flow and activity to be consistently increased in the parahippocampal region across several studies (Speer *et al.* 2000; Loo *et al.* 2003).

Basal ganglia and thalamus

There were inconsistent results of rCBF change after HFL-rTMS in the basal ganglia (Speer *et al.* 2000) whereas activity and rCBF decreased post-LFR-rTMS in the globus pallidus (GP) (Kito *et al.* 2011*a*). Activity and rCBF decreased post-bilateral rTMS in the lentiform nucleus (Takahashi *et al.* 2013). HFL-rTMS caused blood flow and activity to increase

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in the putamen (Li *et al.* 2004). In the thalamus, HFL-rTMS caused rCBF to increase in some studies (Speer *et al.* 2000; Li *et al.* 2004), and to decrease in another (Nahas *et al.* 2001). Bilateral rTMS and LFR-rTMS decreased rCBF in the thalamus (Kito *et al.* 2011*a*; Takahashi *et al.* 2013).

Other brain areas

Cerebellum and midbrain. In the cerebellum, HFL-rTMS increased blood flow (Speer *et al.* 2000; Loo *et al.* 2003) whereas bilateral rTMS decreased it (Takahashi *et al.* 2013). Last, activity and rCBF decreased post-LFR-rTMS in the midbrain (Kito *et al.* 2011*a*).

Functional connectivity

HFL-rTMS increased functional connectivity significantly in the neuroanatomical networks in the dorsolateral frontal loop (i.e. among DLPFC, caudate and GP) in the left hemisphere and the limbic loop [i.e. between the medial orbitofrontal cortex to the ventral striatum (VS)] on both sides within 1 h of stimulation (Shajahan *et al.* 2002). However, in the limbic loop, connectivity of the amygdala to the VS increased on the left, whereas that of the VS to the GP decreased post-HFL-rTMS (Shajahan *et al.* 2002). Further, a recent study has reported that successful accelerated HFL-rTMS (i.e. five HFL treatments per day spread over 4 days) inverted the anti-correlation between the subgenual anterior cingulate cortex (ACC) and parts of the left superior medial prefrontal cortex significantly to a mild positive correlation (Baeken *et al.* 2014). In addition, another study has demonstrated that HFL-rTMS selectively modulated functional connectivity both within and between the central executive network and default mode network (DMN), resulting in an attenuation of abnormal hyperactivity in the DMN (Liston *et al.* 2014).

Neurobiological mechanisms associated with treatment response

As summarized in Table 2, there are several studies that have investigated the neurobiological mechanisms associated with treatment response. Six studies out of 11 are strong studies; however, the findings in these studies have not been replicated. Only one finding, in a relatively weak study, shown in Table 2 has been replicated. In addition, the finding showing a significant increase in glutamate levels in the left DLPFC in MRS after rTMS has not been replicated in strong studies. Therefore, further studies in larger samples and with a control condition are needed to validate these results.

Discussion

The purpose of this systematic review was to summarize and synthesize all of the known neurobiological effects of rTMS applied to the DLPFC in patients with depression. To our knowledge, this is the first attempt to review the literature on the neurobiological effects of rTMS. Our review identified 66 studies evaluating the effects of rTMS on a variety of neurobiological measures in depression.

rTMS alters levels of various neurochemical and electrophysiological parameters including: mRNA expression of particular genes as well as blood flow and activity in brain regions involved in the etiopathogenesis of depression. However, there were conflicting findings on the effect of HFL-rTMS on cortisol levels. The effects of rTMS on BDNF and dopamine are still unclear due to inconsistent results. The effects of rTMS on cortical excitability measured by RMT are unclear; two strong studies showed that LFR and HFL-rTMS did not change RMT, but another strong study showed that LFR-rTMS decreased RMT. Moreover, strong studies demonstrated EEG spectral power increases in the delta, theta, alpha and beta bands as well as CSP increase post-rTMS; however, these findings were not replicated in some weaker-quality studies. An observable trend is that high-frequency rTMS increases rCBF, whereas low-frequency rTMS decreases rCBF, though some findings conflict with this trend. Further, rTMS was shown to increase rCBF in a certain brain region in responders whereas non-responders showed opposite effects, and vice-versa. There is conflicting data on the clinical correlations between blood flow or activity and improvement in depressive symptoms, as several studies suggest that a correlation exists while others do not. Thus, it is crucial that further studies be conducted to resolve conflicting findings regarding the effect of rTMS on regional brain functioning and to what extent stimulation frequency determines circuit activity.

