



## Review

# Effects of repetitive transcranial magnetic stimulation and their underlying neural mechanisms evaluated with magnetic resonance imaging-based brain connectivity network analyses

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## ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain modulation and rehabilitation technique used in patients with neuropsychiatric diseases. rTMS can structurally remodel or functionally induce activities of specific cortical regions and has developed to an important therapeutic method in such patients. Magnetic resonance imaging (MRI) provides brain data that can be used as an explanation tool for the neural mechanisms underlying rTMS effects; brain alterations related to different functions or structures may be reflected in changes in the interaction and influence of brain connections within intrinsic specific networks. In this review, we discuss the technical details of rTMS and the biological interpretation of brain networks identified with MRI analyses, comprehensively summarize the neurobiological effects in rTMS-modulated individuals, and elaborate on changes in the brain network in patients with various neuropsychiatric diseases receiving rehabilitation treatment with rTMS. We conclude that brain connectivity network analysis based on MRI can reflect alterations in functional and structural connectivity networks comprising adjacent and separated brain regions related to stimulation sites, thus reflecting the occurrence of intrinsic functional integration and neuroplasticity. Therefore, MRI is a valuable tool for understanding the neural mechanisms of rTMS and practically tailoring treatment plans for patients with neuropsychiatric diseases.

## 1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) has recently emerged as a central topic of relatively noninvasive brain modulation and rehabilitation techniques used in the treatment of neuropsychiatric diseases [1]. The study of noninvasive brain stimulation models represented by rTMS is one of the fastest-growing fields in physical factor neurorehabilitation therapy [2]. rTMS uses a special stimulation coil

that targets specific brain regions and transmits electromagnetic pulses to induce currents in the brain to regulate neuronal activities [3]. Depending on the intensity, frequency, duration, and target location of different stimuli, rTMS can structurally remodel or functionally induce the activity of specific cortical regions, thus proving to be a valuable tool for the investigation of motor and sensory processes, attention, memory, language, and neural plasticity [3]. The field of rTMS studies requires interdisciplinary research involving clinical neuroscience, biomedicine,

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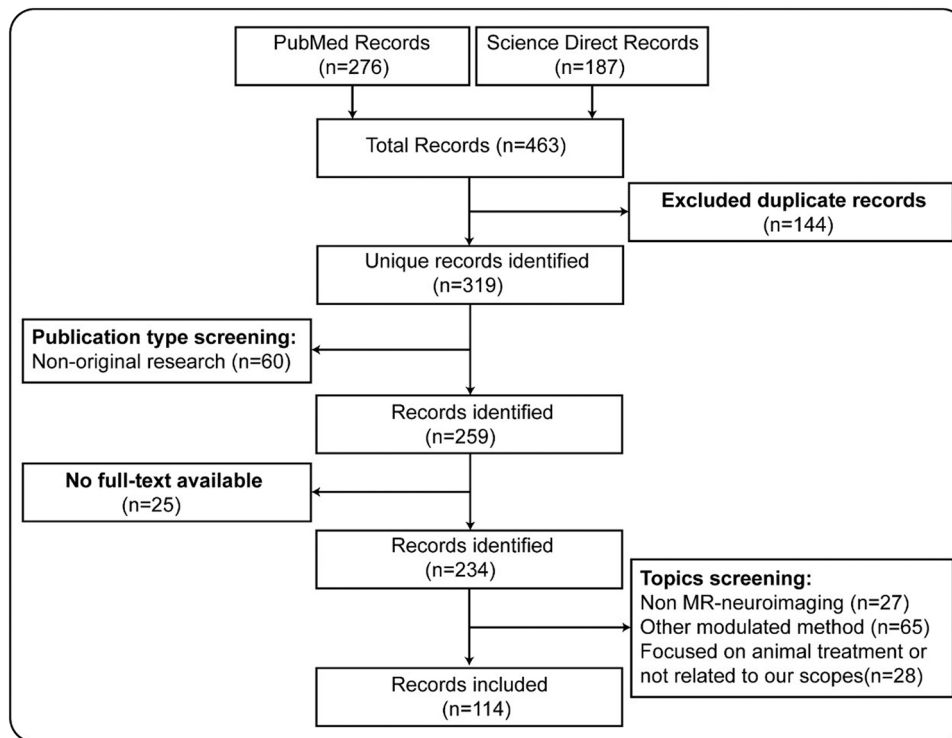


Fig. 1. Flowchart of the literature screening process.

neuroimaging, and other disciplines in order to analyze and understand therapeutic rTMS mechanisms underlying the complex etiology of neuropsychiatric diseases [1–3].

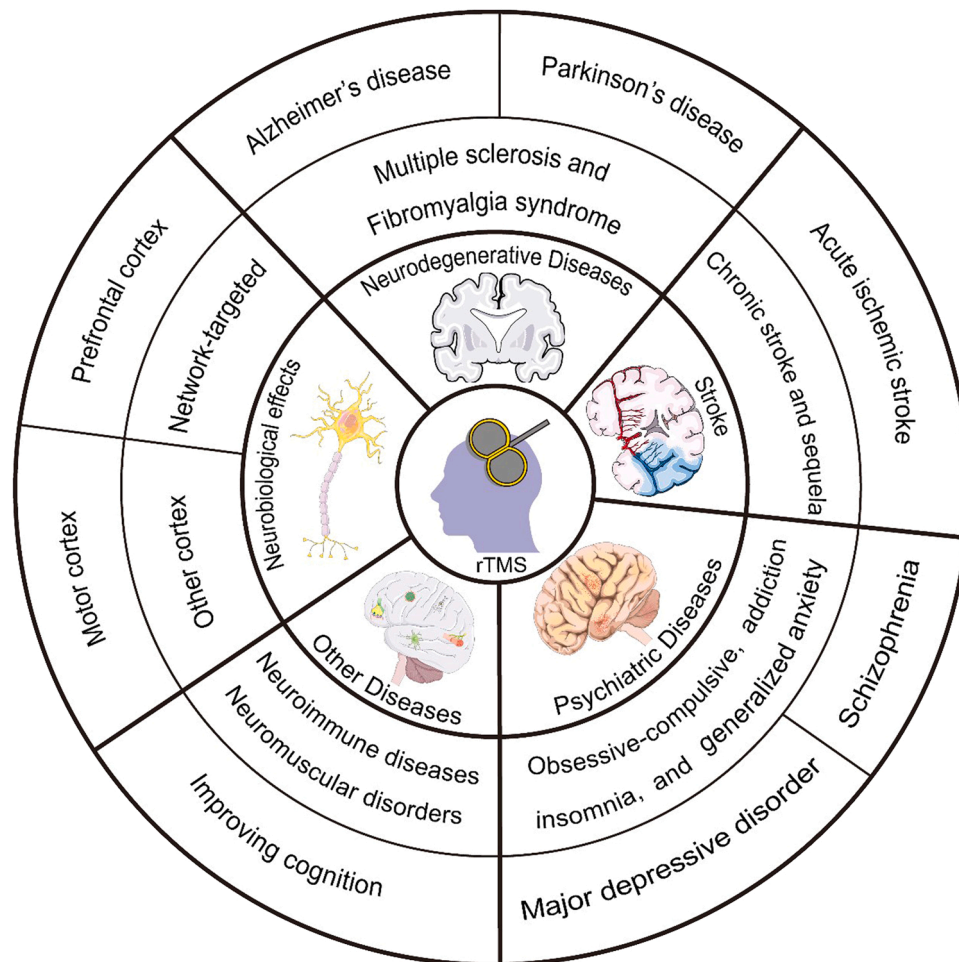
The widespread application of magnetic resonance imaging (MRI) in neuroscience in the past two decades has raised attention from clinical researchers due to its potential use as imaging diagnostic biomarkers [4, 5]. According to recent network research, the brain working mode is an internal interaction connector derived from a systematic network comprised of different scales of regions. Synchronous or continuous spontaneous activities of these regions achieve the overall cognitive function of the brain [1]. Neuroimaging research describes the brain as a group of large-scale, internal, and orderly structural or functional connectivity networks. Brain network models are dynamic systems of neurovascular coupling used to simulate large-scale brain activity or structural damage to the gray and white matter. The elucidation of dynamic interactions of these networks can reasonably explain physiological or pathological cognitive behavior [6–9]. For example, the default mode network (DMN), composed of the medial prefrontal cortex (PFC), hippocampus, and posterior parietal cortex, tends to be negative/inhibitory when performing tasks, whereas various networks independent of the DMN, such as the central executive network, saliency network, and executive control network in the lateral prefrontal and parietal regions, tend to have positive/excitatory activity to varying degrees, according to different brain function tasks [10,11]. Therefore, the transformation from a single brain region to an integrated network of different scales based on neuroimaging usually means that when local neural activity is regulated by noninvasive neural regulation technologies such as rTMS. The changes in the activity of brain regions related to different functions may be reflected by the changes in the interaction and influence of functional connections within a network or between various subnetworks, thus providing an intrinsic integration and neuroplasticity explanation for the neural mechanism of physical regulation [12,13].

