MODERN REVIEW

Western background:

Ancient Greek and Roman physicians, who coined the terms like ‘melancholia’ and ‘mania’, described the symptoms of depression and related disorders. In the fourth century BC, Hippocrates made an early reference to distress and melancholia. He described melancholia (black bile) as a state of “aversion to food, despondency, sleeplessness, irritability and restlessness”. Later, Galen (131-201 A.D.) described melancholia manifesting in “fear and depression, discontent with life and hatred of all people”. Subsequent Greco-Roman medicine not only recognized the symptoms of melancholia in the form of fear, suspicion, aggression and death wishes, but also referred to environmental contributions to melancholia as immoderate consumption of wine, perturbations of the soul due to passion, and disturbed sleep cycle. Many of the original Greek texts on melancholia were transmitted to posterity through medieval Arabic texts in which connections between two major mood states were suggested, and the causes of the disease were speculated to be interactions between temperament, environment and the four humours (i.e. wind, phlegm, yellow bile and black bile). These conditions seem very much similar to ayurvedic description about pathogenesis of disease due to imbalance of the tridoshas.

In the modern era, Robert Burton’s text, Anatomy of Melancholy, published in 1621, was entirely devoted to depression. Burton categorized various forms of melancholy and grief, and also described “causeless melancholia”. Towards the nineteenth century, several attempts were made to clarify the concept of melancholia and bring it closer to what would now be equated with depression. Many physicians such as Esquirol (1820), Samuel Tuke (1813) and Henry Maudsley (1868) attempted to define the causation, nature and presentation of melancholia. French psychiatrist, Jules G.F. Baillarger described the condition for folie a double forme, in which patient become deeply depressed and fall into a stuporous state from which they eventually recover. In 1882, German psychiatrist Karl Kahlbaum, using the term cyclothymia, described mania and depression as stages of the same illness. Emil kraeplin (1899) described a manic depressive psychosis using most of the criteria that psychiatrist now use to establish a diagnosis of bipolar I disorder. In the later part melancholia began to be viewed as an independent disease.

Kraeplin’s work can be seen as culmination of the neurophysiological approach which began with Griesinger and continued to dominate the scene until Freud’s dynamic motivational approach revived interest in the patient as a unique individual with a unique history. What Freud successfully realised was that neurophysiological and psychological knowledge need not be contradictory. Psychoanalysis predominated until the 1970s, which was followed by renewed interest in genetic, biochemical and neuropathological causes of mental disorder which came to be known as biological psychiatry. After the Second World War, the World Health Organization commissioned a task force to review the status of
classification of psychiatry, and produce a revised edition of the International Classification of Diseases. Its subsequent revisions, along with the revised editions of the Diagnostic and Statistical Manual of the American Psychiatric Association, have revolutionized the approach to the study of mental illnesses. These official nomenclatures have established explicit operational criteria for diagnostic categories, including both inclusion and exclusion requirements which means that more is known on what constitutes depression and what does not.

Understanding of the tortuous development of ideas about depression and an awareness of the common obstacles in the past, gives us a greater understanding of the difficulties we could encounter when attempting to make progress in our own time. From looking at the history of ideas on the causation of mental disorder it becomes very apparent that each generation bases its theories of aetiology on the scientific approaches most active at the time. Sometimes psychological ideas prevail, sometimes neuropathological and sometimes genetic. Scientific approaches are also influenced by the wider attitudes of the time, the social, political and cultural climate.

ETYMOLOGY

DEPRESSION:
The word depression is derived from latin ‘depressio’ meaning pressing down. In modern science it is used in various other means like:
- The act of depressing.
- The condition of being depressed.
- An area that is sunk below its surroundings; a hollow.
- The condition of feeling sad or despondent.
- A reduction in activity or force.
- A reduction in physiological vigor or activity: a depression in respiration.
- A lowering in amount, degree, or position.

DEFINITIONS:
Modern science defines depression as a psychiatric disorder characterized by an inability to concentrate, insomnia, loss of appetite, anhedonia, feelings of extreme sadness, guilt, helplessness and hopelessness, and thoughts of death. It is also called ‘clinical depression’. A depressive disorder is an illness that involves the body, mood, and thoughts. It affects the way a person eats and sleeps, the way one feels about oneself, and the way one thinks about things. Clinical depression (also called major-depressive disorder or unipolar depression) is a common psychiatric disorder, characterized by a persistent lowering of mood, loss of interest in usual activities and diminished ability to experience pleasure.
PREVALENCE:
Clinical depression affects about 16% of the population on at least one occasion in their lives. In some countries, such as Australia, one in four women and one in eight men will suffer from depression. The mean age of onset, from a number of studies, is in the late 20s. About twice as many females as males report or receive treatment for clinical depression, though this imbalance is shrinking over the course of recent history; this difference seems to completely disappear after the age of 50 - 55, when most females have passed the end of menopause. It should be noted that these numbers are only for those who report or receive treatment for depression; men are less likely to report feeling depressed, and also less likely to seek treatment, possibly due to gender roles. Clinical depression is currently the leading cause of disability in North America as well as other countries, and is expected to become the second leading cause of disability worldwide (after heart disease) by the year 2020, according to the World Health Organization. In India, 65.4 per 1000 population are affected by mental illnesses, out of which 51 % i.e.31.2 per 1000 Indian population is suffering from depression.

AETIOLOGY:

Social factors associated with Depression
- Stressful life events
  - Interpersonal loss: Death, divorce, discord, isolation
  - Achievement loss: Disappointment, failure, financial problem

- Early Adverse Experiences
  - Inadequate parenting
  - Physical & sexual abuse

Mechanism:
EAEs \(\rightarrow\) Impairment in biological, psychological or social functioning \(\rightarrow\) Depression

Psychological factors associated with Depression
- Negative cognitive style
  - Tendency to view the self, the world, and the future in a negative way

- Rumination
  - Tendency to respond to distress by brooding on the situation in passive, repetitive way

- Interpersonal orientation
  - Tendency to overvalue social connections at the cost of individual autonomy and base one’s self worth on being approved by others

- Achievement orientation
  - Tendency to overvalue achievement and base one’s self worth on accomplishment
Biological factors associated with depression

Genetics

Familial studies: first degree biological relatives of those with MDD have elevated rates (1.5-3 times)

Twin studies: concordance rates for MDD: MZ=54%, DZ=24%

Comparison with Bipolar I

Familial pattern: 7 times higher

Concordance rates: MZ=69%, DZ=19%

Neuroendocrine Functioning

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation and elevated cortisol

Neurotransmitter Activity

Serotonin, norepinephrine, & dopamine anomalies

Brain structure & Functioning

Anomalies in brain tissue and activity pattern in various brain regions (e.g. prefrontal cortex)

According to modern psychiatry the causes are as follow.¹⁴

1) Psychological factors:

Low self-esteem and self-defeating or distorted thinking are connected with depression. Although it is not clear which is the cause and which is the effect, it is known that depressed persons who are able to make corrections in their thinking patterns can show improved mood and self-esteem. Psychological factors related to depression include the complex development of one's personality and how one has learned to cope with external environmental factors such as stress.

- Early experiences – Events such as the death of a parent, abandonment or rejection, neglect, chronic illness, and physical, psychological, or sexual abuse can also increase the likelihood of depression later in life. Post-traumatic stress disorder (PTSD) includes depression as one of its major symptoms.

- Life experiences – Job loss, poverty, financial difficulties, gambling addiction, long periods of unemployment, the loss of a spouse or other family member, divorce or the end of a committed relationship, involuntary celibacy, or other traumatic events may trigger depression. Long-term stress at home, work, or school can also be involved. Bullying in late adolescence is also thought to be a contributing factor.

2) Biological causes:

Biological causes are due to changes in the chemistry of the brain, such as fluctuations in the levels of important hormones. Research data indicate that people suffering from depression have imbalances of neurotransmitters, natural substances that allow brain cells to communicate with one another. Two
transmitters implicated in depression are Serotonin and Norepinephrine. Scientists think a deficiency in serotonin may cause the sleep problems, irritability, and anxiety associated with depression. Likewise, a decreased amount of norepinephrine, which regulates alertness and arousal, may contribute to the fatigue and depressed mood of the illness.\textsuperscript{15} Other researches suggest that impairment of the Hypothalano-Pitutary-Adrenal Axis functioning resulting into hyper secretion of a stress hormone-Cortisol is found in clinically depressed patients.\textsuperscript{16}

3) **Heredity and Genetic factors:**

The tendency to develop depression may be inherited; there is some evidence that this disorder may run in families. A 2004 press release from the National Institute of Mental Health declares "major depression is thought to be 40-70 percent heritable, but likely involves an interaction of several genes with environmental events."\textsuperscript{17} Recent genetic research also supports earlier studies reporting family links in depression. For example, if one identical twin suffers from depression or manic-depressive disorder, the other twin has a 70 percent chance of also having the illness.\textsuperscript{18}

**PREMONITORY SIGNS**

In many cases, depression starts with the birth of the first adverse event faced by the person. Each and every factor like childhood experiences, parent’s attitude and dejection, familial conditions, social and religious background, individual responsibilities, peer pressure, competitive landmarks, failure to sustain one’s own self esteem etc. contribute to the growth of depression with age. In youth and middle age, family and social responsibilities, life’s adversities on the way of success, failure to stand as a developed individual, stressful activities help to manifest depression in its full form. Thus it may develop slowly over a long time period and signs and symptoms have gradual pathogenesis. Sudden crisis in any of the well established area of life like business, relationship, financial condition, etc. may trap the individual into acute depression state without any prior symptomatology.

**CLINICAL MANIFESTATIONS**

The term 'depression' signify many things. It may be viewed as normal when occurring under certain circumstances, for example, in response to a death or loss of business. It is viewed as abnormal when it occurs under inappropriate circumstances, when it is of inappropriate severity, continues for a long time and interferes with a person’s activities of daily living. As a symptom, depression is associated with a number of psychiatric disorders. Depression by itself has a predictable course, associated biological abnormalities, genetic inheritable pattern and treatment response.

