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Review Paper

Neuroplasticity in Major Depressive Disorder: A Systematic Review of Current Insights and Treatment Implications

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ABSTRACT

Major Depressive Disorder (MDD) is associated with impaired Neuroplasticity, which may be essential in understanding the neuroplastic mechanisms underlying MDD in order to improve diagnosis and treatment strategies. This review helps in the synthesis of evidence from recent studies exploring cortical excitability, biomarkers of treatment response, molecular modulation, and structural Neuroplasticity in depression. Findings show that individuals with MDD may exhibit altered cortical inhibition and facilitation compared to healthy controls, with evidence of impaired plasticity in the dorsolateral prefrontal cortex (DLPFC). Neuroplasticity-based measures, such as Transcranial Magnetic Stimulation TMS-evoked potentials, gamma power modulation, and Repetitive Transcranial Magnetic Stimulation rTMS-induced functional connectivity, show potential for treatment prediction. Pharmacological studies highlight serotonergic and noradrenergic modulation roles in enhancing plasticity, while ketamine-induced changes and magnetic seizure therapy provide insights into adaptations in Neuroplasticity. Structural studies reveal hippocampal and cortical thickness alterations, while behavioural interventions like exercise may promote neurocognitive benefits linking to Neuroplasticity. Collectively, the evidence underscores the multifaceted role of Neuroplasticity in MDD and the treatment implications.

Keywords: *Major Depressive Disorder, Neuroplasticity, Repetitive Transcranial Magnetic Stimulation, Transcranial Magnetic Stimulation*

Neuroplasticity is "the ability of the nervous system to modify its activity in response to internal or external stimuli by reorganizing its structure, functions, or connections." (Mateos-Aparicio & Rodríguez-Moreno, 2019). Neuroplasticity is a refers to the neural framework in which various internal processes lead to changes in neurons at both molecular and systemic levels (Serafini, 2012). Neural circuits, brain nuclei, neurons, and synaptic connections experience numerous modifications and significant adaptations throughout life due to environmental influences via mechanisms of neural

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plasticity. Ongoing changes result in the formation of new synapses and the retrogressive removal of existing synapses, alongside alterations in the dendritic tree and spine density that affect the quantity of postsynaptic sites (Serafini, 2012).

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition text revision (DSM-5 TR), Major Depressive Disorder is characterized by the occurrence of at least one major depressive episode without any prior episodes of mania or hypomania. The key aspect of a major depressive episode is the presence of a period lasting a minimum of 2 weeks marked by either a persistently low mood or a noticeable decrease in interest or enjoyment in nearly all activities for most of the day, nearly every day. Additionally, the individual must exhibit at least four other symptoms during this same 2-week timeframe, which can include alterations in appetite or weight, sleep disturbances, and changes in psychomotor activity; reduced energy levels; feelings of worthlessness or excessive guilt; difficulties with thinking, focusing, or making decisions; or thoughts related to death, including suicidal ideation, previous suicide attempts, or a formulated plan for suicide. Depression represents a significant health challenge characterized by a high prevalence and considerable socioeconomic impact in Western societies. It is linked to the shrinkage and impaired function of cortico-limbic areas that regulate mood and emotions. It has been proposed that changes in neurotrophins contribute to diminished neuroplasticity, which may play a causal role in the onset and progression of depression. (Levy et al., 2018). Research has revealed a decline in neuroplasticity among individuals suffering from depression, as well as in animals exposed to stress or various models of depression. Neuroimaging studies have demonstrated that individuals with major depressive disorder (MDD) show reductions in brain volume and diminished connectivity within the prefrontal cortex (PFC) and hippocampus (Evans et al., 2018; MacQueen and Frodl, 2011; Savitz and Drevets, 2009 as cited in Xu et al., 2025). Additionally, some studies have reported alterations in the anterior cingulate cortex, striatum, and amygdala (Gerhard et al., 2016; Gujral et al., 2017 as cited in Xu et al., 2025).

METHODOLOGY

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines. The authors searched from two major databases were PubMed and Google Scholar. The following search terms were used for searching for the articles, which were ‘Neuroplasticity’, ‘Neural Plasticity’, ‘Major Depressive Disorder’, ‘Depression’, ‘Repetitive Transcranial Magnetic Stimulation’, ‘rTMS’, Brain-Derived Neurotrophic Factor, ‘BDNF’, ‘Ketamine’. This approach led the author to enable more relevant articles for investigating Neuroplasticity in Major Depressive Disorder and specific terminologies under Neuroplasticity as Neuroplasticity has many terms under it, which led to the identification of 204 publications.