In this review, we collected data on the brain modulation of participants who received rTMS and analyzed them using brain connectivity network techniques based on MR images to explore the biological effects

of rTMS related to brain regions. We further explained the mechanisms of potential rTMS effects in various neuropsychiatric diseases, involving alterations of multiple brain regions within different functional and structural network modes.

## 2. Literature search and selection strategy

We searched for candidate articles describing the neural mechanisms of rTMS for neuropsychiatric diseases based on brain connectivity analyses in neuroimaging in PubMed and Science Direct databases published between January 1980 and June 2022. The search strategy of key terms used was “(((repetitive transcranial magnetic stimulation OR rTMS) AND ((Magnetic resonance imaging OR MRI) OR (Structural MRI OR sMRI) OR (functional MRI OR fMRI) OR (Blood oxygen level dependence OR BOLD) OR (Diffusion weighted imaging OR DWI) OR (Diffusion tensor imaging OR DTI))) AND (brain connectivity OR brain network)) AND (mechanism)”. The studies were included based on the following inclusion criteria: (1) clinical studies that employed MRI methods in rTMS-treated individuals with neuropsychiatric diseases, or experimental animals studies that refer to biological rTMS mechanisms combined with MRI methods; (2) patients with neuropsychiatric diseases including neurodegenerative diseases, stroke, psychiatric diseases, and others, as well as healthy volunteers for the biological interpretation of brain networks; and (3) original research published in English with the full text available. The following types of studies were excluded: (1) comments, case reports, conference abstracts, book chapters, reviews (including meta-analyses and systematic reviews), letters, editorials, and study designs or protocols; (2) unrelated or irrelevant studies, such as those that did not employ MRI or rTMS techniques to investigate patients with neuropsychiatric diseases or animal models of such disorders; and (3) studies focusing on other topics that are irrelevant to our research purpose. After a detailed evaluation and screening, 114 studies that met our criteria were included and reviewed. A detailed description of the article selection process is shown as a flowchart (Fig. 1).



**Fig. 2.** The main diseases involved in the clinical application of rTMS. Exploration of neurobiological effects and mechanisms of rTMS in various neuropsychiatric diseases were explored involving neurodegenerative diseases, stroke, psychiatric disorders, and other diseases.

### 3. Technical details of rTMS and biological interpretation of brain networks (Fig. 2)

rTMS is a noninvasive neural modulation technique. A coil generates a strong magnetic field that enters the cerebral cortex unimpededly through the skull to painlessly stimulate the target brain area [14]. The coils used in rTMS are generally planar figure-eight-shaped coils, which are composed of two circular vortices made of insulated copper wire with the outer diameter of each vortex being 70–75 mm. The treatment site is determined based on hot spot search or on image-guided navigation, and the left dorsolateral prefrontal area and the primary motor cortex (M1) are often selected as the therapeutic target [15]. A stimulated site is regarded as a hot spot when the electromyography (EMG) amplitude is greater than 50  $\mu\text{V}$  in 5 out of 10 stimulations. When looking for a hot spot, the stimulation intensity is increased slowly from low to high while ensuring that the stimulation intensity is within a safe range. A visual navigation system can provide real-time feedback on the direction of the coil to ensure better accuracy and reliability in the stimulation process. rTMS pulses are repeatedly and rhythmically applied at the target scalp position. According to stimulation frequencies, rTMS can be divided into high- or low-frequency rTMS. High-frequency rTMS generally refers to rTMS with a stimulation frequency greater than or equal to 5 Hz, which promotes cerebral cortical excitability, whereas the frequency in low-frequency rTMS is generally lower than 1 Hz, which inhibits cerebral cortical excitability [16].

In functional MRI (fMRI) research, brain connectivity networks are commonly analyzed, which refers to functionally or structurally relevant

brain regions with or without stimulation or task [4], mainly focusing on sensorimotor, cognitive, emotional, visual, linguistic, and auditory functions. Among them, the most reliable and widely studied resting-state brain network is the DMN, which has been proven to be spontaneously activated in the absence of a clear task, and the activation decreases when the task requires attention [5]. In patients with certain disorders, DMN decreases significantly. This is particularly evident in the lateral and medial occipital posterior cortices, indicating disintegration and fragmentation of the DMN [17]. In addition, dynamic functional connectivity, as a functional connection mode that can reflect time-varying information, has received extensive attention. This connectivity reflects the network flexibility necessary for neural reorganization and deepens the understanding of disease-specific neural processing [12]. The brain network is composed of regions that communicate with each other anatomically and functionally to process information, and their topological structure constitutes a complex simulation network model [7]. fMRI can indirectly visualize neuronal activation and metabolism by reflecting changes in cerebral hemodynamics. Peak activity of calcium signaling plays a key role in the neural mechanism of resting-state blood oxygen level dependent (BOLD) MR signals [18]. Network effects are not only based on local changes in brain regions but also on the comprehensive alteration of the entire network. Following nerve injury, changes in relevant nerve biomarkers are associated with altered network connections in the brain [8]. Psychiatric and neurological diseases can be regarded as systematic brain disorders involving both structural and functional networks. TMS alone cannot elucidate the changes in brain function and their impacts on the

brain tissue of treated patients. Combining rTMS with MRI and brain connectivity network analyses can compensate for this shortcoming because these analyses reflect functional and structural changes of distinct brain regions in response to local rTMS of cortical regions. This is of great significance to the understanding of neural mechanisms and the development of treatment plans for neuropsychiatric diseases [19] (Supplemental Table 1).

#### 4. Exploration of neurobiological rTMS effects with MRI

##### 4.1. Stimulation of the motor cortex

The primary motor cortex (M1) is one of the most common rTMS targets used to explore neurobiological effects in healthy volunteers [20]. The connections between the cortex and related subregions in the cerebellar sensorimotor circuit, as well as the percentages of signal change in the M1 region, are increased after high-frequency rTMS [21, 22]. In particular, the regional homogeneity (ReHo) and degree centrality (DC) are significantly increased in the right cerebellum [23], and widespread changes in the brain at the targeted motor system, as well as remote nonmotor brain networks related to the bodily self-consciousness, are induced by M1 stimulation [24]. A stronger pre-TMS alpha power can reduce TMS-evoked hemodynamic activation throughout the bilateral corticocortical motor system [25]. Some studies have confirmed the correlation between changes in key metabolites associated with cortical neurotransmission and the strength of related brain networks, as well as the relationship between the concentration of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) and rTMS-induced Magnetic resonance spectroscopy [26]. Several studies have shown that the realization of motor function involves the internal connectivity between the pre-supplementary motor area (pre-SMA) and the striatum, as well as between the striatum and the medial part of the globus pallidus [27,28]. However, the region surrounding the sensorimotor module simultaneously increases its internal integration after local inhibitory stimulation, and intermittent theta burst stimulation (iTBS)-induced increases in motor-evoked potentials amplitudes are negatively correlated with motor-related fMRI activity of the left M1 [29,30]. With increased age, the motor cortex network also changes. Both TMS and dynamic causal modeling findings demonstrated the decreasing inhibitory and/or increasing facilitatory influence of the contralateral M1 on the ipsilateral M1 during hand grip tasks with advancing age [31,32]. In addition, Tellelli et al. found that  $B_T$  value (the degree to which task-related activity covaried with peak grip force) in the left ventral premotor cortex was greater in older study participants and in those in whom the contralateral M1 was less responsive to TMS stimulation [33]. Current research methods mainly determine connections based on voxel-to-voxel, seed point-based connectivity analyses, ROI-based graph theory, and whole-brain graph theory. Although rTMS considerably regulates motor networks, it is difficult to determine based on the analysis of brain networks which specific brain regions or subregions are stimulated and altered.

#### 5. Stimulation of the prefrontal cortex

The PFC is also a common rTMS target in healthy individuals. The dorsolateral PFC (DLPFC) plays a crucial role in cognitive and emotional functions. Low-frequency rTMS is mainly applied to the left hemisphere with substantial intranetwork connectivity changes in the DMN, but the regulatory effects on the three subregions of the DLPFC differ depending on the stimulation target determined using the independent components analysis method [34,35]. By contrast, high-frequency rTMS of the left DLPFC can enhance resting brain activity both at targets and remote sites, which are related to memory function coding, although some studies have found that the functional connection between the DLPFC and the left hippocampus was significantly reduced [36–38]. The functions of the ventromedial PFC (vmPFC) are associated with various

social, cognitive, and emotional functions. They are confirmed in healthy participants by rTMS studies targeting the amygdala and vmPFC, which are impaired to a certain extent in some psychiatric diseases [39,40]. Research on the effects of rTMS of the PFC in healthy individuals mainly involves the DLPFC and vmPFC. The PFC is a large and shallow cortical region, which can easily be stimulated and activated to affect the functional plasticity of remote regions or subregions and indirectly modulates the performance of other brain functions.

