Review

Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections

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HIGHLIGHTS

- Depression is associated with significant abnormalities in functional and structural connectivity.
- rTMS for treatment resistant depression modulates connectivity, normalising pre-treatment abnormalities.
- Connectivity imaging can be used to optimise rTMS targeting, explore and predict treatment response.

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a relatively recent addition to the neurostimulation armamentarium for treating individuals suffering from treatment refractory depression and has demonstrated efficacy in clinical trials. One of the proposed mechanisms of action underlying the therapeutic effects of rTMS for depression involves the modulation of depression-associated dysfunctional activity in distributed brain networks involving frontal cortical and subcortical limbic regions, via changes to aberrant functional and structural connectivity. Although there is currently a paucity of published data, we review changes to functional and structural connectivity following rTMS for depression. Current evidence suggests an rTMS-induced normalisation of depression-associated dysfunction within and between large scale functional networks, including the default mode, central executive and salience networks, associated with an amelioration of depressive symptoms. Additionally, changes to measures of white matter microstructure, primarily in the dorsolateral prefrontal cortex, have also been reported following rTMS for depression, possibly reversing depression-associated abnormalities. We argue that measures of functional and structural connectivity can be used to optimise rTMS targeting within the dorsolateral prefrontal cortex and also to explore novel rTMS targets for depression. Finally, we discuss the utility of measures of brain connectivity as predictive biomarkers of rTMS treatment response in guiding therapeutic decisions.

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1. Introduction

A significant number of individuals suffering from major depressive disorder (MDD) fail to achieve an adequate response to currently available treatments and are thus considered to be suffering from treatment resistant depression (TRD). A recent addition to the neurostimulation armamentarium for the treatment of individuals suffering from TRD is repetitive transcranial magnetic stimulation (rTMS). rTMS is a non-invasive technique for which accumulated evidence has demonstrated efficacy and safety for TRD (Perera et al., 2016), where clinical trials report moderate effect sizes (Lam et al., 2008; Schutter, 2009; Slotema et al., 2010; Berlim et al., 2014), and from a patient perspective is generally a well-tolerated treatment approach. Despite nearly two decades of research however, our understanding of the mechanisms of action underlying the therapeutic effects of rTMS for depression is still incomplete, possibly accounting for the modest rates of response to treatment.

One of the proposed mechanisms of action involves the modulation of distributed networks of brain regions distal to the target of stimulation. These distal networks have demonstrated dysregulation in depression and an association with the affective, cognitive and vegetative symptoms of the disorder. Indeed, following rTMS for depression, significant changes in neural activity in fronto-limbic brain regions (e.g., Speer et al., 2000; Catafau et al., 2001; Nahas et al., 2001; Shajahan et al., 2002; Loo et al., 2003; Kito et al., 2008), and in neurobiological processes, including neurotransmission (e.g., Michael et al., 2003; Pogarell et al., 2006; Luborzewski et al., 2007), HPA axis function (e.g., Pridmore, 1999; Zwanzger et al., 2003; Baeken et al., 2009), and neurotrophic factor concentrations (e.g., Yukimasa et al., 2006; Zanardini et al., 2006) have been reported. Considering this mechanism of action, that is, the modulation of distal networks of brain regions associated with diverse neurobiological changes, the connectivity between the rTMS target of stimulation with these distributed networks may provide a key to understanding the mechanisms underlying the therapeutic effects of rTMS for depression. The role of brain connectivity in the mechanisms of action underlying the therapeutic effects of rTMS for depression will be the focus of the current review.

Following an initial review of depression-associated abnormalities in brain connectivity and their relationship to the major symptoms of the disorder, evidence is presented showing significant changes in connectivity within these fronto-limbic networks following rTMS for depression (Kozel et al., 2011; Peng et al., 2012; Baeken et al., 2014; Liston et al., 2014; Salomons et al., 2014). Additionally, evidence is reviewed that suggests that measures of pre-treatment functional connectivity predicts treatment response. The mechanisms of action underlying these rTMS-associated changes in connectivity and their implications for the amelioration of depressive symptoms are then briefly discussed. In the context of these empirical findings, a method for optimisation and individualisation of rTMS targeting utilising brain connectivity neuroimaging is examined. Novel neuroanatomical targets for rTMS are explored in the context of brain connectivity, in an attempt to guide further research and a possible improvement in the efficacy of the technique for treating depression. Finally, the use of brain connectivity measures as biomarkers for predicting a favourable treatment response to guide therapeutic decisions is discussed.

A search of the published literature was conducted utilising the Google Scholar and PubMed databases using the search terms "repetitive transcranial magnetic stimulation", "depression", "major depressive disorder", "treatment resistant depression", in combination with "structural connectivity", "white matter", "diffusion tensor imaging", "diffusion weighted imaging", or "functional connectivity", "resting state network", and "functional magnetic resonance imaging". Additionally, the reference lists of the identified articles, along with meta-analyses, were checked for relevant references.

2. Brain connectivity and depression

The pathophysiology of depression is currently understood to involve significant dysfunction within distributed fronto-limbic networks (e.g., Seminowicz et al., 2004), whose component regions demonstrate complex patterns of interconnectivity. Recent research on brain connectivity has been focussed on two main areas; structural connectivity and functional connectivity. Structural connectivity refers to the anatomical connections of the brain which provide the structural architecture for communication between brain regions. The location of these tracts in the human brain was historically only possible using histological techniques post-mortem, however due to advances in brain imaging techniques it is now possible map them in vivo, utilising a magnetic resonance imaging technique referred to as diffusion weighted imaging (DWI). DWI measures the movement of water molecules in the brain over time, and whose restricted movement, due mainly to the axon membranes, but also a contribution from myelin (Beaulieu, 2002), is used to infer the underlying microstructure of white matter.

