Neurobiology of Depression and Anxiety Among Foundational and Adoloscent Learners

Prof. (Dr.) Amit Kauts[1], Ms. Mankiran Virdhi[2]
[1]*Head, Department of Education, Guru Nanak Dev University, Amritsar*
[2]*Research Scholar, Department of Education, Guru Nanak Dev University, Amritsar*

Abstract: Anxiety and Depression are among the leading pathways that obstacle the growth and development of the foundational stage learners who have just incepted with their journey of formal education and societal relationships. Thus; depression is believed to crop up as a multiplication factor of environmental influences and genetically influenced factors. Thus; the vast number of anxiety disorders pop up during the foundational age of schooling that is characterized as developmental period signalized by versatile changes in the front limbic circuitry. This is the area which plays a pivot role in learning and has been a center of attraction of recent efforts to understand the neurobiological dovetails of disorder of anxiety and depression in the process of growth and development. Thus; the studies of the pediatricians have revealed that the depression and anxiety disorder among the foundational stage learners alter both the function as well as structure of the front limbic circuitry. The amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and hippocampus all play a role in fear conditioning and extinction, and interactions between these areas have been linked to anxiety development. Specifically, children and adolescents with anxiety disorders have changed amygdala sizes and increased amygdala activation in response to neutral and scary stimuli, with the amount of the signal change in amygdala reactivity matching to the severity of symptomatology. Abnormalities in the PFC and ACC, as well as their connections to the amygdala, may indicate impaired top-down regulation or compensatory measures to modulate the heightened amygdala reactivity associated with anxiety. This paper focuses on the neurobiology structural changes of the children having the anxiety and depression as the pivot issues in their normal growth and development procedure.

Keywords: Anxiety, depression, foundational stage learners, adolescent, front limbic circuitry, amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and hippocampus.

INTRODUCTION

Mood and anxiety disorders are distinguished by a range of neuroendocrine, neurotransmitter, and neuroanatomical abnormalities. Everyone has felt dread and worry at some point in their life. Fear is the initial reaction to a specific frightening stimulus. Anxiety, on the other hand, is a less acute but more prolonged reaction to anxiety-inducing stimuli that are recognized. For example, you may feel concerned about the chance of encountering a snake on a trip through the woods, yet you may be terrified if one slithers straight in front of you. In certain circumstances, people experience general anxiety without knowing why. Normally, the brain handles our fear and anxiety such that they don't interfere with our regular functioning. If there is a local threat, different parts of the brain assist us make sense of it by increasing or decreasing our worry and terror. However, for other people, anxiety may be excessive and interfere with their everyday lives. Anxiety becomes an issue when certain brain regions act abnormally (or fail to function), triggering a cascade of improper or unreasonable behaviours. Long-term anxiety like this might be classified as an anxiety disorder. Anxiety disorders, such as panic disorder or social anxiety disorder, may necessitate therapy to enable sufferers to live normal, happy lives. Until recently, scientists assumed that the amygdala, a marble-sized brain region, was the source of fear and anxiety. Some studies have found that monkeys with amygdala impairment were exceptionally calm in the presence of frightening stimuli (such as a nearby snake). Scientists believed that in persons with anxiety disorders, inappropriate dread and anxiety were generated by an overactive amygdala—a simple cause with a simple consequence. The brain is divided into two sections by this work: the cognitive brain and the

emotional brain. The cognitive brain is the frontal lobe, where all of our thoughts and feelings are combined into a single, cohesive experience. Part of the emotional brain is the amygdala, which is situated deep within the brain. This hypothesis holds that anxiety only arises when impulses from the emotional brain overwhelm the cognitive brain and enter the conscious mind. The cognitive brain network takes control and calms the emotional fear network if you can explain, for instance, why snakes are uncommon in the forests where you're trekking. The great level of interconnectedness across neurotransmitter- and neuropeptide-containing circuits in limbic, brain stem, and upper cortical brain regions makes it difficult to identify the most functionally meaningful variations. Furthermore, contextual events and underlying genetic predisposition might cause a basic alteration in brain structure or function, as well as neurotransmitter signalling, which can raise the likelihood of psychopathology. MDD is a common mental condition in primary care settings. Despite greater recognition and treatment by family and primary care physicians, MDD remains a challenging therapy for both clinicians and patients. Recent research has shown that MDD has a significant influence on the brain's structure and function. Research on depression has evolved from a belief in a 'chemical imbalance' in the brain to a more complicated theory incorporating neural networks and plasticity. The network model has improved our understanding of successful therapeutic approaches and their function in minimizing risks OF MDD.