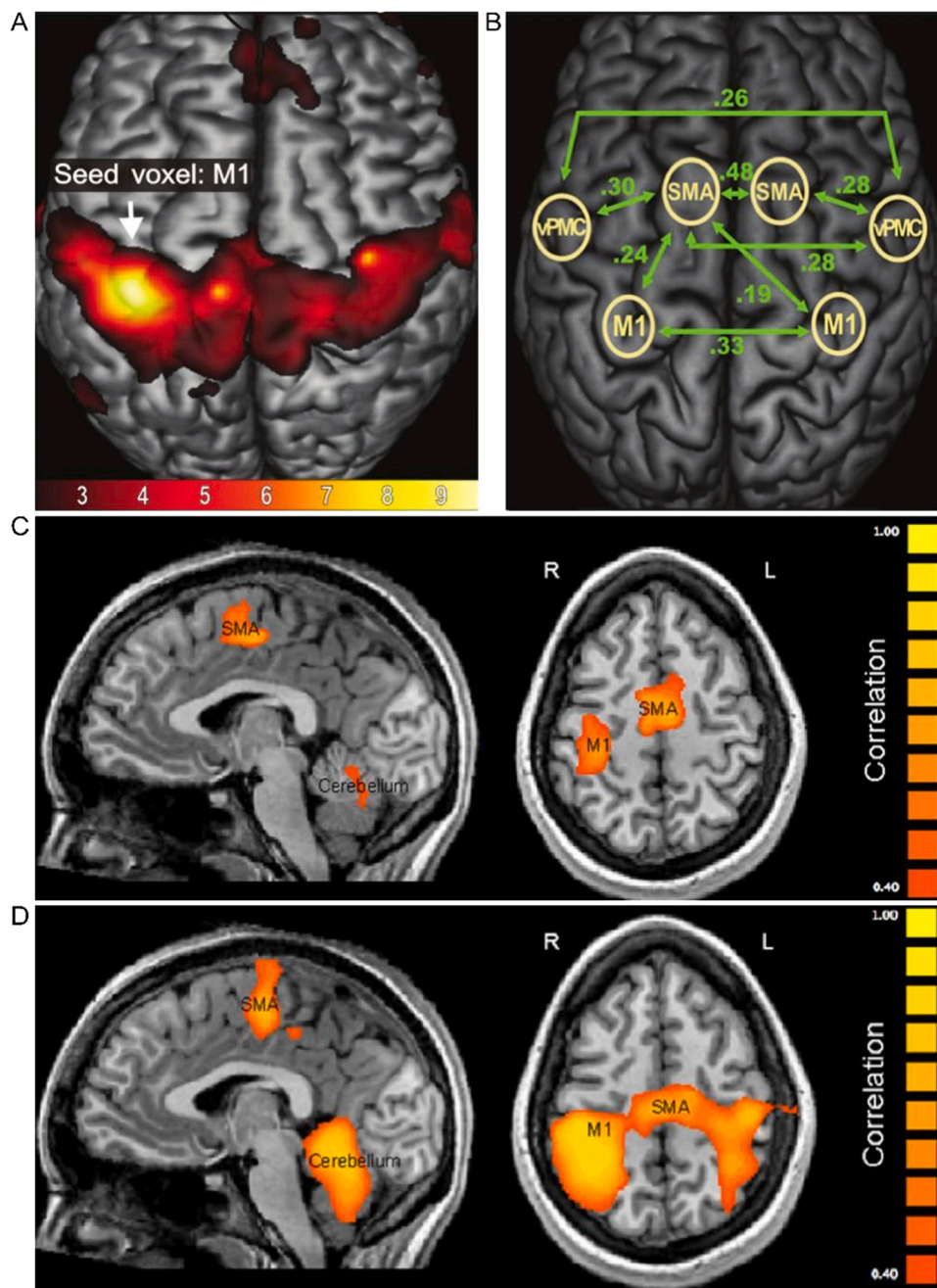
#### 6. Stimulation of other cortical areas

Other cortex targets apart from the motor cortex and PFC are also crucially related to the brain network modulated by rTMS. In general, reduced neural activity within the parietal frontal region, as identified by functional connectivity (FC) analyses, is related to frequent impairment or dysfunctional low configuration of the parietal frontal region in individuals with left space neglect-like behavior, but continuous theta burst stimulation (CTBS) leads to decreased activity in the target region and a compensatory increase in activity in the contralateral ventrolateral anterior temporal lobe [41,42]. After TMS stimulation, the activities of the pons, left temporal lobe, and left insular lobe were decreased, and the amplitude of the visual cortex-related perception threshold changed in correlation with the mental function scale [43–45]. Although the whole-brain correlation between directional functional and structural connectivity was temporarily reduced, Megumi et al. found that resolving this perceptual ambiguity was particularly relevant to the interaction of these parietal regions with the middle temporal visual area [46–48]. In addition, CTBS connected to the right temporoparietal junction leads to a decrease in the degree of connection between this area and the striatum, reflecting the value of delayed reward and selectively affecting the functional network of associative and memory-related cortex areas [49,50]. Hwang et al. found that cranial magnetic stimulation of the superior parietal sulcus, but not of the primary somatosensory cortex, reduced task-specific modulation of the connection pattern between the primary visual cortex and the parahippocampal positional area [51,52]. This may be because CTBS significantly enhanced the self-other distinction among participants with lower empathy comprehension [53,54]. Research has also been carried out on rTMS of several other cortical regions, mainly involving the whole brain, auditory cortex, visual cortex, and cognition-related areas, among others. The different activating and inhibiting effects after stimulation of these regions may explain the pathophysiological characteristics of related diseases.

#### 7. Network-targeted stimulation and its effects

The isolated stimulation of specific cortical areas may have some limitations. Therefore, several studies have applied rTMS to specific brain network regions. The DMN is severely dysfunctional in some forms of psychoses and neurodegenerative diseases, and the plasticity changes of GABA-energetic transmission in the posterior medial area of the DMN increase after theta burst stimulation (TBS) of the left inferior parietal lobe [55]. DMN activity is inhibited as frontoparietal central executive network nodes cause the DMN to move from its normal low-frequency range to a higher frequency [56]. Binney et al. used a combination of fMRI and rTMS in the anterior temporal lobe to measure intrinsic and induced activation changes in the semantic cognitive network, and the results indicated that the functional binding of the left hemispheric semantic network was affected [57]. Similarly, the episodic memory network and cortical-subcortical network related to the reconsolidation of human programmed memory in healthy elderly individuals showed an enhancement of related activities within the network after rTMS [58, 59]. Another study examined visuospatial navigation-related networks using fMRI and TMS. Time-resolved TMS of the parietal and frontal regions showed that both were functionally related to visuospatial processing [60]. There was also a decrease in FC between the





