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Examining Potential Biomarkers for Depression Diagnosis: A Literature Review

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Abstract

Introduction: Biomarkers in depression show potential in providing insight into the pathophysiology of the disorder and subsequent treatment plans. Within research, there have been many prospective biomarkers such as endocrine markers, epigenetics, inflammatory markers, cytokines, neuroimaging, growth factors, and more. Based on recent studies, we propose three promising biomarkers associated with diagnosing major depressive disorder (MDD): growth factors, endocrine markers, and neuroimaging.

Methods: Literature searches were performed using databases PsychINFO, PubMed, and Scopus, and a total of seventeen articles were used.

Results: Physical changes in brain volume and thickness of specific brain regions have been associated with the occurrence of MDD such as reduced hippocampal volume in depressed patients along with thinning of the right para-hippocampus. Additionally, progressive cortical thickening in the left inferior central and pre-frontal gyrus has been observed in patients developing MDD.

Brain derived neurotrophic factor (BDNF), a growth factor, could be a potential biomarker for diagnosing MDD as BDNF plays an important role in neuronal development, neuronal survival, and regulating neurotransmitter systems. Depressed individuals exhibit decreased BDNF levels, specifically in the hippocampus and prefrontal lobes.

Three hormones that have been of primary interest related to MDD biomarkers include cortisol, thyroid stimulating hormone (TSH), and prolactin. These hormones are involved in the diathesis-stress response mediated by the activation of the hypothalamus-pituitary-adrenal (HPA) axis. Elevated levels of these hormones were observed in depressive patients.

Discussion: Following an in-depth analysis of neuroimaging, BDNF, and hormones, differences between MDD patients and control groups were observed. Cortical thickness, functional connectivity, and brain activity (blood flow) alterations were all reported in neuroimaging studies. Mainly, decreases in BDNF levels and alterations of hormones were all observed. Each biomarker requires further investigation and limitations that must be considered.

Conclusion: Overall, the literature review on prospective MDD biomarkers suggests abnormalities in BDNF, cortisol, TSH, and prolactin levels in MDD patients. Structural brain differences were also observed through neuroimaging. Ultimately, studying biomarkers would allow us to better visualize how depression affects the body, allowing for the development of diverse diagnostic and treatment courses.

Keywords: major depressive disorder; neuroimaging; brain derived neurotrophic factor; hormones; cortisol; thyroid stimulating hormone; prolactin

Introduction

Major depressive disorder (MDD) is one of the most common and well-known mood disorders, majorly associated with a shift in an individual's mood [1]. Depression is experienced by almost everyone at some point in their life; however, with the appearance of additional symptoms such as abnormal mood, loss of interest, increased irritability or sadness, disturbed vegetative functions, and abnormal cognition over a prolonged period, it can manifest as a clinical disorder termed Major Depressive Disorder [1-3]. MDD has a high prevalence both in occurrence and lifetime span along with high disease burden rates [4]. Oftentimes, high rates of relapse and recurrence are observed, making this a rather chronic disorder [4]. Current diagnostic criteria come from the symptoms and conditions listed in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [3, 5]. The diagnosis is based on identifying five or more of the characteristic symptoms that persist for at least two weeks [3, 5]. DSM-5 also lists several specifiers for MDD including severity, presence of anxious distress, and

psychotic features, which are used to further characterize a patient's condition [3, 5].

Researchers have taken interest in diagnosing MDD using biological methods. A biological marker, often referred to as a biomarker, can be recognized as cellular, biochemical, or molecular changes in "tissues or body fluids" [6]. Biomarkers are also described as tools used to obtain information about potential causes, diagnoses, and treatments of certain diseases [6]. Examples of biomarkers include proteins, brain imaging, hormone levels, and epigenetics that help to identify disease/illness pathogenesis which in turn can aid in treatment plans and an overall better understanding of the disease/illness [6, 7]. In this review, the authors aim to investigate growth factors, endocrine markers, and neuroimaging as three potential biomarkers for diagnosing MDD as recent literature has shown promising research for these three biomarkers. Biomarkers for MDD and their significance are not entirely understood; however, further investigation into biomarkers appears promising as MDD is a diverse disorder that manifests differently amongst affected individuals [8]. The diverse presentation of MDD often poses challenges in diagnosing and treating patients; therefore, by identifying differing biomarkers in MDD individuals, distinguishing between the different subtypes of depression may be possible and biomarkers may help to develop treatment plans and gain an improved understanding of MDD [6,8,9].

