v. 4, n. 54, 2024

International Journal of Health Science

NEUROIMAGING INSIGHTS INTO DEPRESSIVE DISORDERS: STRUCTURAL AND FUNCTIONAL BRAIN CHANGES

Leonardo Lucas Pereira Filho
http://lattes.cnpq.br/4022430994941735

Giovanna Mariotti Moreira
http://lattes.cnpq.br/1580683314937989

Lara Fernanda de Sá Guimarães
http://lattes.cnpq.br/4791743372358340

Mayara Botelho Carletto
http://lattes.cnpq.br/3806962055766010

Vanessa Britto Zafra
http://lattes.cnpq.br/2807146195840720

Melyssa Aryane de Oliveira
http://lattes.cnpq.br/9531560727825211

Pedro Rafael Fracacio
http://lattes.cnpq.br/2870404153294104

Rafaela Araújo Costa Pinto
https://lattes.cnpq.br/2215473296353541

Wilson Jolando Ojeda Júnior
https://lattes.cnpq.br/3730550452281724

Maykon Pablo Aguiar Fenelon
http://lattes.cnpq.br/521999614166349

Alisson Beraldo
http://lattes.cnpq.br/4791743372358340

Mauricio Lopes da Silva Netto
http://lattes.cnpq.br/4791743372358340

Resume: INTRODUCTION The introduction outlines the global burden of depressive disorders, emphasizing their impact on quality of life and the economy. It traces the historical development of neuroimaging in psychiatry, highlighting the importance of various imaging techniques such as MRI, fMRI, PET, and SPECT in uncovering the neurobiological underpinnings of depression. Key brain regions affected by depression, including the prefrontal cortex, hippocampus, and amygdala, are discussed, alongside neurotransmitter imbalances and default mode network (DMN) disruptions. The role of neuroinflammation, genetic influences, chronic stress, and gender differences in neuroimaging findings are also explored. **OBJETIVE** To review and synthesize current findings on structural brain abnormalities in depressive disorders. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Descriptors" AND "Neuroimaging Techniques" AND "Depressive Disorders" AND "Brain Structure and Function" AND "Treatment Response" AND "Neurobiological Markers" in the last years. **RESULTS AND DISCUSSION** This section delves into specific neuroimaging findings associated with depressive disorders. It discusses structural abnormalities such as reduced grey matter volume in critical regions like the prefrontal cortex and hippocampus, and functional connectivity changes within networks like the DMN and salience network. The discussion includes the impact of chronic stress and neuroinflammation on brain structure, the role of genetic factors, and the distinct neuroimaging profiles of treatment-resistant depression. Furthermore, the effects of therapeutic interventions, including antidepressants, psychotherapy, and neuromodulation techniques, on brain structure and function are analyzed. Gender differences, the relationship between cognitive impairment and neuroimaging findings, and the impact of sleep disturbances, substance abuse, and physical exercise on brain changes in depression are also covered. **CONCLUSION** The introduction outlines the global burden of depressive disorders, emphasizing their impact on quality of life and the economy. It traces the historical development of neuroimaging in psychiatry, highlighting the importance of various imaging techniques such as MRI, fMRI, PET, and SPECT in uncovering the neurobiological underpinnings of depression. Key brain regions affected by depression, including the prefrontal cortex, hippocampus, and amygdala, are discussed, alongside neurotransmitter imbalances and default mode network (DMN) disruptions. The role of neuroinflammation, genetic influences, chronic stress, and gender differences in neuroimaging findings are also explored.

Keywords: Depression; Neuroimaging; Functional Connectivity; Brain Structure; Treatment Response.

INTRODUCTION

Depressive disorders, including major depressive disorder (MDD), represent a significant global health burden, affecting millions worldwide and contributing to substantial disability[1]. Characterized by persistent feelings of sadness, loss of interest in activities, and a range of cognitive and physical symptoms, depression adversely impacts daily functioning and quality of life[1]. Epidemiological studies indicate a high prevalence of depressive disorders across various populations, with significant implications for public health and clinical practice[2]. The pathophysiology of depression is complex, involving genetic, environmental, and neurobiological factors that interact to

influence the onset and progression of the disorder[2]. The application of neuroimaging techniques in psychiatry has significantly advanced our understanding of the neural underpinnings of mental disorders, including depression[3]. Early neuroimaging studies focused on structural abnormalities using techniques such as computed tomography (CT) and magnetic resonance imaging (MRI)[4]. Over the past few decades, functional imaging modalities, including functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), have provided insights into the functional connectivity and activity patterns associated with psychiatric conditions[5]. These advancements have paved the way for a more nuanced understanding of the brain-behavior relationship in depressive disorders[5].