A mild depressed effect or mood does not signify the presence of a serious disorder. To determine whether a depressed mood or effect is of clinical significance, there must be a complete evaluation to
determine the clinical context of the depression. This means that it should be possible to define a threshold at which a constellation of depressive features becomes a condition distinct from the ordinary blues.

According to the current definition, a person who responds to a setback with lowered spirits and self-doubt, difficulty in sleeping and concentration, and decreased appetite and libido for at least 14 days qualifies for diagnosis of a major depression. However, it is necessary to have more specific criteria to differentiate depression from adjustment reactions to life situations, and validate the diagnosis.

**Some important aspects of depression**:¹⁹

- Depression can be incapacitating. In fact, impaired work performance is often an early manifestation.
- Depression is a distinct break from a person’s usual premorbid self.
- The sufferer experiences depression as qualitatively distinct from grief or other understandable reactions to loss or adversity.
- Sometimes there may be a history of similar episodes in the past.
- There may be a history of similar episodes and/or suicide in the family.

The clinical interview is the most effective method for detecting depression. The interview elicits the nature, degree and severity of depressive symptoms. It also helps to identify various types of depression, the course and outcome of the disorders, and various factors like stressors, psychosocial support, physical disorders, concomitant medications, family history and alcohol and substance abuse. The interview helps to determine if the patient has suicidal ideas, and if so, how grave the intention is. It also records the patient’s level of functioning and the presence of psychotic features like delusions or hallucinations.

If there are indications in the history to suspect a medical disorder, appropriate physical examination and laboratory investigations must be carried out to detect the specific disorder. It must also be determined if the disorder has a causal link to the depression.

For the primary care setting, a number of self-reported screening instruments are available which help to identify potentially—depressed patients. Such patients should be further evaluated by clinical interview to determine whether the symptoms meet the criteria for depression.

Several rating scales are also available for doctors. They offer greater specificity to detect depression, and are sensitive to monitor the course of treatment.

**Symptoms of depression**:²⁰

1. Depressed mood
2. Loss of interest and enjoyment
3. Reduced energy, being easily fatigued, diminished activity
4. Marked tiredness on slight effort
5. Reduced concentration and attention on a task
6. Reduced confidence and self-esteem
7. Feeling of guilt and unworthiness
8. Bleak and pessimistic views of the future
9. Ideas or acts of self-destruction or suicide
10. Disturbed sleep
11. Diminished appetite and libido
12. Unexplained physical symptoms.

When these symptoms persist for at least two weeks, social and occupational functioning are significantly impaired, if normal stresses of life do not explain the symptoms and when rest and relaxation have not helped, then the person should consult a doctor for treatment.

Symptomatology of Depression: \(^{21}\)

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Somatic</th>
<th>Psychic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abdominal discomfort</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>2</td>
<td>Anorexia</td>
<td>Diminished interest</td>
</tr>
<tr>
<td>3</td>
<td>Breathlessness</td>
<td>Lack of pleasure</td>
</tr>
<tr>
<td>4</td>
<td>Blurred vision</td>
<td>Sadness of mood</td>
</tr>
<tr>
<td>5</td>
<td>Constipation</td>
<td>Anxiety</td>
</tr>
<tr>
<td>6</td>
<td>Dryness of mouth</td>
<td>Feeling of guilt</td>
</tr>
<tr>
<td>7</td>
<td>Dermatological disturbances</td>
<td>Irritability</td>
</tr>
<tr>
<td>8</td>
<td>Tiredness or fatigability</td>
<td>Despondency</td>
</tr>
<tr>
<td>9</td>
<td>Giddiness</td>
<td>Crying spells</td>
</tr>
<tr>
<td>10</td>
<td>Headache</td>
<td>Helplessness</td>
</tr>
<tr>
<td>11</td>
<td>Heaviness</td>
<td>Hopelessness</td>
</tr>
<tr>
<td>12</td>
<td>Heat flushes</td>
<td>Worthlessness</td>
</tr>
<tr>
<td>13</td>
<td>Insomnia/ Hypersomnia</td>
<td>Lack of confidence</td>
</tr>
<tr>
<td>14</td>
<td>Weight loss /gain</td>
<td>Poor concentration</td>
</tr>
<tr>
<td>15</td>
<td>Palpitation</td>
<td>Decreased self esteem</td>
</tr>
<tr>
<td>16</td>
<td>Chest pain</td>
<td>Unexplained fears or phobias</td>
</tr>
<tr>
<td>17</td>
<td>Sexual disturbances</td>
<td>Suicidal thoughts</td>
</tr>
<tr>
<td>18</td>
<td>Tingling and numbness</td>
<td>Agitation or retardation</td>
</tr>
<tr>
<td>19</td>
<td>Urinary frequency</td>
<td>Negativism</td>
</tr>
<tr>
<td>20</td>
<td>Vague aches and pains</td>
<td>Reduced productivity</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>Decreased memory</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>Loneliness</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>Illusions</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>Hallucinations</td>
</tr>
</tbody>
</table>
Age wise Symptomatology:

Symptoms of depression can be described according to specific age group.

**SYMPTOMS OF CHILDHOOD/ADOLESCENT DEPRESSION**
- Drop in school performance
- Weight loss or gain
- Stomachaches
- Insomnia
- Social withdrawal
- Drug or alcohol abuse
- Isolation
- Apathy
- Fatigue
- Lack of concentration

**SYMPTOMS OF ADULT DEPRESSION**
- Long term sadness
- Feelings of worthlessness or guilt
- Lack of interest in sex
- Loss of concentration
- Loss of interest in activities
- Fatigue
- Weight loss or gain
- Insomnia or oversleeping
- Anxiety
- Suicidal thoughts
- Slowed speech and physical movement
PATHO PHYSIOLOGY OF DEPRESSION:

The enormous progress in the field of neuroscience in the 20th century brought fascinating insights into the nature of mental processes. Starting with neuroanatomy and electrophysiology at the beginning of the 20th century, neuroscience now is an interdisciplinary field occupying many areas of biological investigations, ranging from molecular studies of cell and gene function to brain-imaging techniques, thus broadening our knowledge of the cellular and molecular machinery that regulates behavior. Entered in the 21st century, modern neuroscientists are searching for different basic facts of depression from various aspects like neuro-biology, neuro-chemistry and psychopathology. Different theories are postulated to establish firm scientific foundation in depression. Some of these are discussed below.

NEURO-CHEMISTRY:

Monoamine hypothesis

The first major hypothesis of depression was formulated about 30 years ago and proposed that the main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters Norepinephrine (NE), 5-Hydroxy Triptamine (HT), and/or Dopamine (DA), whereas mania is caused by functional excess of monoamines at critical synapses in the brain. Evidence for this hypothesis came from clinical observations and animal experiments, which showed that the antihypertensive drug reserpine, which causes a depletion of presynaptic stores of NE, 5-HT, and DA, induced a syndrome resembling depression. In contrast to the effects obtained with reserpine, euphoria and hyperactive behavior were observed in some patients being treated with iproniazid, a compound synthesized for the treatment of tuberculosis, which increased brain concentrations of NE and 5-HT by inhibiting the metabolic enzyme MAO. Considering the origin of the noradrenergic, serotonergic, and dopaminergic neurones in the brain and their projections into many areas of the brain, it is clear that monoaminergic systems are responsible for many behavioral symptoms, such as mood, vigilance, motivation, fatigue, and psychomotor agitation or retardation. Abnormal function and the behavioral consequences of either depression or the manic state may arise from altered synthesis, storage, or release of the neurotransmitters, as well as from disturbed sensitivity of their receptors or sub cellular messenger functions.

Disturbances in neurotransmission are the neurobiologic hallmark of depression. Changes have been found in monoamine systems, such as Serotonin (5-HT), Norepinephrine, and Dopamine, as well as other systems, such as corticotropin releasing factor (CRF) and somatostatin. Clinically, the 5-HT and NE systems have been the most thoroughly studied, and it is in these systems that most currently prescribed antidepressants function. Depletion of both 5-HT and NE has been linked to depression; all 5-HT reuptake inhibitors are highly effective antidepressants, and NE reuptake inhibitors are similarly effective for depression. Antidepressant binding to receptor targets results in both the desired clinical outcomes as well as the observed side effects. Serotonergic pathways are believed to function largely in mood, while NE is likely involved with drive and energy state. Both systems function in appetite, sleep regulation, and...
Conceptual study

anxiety. The selective serotonin reuptake inhibitors (SSRIs) are now the most common treatment for depression. Although 5-HT depletion is related to depressive symptoms, depression is also strongly linked with stress, and stress systems in the brain are largely mediated by changes in NE transmission.27

Thus according to this hypothesis, depletion of Serotonin and Norepinephrine at pre-synaptic level due to any reason can cause depression.

PSYCHO PATHOLOGY28:
1) The psychic pain hypothesis29:

Psychic pain, such as depression, is analogous to physical pain. The function of physical pain is to inform the organism that it is suffering damage, to motivate it to withdraw from the source of damage, and to learn to avoid such damage-causing circumstances in the future. Analogously, depression informs the sufferer that current circumstances, such as the loss of a mate, are imposing a threat to biological fitness, it motivates the sufferer to cease activities that led to the costly situation, if possible, and it causes him or her to learn to avoid similar circumstances in the future. Proponents of this view tend to focus on low mood, and regard clinical depression as a dysfunctional extreme of low mood.

2) Rank theory:

If an individual is involved in a lengthy fight for dominance in a social group and is clearly losing, depression causes the individual to back down and accept the submissive role. In doing so, the individual is protected from unnecessary harm. In this way, depression helps maintain a social hierarchy. This theory is a special case of a more general theory derived from the psychic pain hypothesis: that the cognitive response that produces modern-day depression evolved as a mechanism that allows people to assess whether they are in pursuit of an unreachable goal, and if they are, to motivate them to desist.