Neuroimaging is currently being investigated as a potential biomarker for various disorders including MDD, Alzheimer's disease, and schizophrenia [10, 11]. As neuroimaging utilizes various imaging techniques to get an image of the brain or a section of the brain, it is widely used to observe the alterations in neural tissues that lead to a disease phenotype [10]. It has been extensively used to gain insights into the pathophysiology of MDD and many potential biomarkers have been identified as physical changes in brain volume and thickness of certain brain areas [12]. Previous research employing magnetic resonance imaging (MRI) and positron emission tomography (PET) found changes in frontal and limbic regions, specifically the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), hippocampus, and amygdala [11]. Therefore, further such investigations can provide meaningful insights into the causes, diagnosis, and treatment targets of MDD.

Brain derived neurotrophic factor (BDNF) is one of the proposed biomarkers that was examined in this review. BDNF has been associated with neuronal development and maintenance related to changes in synaptic plasticity and, may contribute to key systems in the brain such as neurotransmitter pathways and stress and reward responses that appear altered in patients with various mental illnesses [13-15]. Depressed individuals tend to exhibit reduced BDNF levels which may be involved in the pathology of MDD, specifically in the hippocampus and prefrontal lobes [14, 16].

Increased levels of hormones such as cortisol, TSH, and prolactin have been recognized as another parameter of MDD [17]. These three hormones interact with the hypothalamic-pituitary-adrenal (HPA) that is triggered in response to stress that may contribute to the pathogenesis of MDD [17]. Abnormal cortisol levels in particular have been associated with mental illnesses, treating cortisol levels have shown to improve the wellbeing of mentally ill patients [18]. Increased levels of TSH have been related to metabolic brain alterations resulting in behavioural and cognitive changes associated with depression [19]. Prolactin has shown to be involved in stress responses, and abnormal levels may contribute to abnormal stress responses seen in depressed patients [20]. Additionally, prolactin plays a role in appetite and abnormal levels may lead to weight gain—fluctuations in weight is another key symptom of depression [20].

In this literature review, seventeen articles were reviewed to investigate the role of neuroimaging, brain derived neurotrophic factor (BDNF), and hormones as prospective biomarkers for a MDD diagnosis over the years. The review of seven articles for neuroimaging revealed extensive use of several neuroimaging techniques in probing the biochemical and physiological changes in the brain in response to MDD. Over the years, the use of molecular imaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and diffusion tensor imaging (DTI) have become mainstream approaches. These techniques, accompanied by commonly used tools like functional magnetic resonance imaging (fMRI) and quantitative electroencephalogram (qEEG), identified the ACC, DLPFC, OFC, and amygdala as major regions for predicting biomarkers. The analysis of BDNF as a biomarker encompassed the review of five articles; decreases in BDNF levels in blood samples of those with MDD has been a potential biomarker. Five articles were analyzed to examine three different hormones: dysregulations amongst cortisol, TSH, and prolactin levels from baseline levels have all served as potential biomarkers of MDD.

Methods

A search for articles investigating MDD and potential biomarkers through neuroimaging, BDNF, and hormones was completed by the end date of February 25th, 2024. Three databases were used for the article search and access, namely PsychINFO through Proquest, PubMed, and Scopus. The main search terms used for the first biomarker were "Biomarkers" AND "Major Depressive Disorder" AND "Neuroimaging". For the second biomarker, the search terms included "Biomarkers" AND "Major Depressive Disorder" AND "Brain-derived neurotrophic factor" OR "BDNF". Similarly, the last search was performed with the terms "Biomarkers" AND "Major Depressive Disorder" AND "hormones". From the database search, the authors selected seven articles for neuroimaging, five articles for BDNF, and

five articles for hormones to review. These articles encompass recent developments in the field of biomarkers for MDD. The articles were reviewed using the outlined methods to identify the progression of emerging biomarkers in MDD diagnosis.