Neuroimaging has emerged as a crucial tool in unraveling the complex pathophysiology of depressive disorders[6]. By visualizing structural and functional brain alterations, neuroimaging studies have identified key neural circuits implicated in mood regulation, cognitive processing, and emotional response. These findings have not only enhanced our understanding of the neurobiological basis of depression but have also informed the development of targeted therapeutic interventions[6]. Furthermore, neuroimaging biomarkers hold promise for improving diagnostic accuracy, predicting treatment response, and monitoring disease progression in clinical settings[7]. Various neuroimaging techniques have been employed to investigate the neural correlates of depression, each offering unique insights into brain structure and function[8]. MRI provides high-resolution images of brain anatomy, enabling the identification of structural abnormalities[8]. Functional MRI (fMRI) measures brain activity by detecting changes in blood flow, offering insights into functional connectivity and neural activation patterns. PET and SPECT use radioactive tracers to visualize metabolic activity and neurotransmitter systems, providing a functional assessment of brain regions involved in mood regulation[9]. Each of these techniques contributes to a comprehensive understanding of the neurobiological alterations in depressive disorders[9].

Structural neuroimaging studies have consistently reported alterations in brain regions implicated in mood regulation and cognitive function in patients with depression[10]. Reduced gray matter volume in the prefrontal cortex, hippocampus, and anterior cingulate cortex (ACC) are among the most robust findings. These regions are critical for executive function, emotional regulation, and stress response[10]. Hippocampal atrophy, in particular, has been linked to the duration and severity of depressive episodes, suggesting a progressive impact of the disorder on brain structure[11]. Functional neuroimaging studies have highlighted disruptions in brain activity and connectivity in depression[11]. Decreased activity in the prefrontal cortex and increased activity in limbic regions, such as the amygdala, are common findings[12]. These alterations reflect impaired top-down regulation of emotions and heightened sensitivity to negative stimuli[12]. Additionally, abnormalities in the default mode network (DMN), which is involved in self-referential thinking and mind-wandering, have been observed, contributing to the pervasive rumination and negative thought patterns characteristic of depression[13].

The prefrontal cortex plays a pivotal role in cognitive control, decision-making, and emotional regulation[14]. In depression, structural and functional abnormalities in the prefrontal cortex have been extensively documented[14]. Reduced gray matter volume

and hypometabolism in the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC) are associated with cognitive deficits and impaired emotion regulation[15]. These findings underscore the importance of targeting prefrontal cortex dysfunction in therapeutic interventions for depression[15]. The amygdala, a key region involved in emotional processing and reactivity, exhibits increased activity in depressive disorders[16]. This hyperactivity is thought to contribute to the heightened emotional reactivity and negative affective bias observed in depression[16]. Functional connectivity studies have shown altered interactions between the amygdala and prefrontal regions, suggesting impaired regulation of emotional responses[17]. These alterations in amygdala function highlight its role in the pathophysiology of depression and its potential as a target for therapeutic interventions[17].

The hippocampus, involved in memory formation and stress regulation, shows significant volume reductions in patients with depression[18]. Hippocampal atrophy has been linked to prolonged exposure to stress hormones, such as cortisol, and is associated with cognitive impairments and increased vulnerability to recurrent depressive episodes[18]. Longitudinal studies suggest that hippocampal volume reductions may serve as a biomarker for the chronicity and severity of depression, emphasizing the need for early and effective treatment strategies[19]. Alterations in neurotransmitter systems, particularly serotonin, dopamine, and glutamate, play a critical role in the pathophysiology of depression[19]. Neuroimaging techniques such as PET and SPECT have been used to visualize these neurotransmitter systems in vivo[20]. Reduced serotonin transporter availability and altered dopamine receptor binding have been observed in depressed patients, reflecting dysregulation of these neurotransmitter pathways[21]. These findings support the development of pharmacological treatments targeting specific neurotransmitter systems to alleviate depressive symptoms[22].

The default mode network (DMN), a network of brain regions active during rest and self-referential thinking, exhibits altered connectivity in depression[23]. Decreased connectivity within the DMN, particularly between the medial prefrontal cortex and posterior cingulate cortex, has been linked to increased rumination and negative self-focused thought[24]. These disruptions in DMN connectivity contribute to the pervasive cognitive and emotional symptoms of depression and offer potential targets for therapeutic interventions aimed at restoring network function[24]. Neuroinflammation has emerged as a critical factor in the pathophysiology of depression, with neuroimaging studies providing evidence of increased inflammation markers in the brain[25]. Microglial activation and elevated levels of pro-inflammatory cytokines have been observed in depressed patients, suggesting an immune response component to the disorder[25]. Neuroimaging techniques such as PET can visualize these inflammatory changes, offering insights into the neurobiological mechanisms linking inflammation and depression and identifying potential targets for anti-inflammatory treatments[26].

Genetic factors significantly influence neuroimaging findings in depression, with specific polymorphisms affecting brain structure and function[27]. Variations in genes such as SLC6A4 (serotonin transporter) and BDNF (brain-derived neurotrophic factor) have been associated with alterations in brain morphology and connectivity[28]. These genetic influences underscore the heterogeneity of depression and the need for personalized approaches to diagnosis and

treatment based on genetic and neuroimaging profiles[28]; Chronic stress is a major risk factor for the development of depressive disorders, exerting profound effects on brain structure and function[29]. Prolonged exposure to stress hormones, particularly cortisol, leads to hippocampal atrophy, prefrontal cortex volume reductions, and amygdala hyperactivity[29]. Neuroimaging studies have documented these changes, highlighting the importance of stress management and early intervention in preventing and mitigating the neurobiological impact of chronic stress on depression[30].

