Chapter 4

The neural substrates of different depression symptoms: Animal and human studies

Gunes Unal[a] and Ahmed A. Moustafa[b,c]

[a]*Behavioral Neuroscience Laboratory, Department of Psychology, Boğaziçi University, Istanbul, Turkey,* [b]*School of Psychology & Marcs Institute for Brain and Behaviour, Western Sydney University, Sydney, NSW, Australia,,* [c]*Department of Human Anatomy and Physiology, Faculty of Health Sciences, University of Johannesburg, Johannesburg, South Africa*

Introduction

The neural substrates of different depression symptoms: Animal and human studies

Major depressive disorder (MDD) is the most prevalent form of depressive disorders, yet it constitutes many challenges for accurate diagnosis (Liu & Jiang, 2016). The main difficulty with diagnosis is the ability to successfully eliminate a number of other mood disorders that may share many of the symptoms of MDD (Pies, 2009). Similarity in diagnosis includes not only the depressive disorders, but various anxiety, and bipolar and related disorders that are diagnosed by shared criteria. For MDD diagnosis, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; 2013) lists nine particular symptoms, of which at least five must be present continuously for a minimum of 2 weeks. Either *depressed mood* or a recognizable level of *anhedonia* should be present among these five symptoms. Furthermore, as these individual symptoms are not unique to MDD, particular attention must be given to each symptom to ensure that it is not arising from another medical condition, whether psychological or not. As such, clinical psychologists and psychiatrists usually attempt to confirm that the symptom in question is not attributable to another disease (Bilello, 2016). The difficulty of MDD diagnosis does not only relate to the commonality of symptoms among mood disorders, but also their acuteness and severity of these symptoms. Persistent depressive disorder (i.e. dysthymia), for instance, cannot be separated from MDD purely based on a checklist of symptoms, but requires careful assessment of the frequency and stability of these symptoms. Depressive symptoms, that may appear at varying rates and intensities, emerge due to

The Nature of Depression. https://doi.org/10.1016/B978-0-12-817676-4.00004-3

dysfunction of a wide-range of neuronal circuits and a number of neuromodulator systems (Krishnan & Nestler, 2008; Nestler et al., 2002). Understanding the neural substrates of depressive symptomology, therefore, constitutes a key component for revealing the full etiology of MDD.

Basic and clinical neuroscience have relied on numerous techniques to investigate the neural basis of depression. Significant effort has been placed on neuroimaging studies that compare patients with MDD to healthy participants. These studies were not only useful for revealing disease-specific alterations brain structure, whether reflected as differences in volume, connectivity or metabolic activity, but were also crucial in assessing the effects of various types of antidepressant treatment from pharmacological intervention to physical exercise (Gourgouvelis, Yielder, & Murphy, 2017). The other major approach in investigating the neural substrates of depression and its symptoms was utilizing behavioral and transgenic animal models. While clinical case studies using different neuroimaging techniques provided gross neuroanatomical information, animal models enhanced our understating of the morphological, neuropharmacological and electrophysiological aspects of different symptoms of depression.

Several specific biological correlates have been identified for depression from molecular alterations to network level changes. However, matching individual symptoms to particular neurobiological substrates has been challenging (Post & Warden, 2018). The complex etiology and versatile symptomology of depression often makes it impossible to match a depressive symptom to a specific biological alteration(s). Instead, neural underpinnings of the disease have been studied by considering how much they contribute to the etiology of the disease or, more accurately, how useful they can be for treatment purposes. Furthermore, focusing on individual depressive symptoms has been a technical necessity of non-human animal studies. Basic neuroscience research on depression, whether using well-established behavioral paradigms such as forced swimming-induced stress in rodents (Porsolt, Anton, Blavet, & Jalfre, 1978; Porsolt, Bertin, & Jalfre, 1977; Porsolt, Le Pichon, & Jalfre, 1977) or state-of-the-art transgenic mouse lines (Cryan & Mombereau, 2004; Krishnan & Nestler, 2008) cannot portray the complex human disease in its entirety, but simulate only a handful of its symptoms.

The symptomatological approach to the treatment of depression (i.e., prescribing antidepressants primarily based on how effective they are in eliminating the major symptoms of the disease, as opposed to their known mechanisms of action) has been an effective and popular choice in the clinic. In addition, in basic neuroscience research, the use of animal models which can simulate a subset of the symptoms proved very useful. For these reasons, identifying specific neural substrates for individual depressive symptoms has been the center of attention in both clinical and basic research. However, the complex and versatile etiology of MDD, and the resulting inter-patient variability in symptomology and clinical response, it has been very difficult, and sometimes impossible, to pinpoint independent neurobiological correlates for specific MDD symptoms.

For instance, while *psychomotor retardation* constitutes the key measure of behavioral despair induced by the forced swim test (FST), which is considered the gold standard rodent test for antidepressant effectiveness (Unal & Canbeyli, 2019), not all genetically altered mouse lines produce antidepressant-like behavior in the FST (Cryan & Mombereau, 2004). This chapter, therefore, avoids using subtitles for different depressive symptoms, but lists well-known neural correlates of depression with their identified role in symptomology.

We start with major neuromodulatory systems, namely the serotonergic, noradrenergic and dopaminergic ascending projections. The effects of the former (serotonin) are mostly on mood regulation, whereas the latter (dopamine) is considered the major player in psychomotor symptoms of MDD. We survey adult neurogenesis, especially in relation to anhedonia, and later discuss the related neurotrophic hypothesis of depression. We focus on the network-level understanding of the MDD symptomology by reviewing the cortico-limbic system in relation to the cognitive deficits of MDD (diminished ability to think or concentrate, or indecisiveness) and go over major animal and human studies on the limbic circuitry. We end the chapter by reminding the reader the complex etiology of MDD and the resulting inter-patient variability in its symptomology. While the dysfunction in a specific biological mechanism can contribute to a particular depressive symptom—as discussed in this chapter—it is often not the only underlying factor for that particular symptom. A specific neurobiological dysfunction often contributes to some of the other symptoms through secondary mechanisms. The epiphenomenal nature of depression neurobiology requires a holistic approach to the study of its symptoms.

Neuromodulatory systems: Mood and psychomotor activity

Like many neuropsychiatric diseases, psychopharmacological intervention and experimentation with animal models gave rise to a pharmacological understanding of depression, known as the *monoamine hypothesis* (Delgado, 2000; Hirschfeld, 2000). This hypothesis states depletion of serotonin and catecholamine levels as the main cause of MDD. Placing dysfunction of neurotransmitter/neuromodulator systems at the core of depression was a confrontational idea in psychiatry when it emerged in the 1960s (see Coppen, 1967). However, it gained momentum with the use of tricyclic antidepressants (TCAs), which substantially elevated the mood of MDD patients by blocking the reuptake of serotonin and norepinephrine, and monoamine oxidase inhibitors (MAOIs). This has first led to the *serotonin hypothesis*, which has later evolved to encompass all monoamines (Coppen, 1967; Schildkraut, 1965). Clinical and market success of monoamine agonists, especially selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and serotonin-dopamine reuptake inhibitors (SDRIs) provided support for the monoamine hypothesis, making it the single most important theory for the etiology of MDD.

Monoaminergic pharmacological intervention in MDD leads to versatile clinical outcomes (and side effects), depending on the type of antidepressant, prescription period, and (epi)genetic vulnerability and clinical history of the patient. Fluoxetine, a well-known SSRI with a high prescription rate/market output, has a good success ratio in producing clinical serendipity. The clinical success of an antidepressant treatment, whether self-reported and/or assessed by the health professional, refers to elevated mood often accompanied by a significant reduction in anhedonia (Willner, Scheel-Krüger, & Belzung, 2013). In fact, depressed mood and anhedonia are the must-be-present symptoms for MDD diagnosis (DSM-V, 2013). No antidepressant treatment would be deemed successful without a substantial ameliorative effect in either low mood or loss of interest (i.e. anhedonia). It is therefore evident that a global increase in synaptic serotonin levels has a major antidepressant effect. The same clinical outcomes are observed for SNRIs and SDRIs. SSRIs fluoxetine, sertraline, citalopram, escitalopram and paroxetine as well as SNRIs desvenlafaxine, levomilnacipran, venlafaxine and duloxetine have all been reported to elevate mood,decrease anhedonia and treat cognitive dysfunction at varying levels, depending on the patient. They also lead to similar side effects (nausea, dizziness, headache, dry mouth, etc.) and additional withdrawal issues such as flu-like symptoms and the so called antidepressant discontinuation syndrome (Warner, Bobo, Warner, Reid, & Rachal, 2006). In short, monoaminergic medication does not only have an overall clinical effect, often treating different symptoms of MDD, but also lead to a variety of common side effects.

