Different Mechanisms Between Melancholic and Atypical Depression

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Additional information is available at the end of the chapter

1. Introduction

Major depressive disorder (MDD) is very prevalent and disable psychiatric disorder with prevalence estimates ranging 5% to 20% [1, 2] and has been a growing public health concern due to its recurrent and lethal nature. According to projections, MDD will become the second leading cause of disability worldwide by the year 2020.[3]

Major depressive disorder is considered to be a clinically heterogeneous disorder and the diagnosis is based on a patient's symptoms, not on any laboratory tests. So, the pathophysiology of MDD is not clear. MDD results from multiple genetic factors interacting with many various environmental factors, such as childhood adversity and many life stressful events.[4]

Although work in this area has been inconclusive, many animal, post-mortem, clinical, and genetic studies have produced results implicating at least three neurobiological systems in the pathogenesis of MDD: the monoamine system, the hypothalamic-pituitary-adrenal axis (HPA axis), and neuroplasticity. Additionally, other biological factors, including inflammatory markers, neurophysiologic markers, and neuroimaging markers may be associated with MDD.

Although recent decades have witnessed a tremendous revolution in the development of antidepressant drugs, the neurochemical effects that underlie the therapeutic actions of these agents remain largely unknown.

There has been increasing data showing that depressive disorders are heterogeneous, and therefore, can vary with regard to HPA axis activity, immune function, and treatment response. Considering the biological mechanisms of depressive subtypes, it is helpful to understand the pathogenesis in order to more accurately predict an individual's response to a specific treatment for depression.

Melancholic depression is distinguished by a loss of appetite and sleep; melancholic patients are usually anxious and lose responsiveness to their environments. Those with melancholic depression tend to feel worse in the morning, while those with atypical depression generally feel worse in the evening.

Atypical depression is a subtype of depression that the DSM-5 defines as having the characteristics of reactive mood (including the ability to respond emotionally to environmental cues), increased appetite, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity.[5] Patients with atypical depressive episodes generally have a younger mean age of onset than those with typical depression.[3-7] Individuals with atypical depression are 2- to 3-fold more likely to be women and often have a more chronic, unrelenting course of depression than individuals with typical depression. In a sample of 8116 individuals aged 15–64 years, 17.1% of the patients with a diagnosis of MDD had a history of atypical depression.[13] Of 1500 outpatients studied in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, 18.1% of patients in the trial had depression with atypical features, and women were found to be 70% more likely to have atypical depression.[5] Studies of clinical populations have shown 18–36% of patients with MDD present with atypical depression.[6]

In this chapter, we discuss the biological mechanisms involved in the pathogenesis of depressive subtypes.

2. Different mechanisms between melancholic and atypical depression

2.1. Hormonal axis

MDD generally features the hyperactivity of the hypothalamic-pituitaryadrenal (HPA), a neuroendocrine abnormality[7] In particular, the majority of depressed patients exhibit hypersecretion of cortisol in their plasma, urine, and cerebrospinal fluid (CSF), and a hyperactive cortisol response to adrenocorticotrophic hormone (ACTH).[8-10] To explain the pathophysiology of MDD, the corticosteroid receptor hypothesis has been proposed. It focuses on corticosteroid receptor resistance, which results in a reduction of the negative feedback of cortisol, an increased production of corticotropin-releasing hormone (CRH), and ultimately, hypercortisolism. [8]

Interestingly, the serotonin (5-HT) system is affected by both cortisol and CRH. [9, 11] 5-HT transmission is stimulated by glucocorticoids(GCs) during the stress response.[12] Conversely, during chronic psychosocial stress, 5-HT transmission is impaired and noradrenergic transmission in the hippocampus is suppressed resulting in hypercortisolism, which is similar to the state of depression.[13] Depression may have a genetic component: it has been reported that HPA axis dysregulation could be a genetically determined trait that contributes to an increased susceptibility for depression. However, since the trait is found in both affected subjects and in healthy relatives with a high familial risk, the HPA axis is an interesting candidate endophenotype for affective disorders. [14, 15] Studies regarding the causes of the dysregulated HPA axis in depression have mainly focused on two elements: i) glucocorticoid receptor (GR) feedback mechanisms and ii) the CRH signaling system.

