 Connectivity changes in major depressive disorder after rTMS: a review of functional and structural connectivity data

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Abstract

Aims. In the search for effective therapeutic strategies for depression, repetitive transcranial magnetic stimulation (rTMS) emerged as a non-invasive, promising treatment. This is because the antidepressant effect of rTMS might be related to neuronal plasticity mechanisms possibly reverting connectivity alterations often observed in depression. Therefore, in this review, we aimed at providing an overview of the findings reported by studies investigating functional and structural connectivity changes after rTMS in depression.

Methods. A bibliographic search was conducted on PubMed, including studies that used unilateral, excitatory (≥10 Hz) rTMS treatment targeted on the left dorsolateral prefrontal cortex (DLPFC) in unipolar depressed patients.

Results. The majority of the results showed significant TMS-induced changes in functional connectivity (FC) between areas important for emotion regulation, including the DLPFC and the subgenual anterior cingulate cortex, and among regions that are part of the major resting-state networks, such as the Default Mode Network, the Salience Networks and the Central Executive Network. Finally, in diffusion tensor imaging studies, it has been reported that rTMS appeared to increase fractional anisotropy in the frontal lobe.

Limitations. The small sample size, the heterogeneity of the rTMS stimulation parameters, the concomitant use of psychotropic drugs might have limited the generalisability of the results.

Conclusions. Overall, rTMS treatment induces structural and FC changes in brain regions and networks implicated in the pathogenesis of unipolar depression. However, whether these changes underlie the antidepressant effect of rTMS still needs to be clarified.

Introduction and aims

Depressive disorders are one of the leading causes of disability worldwide, with a high impact on individuals and society in terms of medical costs and loss of productivity (Friedrich et al., 2017). Major depressive disorder (MDD) is one of the most common mental disorders, with an estimated worldwide prevalence rate of 4.7% (Friedrich, 2017). Notably, approximately 15–30% of MDD patients do not respond to two antidepressant drugs, defining the condition as treatment-resistant depression (TRD), which is associated with more severe cognitive impairment, increased comorbidities, increased risk of suicide and higher medical costs (Du et al., 2017; Garay et al., 2017).

Various treatment strategies have been proposed for TRD, including both pharmacological and non-pharmacological approaches (McIntyre et al., 2014). Among the latter, various stimulation techniques have been approved for TRD, such as electroconvulsive therapy, vagus nerve stimulation, deep brain stimulation and repetitive transcranial magnetic stimulation (rTMS) (Akhtar et al., 2016). Specifically for rTMS, this technique is progressively gaining ground as a non-invasive, safe and generally well-tolerated treatment option for MDD and its efficacy in patients with TRD has been confirmed in three large, multicentre, randomised controlled trials (RCTs) (O’Reardon et al., 2007; George et al., 2010; Levkovitz et al., 2015). Briefly, during rTMS sessions, repeated magnetic pulses are delivered through the skull to a specific cortical region; when the magnetic field reaches the neural tissues, a secondary electrical field is generated. The ultimate effect is dependent on stimulation frequency, with high-frequency rTMS associated with increased neuronal excitability and low-frequency stimulations with decreased neuronal excitability (De Risio et al., 2020).

Several mechanisms of action have been postulated for rTMS in the treatment of MDD (Chervyakov et al., 2015). A prominent hypothesis suggests that rTMS induces neuronal plasticity and a restructuration of neuronal networks (Kozyrev et al., 2018). This is relevant since MDD has been associated not only with structural brain alterations, but also with functional...
connectivity (FC) dysfunctions of major brain networks (Schmaal et al., 2020), including the Central Executive Network (CEN), which is involved in cognitive control and emotion regulation, and the Default Mode Network (DMN), which mediates self-referencing and internally oriented processes (Hamilton et al., 2015; Kaiser et al., 2015).

In this framework, the aim of this review is to summarise the evidence on brain structural and FC changes after excitatory rTMS of the left dorsolateral prefrontal cortex (DLPFC) in MDD, and their potential relation with rTMS therapeutic efficacy.

Methods
We performed a bibliographic search on PubMed, with the following query: `(rTMS or TMS or transcranial magnetic stimulation) AND (connectivity or dwi or diffusion) AND (depression)`.

No limitation was posed regarding publication date. We included studies using unilateral, excitatory, high-frequency (≥10 Hz) TMS treatment targeting the left DLPFC. Only studies that investigated brain structural and FC using whole-brain neuroimaging techniques before and after rTMS protocols in depressed patients were included. Studies (a) employing other techniques (e.g. electroencephalogram), (b) based on bilateral or inhibitory rTMS protocols, or (c) targeting areas other than left DLPFC were excluded. The reference list of the selected articles was checked in order to find relevant references not emerged from the main query. Only 13 studies were selected as eligible. Of these, two studies included, in addition to unipolar depressed patients, a small cohort of depressed bipolar disorder type II patients. Finally, nine studies used resting-state functional magnetic resonance imaging (rs-fMRI), three studies employed diffusion tensor imaging (DTI) techniques, and one study employed single-photon emission computed tomography (SPECT).

Results
Connectivity changes induced by rTMS treatment are briefly discussed below, divided according to the investigated connectivity domain. FC results focused on two brain areas, the DLPFC and the subgenual anterior cingulate cortex (sgACC), whose connectivity emerged to be affected by the selected rTMS protocol. Although our focus was on connectivity changes from before to after rTMS, we also listed, when reported, the baseline features predictive of treatment response.

**DLPFC functional connectivity changes**

In an open-label trial on 58 unipolar and bipolar depressed patients evaluating SPECT FC changes before and after 4 weeks of rTMS, Richieri et al. (2018) demonstrated a decrease in FC between the left DLPFC and both the anterior and posterior cingulate cortex and the right medial temporal lobe, key nodes of the DMN. Similarly, in another open-label trial on 17 unipolar and bipolar type II depressed patients and 35 healthy controls (HC) evaluating rs-fMRI connectivity changes before and after 5 weeks of rTMS, Liston et al. (2014) found, at baseline, a decreased FC in patients compared to HC between the left DLPFC and a key region of the DMN, the right parahippocampal gyrus. Moreover, consistently with the results reported by Richieri et al. (2018), the authors observed an rTMS-induced decrease in FC between the left DLPFC and many areas of the DMN, such as the ventromedial prefrontal cortex, the posterior cingulate cortex and the right parahippocampal gyrus. Besides the investigation of FC between DLPFC and DMN areas, Liston et al. (2014) also explored FC between DLPFC and regions that are part of the CEN. Specifically, the authors showed, at baseline, a decreased FC in patients compared to HC between the left DLPFC and multiple areas of the CEN, including the premotor cortex, inferior parietal lobule, precuneus, cerebellum and other areas within the lateral prefrontal cortex. However, the FC reductions in these areas did not change after rTMS.