3) Honest signaling theory:

When social partners have conflicts of interest, 'cheap' signals of need, such as crying, might not be believed. Biologists and economists have proposed that signals with inherent costs can credibly signal information when there are conflicts of interest. The symptoms of major depression, such as loss of interest in virtually all activities and suicidality, are inherently costly, but, as costly signaling theory requires, the costs differ for individuals in different states. For individuals who are not genuinely in need, the fitness cost of major depression is very high because it threatens the flow of fitness benefits. For individuals who are in genuine need, however, the fitness cost of major depression is low because the individual is not generating many fitness benefits. Thus, only an individual in genuine need can afford to suffer major depression. Major depression therefore serves as an honest, or credible, signal of need.

4) Social navigation or niche change theory:

The social navigation, bargaining, or niche change hypothesis suggests that depression, operationally defined as a combination of prolonged anhedonia and psychomotor retardation or agitation, provides a focused sober perspective on socially imposed constraints hindering a person’s pursuit of major fitness enhancing projects. Simultaneously, publicly displayed symptoms, which reduce the depressive's ability to conduct basic life activities, serve as
a social signal of need; the signal's costliness for the depressive certifies its honesty. Finally, for social partners who find it uneconomical to respond helpfully to an honest signal of need, the same depressive symptoms also have the potential to extort relevant concessions and compromises. Depression’s extortionary power comes from the fact that it retards the flow of just those goods and services such partners have come to expect from the depressive under status quo socioeconomic arrangements.

Thus depression may be a social adaptation especially useful in motivating a variety of social partners, all at once, to help the depressive initiate major fitness-enhancing changes in their socioeconomic life. There are extraordinarily diverse circumstances under which this may become necessary in human social life, ranging from loss of rank or a key social ally which makes the current social niche uneconomic to having a set of creative new ideas about how to make a livelihood which begs for a new niche. The social navigation hypothesis emphasizes that an individual can become tightly ensnared in an overly restrictive matrix of social exchange contracts, and that this situation sometimes necessitates a radical contractual upheaval that is beyond conventional methods of negotiation. Regarding the treatment of depression, this hypothesis calls into question any assumptions by the clinician that the typical cause of depression is related to maladaptive perverted thinking processes or other purely endogenous sources. The social navigation hypothesis calls instead for a penetrating analysis of the depressive's talents and dreams, identification of relevant social constraints (especially those with a relatively diffuse non-point source within the social network of the depressive), and practical social problem-solving therapy designed to relax those constraints enough to allow the depressive to move forward with their life under an improved set of social contracts.

5) Bargaining theory:

This theory is similar to the honest signaling, niche change, and social navigation theory. It basically adds one additional element to honest signaling theory. The fitness of social partners is generally correlated. When a wife suffers depression and reduces her investment in offspring, for example, the husband's fitness is also put at risk. Thus, not only do the symptoms of major depression serve as costly and therefore honest signals of need, they also compel social partners to respond to that need in order to prevent their own fitness from being reduced.

PSYCHO-NEURO-ENDOCRINOLOGY:

This science studies the relation between various psychological patterns and their neuronal and endocrinal responses in the body. The Hypothalamic-Pituitary-Adrenal (HPA) axis is the system that manages the body's response to stress. When a threat to physical or psychological well-being is detected, the hypothalamus amplifies production of corticotrophin-releasing factor (CRF), which induces the pituitary to secrete Adreno corticotrophin hormone (ACTH). It then instructs the adrenal gland atop each kidney to release cortisol. Together all the changes prepare the body to fight or flee and cause it to shut down activities that would distract from self-protection. For instance, cortisol enhances the delivery of fuel to muscles. At the same time, CRF depresses the appetite for food and sex and heightens alertness. Chronic
Activation of the HPA axis, however, may lay the ground for illness and, it appears, for depression. As long ago as the late 1960s and early 1970s, several research groups reported increased activity in the HPA axis in unmedicated depressed patients, as evinced by raised levels of cortisol in urine, blood and cerebrospinal fluid, as well as by other measures. Hundreds, perhaps even thousands, of subsequent studies have confirmed that substantial numbers of depressed patients—particularly those most severely affected—display HPA-axis hyperactivity. Indeed, the finding is surely the most replicated one in all of biological psychiatry. Deeper investigation of the phenomenon has now revealed alterations at each level of the HPA axis in depressed patients. For instance, both the adrenal gland and the pituitary are enlarged, and the adrenal gland hyper secretes cortisol. But many researchers at Emory University, have become persuaded that aberrations in CRF-producing neurons of the hypothalamus and elsewhere bear most of the responsibility for HPA-axis hyperactivity and the emergence of depressive symptoms. Notably, study after study has shown CRF concentrations in cerebrospinal fluid to be elevated in depressed patients, compared with control subjects or individuals with other psychiatric disorders. This magnification of CRF levels is reduced by treatment with antidepressants and by effective electroconvulsive therapy. Further, postmortem brain tissue studies have revealed a marked exaggeration both in the number of CRF-producing neurons in the hypothalamus and in the expression of the CRF gene (resulting in elevated CRF synthesis) in depressed patients as compared with controls. Moreover, delivery of CRF to the brains of laboratory animals produces behavioral effects that are cardinal features of depression in humans, such as insomnia, decreased appetite, decreased libido and anxiety.

Considering these views, Serum Cortisol is investigated as biomarker in the present research work to provide scientific evaluation and assessment of therapy.

**NEURO BIOLOGY:**

Recent research has suggested that there may be a link between depression and neurogenesis of the hippocampus. This horseshoe-shaped structure is a center for both mood and memory. Loss of neurons in the hippocampus is found in depression and correlates with impaired memory and dysthemic mood. The hippocampus regains mass when exposed to treatments that increase brain Serotonin, and when regrown, mood and memory tend to be restored. According to some researchers, the Limbic system including Serotonin and Norepinephrine pathways from Locus coerules and Raphe nuclei, Amygdala, Prefrontal cortex, Cingulated gyrus, Septum, Basal ganglia, Fornix and Thalamus are also affected in depression.
Pathophysiology in Depression

Depression is increasingly being viewed as more of a disease of the brain than of the mind. Neuroimaging studies have revealed structural changes in the brains of depressed patients within the neuroanatomical circuit of Nauta termed the limbic-cortical-striatal-pallidal-thalamic tract. The importance of the hippocampus in depressive pathophysiology is now supported by a large body of evidence suggesting that hippocampal volume is reduced in depressed patients. This reduction in volume and the associated deficits in cognitive functioning may occur at their greatest rates in the early years after onset of illness and be greatest in patients with a chronic and recurrent course. Mechanisms proposed to explain hippocampal volume loss in depression include hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and associated glucocorticoid neurotoxicity, decreased levels of brain-derived neurotrophic factor (BDNF) and associated diminished neurogenesis, and loss of plasticity.
Structural Brain Changes in Depression

Unusually high rates of depression are found in neurological diseases associated with both cortical and subcortical atrophy, including Huntington’s disease, post-stroke syndromes, Alzheimer’s disease, epilepsy and Parkinson’s disease. These disorders involve damage to parts of the brain associated with emotional functioning, most notably those in the neuroanatomical circuit of Nauta termed the limbic-cortical-striatal-pallidal-thalamic tract, which are also involved in major depression. Although a direct cause and effect relationship has not been established between structural impairment in neurological disease and depression, it may be that some neurological patients have an increased vulnerability to depression and that when depression occurs it may further contribute to additional structural damage. Neuroimaging studies in depressed patients have also revealed structural changes in the circuit of Nauta, but it is still unclear whether they are the cause or a consequence of the disorder. Although structural changes have been reported in frontal cortex, amygdala and basal ganglia, the most consistent results have been found in the hippocampus. In general, depression seems to be associated with hippocampal volume loss ranging from 8 to 19%. Volume loss may have functional consequences, with reports of associations between acute depression and abnormalities of recollection and declarative memory as well as between depression in remission and impaired verbal memory. Volume loss seems to be directly associated with illness duration and severity of depression, and may be absent in remitted depression. Although it is still unclear as to whether reductions in hippocampal volume antedate illness onset, volumes may decrease at their greatest rate in the early years after onset of depression and with multiple episodes. A large body of evidence in animal studies has also revealed memory deficits and hippocampal damage after exposure to stress. Mechanisms invoked to explain these findings include glucocorticoid neurotoxicity, increased release of excitatory amino acids, inhibition of neurogenesis, loss of plasticity and decreased brain-derived neurotrophic factor (BDNF). It is clear that some of the changes can be reversed by chronic antidepressant drug treatment; tianeptine can reverse stress-induced reductions in hippocampal volume and the associated neuronal atrophy in tree shrews, while a variety of antidepressant treatments including ECT, SSRIs, MAOIs and NRIs reversed hippocampal atrophy and promoted neurogenesis in the dentate gyrus of rat brain. In human studies, successful treatment of depressed patients with a variety of antidepressant medications from TCAs, SSRIs and SNRIs to trazodone and mianserin restored their low serum levels of BDNF to normal. In patients with post-traumatic stress disorder (PTSD), a condition also associated with hippocampal volume loss and a decline in verbal declarative memory, treatment with paroxetine restored both memory and hippocampal volume. Antidepressants may have a neuroprotective effect during depression since hippocampal volume was predicted by the duration of untreated depression whereas there was no relationship between cumulative time treated with antidepressants during depression.
Neurohistological changes – most fundamental explanatory model for depression

**Neuro-histological changes:**

The most fundamental explanatory model for depression

- **Hippocampus**
  - Key structure involved in learning, mood & memory, regulates ANS & Neuroendocrine system
  - Depression
    - Dysthymic mood
    - Impaired memory
    - Disturbance in ANS & NES

- **Meso-limbic circuitry**
  - Depression
    - Regulates response to novelty
    - Anhedonia

- **Pre-frontal cortex**
  - Depression
    - Regulates higher functions like motivation & Judgment
    - Difficulty in concentration
    - Attention deficit
    - Impairment in motivation & judgment

- **Amygdala**
  - Up-regulated anxiety response to minor provocations
  - Involved with social and emotional learning especially emotions like anxiety and fear

**Neuroendocrine**

- **Neurovegetative**
- **Neurocognitive**
- **Neurobehavioral**

**Functional changes in different part of the brain give rise to Depression**
Among the various brain changes induced by stress, the neurohistological changes may be the most fundamental as an explanatory model for depression. This is because changes in neuronal architecture and connectivity would likely cause fundamental and persistent impairments in the functioning of the affected neuronal territories. Thus, the cognitive, affective and behavioral impairments in depression could result from the neurohistological changes (identified in animal models of stress and depression) that develop in the brain territories that sub serve these functions.

