Aalto-yliopisto
Aalto-universitetet
Aalto University

Bachelor's Programme in Electrical Engineering

Functional and structural MRI insight for target selection of multi-locus TMS-based treatment in major depressive disorder

Petra Häggqvist

Bachelor's thesis
2025

Aalto-yliopisto
Aalto-universitetet
Aalto University

Author Petra Häggqvist

Title of thesis Functional and structural MRI insight for target selection of multi-locus TMS-based treatment in major depressive disorder

Programme Electrical Engineering

Major Bioinformation Technology

Thesis supervisor Markus Turunen

Thesis advisor(s) Adj. Prof. Pantelis Lioumis and Prof. Risto Ilmoniemi

Date 12.12.2025 **Number of pages** 35 **Language** English

Abstract

Major Depressive Disorder (MDD) is a prevalent psychiatric condition characterized by persistent low and depressed mood, loss of pleasure and interest, i.e., anhedonia, and suicidal ideation. Despite decades of extensive research, the underlying neurobiological mechanisms of depression remain only partially understood. The current evidence suggests that depression arises from disruptions within and between large-scale brain networks. This bachelor's thesis is a literature review, examining depression and its treatment from the perspective of brain network theory, neuroimaging insight, and the potential of brain stimulation methods in the future. The neuroimaging methods discussed in this thesis include functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), while the stimulation methods focus on transcranial magnetic stimulation (TMS) and its novel, more advanced form, multi-locus TMS.

This thesis explores the utilization of functional and structural MRI (fMRI, DTI) to guide the targeting of multi-locus TMS in depression treatment. In addition, lesion-based approaches, symptom-specific neural circuits, and factors that may explain the variable treatment outcomes of current TMS protocols are discussed. The boarder purpose is to deepen the comprehension of the neural mechanisms underlying depression and the principles of TMS and multi-locus TMS, as well as to identify factors that could improve the precision and efficacy of future treatments.

Modern neuroscience builds on insights yielded from neuroimaging and non-invasive brain stimulation methods. Based on these techniques, psychiatric disorders, such as depression, are increasingly understood as network-level diseases, characterized by altered communication among illness-related brain regions. Depressed individuals present abnormalities within single regions, large-scale networks, and the connections between them, involving both structural and functional changes. Particularly important structures include several regions of the prefrontal cortex and the anterior cingulate cortex. The disorder is conceptualized as an imbalance between hypoactive prefrontal cortex and hyperactive limbic and subcortical structures. This thesis demonstrated that each disrupted brain region can be linked to a large-scale network, which can further be associated with specific symptoms in depression.

While antidepressant medication remains the first-line treatment for MDD, yet at least one third of patients fail to respond adequately even after multiple trials. These patients are diagnosed with treatment-resistant depression, for which treatment alternatives traditionally include psychotherapy and electroconvulsive therapy. The limitations of existing methods, combined with the increasing influence of network-based models of depression, have established brain stimulation methods, especially TMS, as important alternatives for patients who respond poorly to medication. As a non-invasive method, TMS is generally safe, but its antidepressant efficacy varies widely. With standard protocols, clinical success is often modest. Findings explain this to partly result from the largely standardized stimulation parameters, which do not account for individual differences in brain anatomy or network organization. Furthermore, conventional TMS can stimulate only one cortical target at a time, although modern network-based theories highlight disruptions across multiple regions.

To overcome these limitations, improve treatment response, and meet the demands of the current mental health crisis, multi-locus TMS has been developed. Even though some challenges remain and multi-locus TMS is still under development, based on literature, it clearly has the potential to transform the future treatment of psychiatric disorders, including depression. This method enables precise and dynamic control of the induced electric field by utilizing multiple coils, allowing more accurate targeting and the simultaneous stimulation of several brain regions. As such, it aligns with both the network-level basis of MDD and the aims of modern neuroscience, including the development of personalized treatment alternatives. For targeting to be sufficiently precise and individualized, multi-locus TMS must be integrated with neuroimaging methods that provide information about brain structure and connectivity. In the future, it may be possible to combine more than one complementary neuroimaging method to assist in targeting multi-locus TMS-based treatment in MDD.

Keywords Major depressive disorder, neural network theory, neuroimaging, transcranial magnetic stimulation, multi-locus TMS

Aalto-yliopisto
Aalto-universitetet
Aalto University

Tekijä Petra Häggqvist

Työn nimi Toiminnallinen ja rakenteellinen magneettikuvantaminen multi-locus TMS-hoidon kohdentamisen tukena vakavan masennuksen hoidossa

Koulutusohjelma Sähkötekniikan kandidaattiohjelma

Pääaine Bioinformaatioteknologia

Vastuuopettaja Markus Turunen

Työn ohjaaja(t) Dosentti Pantelis Lioumis ja professori Risto Ilmoniemi

Päivämäärä 12.12.2025 **Sivumäärä** 35 **Kieli** englanti

Tiivistelmä

Masennus on yleinen psykiatrinen häiriö, jolle on ominaisimmat oireet ovat pitkäkestoinen matala ja masentunut mieliala, mielihyvän ja mielenkiinnon puute eli anhedonia ja itsetuhoiset ajatukset. Vaikka masennusta on tutkittu laajalti vuosikymmenien ajan, ovat sairauden taustalla olevat neurobiologiset mekanismit edelleen osittain epäselviä. Nykykäsityksen mukaan masennus johtuu aivoverkostojen tasolla ilmenevistä häiriöistä. Tämä kandidaatintyö on kirjallisuustutkimus, joka käsittelee masennusta ja sen hoitoa neuroverkkoteorian, aivokuvantamismenetelmien antaman tiedon sekä aivostimulaatiomenetelmien tulevaisuuden näkökulmasta. Aivokuvantamismenetelmistä tarkastellaan toiminnallista magneettikuvantamista (fMRI) ja diffuusiotensorikuvantamista (DTI), ja aivostimulaatiomenetelmistä keskitytään transkraniaaliseen magneettistimulaatioon (TMS) ja sen uuteen, kehittyneempään versioon, multi-locus TMS-menetelmäään.

Työssä tarkastellaan toiminnallisen ja rakenteellisen magneettikuvantamisen (fMRI, DTI) käyttöä multi-locus TMS-menetelmän kohdentamisessa masennuksen hoidossa, mutta lisäksi käsitellään aivovaurioihin perustuvia lähestymistapoja, oirekohtaisia neuroverkkoja sekä tekijöitä, jotka selittävät nykyisen TMS-hoidon vaihtelevia tuloksia. Tarkoituksena on syventää ymmärrystä masennuksen sekä TMS- ja multi-locus TMS-menetelmän mekanismeista ja tunnistaa tekijöitä, jotka voivat parantaa masennuksen hoidon tarkkuutta ja tehokkuutta tulevaisuudessa.

Moderni neurotiede rakentuu neurokuvantamismenetelmien sekä aivojen ei-invasiivisten stimulaatiomenetelmien antaman tiedon ympärille. Näiden menetelmien perusteella psykiatriset sairaudet, kuten masennus, ymmärretään nykyään hermoverkkosairauksina, joissa sairauteen yhdistettyjen aivoalueiden yhteistoiminta on häiriintynyt. Masennuksen syntymekanismeihin liittyy sekä yksittäisten aivoalueiden, laajempien neuroverkkojen että niiden välisten yhteyksien muutoksia, jotka voivat olla sekä rakenteellisia että toiminnallisia. Masennukselle erityisen keskeisiä rakenteita ovat useat etuotsalohkon alueet ja pihtipoimun etuosa. Häiriön käsitetään johtuvan epätasapainosta hypoaktiivisen etuotsalohkon sekä hyperaktiivisten syvempien ja limbisten aivorakenteiden välillä. Työ osoitti, että masennuksessa häiriintyneet aivoalueet voidaan kukin linkittää osaksi jotakin laajempaa neuroverkkoa, jotka toisaalta voidaan edelleen liittää tiettyihin masennukselle tyypillisiin oireisiin.

Masennuksen primäärihoito on edelleen masennuslääkitys, mutta vähintään kolmasosa potilaista ei reagoi riittävän tehokkaasti useisiin lääkehoitokokeiluihin. Tällöin puhutaan hoitoresistentistä masennuksesta, johon hoitovaihtoehtoina ovat perinteisesti olleet psykoterapia ja sähköhoito. Olemassa olevien menetelmien rajoitteiden sekä masennuksen neuroverkkoteorian vakiintumisen takia erilaiset aivostimulaatiomenetelmät, erityisesti TMS, ovat vakiintuneet hoitovaihtoehdoiksi erityisesti lääkehoitoon tehottomasti reagoiville masennuspotilaille. Ei-invasiivisena menetelmänä TMS-hoito on yleisesti turvallinen, mutta sen tehokkuus masennuksen hoidossa vaihtelee. Hoidon nykyisellä toteutuksella kliininen vaste jää usein keskinkertaiseksi. Tutkimusten perusteella tämä johtuu osittain siitä, että menetelmä perustuu standardoituihin stimulaatioparametreihin, jotka eivät huomioi yksilöllisiä eroja potilaiden aivoanatomian ja neuroverkkojen yhteyksien välillä. Lisäksi nykymuotoista TMS-hoitoa pystytään kohdentamaan vain yhteen aivoalueeseen kerrallaan, vaikka masennuksessa häiriintyneitä alueita on useampi kuin yksi.

Tämänhetkisen TMS-menetelmän rajoitteiden ratkaisemiseksi, hoitovasteen tehostamiseksi ja toisaalta meneillään olevan mielenterveyskriisin taltuttamiseksi on kehitetty multi-locus TMS. Vaikka multi-locus TMS-menetelmän tulevaisuuteen liittyy vielä ratkaisemattomia haasteita ja menetelmä on vasta kehitysvaiheessa, on kirjallisuuden perusteella selvää, että sillä on mahdollisuus mullistaa psykiatristen häiriöiden, kuten masennuksen, hoito tulevaisuudessa. Menetelmä mahdollistaa sähköisen kentän tarkan ja dynaamisen ohjauksen useiden kelojen avulla ja tarjoaa paremman kohdennustarkkuuden ja mahdollisuuden useamman aivoalueen samanaikaiseen stimulointiin. Menetelmä on siten paremmin linjassa sekä masennuksen neuroverkkoteorian että modernin neurotieteen tavoitteiden, kuten personoitujen hoitomuotojen kehittämisen, kanssa. Jotta kohdennus olisi riittävän tarkkaa ja individualisoitua, multi-locus TMS on integroitava toimimaan yhdessä neurokuvantamismenetelmien, kuten fMRI tai DTI, kanssa, jotka antavat potilaskohtaista tietoa aivoista ja sen verkoista. Tulevaisuudessa mahdollista voi olla myös useamman kuin yhden, toistaan täydentävän kuvantamismenetelmän yhdistäminen multi-locus TMS-menetelmän kohdentamiseksi masennuksen hoidossa.

Avainsanat Masennus, neuroverkkoteoria, neurokuvantaminen, transkraniaalinen magneettistimulaatio, multi-locus TMS

Aalto-yliopisto
Aalto-universitetet
Aalto University

Table of contents

Preface and acknowledgements

Writing this bachelor's thesis has been, above all, a rewarding journey of learning. The process has motivated and calmed me considering my possible future in the field of biomedical engineering, which has looked, until recently, quite hazy. Because of this writing journey, I have finally seen concretely how my major positions between medicine and engineering. For these realizations, I am beyond grateful.

Completing this work would not have been possible without the inspiring, intelligent, and helpful people around me during this process. First, I would like to thank my amazing advisors, Pantelis Lioumis and Risto Ilmoniemi – your passionate but relaxed mindset has been contagious. Thank you for giving me such an interesting topic to work on during the final fall of my bachelor's studies and for the commitment and help that you have presented with. A special thanks to Pantelis for coming to listen to our bachelor's seminar. It meant a lot to me.

I would also like to thank Nikos Makris from Harvard Medical School for the inspiring and tireless explanations on the brain anatomy and function, which continued sometimes even in private. Overall, the Special Course in Human Neuroscience, lectured by Nikos, Pantelis and Risto, helped substantially with understanding the bigger picture of my thesis's framework.

Warm thanks to the responsible teacher Markus Turunen and other teachers in the course, who supported the progress along the way. Finally, I would like to thank my dear friend and peer thesis writer, Pihla Happonen, who cheered me on and was always ready to change thoughts on our closely similar thesis subjects.