The main mechanism of action (MOA) of each antidepressant is well-known. While SSRIs, such as fluoxetine, transiently inhibit the reuptake of serotonin molecules already released at the synapse, TCAs additionally occupy certain binding sites of cholinergic, histaminic and adrenergic receptors (Feighner, 1999). In clinical practice, conceptual understanding of the MOA is not the primary concern and most decisions are made case-by-case by observing clinical outcomes: when one medicine does not work for a patient, a different dose or another medication may be prescribed (Bousman et al., 2017). It is this therapeutic power and clinical reliability of the monoaminergic agents which place them at the core of pharmacological treatment of MDD.

Despite the relatively successful clinical application of the monoamine hypothesis, linking different monoamines to specific symptoms of depression is not straightforward. Observing positive clinical effects of the aforementioned psychopharmacological agents is not sufficient to claim that monoaminergic neuromodulators underlie the observed clinical outcome. This is because SSRIs or combination reuptake inhibitors, as well as other monoaminergic agonists, not only affect the synaptic levels of neuromodulator in question, but also alter other molecular mechanisms (Nestler et al., 2002; Willner et al., 2013). In addition to its neuromodulatory effects at the synapse, serotonin functions as a trophic factor during brain development, and knocking out the serotonin plasma membrane transporter (SERT) leads to neurodevelopmental deficits in

transgenic mice (Ansorge, Zhou, Lira, Hen, & Gingrich, 2004). In line with animal studies, polymorphism of the serotonin transporter gene in humans has been associated with anxiety-related traits (Hariri et al., 2002; Lesch et al., 1996), depressive symptoms (Caspi et al., 2003) as well as differential BOLD signaling (i.e. metabolic activity) in the amygdala during fear evoking stimuli (Hariri et al., 2002). Furthermore, levels of serotonin and the brain-derived neurotrophic factor (BDNF), a potent growth factor (Kowiański et al., 2018) and a key regulator of neurogenesis (Zigova, Pencea, Wiegand, & Luskin, 1998) are mutually dependent (Martinowich & Lu, 2008). Due to these and other molecular level-interactions between monoamines and various intracellular mechanisms, the secondary effects of manipulating synaptic levels of serotonin, norepinephrine or dopamine cannot be differentiated from the behavioral effects of primary MOA of a monoaminergic antidepressant. Animal studies, with their controlled nature, provide a relatively better setting to investigate monoaminergic system correlates of individual depressive symptoms and potentially identify symptom-specific treatments.

Perhaps the most important priority of animal research on clinical depression has been to identify and test the effectiveness of potential antidepressants in a reliable way. This led to the invention of two despair-based antidepressant screening tests: the forced swim test (Porsolt et al., 1978; Porsolt, Bertin, et al., 1977; Porsolt, Le Pichon, et al., 1977) and the tail-suspension test (TST; Cryan, Mombereau, & Vassout, 2005; Steru, Chermat, Thierry, & Simon, 1985). Both paradigms, resembling learned helplessness, induce behavioral despair in rodents and assess how much the animals struggle, that is increase their mobility, to get out of the distressing test condition. The main measure of both paradigms therefore resemble *psychomotor retardation* observed in MDD (Avery & Silverman, 1984; Buyukdura, McClintock, & Croarkin, 2011; Unal & Canbeyli, 2019). Both paradigms follow a seemingly mechanistic method by focusing on psychomotor activity rather than on an affective phenomenon such as anxiety-like behavior or anhedonia. In both paradigms, successful antidepressant treatment leads to less retardation/immobility, portrayed as an increased level of struggling in the test phase. Antidepressants that work in the FST by increasing active struggling or mobility in the test phase, often work in the clinical setting and elevate mood in MDD patients. This does not only establish the FST as a reliable, useful antidepressant assessment tool, but it also points out the role of monoaminergic systems in psychomotor symptoms of MDD (Unal & Canbeyli, 2019).

Dopamine, with its well-known role in progressive movement disorders, such as Parkinson's and Huntington's disease, was designated as the major monoamine neuromodulator underlying psychomotor alterations observed in MDD (Bragulat et al., 2007; Martinot et al., 2001; Pizzagalli, 2014). Antagonism of D1 or D2 receptors produce depressive-like behavior in rodents by increasing immobility in the test phase of FST (Klemm, 1989; Yamada, Sugimoto, & Yamada, 2004). In line with this, a PET study tracing [^{18}F]DOPA in MDD

patients with prominent psychomotor retardation found significantly decreased levels of dopamine in the left caudate nucleus (Martinot et al., 2001). Another PET imaging study utilizing [^{11}C]raclopride to assess D2 receptor binding potential suggested that lower levels of extracellular dopamine in caudate-putamen nuclei of both hemispheres underlie psychomotor retardation in depression (Meyer et al., 2006).

There is substantial inter-patient variability in psychomotor symptoms of depression. A depressive period can be accompanied by psychomotor retardation as well as the opposite phenomenon, *psychomotor agitation*. While both may be observed in MDD depending on the patient, frequent transitions between the two is considered as a biomarker for bipolarity. Functional MRI studies show abnormal metabolic activity in dopamine-releasing nuclei or target structures of dopaminergic pathways in bipolar depression (Marchand, Lee, Thatcher, Jensen, et al., 2007; Marchand, Lee, Thatcher, Thatcher et al., 2007). Destabilized functioning of the basal ganglia system and fluctuating levels of synaptic dopamine underlie sudden shifts in mechanical as well as affective symptoms of depression: psychomotor disturbances and mood swings.

As an alternative to behavioral despair that focus on psychomotor activity/retardation, reward-based rodent models have been developed to simulate anhedonia. The sucrose preference test, (Willner, Towell, Sampson, Sophokleous, & Muscat, 1987) for instance, has been useful to assess how well a potential antidepressant may overcome anhedonia, observed as an increased preference of sucrose over water in rodents. These tasks assess so called consummatory behaviors of animals by creating a more natural environment, compared to behavioral despair paradigms that utilize artificial applications such as placing land-based animals (i.e. rodents) in water pools or holding them by the tail for a long time. In this regard, reward-based rodent models such as the sucrose preference test possess good face validity in simulating *loss of pleasure* and decreased motivation, as observed in patients with MDD. Interestingly, however, they are not necessarily as reliable as the FST in assessing the effectiveness of potential antidepressant treatment. The FST, relying on psychomotor measures that reflect secondary (and seemingly mechanical) symptoms of MDD, as opposed to the must-be-present depressive symptom *anhedonia* model used by the sucrose preference test, has been the test of choice for initial assessment of several antidepressants (Unal & Canbeyli, 2019). This phenomenon points to the high level of interaction between the neural substrates of different depressive symptoms.

Adult neurogenesis: Anhedonia

Since its discovery (Altman & Das, 1965; Kaplan & Hinds, 1977), adult hippocampal neurogenesis has attracted special attention in many aspects of neuroscience, emerging as a key contributor for various cognitive and affective phenomena. The neurogenic (reserve) theory, stating that adult hippocampal

neurogenesis provides a great potential for neuronal plasticity in an experience-dependent manner, has been offered as the most prominent factor in the etiology of depression (Gould, Beylin, Tanapat, & Reeves, 1999; Jacobs, van Praag, & Gage, 2000; Kempermann, 2008). According to this theory, depressive symptoms arise from clinically low levels of adult neurogenesis; and accordingly, boosting neurogenesis would be sufficient to treat the disease (Miller & Hen, 2015). This idea could not be tested in humans. However, it has been possible to show that many forms of antidepressant treatment increase neurogenesis levels in the adult hippocampus in animals (Gould, Tanapat, McEwen, Flügge, & Fuchs, 1998; Malberg, Eisch, Nestler, & Duman, 2000; Surget et al., 2011). Based on this observation, in their classical experiment, Santarelli et al. (2003) utilized Serotonin 1A receptor null mice and observed that both the neurogenic and behavioral effects of fluoxetine were lost. Subsequent work has disputed these earlier findings and suggested no role for adult neurogenesis in the antidepressant actions of SSRIs (Holick, Lee, Hen, & Dulawa, 2008; Huang, Bannerman, & Flint, 2008).

