Depression: Current Conceptual Trends

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1.1 Introduction

Sadness is a normal reaction to life's hurdles, hinders, and disappointments. Depression is much more. Whether patients are experiencing emotional pain or feeling lifeless and empty, their symptoms engulf all aspects of their lives, interfering with their ability to be productive, to engage in meaningful relationships, and to attend to activities of daily living. Even basic body functions like eating and sleeping are disrupted and their physical health is often compromised. Feelings of hopelessness and worthlessness can be unrelenting and most affected individuals contemplate dying. Five to fifteen percent do commit suicide.

The World Health Organization (WHO) projects that depression [1, 2] will be second in medical burden only to ischemic heart disease [3]. The annual economic burden of depression in the United States was estimated at approximately $44 billion in 1990. Of the total costs, $12.4 billion was attributed to direct costs, $23.8 billion was associated with indirect costs to employers and society due to absenteeism and decreased worked productivity, and $7.5

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billion was associated with depression-related suicide [4]. Of all depressed individuals, only 10 % meet criteria for severe for treatment-resistant depression (TRD) [5] and account for over half the annual costs associated with treatment for depression [6]. Other studies have confirmed these estimates and shown that annual medical expenditures of TRD patients are double than non-TRD cohorts [7].

The incidence of depression is around 20 % worldwide [8]. Of the 14 million patients with depression in the United States, only 3.2 million are adequately treated following expert guidelines like ones proposed by the American Psychiatric Association [8–10]. The success rate with pharmacological treatments is not high [11], and short-term antidepressant drugs are moderately effective when compared to placebo [12]. Even after achieving a relief from depressive symptoms, 75 % will experience a recurrence of their symptoms [13]. We have shown in a meta-analysis across 2009 patients randomized to active antidepressant or placebo that the relapse rate is 23 and 51 % at 1 year [14]. In TRD patients, relapses can be as high as 50 % within 6 months despite adequate maintenance therapy. In turn, patients with repeated depressive episodes have even higher risks for relapse [15] and become more vulnerable to stress [16], and the course of their illness worsens. All this leads to longer episode durations and shorter inter-episode periods in between [17]. So how does depression develop, what is our current understanding of its pathophysiology, and how can we begin conceptualizing new treatment approaches that could confer long and sustained benefits?

1.2 Genetics of Depression

The vulnerability to depression can be inherited. Individuals with a parent or sibling that has had major depression are 1.5–3 times more likely to develop the condition than those who do not have a close relative with the condition. Bipolar disorder has a stronger genetic influence. Of those with bipolar disorder, approximately 50 % of them have a parent with a history of clinical depression. When a mother or father has bipolar disorder, their child will have a 25 % chance of developing some type of clinical depression.

If both parents have bipolar disorder, the chance of their child also developing bipolar disorder is between 50 and 75 %. Brothers and sisters of those with bipolar disorder may be 8–18 times more likely to develop bipolar disorder and 2–10 times more likely to develop major depressive disorder than others with no such siblings.

For a complex illness like depression, it is unlikely that a single gene will explain it all. So far, the large majority of genetic studies in major depression have focused on the polymorphisms relevant to monoaminergic neurotransmission. The effects though are not large. The polymorphism of the serotonin transporter promoter region (5-HTTLPR) has been linked to bipolar disorder, to suicidal behavior, and to stress vulnerability. It appears that such vulnerability is mostly associated with childhood and developmental trauma. Some studies have attempted to study the association between genes related to neurotoxic or neurotrophic processes, like brain-derived neurotrophic factor (BDNF) with limited results. Others have focused on inflammation, regulation of cortisol secretion by the hypothalamic-pituitary axis, sleep, and circadian rhythms. Whole-genome association studies are expected to yield more results, but the search remains elusive.