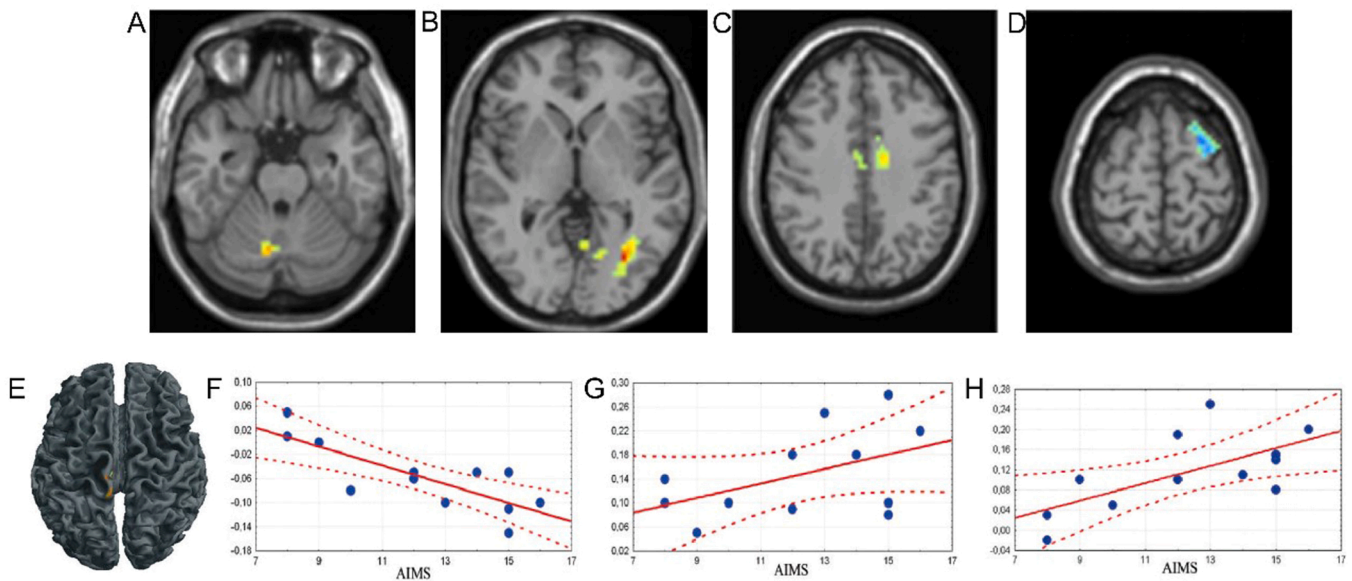
**Fig. 3.** Exploration of neurobiological rTMS effects with resting-state fMRI analysis for the stimulation of the motor cortex and cortico-subcortical neuronal circuitry. (A) Seed-based whole-brain group analysis (seed region: left M1; MNI coordinates  $-36 -24 58$ , the arrow points to the local maximum of the group analysis). Correlated fMRI time courses were not only found in the vicinity of the seed voxel, but also in homotopic regions in the contralateral hemisphere (voxel threshold:  $P < 0.05$ ; color bar represents t-values). (B) Network analysis testing for correlated resting-state activity in key regions of the motor system. BOLD times courses have strongly correlated between resting-state time courses of all 6 motor VOIs (linear Pearson's correlations;  $P < 0.05$ , FDR corrected), especially for interhemispheric connections as well as for intrahemispheric coupling between left SMA and M1, as well as left SMA and right M1. (C, D) The whole brain functional connectivity with M1 in reduced and intact memory modification groups. Disrupted memory modification resulted in weaker correlation of BOLD signal change between the right M1 and the supplementary motor area. Brain areas showing weaker connectivity with the primary cortical region (M1) at retest after reduced (C) and intact (D) memory modification. M1, primary motor cortex; SMA, supplementary motor area; vPMC, ventral premotor cortex. Application in Neurodegenerative Diseases. (A and B were reproduced with the permission of ref. [30], copyright@ Oxford University Press, 2014. C and D were reproduced with the permission of ref. [59], copyright@ Masson, 2014.).

stimulation site (left superior parietal sulcus) and all other areas when the visual attention cortical network was stimulated [61]. These studies carried out rTMS in different brain networks, mainly auxiliary motor areas, default networks, semantic cognitive networks, episodic memory networks, corticosubcortical neural networks, and visual networks. The network mode and its corresponding functions are inhibited or enhanced by the stimulation of different network regions (Fig. 3).

Neurodegenerative diseases comprise various conditions arising from progressive damage to nerve cells and their connections, which are important for cognition, sensation, and motor function. Common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and fibromyalgia syndrome. In recent years, rTMS has been shown to be a promising tool for alleviating the symptoms of neurodegenerative diseases, although its mechanisms are still not well understood. Some researchers have made great efforts to use brain connectivity analyses through neuroimaging to

reveal the underlying mechanisms.

AD is characterized by progressive cognitive decline. TMS has demonstrated efficacy in improving cognitive function and alleviating psychological and behavioral symptoms of dementia in patients with AD. Common targets of TMS in AD treatment include the left DLPFC and temporal lobe. Qin et al. combined fractional amplitude of low-frequency fluctuation and brain connectivity of resting-state fMRI (rsfMRI) analyses to evaluate network changes in patients with mild or moderate AD receiving a combined therapy of TMS and cognitive training [9]. The results indicated that rTMS induced intrinsic brain activity changes through frontolimbic and cerebellothalamocortical pathways. Another study showed that altered hippocampal subregions and network connectivity are related to memory decline in amnesic mild cognitive impairment (aMCI) [38]. rTMS can correct the breakdown in hippocampal subregions and restore connectivity. These changes can help ameliorate the episodic memory decline in patients



**Fig. 4.** Effects of repetitive transcranial magnetic stimulation for patients with Alzheimer's disease. 10 Hz rTMS induced significant changes of fALFF in (A) right cerebellum/declive, (B) left lingual/cuneus, (C) left cingulate gyrus, and (D) left middle frontal gyrus (Significance level was defined at  $p < 0.005$ , cluster size  $> 46$  voxels, AlphaSim corrected). The left side of the image corresponds to the right side of the brain. Color bar represents t values. The warm and cold colors represent higher and lower fALFF after rTMS, respectively. The inferior frontal cortex (IFC) functional connectivity relates to individual difference with AIMS scores for patients with levodopa-induced dyskinesias. The E, F, G, and H demonstrate that the degree of communication (t-scores, y-axis) between the right IFC with the left primary motor cortex (M1), bilateral putamen, and subthalamic nucleus (STN), correlates with increasing motor disability [abnormal involuntary movement scale (AIMS) scores, x-axis] during the ON phase in levodopa-induced dyskinesias (LIDs) patients. Correlation line and confidence intervals are shown in red. (A, B, C and D were reproduced with the permission of ref. [9], copyright@ Oxford University Press, 2015. E, F, G, and H were reproduced with the permission of ref. [67], copyright@ Centauro, 2022).

with aMCI. A randomized controlled study pointed out that rTMS can decrease connectivity within the DMN. This effect is associated with improved cognitive performance in patients with aMCI. Furthermore, the pre-TMS activity level of the DMN predicted rTMS treatment response [62]. Currently, there is no consensus on the rTMS effect that most specifically influences AD symptoms. Further research is needed to explore the underlying mechanisms.

PD is a movement disorder characterized by rigidity, bradykinesia, resting tremor, dysarthria, and postural instability. Previous research has demonstrated that rTMS can improve motor function in PD patients with SMA being the most common target. Different types of motor dysfunction improvements are related to corresponding mechanisms. Regarding bradykinesia, TMS increases caudate nucleus activity and decreases SMA activity in single motor tasks, and this effect is coupled with intensified FC with prefrontal areas [63]. Mi et al. identified that TBS over the SMA can help normalize abnormal FC associated with rigidity and bradykinesia [64]. Volume changes in the globus pallidus after rTMS therapy are mildly associated with motor function improvement, and rTMS can alleviate motor symptoms by modulating the SMA–globus pallidus pathway [65]. Some researchers have focused on targets other than the SMA. Brabenec et al. applied rTMS over the auditory feedback region, i.e., the right posterior superior temporal gyrus, to treat hypokinetic dysarthria in patients with PD [66]. TMS can activate remote fields of the dorsal language stream to enhance articulation performance. Cerasa et al. focused on the inferior frontal cortex and utilized rTMS over this area to prompt levodopa-induced dyskinesia, revealing the role of abnormalities in the cortical-subcortical network in the development of levodopa-induced dyskinesia in treated patients with PD [67]. Considering the variety of PD symptoms, rTMS should target specific brain areas according to the patient's symptoms.

In clinical practice, TMS is rarely used for MS and fibromyalgia syndrome. Some studies have proven the effectiveness of rTMS in alleviating spasticity [68]. The most common TMS target in patients with MS is the primary motor cortex. TMS has compelling effects on the