A reduced sensitivity to cortisol, leading to an impaired negative feedback mechanism has been attributed to resistant GR function. [16] In contrast, the CRH peptide mediates the regulation of the HPA axis as well as autonomic and behavioral responses during stress.[17] Furthermore, the functional action of antidepressants has been linked to the HPA axis.[8, 18] Consequently, a proper clinical response to antidepressant treatment includes the normalization of the dysregulated HPA axis..[9, 19]

Susceptibility to MDD has also been associated with Bcl1 polymorphism, and it was found to be predictive of treatment response.[20] Genetic association studies have yielded preliminary evidence for a role of GR genetic variations in the genetic vulnerability for MDD. Pharmacogenetic studies have investigated polymorphisms in components of the HPA axis in relation to the treatment response to antidepressants. In line with a SNP in the CRH-binding protein[21], a SNP in the FKPB5 protein involved in the regulation of GR sensitivity has been reported to be associated with response to citalopram (Lekman et al., 2008). SNPs in the FKPB5 protein were also associated with response to citalopram in a large cohort study in Munich to TCAs and SSRIs.[22] Taken together, the evidence for a role of GR and the GR gene in the neurobiology of MDD is building rapidly.[23]

Most studies in melancholic depression have found that relative HPA axis hyperactivity occurs, compared to non-depressed states, and that this is more likely to occur in more severe forms of depression.[24] In addition to increased corticotropin-releasing hormone (CRH) production, the overdrive in the HPA axis in depression has been attributed to both glucocorticoids feedback insensitivity and to the overproduction of other corticotrophin secretagogues insensitive to glucocorticoid feedback, such as arginine vasopressin.[25, 26] CRH and arginine vasopressin (AVP) are the main secretagogues of the HPA/stress system. Produced in the parvicellular division of the hypothalamic paraventricular nucleus, the release of these peptides is influenced by input from monoaminergic neurones. In depression, anterior pituitary CRH1 receptors are down-regulated and the resultant response to CRH infusion is blunted. By contrast, vasopressin V3 receptors on the anterior pituitary show an enhanced response to AVP stimulation and this enhancement plays a key role in maintaining HPA hyperactivity.[26]

Contrary to melancholic depression, atypical depression has reversed vegetative symptoms, i.e. hypersomnia and hyperphagia. The patients with melancholic depression show hypercortisolism and more disturbed sleep, as is strongly associated with high nocturnal ACTH and cortisol secretion.[27] Weight loss is correlated with hypercortisolism and dexamethasone non-suppression.[28, 29] Moreover, depressed patients without hypersomnia or increased appetite were shown to have elevated urinary cortisol concentrations as compared to normal morning plasma cortisol levels, as well as and a higher incidence of cortisol non-suppression after dexamethasone compared to normal subjects.[30] In contrast to typically depressed patients, those with hypersomnia and hyperphagia showed no change in morning plasma cortisol and DST.[30, 31]

It has been presented that a relatively hyperactive HPA axis leads to the symptoms of melancholic depression, while a relatively hypoactive stress response leads to the symptoms of atypical depression.[32] That is, CRH hypersecretion and hyposecretion correlate with the

symptomatic pattern of melancholic and atypical depression, respectively. A recent meta-analysis of 40 years of HPA axis research conducted has identified a pattern of relative hypocortisolemia in atypical depression as compared to melancholic depression.[33]

Antonijevic expanded the concept and proposed that clinically relevant differences in the underlying pathophysiology in patients with depression exist, and that the identification of distinct endophenotypes for MDD will not only improve our understanding of the disease, but will also contribute to more specific treatment strategies.[34] Concerning pharmacological treatment, it was reported that the group of patients with atypical depression showed a significantly higher cortisol response to desipramine, a relatively selective noradrenaline reuptake inhibitor, than the group with no atypical symptoms and the group with mood reactivity as the only atypical symptom, indicating that atypical depression may be associated with a smaller impairment of the noradrenaline neurotransmitter system.[35] Similarly, hypersecretion of corticotropin-releasing hormone (CRH) and the resulting hypercortisolism were not found in patients with atypical depression.[36]

2.2. Neurotransmitter system

It has been hypothesized that a deficiency in serotonin is an essential determinant in the pathogenesis of MDD. Consequently, the serotonin system has been thoroughly investigated in a variety of MDD studies. The serotonin system projects from the dorsal raphe nucleus to all regions of the brain, including the cerebral cortex and hippocampus. In depressed patients, the diminished function and activity of the serotonin system has been confirmed in postmortem serotonin transporter and serotonin receptor studies. [citation?]