1.3 Stress and Depression

A stressful psychosocial event either precipitates depressive symptoms or exacerbates a preexisting depressive. The impact of external events is particularly evident in patients who have a genetic vulnerability like the serotonin transporter short allele [18]. Gender and age also modulate the impact of stress [19]. External stressors that originally led to an active episode can exert a positive sensitizing influence, ultimately leading to an autonomous progression of the illness [20, 21]. Patients can often identify what may have triggered their first or second depressive episode, but after a chronic course and repeated episodes, they cannot identify why their symptoms recurred or are surprised to how disproportionate their response to a stressful event is. Post [20] proposes a model of sensitization and kindling to explain the processes occurring in a lifetime of bipolar disorder patients. External stressors originally lead to a depressive

or manic episode and exert a positive sensitizing influence, ultimately leading to an autonomous progression of the illness. Reemergence of symptoms is clearly affected by the underlying state of the brain at the time of stress, and neurotrophic factors can play a role in limiting such progression. Presumably, a similar process occurs in recurrent unipolar depression. Such clinical phenomenon is at the heart of the emergent problem of TRD and has not been adequately studied or modeled in laboratory settings.

The repercussions of stress are determined by a host of characteristics that include its severity, chronicity, and personal relevance to the individual [16, 22, 23]. Chronic stress leads to changes in neurotransmitter neuropeptide concentrations as well as the anatomy of brain structures, which in turn alter the physiology and the adaptive responses of the neocortical regions [24] and cause increased activity in ventral limbic and paralimbic areas [25–29] (the functional neuroanatomy of depression is presented more in details further in this chapter and later in this book). Similar functional changes are associated with sadness, a core symptom of depression and a primary emotional response to loss [30]. These implicated networks receive direct and indirect signals [31] from the internal and external world through the brainstem nuclei, the hypothalamus, the insula, the cingulate, and various secondary associative areas [32]. These various regions play a regulatory role in maintaining homeostasis [33]. Stress can impair the mechanisms that protect the nervous system. It is also known to activate preprogrammed neuronal cell death. In essence, depressed patients are caught in a cycle: stress leads to fundamental alterations in brain chemistry that compromise their ability to cope with one of the initial causes of the illness—stress itself.

Direct Excitotoxicity: Stress causes neuronal damage through either an alteration of cellular energy and a decrease in brain-derived neurotrophic factor (BDNF) expression or through an increase in glutaminergic transmission that results in an increase of intracellular Ca+ and oxygen free radicals [34]. These different pathways promote neuron endangerment and are thought to contribute to the emergence of depressive states. They may also lead to hippocampal atrophy [26, 35], the disruption of activity in connected regions like the amygdala or prefrontal cortex [36], and poor feedback control of

the hypothalamic-pituitary axis (HPA) [37]. Remission may occur when a certain modulation of dysfunctional limbic-cortical interactions takes place [38]. Direct injections of BDNF in the hippocampus also reduce immobility time on the FST [39]. The cAMP response element-binding protein (CREB) is a key mediator of responses that underlie survival, memory, and plasticity of the nervous system. Chronic treatment of rodents with different classes of antidepressants, lithium [40], or electroconvulsive therapy [41] dramatically increases hippocampal levels of CREB gene transcription.

Apoptosis: In parallel, apoptosis, or programmed cell death, also appears to be linked to the pathophysiology of depression [42, 43]. Apoptosis is characterized by structural changes that ultimately lead to cell disintegration. The process is activated by a group of cysteine proteases known as caspases. Bcl-2 and related members of this family of proteins regulate the release of cytochrome *c* from mitochondria into the cytoplasm, which in turn mediates the mitochondrial pathway of apoptosis. It is tightly balanced between antiapoptotic (Bcl-2 and Bcl-xl) and proapoptotic (Bax). Interestingly, both fluoxetine [44] and moclobemide [45] have been demonstrated to upregulate Bcl-2 in purified mitochondria and isolated neural stem cells, respectively. In one of the most comprehensive studies to date, chronic mild stress model and antidepressant drugs exerted opposite effects on Bcl-2, Bcl-xl, and Bax in a region-specific manner in limbic brain regions. We have recently shown that deep brain stimulation to the infra-limbic region also modulates Bcl-2 in the hippocampus. So it appears that without the downregulation of proapototic mechanisms in brain regions and areas critical for mood regulation (like the hippocampus), antidepressants may not exert sustainable therapeutic benefits.