Article selection was carried through the following standardized protocol. The inclusion criteria encompassed the following, which were human studies involving adults aged 18 years and older who have been diagnosed with Major Depressive Disorder (MDD) according to the DSM-5, ICD-10, or similar diagnostic criteria. Studies eligible for inclusion were published in peer-reviewed journals that possess a valid International Standard Serial Number (ISSN). The primary focus was on research examining structural or functional neuroplasticity such as synaptic alterations, neurogenesis, dendritic remodelling, cortical thickness, and functional connectivity in relation to MDD. Research evaluating the effects of treatments whether pharmacological, neuromodulation, psychotherapy, exercise, or

alternative interventions on neuroplasticity in MDD were also included. Included studies must present objective assessments of Neuroplasticity, these may be but not limited to levels of neurotrophic factors in blood or cerebrospinal fluid or indices from neuroimaging, like cortical thickness, hippocampal volume, and functional connectivity. Both observational (cross-sectional, cohort, case-control) and interventional (clinical trial) research designs were accepted. To maintain relevant significance, only studies published from 2015 to 2025 were taken into account in this review. The following were the Exclusion Criteria for this review, which were studies, were excluded if they were case reports, case series, conference abstracts, editorials, or letters. Publications that lack an ISSN or that appear in non-peer-reviewed outlets such as magazines, newsletters, or blogs will be excluded. Research conducted on animals and in vitro studies without direct human data were not considered. Studies concentrating exclusively on psychiatric or neurological disorders other than MDD, without separate analysis of MDD data, were also omitted. Research that does not provide clear measures related to neuroplasticity will be left out of the review. Lastly, duplicate publications or secondary analyses that fail to present new data were excluded as well.

Study Selection and Categorization

Study selection was done through reading through the abstracts and through the inclusion and exclusion criteria. Animal studies, duplicate studies were excluded and only those which were relevant to Neuroplasticity and Major Depressive Disorder were included, as per the inclusion criteria.

Data Collection

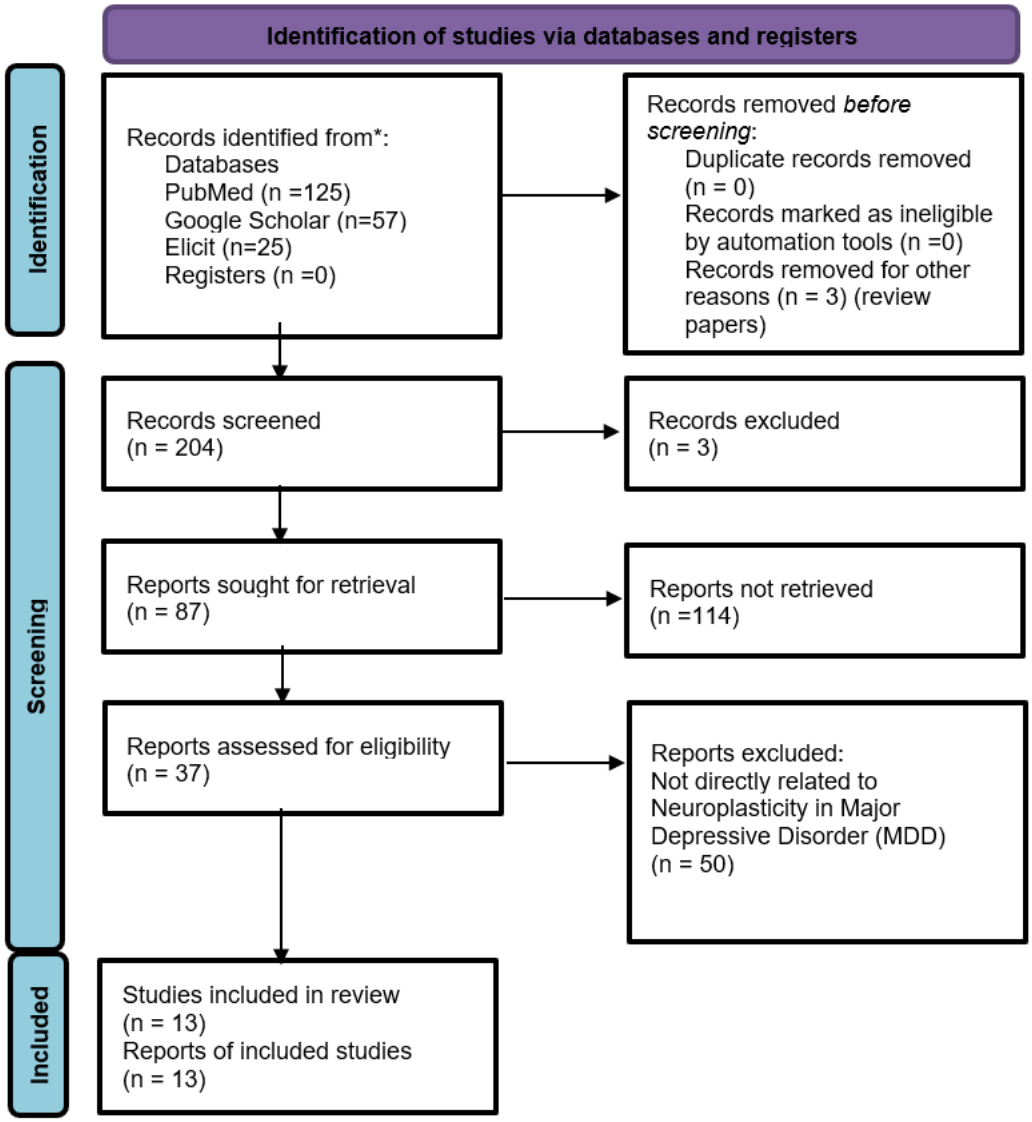
Data extraction was independently executed by the author. Each information were systematically extracted from each eligible article, including the author, year, theoretical/conceptual framework, Research Questions, hypothesis, methodology, analysis and major findings, conclusion, limitations.