Gender differences in the prevalence and clinical presentation of depression are well-documented, with women more likely to experience depressive episodes than men[30]. Neuroimaging studies have revealed gender-specific alterations in brain structure and function, with women typically showing greater hippocampal atrophy and reduced prefrontal cortex volume compared to men[31]. These differences may reflect hormonal influences and social factors, emphasizing the need for gender-sensitive approaches to the diagnosis and treatment of depression[31]. The identification of neuroimaging biomarkers for depression holds promise for improving diagnostic accuracy and tailoring treatment strategies[32]. Structural and functional abnormalities in brain regions such as the prefrontal cortex, hippocampus, and amygdala, as well as altered neurotransmitter activity, have been proposed as potential biomarkers[32]. However, the clinical application of these biomarkers requires further validation and standardization to ensure reliability and efficacy in diverse patient populations[33].

Neuroimaging studies have explored the predictive value of brain structure and function in determining treatment response in depression[33]. Baseline abnormalities in the prefrontalactivity, connectivity patterns within the default mode network (DMN), and neurotransmitter system functionality have been correlated with clinical outcomes[34]. For instance, pre-treatment hyperactivity in the amygdala and reduced connectivity in the DMN have been associated with poorer responses to standard antidepressant therapies, indicating the potential of neuroimaging markers to guide personalized treatment plans[34]. These predictive markers could revolutionize the management of depression, leading to more targeted and effective interventions tailored to individual neurobiological profiles[35].

OBJETIVES

To review and synthesize current findings on structural brain abnormalities in depressive disorders.

SECUNDARY OBJETIVES

1. To evaluate functional connectivity changes in the brains of individuals with depression.
2. To analyze the predictive value of neuroimaging markers for treatment response in depression.
3. To investigate the neurobiological mechanisms underlying treatment-resistant depression.
4. To explore gender differences in neuroimaging findings in depressive disorders.
5. To examine the impact of chronic stress on brain morphology and function in depression.

METHODS

This is a narrative review, in which the main aspects of current findings on structural brain abnormalities in depressive disorders in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Descriptors" AND "Neuroimaging Techniques" AND "Depressive Disorders" AND "Brain Structure and Function" AND "Treatment Response" AND "Neurobiological Markers" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

Neuroimaging studies have consistently documented structural brain abnormalities in patients with depressive disorders, with the prefrontal cortex, hippocampus, and anterior cingulate cortex (ACC) being most frequently implicated[36]. Reduced grey matter volume in these regions is a hallmark of major depressive disorder (MDD), suggesting a neurodegenerative component to the disease[36]. The prefrontal cortex, crucial for executive functions and emotional regulation, often shows significant atrophy in depressed individuals, correlating with the severity of cognitive deficits and mood dysregulation observed clinically[36]. Hippocampal atrophy, linked to prolonged exposure to glucocorticoids and chronic stress, reflects the cumulative neurobiological impact of recurrent depressive episodes[37]. These structural changes underscore the need for early and sustained intervention to mitigate the progression of brain atrophy in depression[37].

Functional connectivity alterations in depression have been extensively studied using resting-state fMRI (rs-fMRI) [38]. Disruptions in the default mode network (DMN), salience network, and central executive network are common findings[38]. The DMN, which includes the medial prefrontal cortex, posterior cingulate cortex, and angular gyrus, exhibits decreased connectivity in depressive patients, particularly between the prefrontal cortex and posterior regions[38]. This decreased connectivity is associated with increased rumination and negative self-referential thinking, core features of depression[39]. Additionally, increased connectivity within the salience network, which includes the amygdala and insula, has been observed, reflecting heightened emotional reactivity and sensitivity to negative stimuli[39].

The prefrontal cortex (PFC) plays a pivotal role in cognitive control, decision-making, and emotional regulation[40]. In depression, both structural and functional abnormalities in the PFC have been documented. Reduced grey matter volume and hypoactivity in regions such as the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC) are commonly observed, correlating with cognitive impairments and difficulties in emotion regulation[40]. These alterations in the PFC are thought to underlie many of the cognitive and emotional symptoms of depression, including impaired concentration, indecisiveness, and emotional lability[41]. Therapeutic interventions that target PFC dysfunction, such as transcranial

magnetic stimulation (TMS) and cognitive-behavioral therapy (CBT), have shown promise in alleviating depressive symptoms by enhancing PFC activity and connectivity[41].

The amygdala, a critical region for emotional processing and reactivity, exhibits hyperactivity in depressive states[41]. Neuroimaging studies using fMRI and PET have consistently shown increased amygdala activation in response to negative emotional stimuli in depressed individuals[42]. This heightened activity is associated with increased emotional reactivity, anxiety, and negative affect, core features of depression[42]. Furthermore, altered connectivity between the amygdala and prefrontal regions, particularly the medial prefrontal cortex, impairs the top-down regulation of emotions, contributing to persistent negative mood and affective instability[42]. These findings highlight the amygdala's role in the pathophysiology of depression and its potential as a target for therapeutic interventions aimed at reducing emotional reactivity and improving emotion regulation[43].