Helsinki, 11th of December in 2025

Petra Häggqvist

Symbols and abbreviations

ACC Anterior cingulate cortex
AG Angular gyrus
AN Attention network
BDNF Brain-derived neurotrophic factor
BOLD Blood oxygen level-dependent
CCN Cognitive control network
DBS Deep brain stimulation
dlPFC Dorsolateral prefrontal cortex
DMN Default mode network
DTI Diffusion tensor imaging
DSM-5 Diagnostic and Statistical Manual of Mental Disorders
ECT Electroconvulsive therapy
FC Functional connectivity
fMRI Functional magnetic resonance imaging
HPA Hypothalamic–pituitary–adrenal
IL-6 Interleukin 6
IPL Inferior parietal lobe
LNM Lesion–network mapping
MDD Major depressive disorder
mPFC Medial prefrontal cortex
mTMS Multi-locus TMS
NAc Nucleus accumbens
NAN Negative affect network
NMDA N-methyl-D-aspartate
OFC Orbitofrontal cortex
PAN Positive affect network
PCC Posterior cingulate cortex
PCG Precentral gyrus
PET Positron emission tomography
PFC Prefrontal cortex
RDoC Research domain criteria
RN Reward network
rTMS Repetitive transcranial magnetic stimulation
SGA Second-generation antipsychotic
sgACC Subgenual anterior cingulate cortex
sgPFC Subgenual prefrontal cortex
SN Salience network
SNR Signal-to-noise ratio
SSRI Selective serotonin reuptake inhibitor
TMS Transcranial magnetic stimulation
TN Threat network
TRD Treatment-resistant depression
VNS Vagus nerve stimulation
VS Ventral striatum

Anterior (a) = In front, before
Dorsal (d) = To the back, upper side, top
Inferior (I) = Below
Lateral (l) = To the sides
Medial (m) = In the middle, close to the medial plane
Parietal (P) = To the wall of a body cavity
Posterior (P) = To the back, after
Subgenual (sg) = “Below the genu” (= knee-like bend) of the corpus callosum in the brain
Ventral (v) = To the front, lower side, stomach

1 Introduction

Major depressive disorder (MDD) is a prevalent psychiatric condition characterized by persistent low mood, anhedonia and suicidal ideation, alongside a heterogeneous array of physical, cognitive, and emotional symptoms [1]. Clinically, MDD is diagnosed when symptoms persist for over two weeks and the patient experiences at least one episode, although most suffer from multiple episodes [2].

Even after numerous trials over the decades, depression is still not fully understood. A range of hypotheses, emphasizing slightly different aspects of depression, have been suggested to explain its mechanisms, such as abnormalities in molecular, endocrine, inflammatory and network-level mechanisms [2]. Furthermore, while significant comorbidity exists between MDD and physical disorders (e.g. cardiovascular, metabolic, neurodegenerative), the underlying mechanisms are not adequately established [3]. Since the 1960s, depression has been recognized as a biological disorder with a neuronal foundation. However, the underlying neural networks of depression, and those of distinct biotypes, remain to be better defined to improve stimulation targets and treatment outcomes [4].

Research conducted with neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), as well as non-invasive brain stimulation studies, such as transcranial magnetic stimulation (TMS), has significantly assisted in understanding the neuronal substrate of depression. According to the studies, it is proposed that depression originates in disrupted communication and coordination within and between key brain regions and networks. Hence, depression should be understood as a circuit of interrelated brain areas with dysfunctional connectivity over separate, focally affected regions with anomalies [5].

MDD is typically defined by hypoactive prefrontal cortex and hyperactive subcortical structures [4]. The essential disrupted brain regions are located especially in prefrontal areas such as the subgenual prefrontal cortex (sgPFC), the dorsolateral prefrontal cortex (dlPFC), and the anterior cingulate cortex (ACC) [5, 6]. Functional connectivity (FC) describes the similar activity of different brain regions, but it does not provide proof of causation. However, causal evidence derives from TMS and lesion studies [6].

The first-line treatment for MDD typically involves antidepressant medication. However, one third to half of patients fail to respond after two to three trials, leading to a diagnosis of treatment-resistant depression (TRD) [7]. In addition to psychotherapy, which is the most traditional nonpharmacological approach to MDD, some TRD patients may benefit from electroconvulsive therapy (ECT). Despite its effectiveness to treating MDD, use of ECT is limited by its invasive nature, as it is conducted under general anesthesia and includes the risk of retrograde amnesia, which may be irreversible in some cases [2]. In the light of these factors, TMS – in the modern era, repetitive TMS (rTMS) – serves as a non-invasive clinical treatment alternative used particularly for TRD patients. The conventional rTMS delivers recurrent magnetic pulses via a coil to stimulate targeted brain regions implicated in depression [7]. The dlPFC is most often targeted, as its modulation indirectly stimulates the subgenual ACC [5].

According to European recommendations, rTMS has an efficacy ranging between 30–64 % [7]. While being a treatment alternative with many benefits and clear potential, rTMS entails also several limitations, as reflected in its modest clinical efficacy. A central limitation of rTMS is its reliance on uniform parameters (e.g., coil location, orientation, stimulation intensity) despite each patient's individual brain anatomy and region connectivity. For instance, the anatomical position and functional connectivity of the dlPFC relative to the motor cortex can differ markedly between patients [8, 9].

This one-size-fits-all approach likely contributes to variable treatment outcomes, highlighting the need for individualized targeting strategies [10].

These unsolved issues related to standard rTMS could be addressed with multi-locus TMS (mTMS), which can be considered an enhanced version of conventional rTMS. It employs multiple overlapping coils to electronically steer the induced electric field within a brain region, enabling rapid and precise targeting. Through standardized algorithms, multi-locus TMS reduces operator-dependent variability while facilitating improved focality and flexible multi-site, network-level stimulation. While further refinements are needed as current standardized algorithms still limit patient-specific individualization, mTMS possesses many features that hold particular promise for treating depression as a disorder of interconnected, disrupted networks in the brain [11, 12].

This thesis is a literature review, aiming to investigate and compare functional and structural MRI (fMRI, DTI) methods in targeting multi-locus TMS for MDD patients. Additionally, this study explores brain lesions as an approach to target mTMS for MDD, considering the causal insight they provide. Furthermore, the goals of this thesis include identifying symptom-specific brain circuits in MDD as well as discussing the reasons behind both positive and negative TMS results. Finally, the broader purpose is to advance understanding of depression, standard and multi-locus TMS and outline directions for future refinement in depression treatment.

This thesis obeys the following structure: after introduction, the second chapter presents the background of MDD, including its diagnosis and characteristics, the major hypotheses underlying its mechanisms, the alterations that occur in the depressed brain, and the current treatment alternatives to the disease. The third chapter addresses the principles, results and potential of neuroimaging methods and TMS-based treatment in depression, focusing on fMRI, DTI, and lesions as well as rTMS and mTMS. In chapter four, the methods utilized in this literature review are described. The fifth chapter summarizes both the second and third chapter and presents the results of this thesis. Finally, the last two chapters discuss the current challenges and future directions of neuroimaging-guided mTMS in depression and conclude the most important answers to the research questions in this thesis.

2 Major depressive disorder

This chapter focuses on major depressive disorder, first presenting the criteria for its diagnosis and the major hypothesis underlying the pathophysiology of depression. Next, the structural and functional alterations in the depressed brain compared to a healthy one are described. The rest of chapter two focuses on treatment-resistant depression and the current treatment approaches to overcome the condition.

As this thesis aims to investigate MDD in the context of developing effective and individualized treatment via neuroimaging and multi–locus TMS, it focuses on novel and relevant studies and recent theories. Therefore, the current theory of network-level disruption underlying depression will be emphasized in this chapter (2.3), while earlier hypotheses will be discussed more briefly (2.2).

2.1 Criteria for diagnosis

According to the *Diagnostic and Statistical Manual of Mental Disorders* [13], MDD is an affective mental disorder, which represents "one of the leading causes of disability worldwide" [14]. As stated by DSM-5, diagnosis of MDD is determined by an experience of at least five of the following nine symptoms [13]:

1. Sustained depressed mood,
2. decreased interest and pleasure in almost all activities, i.e., anhedonia,
3. changes in weight or appetite,
4. insomnia or hypersomnia,
5. psychomotor restlessness, i.e., agitation, or slowing down, i.e., retardation,
6. fatigue or loss of energy,
7. feelings of worthlessness or excessive and inappropriate guilt, which may be delusional,
8. indecisiveness and reduced ability to think or focus,
9. recurrent thoughts of death or suicide.

For the diagnosis, the symptoms must occur during the same, continuous two-week period. The identification of MDD includes that the state of health represents a change from previous condition, and at least one of the symptoms is either depressed mood or anhedonia. Furthermore, the symptoms should induce clinically significant suffering or dysfunction in social, occupational or other significant areas of functioning. The depressive episode should also not result from substance use or another medical condition [13].

2.2 The underlying neural basis of MDD – the major hypotheses

After decades of research, the neural basis of depression remains unclear [5]. As a result of extensive research, several hypotheses regarding the mechanisms of MDD have been proposed. In 2009, aan het Rot et al. suggested that MDD may arise from the cumulative effect of three factors: genetics, childhood trauma, and persistent or recent stress [2]. Furthermore, they highted three major hypotheses underlying MDD: abnormal monoamines, HPA-axis dysregulation, and neurotrophins and neuroplasticity abnormalities [2]. In addition, a theory of impaired inflammatory processes has been proposed later [17].

The monoamine hypothesis explains depression in terms of reduced levels of neurotransmitters, such as serotonin and norepinephrine. This theory is based on observations that numerous antidepressant drugs acutely increase the levels of these neurotransmitters. However, this hypothesis remains insufficient, as decreased serotonin synthesis in depressed patients can be caused by multiple factors: reduced synthesis may lead to depression, depression itself could suppress synthesis, or both could be consequences of a third underlying factor [2].

Beyond monoaminergic imbalance, the hypothalamic–pituitary–adrenal (HPA) axis dysregulation hypothesis links chronic and early-life stress to prolonged epigenetic alterations in the body's stress response system. An epigenetic feature is defined as a firmly heritable phenotype, resulting from alterations in a chromosome without modifications in the DNA sequence [15]. These epigenetic alterations, demonstrated in animal models, affect the regulation of both the HPA-axis and serotonin function and contribute to the onset and persistence of depressive symptoms [2].

According to the neurotrophins and neuroplasticity hypothesis, depression may result from disrupted levels of neurotrophic factors [2], which are proteins that support the growth, survival, and connectivity of both central and peripheral neurons [16]. Neuroplasticity refers to the brain's ability to modify neural connections throughout life, and one of the most important factors to maintain this ability is called the brain-derived neurotrophic factor (BDNF) [2]. A genetic variant of the BDNF gene, known as the "Met" allele, can decrease BDNF transport and secretion, contributing to smaller hippocampal volume and consequently increasing the risk of depression. Disruption in BDNF levels can also occur because of chronic stress, via the hormonal activity of the HPA-axis. These phenomena, combined with stress-induced reductions in serotonin and dopamine levels, may neurobiologically explain anhedonia and the development of MDD in general [2].

The inflammation hypothesis proposes that alterations in inflammatory cytokines, especially interleukin 6 (IL-6), contribute substantially to the development of depression [17]. In 2021, Roohi et al. discussed the role of inflammatory processes in depression, highlighting that IL-6 acts across multiple tissues and that its dysregulation accelerates several depression-relevant events [17]. Many patients with MDD show increased levels of inflammatory cytokines, and the alterations in IL-6 serum levels have been stated as one of the most reproducible anomalies in depression. Roohi and colleagues conclude that cytokines are "involved in almost every predisposing or precipitating risk factor associated with MDD" [17], providing strong evidence for inflammatory involvement in the pathophysiology and symptomatology of depression.

As demonstrated in this chapter, the neural basis of MDD remains complex and not fully understood, despite extensive research. Roohi et al. state the risk factors for MDD to include various features with both familial, developmental, psychological, medical and molecular characteristics associated with genetics, epigenetics, gene expression and the endocrine and immune systems [17]. According to Roohi and colleagues, the current understanding of MDD involves not only neurotransmitter abnormalities but also immune, endocrine, and, most notably, neural circuit dysfunction [17]. Next, this thesis proceeds to address the most recent and recognized theory of MDD, focusing on network-level disruptions in brain circuits.

2.3 Network-level dysfunction theory for depression

Already in 1997, Helen Mayberg was the first to propose a novel model for depression. She suggested that the underlying basis of MDD involves limbic–cortical dysregulation rather than dysfunction of a single brain region [19]. According to this framework, which is now foundational to modern network-level theories of MDD, depression results from disrupted coordination and balance between hypoactive dorsal and hyperactive ventral regions. The model identified three main components [19]:

1. a dorsal compartment, including particularly the dlPFC, dorsal ACC, striatum, and inferior parietal lobe (IPL), linked to cognitive and attentional features of depression,
2. a ventral compartment, involving the HPA-axis, insula, sgACC, and brainstem, associated with somatic and vegetative symptoms of depression,
3. and the rostral cingulate, an isolated region connected to both dorsal and ventral compartments and predictive of antidepressant response.