The second area of brain connectivity research that is attracting a lot of recent attention is functional connectivity, which is inferred by the correlation of neurophysiological events in spatially separated brain regions over time (Friston et al., 1993; van den Heuvel and Hulshoff Pol, 2010). Functional connectivity can be measured via a number of functional imaging techniques including electroencephalography, magnetoencephalography, positron

emission tomography and functional magnetic resonance imaging, however the primary tool currently used is resting-state fMRI, where the low-frequency (<0.1 Hz) spontaneous oscillations in the blood oxygen level dependent (BOLD) signal are correlated in regions considered to be functionally connected. Research has found that these correlated regions are organised into networks, termed intrinsic connectivity networks (ICNs), that subsume similar functions and remain coherent during activity and the resting state (Greicius et al., 2003; Seeley et al., 2007; Yeo et al., 2011; Buckner et al., 2013), and are therefore thought to represent a fundamental aspect of brain organisation.

Research suggests that functional connectivity is constrained by the underlying structural connectivity (Greicius et al., 2009; Honey et al., 2009; van den Heuvel et al., 2009; Van Dijk et al., 2010), however dynamic changes in functional connectivity over time suggest that other complex processes also contribute (Buckner et al., 2013), therefore techniques exploring both types of brain connectivity will provide complementary information into brain function and dysfunction. Indeed, patterns of dysfunction within ICNs and abnormalities in anatomical connectivity have both been identified in association with a number of psychological disorders, including depression (e.g., Menon, 2011).

As rTMS is only currently indicated for TRD, the following sections describing patterns of functional and structural connectivity associated with depression focusses on TRD, however evidence for connectivity abnormalities associated with major depressive disorder (MDD) in general is also presented. The reason this approach was taken was not only the limited published evidence that explores connectivity associated with TRD but that the evidence published to date is ambiguous in terms of whether there are any distinct differences in patterns of connectivity between TRD and non-TRD. While some evidence suggests similar patterns of abnormalities in connectivity between TRD and non-TRD in circuits associated with mood regulation and cognitive processing, with differences only in the degree (Zhou et al., 2011; Peng et al., 2013; De Kwaasteniet et al., 2015; Serafini et al., 2015), other evidence suggests distinct patterns of connectivity associated with TRD when compared to non-TRD (Lui et al., 2011; De Kwaasteniet et al., 2015; Serafini et al., 2015).Therefore, evidence of abnormal patterns of connectivity is presented for MDD in general to provide a more comprehensive overview.

2.1. Functional connectivity and depression

Functional connectivity has mainly been explored within and between three ICNs in association with depression; the default mode network (DMN), the central executive network (CEN), and the salience network (SN). Although research on ICNs and depression is still in its infancy, results published to date show abnormal patterns of connectivity associated with the disorder when compared to healthy individuals (see Fig. 1 for summary). Additionally, changes in connectivity following treatment and patterns of pre-treatment connectivity associated with a favourable clinical response have also been reported; the latter suggesting a role for connectivity measures as potential biomarkers for predicting depression treatment outcome.

The primary brain regions that make up the DMN (Fig. 1a) include the medial prefrontal cortex (ventral, VMPFC and dorsal, DMPFC subdivisions) and the posterior cingulate cortex (PCC), but also include the inferior parietal lobe, and hippocampal formation (Buckner et al., 2008; Andrews-Hanna et al., 2010). The DMN has been shown to decrease in activity during goal-directed tasks and increase activity during self-referential processing, and the 'resting-state' (Gusnard et al., 2001; Raichle et al., 2001).
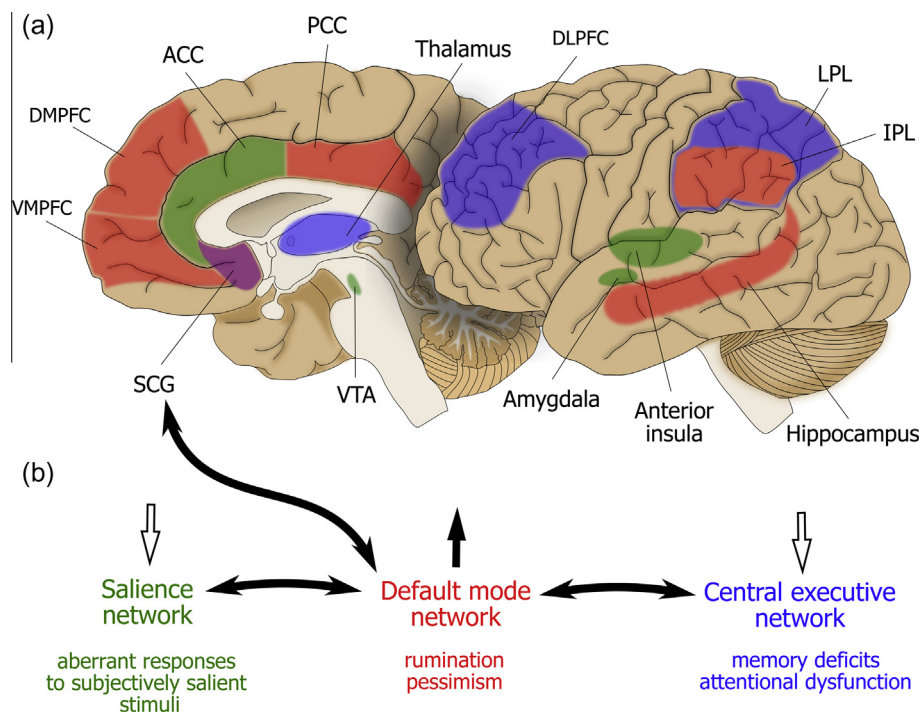

