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Neuroimaging studies in major depressive disorder with suicidal ideation or behaviour among Chinese patients: implications for neural mechanisms and imaging signatures

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ABSTRACT

Major depressive disorder (MDD) with suicidal ideation or behaviour (MDSI) is associated with an increased risk of future suicide. The timely identification of suicide risk in patients with MDD and the subsequent implementation of interventions are crucially important to reduce their suffering and save lives. However, the early diagnosis of MDSI remains challenging across the world, as no objective diagnostic method is currently available. In China, the challenge is greater due to the social stigma associated with mental health problems, leading many patients to avoid reporting their suicidal ideation. Additionally, the neural mechanisms underlying MDSI are still unclear, which may hamper the development of effective interventions. We thus conducted this narrative review to summarise the existing neuroimaging studies of MDSI in Chinese patients, including those involving structural magnetic resonance imaging (MRI), functional MRI, neuronal electrophysiological source imaging of the brain dynamics with electroencephalography and magnetoencephalography. By synthesising the current research efforts in neuroimaging studies of Chinese patients with MDSI, we identified potential objective neuroimaging biomarkers, which may aid in the early identification of patients with MDSI who are at high suicide-related risk. Our findings also offer insights into the complex neural mechanisms underlying MDSI and suggest promising therapeutic targets. Furthermore, we propose future directions to discover novel imaging signatures, improve patient care, as well as help psychiatrists and clinical investigators plan their future research.

INTRODUCTION

Major depressive disorder (MDD) is a serious mental illness where patients usually have deficits in processing negative emotions (ie, hopelessness, sadness, shame and guilt).[1] Reinforcement of negative emotions may drive the generation of suicidal ideation, which involves thinking about, considering or planning suicide.[2] MDD with suicidal ideation or behaviour (MDSI) is associated with an increased risk of future suicide behaviours, which is a serious global health issue and among the leading causes of disability and death across the world.[3] In a previous study, approximately 53% (1750/3275) of patients with MDD expressed suicidal ideation.[4] Among patients with MDD and suicidal ideation, approximately 16%–34% make more than one suicide attempt in their lifetime, nearly 20-fold higher than that of the general population.[5–8] Since the World Health Organization (WHO) declared coronavirus disease 2019 a global public health emergency, suicide risk has increased in both the general population and patients with pre-existing mental disorders, such as MDD.[9] This alarming trend underscores the importance of the timely detection of suicidal ideation in patients with MDD and the subsequent implementation of interventions. According to the ideation-to-action framework, early detection and intervention can prevent the progression from suicidal ideation to suicide attempts, reduce the risk of future suicide and patient suffering, and thereby save lives.[10 11] However, early diagnosis of MDSI and distinguishing between MDSI and patients with MDD without suicidal ideation are challenging. Currently, there is no objective diagnostic method that provides measurable and quantifiable data to assist in an accurate diagnosis of MDSI. In China, the challenge is greater due to the social stigma associated with mental health problems, leading many patients to avoid reporting their suicidal ideation.[12] In addition, understanding of the neural mechanisms underlying MDSI is still limited, which may impede progress in developing effective treatments for this condition.

With the advent of neuroimaging techniques, it is now possible to probe the brain's functional networks, enhancing our

understanding of MDSI and identifying neuroimaging biomarkers associated with or even specific to suicide risk (ie, suicidal ideation and attempt).[13] Recent neuroimaging studies have provided substantial insights, facilitating the early identification of structural and functional alterations in the brain, which could offer potential biomarkers or signatures for diagnosing MDSI. Most current reviews regarding brain biosignatures and suicidal ideation focus on patients with MDD[13] or other mental disorders,[14] without emphasising MDSI specifically. Large-scale systematic reviews, such as those by the Enhancing NeuroImaging Genetics through Meta-Analysis MDD consortium, have analysed data from multiple MDD cohorts worldwide, identifying the structural and functional brain alterations associated with MDD and MDSI.[14] However, these studies have not included patient cohorts from China. To address this gap, we conducted this narrative review of relevant literature identified in the PubMed, China National Knowledge Infrastructure (CNKI) and Wanfang Med Online databases, including studies published both in English and Chinese, with a specific emphasis on aberrant brain structural and functional alterations associated with MDSI. This study aimed to shed light on the intricate neural mechanisms and biosignatures for MDSI among Chinese patients, complementing global research. In addition, the findings of this study could inform potential therapeutic targets, as well as help psychiatrists and clinical investigators in planning future research.

MDSI IN CHINESE PATIENTS

MDD causes considerable suffering for patients and places a heavy burden on their families worldwide.[1 15] Epidemiological studies on MDD showed a pooled prevalence of approximately 2% in the overall global population, affecting nearly 160 million individuals.[16] In China, the prevalence of MDD varies largely between studies.[17–21] Huang *et al* conducted a large cross-sectional study on the epidemiology of mental disorders and reported lifetime and 12-month MDD prevalence rates of 3.4% and 2.1% in adults, respectively.[20] Notably, the prevalence of MDD has been increasing over the past few decades.[22 23]

Suicidal ideation is common in patients with MDD, with numerous studies examining its prevalence both regionally and globally. A meta-analysis of 46 studies comprising 53 598 patients with MDD showed that the global pooled prevalence of suicidal ideation among individuals with MDD was 37.7% (95% CI, 32.3% to 43.4%).[24] In China, an observational study reported a higher incidence of 53.4%.[4]