Dysfunction within the rostral cingulate was proposed to influence remote brain areas regulating mood, cognition, and behaviour. In summary, Mayberg's model defined depression as a network-level disorder, arising from abnormalities across interconnected cortico-striatal and cortico-limbic pathways. The theory was supported by versatile research findings from neuroimaging, lesion-deficit correlational studies as well as clinical, biochemical, electrophysiological, and animal studies [19].

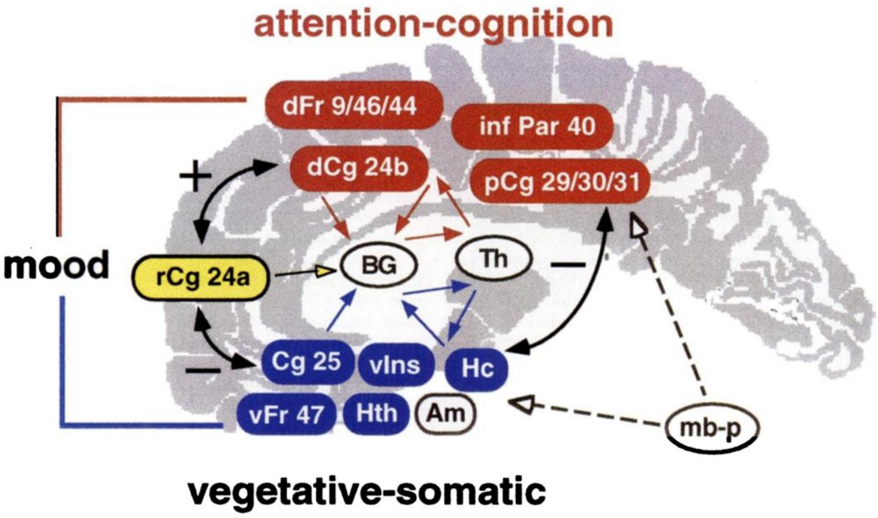

Figure 1. The Limbic-cortical dysregulation model of depression. The dorsal compartment is presented in red, the ventral compartment in blue, and the rostral cingulate in yellow. Sadness and depressive symptoms are connected to decreases in dorsal limbic and neocortical regions (*red areas*) and increases in ventral paralimbic regions (*blue areas*). The model suggests that remission occurs when hyperactive ventral regions are inhibited and the hypoactive dorsal regions are activated (*solid black arrows*). The rostral cingulate (*yellow*) is predicted to somehow participate in the remission to enable these adaptive changes, resulting from the direct anatomical connections to both dorsal and ventral directions. The dotted lines indicate serotonergic projections to limbic, paralimbic, subcortical and cortical areas in both compartments. The illustration is adapted from Mayberg (1997) [19].

Red areas: **dFr** = dorsolateral prefrontal, **inf Par** = inferior parietal, **dCg** = dorsal anterior cingulate, **pCg** = posterior cingulate. *Blue areas*: **Cg 25** = subgenual cingulate, **vIns** = ventral anterior insula, **Hc** = hippocampus, **vFr** = ventral frontal, **Hth** = hypothalamus. *Yellow areas*: **rCg** = rostral cingulate. *White areas*: **mb-p** = midbrain-pons, **BG** = basal ganglia, **Th** = thalamus, **Am** = amygdala. Numbers refer to Brodmann designations.

Additionally in 1997, Drevets et al. reported reduced metabolism in sgACC in depression [20]. The subgenual ACC is a brain structure with multiple connections to different cortical, mood regulating areas, such as the dorsal ACC, medial and lateral OFC, amygdala and dorsomedial thalamus, and in addition, outputs to the brainstem. Therefore, the findings led to the hypothesis of the amygdala-striatal-pallidial-thalamic-cingulate-cortex circuit in depression [5, 20].

By 2008, Drevets and others had further advanced neurocircuitry models for depression [23]. They proposed that the disorder reflects dysfunction within an extended visceromotor network, involving especially the medial PFC and limbic regions, such as the amygdala, striatum, thalamus, and sgACC.

The findings supported a network-level view in which depression stems from impaired communication between prefrontal regulatory systems and limbic emotional circuits, consistent with Mayberg's model suggested over 10 years earlier [23]. Proceeding with this perspective in 2012, Pandaya et al. reviewed depression in the light of recent neuroimaging studies, enabled by novel resting-state connectivity methods [5]. They discussed studies by Anand et al. and Gresius et al., showing decreased ACC connectivity with the amygdala, thalamus, and striatum, as well as abnormalities in the sgACC and thalamus in depressed individuals [5, 21, 22]. Together, these developments reinforced the concept that several interacting neural networks contribute to the pathophysiology of depression [5].

Advances in neuroimaging and increasing awareness of mental disorders have since strengthened the concept of depression as a disorder of network dysfunction [24–27]. In 2020, Spellman and colleagues reported that meta-analyses consistently identify regions altered at the group level in depression, including the dlPFC, orbitofrontal cortex (OFC), ACC, anterior insula, amygdala, hippocampus, basal ganglia, thalamus, and cerebellum [24]. The report pointed out, however, that the circuit-level mechanisms linking these regional dysfunctions to depressive symptoms remain unknown. To clarify depression pathophysiology in the future, Spellman et al. proposed four research priorities: 1) large-scale neuroimaging, 2) longitudinal deep sampling, 3) integration of human neuroimaging and animal neurophysiology, and 4) translational models for developing novel therapeutics, such as rTMS and deep brain stimulation (DBS) [24].

In April 2016, Williams presented a taxonomy to assist in connecting depressive symptoms to underlying individual neural dysfunction [25]. The model identified six large-scale networks and eight core neural biotypes, conceptualized as extremes of hypo- or hyperactivation within and between circuits. Each biotype links to a behavioural or emotional domain and is likely to deviate from conventional diagnostics, with individual overlapping, interacting, and co-occurring [25]. This model was further refined later in 2016, including renaming two networks [26].

The proposed large-scale networks (1.–6.) and the putative biotypes (I–VIII) in depression by Williams [25, 26] include

1. **The default mode network (DMN)**,

which consists of the anterior mPFC, the posterior cingulate cortex (PCC), and angular gyrus (AG). The DMN tends to be upregulated during rest. Furthermore, anterior and posterior regions are observed to define sub-networks of the DMN. The DMN has the biotype **I: rumination**, which is characterized by nonadaptive rumination in depressive thoughts, related to functional overactivation and hyperconnectivity of the DMN. Depression-related anatomical abnormalities in grey and white matter might also contribute to the development of biotype I.

2. **The salience network (SN)**,

which has the core nodes in the ACC, anterior insula, and sublenticular extended amygdala. The SN functions as the detector of salient alterations in the environment, both external and interoceptive. In addition, detections of a separate cingulo-opercular circuit have been observed, including nodes in the anterior mPFC, dorsal ACC, anterior insula, frontal operculum, and anterior thalamus. It has been implicated in the detection of potential mismatches and conflicts. The SN has the biotype **II: anxious avoidance**, referring to difficulties in separating relevant salient events and avoidance of situations that might overstimulate. Biotype of anxious avoidance links to insula and insula-amygdala hypoconnectivity as well as hyperconnectivity in the insula-anterior nodes of DMN. Moreover, the dorsal nodes of SN present both hyper- and hypoconnectivity with posterior precuneus node of the attention network (AN). The direction of alteration between SN-AN varies depending on the importance and the nature of events.

3. **The negative affect network (NAN) [25] / the threat network (TN) [26]**,

including subcortical nodes in the amygdala, brainstem, hippocampus, insula, dorsal mPFC, dorsal ACC, ventral mPFC, and ventral-rostral ACC connections. The NAN includes also two sub-networks, the first consisting of the dorsal and rostral nodes, implicating evaluation and emotion expression, and the second containing the ventral nodes, associated with automatic regulation of negative emotions. The NAN comprises two biotypes, which are **III: negative bias**, and **IV: threat dysregulation**. The negative bias arises from increased insular activation, hyper-responsivity of the amygdala and hyperconnectivity between the anterior modes of NAN and DMN, leading to mood-congruent negative preconceptions. Threat dysregulation refers to abnormal threat processing, related to hyperactivation of the amygdala, hypoactivation of cortical areas and reduced connectivity between amygdala and ventral prefrontal nodes. The development of this biotype might be influenced also by anatomical alterations in depression.

4. **The positive affect network (PAN) [25] / the reward network (RN) [26]**,

characterized by the striatum and especially the nucleus accumbens (NAc), and their cortical projections to the OFC and mPFC. The PAN has two biotypes: **V: anhedonia**, and **VI: context insensitivity**. Anhedonia links to striatal hypoactivation, which connects to the loss of striatal grey matter in MDD, as well as to the hyperactivation of OFC, where the latter might be compensation of the first. Anhedonia might also overlap with the NAN. Context insensitivity occurs also in remitted depression, referring to increased anticipation of reward without sensitivity to the context. It relates to the ACC and midfrontal region overactivation during the anticipation of primary rewards.

5. **The attention network (AN)**,

formed by nodes in the medial superior frontal cortices, anterior insula, anterior IPL, and precuneus, which support alertness, sustained attention, and recollection. The near interplay of AN and DMN is associated with the fluctuation between resting and task-related processing. The AN has one biotype **VII: inattention**, which has been linked to hypoconnectivity within the frontoparietal AN.

6. **The cognitive control network (CCN)**,

comprising the dlPFC, ACC, dorsal parietal cortex, and precentral gyrus (PCG). These regions assist working memory, selective attention, and cognitive flexibility during tasks, and consequently explain the biotype related to the CCN, which is **VIII: cognitive dyscontrol**. This biotype arises from the hypoactivation of the dlPFC and dorsal ACC, which is also understood as one major feature in MDD.

Beyond Williams's model, other interpretations of network dysfunction in depression have been proposed. Li et al. (2018) identified four depression-related networks and emphasized slightly different aspects of the disorder [27]. Their model overlapped substantially with Williams's but offered a more condensed division: affective and reward networks were separated (rather than Williams's negative and positive affect networks), the salience network was incorporated into the affective network, and the attention network was merged into the cognitive control network [25, 27]. Williams's taxonomy was chosen for this thesis because it is more clinically oriented and better suited for identifying disrupted brain regions, networks, and symptom associations in depression. Still, Li et al. importantly noted that depressive symptoms may arise not only from dysfunction *within* networks but also from disrupted interactions *between* them [27].

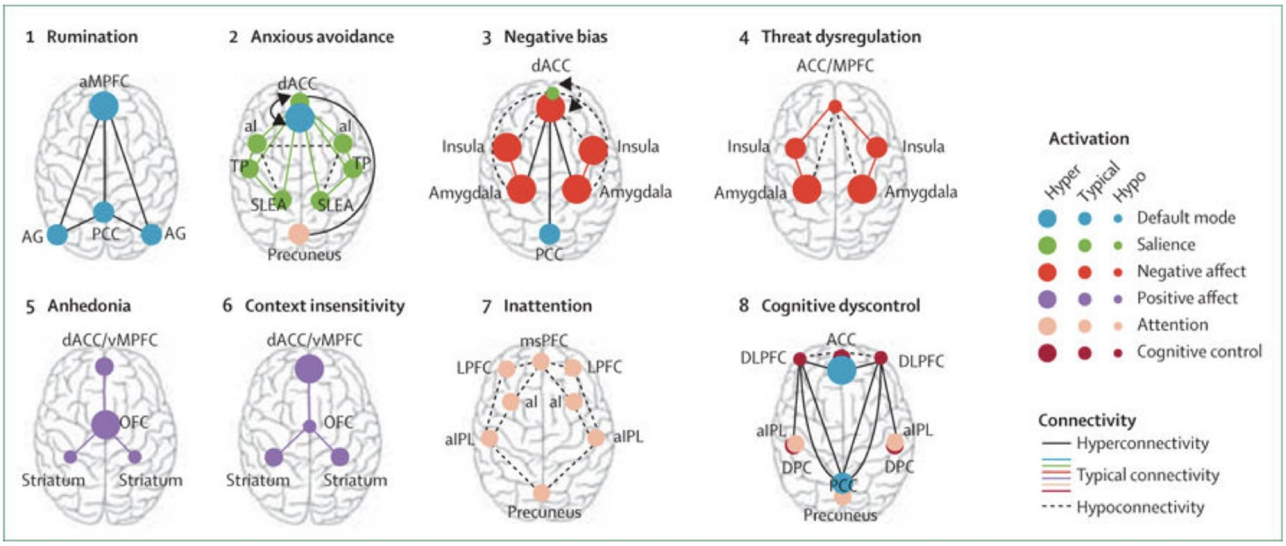

Figure 2. Suggested taxonomy of large-scale networks and the putative biotypes of neural circuit dysfunction in depression. Each large-scale network with its included brain regions is coloured: *blue* = default mode, *green*: salience, *red*: negative affect, *purple*: positive affect, *peach*: attention, *burgundy*: cognitive control. The lines between brain areas represent connectivity. In depression, abnormalities can occur in activity, connectivity or usually both. Explanations on activation and connectivity types are on the right: large sphere indicates hyperactivity in that region, while a small one refers to hypoactivity. Furthermore, black lines represent hyperconnectivity, and dashed lines hypoconnectivity. The coloured lines indicate normal connectivity. The proposed biotypes are associated with one or more large-scale networks in the following way: **I)** Impaired DMN contributes to rumination, **II)** SN, DMN, and AN disruptions contribute to anxious avoidance, **III)** NAN, SN, and DMN anomalies explain negative bias, **IV)** NAN abnormalities cause threat dysregulation, **V)** anhedonia and **VI)** context insensitivity are explained by PAN disruptions, **VII)** inattention results from impaired AN, and **VIII)** dysfunctions in CCN, AN, and DMN contribute to cognitive dyscontrol. The image is adapted from Williams (2016) [25].