Hodes, Hill-Smith, and Lucki (2010) attempted to resolve previous contradictory findings by utilizing TST for behavioral despair and novelty-induced hypophagia test for anhedonia (Dulawa & Hen, 2005) in female mice. They showed that the antidepressant effects of fluoxetine depends on neurogenesis and frontal BDNF levels in a dose-dependent manner (Hodes et al., 2010). Together with previous studies proposing age and sex differences in antidepressant properties of neurogenesis (Hodes, Yang, Van Kooy, Santollo, & Shors, 2009), this finding adds further variability to the neurogenic reserve theory, questioning its external validity. Hippocampal neurogenesis seems to contribute to antidepressant effects of monoaminergic treatment only in adult male rats, but not in female or peripubescent male animals (Hodes et al., 2009).

In spite of the proposed dose-dependent mechanism as well as apparent sex and strain-differences in potential antidepressant properties of adult neurogenesis, the neurogenic hypothesis was supported by experiments in non-human primates for (Perera et al., 2011). Blocking hippocampal neurogenesis by X-ray irradiation abolished the antidepressant effects of fluoxetine treatment in stress-induced adult female bonnet macaques. Importantly, the main measure of depression-like behavior in this study was *anhedonia* (Perera et al., 2011). This finding was replicated in mice that were subjected to chronic mild stress. Once adult neurogenesis was ablated by the same irradiation technique, mice displayed anhedonia reflected by a significant decrease in consummatory behavior (Surget et al., 2011). Based on these studies, impaired adult hippocampal neurogenesis does not seem to constitute a major neuronal signature of clinical depression as initially suggested, but selectively contribute to the anhedonic symptoms of the disease.

The cortico-limbic system: Cognitive impairment

In addition to the aforementioned decrease in motivation—reflected as a reduction in consummatory behavior—animal studies partially ablating the

hippocampal formation or blocking neurogenesis lead to cognitive impairment. This is not surprising since an intact hippocampus is required for declarative memory acquisition and consolidation. Cognitive impairment, which often depends on hippocampal dysfunction, is not listed as a specific symptom of MDD. In contrast, the comorbidity of depression and different forms of cognitive impairment is well documented (Rock, Roiser, Riedel, & Blackwell, 2014). Memory disturbances and faulty prospection, often considered epiphenomena of depression, can be observed in MDD patients (Dillon & Pizzagalli, 2018). A state-of-the-art optogenetic study provided direct support for the involvement of hippocampal neuronal circuits in memory impairment associated with depression (Ramirez et al., 2015). Active dentate gyrus neurons were *tagged* in male mice while they were interacting with the opposite sex. This constitutes a so called appetitive behavior and likely leads to formation of emotionally positive hippocampal memories. Neurons that are activated during this process and potentially contribute to the memory formation constitute an *engram.* Following a 10-day chronic immobilization stress protocol, the tagged engram neurons of the dentate gyrus were optogenetically activated. This had a profound antidepressant effect, as assessed by the TST (i.e. behavioral despair) as well as the reward-based sucrose preference test (Ramirez et al., 2015).

While memory problems are not regarded as a direct consequence of MDD, another particular cognitive dysfunction, *diminished ability to think or concentrate, or indecisiveness*, is considered as a depressive symptom according to DSM-V (2013). A diminished ability to concentrate does not merely refer to a decreased level of vigilance or attention, but cover the (in)ability to make logical mental connections. Neural substrates of this relatively subjective phenomenon have been investigated by functional neuroimaging studies (Mayberg et al., 1999; Rayner, Jackson, & Wilson, 2016). The results point to the role of a wide-range cortico-limbic network, including the amygdaloid complex, hippocampal formation, and prefrontal and cingulate cortices. By assessing resting state connectivity, researchers have revealed particular *functional networks,* such as the autobiographic memory network (AMN) or the cognitive control network (CCN; Rayner et al., 2016), and compared these among MDD patients showing different symptoms and healthy controls (Pizzagalli, 2011; Smith et al., 2009). Irregular activity in functional networks that are primarily composed of the dorsolateral prefrontal cortex (dlPFC) and dorsal anterior cingulate cortex (dACC) was correlated with poor concentration and indecisiveness (Rayner et al., 2016). This indicates a major dysfunction in prefrontal cortex regulation of the downstream limbic structures, including the amygdaloid complex and the hippocampal formation (Mayberg et al., 1999).

Neurotrophic factors and synaptic plasticity

The aforementioned interplay between monoaminergic systems and neurotrophic factors gave rise to the neurotrophic hypothesis of depression (Duman,

Heninger, & Nestler, 1997). This view emphasizes the role of insufficient levels of neurotrophic factors such as BDNF (Deltheil et al., 2008) and a consequently decreased rate of synaptic plasticity through dysfunction or partial blocking of NMDA receptors (Duman & Li, 2012) or receptor subunits (Qiao, An, Xu, & Ma, 2017). In fact, higher levels of BDNF in the frontal cortex is correlated with increased mobility, that is antidepressant-like behavior, in the FST (Borsoi et al., 2015).

Further support for the hypothesis that depression results from interplay between monoaminergic systems and neurotrophic factors come from numerous studies investigating the antidepressant effects of ketamine, a non-competitive NMDA receptor antagonist (Ecevitoglu, Canbeyli, & Unal, 2019). Ketamine, otherwise used as a major anesthetic agent, increases mobility in the FST by an upregulation of BNDF in the hippocampus (Garcia et al., 2008; Yang, Hu, Zhou, Zhang, & Yang, 2013) and prefrontal cortex (Lepack, Fuchikami, Dwyer, Banasr, & Duman, 2014; Zhou et al., 2014). This increase in BDNF levels is regulated by an activation of local AMPA receptors (Zhou et al., 2014) and L-type voltage-dependent calcium channels (Lepack et al., 2014). A recent study showed that isoflurane, another common anesthetic agent, also produces a rapid-onset antidepressant effect through BDNF receptor TrkB signaling (Antila et al., 2017). Other atypical antidepressants that have been used in traditional medicine such as tetrahydroxystilbene glucoside (Wang et al., 2017), andrographolide (Zhang et al., 2019), or crocus sativus/saffron (Ghasemi et al., 2015) also produce antidepressant effects in the FST via an enhancement of the cortical/hippocampal BDNF levels.

MDD patients have clinically low levels of serum and plasma BDNF, which is reversed with successful antidepressant treatment (Molendijk et al., 2010; Zhou et al., 2017). Meta-analysis of clinical data established this key neurotrophin as a biomarker for MDD (Kishi, Yoshimura, Ikuta, & Iwata, 2017; Polyakova et al., 2015). However, no straightforward correlation can be drawn between global levels of BDNF and depressive symptoms. In contrast to the antidepressant properties of hippocampal and prefrontal expression of BDNF or increased TrkB signaling in these structures, infusions of BDNF into the ventral tegmental area (VTA) leads to behavioral despair in rats (Eisch et al., 2003). This finding suggests the need to take a network-level approach to different symptoms of depression, focusing on neuronal circuity rather than wide-spread neuromodulator systems or ubiquitous molecular mechanisms.

The limbic circuitry

The neural circuitry of depression is attributed to several cortical and extracortical limbic structures and the aforementioned cortico-limbic connections that have been implicated in sensory association, emotions, memory and motivation (Nestler et al., 2002). Unlike neurodegenerative diseases, MDD has no pathologic lesion sites marked by degenerating neurons or specific structural

alterations. With interpatient and pharmacokinetic variability are added to this picture, a complete depression circuitry, or a *connectome* for depression, has yet to be produced (Gardner et al., 2014).

In principle, by relying on our current knowledge on functional neuroanatomy, it is possible to make general associations between different depressive symptoms and brain regions involved in MDD. However, it should be noted that going beyond correlations and pinpointing specific structures or neuronal connections as the *cause* of a particular symptom is often a long-shot. This being said, two major lines of research contribute to our network-level understanding of different depressive symptoms: brain imaging studies in depressed patients with diverse symptomology and basic animal research on different neuronal systems that are also involved in depression.