RESULTS

The systematic search in online databases, which were primarily from PubMed and Google Scholar yielded in 207 articles, of which 3 were excluded as they were review papers. The 204 articles were screened, of which 3 were excluded as they were identified as duplicates. The reports sought for retrieval further were 87 articles, of which 114 articles were excluded after screening through their articles and titles. The reports which were assessed for eligibility were 39 articles of which 50 were excluded as they were not directly related to Neuroplasticity in Major Depressive Disorder (MDD) and the studies which were included in the review were 13 and reports of included studies were 13 as they met the inclusion criteria for the final analysis in this systematic review. The screening process is shown in a PRISMA flow diagram in Figure 1.

The studies contained in this review were carried out in 6 countries. Most of the studies were located in Canada (n=4), Japan (n=3), Germany (n=2), Brazil (n=2), Netherlands (n=1), United States (n=1). The articles were published mostly in the time frame between 2016 and 2024. Table 1 (see Appendix) is a summary of detailed study characteristics and critical evaluation.

Figure 1 PRISMA flowchart showing final results



Note. Source: (Page et al., 2021).

DISCUSSION

Neuroplasticity is "the ability of the nervous system to modify its activity in response to internal or external stimuli by reorganizing its structure, functions, or connections." (Mateos-Aparicio & Rodríguez-Moreno, 2019). Neuroplasticity refers to the neural framework in which various internal processes lead to changes in neurons at both molecular and systemic levels (Serafini, 2012).

According to the Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition Text Revision (DSM-5 TR), Major Depressive Disorder is characterized by the occurrence of at least one major depressive episode without any prior episodes of mania or hypomania. The key aspect of a major depressive episode is the presence of a period lasting a minimum of 2 weeks marked by either a persistently low mood or a noticeable decrease in interest or enjoyment in nearly all activities for most of the day, nearly every day. Additionally, the individual must exhibit at least four other symptoms during this same 2-week timeframe,

which can include alterations in appetite or weight, sleep disturbances, and changes in psychomotor activity; reduced energy levels; feelings of worthlessness or excessive guilt; difficulties with thinking, focusing, or making decisions; or thoughts related to death, including suicidal ideation, previous suicide attempts, or a formulated plan for suicide.

The authors have identified major themes through the systematic review of the literature on Neuroplasticity in Major Depressive Disorder.

Theme 1 – Cortical Excitability and Inhibition Dysregulation

Cardinal et al. (2019) conducted a cross-sectional exploratory study comparing the motor cortex inhibition indexed by Transcranial Magnetic Stimulation (TMS) measures Short Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF), along with measures of Descending Pain Modulatory System (DPMS) function and Brain-Derived Neurotrophic Factor (BDNF), in woman with Fibromyalgia (FM) and Major Depressive Disorder (MDD), and in Healthy Controls (HC). Their findings showed that Fibromyalgia (FM) displayed a deteriorated function in cortical inhibition, indexed by higher Short Intracortical Inhibition (SICI) parameter, which indicates reduced inhibition as compared to in Major Depressive Disorder (MDD) and in Healthy Controls (HC). They also found that there is a greater disinhibition of the Descending Pain Modulatory System (DPMS) in Fibromyalgia compared to in Major Depressive Disorder, and of the converse correlation with the Short Intracortical Inhibition (SICI) in Fibromyalgia and not seen in Major Depressive Disorder (MDD). They also showed a positive relationship between the changes in the Numerical Pain Scale (NPS) during Conditioned Pain Modulation Test (CPM-test) with a measure of neuroplasticity composed by the BDNF adjusted index, despite the clinical diagnostic. These suggest that although Fibromyalgia (FM) and Major Depressive Disorder share overlapping symptoms, their underlying neuroplastic mechanisms are quite different, whereby MDD is shown by more impaired inhibitory control within cortical circuits, whereas FM involves a deteriorated function in cortical inhibition and disinhibition in the DPMS.