In suicide victims with MDD, enhanced radioligand binding of an agonist to inhibitory serotonin-1A autoreceptors in the human dorsal raphe nucleus was found, supporting the hypothesis regarding the reduced activity of serotonin neurons.[37] There appears to be a strong trend of decreased 5-HT1A receptor expression in MDD. Biochemically, the polymorphism of the C-1019G promoter (rs6295), a genetic variant of the 5-HT1A receptor, has shown to have the G allele is more frequently in MDD.[38]

Imipramine may be a putative biological marker of depressive disorder. It binds to the serotonin transporter (5-HTT) on platelets, and decreased imipramine binding may indicate depressive disorder. A meta-analysis showed a highly significant decrease in maximal binding values in depressed subject groups, which was further shown to be even greater among those who had been free of medication for 4 weeks at the time of investigation. [39]

Tryptophan hydroxylase (TPH), which has two isoforms (TPH1 and TPH2), is a of the rate-limiting factors in serotonin synthesis. Significantly higher numbers and densities of TPH immunoreactive neurons in the dorsal raphe nuclei of alcohol-dependent, depressed suicide victims compared to controls have been reported. [40] A deficient or impaired serotonin system seems to correlate with depressive disorders, as evidenced by studies on the serotonin receptor, TPH, and 5-HTT.

The norepinephrine (NE) system has been studied in depression, particularly the action of NE reuptake inhibitors. Monoaminergic neurobiology, including norepinephrine, has been

associated with the mechanism of action of serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), tricyclic and monoamine oxidase inhibitor antidepressants. Furthermore, mirtazapine's antidepressant effect seems to be due to the dual enhancement of central noradrenergic and serotonergic neurotransmission stemming from a blockade of adrenergic $\alpha2$ receptors. [41-43]

The dopamine (DA) system has been reported to be highly associated with the symptomatology of depression, as the proposed pathogenesis of melancholic depression involves decreased DA transmission.[44]

In addition to HPA axis activity, distinct alterations of the serotonergic system may also play critical roles in the melancholic and atypical phenotypes, namely a reduced restraint of serotonin synthesis via 5-HT(1A) autoreceptors in the former, and primarily through reduced serotonin synthesis in the latter. Thus, the melancholic subtype with noradrenergic and HPA axis overdrive seems to be associated with reduced 5-HT1A autoreceptor function and, therefore, enhanced serotonergic activation of the HPA axis, as well as an acute phase immune reaction. The latter contributes to HPA axis stimulation and reduces the negative feedback inhibition from corticosteroid receptors. The resulting hypercortisolism can further impair 5-HT1A receptor functions, leading to a vicious circle, which may not be effectively resolved by most selective serotonin reuptake inhibitors (SSRIs).[32, 45] On the other hand, patients with AD and low HPA activity seem to have reduced noradrenergic and serotonergic afferent stimulation, possibly because of reduced serotonin (5-HT) synthesis and, unlike melancholic patients, an unimpaired 5-HT1A autoreceptor function.[32, 46] Moreover, MAOIs have been repeatedly found to be more effective for treating atypical depression than tricyclic antidepressants (TCAs), which have potent noradrenergic properties. This distinction between MAOIs and TCAs may indicate different biological mechanisms at work in patients with atypical or melancholic depression.[18,19] In fact, some researchers have suggested that serotonergic neurotransmission is more relevant than noradrenergic transmission to the pathophysiology of atypical depression.[20] (Fig. 1)

2.3. Neuroinflammatory system

It has been suggested that dysregulation of the immune system, including the cytokine network, is associated with the etiology and pathophysiology of depression.[47, 48] Peripheral cytokines can communicate with brain cells by various mechanisms. Many studies have suggested that imbalances in the cytokine network are associated with the pathophysiology of depression.[49, 50] (please be consistent with your citation system)