Key Brain Structures affected by Stress

In animal models, there are at least three important brain territories in which stress induces significant neurohistological changes. These are the hippocampus, the prefrontal cortex and the amygdala.

1. Stress and the hippocampus

In animal models, stress-induced histological changes in the hippocampus include the following:

- Loss of dendritic spines
- Decrease in the number and length of dendrites
- Loss of synapses
- Loss of glia
- Impairment of neurogenesis
- Possibly, apoptosis (under extreme conditions)

In consequence, there is a reduction in hippocampal volume; such reduction has been observed postmortem in animal models of stress and depression as well as in magnetic resonance imaging (MRI) studies of depressed humans. The functional capacity of a neuron depends on its synaptic networks and connectivity. When dendrites and synapses are lost, this connectivity decreases, and the affected neurons become less effective in the circuits in which they lie. Loss of glia (which also play an important role in neurotransmission), decreased neurogenesis and apoptosis magnify the impairment. The hippocampus has projections to the dorsolateral prefrontal cortex, the ventral tegmental area and the hypothalamus. Stress-induced histological changes in the hippocampus could therefore disturb not only hippocampal functioning but also functioning in these downstream areas.

The hippocampus is a key structure involved in learning and memory, especially explicit (consciously acquired) memory. Perhaps as a result of hippocampal impairment, stressed animals and depressed humans show impaired learning and memory. Insofar as coping necessitates intact learning mechanisms, hippocampal impairment could also explain compromised coping behavior observed in depression.
The dorsolateral prefrontal cortex coordinates with the hippocampus in the regulation of explicit memory. It also subserves other important cognitive functions, such as **attention and concentration**. These cognitive functions are also impaired in depression, perhaps as a downstream effect of hippocampal impairment.\(^\text{71}\)

The ventral tegmental area projects to the nucleus accumbens. Mesolimbic circuitry regulates the response to novelty and the experience of reward. Stressed animals show impaired response to novelty. The parallel in depressed humans could be **anhedonia**. Thus, hippocampal impairment may explain anhedonia as a downstream effect.\(^\text{72}\)

The hypothalamus regulates the autonomic nervous system and the neuroendocrine system. Disturbed hypothalamic inputs, perhaps associated with downstream hippocampal impairment, may explain some of the **neuroendocrine and autonomic nervous system disturbances** that characterize depression.\(^\text{73}\)

### 2. Stress and the prefrontal cortex

In animal models, stress-induced histological changes in the prefrontal cortex include the following:\(^\text{74,75,76,77}\)

- Loss of dendritic spines
- Atrophy of the dendritic tree
- Loss of synapses
- Decreased number and size of glia

Postmortem studies in depressed humans reveal a decrease in neuronal size, a decrease in glial size and number and a decrease in overall cortical thickness.\(^\text{78}\) The prefrontal cortex regulates **cognitive functions such as attention, concentration, learning and memory**. The prefrontal cortex also regulates **higher mental functions such as motivation and judgment**. All these functions are impaired in depression, perhaps as a result of the neurohistological prefrontal changes associated with stress and depression.

### 3. Stress and the amygdala

In animal models, stress-induced histological changes in the amygdala are strikingly different from those in the hippocampus and prefrontal cortex. Changes described include the following:\(^\text{79,80}\)

- Increased dendritic arborization
- Increased synaptogenesis
The resultant increase in amygdalar volume has been described in both stressed animals and depressed humans. The increase is not merely structural; it is functional as well. A recent meta-analysis of 13 MRI studies of the amygdala in unipolar depression however found that amygdalar volume increase was a function of antidepressant treatment. A possible explanation for this discordant result is the varied definition of the boundaries of the amygdala in the different studies, as the amygdala is not a clearly demarcated structure.

The amygdala is involved with social and emotional learning and, especially, with emotions such as anxiety and fear. Fear learning is upregulated in stressed animals, i.e., they show an exaggerated, persistent and more generalized fear response to anxiogenic and noxious stimuli. As a parallel, depressed humans are often anxious and afraid and show an upregulated anxiety response to minor provocations.

Interestingly, animal research shows that whereas stress-induced changes in the hippocampus gradually reverse after the removal of the stress, stress-induced changes in the amygdala do not reverse for weeks or longer. In fact, the persistence of amygdalar changes may explain why depressed humans overreact to stress in a trait-dependent way, why current depression begets future depression, why life events have a cumulative effect in the predisposition to depression and even why physical and sexual abuse of children predisposes to depression during adult life.

What neurohistological changes explain the symptom of depression?

The preceding discussion explains why anxiety, fear, anhedonia, motivational impairment, cognitive deficits, neuroendocrine changes and autonomic nervous system dysfunction may occur in the context of the neurohistological changes induced by stress. It does not explain how or why depression as a symptom develops. Perhaps the best way to address this challenge is to consider that no single neuroanatomical locus explains depression, no more than a single locus in the brain explains happiness or other complex emotions. In other words, depression, like schizophrenia, could be the sum total of disturbances in the functioning of multiple parts of the brain. That is, functional changes in different parts of the brain give rise to neuroendocrine, neurovegetative, neurocognitive, neurobehavioral and other deficits, which, put together, form the depressive syndrome.

Theory of neuroplasticity

Anti neuroplastic changes in depression

Accumulating evidence suggests that there is a rich cross-talk between the neuroimmune system and neuroplasticity mechanisms under both physiological conditions and pathophysiological conditions in depression. Anti-neuroplastic changes which occur in depression include a decrease in proliferation of
neural stem cells (NSCs), decreased survival of neuroblasts and immature neurons, impaired neurocircuitry (cortical–striatal–limbic circuits), reduced levels of neurotrophins, reduced spine density and dendritic retraction.

The review puts forward a model in that both humoral and cellular neuroimmune factors are involved with impairing neuroplasticity under pathophysiological conditions such as depression. Specifically, neuroimmune factors including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α, CD4+CD25+T regulatory cells (T reg), self-specific CD4+T cells, monocyte-derived macrophages, microglia and astrocytes are shown to be vital to processes of neuroplasticity such as long-term potentiation (LTP), NSC survival, synaptic branching, neurotrophin regulation and neurogenesis. In rodent models of depression, IL-1, IL-6 and TNF are associated with reduced hippocampal neurogenesis; mechanisms which are associated with this include the stress-activated protein kinase (SAPK)/Janus Kinase (JNK) pathway, hypoxia-inducible factors (HIF)-1α, JAK-Signal Transducer and Activator of Transcription (STAT) pathway, mitogen-activated protein kinase (MAPK)/cAMP responsive element binding protein (CREB) pathway, Ras-MAPK, PI-3 kinase, IKK/nuclear factor (NF)-κB and TGFβ activated kinase-1 (TAK-1).

Neuroimmunological mechanisms have an active role in the neuroplastic changes associated with depression. Since therapies in depression, including antidepressants (AD), omega-3 polyunsaturated fatty acids (PUFAs) and physical activity exert neuroplasticity-enhancing effects potentially mediated by neuroimmune mechanisms, the immune system might serve as a promising target for interventions in depression.
Figure 1: Neuroimmune factors mediating the relationship between depression-like behaviour and neuroplasticity. This figure illustrates the influence depression has on neuroplasticity and the neuroimmune system. In addition, the influence of neuroimmune factors – both cellular and humoral – on neuroplasticity is outlined. T reg, T regulatory cell; TNF, tumour necrosis factor; IL, interleukin; IFN, interferon; NSC, neural stem cell; BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1; GDNF, glial cell-derived neurotrophic factor; LTP, long-term potentiation.