Fig. 1. Intrinsic connectivity networks (ICN's) and depression. (a) Key nodes of the three main ICN's studied in depression; red = the default mode network, blue = the central executive network, and green = the salience network. (b) Patterns of abnormal functional connectivity within and between ICN's associated with depression and associated symptoms. Black arrows represent hyperconnectivity and white arrows represent hypoconnectivity. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; IPL, inferior parietal lobe; LPL, lateral parietal lobe; PCC, posterior cingulate cortex; SCG, subgenual cingulate gyrus; VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Abnormally increased DMN connectivity has been found in association with depression (Kaiser et al., 2015), including in treatment resistant individuals (Li et al., 2013; Liston et al., 2014), first episode treatment-naïve young adults (Zhu et al., 2012), adults diagnosed with MDD (Sambataro et al., 2014), and in late-life depression (Alexopoulos et al., 2012). Additionally, increased connectivity between the DMN and the subgenual cingulate gyrus (SCG) (Greicius et al., 2007; Liston et al., 2014), the thalamus (Greicius et al., 2007), and decreased connectivity with the bilateral caudate (Bluhm et al., 2009), have also been reported in association with depression. Abnormal DMN connectivity has also demonstrated a relationship to specific depressive symptoms, for example, an association with negative forms of rumination (Berman et al., 2011; Zhu et al., 2012; Hamilton et al., 2015), and pessimism (Alexopoulos et al., 2012) have been reported. Supporting evidence for dysfunction within the DMN and its association with depressive symptomatology comes from task-based fMRI activation studies which have demonstrated a relationship between DMN activity and depression symptom severity (Grimm et al., 2009), as well as some of the prominent features of the depressive disorder, including negative rumination (Hamilton et al., 2011), altered emotion regulation (Sheline et al., 2009) and feelings of hopelessness (Grimm et al., 2009). Considering this evidence, abnormally increased functional connectivity within the DMN appears to be associated with dysfunctional emotion regulation, manifesting as an increased preoccupation with self-referential processes such as negative rumination and pessimism.

The primary nodes of the CEN (Fig. 1a) include the dorsolateral prefrontal cortex (DLPFC) and the lateral posterior parietal cortex, but also include the ventrolateral prefrontal cortex and the thalamus (Seeley et al., 2007). The CEN has also been referred to as the task-positive network due to increased activation of its nodes during goal-directed, cognitively demanding tasks requiring sustained attention, such as working memory tasks (Fox et al., 2005; Seeley et al., 2007). Considering that depression has been associated with significant cognitive deficits, including memory and attentional dysfunction (Austin et al., 2001; Rogers et al., 2004), abnormalities of CEN connectivity may be expected. Indeed, when compared to healthy control subjects, individuals diagnosed with depression have demonstrated hypoconnectivity within the CEN (Alexopoulos et al., 2012; Liston et al., 2014; Kaiser et al., 2015), although increases in functional connectivity have also been reported (Zhou et al., 2010).

The key nodes of the SN (Fig. 1a) include the dorsal anterior cingulate cortex (dACC) and the frontoinsular cortex, but also include subcortical regions, the amygdala and ventral tegmental area (Seeley et al., 2007; Uddin, 2014). The SN is implicated in the detection of personally salient and rewarding stimuli, via the integration of external and internal stimuli, of an emotional, homeostatic and/or cognitive nature, and the guiding of an appropriate behavioural response (Seeley et al., 2007; Menon, 2011; Goulden et al., 2014; Uddin, 2014). Research has demonstrated significantly decreased connectivity within the SN in individuals suffering from depression when compared with healthy subjects, with this aberrant connectivity also demonstrating a significant relationship to depressive symptom severity (Manoliu et al., 2014). Indirectly, a recent meta-analysis demonstrated that when depressed individuals were exposed to negative affective stimuli (i.e., viewing sad faces, viewing negative pictures, reading sad words), there was a significant over-activation in the dACC, the insula and amygdala (Hamilton et al., 2012), all key nodes in the SN. Evidence of dysfunction within the SN associated with depression suggests abnormalities in the detection of personally salient stimuli or a bias towards negatively salient stimuli, which is consistent with the depression-associated preoccupation with a negative view of the self and external events (Beck, 2008).

These large-scale functional networks however do not operate in isolation; complex interactions have been shown to occur, with dysfunction in these dynamics associated with depressive symptomatology (Menon, 2011; Manoliu et al., 2014). For example, aberrant connectivity between networks has been implicated in depression (see Fig. 1b), including abnormal hyperconnectivity between the SN and DMN, and the DMN and CEN (Manoliu et al., 2014; Liston et al., 2014; Kaiser et al., 2015). Individuals suffering from depression have demonstrated DMN dominance over CEN, which correlated with maladaptive rumination (Hamilton et al., 2011). Additionally, abnormal switching between DMN and CEN activity in depression has been suggested as a mechanism underlying the preoccupation with self-referential processes, associated with DMN hyperconnectivity, and deficits in cognitive functioning and goal-directed behaviour, related to CEN hypoconnectivity (Menon, 2011; Manoliu et al., 2014; Kaiser et al., 2015). The SN has been identified as having a causal role in switching between DMN and CEN activity, when resources are required to change from internally to externally focused attention (Sridharan et al., 2008; Menon and Uddin, 2010; Goulden et al., 2014), specifically the anterior insula cortex, which has also demonstrated depression-associated dysfunction. Overall, current evidence has demonstrated significant dysfunction in connectivity within large scale functional neural networks and complex interactions in connectivity between networks, associated with depression.

2.2. Structural connectivity and depression

There is a hypothesis that has been advanced in the literature that depression represents a "disconnection syndrome", whereby abnormalities in white matter microstructure "disconnect" pathways linking frontal cortical and subcortical limbic regions involved in mood regulation and cognitive function (Sexton et al., 2009; Liao et al., 2013). Although the term "disconnection syndrome" was originally applied to a range of neurological disorders (Catani and Ffytche, 2005), in psychiatry it has been predominantly applied to schizophrenia (e.g., Bullmore et al., 1997; Kubicki et al., 2002). Recent evidence for the applicability of the term to depression has emerged from neuroimaging and histological research, which has identified significant abnormalities in white matter pathways in individuals suffering from depression when compared to healthy control subjects, at all stages of the illness.