1.4 Emotion Regulation

Emotion regulation involves the ability to modulate the intensity and quality of responses to emotional stimuli, involving both automatic and controlled regulatory processes [46, 47]. Disruptions in

the control of emotion play a central role in mood and anxiety disorders [48–50]. A feature of depression is the inability to disengage from negative memories, feelings, and thoughts and engage the outside world with flexibility [51–53]. Negative emotions can also distract away from other cognitive demands [54–57] and make patients not able to cope with daily life needs [58]. An effective antidepressant treatment has to reduce this strong focus on negativity and allow the patients to appraise themselves and their world with a wider range of experiences.

Cognitive regulation of emotion involves directing attention to less intense aspects of an emotional stimulus or consciously altering the meaning of an emotion-eliciting stimulus [59, 60]. This "reappraisal" strategy has been shown to decrease the intensity of self-reported negative affective experience [60–62]. It is associated with increased activation in areas of the lateral and medial prefrontal cortex thought to support cognitive control (cf., [63]) and decreased activation of the amygdala, suggesting decreased emotional reactivity [61, 64–69].

1.5 Functional Neuroanatomy of Depression

Pierre Paul Broca first coined the term "limbic," using it to refer to the structures forming a loop in the middle of the brain that he posited were important in regulating emotion [70]. This circuit was further detailed by Papez [71] and elaborated within the larger concept of the triune brain [72]. Schematically, the limbic system and its connected brain stem structures are the middle of three concentric layers and unique to mammals. Alexander and colleagues [73] highlighted the interconnections between the subcortical structures and the prefrontal cortex. They described at least five important ganglia-thalamo-cortical functional working loops. Some researchers have sought to use this framework to explain how prefrontal lobe pathology might result in the symptoms of clinical depression [74].

We have made considerable progress in understanding the brain regions involved in mood dysregulation. Sadness and depressive illness are both associated with decreased activity in dorsal neocortical regions and relative increased activity in ventral limbic

and paralimbic areas [25]. In fact, increased regional cerebral blood flow and metabolism have been shown (but not always [75]) in the amygdala, orbitofrontal cortex, and medial thalamus and decrease in the dorsomedial/dorsal anterolateral PFC, subgenual ACC, and dorsal ACC relative to healthy control subjects. Failure of these subsets is hypothesized to explain the combination of clinical symptoms seen in depressed patients (i.e., mood, motor, cognitive, vegetative symptoms) [76]. These regions may be differentially affected in subtypes of depression [37]. Other important regions include the hippocampus [26], insula [32], and midbrain monoamine nuclei. Underlying structural abnormalities (reduction in volume or glia density) may also contribute to these dysfunctions [27–29]. Other factors to be considered in interpreting these results include the state of the disease, the inherited traits of the individual and genetic susceptibility [77], and the type of response to treatment. Mood, at any given time, is a continuous adaptive process. This implies that although certain localized activity changes can be identified, it is important to begin addressing the dynamic interplay within the system.

Many researchers are attempting to model mood systems based on human and animal known anatomical interconnections. Mayberg proposes that illness remission occurs when there is appropriate modulation of dysfunctional limbic-cortical interactions, an effect facilitated by various forms of treatment from antidepressant psychopharmacology that may initially regulate subcortical areas and later lead to a modulation of prefrontal regions (down-top model) [78]. The reverse may be observed with cognitive psychotherapy (top-down model).

1.6 The Anterior versus Lateral Network: Two Complementary Modes

The prefrontal cortex is divided into distinct cytoarchitectonic regions. While it is widely held that prefrontal cortex is involved in cognitive functions, the most anterior or rostral regions are believed to process higher-order abstract thinking and emotion cognitive integration. The frontopolar and lateral prefrontal cortex are thus anatomically distinct regions and part of two complementary

neuronal networks: one that attends to internal states and another that engages the individual with the outside world. Both networks are intricately tied to depressive symptoms.

The frontal pole has distinctly higher number of dendritic spines per cell and lower density of cell bodies than any other prefrontal region [79, 80]. Its rich connections are directed to the cingulate cortex including subgenual cortex or BA25 and precuneus/posterior cingulate [81], orbitofrontal cortex, and dorsolateral prefrontal cortex [80, 82], all critical regions in mood regulation. The frontal pole is an integrative center for cognitive and emotional processing with higher-level mnemonic control operations, control of emotions, memory, and motivation. The medial prefrontal cortex, which extends to the frontal pole (Brodmann Area 10), is also involved in self-reference [83], in reflective self-awareness [84], and in attributing mental states to others ("the theory of mind") [85].