Results

Neuroimaging

The progression of neuroimaging as a biomarker for MDD was evaluated through a literature review of seven scientific articles, depicting the advancements in the field in the last nine years. The earlier investigations primarily focused on using one neuroimaging technique, usually functional connectivity fMRI, to probe limited pathways affecting the depressive mood such as implicit emotional regulation and reward circuit. These studies were also limited in terms of the small sample size and an emphasis on assessing the antidepressant effects [21]. Research on structural and functional neuroimaging biomarkers suggested the importance of various brain structures for treatment response such as: the prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, amygdala, and insula [22]. Many of these areas were further investigated to explore the diagnostic and treatment response as biomarkers for MDD. AI tools in radiology imaging have been used by researchers to identify complex patterns and quantitatively analyze the imaging data [23]. Deep learning algorithms are widely used for data analysis from scans such as MRI and PET. MDD is not characterized by a single symptom but a heterogeneous mixture of physical, mental, and emotional symptoms. To capture this heterogeneity and the underlying neuroimaging biomarkers, machine-learning programs have been introduced detecting multivariate patterns [24]. Therefore, to accurately use the neuroimaging data acquired from different techniques, multivariate statistical analyses were incorporated with a goal of identifying the biological markers for MDD in order to design diagnostic tools. A meta-analysis study using multivariate analyses revealed that the existing models can diagnose depression with about 75% accuracy, however, further experiments are required to consolidate the use of this system for differential diagnosis of depression [25].

Over the last few years, numerous neuroimaging techniques have been extensively developed to identify biomarkers, such as MRI, magnetoencephalography (MEG), near-infrared spectroscopy (NIRS), among others. The results from a number of MRI and MEG studies identified ACC and DLPFC regions as potential structural biomarkers for MDD [11]. Research based on NIRS evaluated blood flow, blood oxygenation, and brain activities which demonstrated the relevance of frontal regions as potential biomarkers. The EEG studies used measurements such as theta density, gamma rhythms, and sleep EEG, often conducted on MDD patients, revealed the role of the PFC as a biomarker, specifically the ACC, DLPFC, and OFC regions [11].

Additionally, the fronto-limbic network has also been identified as a potential candidate for biomarker evaluation. In the same review, some PET and SPECT studies have been used to monitor the neurotransmitter levels in a brain region using radioligand labels for neurotransmitter receptors. The results from various PET studies probing the levels of neurotransmitters like serotonin, reinforced the importance of prefrontal cortex regions (ACC, DLPFC, and OFC) as promising biomarkers for MDD [11]. Whereas the findings from SPECT studies emphasize the role of midbrain, with a focus on serotonergic biomarkers [11]. Another review on neuroimaging summarized the progress of neuroimaging techniques as MDD biomarkers and described the recent advances in each. EEG, fMRI, NIRS, and molecular imaging techniques (PET and SPECT) have been routinely investigated along with DTI, evaluating the connectivity and abnormalities in the white-matter and volumetric analysis for the changes in hippocampal volume in MDD patients [26]. Recently, a study applied a combined approach to investigate the predictors for MDD diagnosis, wherein they utilized fMRI scans alongside neurotrophic factors (BDNF) and HPA axis secreted hormones such as cortisol and inflammatory factors in MDD patients versus healthy controls. The results suggested the use of single-dimensional multi-indicator and multi-dimensional multi-indicator, limited discriminant analysis (LDA) method for MDD diagnosis models based on discovering the abnormal amplitudes of low-frequency fluctuations (ALFF) in the right caudate nucleus through neuroimaging as well as disrupted serum levels of BDNF, IL-4, and cortisol in MDD patients [26].