aMPFC = anterior medial prefrontal cortex, **AG** = angular gyrus, **PCC** = posterior cingulate cortex (including precuneus), **dACC** = dorsal anterior cingulate cortex, **aI** = anterior insula, **TP** = temporal pole, **SLEA** = sublenticular extended amygdala, **ACC/MPFC** = dorsal medial prefrontal cortex (including dorsal ACC and vMPFC, ventral—subgenual and pregenual— and rostral ACC), **msPFC** = medial superior prefrontal cortex, **LPFC** = lateral prefrontal cortex, **aIPL** = anterior inferior parietal lobule, **MPFC** = medial prefrontal cortex, **vMPFC** = ventromedial prefrontal cortex, **OFC** = orbitofrontal cortex, **ACC** = anterior cingulate cortex, **DLPF** = dorsolateral prefrontal cortex (includes anterior prefrontal cortex and inferior frontal cortex), **PCG** = precentral gyrus, **DPC** = dorsal parietal cortex.

As already demonstrated in the details of the network-level dysfunction hypothesis for depression, the brain exhibits various structural and functional alterations during depression. The next two chapters will discuss these alterations in detail.

2.4 Structural alterations in the depressed brain

Patients with MDD often suffer from structural alterations in both subcortical and cortical brain areas, which are closely related to the illness itself [2, 5, 18]. Based on research, patients suffering from recurrent depressive episodes may possess relatively small hippocampi, even during remission [2, 18]. According to Trifu et al. (2020), hippocampal abnormalities may represent a defining feature of depression, with volumetric reductions potentially underlying memory deficits and other depressive symptoms [18]. This prominent relation reflects hippocampus's essential role as a subcortical region with functions in learning, memory, and context-dependent emotional regulation. Furthermore, hippocampus has also many corticosteroid receptors and strong connections with the hypothalamus [2, 18]. The hypothalamus, in turn, plays a key role in controlling the endocrine and autonomic nervous systems, maintains homeostasis and involves in the body's stress responses commonly disrupted in depression [5, 28].

Beyond the hippocampi, depressive patients experience structural changes also in other subcortical regions, referring especially to the amygdala and ventral striatum (VS) [2, 5, 18]. Patients with MDD diagnosis have been reported to have decreased amygdala core volume [5], which involves significantly in expressing emotions and regulates mood in threating or harmful situations [18]. The VS consists of the nucleus accumbens (NAc) and the large area between the caudate nucleus and the putamen [29]. The VS, especially NAc, forms a significant part of the reward system, NAc being a central structure for reward processing and pleasure information. In addition to abnormalities in the volume of NAc, studies have also found temperate volumetric decreases in the caudate nucleus and putamen of depressive patients [18]. It is consequently concluded that shrinkage (and abnormal activity, discussed later) of the VS is a key factor in anhedonia, one of the core symptoms in MDD [30].

Depressed patients present structural anomalies also in cortical regions, which proceed to explain other aspects of depressive symptoms [2, 5, 18]. These regions include various areas of the prefrontal cortex (PFC), which has a multimodal function as an integrator of sensory-motor information. PFC has three major sections: the dlPFC, the orbital and medial paralimbic cortex, and the ACC [18]. MRI studies have indicated volumetric decreases in overall frontal lobe volume in depression, but especially in the ACC and OFC [2, 5, 18]. The OFC is a subregion of orbital paralimbic cortex, primarily concerned with emotion, memory and the sense of smell [5]. Furthermore, both subgenual and dorsal ACC have been demonstrated with volumetric reductions in depression [2, 5]. The ventral part of ACC has outputs to the hypothalamus, making it a particular area of interest in depression [5]. These reported structural alterations in the cortical areas may be persistent during remission, potentially explaining why patients in remission proceed to overreact to negative stimuli and contributing to the risk of future relapse [2].

2.5 Functional alterations in the depressed brain

In addition to structural changes in the depressed brain, MDD involves also multiple functional abnormalities across subcortical, cortical, and brainstem regions that together regulate emotion, cognition, and neuroendocrine responses [2, 5, 18].

Considering subcortical regions, functional alterations focus on the amygdala, NAc and dorsomedial thalamus [2, 5, 18]. The amygdala shows hyperactivity to negative stimuli and hypoactivity to positive stimuli, consistent with a bias towards negative emotional salience [2, 18]. Neuroimaging studies report increased resting-state metabolism and activation of limbic regions, particularly the amygdala, in both positron emission tomography (PET) and fMRI findings [5]. In contrast, severe or treatment-resistant depression has been associated with amygdala hypometabolism [5]. However, the prolonged amygdala response to negative stimuli supports sustained limbic hyperactivity [5].

Functional alterations reported in the NAc reflect disrupted reward processing and contribute to anhedonia [5, 18]. The dorsomedial thalamus, a key node connecting the PFC, striatum, and amygdala, has shown inconsistent activation findings across studies [5]. Within the brainstem, the nuclei producing serotonin (raphe), norepinephrine (locus coeruleus), and dopamine (substantia nigra, ventral tegmental area) have shown biochemical changes in depression. While chronic antidepressant treatment can increase particularly dopamine transporter levels, abnormal density of serotonin transporter has been reported in depression [18]. This might partly contribute to the inefficacy of antidepressants with many patients.

Cortical areas most consistently implicated in depression include the dorsal and medial PFC, dorsal and ventral ACC, OFC, and insula [5, 18]. The dlPFC has often shown reduced metabolism and blood flow, correlating with impaired problem-solving, poor emotion regulation, and increased suicidal behaviour. These findings led to therapeutic use of TMS targeting the dlPFC, which can normalize its hypoactivity [5]. The ACC is divided into dorsal and ventral parts: the dorsal ACC supports cognitive control and conflict resolution of negative emotional stimuli, whereas the ventral/subgenual ACC connects significantly with limbic and cortical areas regulating mood, including the amygdala, dorsomedial thalamus, and OFC, and projects to hypothalamic and autonomic centres, linking it to stress and endocrine regulation [5]. Furthermore, the insula, particularly its anterior subdivision, contributes to interoception, self-awareness, and emotion, such as disgust. In depression, insular activity increases the response to negative stimuli, and its volume correlates with symptom severity. Some studies, interestingly, report improved insular reactivity after antidepressant treatment [5].

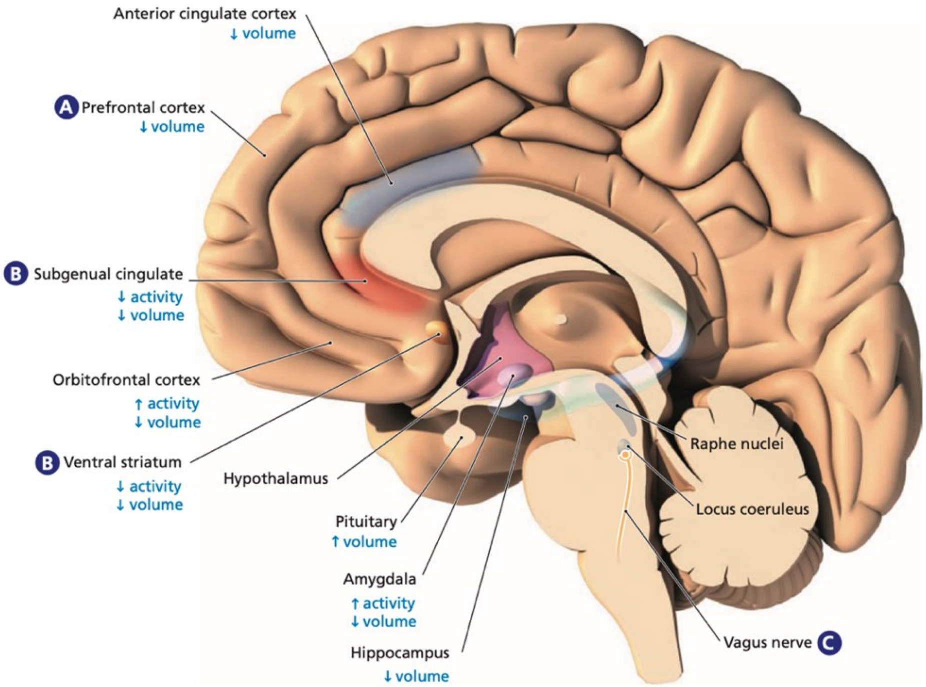

Figure 3. Structural and functional alterations in the depressed brain and the action sites of modern neurostimulation techniques with antidepressant potential. Structural alterations in the depressed brain occur in both cortical and subcortical regions. The ACC, especially the sgACC, might show volume decreases as well as other subregions of the PFC and the OFC. Subcortical regions, such as the amygdala, hippocampus, and the ventral striatum have presented with volumetric reductions. Functional changes have been observed in regions such as the amygdala, VS, OFC, and sgACC. **(A)** TMS of the dlPFC and **(B)** DBS of the sgACC have been shown to have antidepressant effects in patients. **(C)** VNS might have antidepressant properties since it effects on the lorus coeruleus, producing norepinephrine neurons. The image is adapted from aan het Rot et al. [2].

Next, this literature review will address the concept of treatment-resistant depression as well as discuss the present and future treating alternatives for MDD, introducing also transcranial magnetic stimulation. TMS will be examined more profoundly in later chapters.

2.6 Treatment-resistant depression and treatment alternatives

Treatment-resistant depression (TRD) is generally defined as a prolonged, non-responsive form of depression. The common definition of TRD, adopted by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), is "inadequate response to a minimum of two antidepressants despite adequacy of the treatment trial and adherence to treatment" [31]. Although the definitions vary widely depending on their conceptual framework and accurate prevalence estimates are therefore difficult to produce, at least 30% of patients with depression meet the FDA/EMA criteria for TRD [31]. Regardless of the definition, TRD is consistently proven to be costly both individually and societally, demonstrated by markedly higher rates of suicidality and completed suicides among TRD patients [31].

The first-line treatment for MDD is still antidepressant medication, along with the most common non-pharmacological alternative, depression-focused psychotherapy. During the acute phase of depression, especially selective serotonin reuptake inhibitors (SSRIs) remain the most frequent course of action [32]. Often, these two approaches are combined to improve outcomes, especially in severe cases [33]. If two medication trials fail, TRD is diagnosed, and alternative treatments are considered. These alternatives, shown in Table 1 and adapted from McIntyre (2023) and Williams (2016) [25, 31], fall into four categories and are associated with depression networks they aim to target.

In pharmacotherapy, extending, switching or combining antidepressants is common, as response may be delayed with some TRD patients and significant mechanistic differences between antidepressant classes exist [31]. However, in alignment with aan het Rot et al., even the revised monoamine hypothesis fails to explain the complexity of systems implicated in depression, clarifying why the monoamine-targeting antidepressants do not guarantee clinical remission [2].

Beyond standard antidepressants, TRD can be treated with ketamine, esketamine, second-generation antipsychotics (SGAs) or psychostimulants [25, 31, 36]. Ketamine and its S-enantiomer esketamine act primarily on the glutamatergic system as an N-methyl-D-aspartate (NMDA) antagonists and have shown particular benefit for acute suicidality. However, their long-term efficacy, safety, and accessibility remain insufficient [34]. SGAs, especially the combination of olanzapine and fluoxetine, have been reported to be effective, but are associated with tolerability concerns [31, 35]. Psychostimulants, which, similar to antidepressants, influence monoamine metabolism, can relieve overall symptoms, such as inattention, sleepiness and fatigue, but have shown little impact on remission rates [36].