The anterior/medial frontal lobe is also part of a distributed network extending caudally, known as the "default-mode" network [86]. These "resting-state" regions consist of largely medially located brain structures that decrease their activity when individuals attend to cognitively demanding, external stimuli [87].

The mid-lateral frontal regions (BA 9 and 46) maintain preferential bidirectional connections with multimodal temporal areas, on the one hand, and paralimbic areas, such as the cingulate, the retrosplenial cortex, and the rostral temporal cortex, on the other hand [88]. The dorsal regions are involved in the monitoring of information in working memory and the ventral regions are involved in active judgments on information held in posterior cortical association regions that are necessary for active retrieval and encoding of information. They play a critical role in organizing, monitoring, verification of information, attending to emotion stimuli, and reappraisal (Fig. 1.1).

1.7 The Impasse in Mood Disorder Research: The Need for a Paradigm Shift

Since the advent of the first serotonin reuptake inhibitor (SSRI) to the US market back in 1989, the diagnosis and treatment of depression have continued to become more widespread. Yet despite this

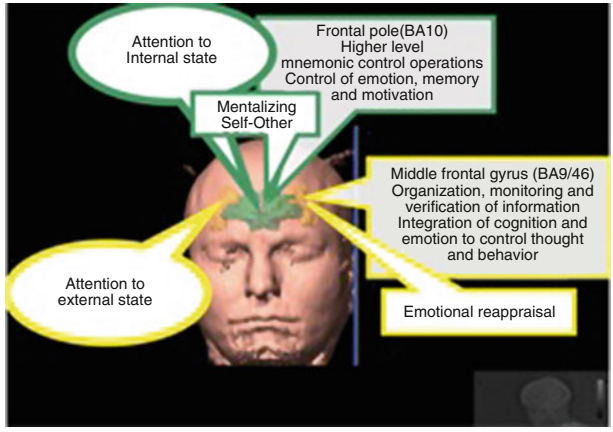

Fig. 1.1 Prefrontal cognitive and emotion integration anterior/medial (*green*) versus lateral (*yellow*) functions. Note that in this proposal, EpCS leads will be placed bilaterally and anterior and lateral prefrontal region (total four leads) to "tap into" both internal and external attention emotion regulation networks

major public health improvement, evidence suggests that treatment-resistant depression is on the rise, and with this serious disease come greater costs and higher morbidity and mortality rates [2]. Even in randomized controlled trials of nonresistant, uncomplicated major depressive disorder (MDD), only 50–60 % respond to any one medication, and of this group, only two-thirds (or 35 % of the initial group) become symptom-free. The Agency for Health Care Policy and Research original meta-analyses were later confirmed in subsequent studies in primary care settings [11]. Similarly, antidepressant drugs are found to have mild to moderate effect sizes when compared to placebo [12]. The results of the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial demonstrate the limitations of a psychopharmacological approach to depression [89]. The STAR-D also illustrates a pattern of diminishing clinical returns: each successive pharmacological treatment failure predicted a worse prognosis of a subsequent trial. The STAR-D showed that after three successive pharmacological treatment strategies at the very best, only 67 % of all patients remit. Practicing clinicians often have to switch their patients to other treatments or combine medications. Even if some

symptom benefit can be obtained with three to four medications simultaneously, the medical risks and side effect burden can become excessive. Unfortunately, even for the few patients who reach remission, a majority relapses within few months. And whereas the original purpose of most widely used antidepressants was for acute treatment, their roles progressed to maintenance and relapse prevention as well as treating bereavement and loss [2].

Some researchers suggest that the increase in indiscriminant antidepressant use is directly associated with the increase in duration of each depressive episode and perhaps is playing a role in the chronicity of the illness [90]. This point is difficult to prove prospectively, but naturalistic studies show that depressive episodes are shorter in nonmedication users than in ones taking prescribed antidepressants (although these studies can be confounded by a different severity or types of depressive illness) [2]. Paradoxically, subjects taking antidepressant medications for longer periods may be more likely to relapse upon discontinuation [91].