Kaneko et al. (2024) conducted a study focusing on neuroplasticity in the Dorsolateral Prefrontal Cortex (DLPFC). They aimed to investigate the differences between 60 individuals who were aged between 18- 85 and were diagnosed with MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and met the criteria of Treatment –Resistant Depression (TRD) and 30 age and sex-matched Health Controls (HC). In order to induce Neuroplasticity, the participants underwent a Paired Associative Stimulation (PAS) paradigm which involved peripheral median nerve stimulation and TMS targeting the left DLPFC. The results of this study showed that the DLPFC-PAS paradigm increased the early component of TMS-evoked potentials (TEP) in the Health Control (HC) Group, which confirmed the successful induction of spike-timing-dependent plasticity in the DLPFC, although the HC group showed a greater increase in TEPs than the TRD group. Their findings provided evidence for impaired Neuroplasticity in the DLPFC of individuals with TRD Event-related spectral perturbation analysis highlighted that the gamma power significantly increased after PAS in the HC group, whereas it was decreased in the TRD group. This gamma power modulation revealed a significant group difference which indicated an inverse relationship for gamma power modulation. It also elucidated in the application of the DLPFC-PAS paradigm to the TRD to be beneficial biomarker for the early diagnosis and treatment for Major Depressive Disorder.

A study conducted by Lissemore et al. (2021), investigated the effects of Venlafaxine pharmacotherapy (≤ 300 mg/day) for 12 weeks on Cortical Inhibition, facilitation and plasticity in Late-Life Depression (LLD) using the Transcranial Magnetic Stimulation (TMS) measures in the motor cortex. The Participants were 68 older adults who were aged 60 and above with Major Depressive Disorder (MDD). They used contralateral Cortical Silent Period (cSP) and paired-pulse paradigms for inhibition or facilitation and paired associative stimulation for short-term plasticity. The findings in this study were that Venlafaxine treatment did not significantly alter cortical inhibition, facilitation, or plasticity after 1 or 12 weeks. It was suggested that age-related changes may be a significant factor driving motor cortex physiologic functioning.

Theme 2: Neuroplasticity as a Biomarker for Treatment Response

Ge et al. (2022) examined whether acute neuroplastic responses induced by acute Repetitive Transcranial Magnetic Stimulation (rTMS) – induced connectivity could predict clinical outcomes in Treatment- Resistant Depression. Cross-sectional changes in functional connectivity induced by a single concurrent rTMS-fMRI session were assessed in 38 outpatients with TRD, in which 26 of them were female of mean age 41.87 years. The participants underwent a 4-week course of rTMS. The rTMS was delivered over the right dorsolateral prefrontal cortex at 1Hz. The results of the study showed that TMS-fMRI induced widespread, transient functional connectivity changes, between prefrontal cortex, motor, parietal, and insular cortices, as well as bilateral thalamic regions. These acute connectivity alterations predicted about 30% variance in the clinical symptom improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) score after rTMS treatment. This highlights that the acute rTMS-induced connectivity changes in the outpatients with TRD, may imply macro-level neuroplasticity.

Dalhuisen et al. (2021) conducted a sham-controlled study investigating the longitudinal effects of Repetitive transcranial magnetic stimulation (rTMS) on the volumes of the hippocampus and amygdala and cortical thickness in patients with chronic Treatment – Resistant Depression (TRD). The participants were patients with a diagnosis of unipolar Major Depressive Disorder (MDD) without psychotic symptoms, with chronic for the last two years and Treatment Resistance. The results were that they found no clinical differences between the active and sham rTMS group. Longitudinal changes in hippocampal and amygdala volume did not differ significantly in the results, although males showed a significant decrease in left amygdala volume, irrespective of treatment group. Changes in cortical thickness of the Para limbic cortex differed significantly between the active and sham groups. The cortical thickness increase of the isthmus of the left cingulate gyrus was greater in the active as compared to the sham rTMS group. This suggested that rTMS can induce neuroplastic changes, particularly in cortical thickness, independent of treatment response.

