Neuroscience of Depression: A Review

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Depression, also used interchangeably with the term clinical depression or major depressive disorder throughout the literature, is considered to be one of the most common forms of psychiatric disorders (De Raedt & Koster, 2010; Gotlib & Hamilton, 2008; Villanueva, 2013). It “is characterized by a profound dysregulation of affect and mood, with association to cognitive dysfunction, sleep and appetite disturbances, fatigue and an array of other metabolic, endocrine and inflammatory conditions” (Villanueva, 2013, p.1). Gotlib and Hamilton (2008) also associated depression with “a sad mood and or loss of interest or pleasure in almost all daily activities, as well as symptoms of weight loss or gain, psychomotor agitation or retardation and concentration difficulties” (p. 159) among others. Depression has been described by the World Health Organization (WHO) as the leading cause of disability worldwide currently, affecting over 121 million people (Cohen, 2012) and predicted to be the second greatest cause of disability by the year 2020 (Cohen, 2012; Gao & Bao, 2011). Depression has also been highlighted by Gao and Bao (2011) “as a major cause of morbidity worldwide and a recurrent life-threatening disorder associated with the risk of suicide” (p.124). Thase (2014) describes depression as a neurobiologically complex disorder with no single identifiable cause, produced by multiple gene alterations and their interactions with various environmental stimuli.

Numerous studies have shown that there are well established cognitive, behavioural and somatic forms of treatment options for depression, but despite this fact, relapse or rate of reoccurrence after remission or recovery remains very high (De Raedt & Koster, 2010). Villanueva (2013) notes that most individuals may experience temporary episodes of depressed mood. According to Gotlib and Hamilton (2008), depression is prevalent in at least 20% of the general population experiencing one
depressed episode, with an 80% relapse rate. Genetics, environmental and social factors have been widely accepted as contributing factors to major depressive disorders. However, it is unclear why some individuals are more prone to developing depression (Villanueva, 2013). Identifying the etiology is therefore important to understanding the onset, maintenance and recovery process of this disorder. The literature reviewed on neuroscience of depression, identified the major causative factors of major depressive disorders, subtypes of depression, gene-environment interactions, neurobiological underpinnings, neurotransmitter, hormonal systems and involvement of cognitive, attentional, and affective factors related to depression.

Due to its heterogeneity, depression has been divided into subtypes with specific symptoms identifiable to each subtype that have been found instrumental in directing treatment goals for patients (Cohen, 2012). According to Singh and Rais (2007), depression is classified into two major groups in the DSM IV TR now DSM-5, but with the criterion for major depressive disorder retained (American Psychiatric Association, 2013). In one group, depression includes bipolar depression, subdivided into bipolar I depression, characteristic of mania, or bipolar II depression/ cyclothymic depression with notable symptom of hypomania. The other group includes unipolar depression or major depressive episode without mania or hypomania. Specific criteria are used to specify groups of symptoms as either catatonia, melancholic, atypical or postpartum and longitudinally organized as chronic, seasonal or rapid cycling on the basis of their severity, which can be mild, moderate, severe or psychotic (Singh & Rais, 2007). A major challenge in the treatment of depression is embedded in the heterogeneity of the disorder. There remain significant differences in symptomatic presentation of patients with depression, including, differences in age of onset, severity of course, treatment response and comorbid conditions (Singh & Rais, 2007). Major depressive disorder is purported by Villanueva (2013) as being spontaneous or resulting from a traumatic emotional experience or merely the symptom of a neurological or endocrine disease, for example, Parkinson disease or hypothyroidism respectively. It was also noted that there is a high prevalence in females, with depression being influenced
by pharmacologic agents, and approximately half the percentage of risk factors attributed to genetic factors (Villanueva, 2013).