Extensive research has been conducted on the effect of MDD on the amygdala, the emotion processing center, on the account of commonly observed aberrant emotional responses in MDD patients. Researchers found that hyperactivity in response to negative stimuli resulted in common chara cteristics of MDD such as emotional reactivity and difficulty in stress-management, whereas hypoactivity of amygdala was observed for positive stimuli [27]. A systematic review of such studies based on the response in amygdala connectivity and activity in the presence of selective serotonin reuptake inhibitors (SSRI) showed a decrease in hyperactivity in the presence of a negative stimulus as well as reduced hypoactivity in response to positive stimuli. When the results were evaluated after eight weeks of SSRI treatment, the event-relation functional connectivity (FC) of amygdala with PFC, ACC, insula, thalamus, caudate nucleus, and putamen was enhanced. Moreover, the post-treatment resting state fMRI exhibited a decrease in short-range functional connectivity strength and effective connectivity with PFC. These regions identified with FC were highly implicated as MDD neuroimaging biomarkers, such as the limbic-cortical-striatal-pallido-thalamic circuit that uses amygdala as a functional modulator in tasks related to cognition and emotion. Research also suggested the functional decoupling between amygdala and striatum (including caudate nucleus and putamen) which has been shown to be associated with anhedonia, a common symptom of MDD encapsulating the inability to feel pleasures [27].

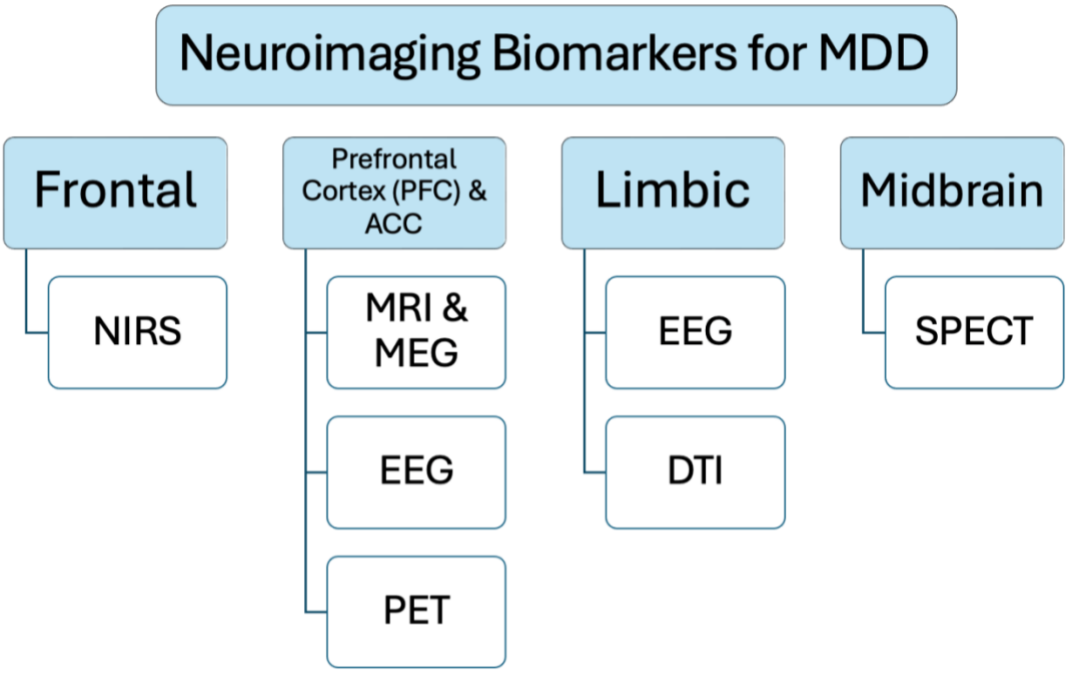

Figure 1. Major neuroimaging biomarkers for MDD identified through an intense literature review. Four brain regions were found to showcase structural and functional changes that can be scanned through various neuroimaging techniques shown above such as NIRS, MRI, EEG, and SPECT. Created using Microsoft Word.