There have been many studies suggesting that proinflammatory cytokines, which initiate inflammatory immune responses, are associated with depression. First, patients and animals administered IL-2 and IFN-α experience "sickness behaviors" that resembled depression: insomnia, decreased appetite, loss of interest, and fatigue.[citation?] These "sickness behaviors" improved when they were treated with antidepressants or when the cytokines were withdrawn.[51, 52] Second, patients with depression that are otherwise healthy seem to have activated inflammatory pathways, with increased pro-inflammatory cytokines, acute-phase proteins, and increased expression of chemokines and adhesion molecules. Third, chronic
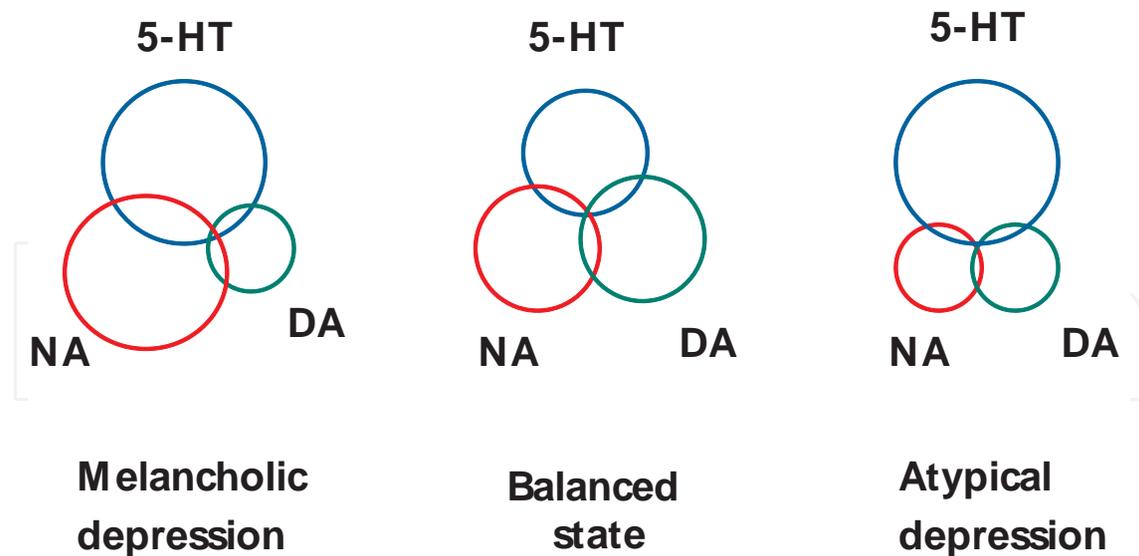
5-HT, serotonin. NA, noradrenaline. DA, dopamine.

Figure 1. Monoamine hypothesis of depression subtype. A simplistic and hypothetical model show that monoamines are differently affected in atypical and melancholic depressions and that monoaminergic neurotransmission is 'out of tune', rather than deficient. The circles represent the increased or decreased monoaminergic functioning and capacity.

inflammatory diseases such as multiple sclerosis and rheumatoid arthritis, are frequently accompanied by depression (See the references in the introduction of [47]).

The pro-inflammatory cytokines have been found to have profound effects on the metabolism of brain serotonin, dopamine, and noradrenaline in mice and rats [53]. Indeed, the activation of inflammatory pathways within the brain is believed to contribute to a confluence of decreased neurotrophic support and altered glutamate release/reuptake, as well as oxidative stress, leading to excitotoxicity and loss of glial elements, consistent with neuropathologic findings that characterize depressive disorders.[48] A recent meta-analysis convincingly suggested that IL-6 and TNF-alpha levels are elevated in depressive patients.[54]

Adipocytes, the source of leptin, also produce cytokines, such as TNF-α and IL-6. Indeed, in obese subjects, it has been estimated that about 30% of the circulating IL-6 is derived from adipose tissue.[55] However, the effects of leptin are generally opposite those of the pro-inflammatory cytokines, and include the induction of anorexia, anhedonia, and increased sympathetic nervous system activity.[56]

The immune system plays an important role in the regulation of leptin production.[79] This communication between the immune and adipose systems is bidirectional, since leptin in turn is involved in the regulation of immune responses. Indeed, leptin regulates pro-inflammatory immune responses, by up-regulating both phagocytosis and the production of pro-inflammatory cytokines. Moreover, leptin deficiency is accompanied by an in-creased susceptibility to endotoxin-induced lethality and a decreased induction of anti-inflammatory cytokines in rodents,[57] thus further suggesting close connections between leptin and the immune system.