Moreover, in an open-label trial on 27 unipolar depressed patients and 27 HC, Zheng et al. (2020) analysed rs-fMRI connectivity changes before and after 2 weeks of rTMS through functional connectivity density, defined as the FC between a voxel and the rest of voxels across the whole brain. Consistently with the results found by Liston et al. (2014), the authors observed, at baseline, a decreased FC in patients compared to HC within the CEN. However, this decreased FC improved after rTMS, contrasting with the null effect of rTMS reported by Liston et al. (2014). Additionally, in an RCT on 21 unipolar depressed patients evaluating rs-fMRI connectivity changes after 2 weeks of real v. sham rTMS, Kang et al. (2016) demonstrated a decreased FC in active compared to sham group between both targeted (left) DLPFC and contralateral DLPFC and between the left DLPFC and left cingulate. Consistently with these results, in an RCT on 33 unipolar depressed patients evaluating rs-fMRI connectivity changes before and after 4 weeks of rTMS, Eshel et al. (2020) observed a decreased FC in active compared to sham group between both targeted (left) DLPFC and contralateral DLPFC and between the left DLPFC and bilateral amygdala. Moreover, the authors demonstrated an increased targeted (left) DLPFC global FC in active compared to sham group. All these post-rTMS changes brought patients closer to the FC values demonstrated in the HC group. Interestingly, the authors also investigated the modulating role of the left DLPFC stimulation on contralateral DLPFC and bilateral amygdala through the analysis of the fMRI blood oxygen level-dependent signal after the left DLPFC single-pulse TMS. The authors found that, in HC, DLPFC stimulation deactivated bilateral amygdala, causing no change in contralateral DLPFC, whereas in patients it failed to deactivate bilateral amygdala and aberrantly activated contralateral DLPFC. Finally, in an RCT on 27 unipolar depressed patients, Iwabuchi et al. (2019) found no difference, after TMS, in FC in the circuit between right amygdala and DLPFC.

**sgACC functional connectivity changes**

In the already cited study carried out by Liston et al. (2014), the authors also explored the sgACC connectivity. Specifically, the authors demonstrated, at baseline, an increase in FC between sgACC and multiple DMN areas, including the ventromedial prefrontal cortex, pregenual anterior cingulate cortex (pgACC) and precuneus, in patients compared to HC, which reverted after rTMS. A similar reversal of the FC alterations between sgACC and pgACC was demonstrated by Baeken et al. (2014), in a study on 20 unipolar depressed patients evaluating rs-fMRI connectivity changes induced by rTMS. Also, Taylor et al. (2018), in an RCT on 32 unipolar depressed patients exploring rs-fMRI connectivity changes before and after 4 weeks of real v. sham rTMS, investigated FC between sgACC and both DMN and CEN. Specifically for the DMN, they demonstrated, in responders (both to real and sham stimulation), a decrease in FC between sgACC and DMN, consistently with the result reported by
DMN and the CEN was found to be positively associated with Stronger baseline FC between sgACC and multiple areas of the Baseline features associated with treatment response

Stronger baseline FC between sgACC and multiple areas of the DMN and the CEN was found to be positively associated with rTMS response (Liston et al., 2014). In contrast, weaker baseline FC between the left DLPFC and cingulate cortex, medial frontal cortex and bilateral medial temporal limbic areas (Richieri et al., 2018) as well as between the bilateral DLPFC and left caudate was found to be positively associated with rTMS response (Kang et al., 2016). Another area whose baseline connectivity was reported to be associated with rTMS response was the right anterior insula (rAI). Specifically, stronger baseline FC between rAI and both DLPFC (Iwabuchi et al., 2019) and posterior cingulate cortex (Taylor et al., 2018) was found to be positively associated with rTMS response.

Discussion

In this review, we summarised the results of studies investigating structural and FC changes after excitatory rTMS on the left DLPFC. Interestingly, the results showed that FC changes in key areas involved in the emotion regulation (i.e. DLPFC and sgACC) and major resting-state networks (DMN, CEN, Salience Network (SN)) were found to be associated with rTMS treatment, possibly mediating rTMS therapeutic efficacy.

In particular, in the reviewed studies, a decrease in FC between DLPFC (Liston et al., 2014; Richieri et al., 2018) or sgACC (Baeken et al., 2014; Liston et al., 2014; Taylor et al., 2018) and DMN areas consistently emerged. Also, stronger baseline rAI connectivity was consistently found to be positively associated with rTMS response, both with DLPFC (Iwabuchi et al., 2019) and with the posterior cingulate cortex (Taylor et al., 2018).

Decreased FC between sgACC and DMN areas

The results on sgACC showed that after rTMS, the increased activity of sgACC (Mayberg et al., 2000, 2005) and the increased connectivity between sgACC and multiple areas, in particular within the DMN (Greicius et al., 2007), found to be associated with depressive symptomatology, seemed to normalise. Notably, this evidence is in line with previous findings showing a similar decrease in hyperactivation and hyperconnectivity of sgACC after very different therapeutic options, such as deep brain stimulation (Mayberg et al., 2005), electroconvulsive therapy (Argyelan et al., 2016), vagus nerve stimulation (Nahas et al., 2007), rTMS targeting the bilateral excitatory dorsomedial prefrontal cortex (Salomons et al., 2014), inhibitory right DLPFC rTMS (Kito et al., 2008), antidepressant drugs (Mayberg et al., 2000; Drevets et al., 2002) and the administration of placebo pills, which can result in a clinical response very similar to the one of antidepressant therapies (Mayberg et al., 2002). Interestingly, the latter therapeutic option could have occurred in the study performed by Taylor et al. (2018) since the decreased FC between sgACC and the DMN and its association with the amelioration of depressive symptomatology reported by this study in the sham group probably suggests a placebo effect of the sham rTMS.