Treatment of depression has long been a hit-and-miss affair. Community surveys have consistently shown that only half of patients with depression are properly diagnosed of whom half receive any form of treatment. Furthermore, of those who actually receive treatment only half receive adequate doses and durations of therapy. Those patients who achieve remission are a rare breed. Failure to receive adequate treatment to full remission carries considerable risks not only for the evolution of the depressive disorder itself but also for extra morbidity and mortality in a wide range of medical illnesses. The economic and social burden of inadequately treated depression is substantial and is considerably greater in the presence of medical comorbidity. Remission of symptoms and a return to full psychosocial functioning has therefore become the new goal of treatment.
The HPA Axis in Depression

The HPA axis and its vulnerability to stress may be the common factor in the hippocampal atrophy and associated memory deficits seen in depression and other disorders such as PTSD. HPA axis hyperreactivity is common across a number of disorders and is not specific to depression. Excessive levels of glucocorticoids produced during HPA axis hyper-reactivity can lead to a state of glucocorticoid neurotoxicity and decreased levels of BDNF with neuronal atrophy in the hippocampus (Figure 2). Although antidepressant treatments of many classes can indirectly up-regulate glucocorticoid receptors and restore HPA axis function, mirtazapine is unique in being able to inhibit cortisol secretion in depressed patients after both acute and chronic administration. All other antidepressants stimulate cortisol secretion, including the other dual action antidepressant shown to produce faster and more remission, venlafaxine, although the doses used were below those needed for venlafaxine to exert its true SNRI effects. Although mirtazapine seems to exert its effects more by its influence upon 5-HT receptors than via any direct antagonism at central glucocorticoid receptors (GR), it may be the antidepressant of choice for reversing hypercortisolaemia and restoring normal HPA axis function. Studies of its influence upon hippocampal deficits in depression, both in volume and memory, are needed, especially since sustained central hypernoradrenergic activity in major depression with melancholia seems to be associated with hypercortisolaemia. Mirtazapine is, above all, a central μ2-adrenoceptor antagonist. Following the early experiments with steroid synthesis inhibitors in mood disorders the glucocorticoid receptor is now seen as a respectable therapeutic target, and direct antagonists of the receptor and of corticotropin-releasing hormone are in clinical development. Early results look promising with the two leading GR antagonists, mifepristone in psychotic depression and ORG 34517 in dexamethasone non-suppressors. It will be interesting to see whether these agents will reverse hippocampal abnormalities of volume and cognition simultaneously with their already demonstrated improvement of treatment outcome in symptomatology.
Glucocorticoid receptors are richly expressed on neurons in the hippocampus and elsewhere in the brain. Mild stress may therefore act through physiological glucocorticoid signaling. Certainly, at physiological levels, the stress hormone cortisol stimulates hippocampal neurons and facilitates learning and memory. At pathological levels, however, cortisol overstimulates the hippocampal neurons and causes dendritic atrophy and loss of synapses; whereas these structural changes are generally reversible, in extreme situations, pathological overstimulation by cortisol can also result in neuronal apoptosis. Glucocorticoid agonism in the medial prefrontal cortex also influences learning and memory: memory consolidation is facilitated, but working memory is impaired.

These neurohistological effects of hypercortisolemia are seen in animal models as well as in humans. In animal models, the neurohistological changes develop in models of stress and depression as well as after chronic administration of corticosteroids to nonstressed animals. In humans, cognitive impairment and reduction in hippocampal volume are described in depression (in which disorder hypercortisolemia is known to occur), in Cushing’s syndrome as well as after the chronic administration of glucocorticoids for...
medical indications. Interestingly, the glucocorticoid receptor antagonist mifepristone has been suggested as a treatment for psychotic depression. It may also attenuate the cognitive impairments associated with depression.

The Role of Cytokines in the Pathophysiology of Major Depression

Recognition that inflammation may represent a common mechanism of disease has been extended to include neuropsychiatric disorders including major depression. Patients with major depression have been found to exhibit increased peripheral blood inflammatory biomarkers, including inflammatory cytokines, which have been shown to access the brain and interact with virtually every pathophysiologic domain known to be involved in depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. Indeed, activation of inflammatory pathways within the brain is believed to contribute to a confluence of decreased neurotrophic support and altered glutamate release/reuptake, as well as oxidative stress, leading to excitotoxicity and loss of glial elements, consistent with neuropathologic findings that characterize depressive disorders. Further instantiating the link between inflammation and depression are data demonstrating that psychosocial stress, a well-known precipitant of mood disorders, is capable of stimulating inflammatory signaling molecules, including nuclear factor kappa B, in part, through activation of sympathetic nervous system outflow pathways. Interestingly, depressed patients with increased inflammatory biomarkers have been found to be more likely to exhibit treatment resistance, and in several studies, antidepressant therapy has been associated with decreased inflammatory responses. Finally, preliminary data from patients with inflammatory disorders, as well as medically healthy depressed patients, suggest that inhibiting proinflammatory cytokines or their signaling pathways may improve depressed mood and increase treatment response to conventional antidepressant medication. Translational implications of these findings include the unique opportunity to identify relevant patient populations, apply immune-targeted therapies, and monitor therapeutic efficacy at the level of the immune system in addition to behavior.
Microglia are primary recipients of peripheral inflammatory signals that reach the brain. Activated microglia, in turn, initiate an inflammatory cascade whereby release of relevant cytokines, chemokines, inflammatory mediators, and reactive nitrogen and oxygen species (RNS and ROS, respectively) induces mutual activation of astroglia, thereby amplifying inflammatory signals within the CNS. Cytokines, including IL-1, IL-6, and TNF-alpha, as well as IFN-alpha and IFN-gamma (from T cells), induce the enzyme, IDO, which breaks down TRP, the primary precursor of 5-HT, into QUIN, a potent NMDA agonist and stimulator of GLU release. Multiple astrocytic functions are compromised due to excessive exposure to cytokines, QUIN, and RNS/ROS, ultimately leading to downregulation of glutamate transporters, impaired glutamate reuptake, and increased glutamate release, as well as decreased production of neurotrophic factors. Of note, oligodendroglia are especially sensitive to the CNS inflammatory cascade and suffer damage due to overexposure to cytokines such as TNF-alpha, which has a direct toxic effect on these cells, potentially contributing to apoptosis and demyelination. The confluence of excessive astrocytic glutamate release, its inadequate reuptake by astrocytes and oligodendroglia, activation of NMDA receptors by QUIN, increased glutamate binding and activation of extrasynaptic NMDA receptors (accessible to glutamate released from glial elements and associated with inhibition of BDNF expression), decline in neurotrophic support, and oxidative stress ultimately disrupt neural plasticity through excitotoxicity and apoptosis.

[5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; GLU, glutamate; IDO, indolamine 2,3 dioxygenase; IFN, interferon; IL, interleukin; NMDA, N-methyl-D-aspartate; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRP, tryptophan]
Psychosocial stressors activate central nervous system stress circuitry, including CRH and ultimately sympathetic nervous system outflow pathways via the locus coeruleus. Acting through alpha and beta adrenergic receptors, catecholamines released from sympathetic nerve endings can increase NF-κB DNA binding in relevant immune cell types, including macrophages, resulting in the release of inflammatory mediators that promote inflammation. Proinflammatory cytokines, in turn, can access the brain, induce inflammatory signaling pathways including NF-κB, and ultimately contribute to altered monoamine metabolism, increased excitotoxicity, and decreased production of relevant trophic factors. Cytokine-induced activation of CRH and the hypothalamic-pituitary-adrenal axis, in turn, leads to the release of cortisol, which along with efferent parasympathetic nervous system pathways (e.g., the vagus nerve) serve to inhibit NF-κB activation and decrease the inflammatory response. In the context of chronic stress and the influence of cytokines on glucocorticoid receptor function, activation of inflammatory pathways may become less sensitive to the inhibitory effects of cortisol, and the relative balance between the proinflammatory and anti-inflammatory actions of the sympathetic and parasympathetic nervous systems, respectively, may play an increasingly important role in the neural regulation of inflammation. CRH, corticotropin-releasing hormone; NF-κB, nuclear factor kappa B.
(a) Activation of NF-kB through Toll-like receptors (TLR) during immune challenge leads to an inflammatory response including (b) the release of the proinflammatory cytokines TNF-a, IL-1 and IL-6. (c) These cytokines, in turn, access the brain via leaky regions in the blood–brain barrier, active transport molecules and afferent nerve fibers (e.g. sensory vagus), which relay information through the nucleus tractus solitarius (NTS). (d) Once in the brain, cytokine signals participate in pathways (indicated in orange) known to be involved in the development of depression, including: (i) altered metabolism of relevant neurotransmitters such as serotonin (5HT) and dopamine (DA); (ii) activation of CRH in the paraventricular nucleus (PVN) and the subsequent production and/or release of ACTH and glucocorticoids (cortisol) and (iii) disruption of synaptic plasticity through alterations in relevant growth factors [e.g. brain-derived neurotrophic factor (BDNF)]. (e) Exposure to environmental stressors promotes activation of inflammatory signaling (NF-kB) through increased outflow of proinflammatory sympathetic nervous system responses [release of norepinephrine (NE), which binds to a (αAR) and b (βAR) adrenoceptors] (orange). (f) Stressors also induce withdrawal of inhibitory motor vagal input [release of acetylcholine (ACh), which binds to the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR)] (blue). (g) Activation of the mitogen activated protein kinase pathways, including p38 and Jun amino-terminal kinase (JNK), inhibit the function of glucocorticoid receptors (GR), thereby releasing NF-kB from negative regulation by glucocorticoids released as a result of the HPA axis in response to stress (blue).
Consolidation of fear memory

The preclinical approaches to PTSD are examining the mechanisms of memory consolidation and how this consolidation process could be interrupted to prevent the development of trauma-related disorders. An excellent review by Ressler and Mayber notes that preclinical studies have demonstrated that memories do not immediately become permanent at the time of initial experience. They exist in a labile state for at least a period of hours and possibly days, during which time they become consolidated into more permanent memory. During this consolidation, molecular, synaptic, neurotransmitter and system-level changes occur consecutively. The neural circuitry implicated in fear memory likely involves complex interactions between the hippocampus (which is involved in short-term memory and probably fears of the context of an event), the amygdala (which is involved in conditioned fear response) and the medial prefrontal cortex (which is believed to extinguish the more primitive subcortical response). The neurocircuitry model of PTSD also implicates the involvement of the amygdala, medial prefrontal cortex and hippocampus. As the hippocampus can process and temporarily store new memory before transferring labile memory to the cortex for permanent storage, it has been suggested that during the immediate period after fear training in an animal model and after a traumatic event in human patients, it may be possible to modulate the consolidation of new fear memories in the process of being formed.