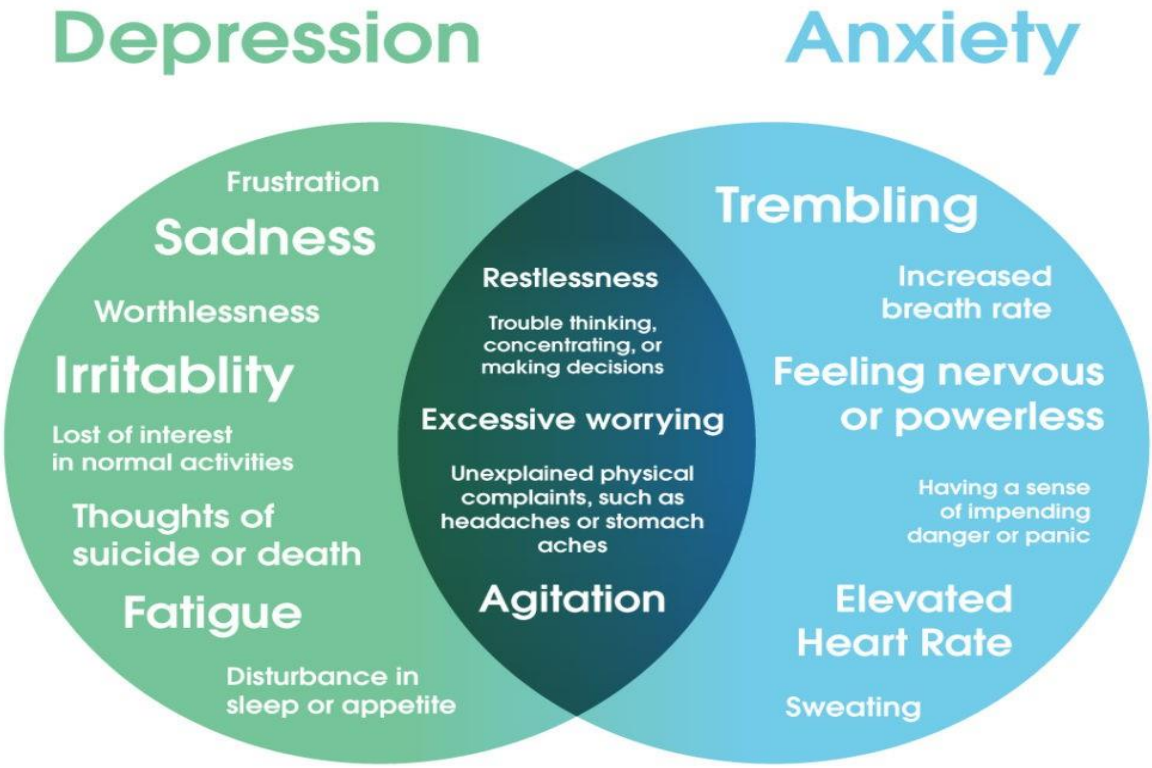

Figure 1: Common neurological and behavioural outcomes of Depression and Anxiety

DEPRESSION AND ANXIETY: NEUROANATOMY

The majority of cases of anxiety disorders occur in childhood, when the prolonged and repetitive experience of anxiety results in specific brain structures that can be observed through neuroimaging. Studies using functional magnetic resonance imaging (fMRI) on generalized anxiety disorder (GAD) have revealed increased activity in the ventrolateral prefrontal cortex, as well as significant activity in the amygdala, particularly when an individual is instructed to focus on their stress, and changes in the Cingular cortex and insular cortex.

Adolescence is characterized by accelerated physical growth, changes in behaviour, cognition, and emotional regulation. The physical changes that occur during this time may lead to long-lasting alterations in different brain regions that may be linked to the emergence of mental health issues in later life. In adolescents, it may be simpler to restructure different brain regions using cognitive behavioural therapy or other modalities than it is in adults. In adults, on the other hand, a variety of therapeutic agents can be used to modify the biochemical structure of the brain.