Currently, healthcare providers largely rely on patient self-reporting to detect suicidal ideation, making early diagnosis of MDSI challenging. No objective diagnostic tool is currently available to distinguish between patients with MDD who have suicidal ideation and those who do not. In China, deep-rooted cultural stigma related to mental illness often discourages patients from reporting their suicidal ideation and may even lead them to avoid discussing symptoms related to mental illnesses.[12] As such, there is a need to develop objective markers for suicidal ideation among patients with MDD, which may assist clinical judgement in the prediction and early identification of those at high risk of suicide-related behaviours, particularly among patients who are reluctant to disclose their suicidal ideation to psychologists and psychiatrists.

FINDINGS FROM NEUROIMAGING STUDIES OF MDSI OR SUICIDE RISK IN CHINESE PATIENTS

Structural neuroimaging studies: brain structural alterations related/specific to MDSI observed in structural magnetic resonance imaging

Various imaging techniques have been employed in structural neuroimaging studies, including magnetic resonance imaging (MRI), computed tomography (CT) and diffusion tensor imaging.[13 14] Among these, MRI has proven to be particularly valuable in capturing detailed images of brain structures and has been instrumental in characterising structural alterations in the brain linked to suicidal ideation in patients with MDSI. Previous neuroimaging studies in Chinese patients with MDD have identified certain structural alterations in the brain regions, such as white matter and grey matter, associated with suicidal ideation (figure 1). Differences in the integrity of white matter have been identified in various areas in the brains of patients with MDSI, including the cingulate gyrus, corpus callosum, posterior limb of the left internal capsule, posterior thalamic radiation (left), superior longitudinal fasciculus, inferior longitudinal fasciculus (right) and cerebral peduncle (figure 1A). Chen *et al* compared microstructural changes in the brains of patients with MDSI (n=44), patients with MDD without suicidal ideation (n=56) and healthy controls (n=55).[25] The voxel-based statistical analysis revealed a characteristic reduction in white matter integrity as quantitatively measured by generalised fractional anisotropy (GFA), specifically showing significantly lower GFA values in the corpus callosum (the largest white matter structure) and the cingulate gyrus (located next to the corpus callosum) in MDSI compared with MDD without suicidal ideation and the healthy controls.[25] Consistently, a disruption in white matter integrity in the corpus callosum was also noted in patients with MDSI (n=34) compared with patients with MDD without suicidal ideation (n=54) and healthy controls (n=57).[26] Furthermore, Zhang *et al* also detected white matter structural changes in the internal capsule, cerebral peduncle, superior longitudinal fasciculus, right inferior longitudinal fasciculus, posterior limb of the left internal capsule and left posterior thalamic radiation in MDSI compared with MDD without suicidal ideation.[25 26]

A number of studies have also demonstrated grey matter changes associated with suicidal ideation in patients with MDD (figure 1B). Zhang *et al* assessed the grey matter volume (GMV) in the prefrontal cortex (PFC), a critical

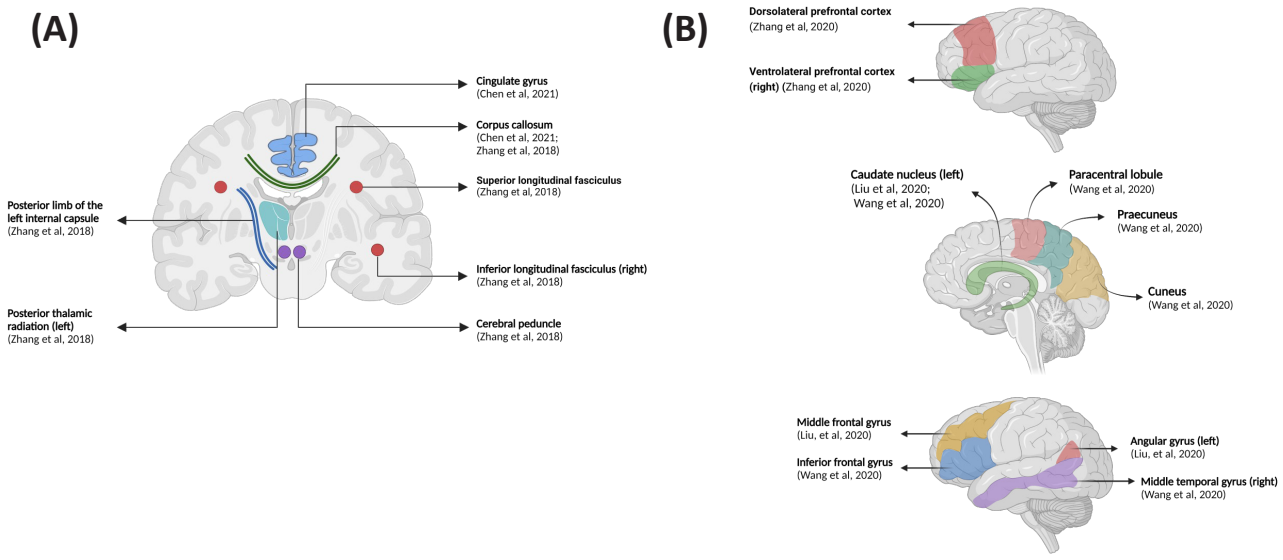

Figure 1 Structural alterations of the brain related/specific to major depressive disorder with suicidal ideation or behaviour (MDSI) observed in structural magnetic resonance imaging. Illustrations of: (A) the areas with potential structural changes in white matter associated with MDSI and (B) the areas with potential volumetric changes in grey matter associated with MDSI.