For example, utilising diffusion tensor imaging (DTI), research has revealed significant reductions in fractional anisotropy (FA), the diffusion metric most widely reported in the literature, in various frontal and limbic regions; in treatment-naïve young adults suffering from a first episode of depression (Li et al., 2007b; Ma et al., 2007; Zhu et al., 2011), adolescents diagnosed with MDD (Cullen et al., 2010), a non-late-onset adult patient group suffering from depression (Zou et al., 2008), late life depression (Taylor et al., 2004; Bae et al., 2006), and in individuals suffering from treatment resistant depression (TRD) (Li et al., 2007a; Peng et al., 2013; de Diego-Adeliño et al., 2014). In fact, higher depression severity was found to predict lower FA values at the whole brain level (de Diego-Adeliño et al., 2014). Additionally, reduced FA values in white matter associated with the anterior cingulate, DLPFC and the insular cortex was found to predict the degree of executive dysfunction in late-life depression (Alexopoulos et al., 2002; Murphy et al., 2007). Meta-analyses have identified a number of white matter pathways that have demonstrated microstructural abnormalities associated with depression, including the superior longitudinal fasciculus, the anterior thalamic radiation, the uncinate fasciculus, the medial forebrain bundle, inferior longitudinal fasciculus, fronto-occipital fasciculus, posterior thalamic radiation and the corpus callosum (Sexton et al., 2009; Murphy and Frodl, 2011; Liao et al., 2013).

Supporting the neuroimaging findings is evidence from post-mortem research in individuals who had suffered from depression, which has shown significantly reduced myelin staining in the deep white matter of the DLPFC (Regenold et al., 2007), and decreases in the expression of oligodendroglia-related genes, genes that code for various aspects of myelin-related functioning, and axon growth and synaptic function, in the temporal cortex (Aston et al., 2005; Sokolov, 2007). Overall, the evidence suggests that a significant disruption to anatomical connectivity within fronto-limbic path-ways is involved in the pathophysiology of depression.

3. rTMS for TRD; modulating dysfunctional connectivity

A number of studies have been published demonstrating changes to measures of functional and structural connectivity fol-lowing various depression treatment modalities. For example, changes in white matter microstructure following ECT (Lyden et al., 2014) and pharmacological treatment (Taylor et al., 2011), and changes to patterns of functional connectivity within ICNs fol-lowing psychotherapy (Crowther et al., 2015) and pharmacological antidepressant treatment (Li et al., 2013), have been reported. The current review however, will be limited to changes following rTMS for depression. There is currently a paucity of published research reporting on the impact that rTMS for depression has on functional and structural connectivity. The studies that have been published show significant changes in connectivity following rTMS, predom-inantly reversing pre-treatment depression-associated abnormali-ties. Additionally, pre-treatment functional connectivity has demonstrated possible utility for predicting rTMS treatment response. rTMS for TRD is applied to the brain at either high fre-quency (HF, $\geqslant 5$ Hz) or low frequency (LF, $\leqslant 1$ Hz), driven by oppos-ing local effects on cortical excitation, whereby HF stimulation has demonstrated an increase and LF stimulation a decrease in local neural activity (Pell et al., 2011), with the targeting of brain regions showing abnormally decreased or increased activity respectively. In the following discussion of rTMS and connectivity, it was consid-ered premature to distinguish between the impact of different stimulation parameters due to a paucity of published evidence, however, stimulation frequency is noted when evidence is pre-sented and the association between stimulation parameters and connectivity is considered an important area of future research.

3.1. rTMS for TRD and functional connectivity

Following rTMS for depression, changes to functional connec-tivity both within and between ICNs has been reported. For exam-ple, following 25 sessions of 10 Hz rTMS to the left DLPFC (the primary target used in rTMS for depression) over 5 weeks in a group of individuals suffering from TRD, pre-treatment hypercon-nectivity within the DMN significantly decreased and had largely normalised relative to a control group, however no changes to pre-treatment abnormal hypoconnectivity within the CEN was observed (Liston et al., 2014). In the same study, changes to con-nectivity between ICNs was also reported, with the induction of an anticorrelation between the DLPFC (CEN node) and the DMN, a pattern of connectivity that wasn't apparent prior to treatment (Liston et al., 2014). Similarly, following 20 sessions of 10 Hz rTMS delivered bilaterally to the dorsomedial prefrontal cortex (DMPFC, a recently investigated rTMS target for depression) an increased anticorrelation between the DMPFC (DMN node) and the insula (SN node), and increased connectivity with the thalamus (CEN node) was found to be associated with a greater clinical response (Salomons et al., 2014).
Resting-state functional connectivity measured at baseline may provide a means by which to predict rTMS treatment response,

especially aberrant connectivity of the SCG. Indeed, abnormal baseline hyperconnectivity between the SCG and VMPFC, DMPFC and PCC (DMN nodes), and the DLPFC and posterior parietal cortex (CEN nodes), was shown to predict a favourable clinical response following left DLPFC rTMS (Liston et al., 2014). Similarly, a positive clinical response was found to correlate with higher baseline DMPFC to SCG (primarily positive), and SCG to DLPFC (primarily negative) functional connectivity, following bilateral DMPFC rTMS (Salomons et al., 2014). Responders to 20 Hz left DLPFC rTMS were also found to have significantly greater baseline hyperconnectivity of the SCG with the superior medial frontal gyrus (DMN node) (Baeken et al., 2014). SCG connectivity with SN nodes has also been implicated in the prediction of a clinical response, with lower base-line connectivity between the SCG and the insula and the amyg-dala, correlating with a more favourable clinical response to DMPFC rTMS (Salomons et al., 2014). In addition to the predictive utility of SCG functional connectivity, one study also found lower baseline connectivity between the DMPFC (DMN node) and the thalamus (CEN), and amygdala (SN), predicted a better clinical response to DMPFC rTMS (Salomons et al., 2014).