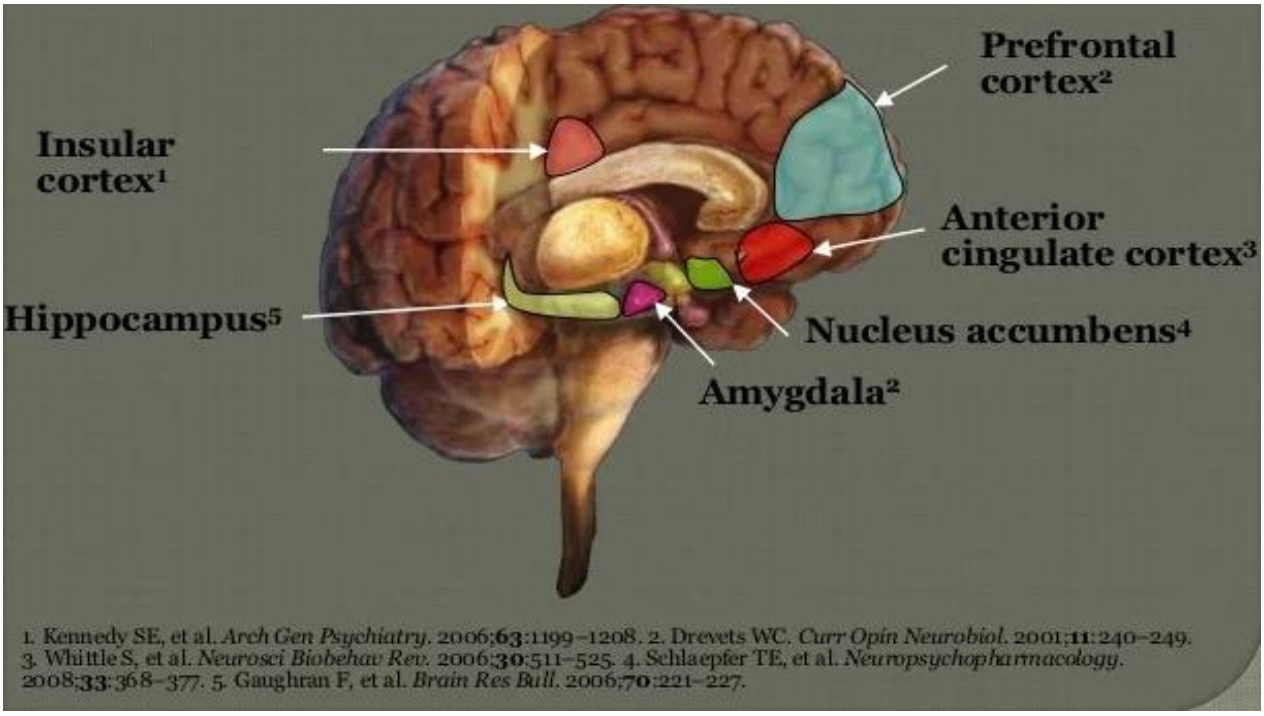

Figure 2: Neuroanatomy of Depression and Anxiety

The prefrontal cortex houses the brain's higher cognitive centres. They engage in social behaviour, planning, and thought processes. The prefrontal cortex is the "newer" (evolutionarily speaking) region of the brain that aids in controlling our emotional reactions.

The majority of emotion processing occurs in older regions of the cortex. The “limbic system” is the aggregate term for these physical brain structures. The hippocampus is a key component of the limbic system and is essential for controlling the hypothalamic-pituitary-adrenal (HPA) axis and the stress response. Neurogenesis and hippocampus expansion are critical for the development of resilience against stress and anxiety. The amygdala, which is involved in the formation of fear and anxiety-related memory and has been shown to be hyperactive in anxiety disorders, is perhaps the most important component of the limbic system that is central to the regulation of emotions. It is well connected to other brain structures like the hippocampus, thalamus, and hypothalamus.

It is crucial to realize that neurotransmitters are the primary means of brain function or communication across different brain networks and centres, independent of physical alterations. Gamma-aminobutyric acid (GABA) is known to have an excitatory effect on emotions, whereas glutamate has an inhibitory effect on emotional responses. It is also commonly known that serotonin, dopamine, and norepinephrine play roles in the pathophysiology of different emotional states. Other neurotransmitters that could be involved in the pathophysiology of anxiety disorders include corticotrophin-releasing factor, neuropeptide Y (NPY), oxytocin (OT), vasopressin (AVP), cholecystokinin (CCK), and galanin (Gal).