cortical area implicated in MDD and suicide, in patients with MDSI (n=35), patients with MDD without suicidal ideation (n=38) and age-matched and gender-matched healthy controls (n=43).[27] Voxel-based morphometric analysis of data collected from T1-weighted imaging, a type of MRI scan that demonstrates differences in the T1 relaxation times of tissues, showed that the GMV in the PFC in patients with MDSI was significantly lower than in patients with MDD without suicidal ideation, suggesting that the reduced volumetric changes of GMV in the PFC may be associated with suicidal ideation in MDD.[27] Interestingly, reductions were noted in regions such as the right ventrolateral PFC, left dorsolateral PFC (DLPFC) and right DLPFC in MDSI compared with MDD without suicidal ideation, suggesting these volumetric changes might contribute to the suicidal ideation in MDD.[27] Similarly, Liu *et al* reported that the GMV values in the right middle frontal gyrus and left angular gyrus were significantly elevated in MDSI compared with MDD without suicidal ideation.[28] Notably, changes in the GMV in specific areas, including the cuneus, precuneus, paracentral lobule, inferior frontal gyrus and caudate nucleus, and local activity in the cuneal and middle temporal gyrus were linked to suicidal ideation in individuals with MDD and those who experienced childhood abuse, with the left caudate nucleus specifically associated with both.[28 29] Considering the interaction effects of childhood abuse and suicidal ideation on the structural changes of the brain, further neuroimaging studies should investigate the role of childhood abuse in the development of suicidal ideation in MDD.[28 29]

These studies collectively suggest that disruption of the white matter integrity and reduction in the GMV in specific brain regions are associated with suicidal ideation in Chinese patients with MDD. However, inconsistencies across studies and limitations in sample sizes indicate the need for further validation to better understand the neural mechanisms involved in suicidal ideation in individuals with MDD.

Functional neuroimaging studies: brain connectivity abnormalities related/specific to MDSI in functional MRI (fMRI)

Resting-state fMRI and task-based fMRI are widely used in mapping brain response during a resting state and an assigned task, respectively, to identify functional alterations in different regions and extensive studies have demonstrated evidence supporting the link between brain connectivity abnormalities and suicidal ideation in patients with MDD.[30–33]

Resting-state fMRI studies of functional connectivity in brain regions

Chen *et al* conducted a resting-state fMRI study involving three groups of subjects: patients with MDSI (n=35), patients with MDD without suicidal ideation (n=32) and healthy controls (n=44).[31] The study used the fractional amplitude of low-frequency fluctuation (fALFF), a resting-state fMRI signal known for reliability in measuring regional spontaneous activity[34] by assessing the relative contribution of low-frequency fluctuations within a specific frequency band to the entire detectable

frequency range. Comparative analysis of the resting-state functional neuroimaging results revealed differences in functional activity among the subjects. Specifically, the analysis of fALFF in several brain regions identified reduced functional activity in the bilateral thalamus and the left cuneus regions associated with suicidal ideation in patients with MDD.[31] Moreover, the seed-based correlation analysis[35 36] was used to measure the functional connectivity, calculated as the correlation of time series for all other voxels in the brain with the time series of a seed voxel or region of interest. It was found that functional connectivity changes in relation to suicidal ideation involved multiple brain regions and complex functional networks. Specifically, patients with MDSI showed greater functional connectivity in the left and right hippocampi compared with patients with MDD without suicidal ideation, possibly as a compensation response to a vulnerable state of the brain to suicide ideation. Du *et al* investigated the differences in resting-state fMRI between patients with MDSI (n=28), those without suicidal ideation (n=20) and healthy controls (n=30).[37] Their results revealed that among patients with MDD, those with suicidal ideation exhibited decreased intrinsic functional connectivity (iFC) between the rostral anterior cingulate cortex (rACC), the orbitomedial PFC and the right middle temporal pole compared with those without suicidal ideation. Additionally, the strength of iFC between the right rACC and the middle temporal pole was positively associated with the severity of suicidal ideation. These findings suggest that disrupted frontolimbic circuits may impact decision-making and emotional processing in patients with MDD and suicidal ideation, providing valuable insights into the underlying pathophysiological mechanisms of this subgroup. Moreover, a previous study found that the severity of suicidal ideation, as measured by the Scale for Suicide Ideation, exhibited a positive correlation with decreased functional connectivity between the perigenual anterior cingulate cortex (pgACC) and the superior frontal gyrus in young adult patients with MDD (aged 18–24 years).[38] However, in the patients without a history of suicidal behaviour, suicidal ideation negatively correlated with increased functional connectivity between the anterior subgenual anterior cingulate cortex and the superior frontal gyrus compared with those with a history of suicidal behaviour. These findings established a connection between suicidal ideation and abnormal functional connectivity patterns in anterior cingulate cortex (ACC) subregions among young adults with MDD and support the link between impaired connectivity within reward networks in ACC subregions and suicidal ideation.