Decreased FC between DLPFC and DMN areas

The DMN is a network of brain areas active when attention is not focused on the outside world, but is engaged in self-referential processing (Gusnard et al., 2001; Raichle et al., 2001). This network, which comprises the medial prefrontal, medial posterior parietal cortex and posterior cingulate cortex, has been repeatedly associated with rumination (Zhou et al., 2020) and (meta)cognitive style in depression (Gusnard et al., 2001; Raichle et al., 2001). Indeed, hyperconnectivity within the DMN has been consistently reported by FC studies in MDD patients (for a review, see Kaiser et al., 2015). Moreover, when attention is focused on the outside world, the FC between DLPFC and DMN decreases (Piccoli et al., 2015; Denkova et al., 2019; Bauer et al., 2020) and, therefore, the decrease in FC between DLPFC and DMN areas observed in the reviewed studies after rTMS treatment in depressed patients could have facilitated the attention towards the outside world, thus avoiding rumination and improving depressive symptomatology.

Baseline connectivity

Concerning baseline features associated with treatment response, an association between stronger baseline rAI connectivity and rTMS response consistently emerged from the reviewed studies.
**Table 1. Connectivity changes in major depressive disorder after rTMS: a review of functional and structural connectivity data**

| Author                      | Study design          | Sample characteristics                                      | Stimulation parameters                        | Imaging parameters           | Statistical analyses                                      | Main results                                                                 |
|-----------------------------|-----------------------|-------------------------------------------------------------|-----------------------------------------------|-------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------|
| Baeken et al. (2014)        | Sham-controlled: Yes  | Pts: 20 (48.8 ± 12.76 years, M/F 7/13)                      | Region: Left DLPFC                            | fMRI (3T)                     | Baseline differences                                      | Post-TMS changes NA                                                        |
|                             | (cross-over after 1   | Brain: NA                                                   | Neuronavigation: Yes                           | Resting state FC method:      | Post-TMS changes NA                                      | NA                                                                          |
|                             | week)                 | Blinded: Single-blind                                       | Intensity (% MT): 110%                        | Seed-based Regions: sgACC     | Relationship with clinical variables                     | NA                                                                          |
|                             | Control group: No     | Psychometric assessments: HAMD17 at baseline, 1 and 2 weeks | Treatment resistance status: Thase & Rush    |                               | Random-effects two-way ANOVA, with age as covariate,     | Post-TMS changes NA                                                        |
|                             |                       | fMRI assessment: fMRI at baseline, 1 and 2 weeks fup        | stage ≥ 3; at least 2 failed trials with     |                               | response (positive, negative) as between-subject factor  | NA                                                                          |
|                             |                       | Neuroimaging assessment:                                     | SSRIs/SSRIs and 1 with TCA                    |                               | and time (baseline, post-treatment) as within-subject    | Relationship with clinical variables                                      |
|                             |                       |                                                             | Medication status: Washout from all         |                               | factor                                                     | At baseline, in Responders v. Non-responders inverse correlation effect   |
|                             |                       |                                                             | medication 2 weeks before                     |                               |                                                           | on FC between sgACC and right pgACC and superior medial frontal gyrus     |
|                             |                       |                                                             | Psychiatric comorbidities: Excluded if         |                               |                                                           | After rTMS, in Responders v. Non-responders inverse       |
|                             |                       |                                                             | suicide attempt within previous 6 months,   |                               |                                                           | correlation effect on FC between sgACC and right pgACC and superior       |
|                             |                       |                                                             | alcohol abuse                                |                               |                                                           | medial frontal gyrus                                                      |
|                             |                       |                                                             | Region: Left DLPFC                           |                               |                                                           |                                                                             |
|                             |                       |                                                             | Neuronavigation: Yes                          |                               |                                                           |                                                                             |
|                             |                       |                                                             | Intensity (% MT): 110%                        |                               |                                                           |                                                                             |
|                             |                       |                                                             | Frequency: 20 Hz                             |                               |                                                           |                                                                             |
|                             |                       |                                                             | Protocol:                                    |                               |                                                           |                                                                             |
|                             |                       |                                                             | Train = 1.9 s; intertrain interval 12 s      |                               |                                                           |                                                                             |
|                             |                       |                                                             | Session = 40 trains                           |                               |                                                           |                                                                             |
|                             |                       |                                                             | Total stimuli per session: 300               |                               |                                                           |                                                                             |
|                             |                       |                                                             | Duration: 4 days/week (5 sessions/day), 1 week|                               |                                                           |                                                                             |
|                             |                       |                                                             |                                                   |                               |                                                           |                                                                             |
| Chen et al. (2020)          | Sham-controlled: Yes  | Pts: Active rTMS: 20 (46.75 ± 5.52 years, M/F 9/11)        | Region: Left DLPFC                           | FMRI (1.5T)                    | Baseline differences                                      | Post-TMS changes NA                                                        |
|                             | Blinded: Double-blind| Brain: NA                                                   | Neuronavigation: No                           | Resting state FC method:      | Post-TMS changes NA                                      | NA                                                                          |
|                             | Control population:   | Blinded: No                                                  | Intensity (% MT): 90%                        | Seed-based Regions: Bilateral | Relationship with clinical variables                     | NA                                                                          |
|                             | Yes                   | Psychometric assessments: HAMD17 at baseline and 4 weeks fup | Frequency: 10 Hz                            | amygdala                      | Random-effects two-way ANOVA, with age as covariate,     | Post-TMS changes NA                                                        |
|                             |                       | Neuroimaging assessment: fMRI at baseline and 12 weeks fup  | Protocol:                                    |                               | response (positive, negative) as between-subject factor  | NA                                                                          |
|                             |                       |                                                             | Train = 4 s; intertrain interval 56 s        |                               | and time (baseline, post-treatment) as within-subject    | Relationship with clinical variables                                      |
|                             |                       |                                                             | Session = 40 trains                           |                               | factor                                                     | At baseline, in Responders v. Non-responders inverse correlation effect   |
|                             |                       |                                                             | Total stimuli per session: 1600 (3200/day)   |                               |                                                           | NA                                                                          |
|                             |                       |                                                             | Duration: 5 days/week, 5 weeks               |                               |                                                           | Relationship with clinical variables                                      |
|                             |                       |                                                             |                                                   |                               |                                                           | At baseline, in active rTMS arm increased FC between left   |
|                             |                       |                                                             |                                                   |                               |                                                           | amygdala and left INS, right IFG, right SFG, right IPL,    |
|                             |                       |                                                             |                                                   |                               |                                                           | right MFG. Higher FC between amygdala and PreCUN            |
|                             |                       |                                                             |                                                   |                               |                                                           | Post-TMS changes                                                        |
|                             |                       |                                                             |                                                   |                               |                                                           | Left AN: In pts v. HC, lower FC between amygdala and left INS, right IFG, right SFG, right IPL, right MFG. Higher FC between amygdala and PreCUN |
|                             |                       |                                                             |                                                   |                               |                                                           | Post-TMS changes                                                        |
|                             |                       |                                                             |                                                   |                               |                                                           | Right AN: In pts v. HC, lower FC between right amygdala and left INS, right IFG, right INS, right IPL, right MFG. Higher FC between amygdala and left PreCUN |
|                             |                       |                                                             |                                                   |                               |                                                           | Post-TMS changes                                                        |
|                             |                       |                                                             |                                                   |                               |                                                           | Left AN: In active rTMS arm increased FC between left amygdala and left INS, right IFG, right INS, right IPL. Right AN: In active rTMS arm increased FC between right amygdala and left INS No changes in the sham-rTMS arm |
|                             |                       |                                                             |                                                   |                               |                                                           | Relationship with clinical variables                                      |
|                             |                       |                                                             |                                                   |                               |                                                           | No changes in the sham-rTMS arm                                        |