3.1.1. Mechanisms underlying functional connectivity change

The mechanisms of action involved in functional connectivity changes, at the cellular level is still poorly understood. Research has shown that the oscillations in the BOLD signal that are used to infer functional connectivity may relate to spontaneous neu-ronal spiking activity (Shmuel and Leopold, 2008), and with rTMS shown to modulate cortical excitability beyond the stimulation train, implicating some form of neural plasticity (Pell et al., 2011), rTMS, via repeated activation of the target region, may change the spontaneous neural activity in proximal and distal brain regions, subsequently altering their functional connectivity. This is observed at the network level, with emerging evidence sug-gesting a causal role for rTMS in regulating both within and between network connectivity. One study, that utilised concurrent TMS and fMRI in healthy subjects, demonstrated that stimulation applied to the DLPFC, one of the major CEN nodes, directly modu-lated connectivity within the DMN, primarily with the medial pre-frontal cortex, and also induced connectivity changes within the CEN (Chen et al., 2013).

Although only speculative, current evidence suggests that an rTMS-induced normalisation of aberrant functional connectivity within and between large scale networks underlies the ameliora-tion of depressive symptomatology. For example, by stimulation of a key CEN node (DLPFC), direct modulation of regions within the DMN and SN may drive changes in abnormal functional con-nectivity via a rebalancing of the dynamics in connectivity and switching of neural activity in these networks; such as a reversal of DMN dominance over CEN, resulting in inhibition of negative rumination and driving improvements in executive functioning.

3.2. rTMS for TRD and structural connectivity

The primary brain region targeted with rTMS for depression has been the DLPFC, which has demonstrated direct anatomical con-nectivity to several fronto-limbic regions related to depressive symptomatology (see Fig. 2), via white matter pathways with depression-associated microstructural abnormalities. The DLPFC is therefore in a prime position to directly modulate the activity in these distal brain regions and to affect changes in the pathways connecting them. Indeed, research in a small TRD patient group has demonstrated a trend towards an increase in FA in the left pre-frontal white matter following 4–6 weeks of daily 10 Hz rTMS to the left DLPFC (Kozel et al., 2011), possibly reversing the decreases in FA in this region associated with depression. Interestingly, the same study (Kozel et al., 2011) found that following treatment,
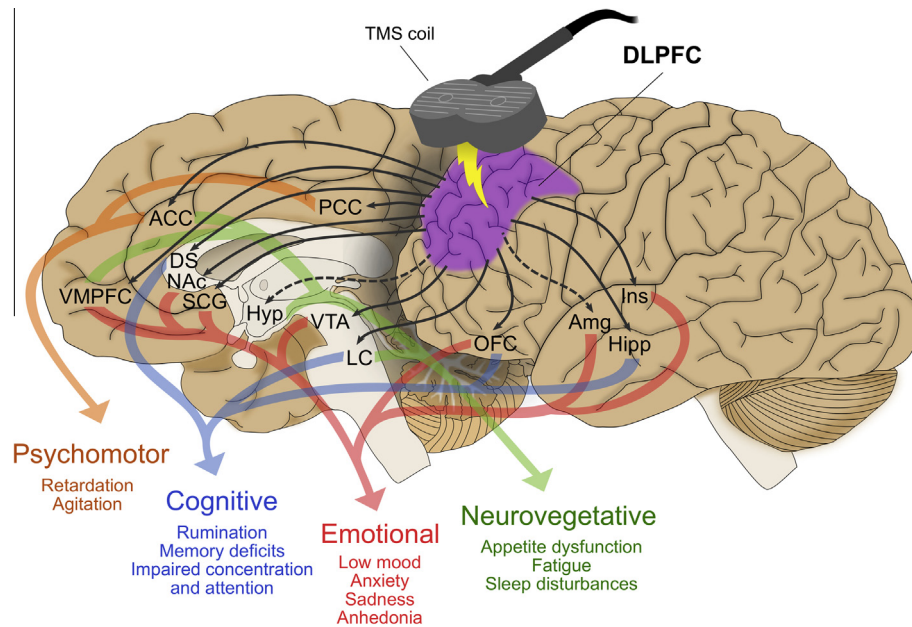
Fig. 2. Anatomical connectivity of the dorsolateral prefrontal cortex (DLPFC) to regions involved in depression symptomatology. Solid arrows represent direct connectivity, dashed arrows represent sparse or indirect connectivity. Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; DLPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; Hipp, hippocampus; Hyp; hypothalamus, Ins, insula; LC, locus coeruleus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SCG, subgenual cingulate gyrus; TMS, transcranial magnetic stimulation; VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

those in the active arm had higher FA in the left versus right prefrontal white matter, a pattern that was not observed in the sham subjects, which the authors cautiously interpret as a positive effect on white matter organisation within the stimulated hemisphere. A more recent and larger study, reported a significant increase in FA in the left middle frontal gyrus following 15 Hz rTMS to the left DLPFC, in an area distal to the stimulation target, with the changes in FA correlating with a reduction in the severity of depressive symptoms (Peng et al., 2012). The same study (Peng et al., 2012) also observed an increase in FA in the anterior lobe of the right cerebellum. The change in FA in the cerebellum however, was not correlated with the improvement in depression symptom severity (Peng et al., 2012).