Advances in functional neuroimaging are beginning to identify the potential etiopathogenic regions and neural circuits of depression. In addition, researchers have begun to apply these techniques to understand the circuit changes induced by rTMS treatment over the DLPFC (Baeken *et al*. 2011). Specifically, the frontal gyrus (Teneback *et al*. 1999; Fitzgerald *et al*. 2007), amygdala (Nadeau *et al*. 2002; Furtado *et al*. 2013), ACC (Nadeau *et al*. 2002), perirhinal cortex (Richieri *et al*. 2012), orbitofrontal cortex (Nadeau *et al*. 2002), insula (Nadeau *et al*. 2002) and precuneus are involved in these regions. Further, resting-state functional connectivity of affective circuitry between the subgenual ACC and left superior prefrontal cortex is altered after successful rTMS treatment (Baeken *et al*. 2014).

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Table 2. *Neurobiological mechanisms associated with treatment response*

Study	Biological measures	rTMS parameters	Depression measures	Findings
Yukimasa *et al.* (2006)	Plasma levels of BDNF measured with the sandwich ELISA method	HFL 20 Hz DLPFC, 80% RMT, 800 pulses/session, 10 sessions	HAM-D 17-item version	In responders and partial responders, BDNF levels significantly increased after rTMS
Luborzewski *et al.* (2007)	Choline and glutamate levels measured with 3.0 T MRS	HFL 20 Hz DLPFC, 100% RMT, 2000 pulses/session, 10 sessions	HAM-D 28-item version	In responders, total choline and glutamate concentrations significantly increased in the left DLPFC after rTMS
Yang *et al.* (2014)	Glutamate levels measured with 3.0 T MRS	HFL 10 Hz DLPFC, 120% RMT, 3000 pulses/session, 15 sessions	HAM-D 17-item version	In responders, glutamate levels significantly increased in the left DLPFC after rTMS
Bajbouj *et al.* (2005*a*)	CSP measured with TMS-electromyography	HFL 20 Hz DLPFC, 100% RMT, 2000 pulses/session, 10 sessions	HAM-D 24-item version	In responders, CSP significantly increased after rTMS
Ozekes *et al.* (2014)	Cordance in theta band power	HFL 25 Hz DLPFC, 100% RMT, 1000 pulses/session, 20 sessions	HAM-D 17-item version	In responders, mean cordance of theta power significantly increased in the prefrontal electrodes after rTMS
Fitzgerald *et al.* (2007)	Middle frontal gyrus (BA9), medial frontal gyrus, inferior frontal gyrus, precentral gyrus, and precuneus measured with 1.5 T functional MRI	LFR 1 Hz DLPFC, 110% RMT, 720 pulses/session, or HFL 10 Hz DLPFC, 100% RMT, 1500 pulses/session, 15 sessions	MADRS	In responders, activation levels were significantly decreased in the bilateral middle frontal gyrus, and left precuneus with LFR-rTMS, whereas activation levels were significantly increased in the left medial frontal gyrus, right inferior frontal gyrus, and left precentral gyrus with HFL-rTMS
Teneback *et al.* (1999)	Inferior frontal lobe, temporal lobe and cingulate measured with SPECT	HFL 20 Hz or 5 Hz DLPFC (or sham rTMS), 100% RMT, 1600 pulses/session, 10 sessions	HAM-D 21-item version	In responders, rCBF was significantly increased in the bilateral inferior frontal lobe and cingulate with HFL-rTMS, whereas rCBF was significantly decreased in the right medial temporal lobe with HFL-rTMS
Nadeau *et al.* (2002)	OFC, insula, amygdala and ACC measured with SPECT	HFL or LFR DLPFC	BDI 21-item version	In responders, rCBF was significantly decreased in the OFC, bilateral insula, right amygdala, ACC with rTMS
Furtado *et al.* (2013)	Amygdala measured with 1.5 T MRI	HFL DLPFC or sequential bilateral HFL + LFR DLPFC	HAM-D 17-item version	In responders, left amygdala volume was increased in trend level with HFL-rTMS

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Table 2 (*cont.*)