Electroconvulsive therapy (ECT), invented already in 1938, remains the most powerful therapy for depression in some specific cases [32, 37]. ECT is conducted under general anesthesia, where electric currents pass through the brain, triggering a short seizure and causing changes in brain chemistry [37]. However, its use is limited by extensive stigma, low availability, and tolerability concerns, including the risk of irreversible retrograde amnesia [2, 31, 37].

Already in the late 1990s, many researchers, including Mayberg, Pandya and Drevets, have highlighted the potential of brain stimulation to both understand and treat depression [5, 19, 23]. Later, as a larger paradigm shift emerged in neuroscience along with the rapid advancements in neuroimaging, this approach has gained broader support, as it aligns with the shift towards network-based and individually treated psychiatric disorders. The therapeutic rationale for brain stimulation rests on the premise that accurately targeted stimulation can normalize disrupted activity within brain circuits by reducing limbic hyperactivity and/or amplifying prefrontal regulation [23]. Clinically established methods include repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) [5, 25, 31].

DBS delivers stimulation to small, deeper brain regions via stereotactically implanted electrodes under the skin. Through white-matter pathways, modulating one node may positively influence connected cortical and subcortical regions involved in depressive symptoms [5]. Despite its potential in treating TRD, DBS is restricted by incomplete knowledge of its exact mechanisms and high suicide rates among treated patients [38]. VNS manages depressive symptoms by applying mild pulses at programmed time intervals to the left vagus nerve, using an implanted pacemaker under the skin. The antidepressant effect of VNS is thought to result from transmitting electric impulses to various emotion-related brain regions, which connect to the vagus nerve through its afferent pathways. These areas include the local coeruleus, dorsal raphe, hypothalamus, thalamus, amygdala, insula, and the cingulate cortex [5]. However, VNS is limited by high costs, procedural complexity, and implant-related complications [31].

Since both DBS and VNS require subcutaneous equipment, TMS distinguishes as a relatively non-invasive, painless and safe brain stimulation method. As this thesis focuses on TMS and the emerging multi-locus TMS, the next chapter discusses these methods in detail, along with the neuroimaging methods required for individualized targeting.

Treatment strategy	**Treatment category**	**DMN**	**SN**	**NAN**	**PAN**	**AN**	**CCN**
Extending antidepressant trial	antidepressants		x		x		
Switching antidepressants	antidepressants		x		x		
Combining antidepressants	antidepressants		x		x		
Ketamine, esketamine	other substances						
SGAs	other substances						
Psychostimulants	other substances					x	
ECT	brain stimulation						
rTMS	brain stimulation	x					x
DBS	brain stimulation		x				
VNS	brain stimulation						
Psychotherapy	non-pharmacological	x		x			
Mindfulness	non-pharmacological	x					
Attention training	non-pharmacological					x	
Cognition training	non-pharmacological						x

Table 1. Alternatives for the management of treatment-resistant depression with their proposed target networks. This table is a combination of two sources, adapted with additions by McIntyre et al. (2023) and Williams (2016) [25, 31]. The treatment options are categorized into antidepressants, other substances, brain stimulation, and non-pharmacological treatments. Clarifications from the table: antidepressants in general (without taking a stand whether it is extending, switching or combining) are proposed to affect particularly the PAN (dopamine-noradrenaline reuptake inhibitors) and SN (serotonin reuptake inhibitors) [25]. The strategy of psychotherapy includes therapies with different emphasis, e.g., cognitive behavioural therapies (NAN) and self-context therapies (DMN). Ketamine-based, ECT or VNS target networks were not suggested by Williams, which is the reason why their network columns remain empty. Williams highlights that the suggestions of the networks and specific treatment options are potentially suitable but speculative.

3 Neuroimaging and TMS in major depressive disorder

Psychiatric research involves field-specific challenges, referring to the absence of clear localization of brain abnormalities and the lack of instantaneous clinical results in treatment. In the last 30 years, the discussion in field has increasingly revolved around a few questions. First, can the diagnosis and treatment be addressed at the brain circuitry level, and second, if so, would the use of neuroimaging be important for identifying and assessing brain circuitries [39]? Based on research, the answer is yes. However, the routine of clinical care in psychiatry has remained quite immutable during the 2000s. Recently, with the establishment of neuroimaging-based modern neuroscience, the field has entered a paradigm shift [26, 39]. The shift circles around the new definition of psychiatric diseases as network-level disorders and focuses on brain connectivity. It will thoroughly change the understanding of the causes, treatment, and prevention of psychiatric diseases, including depression [39].

A major component of the recent paradigm shift in neuroscience is the Research Domain Criteria (RDoC), a novel framework developed by the US National Institute of Health. RDoC integrates several levels of information, from domains, such as cognition and social processes, to basic functions, such as attention and perception, to better understand mental health and brain dysfunction. RDoC acknowledges the network-level basis of mental disorders. For example, the depression-related networks are listed under different domains in the framework: DMN is listed under automatic and regulatory systems, while SN is classified into arousal and regulatory systems [26]. In the context of this thesis, RDoC is most importantly an initiative of personalized medicine [39]. Individualized treatment can be achieved with the help of modern technology, and both TMS and multi-locus TMS, combined with neuroimaging, will play a promising role in pursuing the aims of RDoC.

3.1 Neuroimaging in major depressive disorder

Neuroimaging refers to non-invasive methods that allow the visualization of brain structure and activity. These techniques enable researchers to map brain networks, study the mechanisms underlying neurological and psychiatric disorders, such as depression, and identify biomarkers relevant to diagnosis, treatment response, and personalized medicine. In this way, neuroimaging has revolutionized our ability to understand the brain. The term neuroimaging covers standard methods, such as fMRI, PET, electroencephalogram (EEG), and magnetoencephalogram (MEG), but also more advanced techniques, including DTI and transcranial electrical stimulation (TES) [40]. Each provides different brain insights, and choosing a method fit for purpose is essential.

Through neuroimaging, the structural, functional and network-level alterations in depression, described in chapters 2.3–2.5, have been revealed. Brain connectivity analyses, as highlighted by Williams (2016), have deepened understanding of depression and guided treatment development [25]. By examining individual connectivity profiles, it becomes possible to identify optimal targets for brain stimulation therapies, such as TMS [25]. Supported by literature, this thesis focuses on two complementary neuroimaging techniques widely used in depression research: fMRI, which provides region-specific functional information, and DTI, which provides data on structural connectivity [40]. In addition, insights from lesion studies are also discussed to address the causal perspective in depression [41].

3.1.1 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a powerful, non-invasive neuroimaging tool that uses magnetic fields and radio waves to generate detailed brain images. It measures changes in neural activity indirectly by monitoring the brain blood flow, providing insights into both brain function and structural connectivity [40].

The primary application of fMRI is mapping brain activity, as it can localize responses during specific tasks or stimuli. Identifying the activated brain regions helps to recognize functional networks and understand how different brain regions interact. Functional MRI is also widely used to study cognitive processes, which is relevant to depression due to common cognitive impairments in MDD [40]. For the purposes of this thesis, the most important application of fMRI is investigating neurological and psychiatric disorders and improving targeted treatments for these diseases. Functional MRI is often applied to study precisely depression, and being non-invasive and well-tolerated by patients, it supports repeated measurements and longitudinal studies critical for studying psychiatric abnormalities [40].

Recent advances have further expanded the value of fMRI. Technologies, such as multiband fMRI, increase temporal resolution and allow for real-time monitoring of functional connectivity (FC). Other developments, including resting-state fMRI, graph theories, correlation and component analyses, have enhanced the study of FC, crucial for understanding network-based disorders, such as depression. Higher spatial resolution has been achieved with developments, such as the ultra-high field fMRI, while recent multimodal integrations with EEG and MEG provide complementary temporal and spatial information [40].

Despite its benefits, fMRI still faces limitations that negatively affect its performance. While fMRI offers great spatial resolution, it has relatively poor temporal resolution. This results from the blood oxygen level–dependent (BOLD) signal, reflecting hemodynamic changes that lag behind neural activity by several seconds. Furthermore, its millimeter-scale spatial resolution cannot capture the individual action of neurons or cerebellar areas. Moreover, the data from fMRI is vulnerable to noise from motion, physiological fluctuations, and scanner-related artifacts, reducing the signal-to-noise ratio (SNR). As BOLD is an indirect measure influenced by vascular and metabolic factors, interpreting fMRI findings requires careful consideration [40].

3.1.2 Diffusion tensor imaging

Compared to fMRI, diffusion tensor imaging (DTI) belongs to the category of more advanced neuroimaging techniques. As a form of structural MRI, it is used to illustrate the white matter tracts in the brain by estimating the predominant diffusion direction in voxels. Most often, this is done with a metric called fractional anisotropy, which reflects the water diffusion's directionality and degree of coherence within a voxel. This allows the creation of fiber-orientation maps and the study of white matter connectivity patterns [40].

DTI-based tractography enables examining the long-range structural connections and their abnormalities in neurological disorders. It can also detect white-matter changes associated with learning and practice, making it useful for studying brain plasticity and potentially for future rehabilitation applications. Combined with FC analysis, DTI can be used to connect structural and functional network organizations, offering valuable insights for diagnosis and treatment development [40].

The recent advances in DTI technology include high angular diffusion imaging (HARDI), which better captures complex and crossing fibers. Multi-shell and multi-tissue modelling have enabled the estimation of diffusion parameters across several compartments within one voxel, improving microstructural accuracy. Furthermore, enhanced tractography algorithms have improved the reliability of DTI-based fiber tracking by involving more complex tools, such as probabilistic modelling, constrained spherical deconvolution, and anatomical priors. Future directions involve integrating DTI with other modalities, such as fMRI, to provide complementary information about brain networks [40].

DTI possesses many features that benefit both researchers and patients, but it is still limited. Its diffusion model oversimplifies the behaviour of water in biological tissue, introducing inaccuracies in interpreting diffusion metrics. Moreover, the white matter tract visualizations and connectivity estimations remain imprecise as DTI is applied to also more complex brain regions with fiber crossings or orientation dispersion. DTI is susceptible to noise and artifacts, causing degrading effects in image quality and reliability. Limited spatial resolution and long acquisition times further constrain its ability to resolve fine-scale white matter microstructure [40].

3.1.3 Lesion–symptom mapping

In addition to functional and structural MRI, this thesis considers the value of lesion studies for understanding depression and guiding TMS targeting. Unlike fMRI or DTI, lesion-based insight requires that the depressive symptoms follow a focal brain injury. As stated by Trapp et al. (2023), lesion studies offer a method to identify brain regions causally related to specific functions, such as mood [41]. This approach is logical, given that lesion studies have formed the basis of early and current models of brain function before modern neuroimaging [41].

Lesion–symptom mapping has been successfully applied to investigating depression [41]. Before the large-scale lesion–symptom mapping conducted by Trapp et al. in 2023, there was a relative pause of systematic efforts to use modern lesion tools for depression. Prior results on whether lesion location links to person's risk for or resistance to developing depression were inconsistent, likely due to the multidimensionality of depressive symptoms, different behavioural rating scales across studies, small sample sizes, and approximate lesion location data. Another limitation has been the network-level nature of depression, causing the symptoms to distribute across several regions [41].

More recently, novel imaging methods have been applied to examine the network effects to focal lesions associated with depressive symptoms [41]. Lesion–network mapping (LNM) combines functional imaging results with lesions and connectivity data from healthy controls to infer the network effects of focal lesions. With LNM, researchers have demonstrated that lesions connected to the left PFC are related to higher rates of depression than unrelated lesions [41]. Trapp et al. utilized both conventional and multivariate lesion–symptom mapping as well as functional and structural LNM to conclude that focal lesions to particular nodes of the SN and DMN correlate with higher risk versus resiliency for depressive symptoms. The results suggested that lesions to SN nodes (anterior insula, dlPFC, and left dorsomedial PFC) relate to a greater post-lesion depressive symptom burden, while lesions of DMN nodes (OFC, mPFC, and inferolateral anterior temporal lobe) connected with lower-than expected post-lesion depressive symptoms [41]. The future of lesion studies will focus on lesion–symptom mapping of specific depression subtypes or symptom categories as well as on longitudinal evaluation of the relation between SN/DMN and developing depression after lesion [41].