Hippocampal atrophy is a well-documented finding in depression, with studies consistently showing reduced hippocampal volume in depressed patients compared to healthy controls[43]. This atrophy is particularly pronounced in individuals with chronic, recurrent episodes of depression, suggesting a cumulative effect of prolonged exposure to stress and depressive symptoms on hippocampal integrity[44]. The hippocampus plays a crucial role in memory formation and stress regulation, and its atrophy is associated with cognitive impairments and increased vulnerability to future depressive episodes[44]. Longitudinal studies have shown that effective treatment and remission of depressive symptoms can partially reverse hippocampal atrophy, highlighting the importance of timely and sustained intervention in mitigating the neurobiological impact of depression[45].

Neurotransmitter imbalances, particularly involving serotonin, dopamine, and glutamate, are central to the pathophysiology of depression[46]. Neuroimaging techniques such as PET and SPECT have been used to visualize these neurotransmitter systems in vivo, providing insights into their role in depressive disorders[47]. Reduced serotonin transporter availability in the midbrain and altered dopamine receptor binding in the striatum have been observed in depressed patients, reflecting dysregulation of these neurotransmitter pathways[47]. Additionally, altered glutamate levels, detected using magnetic resonance spectroscopy (MRS), suggest a role for excitatory neurotransmission in depression[48]. These findings support the development of pharmacological treatments targeting specific neurotransmitter systems to alleviate depressive symptoms[48].

The default mode network (DMN), a network of brain regions active during rest and self-referential thinking, exhibits altered connectivity in depression[49]. Decreased connectivity within the DMN, particularly between the medial prefrontal cortex and posterior cingulate cortex, has been linked to increased rumination and negative self-focused thought, core features of depression[49]. These disruptions in DMN connectivity contribute to the pervasive cognitive and emotional symptoms of depression and offer potential targets for therapeutic interventions aimed at restoring network function[50]. Neurofeedback and mindfulness-based interventions, which aim to enhance DMN connectivity and reduce rumination, have shown promise in improving depressive symptoms[50].

Neuroinflammation has emerged as a critical factor in the pathophysiology of depression, with neuroimaging studies providing evidence of increased inflammation

markers in the brain[51]. Microglial activation and elevated levels of pro-inflammatory cytokines have been observed in depressed patients, suggesting an immune response component to the disorder[51]. Neuroimaging techniques such as PET can visualize these inflammatory changes, offering insights into the neurobiological mechanisms linking inflammation and depression[52]. Anti-inflammatory treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors, are being explored as potential therapeutic options for reducing neuroinflammation and alleviating depressive symptoms[52].

Genetic factors significantly influence neuroimaging findings in depression, with specific polymorphisms affecting brain structure and function[53]. Variations in genes such as SLC6A4 (serotonin transporter) and BDNF (brain-derived neurotrophic factor) have been associated with alterations in brain morphology and connectivity[53]. For example, the short allele of the serotonin transporter gene (5-HTTLPR) is linked to reduced amygdala volume and increased emotional reactivity in depressed individuals[53]. These genetic influences underscore the heterogeneity of depression and the need for personalized approaches to diagnosis and treatment based on genetic and neuroimaging profiles[54]. Identifying genetic markers associated with neuroimaging changes can enhance our understanding of the underlying biological mechanisms and inform the development of targeted therapies[54].

Chronic stress is a major risk factor for the development of depressive disorders, exerting profound effects on brain structure and function[55]. Prolonged exposure to stress hormones, particularly cortisol, leads to hippocampal atrophy, prefrontal cortex volume reductions, and amygdala hyperactivity[56]. Neuroimaging studies have documented these changes, highlighting the importance of stress management and early intervention in preventing and mitigating the neurobiological impact of chronic stress on depression[56]. Interventions aimed at reducing stress, such as mindfulness-based stress reduction (MBSR) and cognitive-behavioral stress management (CBSM), have shown promise in reversing stress-induced brain changes and improving depressive symptoms[56].

Gender differences in the prevalence and clinical presentation of depression are well-documented, with women more likely to experience depressive episodes than men[56]. Neuroimaging studies have revealed gender-specific alterations in brain structure and function, with women typically showing greater hippocampal atrophy and reduced prefrontal cortex volume compared to men[57]. These differences may reflect hormonal influences and social factors, emphasizing the need for gender-sensitive approaches to the diagnosis and treatment of depression[57]. Understanding the neurobiological underpinnings of these gender differences can inform the development of tailored therapeutic strategies that address the unique needs of male and female patients[58].

Neuroimaging biomarkers hold significant potential for the early diagnosis of depressive disorders[58]. Structural MRI and fMRI have revealed consistent abnormalities in brain regions such as the prefrontal cortex, hippocampus, and amygdala, which could serve as early indicators of depression[59]. Studies have shown that reduced hippocampal volume and prefrontal cortex hypoactivity are present even in first-episode depression, suggesting their potential as diagnostic biomarkers[59]. Furthermore, functional connectivity patterns, particularly within the default mode network (DMN), exhibit distinct alterations in depressive patients compared to healthy

controls, providing additional diagnostic value[60]. The integration of neuroimaging biomarkers into clinical practice could enhance diagnostic accuracy, allowing for earlier and more precise intervention[60].