In another study by Liao *et al*, resting-state fMRI was performed in patients with MDSI (n=28), patients with MDD without suicidal ideation (n=20) and age-matched, gender-matched and education-matched healthy controls (n=30).[30] Based on the resting-state fMRI data, both static and dynamic brain functional connectomes were constructed. A connectome represents the complete set of neural connections in the brain, while connectomics involves mapping all the brain connections, including structural connectomics and functional connectomics. The results suggested distinct overall topological properties (network strength, network efficiency and small worldness) in patients with MDSI compared with those without suicidal ideation, measured using sparsity-thresholded weighted matrices and computed the area under curve (AUC).[30] In fact, the two studies consistently found differences in topological organisation and better local segregation of the brain network (the cliquishness of a typical neighbourhood[39] at the network level, examined through network-based statistical analysis) in healthy controls compared with patients with MDD with and without suicidal ideation.[30 31] Overall topological properties of the static functional connectome were lower in both MDD groups compared with healthy controls, whereas these properties of the dynamic functional connectome were higher in patients with MDSI compared with patients with MDD without suicidal ideation and healthy controls.[30] Moreover, a connectomics-based model, built on the statistical analysis of the static and dynamic brain functional connectomes of patients with MDD with or without suicidal ideation, showed good performance in distinguishing between the two MDD subgroups. The model achieved an accuracy of 75%, sensitivity of 71% and specificity of 75%.[30] These findings may have clinical implications that the connectomics-based model could assist healthcare providers in identifying patients with MDSI and may hold promise as a non-invasive imaging marker for developing objective diagnostic and predictive tools for MDSI.[30]

The amygdala, an important part of the limbic system in the brain, is involved in emotion processing, stimulus–reward learning and cognitive functioning. In a recent study, Yang *et al* compared the resting-state fMRI-based functional connectivity in four subregions of the amygdala in patients with MDSI (n=59), patients with MDD without suicidal ideation (n=22) and healthy controls (n=60) and found that the regions with significant differences in the omnibus across the three studied groups were distributed across a corticolimbic–corticostriatal circuitry.[40] The regions with significant between-group differences (MDSI vs MDD without suicidal ideation, MDSI vs healthy control) in the functional connectivity of the amygdala were identified. Specifically, disrupted functional connectivity of the lateral amygdala with the caudate, middle temporal gyrus and postcentral gyrus was specific to MDSI, while dysconnectivity of the medial amygdala with the medial superior frontal gyrus and middle temporal gyrus was shared by both MDD groups.[40] Furthermore, patients with MDSI showed lower global functional connectivity and a decreased sigma (small worldness), correlated with the severity of suicidal ideation.[40] A machine learning toolkit based on these findings showed an AUC of 0.82 and an accuracy of 84.09% in distinguishing MDSI from MDD without suicidal ideation, suggesting the good discriminative ability of the toolkit and highlighting the

importance of the amygdala-centred corticolimbic–corticostriatal circuitry as a neural basis for suicidal ideation in MDD. This model may offer a promising approach for the differential diagnosis of patients with MDD with and without suicidal ideation.[40] In support of the above findings, another study of functional connectivity found that suicidal ideation in female patients with first-episode MDD was associated with abnormality in the amygdala neural circuitry, and impairment in the amygdala–precuneus/cuneus functional connectivity may be the characteristic alteration for suicidal ideation.[41]

Alterations in brain dynamics, referring to the patterns of activity and interactions among neurons and neural networks, particularly in regions involved in executive and emotional processing, have been reported in patients with MDSI.[37 42] For instance, Li *et al* assessed the temporal dynamics of intrinsic brain activity in patients with MDSI, MDD without suicidal ideation, and matched healthy controls using resting-state fMRI and constructed a linear model to predict the severity of suicidal ideation.[42] The result indicated a lower temporal variability or dynamics of intrinsic brain activity in patients with MDSI compared with MDD without suicidal ideation, quantified by the variance of the dynamic amplitude of low-frequency fluctuation over time. In particular, reduced brain dynamics were observed in the left orbital frontal cortex, the dorsal PFC (dACC), the left inferior temporal gyrus and the left hippocampus, which are associated with executive and emotional processing.[42] These temporal variabilities showed potential effects in predicting suicidal severity (r=0.43, p=0.030).[42]

Resting-state fMRI studies of functional connectivity in major brain networks

Liu *et al* also carried out a study assessing the brain core network, which is composed of interconnected hub nodes, namely rich-club organisation,[43] analysing the convergence and divergence of global and regional topological properties, as well as the connectivity of neural circuits, in patients with MDSI (n=69), patients with MDD without suicidal ideation (n=58) and cognitively normal controls (n=50).[28] Rich-club organisations consist of rich clubs (linking the rich-club hubs), feeders (linking the rich-club hubs with the non-rich-club hubs) and local connections (linking the non-rich-club hubs).[43] Notably, both MDSI and MDD without suicidal ideation groups showed an impairment of the rich-club organisation compared with the controls. Interestingly, compared with MDD without suicidal ideation, MDSI exhibited differential network connections mainly in the non-core low-level network involving the superior longitudinal fasciculus and the corpus callosum, which were integrated in the default mode network (DMN) and the cognitive control circuit. Using a support vector machine-learning algorithm, the performance evaluation with receiver operating characteristic curve analysis indicated that the feeder connections had a greater ability to differentiate MDSI from MDD without suicidal ideation than rich-club connections or local connections (AUC: 0.79 for the feeder connection, 0.62 for the rich-club or local connection).[28] As such, this study suggested that the feeders might be useful neuroimaging biomarkers for suicidal ideation in patients with MDD.[28]