3.2 Transcranial magnetic stimulation and treatment targeting

Transcranial magnetic stimulation (TMS) is a multifaceted, non-invasive brain stimulation method in which an electric current in a coil (typically a figure-of-eight coil [11]) generates a magnetic field. This field induces an electric field that drives ionic movement in cortical tissue, generating an electric current that depolarizes (or hyperpolarizes) neurons beneath the coil. The movement of charged particles, i.e., the electric current, can produce action potentials and modulate local circuit activity [39, 42]. TMS involves several context-dependent parameters, including the number of total pulses, the frequency of stimulation, the intensity of magnetic stimulation, time duration between each sequence, and target regions stimulated on the cortex. All these factors relate to the bioeffects of the method [42].

Brain stimulation methods, including TMS, aim to normalize brain activity in regions disrupted in depression [27]. TMS has shown promising results in TRD, and repetitive TMS (rTMS) has performed effectively as an antidepressant for adolescents with drug-resistant depression [42]. The first protocols targeted the hypoactive dlPFC, but the clinical efficacy was relatively low. However, advances in neuroimaging-guided TMS and coil designs capable of reaching deeper structures have since improved target selection and response rates [27].

Therapeutically relevant targets extend beyond the dlPFC [27]. Even though current clinical devices stimulate only one brain region at a time, TMS effects are mediated via network-level connectivity. Treatment efficacy depends significantly on the anatomical and functional connectivity profile of the targeted region – for example, Li et al. (2018) demonstrated that rTMS responders and non-responders to dorsal mPFC stimulation showed distinct connectivity patterns within the reward network (PAN [25]) [27]. Such findings highlight the importance of integrating neuroimaging to guide TMS and characterize individual connectivity profiles. Therefore, the advanced approaches, such as neuronavigated multi-locus TMS, have the potential to increase the modest response rates of current rTMS protocols [12]. Chapter 3.2 reviews the benefits and limitations of TMS in depression treatment and explores the potential of multi-locus TMS, focusing on the underlying principles and the factors contributing to previous clinical success and failure.

3.2.1 Repetitive transcranial magnetic stimulation

As implied by its name, repetitive TMS involves not only one but frequent pulses to the targeted cortical region and is now the standard form of TMS. It is currently utilized to treat several psychosocial disorders, including depression. Repetitive TMS is believed to alter synaptic plasticity via long-term potentiation/depression (LTP/LTD) mechanisms, influencing NMDA receptor activity and cortical network dynamics. Although the stimulation is applied locally, its effects achieve deeper regions and more distant neural circuits through connectivity. Repetitive TMS produces activity-dependent neuromodulation, associated with the brain's intrinsic oscillatory rhythms [42].

The frequency of induced pulses in rTMS can be either high-frequency (> 5 Hz), inducing excitatory effects, or low-frequency (<= 1 Hz), inducing inhibitory impacts [42]. When rTMS was first utilized for depression, the treatment site was localized rather straightforwardly in the left dlPFC, using the "5 cm rule": by identifying the so-called motor hot spot and moving the coil 5–5,5 cm anterior to this site in the sagittal plane. However, issues with this approach were apparent already in the early 2000s, reflected in the modest results of positive responses [43].

A major advance emerged in 2012, when Fox et al. introduced connectivity-based targeting. Using resting-state fMRI, they identified dlPFC sites most strongly anti-correlated with the hyperactive sgACC in depression [8]. These sites were typically more anterior and lateral than those selected with the 5 cm rule, highlighting the value of functional connectivity in target selection. However, the solution to targeting may not be as straightforward as this approach indicated [43].

In 2018, Peng et al. outlined three current rTMS protocols in depression treatment: low-frequency stimulation (LF-rTMS) of the left dlPFC, high-frequency stimulation (HF-rTMS) of the right dlPFC, and a combination of the first two. The first protocol has Level A recommendation in European guidelines, supported by promising results. In contrast, the efficacy of the second protocol is only defined as probable, classified as Level B recommendation. However, some studies have yielded results of similar effects from both approaches [42], indicating that individual anatomy and connectivity strongly shape outcomes. While Peng et al. mention that parameters associated with rTMS efficacy include combinations of >1000 pulses per session, stimulation intensity >100% of the motor threshold, and >10 rTMS sessions, the need for further research to determine the most effective parameters is highlighted [42].

Symptom-specific targeting has further refined the field. Siddiqi et al. (2019) identified two symptom clusters responding to distinct dlPFC subregions: a dysphoric cluster responding to a more anterior-lateral site, similar to Fox's target, and a cluster involving anxiety and somatic symptoms, responding best to stimulation within more posterior-medial site [44]. These findings may explain inconsistencies in earlier rTMS results and indicate that different symptom dimensions may require stimulation of totally different circuitries [43].

The variability in clinical outcomes highlights the need for optimized and individualized targeting. Furthermore, the consideration of different protocols and advances in TMS technology arises. Fitzgerald et al. proposed stimulating the dlPFC more broadly to ensure coverage of all relevant areas in all patients, supported by the generally consistent safety record of TMS [43]. Moreover, rTMS has also been applied beyond the dlPFC: studies report apparent therapeutic effects when targeting the dorsal mPFC, OFC, and ACC – regions implicated in depression-related network dysfunction [27]. While rTMS has frequently proved to be efficient in both open and randomized controlled studies, the optimal parameters to ensure individualization in targeting remain unresolved [42, 43]. The clinical utility of the method can only be determined by evaluating its safety, long-term effects, and the increased quality of life for patients [42], which are not quite where they should be yet.

3.2.2 Multi-locus transcranial magnetic stimulation

Even with neuronavigation, conventional TMS devices face a core limitation: altering the stimulation site requires manually repositioning a heavy coil proximal to the scalp, making the procedure slow and cumbersome [11]. To overcome this and to avoid using maximum three large, adjacent coils to enable multi-site stimulation, multi-locus TMS was developed in the late 2010s [11].

Multi-locus TMS (mTMS) is an advanced, still-developing form of TMS that enables the stimulation of different cortical targets without physically moving the coils [12]. Sinisalo et al. (2024) describe it as a "groundbreaking technique" with potential for several clinical applications [12]. Multi-locus TMS uses a stack of overlapping coils, i.e., a coil array, which can be fired simultaneously to target different locations in the cortex. With different pulse combinations and freely chosen time delays between pulses (down to less than a millisecond), the stimulation can be aimed at any network nodes within the coil array's coverage area [12].

Implementing mTMS requires coordinated elements, including coil arrays, electronics, and software [12]. Overlapping electric fields from multiple coils are summed to form new, flexible stimulation fields. Most importantly, the location and orientation of these combination fields differ from what any of the coils could generate alone. Increasing the number of coils expands the ability to shift targets and shape the induced electric field. Compared with conventional TMS, mTMS offers substantially greater flexibility and enables true multi-site stimulation. Technically this is achieved with centrally controlled, independently operating stimulators with dedicated power circuits and high-voltage capacitors, allowing rapid changes in pulse combinations within milliseconds. Advanced power electronics and high-frequency semiconductor technologies enable fast target switching while maintaining control over pulse shapes [12].

Although more complex and physically larger than standard TMS systems, mTMS is electronically steerable, removing the need for manual coil movement and enabling faster and more accurate targeting [11]. Reaching its full potential requires real-time algorithms that integrate data from neuroimaging methods, such as fMRI, DTI, EEG, and MEG, supporting automated and individualized targeting. Future mTMS systems will also utilize closed-loop stimulation that enables automating operations, such as signal preprocessing, real-time analysis, and device control [12]. This interplay between hardware and software is demonstrated in Figure 4.

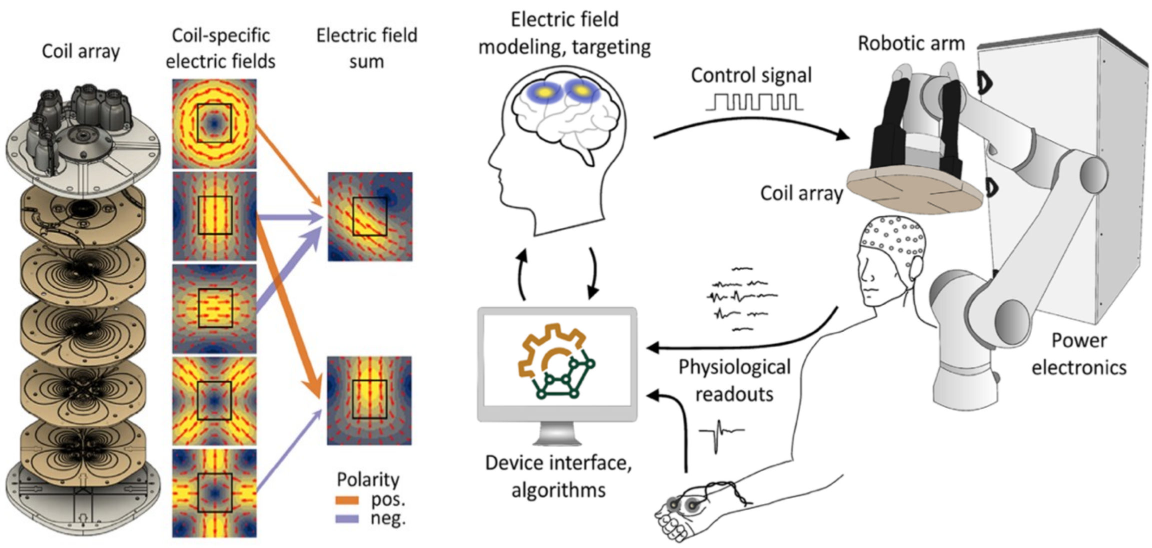

Figure 4. Demonstration of a multi-locus TMS coil array and a schematic illustration of a mTMS system with assisting components. On the left, the mTMS state-of-the-art five coil array is illustrated. Currently, this number of coils is the practical limit, as the cortical field decreases significantly with coil distance. The field patterns of the individual coils are visualized next to the coil array. By combining these fields, mTMS can generate stimulation locations and orientations unattainable with any single coil. The arrow widths represent the relative contributions of individual electric fields, while colours refer to either positive (orange) and negative (blue) polarity. The black box limits the stimulation target under the coil array.
The mTMS paradigm is illustrated on the right. Software and hardware work together to guide the stimulation to desired targets, such as individual nodes within a larger brain network. Algorithms use EEG/MEG information and electric-field modelling to determine optimal pulse combinations, while a robotic arm positions and stabilizes the coil array. The illustrations are adapted from Sinisalo et al. (2024) [12].

As discussed earlier, the structural and functional abnormalities in brain disorders such as MDD rarely stem from a single cortical or subcortical region. Since the disorder derives from disruptions within and between larger networks, multi-site stimulation becomes a logical therapeutic strategy. Control theory further supports this view: a complex state-space system like the brain is very difficult to control via a single-site stimulation alone. Furthermore, neural connections grow stronger when neurons fire together [12]. Studies demonstrating the superior efficacy with multi-site stimulation exist – for instance, Trevizol et al. (2019) showed higher remission rates in treating late-life TRD with bilateral TMS compared to stimulation with only single-hemisphere TMS [45]. For these reasons, multi-locus TMS distinguishes as a promising future treatment alternative for managing network-level diseases, as also emphasized by Sinisalo et al. (2024) [12]. Figure 5 presents possibilities for multi-locus TMS in brain rehabilitation involving network abnormalities and outlines its advantages over conventional rTMS.

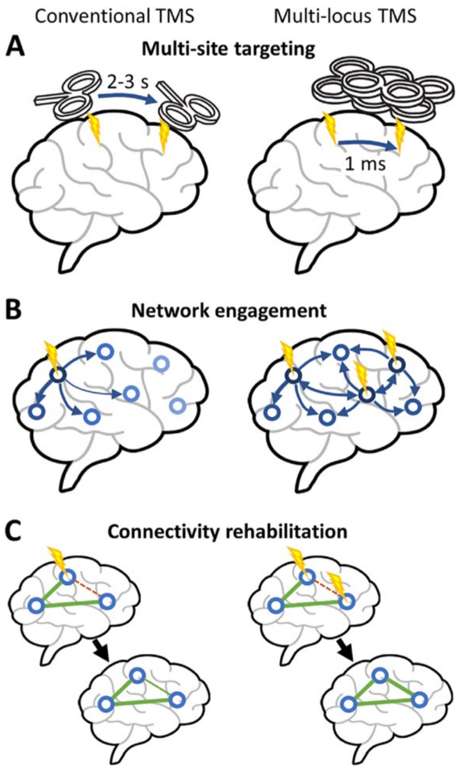

Figure 5. Multi-locus TMS in the context of brain networks. This illustration presents how multi-locus TMS may increase efficacy in network-based disorders compared to TMS currently in clinical use.
(A) Conventional TMS cannot provide simultaneous multi-site stimulation because changing targets requires physically moving the coil. In mTMS, electronic steering enables millisecond-level target shifts. **B)** Conventional TMS can stimulate only one node of a network, limiting its ability to normalize network dynamics, whereas mTMS can deliver rapid, precisely timed pulses that modulate communication between regions more effectively. **C)** As many brain disorders involve weakened inter-regional communication mTMS is expected to increase clinical outcomes by restoring disrupted connections with repetitive, concurrent pulses to interconnected brain nodes. The line widths indicate connection strengths. The illustration is adapted from Sinisalo et al. (2024) [12].