Baseline differences: NA
Post-TMS changes: NA
Relationship with clinical variables: NA
Post-TMS changes: NA
Relationship with clinical variables: NA
Baseline differences: NA
Post-TMS changes: NA
Relationship with clinical variables: NA
Baseline differences: NA
Post-TMS changes: NA
Relationship with clinical variables: NA
Responders 28 (42.25 ± 13.19 years, M/F 11/17), In the active rTMS arm, increase (normalization) in global FC of left DLPFC
In the active rTMS arm, decrease (normalization) in global FC of bilateral amygdalae and right Post-TMS changes
NA

Non-responders 14 (44.07 ± 10.72 years, M7/F7)

In the active rTMS arm, positive correlation between degree of global FC increase of left DLPFC and degree of clinical improvement
In the active rTMS arm, lower baseline FC of left DLPFC predicts greater clinical improvement

Relationship with clinical variables

– Symptoms scores
Linear mixed models (fixed effects of time, global connectivity and time × connectivity) to assess relationship between baseline FC and degree of symptoms scores changes

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Sham-controlled: Yes
Blinded: Yes
Control population: Yes
Psychometric assessments: HAMD at baseline and 4 weeks fup
Neuroimaging assessment: fMRI at baseline and 4 weeks fup

Pts:
- Active rTMS 20 (35.0 ± 6.3 years, M/F 11/17), Sham-rTMS 13 (37.1 ± 11.2, 4/9 M/F)
- HC: 28 (38.9 ± 11.3 years, 15M/13F)

Diagnosis: MDD (DSM-IV)
Severity: HAMD:
- Active rTMS 26.9 ± 7.7
- Sham-rTMS 27.9 ± 6.76

Treatment resistance status: ≥1 but ≤3 failed antidepressant trials

Medication status: Medication-free or washout from all medication 2 weeks before

Psychiatric comorbidities:
Excluded if psychotic disorder, BD, active SUD

Region: Left DLPFC
Neuronalization: Yes
Intensity (% MT): NA
Frequency: 10 Hz
Protocol:
Train = 4 s; intertrain interval 26 s
Session = 75 trains
Total stimuli per session: 3000
Duration: 5 days/week, 4 weeks

fMRI (3T)
Resting state
FC method: Seed-based
Regions: Left DLPFC

Baseline differences
NA

Post-TMS changes
Linear mixed models (fixed effects of time, treatment arm × time) for changes in FC in active rTMS vs. sham rTMS arm.

Relationship with clinical variables
Pearson correlations between changes in FC and changes in symptoms scores
Linear mixed models (fixed effects of time, global connectivity and time × connectivity) to assess relationship between baseline FC and degree of symptoms scores changes

Stronger baseline rACC-IPL FC associated with greater improvement in symptoms score
Stronger sgACC-rDLPFC FC associated with smaller improvement in symptoms scores
sgACC-DLPFC FC AUC for responders/non-remitters classification: 0.87–0.90
rACC-IPL FC AUC for responders/non-remitters classification: 0.75–0.76

Post-treatment relationship with clinical variables
Smaller decrease of sgACC-left fusiform FC associated with greater improvement in symptoms score
Path analysis
Lower baseline sgACC-DLPFC FC > greater decrease of sgACC-fusiform FC > greater improvement in symptoms score

(Continued)
Baseline differences
Post-TMS changes
NA
No change in FC/EC (DLPFC, right anterior INS)
No change in FC (networks)

Post-TMS changes
NA
No change in FC/EC (DLPFC, right anterior INS)
No change in FC (networks)

NA

Post-TMS changes
NA
No change in FC/EC (DLPFC, right anterior INS)
No change in FC (networks)

Baseline differences
NA
Post-TMS changes
RM-ANOVA with stimulation protocol as covariate (DLPFC, right anterior INS)
Randomise permutation-testing (networks)

Baseline differences
NA
Post-TMS changes
RM-ANOVA with stimulation protocol as covariate (DLPFC, right anterior INS)
Randomise permutation-testing (networks)

Baseline differences
NA
Post-TMS changes
RM-ANOVA with stimulation protocol as covariate (DLPFC, right anterior INS)
Randomise permutation-testing (networks)

Post-hoc analyses for hemispheric effect of seed ROI on differences in FC between active- and sham-rTMS arms

Positive correlation between degree of reduction in DLPFC-left caudate FC and degree of residual symptoms score
Kozel et al. (2011)

Sham-controlled: Yes
Blinded: Double-blind
Control population: No
Psychometric assessments: MADRS at baseline
Neuroimaging assessment: MRI at baseline and 4-6 weeks fup

Pts: 8 (44.6 ± 10.2, M/F 1/7)
HC: NA
Diagnosis: MDD (diagnostic criteria NA)
Severity: HAMD > 20 and item 1 score > 2
  • Active rTMS 29.2 ± 5.1
  • Sham rTMS 29.5 ± 2.6
    < 3 years duration
Treatment resistance status: Stage ATHF level 2-4 in current episode, or >1 and ≤3 in a previous episode
Medication status: All medications (except hypnotics or lorazepam) discontinued after randomization
Psychiatric comorbidities: Excluded if depression secondary to substances or medical condition, depression with seasonal pattern, SUD within past year, psychotic disorder, BD, OCD, ED, PTSD

Region: Left DLPFC
Neuronavigation: No
Intensity (% MT): 120%
Frequency: 10 Hz
Protocol:
  • Train = 4 s; intertrain interval 26 s
  • Session = 75 trains
  • Total stimuli per session: 3000
Duration: 5 days/week, 4-6 weeks