The monoamine hypothesis has been supported by structural as well as functional MRI studies that have recorded decreased volume or metabolic activity in brain structures containing monoaminergic cell groups (Sasaki et al., 2008). Decreased serotonergic levels or function in MDD was linked to atrophy in the brainstem raphe nuclei as observed by MRI (Supprian et al., 2004) and transcranial sonography (Budisic et al., 2010). The serotonergic lesion in MDD is accompanied by a decrease in the power of circadian/ultradian rhythms of serotonin as recorded in EEG and resting state fMRI (Salomon & Cowan, 2013). Furthermore, resting state functional connectivity studies showed altered intranuclear (Beliveau et al., 2015) as well as extranuclear/cortical connections of the raphe nuclei (Ikuta et al., 2017) in depression.

Relatively decreased volume and low signaling were also recorded in the locus coeruleus, the noradrenergic center of the brain (Liu et al., 2017; Shibata, Sasaki, Tohyama, Otsuka, & Sakai, 2007). An early study utilizing postmortem examination of brains of MDD patients strengthened this finding by detecting abnormally high levels of tyrosine hydroxylase in the locus coeruleus, indicating suppressed biosynthesis of norepinephrine (Zhu et al., 1999). Recently, a previously understudied nucleus with dense serotonergic and dopaminergic connections, the habenula, attracted attention in depression research (Lawson et al., 2017; Yang, Wang, Hu, & Hu, 2018). Abnormal intranuclear functional connectivity was observed in the habenula of treatment-resistant depression patients (Luan, Zhang, Wang, Zhao, & Liu, 2019), and the lateral nucleus of habenula was suggested as a major therapeutic target for the antidepressant effects of ketamine (Gold & Kadriu, 2019).

Network-level alterations in MDD are not restricted to the monoaminergic nuclei. Supporting the aforementioned theories on adult neurogenesis and neurotrophic factors in the etiology of depression, certain MRI studies detected volumetric changes in the hippocampal formation as well as functional alterations in the fronto-hippocampal network of depressed patients (Campbell & Macqueen, 2004). These findings were associated with different levels of cognitive impairment observed in many MDD patients. However, inconsistent results have been published regarding the hippocampal volume changes

following antidepressant treatment, many reporting no detectable volumetric change (Kraus et al., 2019; Vythilingam et al., 2004). The involvement of the hippocampus in MDD symptomology seems to depend on decreased neurogenesis and neurotrophic factor levels without a noticeable atrophy. Suggested role of the hippocampal formation in anhedonia as well as memory loss associated with depression may be detected at a macroscopic level, but emerge within microcircuits of the hippocampal complex.

Brain imaging studies identified major pathological features within other target limbic regions of ascending monoaminergic projections. The amygdaloid circuit, initially identified as the *emotion center* of the brain (LeDoux, 2000) and the neuronal circuitry where affective (e.g. fear) conditioning is encoded (Pare, Quirk, & Ledoux, 2004) was the usual suspect of early brain imaging experiments in depressed patients. Providing support for early animal studies deeming amygdala as the emotion center of the brain, neuroimaging in healthy participants showed that emotional stimuli consistently activate the amygdala and related limbic and cortical structures (Phan, Wager, Taylor, & Liberzon, 2002; Phillips, Drevets, Rauch, & Lane, 2003). Not surprisingly, in patients with MDD, volumetric alterations (Konarski et al., 2008; Mayberg et al., 1999), resting state network differences (Dutta, McKie, & Deakin, 2014) and abnormal metabolic activity (Beauregard, Paquette, & Levesque, 2006) have been reported in the amygdala as well as structures with dense connections to the amygdaloid circuit, especially the insula, anterior cingulate cortex, middle frontal gyrus, and the dorsomedial, dorsolateral and orbitofrontal prefrontal cortices.

Several structural and functional alterations in the amygdaloid circuit have been associated with depression. However, inconsistent results were published regarding the exact volumetric changes of the amygdala in depressed patients. Many imaging studies reported smaller/shrunk amygdalae in MDD patients compared to healthy participants (Caetano et al., 2004; Hastings, Parsey, Oquendo, Arango, & Mann, 2004; Rosso et al., 2005), while others found it to be enlarged (Frodl et al., 2002; MacMillan et al., 2003). Importantly, brain imaging research with bipolar patients often report enlarged amygdala as well (Altshuler et al., 2000; Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998). Some studies found a correlation between the amygdala size and the severity of the depressive symptoms (Drevets, 1999). The volume and resting state functional connectivity of the amygdala were therefore suggested as biomarkers for bipolar disorder (Ambrosi et al., 2017; Fonseka, MacQueen, & Kennedy, 2018). Many neuroimaging studies also observed decreased volume and/or activity in the aforementioned frontal cortex subregions, especially in the right hemisphere (Mayberg et al., 1999). The positive correlation between amygdala volume/metabolism and severity of depression underlie the role of the amygdaloid circuitry in the defining symptom of the disease: *depressed mood*. An intact amygdala and normal functioning of the aforementioned cortico/fronto-limbic connections are required for healthy mood regulation (Drevets, 1999).

Similar to the so called emotion circuits (LeDoux, 2000), the *reward circuitry* of the brain, including the basal ganglia, was a common region of interest in brain imaging studies (Russo & Nestler, 2013). These experiments have focused on psychomotor alteration, anhedonia and faulty reward processing (Coccurello, 2019; Heshmati & Russo, 2015). The idea stems from basic animal work indicating the involvement of dopaminergic structures and pathways in voluntary motor actions (Buyukdura et al., 2011; Unal & Canbeyli, 2019), goal-directed behavior and reward seeking/processing (Haber, Adler, & Bergman, 2012; Schultz, 1998; Tepper, Abercrombie, & Bolam, 2007). Diminished gray matter volume in the basal ganglia nuclei and smaller globus pallidum were associated with depressive symptoms marked by decreased motivation, anhedonia and slowing psychomotor activity (Onyewuenyi, Muldoon, Christie, Erickson, & Gianaros, 2014).

Volumetric alterations of the basal ganglia gave rise to a novel treatment method for MDD and treatment-resistant depression. Inspired by the effectiveness of deep brain stimulation in Parkinson's disease, pioneering stimulation studies attempted to bring back healthy oscillatory activity in the cortico-striatal-thalamic circuitry to treat depression (Dunlop, Hanlon, & Downar, 2017; Kisely, Li, Warren, & Siskind, 2018). Pilot studies, utilizing deep brain stimulation (DBS) as well as non-invasive transcranial magnetic stimulation (TMS) to target ventral striatum/capsule, medial forebrain bundle or the subcallosal cingulate gyrus produced promising results. Alleviated depressive symptoms include destabilized psychomotor activity and loss of interest or pleasure (Dunlop et al., 2017; Kisely et al., 2018). Altogether, these data suggest that the basal ganglia and wide-ranging dopaminergic circuitry of the brain constitute the basic neuronal signature of psychomotor and motivation related symptoms of MDD. On the contrary, it is important to note that clinical data from brain imaging studies lack the necessary spatial resolution to identify individual contributions of the major dopaminergic pathways to MDD. We can only rely on basic neuroscience research to speculate that abnormal functioning in the nigrostriatal pathway would cause psychomotor symptoms (Groenewegen, 2003; Sobin & Sackeim, 1997; Yin & Yuan, 2017), whereas dysfunction in the mesolimbic and mesocortical pathways likely underlie anhedonia (Haber et al., 2012; Petzinger et al., 2010).

Conclusion: A gestalt understanding of depressive symptoms

This chapter provided a brief review of the identified neural substrates of different depression symptoms. MDD, being a prevalent psychiatric disorder and a global health problem, attracts constant scientific attention both in clinical research and as a useful *model* in basic neuroscience. This results in hundreds, if not thousands, of scientific publications each year, with several contradictory results. A PubMed search for "depression" revealed 23,416 results for 2017 and 24,499 for 2018 (19,813 are published in 2019 as of October). Hence, this chapter surveyed only the major findings in the literature with wide-spread consensus.