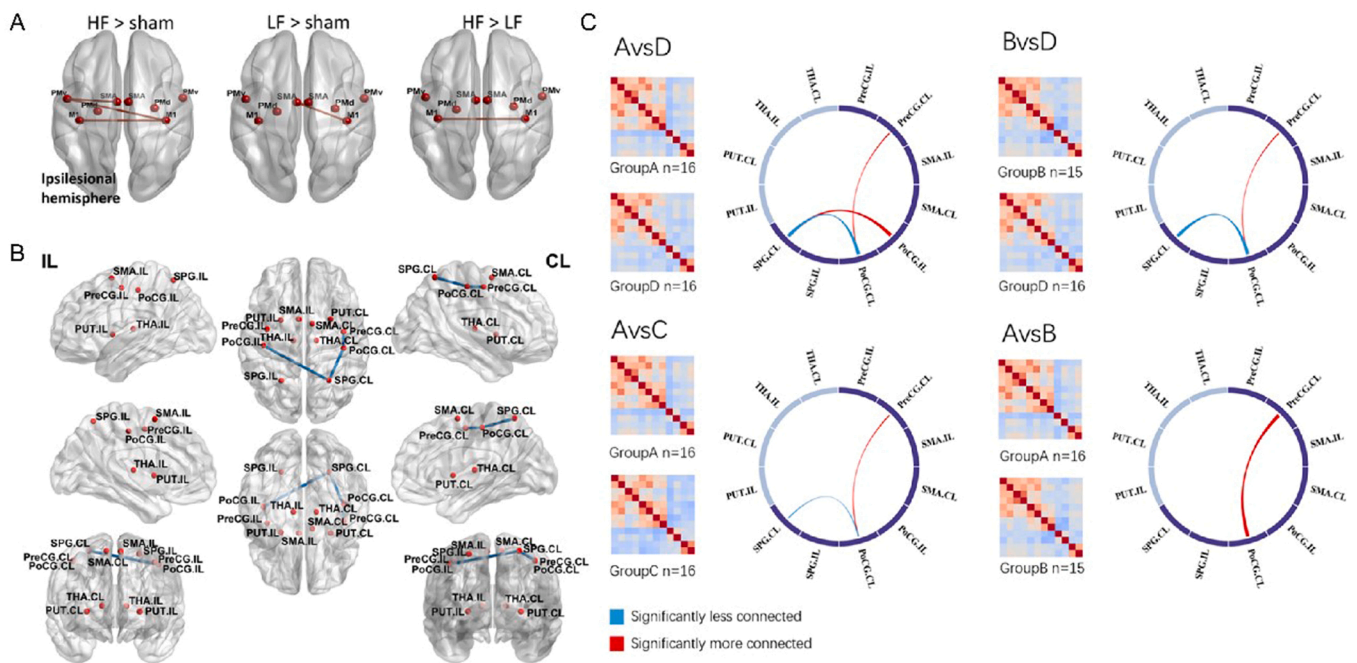
balance of connectivity between the targeted and homologous primary motor cortex [69]. Reorganization of the interhemispheric connectivity balance is essential for the improvement of spasticity. In MS research, due to its dual effects of facilitating and inhibiting movement, rTMS can also be used as a tool for neurophysiological assessment [70]. In managing fibromyalgia syndrome, rTMS over the primary motor cortex can induce connectivity changes in brain areas processing sensory, affective, and cognitive pain information [71]. These effects extend beyond the motor cortex and involve multiple cortical and subcortical network changes related to pain suggesting that the modulating effects of rTMS may be complex and extensive (Fig. 4) (Supplemental Table 2).

## 8. Application in neurovascular diseases

Stroke can cause persistent overall structural and functional changes in the brain. Despite treatment, stroke patients are often affected by disability, sensory dysfunction, cognitive decline, depression, and neurologic pain. TMS has been shown to be a promising tool to modify poststroke symptoms; however, the underlying mechanisms have not been fully understood. Motor dysfunction is the most remarkable manifestation of stroke. The primary motor cortex is the most common rTMS target for poststroke motor dysfunction. Both ipsilesional and contralesional stimulation can be used; however, ipsilesional stimulation of the primary motor cortex can better induce motor cortical excitability and activation in fMRI [72].

Ipsilesional motor cortex stimulation intensifies connectivity with the ipsilesional primary motor cortex and decreases interhemispheric suppression of the contralesional primary motor cortex [73]. TMS reorganizes the FC of inter- and intrahemispheric motor networks to facilitate motor recovery in early stroke patients when combined with rehabilitation therapy [74]. Another study revealed that the beneficial effects of rTMS on motor recovery are through heightening FC between the stimulated site and remote motor control areas [75]. A high level of FC reconstruction indicates a better prognosis [76]. Li et al. discovered





**Fig. 5.** Motor network reorganization after the application of rTMS in stroke. (A) Comparison of the changes in FC from baseline to post-intervention among the three groups. Increased FC displayed after between group comparison. The significant connections are displayed with red lines. The left side of the images refers to the ipsilesional hemisphere. (B) FC comparison between four groups after the treatment. Blue lines indicate significant differences in functional connections ( $P < 0.05$  false discovery rate-corrected). (C) Pairwise comparison between groups of functional connectivity after treatment. The blue line indicates significantly decreased functional connectivity while the red line indicates significantly increased FC after false discovery rate-corrected with  $P < 0.05$ . HF, high-frequency; LF, low-frequency; FC, functional connectivity. PoCG.IL, ipsilesional postcentral gyrus; PoCG.CL, contralesional postcentral gyrus; preCG.IL, ipsilesional precentral gyrus; preCG.CL, contralesional precentral gyrus; THA.IL, ipsilesional Thalamus; THA.CL, contralesional thalamus; SPG.IL, ipsilesional superior parietal gyrus; SPG.CL, contralesional superior parietal gyrus; SMA.IL, ipsilesional supplementary motor area; SMA.CL, contralesional supplementary motor area; PUT.IL, ipsilesional lenticular nucleus, putamen; PUT.CL, contralesional lenticular nucleus, putamen; IL, ipsilesional; CL, contralesional. (A was reproduced with the permission of ref. [75], copyright@ Sage Publications Inc., 2022. B and C were reproduced with the permission of ref. [74], copyright@ Elsevier Science, 2022.)

that after rTMS administration, FC was accentuated in both the ipsilesional and contralesional primary motor cortex, bilateral thalamus, contralesional postcentral gyrus, and SMA, whereas FC was attenuated in the ipsilesional primary motor cortex, inferior and middle frontal gyrus, and postcentral gyrus [77].

Interaction between the contralesional and ipsilesional cortices is important for motor rehabilitation. Stimulation over the contralesional dorsal premotor cortex can have a facilitatory influence on ipsilesional sensorimotor regions involved in movement impairment [78]. Grefkes et al. pointed out that enhanced connectivity between some regions can only be achieved by contralesional rTMS, such as endogenous coupling of the ipsilesional SMA and primary motor cortex [79]. Li et al. also revealed that the enhanced connectivity of the contralesional cortico-cerebellar loop and the reinforcement of interhemispheric connection demonstrates the contralesional compensation promoted by rTMS suggesting complex mechanisms of motor function modulation and reorganization after therapy [80].

rTMS has various effects on the motor cortex and subcortex. The structure and interconnectivity of motor-related brain networks are complicated and still poorly understood. Current studies indicate that rTMS can remodel and reorganize the affected functional network architecture of the motor system and reveal possible underlying mechanisms of rTMS modulation. In patients with subcortical stroke, rTMS can promote the partial reconstruction of the cognitive control domain to improve poststroke cognitive impairment [81]. Cha et al. reported that rTMS over the ipsilesional DLPFC can diminish the inflammatory response and rehabilitate the brain network in patients with poststroke cognitive impairment. TMS can also be used to control central neuropathic pain after stroke by decreasing the activation of the pain network [82]. Other utilization and modulation pathways of rTMS in patients

with stroke require further investigation and exploration (Fig. 5) (Supplemental Table 3).

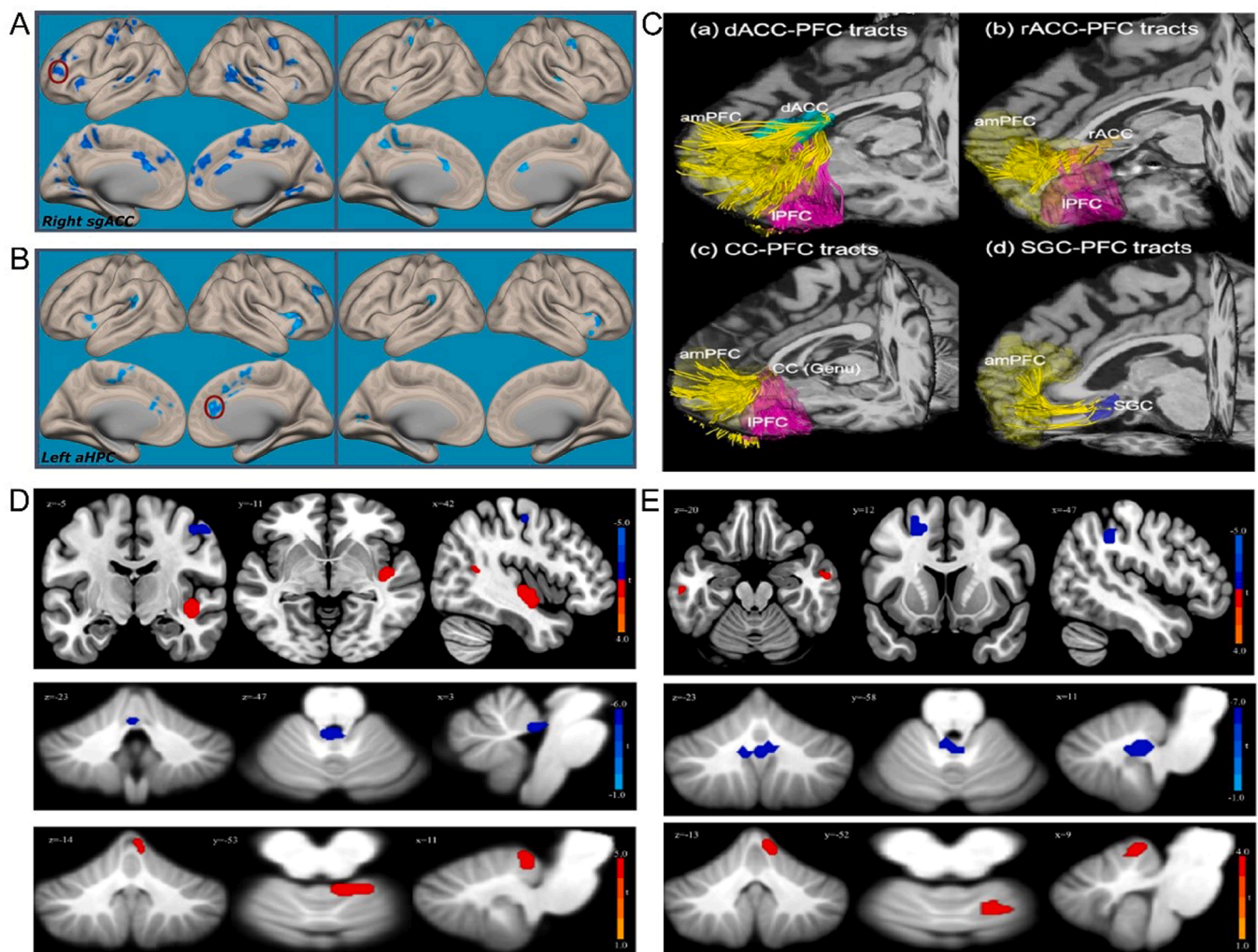
## 9. Application in psychiatric diseases