NEUROENDOCRINE AND NEUROTRANSMITTER PATHWAYS

The neurotransmitters that facilitate communication between these regions must also be taken into account. Patients with anxiety disorders may have enhanced

excitatory neurotransmission by glutamate or decreased inhibitory signalling by γ-aminobutyric acid (GABA) leading to increased activity in emotion-processing brain areas.

Classic neurotransmitters in the central nervous system are frequently co-released with neuropeptides, many of which are produced in limbic areas and might affect the circuitry involved in stress and emotion (Table 1). Many reviews have discussed the functional consequences of these limbic co-localizations (e.g., 6–12). Cholecystokinin (CCK), galanin, neuropeptide Y (NPY), vasopressin (AVP), oxytocin, and corticotropin-releasing factor (CRF) are a few neuropeptides that have been specifically linked to psychopathology. CCK is centrally positioned in multiple limbic regions and can be detected in the gastrointestinal tract and vagus nerve In the brainstem nuclei, galanin and monoamines are co-localized. It controls the neuroendocrine and cardiovascular systems, as well as how people process pain and eat.14–16 NPY is widely expressed in the central nervous system and co-localizes with NE in the amygdala, hippocampus, and hypothalamus. It is well-known for its orexigenic properties. The primary regulator of affiliative, maternal, and reproductive behaviour is oxytocin.17, 18, Central AVP controls fluid homeostasis, but it can also co-localize with CRF to control the HPA axis or with oxytocin to affect affiliative behaviour 19.

GENETIC BENEFACTION IN EMOTIONAL STABILITY

Vulnerability to major depressive disorder (MDD) and anxiety disorders is influenced by both hereditary and environmental factors. The potential genes underlying psychopathology have mostly remained the same in attempts to determine the genetic influence. Scholars have typically focused on the genes whose products control monoaminergic signalling and the HPA axis. The idea that mood and anxiety disorders have a hereditary propensity and that each clinical manifestation results from a combination of environmental and genetic factors is being supported by ongoing research. Specifically, a very diverse range of gene–environment interactions may be made possible by epigenetic factors.

A "developmental dynamic pattern" addressing the impact of genetic variables on individual differences in symptoms of anxiety and depression is strongly supported by the few available longitudinal research. According to this hypothesis, the influence of genes on psychopathology varies, resulting in a distinct pattern of risk factors being linked to distinct developmental phases. This concept stands in stark contrast to the "developmental stable model," which holds that a single set of risk variables that remain constant across an individual's lifespan mediates the genetic contribution to psychopathology. An alternative method of evaluating the influence of genes on psychopathology risk centres on more limited phenotypic traits rather than diagnostic class. A new study evaluated the behavioural traits associated with anxiety in children ages 7 to 9. The idea that genes play a role in both the general propensity for anxiety-related behaviour and particular symptom subtypes is supported by their discovery of both shared and specific genetic effects on anxiety-related behaviour, as well as the lack of a single underlying factor.

ANXIETY (PANIC AND SOCIAL) DISORDER: ANATOMY AND NEUROIMAGING REVELATIONS

Foundational stage learners cum patients with generalized anxiety disorder (GAD) had high ratios of gray matter to white matter in the higher temporal lobe, according to structural MRI studies.113 Children with GAD also show an increase in amygdala volume, which could be related to the amygdala hypertrophy brought on by stress that has been seen in investigations on laboratory animals. Adolescent GAD patients exhibit higher resting vlPFC activity than healthy control subjects in functional MRI investigations. Since there is a negative correlation between the severity of symptoms and vlPFC activity, the increase in vlPFC metabolism is considered a compensatory response rather than the underlying cause of GAD.114 Neuronal vitality in the PFC of GAD patients has been evaluated by measuring the ratio of N-ace-teleoperate to creatine using proton MRS, owing to the reported hypermetabolism in this region. Neuronal viability in the right dorsolateral PFC was higher in GAD patients who did not experience early-life stress, but it was lower in those who self-reported experiencing early-life trauma.