Yet despite their limitations, there is little doubt that pharmacological treatments have definitively helped millions of patients. However, the concern remains that with the lack of reliable biomarkers for the different subtypes of depressive diseases, the use of the same pharmacologic interventions at all stages of acute, recovery, and maintenance treatment of depression may be associated with the emergence of TRD.

1.8 Current Paradigm and Its Limitations

At any given time, mood is a continuous state of adaptive processes. When stress becomes chronic, persistent changes in neurotransmitters and neuropeptide concentrations and the anatomy of brain structures alter the physiology and the responsiveness characteristic of the prestress homeostasis [24]. Adding an exogenous drug propels the system to a third state, where a variable degree of symptom resolution can be associated with side effects, the compliance constraints, and the potential ill effects of being in a pharmacological phase-locked state. To illustrate this point, and borrowing from chemical engineering literature, pharmacotherapy may fit under the descriptions of the process modifications used in

materials science encompassing the use of retardants, catalysts, accelerants, decelerants, or process regulators [92]. In these approaches, we add a chemical substance to a process that is not functioning in an optimal manner, and as a result, we change what was a natural process, to an artificially induced one, with a new and different homeostatic point. This implies that drug therapy does not restore the original homeostasis but introduces another state altogether. This observation is supported by numerous brain imaging studies showing localized brain activity changes with effective treatment but always different from healthy state [93].

Almost all approved antidepressant drugs increase synaptic level of monoamines, particularly norepinephrine (NE) and/or serotonin (5-HT) [94]. More recently, studies into the pathophysiology of depression, coupled with advances in neuronal and intracellular signaling, suggest that we can develop novel interventions and target recently identified brain systems implicated in depression. For example, corticotrophin-releasing factor (CRF) plays a key role in the neurobiology of stress and its relation to depression, and clinical trials involving CRF antagonists are underway. Other neuropeptide receptors are also being investigated such as NK1 and neuropeptide Y. Glutamate and gamma-aminobutyric acid (GABA) are the most common excitatory and inhibitory neurotransmitters, respectively, in the brain. The roles of these neurotransmitters in depression along with neurotrophic factors are becoming clearer, and hence they too are becoming new targets for novel interventions. Most of these newer pharmacological interventions are nonetheless in their early stages of development and have not been appraised in large-scale effectiveness studies. Moreover, all these approaches share a common denominator and constitute the prevailing paradigm in researching and treating mood disorders: exogenous pharmacologic compounds are attempting to compensate for a specific dysfunction in one domain of mood regulation and often only addressing one (of many) hypothesized deficiency. By doing so, exogenous pharmacologic agents produce an altered biosystem, different from the normal homeostasis but associated with depressive symptom resolution.

1.9 Possible Options for the Future

Developing new and effective treatments is not trivial. Nestler et al. [94] have described algorithms for identifying and validating novel treatments. One could use, for example, DNA microarray or mass spectrometry to identify genes or proteins linked in the pathophysiology of depression and later develop specific therapies. Alternatively, studies into the functional neuroanatomy of depression have revealed decreased activity in dorsal neocortical regions and relative increased activity in ventral limbic and paralimbic areas [25]. Illness remission is thought to occur when there is appropriate modulation of dysfunctional limbic-cortical interactions [38]. This can be achieved by various forms of treatment (for review [93]) including antidepressant drugs and psychotherapy. Brain stimulation therapies (BSTs) directly modulate brain function and regulate mood. Each presents with unique characteristics that define its role in the depression therapeutic landscape. Several of these will be detailed is other chapters.

Electroconvulsive therapy (ECT) remains the goal standard for acute treatment of TRD but is associated with very high relapse rates despite maintenance regimen [95] and substantial risks for cognitive impairments [96]. Ultra-brief pulse ECT and magnetic seizure therapy are promising alternatives to classic bilateral ECT. The remission rates in community settings range between 30 and 50 % and are substantially less than that in clinical trials (70–90 %). ECT is thought to enhance gamma-aminobutyric acid (GABAergic) activity in prefrontal cortex which then leads to better limbic governance [97]. We are currently testing a much more focal form of ECT, namely, focal electrically administered seizure therapy (FEAST) that potentially could induce seizure in the right orbitofrontal cortex and spare the medial temporal lobes. If early observations are confirmed, FEAST could potentially lead to a revision of ECT and its drawbacks by completely separating efficacy from cognitive side effects.