Extensive resting-state and task-based fMRI studies on functional connectivity in different regions of interest (ie, the PFC, hippocampus, thalamus) have shown that a number of major brain networks, including the DMN, the frontoparietal network (FPN), the visual network (VN) and the salience network (SN), are associated with suicidal ideation and suicide risk among patients with MDD.[14 44–46] Of these networks, DMN is essential for ruminative thinking and self-reference, while FPN is important in the regulation of emotion and the maintenance of executive functioning, and SN plays a critical role in responding to external stimuli. A decrease in the metabolic activity (glucose metabolism as measured by regional cerebral glucose metabolism (rCMRglu)) of the FPN brain regions has been linked to suicidal ideation or suicide planning in patients with MDD.[47] A previous study of Chinese patients with MDD and suicidal ideation or suicide attempts found that the inter-network gamma connectivity of DMN and FPN is potentially a key neuropathological interaction during the transition from suicidal ideation to suicide attempt.[46] The findings were consistent across studies in different patient populations worldwide, highlighting the functional alterations of these brain networks that are relevant to suicidal ideation and suicide risk among patients with MDD.[46 47]

Task-based fMRI studies

In addition to resting-state fMRI, Dai *et al* performed task-based fMRI (a task involving passively viewing emotional faces) to examine changes in the gamma oscillations, which are crucial for processing negative emotions, in the regions from the DMN, FPN, VN and SN in three groups: patients with MDD and suicidal ideation, patients with MDD and suicide attempt and healthy controls.[46] Interestingly, there was a significant negative correlation between the suicide risk of MDSI and internetwork gamma connectivity of DMN and FPN (p<0.001).[46] Furthermore, such a correlation was not confounded by the severity of depression. On the basis of the impaired gamma functional connectivity of DMN and FPN, a semisupervised algorithm, a machine learning algorithm that uses a combination of labelled and unlabelled data for training, was developed to stratify patients with MDSI into different suicide risk levels, which can be used to predict suicide risk among patients with MDSI.[46]

Positron emission tomography (PET) imaging studies (ie, with ^{18}F-fluorodeoxyglucose (^{18}F-FDG PET)): metabolic activity changes related/specific to MDSI in PET scans

PET, a non-invasive, radiotracer-based imaging modality, provides quantitative binding information, which refers to the specific attachment of a radiotracer to its target within the body.[47] PET has been proven valuable in

imaging brain target areas, enabling the measurement of metabolic activity and receptor occupancy with high contrast and spatial resolution. Globally, most molecular imaging studies with PET related to suicide neurobiology have focused on the major neurotransmitters and their metabolites as well as on their transporters and receptors. van Heeringen *et al* reported that alterations in the regional metabolic activity in the brain using ^{18}F-FDG PET imaging were associated with suicide plans in patients with MDD.[47] rCMRglu was compared between patients with MDD with suicidal thoughts and those with suicide plans. The results showed relative hypometabolism in the right middle frontal gyrus and the right inferior parietal lobe (Brodmann areas 10 and 39), the areas closely associated with decision-making, in particular in exploratory behaviours. However, given the limited number of such studies, it was not possible to suggest a relationship between the binding potential and suicidal ideation.[47] Additionally, no molecular imaging study with PET in Chinese patients with MDSI was identified during our review.

Neuronal electrophysiological source imaging of the brain dynamics with electroencephalography (EEG) and magnetoencephalography (MEG): electronic activity alterations related/specific to MDSI in neuronal electrophysiology

As the brain connectivity evolves over time and is distributed in three-dimensional space, it is important to obtain images of brain dynamics with high temporal and spatial resolution.[48] EEG and MEG are non-invasive methods that allow for viewing brain interactions and complex neural activations. Electrophysiological source imaging, based on EEG and MEG measurements, provides a window to view the brain dynamics by offering intrinsically high temporal resolution and improved spatial resolution when imaging the activity and connectivity of the brain on a large scale and over a wide range.[48] A number of studies with neuronal electrophysiological source imaging of the brain dynamics with EEG and MEG have investigated potential alterations in event-related potential (ERP)-related components (ie, P2, N2) in the electrophysiological neural response to stimuli or specific events in Chinese patients with MDD with or without suicidal ideation.[49–54] The P2 component is associated with cognitive processes such as attention and memory encoding, while the N2 component is linked to conflict monitoring and cognitive control processes.[52] For instance, Zhou *et al* examined ERPs (P300) in patients with MDSI (n=324), patients with MDD without suicidal ideation (n=169) and healthy controls (n=161).[52] The comparative analysis revealed that patients with MDSI had significantly lower P2 intensity compared with those with MDD without suicidal ideation (3.05 vs 3.99 µV, p<0.050), with the latter demonstrating a comparable P2 intensity to that in the normal controls (3.99 vs 4.02 µV, p<0.050). Regarding the component N2, a negative wave appeared at 200–300 ms after a stimulus or event onset. Patients with MDD with and without suicidal ideation exhibited similar N2 wave latencies (205 and 206 ms, respectively), both significantly longer than that in normal control individuals (200 ms, p<0.001).[52] Gao *et al* investigated the relationship between frontal alpha asymmetry characteristics and suicide risk among patients with MDD and found lower left PFC activity and higher right PFC activity in patients with MDD with a history of suicidal attempts.[54] These studies provide initial evidence supporting the changes in neuroelectrophysiological characteristics with EEG/MEG in patients with MDD and MDSI. However, further studies are needed to validate these findings and identify the features with clinical value for differentiating between patients with MDD with and without suicide ideation.