Provocative anxiety-inducing tasks have yielded more robust and interpretable functional brain imaging

(fMRI) results in patients with generalized anxiety disorder (GAD); resting-state fMRI results have typically been inconsistent. The pattern of brain activity observed in anxious patients with GAD is in good agreement with findings from research conducted on laboratory animals, where limbic circuits—specifically, the amygdala—are shown to be key players in the fear response. Indeed, during negative emotional processing, a number of imaging investigations of patients with GAD demonstrate increased activation of the amygdala and insula. Adolescent GAD patients showed an increased right amygdala response when they saw furious faces; this activation was positively connected with the severity of their symptoms. The negative correlation between the activity in the right vlPFC and the overactivity in the right amygdala suggests top-down disinhibition as a possible explanation for the heightened amygdala activity.121 Interestingly, in juvenile GAD patients, a positive therapeutic response to fluoxetine or CBT was predicted by high pretreatment activation of the left amygdala. According to the interpretation of these data, a higher amygdaloid response to negative emotions indicates a better signal-to-noise ratio. Lower pretreatment amygdala activity and higher ACC activity predict a positive treatment response to venlafaxine in adult GAD patients when they watch scared faces. The amygdala activation has clinical usefulness in predicting treatment outcome will require more research.

The amygdala may contribute significantly to anxiety disorders through interconnectivity with brain areas that evaluate social interaction. The thalamus, PFC, and superior temporal gyrus are the brain regions that evaluate social behaviour. Patients with GAD may interpret social behaviour incorrectly due to amygdala activation.

DEPRESSION: NEUROANATOMY AND NEUROIMAGING REVEALTIONS

The function, and abnormal alterations within these intricately linked "limbic" regions have been linked to antidepressant effect and depressions. Reductions in grey-matter volume and glial density have been observed in the prefrontal cortex and hippocampus, regions thought to mediate the cognitive aspects of depression, such as feelings of guilt and worthlessness, in a large body of post-mortem and neuroimaging studies of depressed patients. However, there hasn't been much success in establishing any distinct cause-and-effect correlations of these pathological alterations, and the reported findings are inconsistent and frequently complicated by co-morbid illnesses and medication histories.

Monoamine projections from midbrain and brainstem nuclei—dopamine from the ventral tegmental area (VTA), serotonin from the dorsal raphe in the periaqueductal grey region, and noradrenaline from the locus coeruleus—significantly alter these forebrain networks.

These neurotransmitters not only regulate awareness and alertness but also affect how salient emotional cues are perceived. The involvement of particular hypothalamic nuclei in mediating the neurovegetative symptoms of depression has been examined in more recent research. But, we add a word of caution: the field has frequently used a simplistic "localization of function" approach to examine limbic substrates (for example, amygdala ≈ "fear and anxiety," NAc ≈ "reward"), even though depressive symptoms are likely mediated by dysfunction in a diffuse series of neural networks.

Monoamine projections from midbrain and brainstem nuclei—dopamine from the ventral tegmental area (VTA), serotonin from the dorsal raphe in the periaqueductal grey region, and noradrenaline from the locus coeruleus—significantly alter these forebrain networks.

These neurotransmitters not only regulate awareness and alertness but also affect how salient emotional cues are perceived. The involvement of particular hypothalamic nuclei in mediating the neurovegetative symptoms of depression has been examined in more recent research. But we add a word of caution: the field has frequently used a simplistic "localization of function" approach to examine limbic substrates (for example, amygdala ≈ "fear and anxiety," NAc ≈ "reward"), even though depressive symptoms are likely mediated by dysfunction in a diffuse series of neural networks. It will be important to go beyond monoamine and neurotrophic mechanisms and develop information about antidepressant pharmacogenetics in order to improve the still-low remission rates. Researchers need to investigate the therapeutic potential of viral-mediated gene transfer, which is being successfully used to treat other neuropsychiatric illnesses, as well as the scientific

underpinnings of the effectiveness of deep brain stimulation in depression98. In order to fully utilize preclinical research, the field must continue to enhance animal models using the vast array of molecular and anatomical tools at its disposal. Additionally, a systems approach to the study of depression must be taken, acknowledging the significant bidirectional interactions that exist between the brain and peripheral organs.