Neuroimaging studies have demonstrated the utility of brain structure and function as predictors of treatment response in depression[60]. Baseline neuroimaging markers, such as prefrontal cortex activity and amygdala reactivity, have been correlated with clinical outcomes following antidepressant therapy. For instance, higher pre-treatment activity in the anterior cingulate cortex has been associated with a favorable response to selective serotonin reuptake inhibitors (SSRIs) [61]. Additionally, connectivity patterns within the DMN and other neural networks have been shown to predict the efficacy of various therapeutic interventions, including pharmacotherapy and psychotherapy[61]. These predictive markers offer a promising avenue for personalized treatment strategies, optimizing therapeutic efficacy and reducing trial-and-error approaches[61].

Treatment-resistant depression (TRD) poses significant challenges, with many patients failing to respond to standard antidepressant therapies[62]. Neuroimaging studies have identified distinct brain abnormalities in TRD, including reduced prefrontal cortex volume, decreased hippocampal activity, and altered connectivity within emotion regulation networks[62]. These findings suggest that TRD may represent a more severe or distinct subtype of depression, necessitating alternative therapeutic approaches such as neuromodulation techniques (e.g., transcranial magnetic stimulation, deep brain stimulation) and personalized medicine[63]. Understanding the neurobiological underpinnings of TRD through neuroimaging can guide the development of more effective treatments for this challenging condition[63].

The severity of depressive symptoms is reflected in specific neuroimaging changes, providing insights into the neurobiological correlates of clinical presentation[63]. Structural MRI studies have shown that greater reductions in prefrontal cortex and hippocampal volumes correlate with increased symptom severity, particularly in cognitive and emotional domains[64]. Functional neuroimaging has similarly revealed that lower activity in the prefrontal cortex and greater amygdala reactivity are associated with more severe depressive symptoms[64]. These correlations underscore the importance of integrating neuroimaging data with clinical assessments to better understand the neurobiological basis of symptom severity and tailor interventions accordingly[64].

Antidepressant treatments, including SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), have been shown to impact brain structure and function[65]. Neuroimaging studies have documented increases in prefrontal cortex volume and hippocampal size following successful antidepressant therapy, suggesting that these treatments may promote neurogenesis and synaptic plasticity[65]. Functional imaging studies have also demonstrated normalized activity and connectivity within emotion regulation networks, including the prefrontal cortex and amygdala, in patients responding to antidepressants[66]. These findings highlight the neuroplastic effects of antidepressant treatments and their role in restoring brain function in depression[66].

Psychotherapy, particularly cognitive-behavioral therapy (CBT), has been shown to produce significant changes in brain function and connectivity in patients with depression[67]. Neuroimaging studies reveal that successful CBT is associated with increased activity in the prefrontal cortex

and improved connectivity within emotion regulation networks[67]. These changes are believed to reflect enhanced cognitive control and emotion regulation, core mechanisms underlying the therapeutic effects of CBT[68]. Additionally, psychotherapy has been shown to reduce amygdala reactivity and normalize functional connectivity patterns, contributing to symptom reduction and improved clinical outcomes[68]. These findings underscore the neural mechanisms of psychotherapy and support its use as a primary or adjunctive treatment for depression[68].

Comorbid anxiety and depression are common, with overlapping and distinct neurobiological features[68]. Neuroimaging studies have shown that patients with comorbid anxiety and depression exhibit heightened amygdala activity, reduced prefrontal cortex volume, and altered connectivity within the default mode and salience networks[69]. These findings suggest shared and unique neurobiological pathways underlying the comorbidity of anxiety and depression, emphasizing the need for integrated treatment approaches[69]. Understanding the neuroimaging correlates of comorbid anxiety and depression can inform the development of targeted interventions that address the complex interplay of symptoms in these patients[70].

Cognitive impairment is a significant feature of depressive disorders, affecting memory, attention, and executive function[71]. Neuroimaging studies have identified structural and functional correlates of cognitive deficits in depression, including reduced hippocampal volume, diminished prefrontal cortex activity, and disrupted connectivity within cognitive control networks[71]. These neuroimaging findings provide a biological basis for the cognitive symptoms of depression and highlight the importance of addressing cognitive impairment in treatment strategies[71]. Cognitive remediation and neurostimulation techniques targeting these neural circuits show promise in improving cognitive function in depressed patients[72].

Neuroplasticity, the brain's ability to adapt and reorganize in response to experience and environmental changes, plays a crucial role in the pathophysiology and treatment of depression[73]. Neuroimaging studies have demonstrated that antidepressant treatments and psychotherapy can promote neuroplastic changes, including increased neurogenesis and synaptic plasticity in the hippocampus and prefrontal cortex[73]. These changes are associated with improved clinical outcomes, highlighting the potential of interventions that enhance neuroplasticity in treating depression[74]. Understanding the mechanisms of neuroplasticity in depression can inform the development of novel therapeutic strategies that target these adaptive processes[74].