3.2.1. Mechanisms underlying structural connectivity change

Changes in anatomical connectivity following rTMS for depression, inferred by changes in diffusion imaging metrics, may involve changes to various morphological characteristics of white matter, including myelination, axonal growth, axon diameter and density, and organisation of the white matter tracts. One of the main mechanisms thought to underlie sustained changes to cortical excitability following rTMS is synaptic plasticity, in the form of long term potentiation (LTP) or long term depression, although other potential mechanisms have been suggested (e.g., Pell et al., 2011). Assuming this to be the case, axonal sprouting, which has been shown to occur following stimulation-induced LTP in rats (Adams et al., 1997), may be involved in rTMS-induced changes to white matter microstructure. Also demonstrating an involvement in neuroplasticity, axonal and dendritic growth and remodelling, synapse formation and function, are a family of proteins called neurotrophins (Bibel and Barde, 2000; Huang and Reichardt, 2001). Studies of rTMS in depression have demonstrated an increase in brain derived neurotrophic factor (BDNF) associated with a favourable clinical response (Yukimasa et al., 2006; Zanardini et al., 2006), reversing depression-associated deficits (Karege et al., 2002, 2005; Shimizu et al., 2003; Gonul et al., 2005; Lee et al., 2007; Piccinni et al., 2008, 2009), suggesting a possible association with white matter

microstructural changes following rTMS. Finally, beyond the microstructural level, research has demonstrated evidence of activity-dependent axonal re-routing in long range cortico-cortical connections (Johansen-Berg, 2007), a mechanism that may also underlie diffusion-related changes in white matter pathways via rTMS-induced neuronal activation. These are only a few of the cellular processes, out of many, that may underlie changes in white matter following rTMS, however will have to remain speculative until further empirical testing is undertaken.

In summary, current evidence, although limited, suggests changes in white matter microstructure following rTMS for depression, in pathways proximal and distal to the target of stimulation, and in a direction suggesting a normalisation of depression-associated abnormalities. These changes in white matter microstructure possibly contribute to the amelioration of depression symptomatology via improved connectivity, and therefore restored communication, between frontal cortical and limbic regions, associated with emotion regulation and cognitive processing.

4. Discussion

Despite nearly two decades of research and minor improvements in efficacy via various changes in treatment protocol, including the duration of treatment course and stimulation intensity (Gross et al., 2007; Fitzgerald and Daskalakis, 2013), overall response rates to rTMS for depression continue to be modest, with response rates of 29% to 46% and remission rates of 18% to 31% reported (n = 1371, Berlim et al., 2014; n = 1132, Fitzgerald et al., 2016). One relatively consistent factor in the treatment protocol has been the targeting of the DLPFC and the method by which it is located. Therefore, an opportunity exists to further improve rates of response to rTMS for depression by optimising the method of targeting stimulation and the exploration of novel neuroanatomical targets. This can be achieved by utilising measures of brain connectivity, combined with evidence of the role connectivity plays in rTMS treatment response, and the accumulating evidence of

depression-related abnormalities in connectivity in fronto-limbic pathways involved in emotion regulation and cognitive control. Finally, an improvement in the rate of response to rTMS could be realised if biomarkers of treatment response are used to guide therapeutic decisions. The use of brain connectivity measures to predict rTMS treatment response is discussed below.

4.1. Optimising rTMS targeting of the DLPFC using brain connectivity

The current, standard approach for targeting the DLPFC, in rTMS for depression, involves evoking a response in the abductor pollicis brevis muscle in the thumb by stimulating the contralateral motor cortex and then measuring 5 cm rostrally along the curvature of the scalp, however, this approach has been shown to inaccurately target the DLPFC (Herwig et al., 2001). Additionally, there is also evidence showing significant individual variability in the cytoarchitecture of the DLPFC (Rajkowska and Goldman-Rakic, 1995a, b), and that distinct regions within the DLPFC subsume different functions (Cieslik et al., 2013), which suggests that an individual approach to targeting the DLPFC may be more appropriate. Indeed, by utilising structural MRI, a neuro-navigational approach for locating the DLPFC resulted in an improvement in the efficacy of rTMS for depression over the standard technique (Fitzgerald et al., 2009). Further suggesting that an individualised approach to targeting rTMS may improve clinical outcomes, was a study that found previously reported DLPFC targets with greater clinical efficacy demonstrated stronger functional connectivity (an anti-correlation) with the SCG (Fox et al., 2012a), and that the functional connectivity between the DLPFC and SCG exhibits significant differences between individuals which are reproducible across time (Fox et al., 2012b). Caution is urged however, when considering using functional connections involving the SCG for individuals, due to poor signal to noise ratio, and also that the reproducibility of individual targets using functional connections based on anti-correlations may be reduced when compared with positive correlations (Fox et al., 2012b).

In addition to using functional connectivity, structural connectivity analyses may also provide a strategy for individualising rTMS targeting in the DLPFC. A number of white matter pathways involving the DLPFC have demonstrated significant microstructural abnormalities associated with the depressive illness. These same pathways connect the DLPFC to other cortical and subcortical limbic regions that have demonstrated an involvement in depression symptomatology and the prediction of a favourable clinical outcome. Two such white matter tracts are the cingulum bundle and medial forebrain bundle (MFB), and although they are not the only tracts that connect the DLPFC to regions associated with depression, for example the superior longitudinal fasciculus and the anterior thalamic radiation, evidence is presented that supports a major role for these tracts in depression pathophysiology.

4.1.1. Cingulum bundle

The cingulum bundle is a medial association fibre tract, considered a major component of the limbic system, which connects the DLPFC to the anterior and posterior cingulate, the SCG, DMPFC, parietal cortex and the hippocampus, and has been found to connect key nodes of the DMN (van den Heuvel et al., 2009). Depression research, utilising diffusion MRI, has demonstrated white matter microstructural abnormalities in the cingulum bundle (i.e. reduced FA) (Cullen et al., 2010; Kieseppä et al., 2010; de Diego-Adeliño et al., 2014), and also a correlation between measures of white matter microstructure and executive functioning (Schermuly et al., 2010). Interestingly, never depressed individuals with a family history of depression demonstrated a significant reduction in FA bilaterally in the cingulum when compared to a group without family histories of depression (Keedwell et al.,

2012), suggesting a vulnerability to depression associated with white matter microstructural abnormalities in the cingulum. Additionally, the same study (i.e., Keedwell et al., 2012), found that the reduction in FA in the cingulum correlated with anhedonia, a key symptom of depression. Further, pre-treatment FA in the cingulum bundle predicted remission following pharmacological antidepressant treatment (i.e., two SSRI's and an SNRI) (Korgaonkar et al., 2014). Therefore, considering the role of the cingulum bundle in the pathophysiology of depression and treatment response, mapping the extent of the tract in individuals suffering from depression, may provide a more refined rTMS target within the DLPFC, with greater connectivity to, and therefore ability to modulate activity within, emotion regulating and cognitive processing regions.