Cognitive and clinical neuroscience studies utilizing brain imaging in patients and healthy controls provide the gross neuroanatomical substrates of some of the symptoms. These were recorded as volumetric alterations in specific structures, changes in metabolic activity (e.g. BOLD signal) or differences in fMRI-defined functional networks. Behavioral and systems neuroscience research revealed the molecular, neurochemical and neuronal circuit-level pathologies underlying depression. Some of these animal studies are not closely related to clinical depression, as they have not used an animal model of depression and did not induce despair/stress, but merely investigated normal functioning of neural systems, such as the basal ganglia (Smith, Pare, & Sidibe, 2004; Tepper et al., 2007) or amygdaloid circuitry (Pare et al., 2004), which are known or hypothesized to have a role in the disease. Integrating data from human and animal work is the key to a holistic understanding of depression and its symptoms. The individual symptoms of depression, as detailed in this chapter, cannot be linked exclusively to a particular neural substrate, but often result by a combination of a number of alterations at the chemical, molecular, cellular and network level. Hence, relatively speaking, one particular depressive symptom may be *more* related to the dysfunction in a specific brain region or neuronal circuit then other regions or circuits. But these other regions or circuits may still contribute to the symptom at varying degrees. Here, we argue that it is important to keep the epiphenomenal aspects of depression in mind and avoid making unrealistic matchings between individual symptoms and handpicked neurobiological substrates. The complex etiology of depression, together with the relatively high inter-patient variability in symptomatology and clinical outcome, require a Gestalt approach to the multifaceted disease.

References

Altman, J., & Das, G. D. (1965). Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *Journal of Comparative Neurology*, *124*(3), 319–335. https://doi.org/10.1002/cne.901240303.

Altshuler, L. L., Bartzokis, G., Grieder, T., Curran, J., Jimenez, T., Leight, K., et al. (2000). An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. *Biological Psychiatry*, *48*(2), 147–162. https://doi.org/10.1016/s0006-3223(00)00836-2.

Altshuler, L. L., Bartzokis, G., Grieder, T., Curran, J., & Mintz, J. (1998, July). Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: An MRI study demonstrating neuroanatomic specificity. *Archives of General Psychiatry, United States*. https://doi.org/10.1001/archpsyc.55.7.663.

Ambrosi, E., Arciniegas, D. B., Madan, A., Curtis, K. N., Patriquin, M. A., Jorge, R. E., et al. (2017). Insula and amygdala resting-state functional connectivity differentiate bipolar from unipolar depression. *Acta Psychiatrica Scandinavica*, *136*(1), 129–139. https://doi.org/10.1111/acps.12724.

Ansorge, M. S., Zhou, M., Lira, A., Hen, R., & Gingrich, J. A. (2004). Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science (New York, NY)*, *306*(5697), 879–881. https://doi.org/10.1126/science.1101678.

Antila, H., Ryazantseva, M., Popova, D., Sipilä, P., Guirado, R., Kohtala, S., et al. (2017). Isoflurane produces antidepressant effects and induces TrkB signaling in rodents. *Scientific Reports*, *7*(1), 7811. https://doi.org/10.1038/s41598-017-08166-9.

Avery, D., & Silverman, J. (1984). Psychomotor retardation and agitation in depression: Relationship to age, sex, and response to treatment. *Journal of Affective Disorders*, *7*(1), 67–76. https://doi.org/10.1016/0165-0327(84)90066-1.

Beauregard, M., Paquette, V., & Levesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Neuroreport*, *17*(8), 843–846. https://doi.org/10.1097/01.wnr.0000220132.32091.9f.

Beliveau, V., Svarer, C., Frokjaer, V. G., Knudsen, G. M., Greve, D. N., & Fisher, P. M. (2015). Functional connectivity of the dorsal and median raphe nuclei at rest. *NeuroImage*, *116*, 187–195. https://doi.org/10.1016/j.neuroimage.2015.04.065.

Bilello, J. A. (2016). Seeking an objective diagnosis of depression. *Biomarkers in Medicine*, *10*(8), 861–875. https://doi.org/10.2217/bmm-2016-0076.

Borsoi, M., Antonio, C. B., Viana, A. F., Nardin, P., Goncalves, C.-A., & Rates, S. M. K. (2015). Immobility behavior during the forced swim test correlates with BNDF levels in the frontal cortex, but not with cognitive impairments. *Physiology & Behavior*, *140*, 79–88. https://doi.org/10.1016/j.physbeh.2014.12.024.

Bousman, C. A., Forbes, M., Jayaram, M., Eyre, H., Reynolds, C. F., Berk, M., et al. (2017). Antidepressant prescribing in the precision medicine era: A prescriber's primer on pharmacogenetic tools. *BMC Psychiatry*, *17*(1), 60. https://doi.org/10.1186/s12888-017-1230-5.

Bragulat, V., Paillere-Martinot, M.-L., Artiges, E., Frouin, V., Poline, J.-B., & Martinot, J.-L. (2007). Dopaminergic function in depressed patients with affective flattening or with impulsivity: [18F] fluoro-L-dopa positron emission tomography study with voxel-based analysis. *Psychiatry Research*, *154*(2), 115–124. https://doi.org/10.1016/j.pscychresns.2006.07.002.

Budisic, M., Karlovic, D., Trkanjec, Z., Lovrencic-Huzjan, A., Vukovic, V., Bosnjak, J., et al. (2010). Brainstem raphe lesion in patients with major depressive disorder and in patients with suicidal ideation recorded on transcranial sonography. *European Archives of Psychiatry and Clinical Neuroscience*, *260*(3), 203–208. https://doi.org/10.1007/s00406-009-0043-z.

Buyukdura, J. S., McClintock, S. M., & Croarkin, P. E. (2011). Psychomotor retardation in depression: Biological underpinnings, measurement, and treatment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(2), 395–409. https://doi.org/10.1016/j.pnpbp.2010.10.019.

Caetano, S. C., Hatch, J. P., Brambilla, P., Sassi, R. B., Nicoletti, M., Mallinger, A. G., et al. (2004). Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry Research*, *132*(2), 141–147. https://doi.org/10.1016/j.pscychresns.2004.08.002.

Campbell, S., & Macqueen, G. (2004). The role of the hippocampus in the pathophysiology of major depression. *Journal of Psychiatry & Neuroscience: JPN*, *29*(6), 417–426.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science (New York, NY)*, *301*(5631), 386–389. https://doi.org/10.1126/science.1083968.

Coccurello, R. (2019). Anhedonia in depression symptomatology: Appetite dysregulation and defective brain reward processing. *Behavioural Brain Research*, *372*, 112041. https://doi.org/10.1016/j.bbr.2019.112041.

Coppen, A. (1967). The biochemistry of affective disorders. *The British Journal of Psychiatry: The Journal of Mental Science*, *113*(504), 1237–1264. https://doi.org/10.1192/bjp.113.504.1237.

Cryan, J. F., & Mombereau, C. (2004). In search of a depressed mouse: Utility of models for studying depression-related behavior in genetically modified mice. *Molecular Psychiatry*, *9*(4), 326–357. https://doi.org/10.1038/sj.mp.4001457.

Cryan, J. F., Mombereau, C., & Vassout, A. (2005). The tail suspension test as a model for assessing antidepressant activity: Review of pharmacological and genetic studies in mice. *Neuroscience & Biobehavioral Reviews*, *29*(4), 571–625. https://doi.org/10.1016/j.neubiorev.2005.03.009.

Delgado, P. L. (2000). Depression: The case for a monoamine deficiency. *The Journal of Clinical Psychiatry*, *61*(Suppl 6), 7–11.

Deltheil, T., Guiard, B. P., Cerdan, J., David, D. J., Tanaka, K. F., Reperant, C., et al. (2008). Behavioral and serotonergic consequences of decreasing or increasing hippocampus brain-derived neurotrophic factor protein levels in mice. *Neuropharmacology*, *55*(6), 1006–1014. https://doi.org/10.1016/j.neuropharm.2008.08.001.

Dillon, D. G., & Pizzagalli, D. A. (2018). Mechanisms of memory disruption in depression. *Trends in Neurosciences*, *41*(3), 137–149. https://doi.org/10.1016/j.tins.2017.12.006.

Drevets, W. C. (1999). Prefrontal cortical-amygdalar metabolism in major depression. *Annals of the New York Academy of Sciences*, *877*, 614–637. https://doi.org/10.1111/j.1749-6632.1999.tb09292.x.

Dulawa, S. C., & Hen, R. (2005). Recent advances in animal models of chronic antidepressant effects: The novelty-induced hypophagia test. *Neuroscience and Biobehavioral Reviews*, *29*(4–5), 771–783. https://doi.org/10.1016/j.neubiorev.2005.03.017.

Duman, R. S., Heninger, G. R., & Nestler, E. J. (1997). A molecular and cellular theory of depression. *Archives of General Psychiatry*, *54*(7), 597–606. https://doi.org/10.1001/archpsyc.1997.01830190015002.