Kopelman et al. (2023) conducted a randomized controlled trial to examine the rapid neuroplasticity changes and treatment response to intravenous ketamine in 98 adults of 18 and above age with moderate-to-severe unipolar depression who had failed at least one antidepressant, and were also individuals with Treatment-resistant Depression (TRD). A randomization of 2:1 to a single infusion of Ketamine (0.5 mg/kg IV over 40 min) vs. vehicle (50 ml 0.9% NaCl) completed diffusion tensor imaging (DTI) assessments at pre-infusion baseline and 24-h post-infusion. DTI mean diffusivity (DTIMD), a putative marker of microstructural neuroplasticity in gray matter, was calculated for 7 regions of interest (left

and right (Brodmann area 10) BA10, amygdala, and hippocampus; and ventral Anterior Cingulate Cortex) and compared to clinical response measured with the Montgomery-Asberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptoms-Self-Report (QIDS-SR). The findings suggested that a proxy for structural neuroplasticity was associated with treatment response to ketamine in a subset of the relevant brain regions for depression.

Yonezawa et al. (2023), conducted a post-hoc reanalysis of a double-blind, placebo-controlled RCT examined predictors of antidepressant response to intravenous Ketamine (0.5-1.0 mg/kg) in Treatment-Resistant Depression (TRD) Among 31 patients, logistic regression analysis showed that age of onset was significantly associated with a greater clinical response three days after ketamine infusion, while no associations were found with sex, baseline depression severity, or dissociative symptoms with Clinician-Administered Dissociative States Scale (CADSS). These findings may suggest that early-onset TRD may characterize by impaired glutamatergic signalling and reduced neuroplasticity.

Sun et al. (2018), investigated the effects of Magnetic Seizure Therapy (MST) on Suicidal Ideation and Neuroplasticity in 23 patients with Treatment-resistant Depression (TRD), the mean age of the participants were 45 ± 12.2 years, of which 11 were males. The study showed that MST produced significant resolution of suicidal ideation, and also produced neuroplasticity in the brain. MST increased cortical-evoked activity (CEA) in prefrontal cortex of patients with TRD and not in the motor cortex. The MST decreased cortical inhibition, which was greatest in patients with significant suicidal ideation reduction, was seen. The long-interval cortical inhibition (LICI) reduction can help in the identification of patients achieving resolution of suicidal ideation with 90% sensitivity and 88% specificity. The increase in CEA and concomitant correlation of LICI decrease with the reduction of suicidal ideation may imply MST can achieve its therapeutic effects through the improvement of LTP-like plasticity.

Theme 3: Molecular and Neurotransmitter Modulation of Plasticity

Kuo et al. (2016) investigated how chronic serotonergic enhancement through selective serotonin reuptake inhibitor (SSRI) (citalopram, 20mg/day for 14-35 days) modulates by transcranial direct current stimulation (tDCS) -induced neuroplasticity in the primary motor cortex of 12 healthy participants (5men, 7 women, aged 27.5 ± 4 years). Using a partially, double-blinded, placebo controlled, crossover design, the study compared plasticity after anodal tDCS (LTP-like) and cathodal tDCS (LTD-like) under both placebo and chronic SSRI administration with N-methyl-D-aspartate (NMDA) receptor antagonism. The results of the present study show that chronic application of SSRI in healthy humans increased and extended the duration of the facilitation induced by anodal tDCS for more than 24 h after intervention, whereas it turned cathodal tDCS-induced inhibition into facilitation. These findings support the impact on neuroplasticity to be relevant for therapeutic effects of serotonergic enhancement. Although this study focused on healthy participants only, this may not be generalizable to patients with Major Depressive Disorder (MDD).

Kuo et al. (2017) investigated the acute and chronic effects of noradrenergic enhancement through reboxetine on transcranial direct current stimulation (tDCS) -induced neuroplasticity in 16 healthy participants. The study explored the impact of single dose and chronic administration of the selective noradrenaline reuptake inhibitor (NRI) reboxetine (RBS) on plasticity induced tDCS through a double-blinded, placebo-controlled randomized crossover

study. The results of this study showed that single dose administration of the selective NRI RBX increased LTP-like plasticity induced by anodal tDCS, although it turned cathodal tDCS-induced LTD-like plasticity into facilitation in healthy participants. Under chronic administration, the LTP-like effects of anodal tDCS were prolonged for more than 24 h after intervention, and thus lasted relatively longer than those under single dose administration or placebo medication. Although this study focused on healthy participants only, this may not be generalizable to patients with Major Depressive Disorder (MDD).