Psychiatric diseases are disorders that disturb thinking, mood, behavior, and emotional regulation. This increases the risk of suicide, pain, disability, and loss of freedom. Common psychiatric diseases include major depressive disorder (MDD), obsessive-compulsive disorder (OCD), schizophrenia, generalized anxiety disorder, and addiction. In recent years, rTMS has shown in patients with psychiatric diseases its therapeutic efficacy, a decrease in suicide risk, and an improvement of psychiatric symptoms through multiple underlying mechanisms (Supplemental Table 4).

## 10. Major depressive disorder

MDD is a common psychiatric disorder. Patients with MDD experience depressive mood, lack of energy and motivation, feelings of guilt, cognitive dysfunction, and suicidal ideation. Depression influences the distribution of differentiated connections in limbic and cortical brain regions, including the DLPFC, hippocampus, amygdala, nucleus accumbens, and vmPFC. Among those, the DLPFC is the most common rTMS target [83–85]. High-frequency stimulation of the left DLPFC and low-frequency stimulation of the right DLPFC are effective protocols for treating MDD [86]. TMS has shown remarkable effects on functional activation and connectivity networks, as well as structural connectivity networks in patients with MDD [87].

Previous studies have demonstrated that rTMS can directly increase local neural activity in the precuneus, frontal gyrus, temporal gyrus, and



**Fig. 6.** Application in psychiatric diseases and disorders. (A) Post-TMS changes in connectivity between the right sgACC and the precuneus/PCC, dorsomedial prefrontal cortex, DACC, left DLPFC, bilateral insula, and visual processing regions were associated with PTSD improvement (left); precuneus/PCC, dACC, and somatosensory/motor anticorrelations were inversely associated with reduced MDD symptoms (right). (B) Post-TMS changes in connectivity between left aHPC and SN network regions are inversely associated with PCL (left) and IDSSR (right) improvement. Images only include regions that survived cluster-based FDR  $p < 0.05$  and LOOCV. (C) Diffusion-MRI tractography showing fiber bundles connected to different subregions of the left PFC and four MDD-related deep-brain regions: (a)-(c) illustrate the fiber bundles that connect the amPFC (yellow), IPFC (magenta) and the dACC, the rACC, and the genu of CC, respectively, and (d) illustrate the fiber bundles between the amPFC and the SGC. There is no connection between IPFC and SGC. In schizophrenia patients with auditory verbal hallucination: (C) The dorsal DN FC alternations with the cerebral cortical areas in the pretreatment patients compared to controls; The dorsal DN FC alternations with the cerebellar area in the posttreatment patients compared to controls. FDR correction, size  $> 50$ ,  $p < 0.05$ . (D) The ventral DN FC alternations with the cerebral cortical areas in the pretreatment patients compared to controls; The ventral DN FC alternations with the cerebellar area in the pretreatment patients compared to controls. The ventral DN FC alternations with the cerebellar area in the post-treatment patients compared to controls. FDR correction, size  $> 50$ ,  $p < 0.05$ . sgACC, subgenual Anterior Cingulate Cortex; PCC, Posterior Cingulate Cortex; DACC, Dorsal Anterior Cingulate; DLPFC, Dorsolateral Prefrontal Cortex; PTSD, Posttraumatic Stress Disorder; MDD, Major Depressive Disorder; aHPC, Anterior Hippocampus; DN, Default Network; PCL, PTSD Checklist; IDSSR, Inventory of Depressive Symptomatology–Self-Report; FDR, false discovery rate; LOOCV, leave-one-out cross-validation; PFC, prefrontal cortex; amPFC, anterior medial PFC; IPFC, lateral PFC; rACC, rostral Anterior Cingulate Cortex; CC, corpus callosum; SGC, subgenual cingulate cortex; FC, functional connectivity.

(A was reproduced with the permission of ref. [84], copyright@ Elsevier Inc., 2018. B was reproduced with the permission of ref. [87], copyright@ Elsevier BV, 2022. C and D were reproduced with the permission of ref. [107], copyright@ Pergamon, 2022.)

limbic lobe. These effects can also enhance bidirectional connectivity from the middle frontal to the inferior temporal gyri [88,89]. TMS can also induce better engagement of the DLPFC in controlling the amygdala [90,91]. Regarding structural connectivity, TMS can induce neuroplastic changes in the hippocampus, prefrontal network, and structural covariance network [92,93]. In addition, microstructural changes in the lateral prefrontal and anteromedial white matter are also related to treatment response after rTMS therapy [87]. Treatment-induced brain structural and architectural changes provide a new perspective for understanding the neural mechanism of TMS effects. Other targets of rTMS

are also being investigated. Salomons et al. chose the dorsomedial PFC, and their results indicate that symptom improvement correlates with increased dorsomedial PFC–thalamic connectivity and reduced subgenual cingulate cortex–caudate connectivity [94].

Despite multiple advances in mental health management, suicide remains a leading cause of death in patients with MDD. TMS can effectively reduce suicide risks by restoring the impaired FC between the left executive control network and sensory-motor network, DMN, and precuneus network [95,96]. Barredo et al. discovered that rTMS diminishes FC between the dorsal striatum and frontopolar cortex, which



induces a decrease in suicidal ideation in 65% of the participants [97].

rTMS can also provide partial symptom relief in treatment-resistant depression. White matter fractional anisotropy in the left middle frontal gyrus and connectivity between the precuneus and both subgenual anterior cingulate cortices are increased in treatment-resistant patients after therapy [98,99]. Additionally, FC of the anterior cingulate cortex is a possible predictor of stimulation outcome [100]. Some rTMS effects have been observed in other types of depression. In patients with postpartum depression, rTMS increases connectivity between the left and right hemispheres and reconstructs the intrinsic functional architecture of interhemispheric communication to relieve postpartum depressive symptoms [101]. In patients with poststroke depression, TMS modulates the medial PFC and posterior cingulate cortex within the DMN [102]. In patients with PD-related depression, brain activity decreases in the right DLPFC after TMS administration and increases for the connections of the cerebellum and left fusiform gyrus, as well as the left DLPFC and anterior cingulate gyrus. These effects differ from those of antidepressant drugs [103]. All evidence proves that TMS is an effective approach to effectively restore abnormal brain network functions, which is consistent with the improvement of depressive symptoms. However, the explanation of the antidepressant effects needs further investigation due to the currently poor understanding of the pathophysiology of depression (Fig. 6).