The interaction between the environment and genetic composition has been recognized as being influential in individual’s predisposition to depression, with environmental stressors being the major trigger for an initial development (Thase, 2014). Thase (2014), De Raedt and Koster (2010) and Risch et al. (2009) made reference to a prominent study done by Caspi et al. (2003), wherein the serotonin transporter gene 5-HTTLPR was identified as a predictor of a diagnosis of major depressive disorder. In the same study, gene 5-HTTLPR predicted increased depressive symptoms and suicidality in the presence of stressful life events. Although this claim has been refuted by Risch et al. (2009), Thase (2014) reported that individuals with depression were carriers of two (2) copies of the long allele of the gene, functional in the serotonergic neurotransmission and two (2) copies of the short allele which are less functional, or that they may carry one of each gene. The findings revealed that individuals aged 21-26 years carrying one or two copies of the short allele of the 5-HTT gene, exhibited greater risk of developing depression in the presence of stressful life events; suggesting that the genetic characteristic of individuals moderates their response to environmental stimuli (Thase, 2014). Thase (2014) further theorized that genetic vulnerability might be involved in the changes within the brain resulting from repeated exposure to environmental factors that have remained a potent contributor in gene-environment interactions.

A relationship between hyperactivity or reactivity of the amygdala and volume reduction has been identified in the anterior cingulate cortex of individuals with the short allele, in response to environmental stress. According to Thase (2014), this relationship reflects an inherited vulnerability to emotional reactivity that has been implicated in depression. Thase (2014) further suggested that once these patterns of vulnerability have been established, new episodes may emerge after progressively less provocation and eventually; episodes may also appear spontaneously.

Several clinical studies have indicated that depression may be associated with the inability of neural systems to exhibit adaptive plasticity (Villanueva, 2013; Dwivedi, 2009). These researchers identified the brain derived neurotrophic
factor (BDNF) and its crucial role in the genesis of major depressive disorder. Specifically the studies recorded significant depletion of BDNF and its regulated genes – including TrkB of the tyrosine kinase receptor family – in brain samples, serum levels and circulating lymphocytes of depressed individuals (Villanueva, 2013; Dwivedi, 2009). Such depletion was observed to occur during individuals’ exposure to stressful situations, whilst persistent stress resulted in atrophy of the hippocampus; however, the process by which a decrease in this neurotrophin leads to depression is unclear (Dwivedi, 2009). One explanation was that brain derived neurotrophic factor itself is implicated in producing antidepressant effects and is upregulated with antidepressant treatments (Villanueva, 2013; Dwivedi, 2009).

Within the brain, there are key structures that are essentially associated with the neurobiology of depression and the expression of emotional states, namely the prefrontal cortex, orbital and dorsolateral aspect, the subgenual anterior cingulate cortex, and the limbic system inclusive of the amygdala and hippocampus (Thase, 2014; Golib & Hamilton, 2008). In examining these structures, researchers have focused extensively on the amygdala as the foremost brain region, which plays a key role in processing of emotionally mediated attention, and assigning of negative and positive affective significance in remembering emotional events. On the other hand, the subgenual anterior cingulate cortex is described as critical in regulating certain emotions and the area of appreciation and anticipation of rewards within the brain (Thase, 2014; De Raedt & Koster, 2010; Golib & Hamilton, 2008). Initiation and regulation of emotion specific to depression has also been linked to the dorsolateral prefrontal cortex (DLPFC) (De Raedt & Koster, 2010). The hippocampus, however, has been implicated in the retrieval and storage of new memories, and considered as the site of neurogenesis providing the feedback inhibition to the hypothalamus-pituitary-adrenal (HPA) axis in stress response (Thase, 2014; Golib & Hamilton, 2008).

From a review of neuroimaging research, Thase (2014) noted that these aforementioned regions of the brain have been identified as either exhibiting increased or decreased cerebral blood flow, glucose metabolism and structural volume loss within interconnected neurologic circuits.
and glial cell density in depressed individuals. Drevets, Savitz & Trimble (2008) reported that the anterior cingulate cortex was abnormally reduced with notable gray matter volume deficit in individuals with major depressive disorder. Other studies suggested increased activity along amygdala and orbital cortex and decreased activity most often in the dorsolateral prefrontal cortex of depressed patients, suggesting that depression is associated with disruptions within multiple linked regions of the brain rather than any one structure (Thase, 2014; Gotlib & Hamilton, 2008).