Brunoni et al. (2020), investigated if single nucleotide polymorphisms (SNPs) which are associated with neuroplasticity and the activity of monoamine neurotransmitters, such as the brain-derived neurotrophic factor (BDNF, rs6265), the serotonin transporter (SLC6A4, rs25531), the tryptophan hydroxylase 1 (TPH1, rs1800532), the 5-hydroxytryptamine receptor 2A (HTR2A, rs6311, rs6313, rs7997012), and the catechol-O-methyltransferase (COMT, rs4680) genes, are associated with efficacy of transcranial direct current stimulation (tDCS) in major depression. The findings suggest that, despite the theoretical role of BDNF and serotonin-related polymorphisms in synaptic plasticity and antidepressant response, no single genetic marker could be linked to efficacy in this trial. The authors conclude that larger, combined datasets are needed to clarify the genetic underpinnings of neuroplasticity-related treatment effects in depression.

Theme 4: Structural and Macro-Level Neuroplasticity

Hayasaka et al. (2017) investigated structural alterations in the hippocampus (HIPP) and amygdala (AM) following Repetitive transcranial magnetic stimulation (rTMS) in patients with unipolar major depression. 28 patients with a mean age of 48.3 ± 12.4 years, 39.2% of which were female, participated in this study. Results showed a significant 3.4% increase in the left Hippocampus volume in patients with depression after a course of 10 sessions of rTMS over the left DLPFC. In contrast, the right HIPP and bilateral AM volumes were not significantly affected. Although the authors reported it is difficult to pinpoint the histological nature of the observed increase in volume. The underlying causes of an increase in gray matter volume can be attributed to various other mechanisms, such as an increase in cell size, neurogenesis, gliogenesis, spine density, blood flow, and interstitial fluid. They state that the HIPP volume increase is a consequence of a combination of the above-mentioned effects and the increase in the hippocampus volume cannot be attributed to neuroplasticity without further research.

Gourgouvelis et al. (2017) conducted a pilot study which used a subsequent memory paradigm to investigate the effects of an eight- week exercise intervention on hippocampal function in 8 low-active healthy and 8 low –active individuals with Major Depressive Disorder (MDD). Results of this study suggested that improvements in aerobics fitness from the intervention possibly promote neural processing efficiency during memory encoding processes. The neurocognitive benefits associated with exercise, which may be cerebral blood flow and neural growth factors, specifically Brain- Derived Neurotrophic Factor (BDNF), which is in turn a key mediator of Neuroplasticity in the brain. The limitation of this study is that it has a small sample size and therefore can be difficult to generalise.

Limitations

Some limitations of the present review are, firstly the heterogeneity of the study designs, relatively small and specialized samples of each study and a focus on markers of plasticity that may not fully capture neural adaptations. Secondly, the findings from healthy controls

or specific age groups, samples and differing multicultural contexts may not generalise to the broader populations of Major Depressive Disorder in relation to Neuroplasticity.

CONCLUSION

Evidence shows that Neuroplasticity is a core mechanism in the pathophysiology and treatment of Major Depressive Disorder (MDD). Emerging biomarkers of plasticity may help in predicting treatment outcomes. Although future large-scale, longitudinal and multimodal studies are required and beneficial to validate these findings and translate them into clinical applications.

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Conflict of Interest
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APPENDIX

Table 1 Studies Included in the Systematic Review

Author/ Year	Research Question(s)/hypothesis/objectives	Methodology	Analysis and Major findings	Conclusions/limitations
(Kaneko et al., 2024)	They aimed to investigate the differences in neuroplasticity between 60 individuals with TRD and 30 age- and sex-matched healthy controls (HCs). To induce neuroplasticity, participants underwent a paired associative stimulation (PAS) paradigm involving peripheral median nerve stimulation and transcranial magnetic stimulation (TMS) targeting the left dorsolateral prefrontal cortex (DLPFC)	Neuroplasticity was assessed by using measurements combining TMS with EEG before and after paired associative stimulation (PAS). Sample: 60 individuals with TRD and 30 age- and sex-matched healthy controls. Design: Experimental, case-control study. Tools: Paired associative stimulation (PAS) combining peripheral median nerve stimulation with TMS targeting the left DLPFC; neuroplasticity assessed via TMS-EEG measures (TMS-evoked potentials, gamma power modulation).	Both groups showed increased early TMS-evoked potentials (TEPs) after PAS. The increase was significantly greater in HCs compared to TRD patients. Gamma power increased after PAS in HCs but decreased in TRD patients, showing a significant group difference. Findings suggest impaired neuroplasticity in the DLPFC of TRD patients.	Concluded that neuroplasticity is impaired in TRD, particularly reflected in abnormal gamma power modulation in the DLPFC. Limitations: TRD-specific sample (not all MDD patients), lack of longitudinal follow-up, and unclear generalizability to less severe depression or other brain regions.
(Dalhuisen et al., 2020)	Does rTMS lead to longitudinal changes in hippocampus/amygdala volume and cortical thickness in chronic TRD?	Sham-controlled study; 31 chronic TRD patients (active rTMS N=15; sham N=16); 20 sessions	No significant clinical differences between groups. No significant changes in hippocampal/amyg	rTMS induces neuroplastic cortical changes even if clinical response is absent. Limitations: small sample, short