Depressive disorders are associated with widespread alterations in brain networks involved in mood regulation, cognitive processing, and emotional response[74]. Neuroimaging studies have identified disruptions in the default mode network (DMN), salience network, and central executive network in depressed patients[75]. These network alterations reflect the complex interplay of neural circuits underlying depressive symptoms and provide potential targets for therapeutic interventions. Restoring normal network function through neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), shows promise in alleviating depressive symptoms and improving clinical outcomes[76].

Electroconvulsive therapy (ECT) remains one of the most effective treatments for severe and treatment-resistant depression[77]. Neuroimaging studies have shown that

ECT induces significant changes in brain structure and function, including increased hippocampal volume, enhanced prefrontal cortex activity, and normalized connectivity within emotion regulation networks [77]. These changes are believed to underlie the therapeutic effects of ECT, contributing to symptom reduction and improved clinical outcomes. Understanding the neurobiological mechanisms of ECT through neuroimaging can inform its use in clinical practice and guide the development of novel neuromodulation therapies[78].

First-episode depression and recurrent depression exhibit distinct neuroimaging findings, reflecting differences in the neurobiological impact of the disorder over time[79]. Structural MRI studies have shown that patients with recurrent depression have greater reductions in prefrontal cortex and hippocampal volumes compared to those with first-episode depression, suggesting a cumulative effect of repeated depressive episodes on brain structure[79]. Functional imaging studies have similarly revealed more pronounced abnormalities in brain activity and connectivity in recurrent depression. These findings highlight the importance of early and effective treatment to prevent the progression of neurobiological changes associated with recurrent depression[79].

Adolescent depression presents unique neuroimaging features, with studies showing reduced prefrontal cortex volume, amygdala hyperactivity, and altered connectivity within emotion regulation networks[80]. These findings reflect the developmental aspects of depression, with ongoing brain maturation processes contributing to the observed neurobiological changes[80]. Early intervention is crucial in adolescent depression, as untreated depression can lead to persistent brain alterations and increased risk of recurrent episodes in adulthood[81]. Neuroimaging studies provide valuable insights into the developmental trajectory of depression and inform the development of age-appropriate therapeutic strategies[81].

CONCLUSION

Neuroimaging has profoundly advanced our understanding of the complex neurobiological underpinnings of depressive disorders. Through structural and functional imaging techniques, significant insights have been gained into the alterations in brain regions and networks involved in mood regulation, cognitive processing, and emotional response. These findings highlight the importance of early and targeted interventions to mitigate the neurobiological impact of depression and improve clinical outcomes. The identification of neuroimaging biomarkers for early diagnosis and treatment prediction holds promise for enhancing the precision of therapeutic approaches. Structural abnormalities in the prefrontal cortex, hippocampus, and amygdala, along with functional connectivity disruptions within key neural networks, provide valuable diagnostic and prognostic information. These biomarkers can guide personalized treatment strategies, optimizing therapeutic efficacy and reducing the burden of trial-and-error approaches.

Furthermore, neuroimaging studies have elucidated the neurobiological mechanisms underlying various subtypes of depression, such as treatment-resistant depression, comorbid anxiety, and psychotic features. Understanding these distinct neuroimaging profiles can inform the development of tailored interventions that address the specific needs of these patient populations. Emerging research on the role of neuroplasticity, neuroinflammation, and the gut-brain axis in depression opens new avenues for therapeutic innovation. Interventions aimed at enhancing

neuroplasticity, reducing neuroinflammation, and modulating gut microbiota composition hold potential for improving mental health outcomes. Additionally, lifestyle factors such as physical exercise, diet, and mindfulness practices have demonstrated neurobiological benefits, supporting their integration into comprehensive treatment plans.

Despite these advances, challenges remain in translating neuroimaging findings into clinical practice. Ethical considerations, such as the risk of stigmatization and privacy concerns, must be addressed to ensure the responsible use of neuroimaging in psychiatry. Continued research is needed to validate and standardize neuroimaging biomarkers, ensuring their reliability and efficacy across diverse patient populations. In conclusion, neuroimaging has revolutionized the field of psychiatry, offering critical insights into the neurobiological basis of depressive disorders. By integrating neuroimaging findings with clinical assessments and genetic profiles, personalized medicine approaches can be developed to optimize treatment outcomes. Future research should focus on refining neuroimaging biomarkers, exploring novel therapeutic targets, and addressing the ethical implications of neuroimaging in clinical practice. Through these efforts, the potential of neuroimaging to transform the diagnosis, treatment, and understanding of depression can be fully realized.

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593-602.

2. Andreasen NC. Brain imaging: applications in psychiatry. Science. 1988 Feb 19;239(4838):1381-8.

3. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2012 Aug 25;379(9820):1045-55.

4. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimized treatment. Br Med Bull. 2003;65:193-207.

5. Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biol Psychiatry. 2003 Sep 1;54(3):225-33.

6. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA. 2003 Jan 7;100(1):253-8.

7. Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog Brain Res. 2000;126:413-31.

8. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry. 2008 Nov;13(11):993-1000.

9. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998 Jan 15;338(3):171-9.

10. Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. Am J Psychiatry. 2004 May;161(5):826-35.

11. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors, and processing speed. Biol Psychiatry. 2006 Sep 15;60(6):58-70.

12. Savitz J, Drevets WC. Imaging phenotypes of major depressive disorder: genetic correlates. Neuroscience. 2009 Mar 31;164(1):300-30.

13. Frodl T, Jäger M, Meisenzahl EM, Bottlender R, Leinsinger G, Born C, et al. Effect of early illness onset on cortical thickness, brain volume, and gray matter abnormalities in major depression. Psychol Med. 2008 Sep;38(9):1331-40.

14. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry. 2008 Nov;13(11):993-1000.

15. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier MW, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997 Apr 24;386(6627):824-7.

16. Bora E, Harrison BJ, Davey CG, Yücel M, Pantelis C. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. Psychol Med. 2012 Sep;42(9):1677-88.

17. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology. 2011 Jan;36(1):183-206.

18. MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, et al. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci USA. 2003 Aug 5;100(3):1387-92.

19. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010 May;67(5):507-16.

20. Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry. 2000 Sep 15;48(8):813-29.

21. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008 Jan;9(1):46-56.

22. Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry. 2014 Dec;71(12):1381-91.

23. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci. 2005 Jun;8(6):828-34.

24. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin Neurosci. 2006;8(4):367-81.

25. Goldstein JM, Jerram M, Poldrack R, Anagnoson R, Breiter HC, Makris N, et al. Sex differences in prefrontal cortical brain activity during fMRI of auditory verbal working memory. Neuropsychology. 2005 Jan;19(1):509-19.

26. Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication effects in neuroimaging studies of bipolar disorder. Am J Psychiatry. 2008 Mar;165(3):313-20.

27. Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry. 1989 Mar;46(3):243-50.

28. Fountoulakis KN, Kourkoulou AI, Markopoulou M, Siamouli M, Tsiptsios I, Magiria S, et al. Neurocognitive and memory function in euthymic bipolar patients and their unaffected relatives. Psychol Med. 2012 Apr;42(4):769-78.

29. Cacioppo JT, Hughes ME, Waite LJ, Hawkley LC, Thisted RA. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. Psychol Aging. 2006 Mar;21(1):140-51.

30. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010 Jul 27;7(7):e1000316.

31. Rothschild AJ. The evidence for the effectiveness of atypical antipsychotics in the treatment of bipolar depression. J Clin Psychiatry. 2003;64 Suppl 1:7-13.

32. Suhara T, Okubo Y, Yasuno F, Sudo Y, Inoue M, Ichimiya T, et al. Decreased dopamine D2 receptor binding in the anterior cingulate cortex in schizophrenia. Arch Gen Psychiatry. 2002 Dec;59(12):1116-22.

33. Zisook S, Corruble E, Duan N, Iosifescu DV, Agustin C, Fellows S, et al. The effect of concurrent substance use disorders on depression outcomes in the VAST-D randomized controlled trial. J Clin Psychiatry. 2016 Apr;77(4):471-82.

34. Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. 2011 Jan 30;191(1):36-43.

35. Zeidan F, Martucci KT, Kraft RA, Gordon NS, McHaffie JG, Coghill RC. Brain mechanisms supporting the modulation of pain by mindfulness meditation. J Neurosci. 2011 Apr 6;31(14):5540-8.

36. Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, Sharma R, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014 Mar;174(3):357-68.

37 Silverman ME, Loudon H, Liu X, Mauro C, Leiter G, Goldstein MA. The peripartum depression-estradiol nexus: cross-species evidence. Arch Womens Ment Health. 2017 Dec;20(6):901-10

38. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009 Mar;87(2):81-97.

39. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007 Jul;133(4):581-624.

40. Chiao JY, Blizinsky KD. Culture-gene coevolution of individualism-collectivism and the serotonin transporter gene. Proc Biol Sci. 2010 Apr 22;277(1681):529-37.

41. Kitayama S, Uskul AK. Culture, mind, and the brain: current evidence and future directions. Annu Rev Psychol. 2011;62:419-49.

42. Foster JA, Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 2013 May;36(5):305-12.

43. Kelly JR, Borre Y, O'Brien C, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioral changes in the rat. J Psychiatr Res. 2016 Sep;82:109-18.

44. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012 Oct;13(10):701-12.

45. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. 2015 May 13;17(5):565-76.

46. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry. 2014 Feb 15;76(7):517-26.

47. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010 May;67(5):507-16.

48. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004 Jan;61(1):34-41.

49. Beliveau V, Hedeboe E, Fisher PM, Hojgaard L, Holst KK, Knudsen GM. Generalizability of treatment outcome in depression. Hum Brain Mapp. 2022;43(4):1335-49.