Duman, R. S., & Li, N. (2012). A neurotrophic hypothesis of depression: Role of synaptogenesis in the actions of NMDA receptor antagonists. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences*, *367*(1601), 2475–2484. https://doi.org/10.1098/rstb.2011.0357.

Dunlop, K., Hanlon, C. A., & Downar, J. (2017). Noninvasive brain stimulation treatments for addiction and major depression. *Annals of the New York Academy of Sciences*, *1394*(1), 31–54. https://doi.org/10.1111/nyas.12985.

Dutta, A., McKie, S., & Deakin, J. F. W. (2014). Resting state networks in major depressive disorder. *Psychiatry Research*, *224*(3), 139–151. https://doi.org/10.1016/j.pscychresns.2014.10.003.

Ecevitoglu, A., Canbeyli, R., & Unal, G. (2019). Oral ketamine alleviates behavioral despair without cognitive impairment in Wistar rats. *Behavioural Brain Research*, *372*, 112058. https://doi.org/10.1016/j.bbr.2019.112058.

Eisch, A. J., Bolanos, C. A., de Wit, J., Simonak, R. D., Pudiak, C. M., Barrot, M., et al. (2003). Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: A role in depression. *Biological Psychiatry*, *54*(10), 994–1005. https://doi.org/10.1016/j.biopsych.2003.08.003.

Feighner, J. P. (1999). Mechanism of action of antidepressant medications. *The Journal of Clinical Psychiatry*, *60*(Suppl 4), 3–4.

Fonseka, T. M., MacQueen, G. M., & Kennedy, S. H. (2018). Neuroimaging biomarkers as predictors of treatment outcome in major depressive disorder. *Journal of Affective Disorders*, *233*, 21–35. https://doi.org/10.1016/j.jad.2017.10.049.

Frodl, T., Meisenzahl, E., Zetzsche, T., Bottlender, R., Born, C., Groll, C., et al. (2002). Enlargement of the amygdala in patients with a first episode of major depression. *Biological Psychiatry*, *51*(9), 708–714. https://doi.org/10.1016/s0006-3223(01)01359-2.

Garcia, L. S. B., Comim, C. M., Valvassori, S. S., Réus, G. Z., Barbosa, L. M., Cristina, A., et al. (2008). Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, *32*, 140–144. https://doi.org/10.1016/j.pnpbp.2007.07.027.

Gardner, A., Åstrand, D., Öberg, J., Jacobsson, H., Jonsson, C., Larsson, S., et al. (2014). Towards mapping the brain connectome in depression: Functional connectivity by perfusion SPECT. *Psychiatry Research: Neuroimaging*, *223*(2), 171–177. https://doi.org/10.1016/j.pscychresns.2014.05.008.

Ghasemi, T., Abnous, K., Vahdati, F., Mehri, S., Razavi, B. M., & Hosseinzadeh, H. (2015). Antidepressant effect of *Crocus sativus* aqueous extract and its effect on CREB, BDNF, and VGF transcript and protein levels in rat hippocampus. *Drug Research*, *65*(7), 337–343. https://doi.org/10.1055/s-0034-1371876.

Gold, P. W., & Kadriu, B. (2019). A major role for the lateral habenula in depressive illness: Physiologic and molecular mechanisms. *Frontiers in Psychiatry*, *10*, 320. https://doi.org/10.3389/fpsyt.2019.00320.

Gould, E., Beylin, A., Tanapat, P., Reeves, A., & Shors, T. J. (1999). Learning enhances adult neurogenesis in the hippocampal formation. *Nature Neuroscience*, *2*(3), 260–265. https://doi.org/10.1038/6365.

Gould, E., Tanapat, P., McEwen, B. S., Flügge, G., & Fuchs, E. (1998). Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proceedings of the National Academy of Sciences*, *95*(6), 3168–3171. https://doi.org/10.1073/pnas.95.6.3168.

Gourgouvelis, J., Yielder, P., & Murphy, B. (2017). Exercise promotes neuroplasticity in both healthy and depressed brains: An fMRI pilot study. *Neural Plasticity*, *2017*, 8305287. https://doi.org/10.1155/2017/8305287.

Groenewegen, H. J. (2003). The basal ganglia and motor control. *Neural Plasticity*, *10*(1–2), 107–120. https://doi.org/10.1155/NP.2003.107.

Haber, S. N., Adler, A., & Bergman, H. (2012). The basal ganglia. In J. K. Mai, & G. Paxinos (Eds.), *The human nervous system* (3rd ed., pp. 678–738). San Diego: Academic Press. https://doi.org/10.1016/B978-0-12-374236-0.10020-3 (chap. 20).

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science (New York, NY)*, *297*(5580), 400–403. https://doi.org/10.1126/science.1071829.

Hastings, R. S., Parsey, R. V., Oquendo, M. A., Arango, V., & Mann, J. J. (2004). Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *29*(5), 952–959. https://doi.org/10.1038/sj.npp.1300371.

Heshmati, M., & Russo, S. J. (2015). Anhedonia and the brain reward circuitry in depression. *Current Behavioral Neuroscience Reports*, *2*(3), 146–153. https://doi.org/10.1007/s40473-015-0044-3.

Hirschfeld, R. M. (2000). History and evolution of the monoamine hypothesis of depression. *The Journal of Clinical Psychiatry*, *61*(Suppl 6), 4–6.

Hodes, G. E., Yang, L., Van Kooy, J., Santollo, J., & Shors, T. J. (2009). Prozac during puberty: Distinctive effects on neurogenesis as a function of age and sex. *Neuroscience*, *163*(2), 609–617. https://doi.org/10.1016/j.neuroscience.2009.06.057.

Hodes, G. E., Hill-Smith, T. E., & Lucki, I. (2010). Fluoxetine treatment induces dose dependent alterations in depression associated behavior and neural plasticity in female mice. *Neuroscience Letters*, *484*(1), 12–16. https://doi.org/10.1016/j.neulet.2010.07.084.

Holick, K. A., Lee, D. C., Hen, R., & Dulawa, S. C. (2008). Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *33*(2), 406–417. https://doi.org/10.1038/sj.npp.1301399.

Huang, G.-J., Bannerman, D., & Flint, J. (2008, February). Chronic fluoxetine treatment alters behavior, but not adult hippocampal neurogenesis, in BALB/cJ mice. *Molecular Psychiatry, England*. https://doi.org/10.1038/sj.mp.4002104.

Ikuta, T., Matsuo, K., Harada, K., Nakashima, M., Hobara, T., Higuchi, N., et al. (2017). Disconnectivity between Dorsal Raphe nucleus and posterior cingulate cortex in later life depression. *Frontiers in Aging Neuroscience*, *9*, 236. https://doi.org/10.3389/fnagi.2017.00236.

Jacobs, B. L., van Praag, H., & Gage, F. H. (2000). Adult brain neurogenesis and psychiatry: A novel theory of depression. *Molecular Psychiatry*, *5*(3), 262–269.

Kaplan, M. S., & Hinds, J. W. (1977). Neurogenesis in the adult rat: Electron microscopic analysis of light radioautographs. *Science*, *197*(4308), 1092–1094. https://doi.org/10.1126/science.887941.

Kempermann, G. (2008). The neurogenic reserve hypothesis: What is adult hippocampal neurogenesis good for? *Trends in Neurosciences*, *31*(4), 163–169. https://doi.org/10.1016/j.tins.2008.01.002.

Kisely, S., Li, A., Warren, N., & Siskind, D. (2018). A systematic review and meta-analysis of deep brain stimulation for depression. *Depression and Anxiety*, *35*(5), 468–480. https://doi.org/10.1002/da.22746.

Kishi, T., Yoshimura, R., Ikuta, T., & Iwata, N. (2017). Brain-derived neurotrophic factor and major depressive disorder: Evidence from meta-analyses. *Frontiers in Psychiatry*, *8*, 308. https://doi.org/10.3389/fpsyt.2017.00308.

Klemm, W. R. (1989). Drug effects on active immobility responses: What they tell us about neurotransmitter systems and motor functions. *Progress in Neurobiology*, *32*(5), 403–422.

Konarski, J. Z., McIntyre, R. S., Kennedy, S. H., Rafi-Tari, S., Soczynska, J. K., & Ketter, T. A. (2008). Volumetric neuroimaging investigations in mood disorders: Bipolar disorder versus major depressive disorder. *Bipolar Disorders*, *10*(1), 1–37. https://doi.org/10.1111/j.1399-5618.2008.00435.x.

Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., & Moryś, J. (2018). BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. *Cellular and Molecular Neurobiology*, *38*(3), 579–593. https://doi.org/10.1007/s10571-017-0510-4.

Kraus, C., Seiger, R., Pfabigan, D. M., Sladky, R., Tik, M., Paul, K., et al. (2019). Hippocampal subfields in acute and remitted depression—an ultra-high field magnetic resonance imaging study. *The International Journal of Neuropsychopharmacology*, *22*(8), 513–522. https://doi.org/10.1093/ijnp/pyz030.

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*(7215), 894–902. https://doi.org/10.1038/nature07455.

Lawson, R. P., Nord, C. L., Seymour, B., Thomas, D. L., Dayan, P., Pilling, S., et al. (2017). Disrupted habenula function in major depression. *Molecular Psychiatry*, *22*(2), 202–208. https://doi.org/10.1038/mp.2016.81.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, *23*, 155–184. https://doi.org/10.1146/annurev.neuro.23.1.155.

Lepack, A. E., Fuchikami, M., Dwyer, J. M., Banasr, M., & Duman, R. S. (2014). BDNF release is required for the behavioral actions of ketamine. *The International Journal of Neuropsychopharmacology*, *18*(1). https://doi.org/10.1093/ijnp/pyu033.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science (New York, NY)*, *274*(5292), 1527–1531. https://doi.org/10.1126/science.274.5292.1527.

Liu, K. Y., Marijatta, F., Hämmerer, D., Acosta-Cabronero, J., Düzel, E., & Howard, R. J. (2017). Magnetic resonance imaging of the human locus coeruleus: A systematic review. *Neuroscience & Biobehavioral Reviews*, *83*, 325–355. https://doi.org/10.1016/j.neubiorev.2017.10.023.

Liu, X., & Jiang, K. (2016). Why is diagnosing MDD challenging? *Shanghai Archives of Psychiatry*, *28*(6), 343–345. https://doi.org/10.11919/j.issn.1002-0829.216073.

Luan, S.-X., Zhang, L., Wang, R., Zhao, H., & Liu, C. (2019). A resting-state study of volumetric and functional connectivity of the habenular nucleus in treatment-resistant depression patients. *Brain and Behavior*, *9*(4). https://doi.org/10.1002/brb3.1229.

MacMillan, S., Szeszko, P. R., Moore, G. J., Madden, R., Lorch, E., Ivey, J., et al. (2003). Increased amygdala: Hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *Journal of Child and Adolescent Psychopharmacology*, *13*(1), 65–73. https://doi.org/10.1089/104454603321666207.

Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *The Journal of Neuroscience*, *20*(24), 9104–9110. https://doi.org/10.1523/JNEUROSCI.20-24-09104.2000.

Marchand, W. R., Lee, J. N., Thatcher, G. W., Jensen, C., Stewart, D., Dilda, V., et al. (2007). A functional MRI study of a paced motor activation task to evaluate frontal-subcortical circuit function in bipolar depression. *Psychiatry Research*, *155*(3), 221–230. https://doi.org/10.1016/j.pscychresns.2007.03.003.

Marchand, W. R., Lee, J. N., Thatcher, J., Thatcher, G. W., Jensen, C., & Starr, J. (2007). A preliminary longitudinal fMRI study of frontal-subcortical circuits in bipolar disorder using a paced motor activation paradigm. *Journal of Affective Disorders*, *103*(1–3), 237–241. https://doi.org/10.1016/j.jad.2007.01.008.

Martinot, M., Bragulat, V., Artiges, E., Dolle, F., Hinnen, F., Jouvent, R., et al. (2001). Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. *The American Journal of Psychiatry*, *158*(2), 314–316. https://doi.org/10.1176/appi.ajp.158.2.314.

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and serotonin: Role in mood disorders. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *33*(1), 73–83. https://doi.org/10.1038/sj.npp.1301571.

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., et al. (1999). Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *The American Journal of Psychiatry*, *156*(5), 675–682. https://doi.org/10.1176/ajp.156.5.675.

Meyer, J. H., McNeely, H. E., Sagrati, S., Boovariwala, A., Martin, K., Verhoeff, N. P. L. G., et al. (2006). Elevated putamen D(2) receptor binding potential in major depression with motor retardation: An [11C]raclopride positron emission tomography study. *The American Journal of Psychiatry*, *163*(9), 1594–1602. https://doi.org/10.1176/ajp.2006.163.9.1594.

Miller, B. R., & Hen, R. (2015). The current state of the neurogenic theory of depression and anxiety. *Current Opinion in Neurobiology*, *30*, 51–58. https://doi.org/10.1016/j.conb.2014.08.012.

Molendijk, M. L., Bus, B. A. A., Spinhoven, P., Penninx, B. W. J. H., Kenis, G., Prickaerts, J., et al. (2010). Serum levels of brain-derived neurotrophic factor in major depressive disorder: State-trait issues, clinical features and pharmacological treatment. *Molecular Psychiatry*, *16*, 1088. https://doi.org/10.1038/mp.2010.98.

Nestler, E. J., Barrot, M., DiLeone, R. J., Eisch, A. J., Gold, S. J., & Monteggia, L. M. (2002). Neurobiology of depression. *Neuron*, *34*(1), 13–25. https://doi.org/10.1016/S0896-6273(02)00653-0.

Onyewuenyi, I. C., Muldoon, M. F., Christie, I. C., Erickson, K. I., & Gianaros, P. J. (2014). Basal ganglia morphology links the metabolic syndrome and depressive symptoms. *Physiology & Behavior*, *123*, 214–222. https://doi.org/10.1016/j.physbeh.2013.09.014.

Pare, D., Quirk, G. J., & Ledoux, J. E. (2004). New vistas on amygdala networks in conditioned fear. *Journal of Neurophysiology*, *92*(1), 1–9. https://doi.org/10.1152/jn.00153.2004.

Perera, T. D., Dwork, A. J., Keegan, K. A., Thirumangalakudi, L., Lipira, C. M., Joyce, N., et al. (2011). Necessity of hippocampal neurogenesis for the therapeutic action of antidepressants in adult nonhuman primates. *PloS One*, *6*(4). https://doi.org/10.1371/journal.pone.0017600.

Petzinger, G. M., Fisher, B. E., Van Leeuwen, J.-E., Vukovic, M., Akopian, G., Meshul, C. K., et al. (2010). Enhancing neuroplasticity in the basal ganglia: The role of exercise in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *25 Suppl 1*(0–1), S141–S145. https://doi.org/10.1002/mds.22782.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, *16*(2), 331–348. https://doi.org/10.1006/nimg.2002.1087.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, *54*(5), 504–514. https://doi.org/10.1016/s0006-3223(03)00168-9.

Pies, R. W. (2009). Depression and the pitfalls of causality: Implications for DSM-V. *Journal of Affective Disorders*, *116*(1–2), 1–3. https://doi.org/10.1016/j.jad.2008.11.009.

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *36*(1), 183–206. https://doi.org/10.1038/npp.2010.166.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393–423. https://doi.org/10.1146/annurev-clinpsy-050212-185606.

Polyakova, M., Stuke, K., Schuemberg, K., Mueller, K., Schoenknecht, P., & Schroeter, M. L. (2015). BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis. *Journal of Affective Disorders*, *174*, 432–440. https://doi.org/10.1016/j.jad.2014.11.044.

Porsolt, R. D., Bertin, A., & Jalfre, M. (1977). Behavioral despair in mice: A primary screening test for antidepressants. *Archives Internationales de Pharmacodynamie et de Therapie*, *229*(2), 327–336.

Porsolt, R. D., Le Pichon, M., & Jalfre, M. (1977). Depression: A new animal model sensitive to antidepressant treatments. *Nature*, *266*(5604), 730–732.

Porsolt, R. D., Anton, G., Blavet, N., & Jalfre, M. (1978). Behavioural despair in rats: A new model sensitive to antidepressant treatments. *European Journal of Pharmacology*, *47*(4), 379–391. https://doi.org/10.1016/0014-2999(78)90118-8.

Post, R. J., & Warden, M. R. (2018). Depression: The search for separable behaviors and circuits. *Current Opinion in Neurobiology*, *49*, 192–200. https://doi.org/10.1016/j.conb.2018.02.018.