BDNF

In addition to neuroimaging as a biomarker, researchers were also interested in investigating biomarkers for MDD to distinguish between other mental illnesses. Through an analysis of five articles, BNDF as a biomarker has become increasingly prevalent due to its role in neuronal growth and maintenance [28]. The role of BDNF has been underlined for its role in mood disorders, where disrupted BDNF production may lead to MDD symptoms [28]. To measure BDNF levels as a biomarker for MDD, researchers used blood serum levels of participants. Aside from neuronal tissues, BDNF is also produced in non-neuronal tissues such as the peripheral tissues. Past literature has revealed that peripheral growth factors such as BDNF have crossed the blood-brain barrier and travel into the brain, allowing for behavioral and cellular changes [29]. Researchers reported lowered proBDNF and mature BDNF levels in unmedicated patients with MDD compared to control groups [29]. Similarly, BDNF was examined through blood samples as a biomarker of MDD; lower BDNF levels were predicted due to elevated stress levels in individuals with MDD, and in turn, lower BDNF levels resulting in altered synaptic plasticity as BDNF is essential in maintaining synaptic plasticity [29]. Through blood samples it was found that the BDNF levels were lower than average in individuals with MDD, consistent with previous literature [29]. Lower BDNF levels have been associated with the shrinkage of brain areas that are linked with abnormal depressive behavior, due to BDNF's role in the neurotrophic hypothesis stating that BDNF is important for neurological pathways that are associated with MDD [30]. After examining BDNF levels in patients, researchers found overall lower BDNF levels in the MDD group [30, 31]. Moreover, when researchers investigated the BDNF gene and Val66Met variation, they concluded that BDNF is not a useful indicator for MDD as a diagnostic tool as there was only a significant difference when patients already received their MDD diagnosis [15].

Hormones

Furthermore, aside from neuroimaging and BDNF as potential biomarkers, there has been research investigating hormone levels, specifically cortisol, TSH, and prolactin as potential biomarkers over the years. After investigating five articles, cortisol, TSH, and prolactin have shown dysregulations in those with MDD.

Researchers have shown that elevated cortisol levels can be an indicative response of stress within individuals with MDD [32]. A systematic review investigated multiple potential MDD biomarkers including neuroimaging, hormones, and other factors that determined cortisol levels as the only significant indicator of diagnosing and predicting relapse of MDD [33]. The authors also highlight a connection between higher serum cortisol levels and severity of MDD symptoms, suggesting that cortisol could assess the intensity of MDD symptoms [34]. However, an article published in 2021 demonstrated that serum cortisol levels may be indicative of MDD duration rather than being useful as a

potential diagnostic tool [35]. Additionally, cortisol levels are oftentimes associated with various disorders which can make diagnosing MDD difficult using cortisol serum levels [36].

TSH was also investigated as a prospective hormone biomarker for MDD. Authors have underlined how thyroid disorders can present as MDD, since thyroid disorders can imitate symptoms of MDD [36]. Furthermore, some patients diagnosed with MDD have also been found to concurrently have thyroid disorders. It is thought that both MDD and thyroid disorders disrupt similar pathways in the human body. Results showed that an elevation in TSH levels and depression are correlated, serving as a potential biomarker for MDD [36]. The importance of screening depressed patients for subclinical hypothyroidism is highlighted in literature [36]. Further investigation of subclinical hypothyroidism diagnosis alongside MDD was performed and the findings suggest an autoimmune response affecting TSH levels within MDD groups [37].

The last potential hormone as a biomarker that was investigated were prolactin levels in MDD patients. Previous literature has shown heart health issues associated with MDD, as a result they examined prolactin [20]. Results indicated that prolactin levels in patients with MDD are elevated compared to the control group through plasma level analysis. Prolactin levels increased in the plasma samples MDD group averaging at 8.79 ± 5.16 ng/mL compared to controls with levels at 7.03 ± 4.78 ng/mL [20]. The female group also showed increased prolactin levels compared to males. Dysregulated prolactin levels are thought to be associated with key MDD symptoms such as anxiety, somatization, and hostility [20].

Table 1. Summary of the MDD biomarkers discussed in this review, along with their role in the brain and differences in levels observed in healthy versus MDD individuals where these biomarkers represent potential diagnostic tools for MDD