Transcranial magnetic stimulation (TMS) is a noninvasive technique whereby rapid oscillations in electrical and then magnetic energy depolarize cortical cells. Prefrontal TMS, repeated over several weeks, has clinically significant antidepressant

effects in moderate TRD [98, 99]. However, the effect sizes are variable and not always positive. Clinical and imaging data [100] imply that higher number of stimuli per session and longer treatment courses are more effective. Maintenance studies are starting to be developed.

Vagus nerve stimulation (VNS) therapy is the first BST to be US FDA approved for TRD. It involves implanting a pacemaker-like generator in the anterior chest wall and the leads around the left vagus nerve. In naturalistic follow-ups, 30–40 % of studied cohorts responded by 1 year. Two-thirds of early responders showed continued clinical benefit after 12 months and 50 % after 24 months [101]. Using real-time VNS and fMRI, we demonstrated that chronic intermittent VNS is associated with deactivations of medial prefrontal cortex [102]. These brain changes gradually occur over time and may explain the slow onset of its therapeutic action [101].

Deep brain stimulation (DBS) involves the placement of multi-contact electrodes in subcortical regions also connected to a pacemaker-like generator. DBS is routinely performed for refractory Parkinson's disease [103] and various other neurological syndromes [104]. Several successful open-label studies have been published with small samples of TRD patients using high-frequency DBS to the caudate nucleus [105], anterior thalamic nuclei [106], subgenual cingulate [107], the anterior limb of the internal capsule [108], or the nucleus accumbens [109] with up to 35 % remissions at 6-month open follow-up [107]. At present, two randomized placebo-controlled studies targeting the subgenual cingulate and the ventral capsule/ventral striatum are underway (see Chap. 7 for details).

Epidural prefrontal cortical stimulation (EpCS) involves the placement of multi-contact stimulating paddles over specific cortical regions and connected to a pacemaker-like generator. It modulates local and subcortical regions depending on stimulation intensity, frequency, and duration. The bilateral four paddle EpCS approach we pioneered in 2008 showed promising improvements in depressive symptoms and a number of behavioral measures associated with in self-awareness, internal monitoring, and regulatory executive functions. Out of five severely TRD patients, three

met criteria for remission at 7 months and 24 months follow-ups [110]. Separately from our work, an industry-sponsored study (North Star) reported on the feasibility, safety, and efficacy of *unilateral* left dorsolateral prefrontal EpCS [111]. Twelve TRD patients were randomized to active or sham single blind for 8 weeks' treatment with an adaptive open design follow-up. No significant difference across conditions was noted during the sham-controlled phase after 2 months. Active left DLPFC EpCS proceeded to have a gradual improvement from 8 to 16 weeks with 21 % ± 23 and 26 % ± 29 changes from baseline. The results also showed that the placement of their single cortical lead paddle over left DLPFC was critical for their response rate. The more anterior the paddle was, the better the response. Interestingly, we had shown a similar relationship in a larger cohort of 59 patients enrolled in an RCT with noninvasive left DLPFC TMS [112].

1.10 Final Discussion

Our field has been divided on continuing with the legacy of DSM and a more theoretically driven, biologically based, phenomenologically linked diagnostic approach to depression. With the current approach requiring five out of eight primary criteria to diagnose major depression, one can imagine the number of combinations that could exist. This likely means that we have been diagnosing and studying different disease processes under one heading. No wonder that our treatments have not been that successful.

While there may be multiple reasons to precipitate a first depression episode, whether it is a social stressor, a genetic loading, an acute medical illness, or an exposure to a toxin, it appears that over time, and with repeated relapses, patients progress to become more treatment resistant. This backdrop represents a more homogeneous group of patients where we are more likely to uncover a common underlying pathophysiology. The challenge would be to generalize it back to the predominant depressed subtypes.

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