Study	Biological measures	rTMS parameters	Depression measures	Findings
Baeken *et al.* (2014)	rsFC between subgenual ACC and parts of the left superior medial prefrontal cortex	HFL 20 Hz DLPFC, 110% RMT, 1560 pulses/session, five sessions/day, spread over 4 days, 20 sessions	HAM-D 17-item version	In responders, subgenual ACC rsFC correlation between the perigenual anterior cingulate and superior medial frontal gyrus became significantly stronger with accelerated HFL-rTMS
Richieri *et al.* (2012)	Perirhinal cortex measured with SPECT	HFL 10 Hz DLPFC, 120% RMT, 2000 pulses/session, or LFR 1 Hz DLPFC, 120% RMT, 360 pulses/ session, 20 sessions	BDI 13-item version (BDI short-form)	In responders, rCBF in the left perirhinal cortex significantly decreased with rTMS in the whole group

rTMS, Repetitive transcranial magnetic stimulation; brain-derived neurotrophic factor; ELISA, enzyme-linked immunosorbent assay; HFL, high-frequency left-sided; dorsolateral prefrontal cortex; RMT, resting motor threshold; HAM-D, Hamilton Depression Rating Scale; MRS, magnetic resonance spectroscopy; CSP, cortical silent period; BA, Brodmann area; MRI, magnetic resonance imaging; LFR, low-frequency right-sided; MADRS, Montgomery-Åsberg Depression Rating Scale; SPECT, single photon emission computed tomography; rCBF, regional cerebral blood flow; OFC, orbitofrontal cortex; ACC, anterior cingulated cortex; BDI, Beck Depression Inventory; rsFC, resting-state functional connectivity.

Neurochemical factors that affect neuroplasticity such as BDNF and glutamate underlie dysregulation of the corresponding neural networks in depression and these seem to be modified by rTMS treatment (Yukimasa *et al*. 2006; Luborzewski *et al*. 2007; Yang *et al*. 2014). In addition, neurophysiological findings such as CSP increase (Bajbouj *et al*. 2005*a*) as well as prefrontal cordance increase in the theta band (Ozekes *et al*. 2014) following successful rTMS may reflect the improvement of the cortical $GABA_B$ receptor-mediated inhibitory functioning, and increased metabolic activity and blood flow perfusion in frontal regions, seen with rTMS of the DLPFC. More comprehensive studies that include multimodal biological markers are needed to better understand the antidepressant mechanism of DLPFC-rTMS treatment. By further elucidating these mechanisms the researchers may be able to individualize parameters of stimulation to enhance efficacy.

Study limitations

While this review summarized the neurobiological effects of rTMS in patients with depression, there are some limitations. First, this study only reviewed primary studies in English; our search terms identified several studies that examined the neurobiological effect of rTMS in depression that were either not written in English or presented at scientific conferences as abstracts. These studies may alter the scope of understanding of the effect of rTMS. In addition, our review only examined the effect of rTMS when delivered to either the left or right DLPFC. Including studies that only examined rTMS stimulation over these areas also limits our understanding of the full breadth of the biological effect of rTMS because stimulation of different areas of the brain may elicit alterations in other circuits (Conca *et al*. 2002; Baeken & De Raedt, 2011). It is also important to note that results from the studies included in this review may not solely reflect the effect of rTMS; as many of the participants were on antidepressant medications. These pharmacological agents also affect neurobiological function (Oberlander *et al*. 2009). Thus, the effect of rTMS treatment may be confounded by concomitant antidepressant use in these studies. As well, the relatively small number of studies that examined individual biological mechanisms prevented a quantitative meta-analysis. Last, the heterogeneity, including the time of the post-assessment, in the studies reviewed prevents definitive conclusions from being drawn on the effect of rTMS on neurobiological parameters.

Conclusion

There was a large degree of heterogeneity in the rTMS parameters of treatment, study approach, and these variations in procedures probably affected the ability to coherently summarize findings of the various

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studies. Despite this, the findings of this review will be able to direct future research focused on the effect of rTMS on various neurobiological factors. Overall, there were very few findings that were replicated in multiple strong studies. While there have been some corroboration and replication of some of the stronger findings, many mechanisms demonstrated conflicting findings. As rTMS continues to be adopted by more treatment providers, the mechanism of its neurobiological effects needs to be better understood. Well-designed rTMS studies, using a constant set of parameters, that include multi-modal measurements of putative neurobiological mechanisms, are still greatly needed.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715001609

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Declaration of Interest

None.

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