MRI DTI (3 T)
Resting state FC method: FA
Regions: PFC (bilateral)
Baseline differences
Post-TMS changes
  • Increased FA in left PFC in active v. sham rTMS (trend level significance)

Baseline differences
Post-TMS changes
  • Increased FA in left PFC in active v. sham rTMS (trend level significance)

Relationship with clinical variables
NA

Liston et al. (2014)

Sham-controlled: No
Blinded: NA
Control population: Yes
Psychometric assessments: HAMD24 at baseline and 5 weeks fup
Neuroimaging assessment: fMRI at baseline and 5 weeks fup

Pts: 17 (42.3 ± 17.3 years, M/F 3/14)
HC: 35 (36 ± 16 years, M/F 12/23)
Diagnosis: 14 MMD, 3 BD II depression (DSM-IV)
Severity: NA
Treatment resistance status: At least 2 failed antidepressant trials
Medication status: No changes in the previous 4 weeks
Psychiatric comorbidities: Excluded if any other psychiatric disorder, depression with psychotic features, suicidal ideation/behaviour, SUD in the past 3 years

Region: Left DLPFC
Neuronavigation: No
Intensity (% MT): 120%
Frequency: 10 Hz
Protocol:
  • Train = 4 s; intertrain interval 26 s
  • Session = 75 trains
  • Total stimuli per session: 3000
Duration: 5 days/week, 5 weeks

fMRI (3 T)
Resting state FC method: Seed-based
Regions: Left DLPFC, sgACC, DMN, CEN. Two FC maps:
  • Within-network (DLPFC:DMN, sgACC:DMN)
  • Between-network (DLPFC:sgACC, sgACC:CEN)
Baseline differences
Post-TMS changes
  • Increased FC in left PFC v. right PFC (trend level significance)
  • Increased in particular the reduction in FC between DLPFC and vmPFC (trend level significance)

Baseline differences
Post-TMS changes
  • Increased in particular the reduction in FC between DLPFC and vmPFC (trend level significance)

Relationship with clinical variables
ANCOVA of baseline FC in Responders v. Non-responders, with age, sex, baseline HAM-D score and lifetime number of antidepressant trials as covariates

Baseline differences
Post-TMS changes
  • In pts v. HC, FC:
    • Within-CEN: Reduced. In particular, reduced FC between left DLPFC and premotor cortex, posterior parietal areas, bilateral cerebellum, lateral PFC
    • Within-DLN: Increased. In particular, increased FC between sgACC and vmPFC, pgACC, thalamus, preCUN
    • sgACC-CEN: Increased FC between sgACC and caudate nucleus and bilateral posterior parietal areas
    • DLPFC-DN: Reduced FC between DLPFC and right parahippocampal area

Post-TMS changes
  • Within-DLN: Normalization of FC. Reduction in FC between sgACC and vmPFC, pgACC and preCUN
  • sgACC-CEN: No change in FC (increased FC persisted)
  • DLPFC-DN: Increased in magnitude of FC reduction between DLPFC and right parahippocampal area. Reduction in FC between DLPFC and vmPFC and PCC

(Continued)
| Author | Study design | Sample characteristics | Stimulation parameters | Imaging parameters | Statistical analyses | Main results |
|--------|--------------|------------------------|------------------------|-------------------|---------------------|--------------|
| Peng et al. (2012) | Sham-controlled: Yes Blinded: Double-blind Control population: Yes Psychometric assessments: BDI and HAMD17 at baseline and 4 weeks fup Neuroimaging assessment: MRI at baseline and 4 weeks fup | Pts: 30 (26.86 ± 5.27 years, M/F 19/11) HC: 25 (28.240 ± 4.980 years, M/F 14/11) Diagnosis: MDD (DSM-IV) Severity: NA Treatment resistance status: At least 2 failed antidepressant trials Medication status: Switch to escitalopram 2 weeks before Psychiatric comorbidities: Excluded if any psychiatric disorder Region: Left DLPFC Neuronavigation: No Intensity (% MT): 110% Frequency: 15 Hz Protocol: Train = 4 s; intertrain interval 29 s Session = 50 trains Total stimuli per session: 3000 Duration: 5 days/week, 4 weeks MRI DTI (3T) FC method: FA Regions: Whole-brain Baseline differences Two-sample t-tests on a voxel-by-voxel basis for differences in FA Post-TMS changes Two-factor repeated-measures ANOVA for main effects of groups (active v. sham), treatment times (pre v. post-rTMS) and group × time Two-sample t-tests and paired t-tests between pre- and post-treatment FA in active and sham groups Relationship with clinical variables Pearson correlation between FA and symptoms scores (pre- and post-rTMS) | Relationship with clinical variables DLPFC FC at baseline not a significant predictor Increased FC between sgACC and DMN (vmPFC, dmPFC, pgACC, PCC) at baseline associated with better response Increased FC between sgACC and CEN at baseline associated with better response |
| Richieri et al. (2018) | Sham-controlled: No Blinded: NA Control population: Yes Psychometric assessments: BDI, STAI-Y at baseline and 4 weeks fup Neuroimaging assessment: SPECT at baseline only | Pts: 58 (53.8 ± 14.0 years, M/F 21/37) HC: 55 (49.8 ± 16.6 years, M/F 23/32) Diagnosis: 44 MDD, 14 BD II depression (DSM-IV) Severity: BDII mean 25.9 ± 9.5 Duration 17.3 ± 8.1 months Treatment resistance status: At least 2 failed trials with two different antidepressants MSM mean 8.7 ± 2.1 Medication status: No changes in the previous 2 weeks No washout Psychiatric comorbidities: Excluded if depression with psychotic features Region: Left DLPFC Neuronavigation: No Intensity (% MT): 120% Frequency: 10 Hz Protocol: Train = 5 s; intertrain interval 25 s Session = 60 trains Total stimuli per session: 2000 Duration: 5 days/week, 4 weeks SPECT, 99mTc-ECD Resting state FC method: Inter-regional correlation of normalized perfusion values (full factorial model) Regions: Left DLPFC Baseline differences Full factorial model of analysis with normalized L DLPFC perfusion values as an interaction covariate to study inter-regional correlation, between patients and HC Post-TMS changes NA Relationship with clinical variables Pearson correlation between L DLPFC perfusion and clinical variables, including age, gender, BDI and HAMD scores as covariates Spearman correlation between FC and symptoms scores in Responders and Non-responders Multiple logistic regression models to classify responder v. non-responder on the basis of baseline FC | Relationship with clinical variables In Responders v. HC, higher baseline FC between left DLPFC and right cerebellum Post-TMS changes In Responders v. Non-responders, higher baseline FC between left DLPFC and right cerebellum |
### Tateishi et al. (2019)