Hypersomnia is one of the main symptoms of atypical depression. Cytokines are important sleep regulatory substances among many factors that are involved in sleep regulation. Among cytokines, interleukin IL-1 and TNF-α have been determined to be important sleep-promoting substances. Early studies in humans have shown that sleep onset is associated with the increased activity of IL-1, followed by elevations of IL-2 that appeared to be related to a decline in plasma cortisol and the appearance of slow wave sleep.[58] IL-4, one of the anti-somnogenic cytokines, inhibits the production or release of other substances implicated in sleep regulation, such as nuclear factor kappa B.

Atypical depression has been linked to decreased IL-4 and increased IL-2 compared to individuals without atypical features in one study,[59] while another study reported decreased IL-2 in atypical depression compared with controls.[60] Individuals with atypical depression had significantly higher levels of inflammatory markers than persons with melancholic depression and controls.[61] Overall, findings on inflammatory markers among those with melancholic versus atypical depression have been contradictory. Taking into consideration a meta-analysis that body mass index may interact with C-reactive protein and IL-6 to yield a potential tri-directional relationship between adiposity, inflammation and depression,[62] the high BMI levels of those with atypical depression may indicate a differential association between atypical depression with inflammation compared with melancholic depression, as was also postulated.[32]

2.4. Neuroplasicity

A time-lag in clinical response after the administration of an antidepressant drug suggests that alterations in monoamine metabolism alone cannot explain the entire antidepressant effect. In this respect, it was suggested that the mechanism of action of antidepressant drugs may be associated with intracellular signal transduction pathways that are linked to the expression of specific genes.[63]

The neuroplasticity hypothesis proposes that depression results from an inability to make the appropriate neuronal proliferation in response to stress.[64] Brain-derived neurotrophic factor (BDNF), an important member of the neurotrophin family, is a key component of the neuro-plasticity hypothesis. The molecule acts on neurons at both presynaptic and postsynaptic sites by binding to its tyrosine kinase receptor (TrkB), resulting in the internalization of the BDNF TrkB complex-signaling endosome. [65]

A growing body of evidence shows similar results through the direct measurements of BDNF in the serum and plasma. [66-68] Antidepressants lead to the up-regulation of the cAMP response element-binding (CREB) protein and an increase in the expression of neurotrophic factors through their stimulation of intracellular pathways. By taking antidepressants, depressed patients increase their serum BDNF levels close to the physiological level. [69-71] Furthermore, studies show that the enhancement of BDNF expression may be an important element in the clinical response to antidepressant treatment. [72] The BDNF molecule has been shown to likely contribute to the ''final common pathway'' for different antidepressant approaches. The various antidepressant approaches include: antidepressants [73], electrocon-vulsive therapy [73, 74], exercise [75, 76], and repetitive transcranial magnetic stimulation. [77]

A meta-analysis including 1504 subjects indicated that BDNF levels increased significantly after antidepressant treatment and that there was a significant correlation between changes in BDNF levels and depression scores. The researchers also found a difference between pre-treatment patients and healthy controls and a small, but significant, difference between treated patients and healthy controls. [78]

Low serum BDNF levels have been found in depressed patients, however, no study has systematically investigated whether depression subtypes contribute to the low BDNF levels found in depressed subjects. One study including 1070 patients with a diagnosis of major depressive disorder within the past 6-month diagnosis from the Netherlands Study of Depression and Anxiety (NESDA) was reported. The Composite International Diagnostic Interview (CIDI) and Inventory of Depressive Symptoms (IDS) items were tested individually in separate multiple regression analyses with serum BDNF level as the dependent variable and the CIDI or IDS item as an independent variable. Subsequently, BDNF levels were compared between patients with seasonal affective disorder (based on the Seasonal Pattern Assessment Questionnaire) and melancholic depression, atypical depression, and moderate depression (based on a latent class analysis). Serum BDNF levels did not significantly differ between patients with melancholic depression, atypical depression, and moderate depression.[79]