Role of hippocampal neurogenesis in memory consolidation

In rodents, primates and humans, the dentate gyrus in the hippocampus is one of the two brain regions with lifelong neurogenesis. Despite the wealth of accumulating data on the characteristics of neurons in newborns, the specific contribution of their generation to memory formation by the hippocampus remains unclear. Recently, Kitamura and colleagues showed that severe impairment of hippocampal neurogenesis attenuated the loss of hippocampus-dependent remote contextual fear memory in mice, while conversely, exercise on a running wheel, which promotes neurogenesis, increased the rate of loss of hippocampus-dependent contextual fear memory. The hippocampus-dependent periods for fear memory are modulated by various conditions. Independent lines of evidence strongly suggest that the level of hippocampal neurogenesis plays a role in determining the hippocampus-dependent period of memory in adult rodents. In short, the level of hippocampal neurogenesis was able to be modulated and was associated with a causal relationship between adult neurogenesis and the hippocampus-dependent period of fear memory. Therefore, it is theoretically possible that promoting adult neurogenesis early in the transition period might facilitate the clearance of fear memory from the hippocampus (Figure 6).
Figure 6: Neurogenesis by Omega 3 fatty acid supplementation

Figure 2 Schematic illustration of the development of posttraumatic stress disorder (PTSD) focusing on modulating the consolidation of fear memory through neurogenesis by omega-3 fatty acid supplementation. The strength and regulation of fear memory is affected by many factors both before and after the fearful and traumatic event occurs. Genetic and environmental factors as well as brain function and structure are associated with the risk of such an experience. Acquired memories undergo a period of consolidation, in which they shift from a labile state to a more permanent state. Memories are initially dependent on the hippocampus, but hippocampal dependency progressively decays over time, a process that is associated with a gradual increase in dependency on the neocortex. We propose that promoting adult neurogenesis by omega-3 fatty acid supplementation early in the transition period might facilitate clearance of fear memory from the hippocampus and consequently minimize PTSD symptoms (dotted arrows and box).
Dietary Omega-3 and Clinical Depression

Brain development is a complex interactive process in which early disruptive events can have long-lasting effects on later functional adaptation. It is a process that is dependent on the timely orchestration of external and internal inputs through sophisticated intra- and intercellular signaling pathways\textsuperscript{120}.

Nerve tissue possesses one of the highest concentrations of fatty acids in the body, with approximately 50–60% of the dry weight of the adult brain comprised of lipids, of which approximately 35% are in the form of long-chain polyunsaturated fatty acids (LCPUFA), mainly arachidonic acid (20 : 4n-6; AA) and DHA (22 : 6n-3). These LCPUFA are derived through biosynthesis from their respective dietary essential fatty acid (EFA) precursors, linoleic acid (18 : 2n-6) and \(\alpha\)-linolenic acid (18 : 3n-3; LNA), or they can be obtained directly from dietary sources such as eggs, fish and meat or, more recently, from single-cell oils\textsuperscript{121}. These long-chain fatty acids provided in food are essential for both the structure and function of nerve cells. The three most nutritionally important omega-3 fatty acids are alpha-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Alpha-linolenic acid is one of two fatty acids traditionally classified as "essential." The other fatty acid traditionally viewed as essential is an omega 6 fat called linoleic acid. These fatty acids have traditionally been classified as "essential" because the body is unable to manufacture them on its own and because they play a fundamental role in several physiological functions. As a result, we must be sure our diet contains sufficient amounts of both alpha-linolenic acid and linoleic acid. Long-chain polyunsaturated fatty acids (LCPUFA), specifically arachidonic acid and docosahexaenoic acid (DHA), accrue rapidly in the grey matter of the brain during development, and brain fatty acid (FA) composition reflects dietary availability\textsuperscript{122}. Further, Linoleic and a-linolenic acid are essential for normal cellular function, and act as precursors for the synthesis of longer chained polyunsaturated fatty acids (PUFAs) such as arachidonic (AA), eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), which have been shown to partake in numerous cellular functions affecting membrane fluidity, membrane enzyme activities and eicosanoid synthesis. The brain is particularly rich in PUFAs such as DHA, and changes in tissue membrane composition of these PUFAs reflect that of the dietary source. The decline in structural and functional integrity of this tissue appears to correlate with loss in membrane DHA concentrations. Arachidonic acid, also predominant in this tissue, is a major precursor for the synthesis of eicosanoids, that serve as intracellular or extracellular signals. With aging comes a likely increase in reactive oxygen species and hence a concomitant decline in membrane PUFA concentrations, and with it, cognitive impairment. Neurodegenerative disorders such as Parkinson's and Alzheimer's disease also appear to exhibit membrane loss of PUFAs. Thus it may be that an optimal diet with a balance of n-6 and n-3 fatty acids may help to delay their onset or reduce the insult to brain functions which these diseases elicit\textsuperscript{123}. 
Omega-3 fatty acids are long-chain polyunsaturated fatty acids found in various plant and marine life\textsuperscript{124}. The marine-based omega-3 fatty acids primarily consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and appear to be highly biologically active. In contrast, those from plants (flaxseed, walnuts, and canola oil) are usually in the form of the parent omega-3 fatty acid, alpha-linolenic acid. Although dietary alpha-linolenic acid can be endogenously converted to EPA and DHA (see the metabolic pathways in Figure 7), research suggests that this occurs inefficiently to only 10\%–15\%\textsuperscript{125}. In the last 150 years, rapid expansion in Western populations has been associated with a change in diet, with omega-3 polyunsaturated fatty acids from fish, wild game, and plants being replaced by saturated fats from domestic animals and omega-6 polyunsaturated fatty acids from common vegetable oils (corn, safflower, and soybean) and other sources. These changes have resulted in a large increase in the ratio of omega-6 to omega-3 fatty acids in the general diet from 1:1 to more than 10:1\textsuperscript{126,127}. This has resulted in a high proportion of the common omega-6 fatty acid arachidonic acid, rather than EPA, in the cell membranes of most tissues, leading in turn to a high proportion of inflammatory eicosanoids\textsuperscript{128}. As shown in Figure 7, an increase in arachidonic acid also affects the production of EPA and DHA, owing to competition for metabolizing enzymes. Such dietary changes in fatty acid intake have been held to have numerous pathological consequences. In relation to depression, both Smith\textsuperscript{129} and Hibbeln and Salem\textsuperscript{130} suggested that the sharp rises in rates of depression and other neurological disorders in the 20th century are being fueled by increased consumption of vegetable oils rich in omega-6 fatty acids. Indirect support for that hypothesis emerges from data indicating high levels of inflammatory eicosanoids derived from arachidonic acid in both patients with unipolar depression and those with bipolar depression\textsuperscript{131}.

**Figure 7: Metabolic pathways for Polyunsaturated Fatty Acids**

<table>
<thead>
<tr>
<th>Omega-6 Series</th>
<th>Metabolic Enzymes</th>
<th>Omega-3 Series</th>
<th>Dietary Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linolenic acid (18:2n-6)</td>
<td>Delta-6-desaturase</td>
<td>Alpha-linolenic acid (18:3n-3)</td>
<td>Flaxseed oil, walnuts, canola</td>
</tr>
<tr>
<td>Gamma-linolenic acid (18:3n-6)</td>
<td></td>
<td>Steridonic acid (18:4n-3)</td>
<td></td>
</tr>
<tr>
<td>Dihomo-gamma-linolenic acid (20:3n-6)</td>
<td>Elongase</td>
<td>Eicosatetraenoic acid (20:4n-3)</td>
<td></td>
</tr>
<tr>
<td>Arachidonic acid (20:4n-6)</td>
<td>Delta-5-desaturase</td>
<td>Eicosapentaenoic acid (EPA) (20:5n-3)</td>
<td>Fish oil</td>
</tr>
<tr>
<td>Adrenic acid (22:4n-6)</td>
<td>Elongase</td>
<td></td>
<td>Retroconversion</td>
</tr>
<tr>
<td>Docosapentaenoic acid (22:5n-6)</td>
<td>Delta-4-desaturase</td>
<td>Docosapentaenoic acid (22:5n-3)</td>
<td>Fish oil, breast milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docosahexaenoic acid (DHA) (22:6n-3)</td>
<td></td>
</tr>
</tbody>
</table>
Possible Mechanisms for Links between Fatty Acid Abnormalities and Mood Disorders

Several neurophysiological mechanisms have been proposed to explain the relationship between omega-3 polyunsaturated fatty acids and depression, such as the one proposed by Mamalakis et al.\textsuperscript{132}. The two omega-3 fatty acids, EPA and DHA, appear to decrease the production of inflammatory eicosanoids from arachidonic acid by means of two mechanisms\textsuperscript{133}. First, they compete with arachidonic acid for incorporation into membrane phospholipids, decreasing both cellular and plasma levels of arachidonic acid. Second, EPA competes with arachidonic acid for the cyclo-oxygenase enzyme system, inhibiting the production of proinflammatory eicosanoids derived from arachidonic acid (e.g., prostaglandins, leukotrienes, and thromboxanes), and prostaglandin E2 and thromboxane B2 have been linked to depression. DHA and EPA also inhibit the release of proinflammatory cytokines, such as interleukin-1 beta, interleukin-2, interleukin-6, interferon-gamma, and tumor necrosis factor alpha, which depend on eicosanoid release and are also associated with depression\textsuperscript{134}. Further, omega-3 fatty acids affect brain-derived neurotrophic factor, which encourages synaptic plasticity, provides neuroprotection, enhances neurotransmission, and has antidepressant effects\textsuperscript{135}.

Another possible mechanism relates to the abundance of DHA in CNS membrane phospholipids, where it plays a vital role in maintaining membrane integrity and fluidity\textsuperscript{136}. By varying lipid concentrations in cell membranes, changes in fluidity can affect either the structure or functioning of proteins embedded in the membrane, including enzymes, receptors, and ion channels, leading to changes in cellular signaling. Support for involvement of omega-3 fatty acids in receptor functioning, neurotransmitter levels, and the metabolism of monoamines implicated in depression has been provided by animal studies\textsuperscript{137,138}.