According to De Raedt and Koster (2010) there are many studies that identify stressors as generators of biological change both at the hormonal and neurochemical levels over an extended period of time. The hypothalamus-pituitary-adrenal axis is central to the stress response in normal situations, wherein perception of stressors stimulate the release of corticosteroids in subcortical regions located in the limbic system (De Raedt & Koster, 2010). De Raedt and Koster deduced that activating inputs from these regions of the brain and other related areas, reaches the hypothalamus and provokes the release of adrenocorticotropic hormone releasing factor that activates the secretion of adrenocorticotropic hormone in the pituitary. This hormone then travels via the bloodstream to the adrenal cortex where receptors are targeted to release glucocorticoid hormones or cortisol, influencing the inhibitory feedback mechanism through the glucocorticoid receptors and mineralocorticoid receptors respectively, in regulating the stress response after the threat has passed (Gao & Bao, 2011; De Raedt & Koster, 2010).

De Raedt and Koster’s (2010) conceptual framework stipulates that the hypothalamic-pituitary-adrenal axis becomes increasingly impaired following periods of excess cortisol during depressive episodes or stressful environments, making it more reactive to stressors. This hyperactivity has been found to be as a result of dysfunctional glucocorticoid mediated feedback inhibition and one of the most consistent biological findings in depression. This response subsequently leads to decreased activity in the dorsolateral prefrontal cortex area, mediated specifically by the serotonin metabolism, and by contrast prolonged activation of the amygdala (De Raedt & Koster, 2010).
Villanueva (2013) associated major depressive disorder with maladaptive responses to stress resulting from a dysfunctional hypothalamic-pituitary-adrenal axis and hormonal alterations. Hypothalamic-pituitary-adrenal axis functioning and the monoaminergic neurotransmission implicated in the pathogenesis of depression, which contains serotonin, norepinephrine and dopamine (Gao & Bao, 2011) and specifically serotonin metabolism, have been suggested by De Raedt and Koster (2010) as being interrelated, with reciprocal causal interactions between the hypothalamic-pituitary-adrenal axis and the 5-hydroxytryptamine (5-HT) system. The serotonergic neurotransmission important for depression and the mutual relationship between the hypothalamic-pituitary-adrenal axis function and serotonin metabolism, are also theorized by De Raedt and Koster (2010), as being dependent on genetic vulnerability factors and their relation to the 5-HT1A and 5-HT2A receptors located at cortical and subcortical regions of the brain (pp.57-58). Depressed mood highlighted by Gao and Bao (2011) as the core symptom of major depressive disorder, was suggested to be induced by lowering of the availability of serotonin in only some vulnerable individuals, deducing that there is no simple direct relationship between changes in the monoaminergic systems and the occurrence of depression.

Monoaminergic systems however, are purported as exerting only partial influence on depressive symptoms, with a vast amount of evidence indicating that neuropeptides such as corticotrophin releasing hormones and amino acid neurotransmitters integral in synaptic transmission and neural circuit, have been involved in clinical signs and pathogenesis of depression (Gao & Bao, 2011). In their review Gao and Bao (2011) identified L-glutamic acid (glutamate) and y-aminobutyric acid (GABA) as being the principal excitatory and inhibitory neurotransmitters within the central nervous system. They added that, in comparison to monoamine neurotransmitters that account for 5% of total synapse in the brain, glutamate and GABA are thought to estimate at least 50% of the total synapses. The regulatory roles of the excitatory glutamatergic system in regulating synaptic plasticity, learning and memory and inhibitory GABAergic system, which modulate behavioural and physiological
mechanisms, have been suggested as being interactive in the functions of the hypothalamic-pituitary-adrenal axis and its involvement in depression (Gao & Bao, 2011).

Gao and Bao (2011) concluded that interactions between several neurologic structures and processes explained depression; namely, hyperactivity of the hypothalamic-pituitary-adrenal axis and glutamatergic system, and hypoactivity of the GABAergic transmission. The researchers recommended that treatment approaches should aim at regulating excitation of inhibition of corticotrophin releasing hormone, thereby enhancing normal hypothalamic activity. De Raedt and Koster (2010) noted that treatment with selective serotonin reuptake inhibitors (SSRIs), which temporarily normalizes 5-HT functioning has also been associated with normalization of the hypothalamic-pituitary-adrenal system functions. De Raedt and Koster (2010) contend that serotonin which is mainly synthesized in the brain, is instrumental in the role of cognition and emotion with implications for affective disorders as in the case of depression. They suggested that the serotonin system is related to emotion regulation by way of its effects on attentional control over negative stimuli, modulating the responsiveness of the amygdala and its connectivity with the anterior cingulate cortex (De Raedt & Koster, 2010).