4.1.2. Medial forebrain bundle

The MFB, a key pathway of the reward system, is a projection tract connecting the ventral tegmental area (VTA) with the nucleus accumbens (NAc), hypothalamus, then on to frontal cortical regions, including the orbitofrontal cortex and the DLPFC (Zahm, 2006; Coenen et al., 2012). The MFB has been found to exhibit significant white matter microstructural abnormalities associated with depression, predominantly reductions in FA, which have also demonstrated a correlation with overall depression severity, anhedonia and sadness (Blood et al., 2010; Bracht et al., 2014, 2015), suggesting that the integrity of the MFB is important for emotion regulation and is a possible target pathway for depression treatment. Supporting the use of the MFB as a target for depression treatment and diffusion imaging as a targeting strategy, a pilot study that used DTI to individually target deep brain stimulation to the supero-lateral branch of the MFB (slMFB), proximal to the VTA, was shown to have rapid antidepressant effects in a group suffering a severely treatment-resistant depression (Schlaepfer et al., 2013). Interestingly, a tractographic study of the four brain regions used historically as surgical ablation targets to treat severe treatment refractory depression, found that each of the sites had shared connectivities with the slMFB (Schoene-Bake et al., 2010), further implicating the importance of this white matter tract in a clinical recovery from depression. Therefore, utilising diffusion MRI to map the MFB in individuals, focusing on the supero-lateral branch, and assessing regions of greater anatomical connectivity with the DLPFC, may provide rTMS stimulation targets with a greater ability to directly modulate reward-related circuitry.

4.2. Novel rTMS targets for depression using brain connectivity

In addition to providing an individualised approach to DLPFC targeting, functional and structural connectivity analyses may also lead to the identification of novel rTMS targets for treating depression. The exploration of novel targets for rTMS needs to take into account the limitation of the technique to the focal stimulation of superficial cortical regions but also to keep in mind that modulation of distal regions via transsynaptic connectivity is one of the putative mechanisms by which rTMS exerts its therapeutic effects. A number of alternative cortical rTMS targets have been suggested for treating TRD, including the cerebellum (Schutter and van Honk, 2005; Wu and Baeken, 2016) and the ventro-lateral prefrontal cortex (Downar and Daskalakis, 2013). The parietal cortex and the dorsomedial prefrontal cortex (DMPFC), with extensive connectivity to networks of regions associated with emotion regulation and cognitive processing (Downar et al., 2016), and key regions involved in a favourable clinical response to rTMS for depression, suggest that they are excellent candidates as alternative rTMS targets.

4.2.1. Parietal cortex

Abnormalities in both functional and structural connectivity have been reported in the parietal cortex in association with depression, for example, reduced functional connectivity between the right parietal lobe and the DLPFC, both key nodes of the CEN (Ye et al., 2012; Liston et al., 2014), and significant reductions in FA in the parietal portion of the superior longitudinal fasciculus (SLF) (Zou et al., 2008; Wu et al., 2011). In support of using the parietal cortex as an rTMS target for depression, rTMS research in healthy subjects has demonstrated significantly reduced ratings of depressive mood following 2 Hz rTMS to the right parietal cortex in a placebo controlled study (van Honk et al., 2003). Similarly, rTMS to the left parietal cortex in healthy subjects, utilising resting-state fMRI to individually target stimulation to a parietal region with high functional connectivity to the hippocampus, found an enhancement in associative memory and an increase in functional connectivity between the stimulation target and hippocampus (Wang et al., 2014), suggesting a possible target for ameliorating memory deficits associated with depression. Finally, clinical research has also provided evidence that 2 Hz rTMS to the right parietal cortex in a group suffering from depression, demonstrated significant antidepressant effects compared to sham, for partial responders when compared with non-responders (Schutter et al., 2009).

To aid in the identification of individual rTMS targets within the parietal cortex measures of structural and functional connectivity may be utilised, for example, by mapping regions of higher functional connectivity between the posterior parietal cortex and the SCG, which has been shown to predict a greater clinical response to DLPFC rTMS for depression (Liston et al., 2014). The parietal cortex, via the SLF and the cingulum bundle, has direct anatomical connections to key fronto-limbic regions associated with emotion regulation and cognitive processing, including the DLPFC, SCG and the hippocampus. Therefore, mapping the architecture of these tracts using diffusion imaging and tractography may also provide individual rTMS targets within the parietal cortex.

4.2.2. Dorsomedial prefrontal cortex

A study that used resting-state MRI to explore for unique patterns of functional connectivity in depression found that the DMPFC demonstrated increased connectivity with all three ICNs studied (i.e., the CEN, DMN, and an affective network), a pattern that was not observed in a healthy control group (Sheline et al., 2010), suggesting a central role for this brain region in the pathophysiology of depression. The DMPFC is also connected to the SCG, via the cingulum bundle (Croxson et al., 2005), a region whose pre-treatment functional connectivity has demonstrated a utility for predicting rTMS treatment response (Baeken et al., 2014; Liston et al., 2014; Salomons et al., 2014), and is considered a key region involved in emotion regulation (Mayberg et al., 1999; Phillips et al., 2003). Based on the argument that stimulation of the DMPFC might have a more direct effect on the emotion-regulating regions of the brain than the DLPFC, recent rTMS research found that the DMPFC may indeed be an efficacious target for treating depression (Downar et al., 2014; Salomons et al., 2014; Bakker et al., 2015; Schulze et al., 2016).