Another study with same subjects (NESDA) examined the association between serum levels of BDNF and plasma levels of IL-6 and TNF-α in patients with MDD (n = 1070) and non-depressed controls (n = 379). Multiple regression analyses with serum BDNF as the dependent variable was used and the presence of BDNF–cytokine associations in DSM-IV-assigned melancholic MDD patients was tested. Stratified analyses showed that BDNF levels are indeed positively associated with IL-6 levels in MDD patients, but not in non-depressed controls. When further stratified for melancholic and non-melancholic MDD, IL-6 emerged as a robust positive predictor of BDNF only in the melancholic sample, wherein serum BDNF levels were accordingly enhanced. Post-hoc exploratory analyses verified an accentuated positive association of BDNF levels with leucocyte counts in melancholia. No significant associations emerged between BDNF and TNF-α.[80] Another study found that IL-6 and TNF-α specifically enhanced BDNF secretion in monocytes, whereas typical Th1- and Th2-cytokines did not show any effect on monocytes. Otherwise, only IL-6 and tumor necrosis factor-alpha (TNF-α) were found to have the ability to enhance extracellular BDNF levels in human monocytes. Intriguingly, levels of BDNF in antidepressant-free melancholics – the group presenting with the most clear-cut BDNF–IL-6 association – was not significantly different from both non-melancholics and controls, suggesting that low serum BDNF may not be a hallmark of melancholia.[81]. This finding is concordant with a recent study showing that serum BDNF levels of antidepressant-free melancholic patients are not different from healthy controls [82].

Although BDNF is believed to be transported over the blood – brain barrier [83], and significant correlations have been found between peripheral BDNF and measures of central neuroplasticity [84], we cannot be sure that measuring serum BDNF reflects the brain expression of BDNF adequately. Currently, however, measuring BDNF in the peripheral blood is the only feasible method as other methods would be far more invasive.

Conclusively, these few studies suggest that there is not much possibility of different neuro-plastic mechanisms between atypical and melancholic depression.

2.5. Neuroimaging factor

Recent neuroimaging studies have focused on the neurobiological differences between healthy controls and abnormalities associated with MDD, such as dysfunctional or structural differences in cerebral regions, including the prefrontal cortex, amygdala, anterior cingulate cortex (ACC), and hippocampus. [85-88]

Regional CBF and metabolism are consistently increased in the amygdala, orbital cortex, and medial thalamus, and decreased in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex ventral to the genu of the corpus callosum (subgenual PFC) on positron emission tomography (PET) imaging studies in MDD subjects without medication, as compared to healthy controls. [89, 90] These circuits have also been implicated more generally in emotional behavior.

Previous structural magnetic resonance imaging (MRI) studies using region-of-interest (ROI) analyses have shown a variety of inconsistent findings. [91, 92] These inconsistencies can likely be explained by variability in the ROI criteria between studies and inconsistency in ROI validation.[91, 93, 94] Consequently, voxel-based morphometry (VBM)[95] is being increasingly used as a viable alternative methodology for detecting structural abnormalities in patients with neuropsychiatric disorders, including MDD.[96-99] Previous MDD VBM studies have also shown reduced gray matter density in the hippocampus. [97, 98, 100] Recently, it has been reported that the gray matter density of several regions associated with emotion regulation, particularly dorsal raphe nucleus, was lower in MDD patients.[101]

Because depression is heterogeneous, subtyping the disease will be helpful for understanding imaging results. However, there are few imaging studies which were done according to depression subtype. There is no VBM study.

One chimeric faces study measured of perceptual asymmetry and showed that those with atypical depression differed from those with typical depression and controls in showing abnormally large right hemisphere bias. A chimeric face consists of fusion of a neutral right half-face with a smiling left half-face. Its mirror image (creating a neutral left half-face fused with a smiling right half-face) is randomly placed above or below. The task is to quickly determine which of the two faces is happier. Preference for choosing one side as happier relative to the other has been interpreted as reflecting increased activation of the contralateral parietal lobe,[102] although inhibitory mechanisms could also be hypothesized. This was present in patients having either MDD or dysthymia and was not related to anxiety, physical anhedonia, or vegetative symptoms. In contrast, patients with melancholic depression showed essentially no right hemisphere bias. The authors suggest that this is further evidence that atypical depression is a biologically-distinct subtype and underscores the importance of this diagnostic distinction for neurophysiologic studies.[103]

Single photon emission computerized tomography (SPECT) in 50 depressed patients with MDD, including subtype assessment indicated differential brain activity in patients with

atypical depression compared with typical depression. [104] Patients with melancholic depression (N=16) and patients with undifferentiated depression (N=20) each differed from controls (N=20) in 10 brain regions, but did not differ from each other in any of the 17 regions. In contrast, patients with atypical depression (N=14) differed from patients with melancholic depression in nine regions and from patients with undifferentiated depression in 10 regions, while showing differences from controls in five brain regions. In two brain regions, patients with atypical depression differed from both controls and at least one of the other depressed groups (Table 1). Conclusively, those with atypical depression had increased frontal, temporal, and parietal perfusion coupled with decreased occipital perfusion, relative to the other two depressed groups. Patients with atypical depression also had increased right frontal perfusion, whereas those with melancholia and undifferentiated depression had decreased perfusion in the majority of nonoccipital regions, relative to controls. Thus, all three depressed groups showed abnormal perfusion, but the patterns differed. Melancholia and undifferentiated depression had similar patterns of abnormal perfusion that differed from those with atypical depression.