**Sham-controlled:** No  
**Blinded:** NA  
**Control population:** No  
**Psychometric assessments:** BDI, HAMD24, WCST, WFT and SCT at baseline and 6 weeks fup  
**Neuroimaging assessment:** MRI at baseline and 6 weeks fup  

**Pts:** 12; (52.8 ± 17.8 years, M/F 5/7)  
**Region:** Left DLPFC  
**Neuronavigation:** No  
**Intensity (% MT):** 100%  
**Frequency:** 10 Hz  
**Protocol:** Train = 4 s; 26 s intertrain interval  
**Session:** 40 trains  
**Total stimuli per session:** 3600  
**Duration:** 5 days/week, 6 weeks  

**MRI DTI (3T)**  
**Resting state FC method:** FA  
**Regions:** Bilateral SFG and MFG  
**Baseline differences:** NA  
**Post-TMS changes:**  
One-sample paired t-test for FA changes  
**Relationship with clinical variables:**  
Spearman correlation between degree of FA changes and symptoms scores changes  

### Taylor et al. (2018)

**Sham-controlled:** Yes  
**Blinded:** Double-blind  
**Control population:** No  
**Psychometric assessment:** MADRS, HRSD17, QIDS, GAD7, WASA, GAF at baseline, weekly and 4 weeks fup  
**Neuroimaging assessment:** fMRI at baseline and 4 weeks fup  

**Pts:**  
- Active rTMS 16 (46.9 ± 10.7 years, M/F 5/11)  
- Sham rTMS: 16 (44.13 ± 11.1 years, M/F 6/10)  
**Region:** Left DLPFC, region with maximal negative correlation with sgACC  
**Neuronavigation:** No  
**Intensity (% MT):** 100%  
**Frequency:** 10 Hz  
**Protocol:** NA  
**Total stimuli per session:** 3600  
**Duration:** 5 days/week, 4 weeks  

**Baseline differences:** NA  
**Post-TMS changes:**  
Seed-to-whole-brain FC: Regression models with baseline MADRS and mean FD change as covariates  
Seed-to-network FC: ANCOVA for each seed, with seed-to-network values and time as repeated measures, group as a between-subject factor, mean FD change and baseline MADRS as covariates  
**Relationship with clinical variables:**  
Seed-to-whole-brain FC: Regression models with baseline MADRS and mean FD change as covariates, to assess relationship between symptoms scores change and FC change  
Seed-to-network FC: ANCOVA for each seed, with seed-to-network values and time as repeated measures, group as a between-subject factor, mean FD change and baseline MADRS as covariates, to test baseline FC as a predictor of symptoms scores changes  

**Baseline differences:** NA  
**Post-TMS changes:**  
Seed-to-whole-brain FC: Regression models with baseline MADRS and mean FD change as covariates, to test baseline FC as a predictor of symptoms scores changes  

(Continued)
| Author | Study design | Sample characteristics | Stimulation parameters | Imaging parameters | Statistical analyses | Main results |
|--------|-------------|------------------------|------------------------|--------------------|---------------------|--------------|
| Zheng et al. (2020) | Sham-controlled: No Blind: NA | Control population: Yes | Psychometric assessments: HAMD17, HAMA at baseline and 2 weeks fup | Neuroimaging assessment: MRI at baseline and 2 weeks fup | Region: Left DLPFC Neurorunation: No Intensity (% MT): 100% Frequency: 10 Hz Protocol: Train = 4 s; intertrain interval 26 s Session = 50 trains Total stimuli per session: 1500 Pts: 27 (41.22 ± 12.71 years, 8M/19F) HC: 27 (41.00 ± 8.04 years, M/F 6/21) Diagnosis: MDD (DSM-IV) Severity: HAMD 23.89 ± 4.47 Treatment resistance status: NA Medication status: Previously medicated for less than a week. Washout from all medication 1 month before Psychiatric comorbidities: Excluded if psychotic disorder, SUD, alcohol abuse | MRI (3T) Resting state FC method: ALFF, FCD Regions: CEN, DMN and SN | Baseline differences Two-sample t-tests for differences in FC between pts and HC Post-TMS changes Paired t-tests for differences in FC between pre- and post-rTMS Relationship with clinical variables Pearson correlation between ALFF/FCD and symptom scores at baseline Pearson correlation between ALFF/FCD and symptom scores changes Baseline differences In pts v. HC: • ALFF increased in right OFC and decreased in left striatal cortex and medial PFC. No differences in ALFF in DMN, CEN and SN • FCD increased in right dACC and OFC and decreased in right IPL. FCD decreased in CEN Post-TMS changes • ALFF increased in left DLPFC and SFG. No differences in ALFF in CEN, DMN or SN • FCD increased in right dACC and STG, decreased in bilateral LG. FCD increased in CEN Relationship with clinical variables At baseline, FCD in CEN negatively correlated with HAM-A No correlations between changes in ALFF or FCD and changes in symptoms scores after rTMS |
Anterior insula (AI) is part of the SN, a key circuit directing attention and cognitive control (Menon, 2015), and comprising not only the AI but also the dorsal anterior cingulate cortex, amygdala, ventral striatum and substantia nigra/ventral tegmental area. Specifically, AI, and especially the rAI, is crucial to detect and select salient stimuli as well as to interact with other neurocognitive systems, including the DMN and the CEN, by activating or deactivating them according to circumstances (Menon, 2015). Notably, this structure has been often found impaired in depressive disorders (Grimm et al., 2009; Sheline et al., 2009). Therefore, the stronger baseline FC between rAI and selective areas within the CEN (i.e. DLPFC) and within the DMN (i.e. posterior cingulate cortex), which was consistently found to be positively associated with rTMS response (Taylor et al., 2018; Iwabuchi et al., 2019), could point towards the hypothesis that rTMS treatment improves the communication between the rAI and these neurocognitive systems, which in turn may have positive effects on depressive symptomatology.