The DMPFC has demonstrated significant functional segregation into regions that subsume differing high level cognitive functions (Eickhoff et al., 2016), suggesting that a more refined approach to targeting DMPFC rTMS might be possible. Indeed, a caudal-left subregion of the DMPFC was found to have functional connectivity to the SN, specifically the anterior cingulate cortex and the anterior insula (Eickhoff et al., 2016). Research suggests that the SN, primarily the fronto-insula cortex, plays a causal role in driving switching between DMN and CEN (Sridharan et al., 2008; Goulden et al., 2014), and that depression is associated with abnormal switching between DMN and CEN (e.g., Menon, 2011; Manoliu et al., 2014) and DMN dominance over CEN (Hamilton et al., 2011). Therefore, left-caudal DMPFC rTMS, may stimulate the anterior insula cortex, via direct anatomical connectivity (Ghaziri et al., 2015), and drive changes in functional connectivity between the DMN and CEN in a direction conducive to the amelioration of depressive symptoms. Indeed, DMPFC rTMS has demonstrated changes in functional connectivity between the DMPFC and the insula, associated with a better clinical response (Salomons et al., 2014).

The decision as to which target should be utilised in clinical practice will primarily depend on the efficacy that has been demonstrated in clinical trials, however with increasing neuroimaging evidence demonstrating significant inter-individual variability in functional and structural connectivity, combined with heterogeneity in the clinical presentation of depression, an individualised approach to rTMS targeting may be more appropriate. For example, an individualised approach may be driven by the type of depression experienced, such as melancholic depression, a depression subtype characterised by pervasive anhedonia (Harald and Gordon, 2012), where white matter microstructural abnormalities in the medial forebrain bundle (MFB) have been found to be greater in melancholic when compared to non-melancholic groups (Bracht et al., 2014). Therefore, cortical targets with connections to the MFB, a projection tract connecting the frontal cortex to key regions of the reward system that has been successfully targeted with deep brain stimulation for TRD, partly due to its association with anhedonia (Schlaepfer et al., 2013), may prove an appropriate rTMS target for the melancholic subtype of depression. This approach however, makes the assumption that stimulating pathways with abnormalities in connectivity is best for ameliorating depressive symptoms, whereas stimulating intact pathways with connections to emotion regulating and cognitive processing networks may be a superior approach. This issue will need to be addressed with future empirical research and could be critical to brain stimulation targeting for depression treatment. An individualised approach to targeting will also benefit from the emerging body of neuroimaging evidence that demonstrates patterns of pre-treatment connectivity that predict rTMS treatment response.

4.3. Predicting rTMS treatment response using brain connectivity

Pre-treatment measures of functional connectivity have demonstrated promise as predictive biomarkers of treatment response to rTMS for depression. Current evidence has highlighted aberrant functional connectivity of the SCG, especially higher connectivity with nodes of the DMN, but also higher connectivity with nodes of the CEN and lower connectivity with nodes of the SN, all predicting a favourable clinical response (e.g., Baeken et al., 2014; Liston et al., 2014; Salomons et al., 2014). The SCG is a region increasingly identified in the pathophysiology of depression (Drevets et al., 1997, 2002; Drevets, 1999, 2000; Botteron et al., 2002) and has been used successfully as the target of deep brain stimulation for a severely treatment resistant form of depression (Mayberg et al., 2005; Lozano et al., 2008; Anderson et al., 2012). Supporting the importance of the SCG in depression treatment outcomes is evidence demonstrating the predictive utility of pre-treatment activity in the SCG via various other treatment modalities, including psychotherapy, pharmacotherapy and sleep deprivation (Mayberg et al., 1997; Wu et al., 1999; Siegle et al., 2006; Konarski et al., 2009). Finally, in addition to patterns of functional connectivity involving the SCG, other patterns of functional connectivity between the DMN, CEN and SN have also demonstrated promise for predicting rTMS treatment response, and therefore should be part of future research into predictive biomarkers.

Although only a few studies have been published to date, and with sample sizes that preclude the exploration of measures of white matter microstructure as a clinical predictor for rTMS for depression, evidence from other depression treatment modalities suggest utility for predicting a clinical response. Diffusion metrics within fronto-limbic white matter tracts, including the cingulum bundle, superior longitudinal fasciculus, and uncinate fasciculus, have been shown to predict a favourable clinical response to various depression treatment modalities, including deep brain stimulation (Riva-Posse et al., 2014) and ECT (Lyden et al., 2014), and also to pharmacological antidepressant treatment (Alexopoulos et al., 2002, 2008; Korgaonkar et al., 2014). This evidence may guide future research into the use of measures of white matter microstructure as predictors of clinical response to rTMS for depression, keeping in mind however that rTMS may ameliorate depressive symptoms via unique neural pathways compared to other depression treatment modalities (e.g., Seminowicz et al., 2004). Additionally, future research may also assess the relationship between some of the potential clinical predictors of rTMS response, such as length of current depressive episode, age, and degree of treatment resistance (Fitzgerald et al., 2016; Wu and Baeken, 2016) and their impact on functional and structural connectivity as a means to developing a robust and clinically applicable predictor of rTMS response.

5. Conclusions

Advances in neuroimaging technology have allowed research into brain connectivity and its dysfunction associated with psychopathology, and has thus advanced our understanding of depression as a dysfunction in large scale neural networks where disconnections between predominantly fronto-limbic regions underlies the key symptomatology. Measures of functional and structural connectivity have also advanced our understanding of the mechanisms of action underlying the therapeutic effects of rTMS for depression at the network level, and although a paucity of research has been published to date, significant changes to connectivity have been reported in directions suggesting a normalisation of depression-associated abnormalities. Additionally, aberrant pre-treatment functional connectivity, especially increased connectivity of the subgenual cingulate gyrus with nodes of the default mode network, shows promise as a biomarker for predicting rTMS treatment response. Utilising this evidence, optimisation and individualisation of rTMS targeting, and the exploration of alternative rTMS targets may lead to a better clinical response to rTMS treatment for depression.

Conflict of interest

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