Biomarker	Role in the Brain	Differences in Healthy vs MDD Individuals
Neuroimaging	Neuroimaging biomarkers represent various brain regions and can be used to describe the pathophysiology of MDD [11]. Images of the brain can reveal tissue composition and alterations in diseased phenotypes [10]. Neuroimaging techniques include: MRI, EEG, fMRI, MEG, NIRS, PET, SPECT.	In MDD individuals, physical changes in brain volume and thickness of specific brain regions have been seen. The frontolimbic regions such as the prefrontal cortex, anterior cingulate cortex, hippocampus, amygdala, and insula were identified as neuroimaging biomarkers for MDD [22].
BDNF	BDNF is classified as a growth factor in the brain that is vital for neuronal development and survival [13-15]. BDNF is also involved in regulating neurotransmitter systems such as the stress and reward responses in the brain [13-15].	A decrease in BDNF levels in the hippocampus and prefrontal lobe have been found in MDD patients [14,16]. Reduced BDNF levels have been detected in blood samples of MDD individuals [29].
Cortisol	Cortisol is a steroid hormone that can bind to glucocorticoid receptors that are found throughout the body resulting in a wide range of effects on the body [18]. Cortisol impacts the body's metabolism and nervous systems mainly [18]. Stress increases cortisol levels in the body, triggering the HPA axis [18].	Abnormal cortisol levels have been found in patients with MDD–specifically higher serum cortisol levels [18, 35]. Higher serum cortisol levels have been linked to increasing severity of MDD symptoms [34].
TSH	TSH is a hormone that acts on the thyroid gland to generate thyroxine (T4) and triiodothyronine (T3), and maintains endocrine functions [36-37]. Thyroid hormones are important for brain and metabolic functioning as well as overall growth [38].	Dysregulation in TSH levels and MDD are correlated [34]. Elevated levels of TSH have been related to metabolic brain changes, leading to behavioural and cognitive changes associated with MDD patients [19].
Prolactin	Prolactin is classified as a polypeptide hormone and it is thought to impact a wide variety of mechanisms within the body including the stress responses [20]. Prolactin may also contribute to one's appetite [20].	Patients with MDD have demonstrated increased prolactin levels through plasma analysis [20]. Abnormal levels of prolactin contribute to abnormal stress responses seen in MDD patients [20]. Changes in prolactin levels may contribute to weight gain (key symptom of MDD) [20].

Discussion

The primary goal of this literature review was to identify and propose potential biomarkers in diagnosing MDD. Depression is one of the most common mental illnesses worldwide and MDD has one of the top disease burden rates [39]. The etiology of MDD is thought to be composed of both environmental and genetic factors, making MDD a complex and intricate illness [40]. Currently, MDD is diagnosed through the DSM-5 manual in the form of behavioral symptoms [5]. Future research aims to compose potential biological markers that may be found across individuals with MDD to enhance diagnosis and treatments for the illness. After a comprehensive analysis of recent developments of neuroimaging, BDNF, and hormones as potential biomarkers for MDD, studies have shown promising results that require further investigations and key limitations that must be considered.

Various imaging techniques, such as MRI, NIRS, and EEG are currently used to identify potential biomarkers for MDD and indicators for treatment response [11, 26]. Several neuroimaging biomarkers located at frontolimbic regions such as the prefrontal cortex, anterior cingulate cortex, hippocampus, amygdala, and insula were identified [22]. Further review of literature revealed limitations of biomarker studies examined here such as use of just one neuroimaging technique–opposed to a combination–and small sample size [21].

Results illustrate the importance of BDNF in the pathology of MDD as researchers report lower proBDNF and mature BDNF levels in unmedicated patients with MDD compared to the control group [28]. Through blood samples, researchers concluded BDNF levels were lower than average in individuals that have MDD [29]. When investigating the BDNF gene, researchers demonstrated that BDNF may be altered when patients undergo and experience MDD rather than BDNF alterations being an initial risk factor for the disease [15].

Furthermore, there has also been an interest in investigating hormones as a potential biomarker for MDD, such as cortisol, TSH, and prolactin. In a systematic review, altered cortisol levels were found to be the only significant indicator of diagnosing and predicting relapse of MDD [33]. The authors discussed the significance of symptom severity relating to cortisol levels as a biomarker. Dysregulation in TSH and depression appear to be correlated, specifically elevated levels of TSH [36]. Both subclinical hypothyroidism and autoimmune thyroiditis have been linked to individuals with MDD where TSH levels are abnormal; however, whether abnormal TSH levels lead to depressive symptoms or vice versa is still not completely understood [37]. Elevated prolactin levels in patients with MDD compared to the control group through plasma levels have been found. Dysregulated prolactin levels are thought to be associated with key MDD symptoms such as anxiety, somatization, and hostility [20].