Region	M vs. C	U vs. C	A vs. C	A vs. M	A vs. U	M vs. U
Brain stem						
Right frontal			↑	↑	↑	
Left frontal	↓			↑		
Right parietal	↓	↓	↓			
Left parietal	↓	↓	↓			
Right medial temporal	↓	↓		↑	↑	
Left medial temporal		↓		↑	↑	
Right lateral temporal	↓	↓		↑	↑	
Left lateral temporal	↓	↓		↑	↑	
Right occipital				↓	↓	
Left occipital		↓	↓	↓		
Right thalamus					↑	
Left thalamus	↓		↓			
Right globus pallidus						
Left globus pallidus	↓	↓			↑	
Right caudate	↓	↓			↑	
Left caudate	↓	↓		↑	↑	

A, atypical depression. C, control. M, melancholic depression. U, undifferentiated depression.

↑ , first group is significantly increased relative to the second group.

↓ , first group is significantly decreased relative to the second group.

Table 1. Perfusion findings of depressed patients and controls [129], adapted from [105].

These imaging studies are consistent, suggesting that atypical depression does not have the biological features of melancholia.

3. Conclusions

Major depressive disorder is considered to be a clinically heterogeneous disorder and the diagnosis is based on a patient's symptoms, not on any laboratory tests. Consequently, MDD's pathophysiology is unsettled. Currently, researchers have determined that MDD results from the interaction of multiple genetic factors and various environmental factors, such as childhood adversity and many stressful life events. Although the development of antidepressant drugs has skyrocketed in recent decades, the neurobiological effects underlying the therapeutic actions of these agents remain poorly understood. Considering the biological mechanism of depressive subtypes, it is helpful to understand the pathogenesis of each depressive disorder in order to predict an individual's response to treatment for MDD. For example, melancholic depression is associated with hyperactivity of the HPA axis while atypical depression is associated with hypoactivity of the HPA axis. Researchers have searched for biological mechanisms according to depression subtypes in an effort tto understand the pathogenesis of depression subtypes.

Concerning pharmacological treatment, it was reported that the group of patients with atypical depression showed a significantly higher cortisol response to desipramine, a relatively selective noradrenaline reuptake inhibitor, than a group with no atypical symptoms and a group with mood reactivity as the only atypical symptom, indicating that atypical depression may be associated with a smaller impairment of the noradrenaline neurotransmitter system. Similarly, hypersecretion of corticotropin-releasing hormone (CRH) and the resulting hyper-cortisolism were not found in patients with atypical depression. Imaging studies are consistent with that finding, suggesting that atypical depression does not have the biological features of melancholia.

The results are summarized in Table 2.

Melancholic depression	Atypical depression
DSM-5 subsymptoms per subtype[5]:	
A. One of the following:	A. Mood reactivity
1. Loss of pleasure	
2. Lack of reactivity to usually pleasurable stimuli	
B. Three of following:	B. Two of the following:
1. Depressed mood with profound despondency, despair , moroseness	1. Weight gain/increase in appetite
2. Symptoms at worst in morning	2. Hypersomnia
3. Early-morning awakening	3. Leaden paralysis
	4. Interpersonal rejection sensitivity

Melancholic depression	Atypical depression
4. Psychomotor agitation/retardation	C. Criteria are not met for "with melancholic features" or
5. Anorexia or weight loss	"with catatonia" during the same episode.
6. Guilt	
Neurobiological mechanisms per subtype:	
Increased sympathetic activity	Decreased sympathetic activity
Hyperactive HPA axis	Hypoactive HPA axis
Activated CRF system	CRF deficiency
Increased susceptibility for infection	Increased susceptibility for inflammation
Low BDNF	Low BDNF
	Increased right frontal or parietal region in imaging studies

DSM, Diagnostic and Statistical Manual of Mental Disorders.

Table 2. Different clinical symptoms and biological mechanisms between melancholic and atypical depression based on the DSM-5

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