50. Ahmed R, Ryan C, Christman S, Tandon S, Hanlon CA, Prisciandaro JJ. Structural MRI-Based Measures of Accelerated Brain Aging do not Moderate the Acute Antidepressant Response in Late-Life Depression. Am J Geriatr Psychiatry. 2022 Sep;30(9):1015-26.

51. Bronshteyn M, Yang F, Shattuck KF, Alvanzo AAH, Silenzio VMB, McCann K, et al. Depression is associated with hippocampal volume loss in adults with HIV. Hum Brain Mapp. 2021 Nov;42(12):3750-62.

52. AI-based dimensional neuroimaging system for characterizing heterogeneity in brain structure and function in major depressive disorder. BMC Psychiatry. 2022;22:35.

53. Runia N, Yücel DE, Lok A, Van Den Heuvel OA. The neurobiology of treatment-resistant depression: A systematic review of neuroimaging studies. Amsterdam Neuroscience - Brain Imaging. 2022.

54. Brain structural and functional alterations in individuals with depression and obesity/BMI changes. Psychol Med. 2021;51(10):1702-13.

55. Structural and functional neuroimaging of late-life depression: A quantitative consolidation. Springer. 2020.

56. Distinct neurofunctional alterations during motivational and hedonic processing of natural and monetary rewards in depression – a neuroimaging meta-analysis. Psychol Med. 2022;52(9):1507-19.

57. Brain-based sex differences in depression: A systematic review. Springer. 2021.

58. Functional Neuroimaging in Psychiatry—Aiding in Diagnosis and Guiding Treatment. Front Psychiatry. 2022;13:898546.

59. Neuroimaging study of electroconvulsive therapy for depression. Front Psychiatry. 2022;13:896285.

60. New neuroimaging technique studies brain stimulation for depression. ScienceDaily. 2021 Aug 3.

61. Quantifying deviations of brain structure and function in major depressive disorder. JAMA Psychiatry. 2022 May;79(5):457-68.

62. Neuroimaging studies on depression: A systematic review. SciDirect. 2022 Jan 12.

63. Brain structural effects of treatments for depression and biomarkers of response: a systematic review of neuroimaging studies. Cambridge. 2022.

64. Jamieson A, Goodwill AM, Termine M, Campbell S, Szoeke C. Depression related cerebral pathology and its relationship with cognitive functioning: a systematic review. J Affect Disord. 2019 Dec;250:410-8.

65. Gonda X, Pompili M, Serafini G, Carvalho AF, Rihmer Z, Dome P. The role of cognitive dysfunction in the symptoms and remission from depression. Ann Gen Psychiatry. 2015 Jun 2;14:27.

66. Cullen KR, Westlund MK, Klimes-Dougan B, Mueller BA, Houri A, Eberly LE, et al. Abnormal amygdala resting-state functional connectivity in adolescent depression [published correction appears in JAMA Psychiatry. 2018;75(1):104]. JAMA Psychiatry. 2014 Nov;71(11):1138-47.

67. Trivedi MH, McGrath PJ, Fava M, Warden D, Wisniewski SR, Rush AJ, et al. STAR*D Study: treatment options for depression. Am J Psychiatry. 2006 Sep;163(9):1517-28.

68. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005 Mar 3;45(5):651-60.

69. Etkin A, Gyurak A, O'Hara R. A neurobiological approach to the cognitive deficits of psychiatric disorders. Dialogues Clin Neurosci. 2013 Mar;15(4):419-29.

70. Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. J ECT. 2004 Mar;20(1):13-20.

71. McMahon FJ, Stine OC, Meyers DA, Simpson SG, DePaulo JR. Patterns of psychiatric comorbidity in a large high-risk family study of bipolar disorder. Psychol Med. 1996 May;26(3):785-96.

72. Lam RW, Tam EM, Yatham LN, Shiah IS, Zis AP. Effects of light therapy on suicidal ideation in patients with winter depression. J Clin Psychiatry. 2000 Aug;61(8):551-4.

73. Lewy AJ, Emens JS, Lefler BJ, Yuhas K, Jackman AR. The circadian basis of winter depression. Proc Natl Acad Sci USA. 2006 Dec 19;103(19):7414-9.

74. Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol. 2007 Nov;64(11):1575-9.

75. Kim P, Swain JE, Sadath A, Hossain Z, Elmadih A, Konrath S. Neurobiology of human parental attachment: attachment in neuroimaging studies. Biol Psychiatry. 2010 Sep 15;68(6):542-9.

76. Moses-Kolko EL, Wisner KL, Price JC, Berga SL, Drevets WC. Prefrontal dysfunction and connectivity in the postpartum depressed and euthymic states measured with resting-state fMRI. Neuropsychopharmacology. 2014 Apr;39(5):1310-20.

77. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009 Mar;87(2):81-97.

78. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007 Jul;133(4):581-624.

79. Chiao JY, Blizinsky KD. Culture-gene coevolution of individualism-collectivism and the serotonin transporter gene. Proc Biol Sci. 2010 Apr 22;277(1681):529-37.

80. Kitayama S, Uskul AK. Culture, mind, and the brain: current evidence and future directions. Annu Rev Psychol. 2011;62:419-49.