Without hesitation, multi-locus TMS holds great promise for future research and clinical applications. However, as discussed in the article by Sinisalo et al. and in private conversations with the inventors and researchers of the technology, a few important challenges remain [12, 46]. Safety considerations include the need for stronger hearing protection and careful monitoring of the coil temperature, caused by higher impulse noise and heat accumulation per pulse. Designing a modular mTMS device that is both robust and maintainable also poses technical difficulties. The modern technology utilized to reach the full potential of mTMS must be accessible for research groups and hospitals – this is essential for engaging the patients that could benefit from this method. Like conventional TMS, multi-locus TMS cannot deliver straightforward focal stimulation to deeper brain structures and still relies on standardized algorithms, highlighting the ongoing need for individualized targeting [46]. As Sinisalo et al. note, mTMS could develop into a revolutionary tool for treating several disorders in the brain [12], but to unlock its full capacity, more research, multimodal integration and clinical trials are required.

4 Methods

4.1 Databases and search strategy

This thesis is a literature review, intending to investigate, combine, and critically analyze the existing literature on MDD, neuroimaging techniques, TMS, and multi-locus TMS. As the literature around depression-related themes is extensively abundant, limiting the addressed sources was crucial. The references included have been chosen by obeying the following criteria:

1. the reference is recent, novel or temporally significant,
2. the reference is principal work, a pioneer in its field or generally recognized,
3. the reference is simple and comprehensible enough, written in a way that it assists the writer's comprehension on a complex topic.

The major databases used were open access or allowed for viewing via Aalto university access. These refer mainly to Google Scholar, PubMed and ScienceDirect. Some sources that seemed feasible were not permitted for viewing, and for these reasons accessibility became the main criteria for choosing the database.

A major reference used in this thesis was chosen for special reasons. The network model for depression, suggested by Williams in April and September 2016, was chosen out of all options, as it served the purpose of the thesis best. Since the model is more clinically oriented and diagnostically applicable as it introduces symptom-specific biotypes, it works better for this thesis than some other models that exist. It aligns with the aims of combining brain regions, networks and symptoms in depression, and, on the other hand, assists in understanding the potential of multi-locus TMS in depression treatment. In addition, a lecture held by HUS clinical psychiatric researcher, Tuukka Raj, utilized this specific model in November 2025, validating the selection of William's model for this thesis.

Also deserving a separate mention, material from the Special Course in Human Neuroscience, lectured by professors Lioumis, Ilmoniemi and Makris in 2025 at Aalto university, was included in this thesis. The course helped with understanding the bigger picture of the paradigm shift in modern neuroscience, gave motivation and inspiration for the thesis, and served as a guide in understanding the complex brain anatomy in detail.

4.2 Use of artificial intelligence

This thesis is original work of the writer. However, AI tools have been used in some tasks for assistance. This refers to assistance in academic writing, grammatic correctness, and finding synonyms. AI has also briefly been used to help in ideas and planning during the first weeks. As the material in the field of depression is extremely broad, AI has been used to search relevant references and translate or explain some material that has felt difficult to understand. In the final phase of writing, some summarizing help has been utilized to minimize repetition, additionally to fitting into desired number of pages.

5 Results

Area	Network	Symptoms in MDD
dlPFC	CCN, AN	Impaired problem-solving, working memory and top-down attention control, poor emotion regulation, suicidal ideation and behaviour, ***treatment sensitivity***
mPFC	DMN, NAN, PAN, AN	Depressive rumination, negative self-focus, reduced top-down emotional control, weaker processing of reward experiences, ***treatment resistance***
ACC	SN, NAN, PAN, CCN	Impaired conflict monitoring, anxious avoidance, over-processing of conflict signals, poor downregulation of threat, decreased contextual flexibility
PCC	DMN	Stuck internal focus, interference of default mode network and its functions during tasks, ***treatment sensitivity***
OFC	PAN	Reduced valuation, consummatory anhedonia, weak reward updating
DPC	CCN	Difficulties with goal maintenance and task rules
Insula	SN, NAN, AN	Exaggerated salience of negative stimuli and interpersonal cues, heightened self-awareness and self-criticism, increased bodily response to threat, overall symptom severity
Amygdala	SN, NAN	Exaggerated salience of negative stimuli and threat response, negative emotional bias
Hippocampus	DMN, NAN	Overgeneral memory, memory deficits, negative memory bias
Striatum	PAN	Motivational anhedonia, subdued reward anticipation, weak reward updating
Precuneus	AN	Attention shifting to threat or worry
PCG	CCN	Impaired ability to perform tasks
AG	DMN	Stuck internal focus
aIPL	AN	Attention shifting to threat or worry

Table 2. The relationship between the disrupted brain regions, networks, and symptoms in MDD. This table holds the results of this thesis and connects the complex relations between brain regions, networks and symptoms in depression. The references for this table are mainly from Williams (2016) [25, 26], with additions from also other sources [5, 47, 48]. Comparing the articles by Williams in April 2016 versus September 2016, the main difference is that in the latter the negative affect network is called the threat network and the positive affect network is called the reward network. In the latter article, hippocampus is included in the threat network [26], but some sources include it in DMN [47]. This thesis uses mainly the terms negative and positive affect network. The third column holds the region-network related symptoms, but also ***treatment sensitivity*** and ***treatment resistance***, which have been associated with hypoconnective PCC and the left dlPFC, and hyperconnective anterior mPFC, respectively [26, 42].

6 Discussion

One aim of this literature review was to identify symptom-specific brain regions and networks in depression to support the target selection for multi-locus TMS. The key findings are summarized in Table 2 in chapter five. If the clinical relevance of a region is defined by its involvement in multiple large-scale networks, the most critical areas disrupted in depression are the mPFC (DMN, NAN, PAN, AN), ACC (SN, NAN, PAN, CCN), and insula (SN, NAN, AN). Each of these participates in at least three networks and is therefore linked to the multifaceted symptom profile of depression. Symptom severity is already known to relate to these regions, most notably to the insula, which has been associated with overall symptom burden [26, 48]. This suggests that, without information at the individual level, these regions could be considered primary targets for multi-locus TMS, either through direct stimulation or via connectivity-based approaches.

However, the literature also suggests that hyperconnective anterior mPFC in DMN is associated with treatment resistance [26], which may limit the efficacy of its stimulation. In contrast, hypoconnective PCC node in DMN has been linked to treatment sensitivity [26], indicating possible therapeutic efficacy in future depression treatment. Furthermore, targeting the dlPFC, as the standard clinical target, is supported by its association with suicidal behaviour [5], which is one of the most severe, high-risk symptoms of depression. Even though the dlPFC has been proven to be responsive to rTMS [42], the overall response rates of dlPFC link strongly to anticorrelation with the commonly hyperactive sgACC [8]. Previous results, both clinical responses of rTMS [42] and lesion-based studies [41], indicate that generally the left dlPFC may be more associated with depression than the right.

As noted earlier, suicidal ideation and behaviour are among the most dangerous but also disease-specific symptoms for depression. Suicidality, however, occurs commonly in addiction too, which, similar to MDD, is now understood as a network-level disorder [49]. In addiction, the primary disrupted network is the reward network (or positive affect network), leading to typical addictive symptoms, such as relapse and craving [50]. Disruptions in this network are also characteristic of depression, contributing especially to anhedonia and impaired reward processing and motivation. This shared feature, altered reward network, may represent a promising future direction for research on the origin and management of suicidal behaviour.

Given the focus of this thesis, using neuroimaging to guide the target selection for multi-locus TMS, it is evident that functional and structural MRI are essential for individualizing mTMS-based treatment in depression. Based on the literature and previous results with rTMS, fMRI and DTI are well-suited for this purpose (alongside with EEG and MEG) [2, 5, 12, 18, 40, 51], as depression involves both functional and structural alterations that these methods respectively capture. The results of this thesis support integrating both fMRI and DTI in future mTMS protocols, as they offer complementary information and are jointly required to obtain individual FC data. Their strengths also offset one another, with fMRI offering superior spatial resolution and DTI compensating for temporal limitations. These methods are also developing and improving continuously [40]. In addition, causal insight from lesion-based methods can support targeting [41].

Consistent with Sinisalo et al. (2024), multi-locus TMS may soon outperform current rTMS by enabling precise, multi-site stimulation guided by real-time neuroimaging feedback. Combining MRI, particularly fMRI and DTI, with network-based models of depression would allow mTMS not only to reach targets inaccessible to standard rTMS, but also to avoid stimulating critical neighboring or connected regions [12]. Achieving this will require seamless integration with multiple neuroimaging methods and automated algorithms within a closed-loop system, enabling personalized identification of hotspots, optimal coil orientation, and stimulation timing. Stimulation could also be synchronized with intrinsic brain rhythms, potentially influencing whether the effect is excitatory or inhibitory [12]. The development of such paradigms could benefit from rapidly advancing AI-based tools.

Several questions remain, particularly regarding the implementation of a dynamic, individualized and feedback-based mTMS paradigm: if stimulation parameters adjust continuously in real time, how should the dosing be determined? During multi-site stimulation, should the limits be dictated by connectivity, induced brain activity, or electric field distributions [12]? Additionally, further research is required to determine how patient biotypes influence responsiveness to TMS-based treatments. Despite these open questions, the future MDD treatment will likely involve neuronavigated multi-locus TMS.

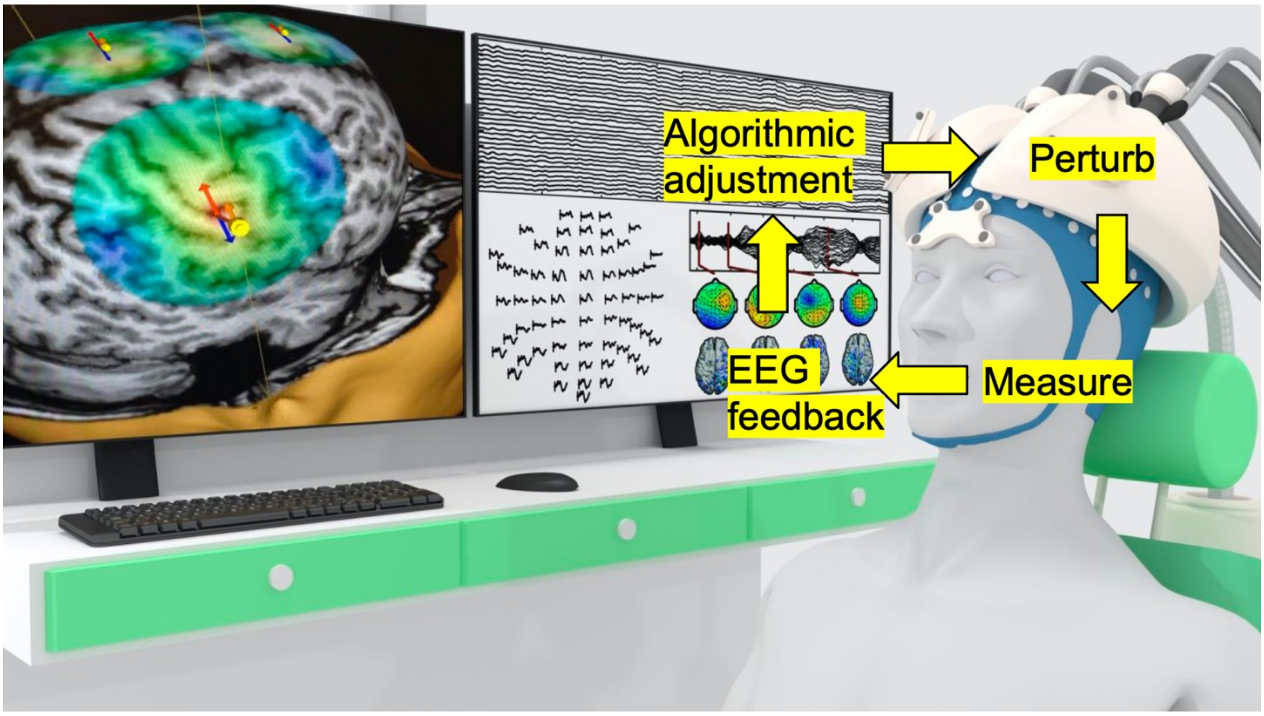

Figure 6. The future (> 2026) closed-loop paradigm of multi-locus TMS, by Lioumis (2025) [39]. This response-guided closed loop paradigm of multi-locus TMS utilizes EEG to provide the feedback signal from each perturb, i.e., stimulation. These responses are measured, demonstrated with EEG, and then integrated with algorithms that are adjusted based on responses. The next stimulation is given based on previous responses. In the future, this paradigm could be improved by adding real-time structural and functional MRI methods to help guide the stimulation, focusing on evoked or altered activity and connectivity. The illustration is adapted from Lioumis (2025) [39].