**Structural connectivity changes**

The three DTI studies here reviewed (Kozel et al., 2011; Peng et al., 2012; Tateishi et al., 2019) reported increased FA, which suggests an improvement of white matter tracts integrity, in regions within the prefrontal lobe after rTMS treatment. These findings suggest the presence of a normalizing effect of rTMS treatment on prefrontal tracts, which have been often found to be characterised by reduced FA in MDD (Korgaonkar et al., 2011; Chen et al., 2016), similarly to what has been found for antidepressant treatments (Zeng et al., 2012; Gryglewski et al., 2020). Therefore, these studies support the hypothesis of a relationship between white matter abnormalities and depressive symptomatology (Walther et al., 2012; Coloigner et al., 2019; Hej et al., 2019), although a clear relationship between white matter deficits and MDD is currently lacking, mainly due to the heterogeneities observed between the studies (Coloigner et al., 2019). This is true also for the results reported by the three reviewed studies, since increased prefrontal FA was observed both in the left (Kozel et al., 2011; Peng et al., 2012) and in the right (Tateishi et al., 2019) sides. Therefore, these contrasting results warrant the need for future studies to better clarify the relationship between rTMS treatment and structural connectivity changes in MDD.

**Limitations and conclusions**

The reviewed studies suffer from some limitations. First, the sample size was often modest and some studies (Liston et al., 2014; Richieri et al., 2018) also included a mixed sample of unipolar and bipolar depressed patients, possibly decreasing the statistical power of the statistical analyses. Second, the majority of patients were concomitantly treated with medications, so the observed connectivity changes could be linked to concomitant psychotropic drugs, or placebo effects in open-label studies. Third, the stimulation parameters of rTMS were heterogeneous in terms of TMS frequency, number of sessions, timing and concomitant treatments, possibly influencing the connectivity changes observed.

In conclusion, the abovementioned results support the hypothesis that rTMS induces neuronal plasticity and reorganisation of key networks in the pathogenesis of unipolar depression. However, whether these changes underlie the antidepressant effect of rTMS is not defined yet. Further studies including larger and more homogeneous samples are needed to better clarify the effect of rTMS on brain connectivity and the relationship with its therapeutic effect in unipolar depression.

**Data.** All data described in this review have been included in Table 1.

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**References**

Akhtar H, Bukhari F, Nazir M, Anwar MN and Shahzad A (2016) Therapeutic efficacy of neurostimulation for depression: techniques, current modalities, and future challenges. *Neuroscience Bulletin* 32, 115–126.

Argyel M, Lenz C, Kaliora S, Sarpal DK, Weissman N, Kingsley PB, Malhotra AK and Petrides G (2016) Subgenual cingulate cortical activity predicts the efficacy of electroconvulsive therapy. *Translational Psychiatry* 6, e789.

Baeken C, Marinazzo D, Wu G-R, Van Schuerbeek P, De Mey J, Marchetti I, Vanderhasselt M-A, Remue J, Luytaert R and De Raedt R (2014) Accelerated HF-rTMS in treatment-resistant unipolar depression: insights from subgenual anterior cingulate functional connectivity. *The World Journal of Biological Psychiatry* 15, 286–297.

Bauer CCC, Rozenkrantz L, Caballero C, Nieto-Castanon A, Scherer E, West MR, Mraxeck M, Phillips DT, Gabrieli JDE and Whitfield-Gabrieli S (2020) Mindfulness training preserves sustained attention and resting state anticorrelation between default-mode network and dorsolateral prefrontal cortex: a randomized controlled trial. *Human Brain Mapping* 41, 5356–5369.

Chen G, Hu X, Li L, Huang X, Lui S, Kuan W, Ai H, Bi F, Gu Z and Gong Q (2016) Disorganization of white matter architecture in major depressive disorder: a meta-analysis of diffusion tensor imaging with tract-based spatial statistics. *Scientific Reports* 6, 21825.

Chen F, Gu C, Zhai N, Duan H, Zhai A and Zhang X (2020) Repetitive transcranial magnetic stimulation improves amygdala functional connectivity in major depressive disorder. *Frontiers in Psychiatry* 11, 732.

Cherysaykov AV, Chernyaysky AV, Sinitsyn DO and Piradov MA (2015) Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. *Frontiers in Human Neuroscience* 9, 303.

Coloigner J, Batall J-M, Commovick O, Corouge I, Robert G, Barilott C and Drapier D (2019) White matter abnormalities in depression: a categorical and phenotypic diffusion MRI study. *NeuroImage: Clinical* 22, 101710.

Denkova E, Nomi JS, Uddin IQ and Jha AP (2019) Dynamic brain network configurations during rest and an attention task with frequent occurrence of mind wandering. *Human Brain Mapping* 40, 4564–4576.

De Risio L, Borgi M, Pettorossi M, Miuli A, Ottomana AM, Sociali A, Martinotti G, Nicolò G, Macri S, di Giannantonio M and Zoratto F (2020) Recovering from depression with repetitive transcranial magnetic stimulation (rTMS): a systematic review and meta-analysis of preclinical studies. *Translational Psychiatry* 10, 393.

Drevets WC, Bogers W and Raichle ME (2002) Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *European Neuropsychopharmacology* 12, 527–544.

Du L, Liu H, Du W, Chao F, Zhang L, Wang K, Huang C, Gao Y and Tang Y (2017) Stimulated left DLPFC-nucleus accumbens functional connectivity predicts the anti-depression and anti-anxiety effects of rTMS for depression. *Translational Psychiatry* 7, 3.

Eshel N, Keller CJ, Wu W, Jiang J, Mills-Finnerty C, Huemer J, Wright R, Fonzo GA, Ichikawa N, Carreon D, Wong M, Yee A, Shipgel E, Guo Y, McTeague L, Maron-Katz A and Etkin A (2020) Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. *Neuropsychopharmacology* 45, 1018–1025.

Friedrich MJ (2017) Depression is the leading cause of disability around the World. *JAMA* 317, 1517.

Garay RP, Zarate CA, Charpeaud T, Citrome L, Correll CU, Hameg A and Illoca P-M (2017) Investigational drugs in recent clinical trials for...
treatment-resistant depression. Expert Review of Neurotherapeutics 17, 593–609.

Ge R, Downar J, Blumberger DM, Daskalakis ZJ and Vila-Rodriguez F (2020) Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. Brain Stimulation 13, 206–214.

George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarowski P, Holtzheimer PE, Schwartz T and Sackeim HA (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Archives of General Psychiatry 67, 507.

Greicius MD, Flores BH, Monen V, Glover GH, Sulsmon HB, Kenna H, Reiss AL and Schatzberg AF (2007) Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biological Psychiatry 62, 429–437.

Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, Ernst J, Hell D, Boeker H and Northoff G (2009) Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. Neropsychopharmacology 34, 932–943.

Gryglewski G, Seiger R, Baldinger-Melich P, Unterholzer J, Spurny B, Vanicek T, Hahn A, Kasper S, Frey R and Lanzenberger R (2020) Changes in white matter microstructure after electroconvulsive therapy for treatment-resistant depression. International Journal of NeuroPsychopharmacology 23, 20–25.