Neuroimaging studies (MRI, fMRI, PET, EEG/MEG, alone or in combination) focusing on changes in the brain structure, function or activity in response to antidepressant treatment for MDSI

The integration of electrophysiological source imaging with EEG and MEG with fMRI holds promise for enhancing both spatiotemporal resolution and specificity. However, as of the review cut-off, studies on electrophysiological source imaging in combination with fMRI in basic and clinical neuroscience research are lacking in Chinese patients with MDSI.

IMPLICATIONS FOR DETERMINING THE POTENTIAL NEURAL MECHANISMS UNDERLYING SUICIDAL IDEATION IN CHINESE PATIENTS WITH MDD

The neurobiological mechanisms underlying suicidal ideation in individuals with MDD are complex and challenging to determine. Advancements in structural and functional brain imaging have shed light on the underpinnings of MDD-related suicidal ideation. Through a comprehensive analysis of the major findings from structural and functional imaging studies, particularly those using MRI and fMRI, we propose potential neural mechanisms underlying suicidal ideation in Chinese patients with MDD. Specifically, based on structural brain abnormalities in white and grey matter, as well as functional connectivity alterations in patients with MDSI compared with those without suicidal ideation (table 1), we hypothesised that disruptions in the frontolimbic system, especially DLPFC, ACC, the amygdala and the hippocampus of the limbic system and related interconnected networks could potentially be the core pathological alterations contributing to suicidal ideation in MDD.

The DLPFC, nestled within the frontal lobes of the brain, is involved in a range of cognitive processes.[55 56] It functions as a central hub for decision-making, impulse control and regulating emotions, thereby playing a pivotal role in making rational decisions and curbing impulsive behaviours. Several studies using structural and functional neuroimaging techniques have revealed impairments in the DLPFC among Chinese patients with MDSI.[27 46] In a study by Zhang *et al*, significantly

Table 1 Alterations in activity, functional connectivity and neural network gamma interaction in different brain areas of patients with MDSI

Brian areas	Activity	FC	Networks gamma interaction	References
Cortical areas				
Left cuneus	↓			Chen *et al*[25]
rACC, OMPFC and TPOmid		↓*		Du *et al*[37]
pgACC and SFG		↓		Qiu *et al*[38]
MPFC, PCC, precuneus and LPC (DMN) DLPFC, ACC, FEF, PPC and IPS (FPN)			↓†	Dai *et al*[46]
Subcortical areas				
Bilateral thalamus	↓			Chen *et al*[25]
Bilateral hippocampus	↑	↑		Chen *et al*[25]
Lateral amygdala and caudate		↓		Yang *et al*[40]

The arrows, whether indicating an increase or decrease, were quantified based on resting-state functional magnetic resonance imaging data.
*Intrinsic functional connectivity.
†Inter-network gamma connectivity with FPN and DMN.
ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; FC, functional connectivity; FEF, frontal eye fields; FPN, frontoparietal network; IPS, intraparietal sulcus; LPC, lateral parietal cortex; MDSI, major depressive disorder with suicidal ideation or behaviour; MPFC, medial prefrontal cortex; OMPFC, orbitomedial prefrontal cortex; PCC, posterior cingulate cortex; pgACC, perigenual anterior cingulate cortex; PPC, posterior parietal cortex; rACC, rostral anterior cingulate cortex; SFG, superior frontal gyrus; TPOmid, right middle temporal pole.

decreased GMV was observed in the left and right DLPFC in patients with MDSI compared with those without suicidal ideation. Additionally, Dai *et al* demonstrated that functional impairment of the DLPFC was associated with suicidal ideation in patients with MDD (table 1). These findings suggest that structural shrinkage, potentially indicating neuron loss, along with functional impairment, may contribute to challenges in regulating negative emotions and intrusive thoughts, thereby increasing the risk of suicidal ideation, particularly under stress.