CONCLUSION

We discovered that depression is associated with a wide range of anomalies at several levels of neuroscientific description, including molecules and cells, brain circuits, and cognitive functions. Based on this brief overview, we have identified three potential lines of future scientific inquiry: the first is the development of an integrated neuroscientific model of depression (and antidepressant treatment) that provides mechanistic links between abnormalities (and the effects of antidepressant interventions) at various levels of neuroscientific description and distinguishes distinct pathophysiological trajectories leading to depressive symptomatology. Second, the quest for aetiological and pathophysiological variables involved in the genesis of depression should continue, particularly outside of the brain's immediate borders. Third, a greater emphasis on translational activities that utilize known basic. Going forward, it will be critical to pursue a thorough, biologically based knowledge of GAD, particularly in the context-relevant RDoC anxiety components (e.g., prolonged threat, acute threat). Furthermore, treatments must be developed using a comprehensive neurobiological framework (e.g., genes, brain, psychophysiology, behaviour), and the timing of treatment implementation must be empirically tested to determine the most impactful timing for producing the optimal treatment trajectory. This is especially relevant for anxiety disorders, which frequently appear in school-aged children during other critical neurodevelopmental processes (e.g., synaptogenesis, myelination, and synaptic pruning).52 Other major factors are the variable character of symptoms in clinical populations and the low power of many neuroimaging investigations. These constraints highlight the need of study replication, which is not common in science today. Data sharing (e.g., in accordance with NIMH priorities), such as making study data sets publicly available, can considerably assist scientists in their quest of replication. Future directions in personalized medicine must consider not only treatment targets and optimal timing (for example, the developmental window from which to produce the quickest, most long-lasting, positive outcomes), but also the limitations of this research, which argue for replication and improved data sharing systems.

REFERENCE

[1] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Washington, DC: American Psychiatric Association, 2013. [Google Scholar]

[2] Barrera G, Echevarria DJ, Poulin JF, et al. One for all or one for one: does transmission unify the concept of a brain galanin “system” or clarify any consistent role in anxiety? *Neuropeptides.* 2005; 39:289–292. [PubMed] [Google Scholar]

[3] Cole RL, Sawchenko PE. Neurotransmitter regulation of cellular activation and neuropeptide gene expression in the paraventricular nucleus of the hypothalamus. *J Neurosis.* 2002; 22:959–969. [PMC free article] [PubMed] [Google Scholar]

[4] Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 2008; 213(1): 93–118. [PMC free article] [PubMed] [Google Scholar]

[5] Gysling K, Forray MI, Haeger P, et al. Corticotropin-releasing hormone and urocortin: redundant or distinctive functions? *Brain Res Brain Res Rev*. 2004; 47:116–125. [PubMed] [Google Scholar]

[6] Honkaniemi J, Pelto-Huikko M, Rechardt L, et al. Colocalization of peptide and glucocorticoid receptor immunoreactivities in rat central amygdaloid nucleus. *Neuroendocrinology*. 1992; 55:451–459. [PubMed] [Google Scholar]

[7] Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *Am J Psychiatry* 2014; 171(4): 395–397. [PubMed] [Google Scholar]

[8] Lang PJ, McTeague LM, Bradley MM. RDoC, DSM, and the reflex physiology of fear: a bidimensional analysis of the anxiety disorders

spectrum. *Psychophysiology* 2016; 53(3): 336–347. [PMC free article] [PubMed] [Google Scholar]

[9] Nutt DJ. Neurobiological mechanisms in generalized anxiety disorder. *J Clin Psychiatry* 2001; 62: 22–27. [PubMed] [Google Scholar]

[10] Palkovits M. Stress-induced expression of co-localized neuropeptides in hypothalamic and amygdaloid neurons. *Eur J Pharmacol.* 2000; 405:161–166. [PubMed] [Google Scholar]

[11] Smoller JW. Disorders and borders: psychiatric genetics and nosology. *Am J Med Genet B Neuropsychiatry Genet* 2013; 162(7): 559–578. [PubMed] [Google Scholar]

[12] Roiser JP, Elliott R, Sahakian BJ (2012) Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology* 37(1): 117–136.

[13] Watts AG. The impact of physiological stimuli on the expression of corticotropinreleasing hormone (CRH) and other neuropeptide genes. *Front Neuroendocrinal.* 1996; 17:281–326. [PubMed] [Google Scholar]

[14] Warren MB, Pringle A, Harmer CJ (2015) A neurocognitive model for understanding treatment action in depression. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 370(1677): 20140213.

[15] Whitfield-Gabrieli S, Ford JM (2012) Default mode network activity and connectivity in psychopathology. *Annual Review of Clinical Psychology* 8(1): 49–76

[16] Wichers M, Geschwind N, van Os J, et al. (2010) Scars in depression: Is a conceptual shift necessary to solve the puzzle? *Psychological Medicine* 40(3): 359–365.

[17] Yüksel C, Öngür D (2010) Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biological Psychiatry* 68(9): 785–794.