Qiao, H., An, S.-C., Xu, C., & Ma, X.-M. (2017). Role of proBDNF and BDNF in dendritic spine plasticity and depressive-like behaviors induced by an animal model of depression. *Brain Research*, *1663*, 29–37. https://doi.org/10.1016/j.brainres.2017.02.020.

Ramirez, S., Liu, X., MacDonald, C. J., Moffa, A., Zhou, J., Redondo, R. L., et al. (2015). Activating positive memory engrams suppresses depression-like behaviour. *Nature*, *522*, 335. https://doi.org/10.1038/nature14514.

Rayner, G., Jackson, G., & Wilson, S. (2016). Cognition-related brain networks underpin the symptoms of unipolar depression: Evidence from a systematic review. *Neuroscience & Biobehavioral Reviews*, *61*, 53–65. https://doi.org/10.1016/j.neubiorev.2015.09.022.

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029–2040. https://doi.org/10.1017/S0033291713002535.

Rosso, I. M., Cintron, C. M., Steingard, R. J., Renshaw, P. F., Young, A. D., & Yurgelun-Todd, D. A. (2005). Amygdala and hippocampus volumes in pediatric major depression. *Biological Psychiatry*, *57*(1), 21–26. https://doi.org/10.1016/j.biopsych.2004.10.027.

Russo, S. J., & Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nature Reviews: Neuroscience*, *14*(9), 609–625. https://doi.org/10.1038/nrn3381.

Salomon, R. M., & Cowan, R. L. (2013). Oscillatory serotonin function in depression. *Synapse (New York, NY)*, *67*(11), 801–820. https://doi.org/10.1002/syn.21675.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., et al. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science (New York, NY)*, *301*(5634), 805–809. https://doi.org/10.1126/science.1083328.

Sasaki, M., Shibata, E., Tohyama, K., Kudo, K., Endoh, J., Otsuka, K., et al. (2008). Monoamine neurons in the human brain stem: Anatomy, magnetic resonance imaging findings, and clinical implications. *Neuroreport*, *19*(17), 1649–1654. https://doi.org/10.1097/WNR.0b013e328315a637.

Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. *The American Journal of Psychiatry*, *122*(5), 509–522. https://doi.org/10.1176/ajp.122.5.509.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*(1), 1–27. https://doi.org/10.1152/jn.1998.80.1.1.

Shibata, E., Sasaki, M., Tohyama, K., Otsuka, K., & Sakai, A. (2007). Reduced signal of locus ceruleus in depression in quantitative neuromelanin magnetic resonance imaging. *Neuroreport*, *18*(5), 415–418. https://doi.org/10.1097/WNR.0b013e328058674a.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106.

Smith, Y., Raju, D. V., Pare, J.-F., & Sidibe, M. (2004). The thalamostriatal system: A highly specific network of the basal ganglia circuitry. *Trends in Neurosciences*, *27*(9), 520–527. https://doi.org/10.1016/j.tins.2004.07.004.

Sobin, C., & Sackeim, H. A. (1997). Psychomotor symptoms of depression. *The American Journal of Psychiatry*, *154*(1), 4–17. https://doi.org/10.1176/ajp.154.1.4.

Steru, L., Chermat, R., Thierry, B., & Simon, P. (1985). The tail suspension test: A new method for screening antidepressants in mice. *Psychopharmacology*, *85*(3), 367–370. https://doi.org/10.1007/BF00428203.

Supprian, T., Reiche, W., Schmitz, B., Grunwald, I., Backens, M., Hofmann, E., et al. (2004). MRI of the brainstem in patients with major depression, bipolar affective disorder and normal controls. *Psychiatry Research*, *131*(3), 269–276. https://doi.org/10.1016/j.pscychresns.2004.02.005.

Surget, A., Tanti, A., Leonardo, E. D., Laugeray, A., Rainer, Q., Touma, C., et al. (2011). Antidepressants recruit new neurons to improve stress response regulation. *Molecular Psychiatry*, *16*(12), 1177–1188. https://doi.org/10.1038/mp.2011.48.

Tepper, J. M., Abercrombie, E. D., & Bolam, J. P. (2007). Basal ganglia macrocircuits. *Progress in Brain Research*, *160*, 3–7. https://doi.org/10.1016/S0079-6123(06)60001-0.

Unal, G., & Canbeyli, R. (2019). Psychomotor retardation in depression: A critical measure of the forced swim test. *Behavioural Brain Research*, *372*, 112047. https://doi.org/10.1016/j.bbr.2019.112047.

Vythilingam, M., Vermetten, E., Anderson, G. M., Luckenbaugh, D., Anderson, E. R., Snow, J., et al. (2004). Hippocampal volume, memory, and cortisol status in major depressive disorder: Effects of treatment. *Biological Psychiatry*, *56*(2), 101–112. https://doi.org/10.1016/j.biopsych.2004.04.002.

Wang, H., Zhao, Y., Wang, Y.-J., Song, L., Wang, J.-L., Huang, C., et al. (2017). Antidepressant-like effects of tetrahydroxystilbene glucoside in mice: Involvement of BDNF signaling cascade in the hippocampus. *CNS Neuroscience & Therapeutics*, *23*(7), 627–636. https://doi.org/10.1111/cns.12708.

Warner, C. H., Bobo, W., Warner, C., Reid, S., & Rachal, J. (2006). Antidepressant discontinuation syndrome. *American Family Physician*, *74*(3), 449–456.

Willner, P., Scheel-Krüger, J., & Belzung, C. (2013). The neurobiology of depression and antidepressant action. *Neuroscience & Biobehavioral Reviews*, *37*(10 Part 1), 2331–2371. https://doi.org/10.1016/j.neubiorev.2012.12.007.

Willner, P., Towell, A., Sampson, D., Sophokleous, S., & Muscat, R. (1987). Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. *Psychopharmacology*, *93*(3), 358–364. https://doi.org/10.1007/bf00187257.

Yamada, J., Sugimoto, Y., & Yamada, S. (2004). Involvement of dopamine receptors in the anti-immobility effects of dopamine re-uptake inhibitors in the forced swimming test. *European Journal of Pharmacology*, *504*(3), 207–211. https://doi.org/10.1016/j.ejphar.2004.09.057.

Yang, C., Hu, Y.-M., Zhou, Z.-Q., Zhang, G.-F., & Yang, J.-J. (2013). Acute administration of ketamine in rats increases hippocampal BDNF and mTOR levels during forced swimming test. *Upsala Journal of Medical Sciences*, *118*(1), 3–8. https://doi.org/10.3109/03009734.2012.724118.

Yang, Y., Wang, H., Hu, J., & Hu, H. (2018). Lateral habenula in the pathophysiology of depression. *Current Opinion in Neurobiology*, *48*, 90–96. https://doi.org/10.1016/j.conb.2017.10.024.

Yin, Y., & Yuan, Y. (2017). The dopaminergic polymorphisms in psychomotor retardation of depression: A pathway-based imaging genetics association study. *European Psychiatry*, *41*, S145–S146. https://doi.org/10.1016/j.eurpsy.2017.01.1989.

Zhang, J.-J., Gao, T.-T., Wang, Y., Wang, J.-L., Guan, W., Wang, Y.-J., et al. (2019). Andrographolide exerts significant antidepressant-like effects involving the hippocampal BDNF system in mice. *The International Journal of Neuropsychopharmacology*, *22*(9), 585–600. https://doi.org/10.1093/ijnp/pyz032.

Zhou, C., Zhong, J., Zou, B., Fang, L., Chen, J., Deng, X., et al. (2017). Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression. *PloS One*, *12*(2). https://doi.org/10.1371/journal.pone.0172270.

Zhou, W., Wang, N., Yang, C., Li, X.-M., Zhou, Z.-Q., & Yang, J.-J. (2014). Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *29*(7), 419–423. https://doi.org/10.1016/j.eurpsy.2013.10.005.

Zhu, M. Y., Klimek, V., Dilley, G. E., Haycock, J. W., Stockmeier, C., Overholser, J. C., et al. (1999). Elevated levels of tyrosine hydroxylase in the locus coeruleus in major depression. *Biological Psychiatry*, *46*(9), 1275–1286. https://doi.org/10.1016/s0006-3223(99)00135-3.

Zigova, T., Pencea, V., Wiegand, S. J., & Luskin, M. B. (1998). Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb. *Molecular and Cellular Neurosciences*, *11*(4), 234–245. https://doi.org/10.1006/mcne.1998.0684.