### 11. Schizophrenia (with or without Auditory Hallucinations)

In patients with schizophrenia, rTMS improves the negative symptoms based on the regulatory neural network, especially when rTMS is combined with fMRI, and can be used as a research modality of neural regulatory mechanisms [104]. A novel patterned rTMS technique called TBS can enhance the strength of this network connection correlating with the improvement of negative symptoms in patients with schizophrenia [104]. Auditory hallucinations are the most prominent features of schizophrenia [105]. TMS has been proven to be beneficial in relieving the perception of auditory hallucinations. Gromann et al. applied rTMS to the right motor cortex. Compared to the control group, the treatment group showed increased connectivity of the right temporoparietal cortex with the DLPFC and angular gyrus [106]. Xie et al. selected the left temporoparietal junction as the stimulation site. TMS modulated the neural circuits of the cerebellar dentate nucleus subdomains thereby decreasing the pathological FC of the dentate nucleus and temporal lobes [107] (Fig. 6).

### 12. Other psychiatric diseases

OCD is characterized by obsessive and compulsive behaviors. Many patients with OCD respond unsatisfactorily to psychological and pharmacological therapies and need alternative treatment options such as TMS. Ji et al. chose the pre-SMA areas as TMS targets. After treatment, the connectivity strength of the targeted network was decreased compared to that of the sham-treated group [108]. Dunlop et al. demonstrated that TMS of the DLPFC can reduce corticostriatal hyperconnectivity [109]. The alleviation of pathological brain connection strength in this network played a central role in the therapeutic mechanism of rTMS.

Substance addiction is a special psychiatric condition. In patients with heroin addiction, rTMS with the DLPFC as the target can modulate the coupling of executive control and the DMN, reducing spontaneous drug craving [109]. In chronic cocaine users, rTMS has the potential to reconstruct cortical facilitation related to elevated BOLD signals, indicating a potential target for patients with addiction [110]. In patients with methamphetamine addiction, the increase in FC between the inferior parietal lobule and the DLPFC is related to craving reduction after rTMS therapy [111]. In smokers, TMS over the DLPFC decreased the FC of the orbitofrontal cortex to facilitate smoking cessation [112, 113]. Therefore, rTMS can modulate specific brain networks to treat

various substance addictions depending on the target region.

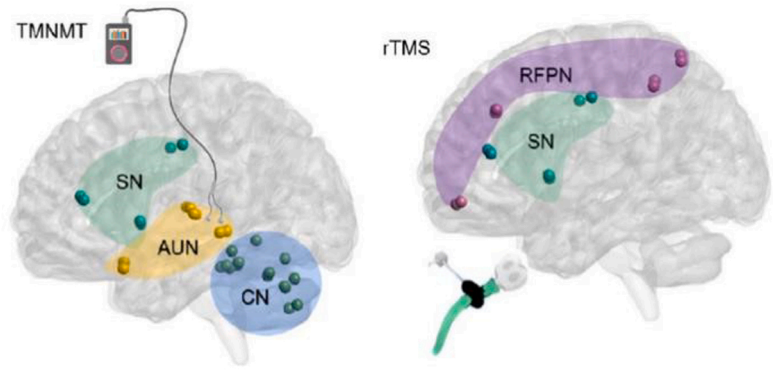
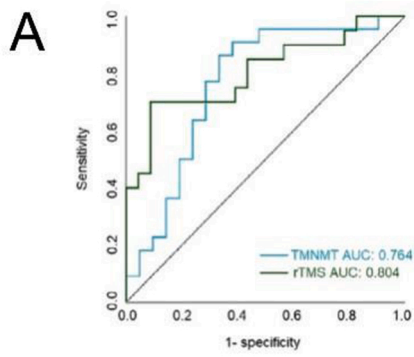
rTMS decreases connectivity between the left medial frontal gyrus and right insula in patients with insomnia [88]. The reduced amygdala connectivity with the posterior DMN after TMS treatment is associated with symptom improvement in patients with borderline personality disorders [114]. In patients with generalized anxiety disorder, TMS facilitates normalization of the FC of the dorsal anterior cingulate, which correlates with an improvement in worry symptoms [115]. TMS can also help reconstruct the FC for language, salience, and sensorimotor networks in patients with disordered consciousness after traumatic brain injury [116].

rTMS has multiple effects depending on the psychiatric disease. Most research on the neural mechanisms of TMS in treating psychiatric diseases concentrates on MDD. Future studies should focus on pathological brain network mechanisms and potential rTMS regulatory mechanisms due to the complexity and diverse phenotypes of psychiatric diseases.

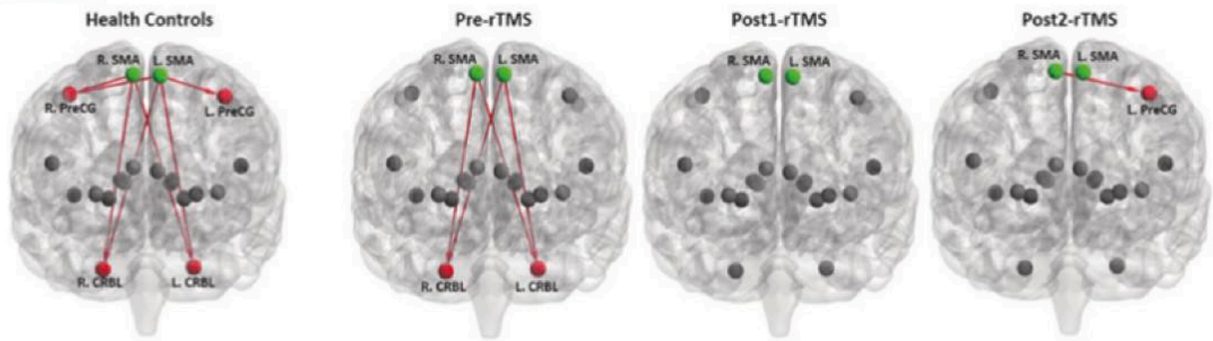
### 13. Application in other diseases

The Val66Met gene polymorphism of the brain-derived neurotrophic factor is related to the individual variability of episodic memory, hippocampal volume, and TMS effects during motor learning tasks. It has a significant impact on neural plasticity by regulating protein expression levels affected by rTMS focusing on cognition-related brain networks [117]. Resting-state FC analyses can predict the clinical results of rTMS in patients with tinnitus [118]. The left-brain regions associated with autonomous swallowing were widely overactivated in a study of FC changes associated with functional dysphagia after rTMS targeting the SMA [119]. rTMS can partly restore the impaired structural brain connectivity in spastic cerebral palsy at different node levels [120]. Goto et al. have shown that the thalamic cortical tract plays a role in the analgesic effects of rTMS, and the efficacy of rTMS in patients with central poststroke pain can be predicted by fiber tracking using diffusion tensor imaging (DTI) [121]. rTMS is not only effective for the treatment of central nervous system-related diseases but also for the therapy of inflammatory or endocrine diseases. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common antibody-mediated autoimmune encephalitis. The rTMS-induced plasticity of the brain FC network indicated the severity of NMDAR encephalitis [122]. DeVoto et al. performed rTMS in the bilateral insular and PFC of the brain. The results showed that rTMS can promote weight loss in obese patients and prevent the occurrence of cardiac metabolic complications such as type 2 diabetes mellitus [123]. In addition, rTMS has shown its application value in diseases related to neuromuscular disorders. Chen et al. used a procedure known as free functioning muscle transfer to restore motor function in selected patients with severe neuromuscular injury and studied the reorganization of the motor system using rTMS and fMRI. The results showed that the motor threshold and short-term intracortical inhibition on the transplanted side were decreased at rest but did not decrease during muscle activation [124].

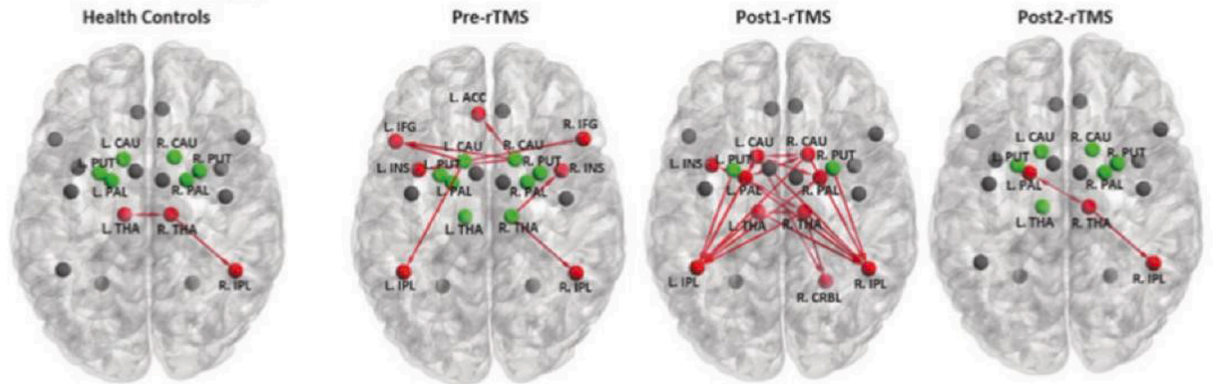
Previous studies have confirmed that rTMS also has great value in improving cognition. rTMS of the local left inferior frontal junction network can attenuate attentional blink and improve cognitive deficits to a certain extent [125]. However, differential connectivity from the frontal area may indicate how deliberate control monitors and corrects errors and biases in decision-making [126]. Siuda-Krzywicka et al. used fMRI and rTMS to investigate the extensive reorganization of brain activity in Braille learning in adults with normal vision. The results showed that the resting-state connection between the visual and somatosensory cortices was enhanced after rTMS [127]. The spatial mechanisms within the dorsal visual pathway contribute to the configural processing of facial features and, more broadly, the dorsal stream may contribute to the veridical perception of faces when rTMS is used to study the spatial relationship between facial features [128]. Although rTMS has extensive applications in neuromuscular movement, neuroimmune disorders, learning and memory, and cognitive enhancement, there is still a huge