The ACC, a small region located in the medial frontal lobe of the brain, plays a critical role in emotion regulation, decision-making, conflict monitoring and empathy.[57 58] The ACC acts as a central hub connecting various brain networks, and its dysfunction could have broad repercussions, potentially disrupting the balance between emotional and cognitive processes. Functional disruption of the ACC and its subareas (ie, pgACC, rACC, dACC) has been consistently demonstrated in various neuroimaging studies involving Chinese patients with MDSI.[37 38 42 46] A number of fMRI studies have highlighted key findings regarding the ACC, and its three main subareas, as summarised in table 1. For instance, Du *et al*[37] found that patients with MDSI exhibited a reduction in iFC between the rACC, the orbitomedial PFC and the right middle temporal pole compared with those without suicidal ideation. Moreover, the strength of the iFC between the right rACC and the middle temporal pole was positively associated with the severity of suicidal ideation. Similarly, Qiu *et al*[38] reported a positive association between the severity of suicidal ideation and decreased functional connectivity between the pgACC and the superior frontal gyrus in young adult Chinese patients with MDD. Another study by Li *et al*[42] also identified a reduction in the brain dynamics in the dACC. These consistent findings of impaired ACC function and altered connectivity patterns may indicate a dysregulation of the brain networks involved in emotional processing and self-referential thinking, thus contributing to the emergence of suicidal thoughts.

The limbic system, primarily consisting of the hippocampus, amygdala and hypothalamus, serves as the emotional command centre.[59] Dysfunctions within this system have been linked to heightened emotional reactivity, negative feelings and difficulties in regulating emotions, all of which can increase vulnerability to suicidal ideation. Specifically, neuroimaging studies in Chinese patients with MDSI have revealed abnormalities in the hippocampus and amygdala compared with MDD without suicidal ideation.[31 40] These alterations may contribute to a hyperactive response to stress and heightened emotional sensitivity, potentially leading to a negative bias in interpreting stressful life events, and ultimately, the emergence of suicidal thoughts. Additionally, the functional connectivity between the amygdala and the precuneus within the DMN was identified to be impaired in patients with MDSI, and this alteration may also play a role in the development of suicidal ideation in MDD. The interconnection within the frontolimbic circuits is crucial for emotion regulation and cognitive control. Disruptions in this connectivity, such as diminished connectivity between these specific cortical and subcortical brain

areas, can further contribute to the development and persistence of suicidal ideation in patients with MDD. These findings suggest that targeting these specific brain areas and their interactions may provide potential avenues for developing interventions for patients with MDD who are at higher risk of suicidal ideation. However, the proposed neural mechanisms should be considered preliminary due to the limited and inconsistent results across studies to date, and the involvement of other brain regions and neurotransmitters in the complexity of suicidal ideation. Further research is needed to fully comprehend these mechanisms and guide the development of new and more effective interventions for suicidal ideation among individuals with MDD.

IMPLICATIONS FOR NOVEL NEUROIMAGING BIOMARKERS/SIGNATURES IN THE EARLY IDENTIFICATION AND DIAGNOSIS OF SUICIDAL IDEATION AMONG CHINESE PATIENTS WITH MDD

The development of objective, non-invasive biomarkers for the early identification and diagnosis of suicidal ideation among patients with MDD is one of the key priorities within the field of psychiatry. Advanced neuroimaging technologies have identified aberrant brain structural and functional alterations associated with suicidal ideation, which may hold promise as potential biomarkers or signatures for the early identification and diagnosis of suicidal ideation in patients with MDD.[28 30 40 42] Convergent findings emerging from the important reviewed literature on potential neuroimaging signatures associated with suicidal ideation and neuroimaging-derived predictive models are summarised in table 2.[28 30 40 42] It is worth noting that the models reported to date have shown good discriminative ability in predicting suicidal ideation among patients with MDD (table 2). As such, neuroimaging-based models may serve as a novel diagnostic tool to model psychiatric disorder phenotypes, complementing conventional diagnostic methods and aiding in the early identification of suicidal ideation. The development and identification of new neuroimaging biomarkers hold significant clinical implications. The use of these biomarkers can aid in predicting suicidal ideation among patients with MDD and help guide clinical judgement to identify patients with MDD at high suicide-related risk, particularly those who may be unwilling to or may not voluntarily report their suicidal ideation to healthcare providers. Also, neuroimaging biomarkers have the potential to uncover the complex and intricate pathological mechanisms involved in suicidal ideation among patients with MDD, thereby facilitating the identification of potential therapeutic targets.

Currently, neuroimaging is not a standard practice and despite the recent progress in the field, syndromic identification and differentiation based on neuroimaging is not fully feasible. As proposed in this review, the integration of the objective diagnostic markers evaluated through MRI scans into clinical practice requires careful consideration of diagnostic ethics, which must be thoroughly deliberated in the future before implementation.

Table 2 Summary of potential neuroimaging signatures for suicidal ideation in patients with MDD and the performance of the reported neuroimaging-derived predictive models

References	Type of fMRI/study subjects	Main brain functional changes	Performance metrics of the reported neuroimaging-derived predictive models
Liao *et al*[30]	rs-fMRI/MDSI (n=28); MDD without SI (n=20) and HC (n=30)	Lower overall topological properties of the static functional connectome in MDSI versus MDD without SI. Higher properties of the dynamic functional connectome in MDSI versus MDD without SI.	Accuracy, 75%; sensitivity, 71%; specificity, 75%
Yang *et al*[40]	rs-fMRI/MDSI (n=59); MDD without SI (n=22) and HC (n=60)	Aberrant functional connectivity of the lateral amygdala with caudate, middle temporal gyrus and postcentral gyrus specific to MDSI versus MDD without SI.	AUC, 0.82; accuracy, 84.09%
Li *et al*[42]	rs-fMRI/MDSI; MDD without SI and HC	Lower brain dynamics in the left orbital frontal cortex, the dorsal anterior cingulate cortex, the left inferior temporal gyrus and the left hippocampus in MDSI versus MDD without SI.	The linear model shows significant correlations of the temporal variabilities with the severity of suicidal ideation. R=0.43; p=0.030
Liu *et al*[28]	rs-fMRI/MDSI (n=69); MDD without SI (n=58) and HC (n=50)	Differential network connections on the non-core low-level network involving the superior longitudinal fasciculus and the corpus callosum integrated in the DMN and the cognitive control circuit.	AUC, 0.79 for the feeder connection; AUC, 0.62 for the rich-club or local connection