Gusnard DA, Akbudak E, Shulman GL and Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relating to a default mode of brain function. Proceedings of the National Academy of Sciences 98, 4259–4264.

Hamilton JP, Farmer M, Fogelmark P and Gotlib IH (2015) Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. Biological Psychiatry 78, 224–230.

Heij GJ, Penninx BWHJ, van Velzen LS, van Tol M-J, van der Wee NJA, Veltman DJ and Aghajani M (2019) White matter architecture in scale network dysfunction in major depressive disorder: a meta-analysis of neuropsychiatric studies. European Archives of Psychiatry and Clinical Neuroscience.

Kozyrev V, Staadt R, Eysel UT and Jancke D (2012) Rumination, the default-mode network, and the dark matter of clinical depression. Proceedings of the National Academy of Sciences 109, 2171–2176.

Kose S, Li X, Lim KO, Trivedi MH and George MS (2011) Loss of white matter integrity in major depressive disorder: abnormally increased contributions from subgenual anterior cingulate cortex in treatment-resistant depression. Archives of General Psychiatry 68, 517–526.

Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S and Jerabek PA (2000) Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biological Psychiatry 48, 830–843.

Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S and Jerabek PA (2002) The functional neuroanatomy of the placebo effect. American Journal of Psychiatry 159, 728–737.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schweibl JM and Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45, 651–660.

McIntyre RS, Filetou M-J, Martin L, Patry S, Carvalho A, Cha DS, Barakat M and Miguez M (2014) Treatment-resistant depression: definition, review of the evidence, and algorithmic approach. Journal of Affective Disorders 156, 1–7.

Menon V (2015) Large-scale functional brain organization. Brain Mapping: An Encyclopedic Reference, 2, 449–459.

Nahas Z, Teneback C, Chae J-H, Mu Q, Molnar C, Kozel FA, Walker J, Anderson B, Koola J, Kose S, Lomarev M, Bohnke DE and Geers MG (2007) Serial vagus nerve stimulation functional MRI in treatment-resistant depression. Neurpsychopharmacology 32, 1649–1660.

O’Reardon JP, Sulsmon HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS and Sackeim HA (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biological Psychiatry 62, 1208–1216.

Peng H, Zheng H, Li L, Liu J, Zhang Y, Shan B, Zhang L, Yin Y, Liu J, Wu Z, Jia L, Yang H and Zhang Z (2012) High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression. Journal of Affective Disorders 136, 249–257.

Piccoli T, Valente G, Linden DEJ, Re M, Esposito F, Sack AT and Salle FD (2015) The default mode network and the working memory network are not anti-correlated during all phases of a working memory task. PLoS ONE 10, e0123354.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA and Shulman GL (2001) A default mode of brain function. Proceedings of the National Academy of Sciences 98, 676–682.

Richiari R, Verger A, Boyer L, Bouckine M, David A, Lançon C, Cormolacce M and Guedel E (2018) Predictive value of dorso-lateral prefrontal connectivity for rTMS treatment in treatment-resistant depression: A brain perfusion SPECT study. Brain Stimulation 11, 1093–1097.

Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P and Downar J (2014) Resting-state cortico-thalamic-striallial connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. Neurpsychopharmacology 39, 488–498.

Schmaal L, Pozzi E, Ho TC, van Velzen LS, Veer IM, Opel N, Van Someren EJW, Han ILM, Aftanas I, Aleman A, Baune BT, Berger K, Blanken TF, Capitão L, Couvy-Duchesne B, Cullen KR, Dammann O, Davey C, Erwin-Grabner T, Evans J, Frodl T, Fu CHY, Godlewksa B, Gottlib IH, Goya-Maldonado R, Grab HE, Groenewald NA, Grotegerd D, Gruber O, Gutman BA, Hall GB, Harrison BJ, Hatton SN, Hermsdorff M, Hickie IB, Hilland E, Irunugo B, Jonassen R, Kelly S, Kircher T, Klimes-Dougan B, Krug A, Landro NR, Lagopoulos J, Leerssen J, Li M, Linden DEJ, MacMaster FP, McIntosh AM, Mehler DMA, Nomad I, Penninx BWJH, Portella MJ, Reneman L, Renteria ME, Sacchet MD, Sämann PG, Schraette A, Sim K, Soares JC, Stein DJ, Tozzi L, van Der Wee JNA, van Tol M-J, Vermeiren R, Vives-Gilbert Y, Walter H, Wilson M, Whalley HC, Witter K, Whittle S, Wright MJ, Yang TT, Zarate C, Thomopoulos SI, Jahanzhad N, Thompson PM and Veltman DJ (2020) ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. Translational Psychiatry 10, 172.
Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, Mintun MA, Wang S, Coalson RS and Raichle ME (2009) The default mode network and self-referential processes in depression. Proceedings of the National Academy of Sciences 106, 1942–1947.

Tateishi H, Nishihara M, Kawaguchi A, Matsushima J, Murakawa T, Haraguchi Y, Kunitake Y, Maekawa T, Kato TA, Asami T, Mizoguchi Y and Monji A (2019) Improvement of frontal lobe dysfunction and white matter integrity by rTMS in treatment-resistant depression. Neuropsychiatric Disease and Treatment 15, 3079–3087.

Taylor SF, Ho SS, Abagis T, Angstadt M, Maixner DF, Welsh RC and Hernandez-Garcia L (2018) Changes in brain connectivity during a sham-controlled, transcranial magnetic stimulation trial for depression. Journal of Affective Disorders 232, 143–151.

Walther S, Hügli S, Höfle O, Federspiel A, Horn H, Bracht T, Wiest R, Strik W and Müller TJ (2012) Frontal white matter integrity is related to psychomotor retardation in major depression. Neurobiology of Disease 47, 13–19.

Zeng L-L, Liu L, Liu Y, Shen H, Li Y and Hu D (2012) Antidepressant treatment normalizes white matter volume in patients with major depression. PLoS ONE, 7, e44248.

Zheng A, Yu R, Du W, Liu H, Zhang Z, Xu Z, Xiang Y and Du L (2020) Two-week rTMS-induced neuroimaging changes measured with fMRI in depression. Journal of Affective Disorders 270, 15–21.

Zhou H-X, Chen X, Shen Y-Q, Li L, Chen N-X, Zhu Z-C, Castellanos FX and Yan C-G (2020) Rumination and the default mode network: meta-analysis of brain imaging studies and implications for depression. NeuroImage 206, 116287.