7 Conclusion

This bachelor's thesis examined MDD and its treatment from the perspective of modern neuroscience, neural network theory, neuroimaging, and non-invasive brain stimulation, with a focus on TMS and the emerging multi-locus TMS. MDD is a network-level disorder characterized by hypoactive prefrontal regions and hyperactive limbic and subcortical structures, with substantial individual variability in brain anatomy, function and connectivity. This review identified symptom-specific large-scale networks and highlighted key regions, i.e., ACC, PCC, mPFC, dlPFC, and insula, whose involvement was concluded to indicate overall symptom severity or multidimensionality, or treatment sensitivity. Consequently, these areas were suggested as potential targets of multi-locus TMS. As nearly half of the patients fail to respond to first-line antidepressant medication and meet the criteria for treatment-resistant depression, an urgent need for individualized treatment built on network-based neuroscience exists. This thesis concludes that fMRI and DTI, supported by lesion-based approaches, provide complementary and, in the case of lesions, causal insights that can guide multi-locus TMS targeting. By integrating these imaging tools with multi-locus TMS, which enables precise, automated, multi-site stimulation, depression treatments could transform towards highly personalized and circuit-specific interventions that address the heterogenetic nature of depression. Although some technological and conceptual questions remain, such as algorithm individualization, determining real-time dosing, and understanding the influence of patient biotypes, the future prospects of multi-locus TMS as a transformative, network-based therapy for MDD seem hopeful.

8 References

[1] Marx W, et al. Major depressive disorder. *Nature Reviews Disease Primers*. 2023;9(44).
Available from: https://doi.org/10.1038/s41572-023-00454-1

[2] aan het Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. *CMAJ*. 2009;180(3):305–313.
Available from: https://doi.org/10.1503/cmaj.080697

[3] Berk M, et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. *World Psychiatry*. 2023;22(3):366–387.
Available from: https://doi.org/10.1002/wps.21110

[4] Croset L. Activity and functional connectivity of key nodes in depression network: A resting state EEG study. Master's thesis. 2024.

[5] Pandya M, Altinay M, Malone DA, Anand A. Where in the Brain Is Depression? *Current Psychiatry Reports*. 2012;14:634–642.
Available from: https://doi.org/10.1007/s11920-012-0322-7

[6] Downar J, Daskalakis ZJ. New Targets for rTMS in Depression: A Review of Convergent Evidence. *Brain Stimulation*. 2013;6(3):231–240.
Available from: https://doi.org/10.1016/j.brs.2012.08.006

[7] Lacroix A, et al. Predictors of clinical response after rTMS treatment of patients suffering from drug-resistant depression. *Translational Psychiatry*. 2021;11:587.
Available from: https://doi.org/10.1038/s41398-021-01555-9

[8] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate. *Biological Psychiatry*. 2012;72(7):595–603.
Available from: https://doi.org/10.1016/j.biopsych.2012.04.028

[9] Cash RFH, et al. Subgenual Functional Connectivity Predicts Antidepressant Treatment Response to Transcranial Magnetic Stimulation: Independent Validation and Evaluation of Personalization. *Biological Psychiatry*. 2019;86(2):E5–E7.
Available from: https://doi.org/10.1016/j.biopsych.2018.12.002

[10] Lefaucheur JP, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*. 2014;125(11):2150–2206.
Available from: https://doi.org/10.1016/j.clinph.2014.05.021

[11] Koponen LM, Nieminen JO, Ilmoniemi RJ. Multi-locus transcranial magnetic stimulation–theory and implementation. *Brain Stimulation*. 2018;11(4):849–855.
Available from: https://doi.org/10.1016/j.brs.2018.03.014

[12] Sinisalo H, et al. Modulating brain networks in space and time: Multi-locus transcranial magnetic stimulation. *Clinical Neurophysiology*. 2024;158:218–224.
Available from: https://doi.org/10.1016/j.clinph.2023.12.007

[13] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR™). Washington, DC: American Psychiatric Publishing. 2022;183–187.

[14] Yan G, et al. Global, regional, and national temporal trend in burden of major depressive disorder from 1990 to 2019: An analysis of the global burden of disease study. *Psychiatry Research*. 2024;337:115958.
Available from: https://doi.org/10.1016/j.psychres.2024.115958

[15] Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. *Genes & Development*. 2009;23:781–783.
Available from: https://genesdev.cshlp.org/content/23/7/781.full.

[16] Skaper SD. The Neurotrophin Family of Neurotrophic Factors: An Overview. *Neurotrophic Factors. Methods in Molecular Biology, vol. 846*. Humana Press. 2012;846:1–12.
Available from: https://doi.org/10.1007/978-1-61779-536-7_1

[17] Roohi E, Jaafari N, Hashemian F. On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? *Journal of Neuroinflammation*. 2021;18:45.
Available from: https://doi.org/10.1186/s12974-021-02100-7

[18] Trifu SC, Trifu AC, Aluas E, Tataru MA, Costea RV. Brain changes in depression. *Romanian Journal of Morphology and Embryology*. 2020;61(2).
Available from: https://doi.org/10.47162/RJME.61.2.06

[19] Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. The *Journal of Neuropsychiatry and Clinical Neuroscience*. 1997;9(3).
Available from: https://doi.org/10.1176/jnp.9.3.471

[20] Drevets WC, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–827.
Available from: https://doi.org/10.1038/386824a0

[21] Anand A, et al. Activity and Connectivity of Brain Mood Regulating Circuit in Depression: A Functional Magnetic Resonance Study. *Biological Psychiatry*. 2005; 57(10):1079–1088.
Available from: https://doi.org/10.1016/j.biopsych.2005.02.021

[22] Greicius MD, et al. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*. 2007; 62(5):429–437.
Available from: https://doi.org/10.1016/j.biopsych.2006.09.020

[23] Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure and Function*. 2008;213:93–118.
Available from: https://doi.org/10.1007/s00429-008-0189-x

[24] Spellman T, et al. Toward Circuit Mechanisms of Pathophysiology in Depression. *The American Journal of Psychiatry*. 2020;177(5).
Available from: https://doi.org/10.1176/appi.ajp.2020.20030280

[25] Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. The *Lancet Psychiatry*.2016;3(5):472–480.
Available from: https://doi.org/10.1016/S2215-0366(15)00579-9

[26] Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. *Depression and Anxiety*. 2016;34(1):9–24.

Available from: https://doi.org/10.1002/da.22556

[27] Li BJ, et al. A brain network model for depression: From symptom understanding to disease intervention. *CNS Neuroscience and Therapeutics*. 2018;24(11):1004–1019.
Available from: https://doi.org/10.1111/cns.12998

[28] Saper CB, Lowell BB. The hypothalamus. *Current Biology*. 2014;24(23): R1111–R1116.
Available from: https://doi.org/10.1016/j.cub.2014.10.023

[29] Haber SN. Neuroanatomy of reward: a view from the ventral striatum. *Neurobiology of Sensation and Reward*. Boca Raton (FL): CRC Press/Taylor & Francis. 2011. Chapter 11.

[30] Sobstyl M, Prokopienko M, Pietras T. The ventral capsule and ventral striatum — stereotactic targets for the management of treatment-resistant depression. A systematic literature review. *Frontiers in Psychiatry*. 2023;14:1100609.
Available from: https://doi.org/10.3389/fpsyt.2023.1100609

[31] McIntyre RS, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. 2023;22(3):394–412.
Available from: https://doi.org/10.1002/wps.21120

[32] Karrouri R, Hammani Z, Benjelloun R, Otheman Y. Major depressive disorder: Validated treatments and future challenges. *World Journal of Clinical Cases*. 2021;9(31):9350–9367.
Available from: https://doi.org/10.12998/wjcc.v9.i31.9350

[33] Dunlop BW. Evidence-Based Applications of Combination Psychotherapy and Pharmacotherapy for Depression. *Focus*. 2016;14(2).
Available from: https://doi.org/10.1176/appi.focus.20150042

[34] Yavi M, et al. Ketamine treatment for depression: a review. *Discover Mental Health*. 2022;2(9)
Available from: https://doi.org/10.1007/s44192-022-00012-3

[35] Nelson JC, Papakostas GI. Atypical Antipsychotic Augmentation in Major Depressive Disorder: A Meta-Analysis of Placebo-Controlled Randomized Trials. *The American Journal of Psychiatry*. 2009;166(9).
Available from: https://doi.org/10.1176/appi.ajp.2009.09030312

[36] Janela D, Jerónimo J, Rema J P, Telles-Correia D, Novais F. Psychostimulant Augmentation of Antidepressant Therapy in Depression: a Systematic Review and Meta-Analysis. *Current Treatment Options in Psychiatry*. 2023;10:492–510.
Available from: https://doi.org/10.1007/s40501-023-00307-4

[37] Trifu S, et al. Efficacy of electroconvulsive therapy as a potential first-line treatment for major depressive disorder (Review). *Experimental and Therapeutic Medicine*. 2021;22(5):1281
Available from: https://doi.org/10.3892/etm.2021.10716

[38] Wu Y, et al. Deep Brain Stimulation in Treatment-Resistant Depression: A Systematic Review and Meta-Analysis on Efficacy and Safety. *Frontiers in Neuroscience*. 2021; 15:655412.
Available from: https://doi.org/10.3389/fnins.2021.655412

[39] Makris N, Lioumis P, Ilmoniemi R. Special Course in Human Neuroscience: Brain circuits: Principles of neuroanatomy in neuroimaging and brain stimulation. Lectures and course material. Aalto university. 2025.

[40] Yen C, Lin C-L, Chiang M-C. Exploring the Frontiers of Neuroimaging: A Review of Recent Advances in Understanding Brain Functioning and Disorders. *Life*. 2023;13(7):1472.
Available from: https://doi.org/10.3390/life13071472

[41] Trapp NT, et al. Large-scale lesion symptom mapping of depression identifies brain regions for risk and resilience. *Brain*. 2023;146(4):1672–1685.
Available from: https://doi.org/10.1093/brain/awac361

[42] Peng Z, et al. Mechanism of Repetitive Transcranial Magnetic Stimulation for Depression. *Shanghai Archives of Psychiatry*. 2018;30(2):84–92.
Available from: https://doi.org/10.11919/j.issn.1002-0829.217047

[43] Fitzgerald PB. Targeting repetitive transcranial magnetic stimulation in depression: do we really know what we are stimulating and how best to do it? *Brain Stimulation*. 2021;14(3):730–736.
Available from: https://doi.org/10.1016/j.brs.2021.04.018

[44] Siddiqi SH, et al. Distinct Symptom-Specific Treatment Targets for Circuit-Based Neuromodulation. *The American Journal of Psychiatry*. 2020;177(5).
Available from: https://doi.org/10.1176/appi.ajp.2019.19090915

[45] Trevizol AP, et al. Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant late-life depression. *International Journal of Geriatric Psychiatry*. 2019;34(6):822–827.
Available from: https://doi.org/10.1002/gps.5091

[46] Lioumis P, Ilmoniemi R. Private conversations about challenges and future directions of multi-locus TMS in depression treatment. Aalto university. 2025.

[47] Jones DT, Mateen FJ, Lucchinetti CF, Jack CR, Welker KM. Default Mode Network Disruption Secondary to a Lesion in the Anterior Thalamus. *Jama Neurology*. 2011;68(2):242–247.
Available from: https://doi.org/10.1001/archneurol.2010.259

[48] Manoliu A, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Frontiers in Human Neuroscience*. 2014;7.
Available from: https://doi.org/10.3389/fnhum.2013.00930

[49] Tolomeo S, Yu R. Brain network dysfunctions in addiction: a meta-analysis of resting-state functional connectivity. *Translational Psychiatry*. 2022;12:41.
Available from: https://doi.org/10.1038/s41398-022-01792-6

[50] Cooper S, Robison AJ, Mazei-Robison MS. Reward Circuitry in Addiction. *Neurotherapeutics*. 2017;14(3):687–697.
Available from: https://doi.org/10.1007/s13311-017-0525-z

[51] Zhang K, et al. Molecular, functional, and structural imaging of major depressive disorder: Recent progress and clinical relevance. *Neuroscience Bulletin*. 2016;32:273–285.
Available from: https://doi.org/10.1007/s12264-016-0030-0