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		over 4 weeks; MRI for hippocampal/amygdala volume & paralimbic cortical thickness	dala volumes overall; males showed left amygdala decrease. Significant cortical thickness increase in left cingulate gyrus isthmus in active vs sham rTMS	treatment duration, chronic population may need more intensive rTMS
(Gourgouvelis et al.,2017)	Does an 8-week exercise intervention modulate hippocampal activity and improve mood in low-active healthy and MDD participants?	Pilot study; low-active healthy (n=8) and low-active MDD (n=8) adults; 8-week supervised exercise program; fMRI with subsequent memory paradigm; depression scores measured	MDD group showed significant improvement in depression scores ($p<0.0001$); memory performance unchanged in both groups; marginally significant decrease in hippocampal activity across both groups; whole-brain analysis showed similar deactivation in memory-associated regions	Exercise may enhance neural efficiency and improve mood in MDD without necessarily changing memory performance. Limitations: very small sample, pilot design, limited statistical power
(Sun et al., 2018)	Does MST reduce suicidal ideation and produce neuroplastic changes in patients with treatment-resistant depression?	Open-label intervention; n=23 TRD patients; MST treatment course; TMS-EEG measured cortical-evoked activity (CEA) and long-interval cortical inhibition (LICI) in DLPFC and motor cortex; suicidal ideation assessed via SSI	44.4% of patients experienced resolution of suicidal ideation; MST increased CEA in frontal-central electrodes; LICI decreased in responders; reduction in SSI correlated with LICI decrease ($rho=0.73$, $p<0.05$); no motor cortex effects	MST produced neuroplasticity in the frontal cortex and reduced suicidal ideation; LTP-like plasticity may underlie therapeutic effect; small sample, open-label design
(Lissemore et al., 2021)	Does venlafaxine treatment modify cortical inhibition, facilitation, or plasticity in late-life depression?	Open-label trial; n=68 patients with late-life depression; 12-week venlafaxine treatment (≤300 mg/d); TMS with EMG recordings from right hand;	Venlafaxine did not significantly change cortical inhibition, facilitation, or plasticity at 1 or 12 weeks; depressive symptom	Venlafaxine does not modulate motor cortical inhibition/plasticity despite improving depressive symptoms; findings limited to motor cortex

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		measures: contralateral cortical silent period, paired-pulse short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), paired associative stimulation (PAS)	improvements were not associated with cortical physiology changes	
(Brunoni et al., 2019)	Investigate whether SNPs associated with neuroplasticity and monoamine function are associated with efficacy of tDCS and escitalopram in major depression.	Ancillary analysis of ELECT-TDCS trial; N=195 adults with moderate-to-severe unipolar depression; randomized to escitalopram/tDCS-sham (n=75), tDCS/placebo-pill (n=75), placebo-pill/sham-tDCS (n=45); genotyped for BDNF, HTR2A, TPH1, SLC6A4, COMT; depressive symptoms measured using standard rating scales.	No SNPs were significantly associated with treatment response in any group or in exploratory analyses; pairwise comparisons also showed no allele-related differences.	Genetic variation in these candidate neuroplasticity/monoamine genes did not predict response to tDCS or escitalopram; study limited by sample size for pharmacogenetic analyses.
(Hayasaka et al., 2017)	Investigate structural alterations in the hippocampus and amygdala following high-frequency left prefrontal rTMS in patients with depression.	Open-label study; 28 patients with depression; 10 daily 20-Hz left DLPFC rTMS sessions over 2 weeks; MRI scans at baseline and post-treatment; HAM-D17 for clinical symptoms; manual tracing of hippocampus and amygdala volumes.	Left hippocampal volume increased significantly (+3.4%) post-rTMS; no significant change in amygdala; no correlation between hippocampal volume increase and HAM-D17 improvement.	Left prefrontal rTMS induces structural neuroplasticity in the ipsilateral hippocampus; clinical improvements may not directly correspond to hippocampal volumetric changes; small sample and lack of sham control limit generalizability.
(Yonezawa et al., 2024)	To identify demographic and clinical factors associated with response to intravenous ketamine in TRD	Secondary analysis of a double-blind, randomized, placebo-controlled trial; N = 31 TRD patients (13	Logistic regression: later age of onset positively correlated with treatment response at 3 days (β =	Later disease onset predicts better short-term response; limitations include small sample size and short follow-up period; results may