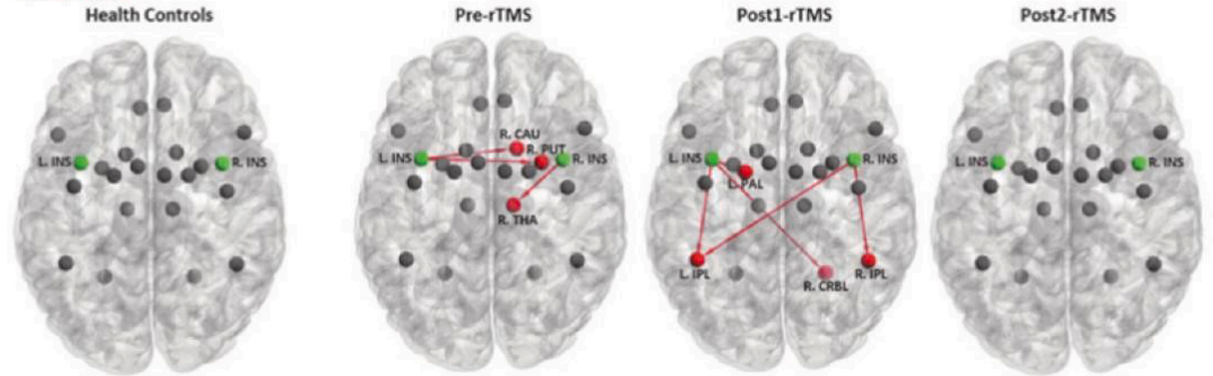
**B** Seed : SMA



Seed : Thalamus and Basal ganglia



Seed : Insula



(caption on next page)

**Fig. 7.** Application in other diseases or disorders. (A) The receiver operating characteristic (ROC) curves were used to characterize the overall predictive value for rTMS and tailor-made notch music training (TMNMT) treatments of tinnitus patients (rTMS=green; TMNMT=blue). Optimal functional network connections (FNCs) features with the highest AUC for each treatment: the FNC in the SN-RFPN for rTMS, the combination of FNCs in the AUN-SN and AUN-CN for TMNMT, respectively. (B) Connectivity analysis of the serial fMRI study in the functional dysphagia patients and healthy controls using the different brain structures as seed areas (FDR-corrected  $p < 0.05$ ). Seed of SMA: healthy controls exhibited positive connectivity with the bilateral PCG and cerebellum; in the right SMA seed, and healthy controls exhibited positive connectivity with the bilateral cerebellum and right PCG. However, the patient showed positive connectivity with the bilateral cerebellum in both SMA seeds before rTMS. After the rTMS treatment, the patient did not show significant connectivity with ROIs in the bilateral SMA seeds; however, connectivity was recovered between the left SMA (seed area) and the left PCG (target area) in post2-rTMS. Seed of thalamus and BG: Significant positive connectivity with the ROIs in the bilateral BG seeds and bilateral thalamus was noted. Seed of Insula: there are no significant connections with both insula in healthy controls, and the patient's neural connectivity with the insula seed differed in post2-rTMS. BG, basal ganglia; FDR, false discovery rate; ROIs, regions of interest. SMA, supplementary motor area; PCG, precentral gyrus. (A was reproduced with the permission of ref. [118], copyright@ Elsevier, 2022. B was reproduced with the permission of ref. [119], copyright@ Mary Ann Liebert, Inc, 2021.)

scope and great potential to be explored for its clinical and rehabilitation applications (Fig. 7, Supplemental Table 5).

#### 14. Conclusions

We have reviewed the technical details of rTMS and the biological interpretation of brain networks identified by MRI. Furthermore, we provided a comprehensive summary of the neurobiological effects and mechanisms of rTMS used for the rehabilitation of neuropsychiatric diseases. Combined with MRI and brain connectivity network analyses, which can reflect alterations induced by local rTMS and subsequent functional and structural connectivity changes of adjacent and separated brain regions related to stimulation sites, this provides a tool to understand the neural mechanisms and to tailor treatment plans for patients with neuropsychiatric diseases.

Based on the neurobiological rTMS effects in healthy volunteers, functional networks activities of cortical and subcortical motor systems are strengthened or suppressed, and concentrations of important metabolites related to neurotransmission change in key brain regions of the related networks after rTMS of the primary motor cortex. Stimulation of the DLPFC and vmPFC cause changes in FC networks related to cognitive and emotional functions and indirectly participate in the execution of functions of other remote brain networks. In addition, neurobiological effects are involved in the whole brain, auditory cortex, and visual cortex. Different effects in specific brain networks can explain the pathophysiological characteristics of neuropsychiatric diseases and objectively demonstrate gradual changes in the stimulation-induced activation or inhibition of the related brain regions.

Brain connection analysis using neuroimaging can theoretically reveal the neural mechanisms underlying neuropsychiatric disorders and their treatment-related rTMS modulation. Different clinical phenotypes correspond to different neural circuits involved in neurodegenerative diseases. After rTMS, the plasticity of the functional connection changes. This reflects the neuropathological mechanisms and characterizes the significance of different cortical and subcortical networks. rTMS has multiple effects on the motor cortex and cognition-related circuits in patients with stroke. It can remodel abnormal network systems and reveal potential rTMS mechanisms by improving motor and cognitive impairments after stroke. rTMS has multiple effects on various psychiatric disorders owing to the complexity and diversity of their phenotypes. For example, rTMS can effectively restore the relevant brain network status of patients with psychiatric disorders, and the plasticity changes in the network triggered by rTMS are consistent with the cognitive improvements of affected patients. In addition, rTMS has been widely used for neuromuscular movement disorders, neuroimmune diseases, cognitive enhancement, and learning and memory impairments. The therapeutic mechanisms of rTMS need to be further explored because of the potential application of rTMS in clinical practice and rehabilitation.

In conclusion, rTMS effects on different functional brain regions can be explained by corresponding neurobiological changes elucidated in MRI-derived brain connectivity network analyses. rTMS has important

and valuable clinically modulated effects on common neuropsychiatric diseases corresponding to different neural rehabilitation mechanisms. These mechanisms can be reasonably evaluated and elaborated with MRI-based brain connection analyses. In view of the diversity of neuropsychiatric diseases, the neural mechanisms underlying treatment effects by rTMS still need to be continuously improved. This is expected to further advance and expand the clinical application scope of rTMS in the future. MRI-based brain connectivity network analyses will help provide a scientific basis for improving the reliability and accuracy of its interpretation for monitoring patients with neuropsychiatric diseases after rTMS treatment.

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#### Ethical statement

Hereby, I consciously assure that for the manuscript /insert title/ the following is fulfilled:

- 1) This material is the authors' own original work, which has not been previously published elsewhere.
- 2) The paper is not currently being considered for publication elsewhere.
- 3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
- 4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
- 5) The results are appropriately placed in the context of prior and existing research.
- 6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
- 7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

I agree with the above statements and declare that this submission follows the policies of Solid State Ionics as outlined in the Guide for Authors and in the Ethical Statement.



## CRediT authorship contribution statement

**Han Xiaowei:** Investigation, Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition. **Zhu Zhen-gang:** Investigation, Writing – original draft. **Luan Jixin:** Visualization, Writing – original draft. **Lv Pin:** Methodology, Visualization. **Xin Xiaoyan:** Validation, Visualization. **Zhang Xin:** Funding acquisition, Visualization. **Shmuel Amir:** Validation, Visualization. **Yao Zeshan:** Validation, Visualization. **Ma Guolin:** Conceptualization, Funding acquisition, Supervision, Visualization. **Zhang Bing:** Conceptualization, Funding acquisition, Supervision, Visualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejro.2023.100495](https://doi.org/10.1016/j.ejro.2023.100495).

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