The hypothesis that omega-3 polyunsaturated fatty acids can affect cell membrane fluidity is supported by a recent study using magnetic resonance imaging\textsuperscript{139}. Twelve women with bipolar disorder received omega-3 fatty acids for 4 weeks and were contrasted with two nontreatment groups. T2 whole-brain relaxation times were used to detect changes in membrane fluidity, measured at baseline and 4 weeks after treatment initiation. The bipolar subjects receiving omega-3 fatty acids had significant decreases in T2 values, with a dose-dependent effect shown by subdividing the treatment group into patients receiving a high dose (10 g/day) and those receiving a low dose (2 g/day). Another postulated, more direct mechanism involves gene expression and the binding of fatty acids to specific nuclear receptors early in life, leading to genetic transcription\textsuperscript{140} and predisposing to a range of diseases with DHA and EPA depletion later in life, such as Alzheimer’s disease, cardiac disease, and depression.
Omega-3 fatty acids and hippocampal neurogenesis\textsuperscript{141}

A growing number of epidemiological studies have suggested an association between mental health and reduced dietary intake of omega-3 fatty acids, essential fatty acids that humans cannot synthesize de novo. Recent clinical trials are supportive of omega-3 fatty acid supplementation in reducing depressive symptoms, although it reduces anxiety symptoms only slightly\textsuperscript{142,143}. Based on the animal research to date, omega-3 fatty acids are the most promising candidate for dietary intervention in the aftermath of a traumatic event to facilitate adult hippocampal neurogenesis. Animal studies have revealed that short-term augmentation of dietary omega-3 fatty acids relative to omega-6 fatty acids up-regulated adult neurogenesis\textsuperscript{144}, and that dietary omega-3 fatty acids elevated levels of brain-derived neurotrophic factor (BDNF) which promotes neuronal survival and growth\textsuperscript{145,146}. Further, docosahexaenoic acid (DHA, 22:6n-3), a 22-carboned omega-3 fatty acid, promoted the development of hippocampal neurons in vitro by increasing neurite extension and branching\textsuperscript{147} as well as the maturation of neurons and hippocampal neurogenesis in adult rats\textsuperscript{148}. Venna and colleagues have shown that the increase in newborn hippocampal cells by polyunsaturated fatty acids occurred in parallel with an increase in hippocampal volume and overexpression of BDNF mRNA and protein in the hippocampus\textsuperscript{149}. BDNF influences the survival of existing neurons and the growth and differentiation of new neurons, and is also implied in the regulation of various neurotransmitter systems\textsuperscript{150,151}. Moreover, BDNF infused directly into the dorsal hippocampus of rats significantly increased the granule cell layer, indicating neurogenesis\textsuperscript{152}. Wu and Gomez-Pinilla have indicated that DHA dietary supplementation enhanced the effects of exercise on cognition and BDNF-related synaptic plasticity\textsuperscript{153}. Evidence has accumulated that omega-3 fatty acids have an influence on hippocampal neurogenesis by increasing BDNF. In addition, Watanabe and colleagues have revealed that brain fatty acid binding protein 7 (Fabp7) which preferentially binds DHA, plays a significant role in neurogenesis, most likely through maintenance of neural stem/progenitor cells\textsuperscript{154}. The possible effects of omega-3 fatty acids on brain structures are also highlighted by clinical observation. A significant correlation was found between omega-3 fatty acid consumption and gray matter volume of the amygdala, hippocampus and anterior cingulate gyrus in healthy adults\textsuperscript{155}. Conversely, a selective deficit of DHA was reported in the postmortem frontal cortex of patients with depressive disorder\textsuperscript{156}. Hippocampal volume appears to be diminished in PTSD in some\textsuperscript{157,158,159,160,161,162,163,164,165,166,167,168,169,170} but not all studies\textsuperscript{171,172,173,174,175,176,177}. The author and colleagues have reported smaller volumes of the amygdala and hippocampus in a cohort of breast cancer survivors experiencing intrusive recollections of traumatic memory, compared to survivors without intrusive recollections\textsuperscript{178,179}. Furthermore, a significant negative correlation has been shown between script-driven enhanced emotional memory about MVA and urgent surgery and hippocampal volume in healthy women\textsuperscript{180}. Two studies have suggested that hippocampal volume might increase following treatment with antidepressants\textsuperscript{181,182}. While the origin of small hippocampal volume is unknown, the result of one twin study suggested that small hippocampal volume
might be a familial risk factor for developing PTSD\textsuperscript{183}. As well, the nutritional environment, including omega-3 fatty acids, may contribute to hippocampal volume.

**Impact of diet on Adult Hippocampal Neurogenesis**\textsuperscript{184}

As much as diet has an impact on cardiovascular health, cancer risks and longevity, it has also an impact on mental health. Research over the last 5 years has now clearly established that our learning and memory abilities, as well as our mood, can be influenced by diet, not only during development, but also during adulthood\textsuperscript{185}. For example, low intake of omega-3 fatty acids is associated with several forms of cognitive decline in the elderly\textsuperscript{186}, whereas a diet rich in it is associated with the prevention of cognitive decline\textsuperscript{187}. Interestingly, rodents with omega-3 fatty acids deficiency showed impaired performance in spatial memory tasks, which could be rectified after dietary replenishment\textsuperscript{188}. Moreover, omega-3 fatty acid concentrations are lower in patients with depression\textsuperscript{189}, and its supplementation has even emerged as a potential treatment for depression\textsuperscript{190,191}. Likewise, the intake of flavonoids is positively correlated with cognitive function\textsuperscript{192} and mood\textsuperscript{193}. Although these studies emphasize an important role of diet on mental health, further work is necessary to determine the mechanisms underlying these behavioural effects. One of the brain structures associated with learning and memory, as well as mood, is the hippocampus. Interestingly, the hippocampus is one of the two structures in the adult brain where the formation of newborn neurons, or neurogenesis, persists. Adult hippocampal neurogenesis (AHN) has been linked directly to cognition and mood\textsuperscript{194}; therefore, modulation of AHN by diet could emerge as a possible mechanism by which nutrition impacts on mental health. In this study, we give an overview of the mechanisms and functional implications of AHN and summarize recent findings regarding its modulation by diet.

**Adult Hippocampal Neurogenesis (AHN) & Mood Regulation**

Recently, it has been proposed that AHN might play a role in mood regulation and in the aetiology of major depression\textsuperscript{195,196}. This idea arises from two lines of evidence. The first is that AHN is reduced by stressful experiences, a causal factor in the pathogenesis of major depression. Moreover, AHN is reduced in animal models of depression\textsuperscript{197}. The second line of evidence indicates that many treatments for depression have been shown to enhance neurogenesis in laboratory animals; these factors include electroconvulsive therapy (ECT)\textsuperscript{198} and common antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs)\textsuperscript{199}. The long time scale for recovery when humans are treated pharmacologically for depression (several weeks) parallels the long time scale of stimulated neurogenesis that is induced by ECT and SSRIs in nondepressed animals\textsuperscript{200,201}. Moreover, the effects of SSRIs on neurogenesis are selective for the hippocampus, leaving the ongoing stem cell proliferation in the SVZ unchanged\textsuperscript{202}. Finally, in several animal models of depression, disruption of neurogenesis blocks the behavioural efficacy of SSRIs\textsuperscript{203}. One of the mechanisms
Conceptual study

thought to mediate reduction of AHN by stress is the elevation of corticosterone by an activated hypothalamic–pituitary–adrenal axis. Indeed, corticosterone decreases cell proliferation, whereas adrenalectomy increases AHN. Moreover, glucocorticoid levels are increased in a variety of stress paradigms and adrenalectomy prevents the stress-induced suppression of AHN\(^\text{204}\). One of the molecular candidates for mediating both neurogenic and behavioural effects of antidepressant is BDNF. Indeed, the levels of BDNF expression and AHN are co-regulated by both stress and antidepressants\(^\text{205}\). Moreover, infusion of BDNF into the dentate gyrus mimics the effect of antidepressants, but antidepressants fail to increase AHN with compromised BDNF-TrkB signalling, suggesting that this pathway is required for neurogenesis induced by antidepressants\(^\text{206}\).

Adult hippocampal neurogenesis in CNS pathologies AHN responds to neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases. Conflicting observations have been reported on the level of AHN in Alzheimer’s disease mouse models, but the majority reports a decrease\(^\text{207}\). Mouse models of Parkinson’s disease over-expressing the wild-type human a-synuclein show a decrease in the survival rate of newborn hippocampal neurons\(^\text{208}\). AHN is also influenced by many other pathological conditions. For example, it is increased in epilepsy\(^\text{209}\) and stroke\(^\text{210}\), whereas it is decreased in HIV infection\(^\text{211}\), and the integration of newborn neurons is disrupted by CNS inflammation\(^\text{212}\). It is apparent that AHN is influenced by neurological diseases; however, further studies are needed to understand the roles and consequences of AHN changes in pathological events. Dietary modulation of adult hippocampal neurogenesis Diet is another important environmental factor that can influence AHN.

Diet can impact on AHN from four different levels: calorie intake, meal frequency, meal texture and meal content. Not only do these four parameters modulate AHN in rodents, but independent rodent studies and intervention or epidemiological studies in human have shown that they also modulate cognitive performance and mood.

1. Calorie restriction can extend lifespan, improve behavioural outcomes in some experimental animal models of neurodegenerative disorders and enhance spatial learning\(^\text{213}\). It was shown more recently that a reduction in calorie intake of 30–40% increases AHN in rodents, and that this effect is partly mediated by BDNF\(^\text{214,215}\).

2. It is also found that independent of calorie intake, meal frequency is a key player in modulating AHN. Indeed, without reducing calorie intake, extending the time between meals increases AHN. It also changes hippocampal gene expression and correlates with performance in hippocampus-dependent tasks and mood (S. Thuret, unpublished data). However, further studies are ongoing to understand the mechanisms by which calorie restriction and meal frequency modulate AHN and mental health.
Figure 8:
Overview of physiological and environmental modulation of adult hippocampal neurogenesis and its impact on learning and memory abilities and mood.

The dotted square contains the enlarged hippocampus.

The red dots symbolize newborn neurons in the dentate gyrus (DG).