AUC, area under the receiver operating characteristic curve; DMN, default mode network; fMRI, functional magnetic resonance imaging; HC, health control; MDD, major depressive disorder; MDSI, major depressive disorder with suicidal ideation; SI, suicidal ideation.

LIMITATIONS AND FUTURE DIRECTIONS

The existing studies covered in the present review have some limitations, underscoring the need for future investigation. The majority of the findings were obtained from observational studies with a cross-sectional design and relatively small sample sizes, emphasising the necessity for future investigations with larger sample sizes and longitudinal design to identify new and better neuroimaging markers/signatures for suicidal ideation among patients with MDD. Also, variations in protocols applied for structural and functional imaging of the brain and data extraction have led to inconsistent and contradictory findings across studies. To address this issue, the standardisation of methods for neuroimaging studies is critical. In addition, most of the previous studies focused on adult patients and the findings were obtained by analysing data from a combined group of patients without considering subgroup populations, such as college students and females with postpartum depression. There is a critical gap in the neuroimaging literature concerning the differences between sexes, despite extensive evidence demonstrating distinct features and suicide risk between sexes.[60–62] Furthermore, MDD may have distinct aetiological factors and underlying mechanisms in different patient subgroups, highlighting the need for careful consideration of specific subgroups when planning future studies. These subgroups may include, but are not limited to, adolescents, college students and females, especially those with postpartum depression, which has a worldwide prevalence of 17.22% among women after childbirth.[63] With these results of the brain structural changes associated with MDSI, it would be helpful to validate these neuroimaging findings in brain mortem tissues from the brain banks platform in China. Resting-state fMRI and task-based fMRI studies may help identify suicidal ideation-associated or suicidal ideation-specific alterations. However, few studies employ these approaches, highlighting the need for future research to incorporate these methods. Moreover, PET imaging studies with a focus on microglial activation and neuroinflammation allow quantitative assessment of changes in relation to or specific to suicidal ideation among patients with MDD.[64] As of the review cut-off, no molecular imaging study using PET in a Chinese patient population with MDSI was identified. Given the intriguing and significant role of microglial activation in neuropsychiatric disorders and suicide,[65–68] there is a need for PET imaging studies, particularly focusing on microglial activation between MDSI and MDD without suicidal ideation in Chinese patients. It is worth mentioning that imaging genetics,[69–71] an emerging field that links brain structure, function and wiring with genotypes and characterises the genetic basis of the structural and functional alterations of the brain that may exert a critical role in MDSI, may facilitate the identification and development of imaging markers for suicidal ideation among patients with MDD. Imaging transcriptomics enables the identification of associations between gene expression and the brain structure, function or metabolic pathway associated with suicidal ideation in patients with MDD. However, genetic neuroimaging is limited in Chinese patients with MDD with or without suicidal ideation, underscoring the need for further research.

Research on the neural circuitry related to suicidal thoughts and behaviours is also crucial. Initial neuroimaging studies have laid the groundwork, despite their relatively small sample size and heterogeneity of the research results to date. Integrating data from multiple studies to expand the population can aid in addressing the challenges posed by the small sample sizes and enhance our understanding of how suicide risk evolves over time. Defining at-risk subgroups by risk experiences and psychopathology subtypes could provide a clearer picture of the neural changes associated with suicide risk, both current and lifetime. It would also be beneficial to expand research efforts examining the structural and functional changes related to intervention responses. Such research efforts may lead to important findings that may help predict suicide risk and aid in developing new prevention models.

CONCLUSIONS

In summary, the research efforts in neuroimaging studies of MDD with or without suicidal ideation in Chinese patients to date suggest that structural and functional changes in the brain may be related or specific to MDSI. The initial findings of these neuroimaging studies have laid important groundwork in this area despite certain limitations, such as heterogeneity as well as the small sample sizes in studies, with some convergent findings showing promise. The specific neuroimaging alterations in MDSI as identified in this review may hold potential as objective non-invasive biomarkers and signatures for distinguishing MDSI and MDD without suicidal ideation. Furthermore, a number of neuroimaging-based predictive models have been established, and the performance evaluation metrics have suggested that they have a good ability to distinguish between Chinese patients with MDSI and MDD without suicidal ideation. As such, the findings described in the present review have clinical implications for aiding suicidal ideation diagnosis in patients with MDD, potentially enabling early identification of those at high suicide-related risk. Moreover, they contribute to understanding the complex neural mechanisms underlying suicidal ideation among patients with MDD and provide potential therapeutic targets. Future research directions should address current study limitations and aim to discover novel and better imaging signatures that could benefit affected patients and their families. Additionally, the findings in the review can assist psychologists and clinical investigators in planning future research.

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