According to De Raedt and Koster (2010) the anterior cingulate cortex has been implicated in attentional, cognitive and affective factors of depression, where signals are relayed to the dorsolateral prefrontal cortex to alter the direction of attention or modify processing resources. This in turn sends signals to the subcortical system where emotions processed by the amygdala are suppressed via connections with the orbitofrontal cortex. Abnormalities in the dorsolateral prefrontal cortex and the anterior cingulate cortex activity have been observed during task-related emotional processing such as attention and working memory tasks, in depressive conditions (De Raedt & Koster, 2010; Quinn, Harris, Felmingham, Boyce & Kemp, 2012). Attentional factors are considered by De Raedt and Koster (2010) as being of critical importance in understanding vulnerability to depression, and are centrally related to biological processes affected by recurrent depressive episodes, cognitive and affective processes. They characterized depression by
specific attentional bias in information processing, where emotional disorders are guided by cognitive schemas and in the case of depression, negative schemas involving loss and failure that remain latent and are activated by relevant stimuli (De Raedt & Koster, 2010).

In their framework, De Raedt and Koster (2010) assumed that depression becomes more severe or persistent because negative thinking patterns become more reactive to stressors and negative mood after each successive depressive episode, indicative of latent cognitive vulnerability for depression. They deduced that the course of depression is strongly influenced by how individuals respond to depressive symptoms and that they are likely to experience an extended depressive episode if they engage in uncontrolled ruminative thinking about the causes and consequences of their depression (De Raedt & Koster, 2010).

Cooney, Joormann, Eugene, Dennis and Gotlib (2010) describe rumination as the recursive pattern of focused thinking on one’s negative mood, and this has been shown to increase vulnerability for depression, by prolonging and deepening episodes of depression and increasing the likelihood of developing future episodes. Rumination is said to be associated with biases in negative processing of emotional content and associated with the region of the brain related with the representation of one’s self (Cooney et al. 2010). The medial prefrontal cortex, implicated in mediating “self-referential content as well as increased activity in the limbic system have been suggested by as contributing to ruminative self-focus that characterizes depressed individuals” (Cooney et al., 2010, p. 471). De Raedt and Koster (2010) have stipulated reduced attentional control as being characteristic of depressive episodes. Depressed individuals were considered as exhibiting significant attentional bias toward negative stimuli and these attentional factors and information processing biases played an integral role in the etiology, maintenance and recurrence of depression (De Raedt & Koster, 2010).

Depression generally considered as being associated with a wide range of affective, somatic symptoms and cognitive deficit, has been strongly related to biased recall of information, with greater recall of the negative information than of neutral or positive information (De Raedt & Koster, 2010). The scholars concluded that impaired attentional control associated with
the emotional reactivity preceding depressive symptoms enhance elaboration of negative information and the development of depression (De Raedt & Koster, 2010). An alternate view highlighted by Panksepp, Wright, Dobrossy, Schlaepfer and Coenen (2014) is that affective arousals govern the words and intonations applied in communicating conveying feelings clearly. In their article, the basic affective systems relevant to depression were identified as being: seeking, implicated in the amotivational and feeling of dysphoria associated with depression, panic where the brain stress axis namely corticotrophin releasing factor is indicated, and play. They suggest that sustained overactivity of the ‘panic’ and underactivity of the ‘seeking’ and ‘play’ networks contributes to depression considerably (Panksepp et al. 2014).

In conclusion, the neuroscience of depression encompasses functional integration between cognitive and neurobiological states, in which vulnerability relates to a dysfunctional reaction to environmental or external stressors. Negative thinking patterns have increased with depressive episodes and have been found to remain even after recovery or remission. In considering the heterogeneity of depression there is doubt regarding the reason some individuals become more reactive to stressors that leads to depressive episodes and others are not. Understanding the subtypes of depression, gene-environment interactions, neurobiological underpinnings, neurotransmitter, hormonal systems and involvement of cognitive, attentional, and affective factors and their relation to depression has to a certain degree elucidated conditions for therapeutic interventions that target emotional regulation and restoration of stress reactivity. Interrelatedness between brain structures and processes, the environmental and psychosocial factors have been implicated in depression (Raedt & Koster, 2010).

References


NEUROSCIENCE OF DEPRESSION