Amongst the findings for each biomarker, key limitations should also be considered. For neuroimaging studies, many region-of-interest methods are used that limit the scans that are analyzed, incorporating bias into the study. Additionally, the use of treatments such as antidepressants and comorbid disorders with MDD need to be monitored throughout the study as these factors may alter the findings. Due to the complexity of MDD, the use of multiple biomarkers is necessary at this stage in research to encompass a well-informed diagnosis of MDD. Timing as to when to look for the biomarker is also a concern, as different stages of MDD can alter the levels of BDNF and hormones as well as neuroimaging scans in the individual. Additionally, the levels of BDNF within the blood samples obtained from patients are thought to be composed of both peripheral tissue and neuronal BDNF. However, blood samples can pose a limitation as the blood BDNF levels are BDNF levels that has passed the brain-blood barrier essentially not encompassing the levels within the brain [29]. In relation to hormones as potential biomarkers, measurements of participants before an MDD episode are needed to provide baseline measurements for the individual themselves. Moreover, the demographics (e.g., age, gender, race, income) of an affected individual with a complex disorder such as MDD may manifest in a different manner, and so differences in symptoms across individuals should also be evaluated.

This literature review identified notable biomarkers that have the potential in the field to serve as useful factors to diagnose depression. That said, there are a number of limitations within this analysis. Due to the scope of this review, a comprehensive and systematic search of all articles published investigating biomarkers in depression was not conducted. Additionally, the articles analyzed were limited to the databases chosen by the authors, resulting in a possible selection bias of publications. Furthermore, the review highlights notable research developments through the form a timeline in the field and focuses on neuroimaging, BDNF, and hormones as biomarkers, however, does not provide a comprehensive summary of all possible and previously investigated biomarkers in the field.

Conclusions

Over the years, several neuroimaging techniques have been used to investigate regions of the brain as potential biomarkers for MDD. Neuroimaging studies have shown that PET, SPECT, and DTI are the main neuroimaging techniques used. Additionally, both fMRI and qEEG identified key regions ACC, DLPFC, OFC, and the amygdala as major regions for MDD biomarkers. The BDNF levels collected from blood samples may be useful as a potential biomarker in patients with MDD as lower BDNF levels have been found in individuals with MDD. Elevated cortisol, TSH, and prolactin levels have been found in individuals with MDD. Researchers especially highlight the urgency of screening depressed patients for subclinical hypothyroidism. Biomarkers often overlap for

mood disorders, and therefore having multiple biomarkers that distinguish individuals with MDD will aid in the diagnosis and treatment of this disorder. Overall, further investigation into neuroimaging, BDNF, and hormones (TSH, cortisol, prolactin) as biomarkers for MDD is needed for diagnoses and treatment options.

List of Abbreviations Used
ACC: anterior cingulate cortex
AI: artificial intelligence
ALFF: abnormal amplitudes of low-frequency fluctuations
BDNF: brain derived neurotrophic factor
DLPFC: dorsolateral prefrontal cortex
DSM-5: diagnostic and statistical manual of mental disorders 5th edition
DTI: diffusion tensor imaging
FC: functional connectivity
fMRI: functional magnetic resonance imaging
HPA: hypothalamus-pituitary-adrenal
MDD: major depressive disorder
MEG: magnetoencephalography
MRI: magnetic resonance imaging
NIRS: near-infrared spectroscopy
OFC: orbitofrontal cortex
PET: positron emission tomography
PFC: prefrontal cortex
qEEG: quantitative electroencephalogram
SPECT: single-photon emission computed tomography
SSRI: selective serotonin reuptake inhibitors
TSH: thyroid stimulating hormone

Conflicts of Interest
The authors declare that they have no conflicts of interest**.**

Ethics Approval and/or Participant Consent
Ethics approval and/or participant consent was not required as a literature review was performed.

Authors' Contributions
GKD: Performed literature searches, analyzed primary and review articles, drafted and revised the manuscript.
SCG: Performed literature searches, analyzed primary and review articles, drafted and revised the manuscript.

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