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		women; mean age 48.4 ± 10.9 years); intravenous ketamine 0.5 or 1.0 mg/kg; outcome measured with HAM-D-6 and Clinician-Administered Dissociative States Scale	0.08, p = 0.037); no significant associations with age, sex, baseline HAM-D-6, or dissociative score; multiple regression showed no significant predictors for % change in HAM-D-6	not generalize to all TRD patients
(Kopelman et al., 2023)	Does acute intravenous ketamine induce rapid neuroplasticity changes within 24 hours, and are these changes associated with clinical response in treatment-resistant depression (TRD)?	98 unipolar depressed adults with TRD; randomized 2:1 to ketamine (0.5 mg/kg) or saline; diffusion tensor imaging (DTI) at baseline and 24 h; depression measured via MADRS and QIDS-SR	Greater DTI-MD decrease (indicative of enhanced neuroplasticity) in several regions correlated with larger improvements in depression; left BA10 and left amygdala effects mainly in ketamine group; mixed/region-specific effects in hippocampus	Ketamine's acute antidepressant effects may be mediated by rapid neuroplasticity; regional heterogeneity observed; only a single post-infusion time point; complex and sometimes inverse associations in hippocampus
(Ge et al., 2022)	Can acute functional connectivity changes induced by rTMS predict clinical response in treatment-resistant depression?	N = 38 outpatients with TRD (26 female, mean age 41.87); single concurrent rTMS-fMRI session; followed by 4-week course of 1 Hz rTMS over right DLPFC	Acute rTMS induced widespread functional connectivity changes; connectome-based predictive modelling showed rTMS-induced connectivity predicted ~30% of variance in MADRS improvement; key predictive connections involved prefrontal, motor, parietal, insular, and thalamic regions	Acute functional connectivity changes may index macro-level neuroplasticity relevant to rTMS response; sample size moderate; single site; only right DLPFC stimulation
(Kuo et al., 2016)	Does acute vs. chronic administration of the NRI reboxetine affect tDCS-induced plasticity in	16 healthy volunteers; double-blind, placebo-	Chronic RBX enhanced and prolonged anodal tDCS-induced	Chronic noradrenergic enhancement has a strong impact on

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	humans?	controlled, randomized crossover design; single dose (8 mg) or 21-day chronic RBX; anodal/cathodal tDCS applied to primary motor cortex; plasticity monitored via TMS-elicited motor-evoked potentials	LTP-like plasticity (>24 h); chronic RBX converted cathodal tDCS-induced LTD-like plasticity into facilitation (120 min); single dose had lesser effects	human neuroplasticity; may explain delayed therapeutic effects of NRIs in depression; limitation: healthy volunteers, small sample size, motor cortex only
(Kuo et al., 2017)	Does chronic SSRI (citalopram) administration facilitate excitatory tDCS-induced neuroplasticity in healthy humans, and is this effect glutamate-dependent?	12 healthy adults; partially double-blind, placebo-controlled, randomized crossover; interventions: anodal/cathodal tDCS combined with placebo, citalopram (20 mg/day for 35 days), and dextromethorphan (NMDA antagonist); motor-evoked potentials measured via TMS	Chronic citalopram increased and prolonged LTP-like plasticity induced by anodal tDCS for >24 h; cathodal tDCS-induced LTD-like plasticity converted into facilitation; effects blocked by dextromethorphan	Chronic serotonergic enhancement strengthens LTP-like glutamatergic plasticity, potentially explaining delayed clinical effects of SSRIs; limitation: small sample, healthy subjects only
(Cardinal et al., 2019)	Objectives: 1) Compare motor cortex inhibition (SICI, ICF) and DPMS function among FM, MDD, HC. 2) Compare these measures between FM and MDD adjusted for BDNF. 3) Examine correlation between DPMS function and BDNF-adjusted indices regardless of diagnosis.	Cross-sectional exploratory study; 63 women aged 18–75 (FM=18, MDD=19, HC=29); Tools: TMS (SICI, ICF), CPM-test (NPS change), serum BDNF levels	MANCOVA: SICI higher in FM vs MDD (53.4%) and vs HC (66.99%). DPMS inhibitory potency lower in FM vs MDD (112.29%). BDNF higher in FM vs MDD (35.7%). In FM, SICI negatively correlated with DPMS function (Rho=-0.49). BDNF positively correlated with DPMS disinhibition.	FM differs from MDD in neurophysiological substrates: higher cortical inhibition, lower DPMS function, higher BDNF. Suggests up-regulation of intracortical inhibitory networks and disrupted descending pain modulation in FM. Limitations: small sample, cross-sectional, only women.