Figure 9:
Overview of the impact of diet on adult hippocampal neurogenesis.
The red dots symbolize newborn neurons in the dentate gyrus of the hippocampus.
3. Interestingly, food texture also has an impact on AHN; rats fed with a soft diet, as opposed to a solid/hard diet, exhibit decreased hippocampal progenitor cell proliferation. The authors hypothesize that chewing resulting in cell proliferation is related to corticosterone levels\textsuperscript{216}. Interestingly, independent studies have shown impairment in learning and memory abilities with similar soft diets\textsuperscript{217, 218}. If chewing plays a role in AHN, these data could be particularly relevant to the ageing population with cognitive decline where dental weakening might limit the chewing ability.

4. Meal content offers the most flexibility to regulate AHN, as a variety of bioactives/nutrients have been identified as potential modulators. For example flavonoids, which are enriched in foods such as cocoa and blueberries, have been shown to increase AHN in chronically stressed rats\textsuperscript{219}, and the authors hypothesized that this effect might be mediated by BDNF. Moreover, independent studies have shown that treatment with flavonoids improves symptoms of depression\textsuperscript{220} and improves spatial working memory in ageing rats\textsuperscript{221}. Interestingly Williams et al. have also identified BDNF as a potential mediator of the effect of flavonoids on cognition\textsuperscript{222}. Deficiency in zinc inhibits AHN\textsuperscript{223} and induces depression in rodents\textsuperscript{224}, whereas independent intervention studies have shown the efficacy of zinc supplements in improving symptoms of depression\textsuperscript{225}. Corniola et al. hypothesized that zinc plays a role in AHN by regulating p53-dependent molecular mechanisms that control neuronal precursor cell proliferation and survival\textsuperscript{226}. Some bioactives act in a dose-dependent manner on AHN. Some can induce AHN at low doses or at a very precise physiological dosage and inhibit AHN at high doses. For example, excess retinoic acid decreases AHN and leads to depressive behaviour and impaired spatial learning in rodents\textsuperscript{227,228}. A deficiency in retinoic acid will lead to similar effects on AHN and mental health, but its effects are reversed by re-establishing a normal level\textsuperscript{229}. Caffeine is another dose-dependent bioactive. Indeed, consumed at low doses chronically, Han et al. have shown that it decreases AHN and performance in hippocampus-dependent learning tasks in rodents. Interestingly, at supraphysiological doses, there is an increase in proliferation of neuronal precursors\textsuperscript{230}. However, neurons induced in response to supra-physiological levels of caffeine have a lower survival rate than control cells and increased proliferation does not yield an increase in AHN\textsuperscript{231}. Curcumin is a natural phenolic component of yellow curry spice that increases AHN in rodents\textsuperscript{232} and epidemiological studies have reported better cognitive performance from curry consumption in ageing populations\textsuperscript{233}. Moreover, in vitro studies have shown that curcumin exerted biphasic effects on progenitor cells; low concentrations stimulated cell proliferation, whereas high concentrations were cytotoxic. Curcumin activates extracellular signal-regulated kinases (ERKs) and p38 kinases, cellular signal transduction pathways known to be involved in the regulation of neuronal plasticity and stress responses\textsuperscript{234}. 
Finally, it is important to note that independent of calorie intake, diets with high-fat content are detrimental and impair AHN in male rats. The authors hypothesize that high dietary fat intake disrupts AHN through an increase in serum corticosterone levels, and that males are more susceptible than females\(^{235}\).

BDNF and corticosterone levels appear to be common protagonists of dietary modulated AHN; however, they are unlikely to be the only mediators. For example, further studies will need to be done to investigate if dietary factors modulate AHN by modifying the neurogenic niche. The vasculature\(^ {236}\) and astrocytes\(^ {237}\) are important constituents of the neurogenic niche and interestingly flavanol-rich foods can positively enhance cortical blood flow\(^ {238,239}\) and are regulators of astrocytic signalling pathways and gene expression\(^ {240}\). Such changes in the neurogenic niche in response to flavanoids might underpin neuro-cognitive improvements through the concurrent promotion of adult hippocampal neurogenesis. Forthcoming studies will not only need to refine the molecular mechanisms by which food intake influences AHN, but also consider the role of epigenetic mechanisms. Indeed, there is increasing evidence that epigenetic mechanisms underlie both AHN\(^ {241}\) and changes in gene expression in response to diet\(^ {242}\). Future research will need to investigate if diet can modulate AHN through epigenetic changes.

Table 1: modulation of Adult Hippocampal Neurogenesis (AHN) by diet\(^ {243}\)

<table>
<thead>
<tr>
<th>Diet</th>
<th>Study model</th>
<th>Effect on AHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloric/dietary restriction</td>
<td>Rat</td>
<td>Increased survival(^ {244})</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Increased survival(^ {245,246,247,248})</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>Rat</td>
<td>Increased DHA(^ {249})</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Rat, chronically stressed</td>
<td>Increases proliferation(^ {250})</td>
</tr>
<tr>
<td>Blueberry</td>
<td>Rat, chronically stressed</td>
<td>Increases proliferation(^ {251})</td>
</tr>
<tr>
<td>Curcumin low concentration</td>
<td>Mouse</td>
<td>Increases proliferation(^ {252})</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>Rat</td>
<td>Decreased proliferation(^ {253})</td>
</tr>
<tr>
<td>Thiamine deficiency</td>
<td>Mouse</td>
<td>Decreased proliferation(^ {254})</td>
</tr>
<tr>
<td>Zinc deficiency</td>
<td>Rat male</td>
<td>Decreased proliferation(^ {255})</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>Mouse</td>
<td>Decreased proliferation(^ {256})</td>
</tr>
<tr>
<td>High fat</td>
<td>Male rate</td>
<td>Decreased proliferation(^ {257})</td>
</tr>
<tr>
<td></td>
<td>Female rat</td>
<td>No change</td>
</tr>
<tr>
<td>Soft diet</td>
<td>Rat</td>
<td>Decreased proliferation(^ {258})</td>
</tr>
<tr>
<td>Caffeine At physiologically relevant doses</td>
<td>Mouse</td>
<td>Decreased proliferation(^ {259})</td>
</tr>
<tr>
<td>At supraphysiological doses</td>
<td>Mouse</td>
<td>Increased proliferation / decreased survival(^ {260})</td>
</tr>
<tr>
<td>Low dose chronically</td>
<td>Rat</td>
<td>Decreased proliferation(^ {261})</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Rat</td>
<td>Decreased proliferation(^ {262,263})</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>Decreased proliferation(^ {264})</td>
</tr>
</tbody>
</table>
Table 2: modulation of learning and memory and depressive behavior by diet

<table>
<thead>
<tr>
<th>Diet</th>
<th>Effect on learning</th>
<th>Effect on depressive behavior</th>
<th>Study model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloric/dietary restriction</td>
<td>Enhanced spatial learning in aged rats(^{266})</td>
<td></td>
<td>Rat</td>
</tr>
<tr>
<td></td>
<td>Enhanced cognitive performance in females only(^{267})</td>
<td></td>
<td>Rat</td>
</tr>
<tr>
<td></td>
<td>Increased learning and motor performance(^{268})</td>
<td></td>
<td>Mouse</td>
</tr>
<tr>
<td></td>
<td>Increased learning consolidation(^{269})</td>
<td></td>
<td>Mouse</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>Improved EPA(^{270})</td>
<td>Delayed onset of depressive periods(^{271})</td>
<td>Human (bipolar)</td>
</tr>
<tr>
<td></td>
<td>Decreased(^{272})</td>
<td>No benefit 6g/day EPA(^{273})</td>
<td>Human (bipolar)</td>
</tr>
<tr>
<td></td>
<td>Improvement with 1g/day EPA(^{274})</td>
<td>Various effects with various concentrations of various fatty acids(^{275})</td>
<td>Human</td>
</tr>
<tr>
<td></td>
<td>Improved spatial memory(^{276})</td>
<td>Improved acquisition and retention in a T-maze foot shock avoidance test(^{277})</td>
<td>Mouse (Alzheimer model)</td>
</tr>
<tr>
<td></td>
<td>Improved(^{278})</td>
<td>Improved(^{279})</td>
<td>Rat</td>
</tr>
<tr>
<td>Flavonoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blueberry</td>
<td>Increased spatial memory(^{300})</td>
<td>Improved(^{280})</td>
<td>Rodents</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Improved cognitive performance(^{281})</td>
<td>Improved(^{282})</td>
<td>Human</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>Impaired spatial learning and memory(^{282})</td>
<td>Impaired relation memory(^{283})</td>
<td>Mouse adult</td>
</tr>
<tr>
<td>Zinc</td>
<td>Impaired(^{284})</td>
<td>Impaired(^{285})</td>
<td>Human</td>
</tr>
<tr>
<td></td>
<td>Impaired(^{286})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High fat</td>
<td>Decreased spatial learning(^{287})</td>
<td>Decreased learning memory and increased risk for dementia(^{288})</td>
<td>Rat</td>
</tr>
<tr>
<td>High sugar</td>
<td>Impaired spatial learning(^{289})</td>
<td></td>
<td>Rat</td>
</tr>
<tr>
<td>Low glucose (extracellular)</td>
<td>Impaired memory(^{290})</td>
<td></td>
<td>Rat aged</td>
</tr>
<tr>
<td>Soft diet</td>
<td>Impairment of learning ability and memory(^{291})</td>
<td></td>
<td>Rat Alzheimer model</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Improved object recognition(^{292})</td>
<td></td>
<td>Rat (Alzheimer model)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Improved associative learning with moderate chronic consumption(^{294})</td>
<td>Reduced risk(^{293})</td>
<td>Human</td>
</tr>
<tr>
<td></td>
<td>Deficit(^{295})</td>
<td></td>
<td>Mouse male</td>
</tr>
</tbody>
</table>
It is now getting clearer that AHN affects cognition and mood. It is also firmly established that nutrition has an impact on cognition and mood. Therefore, AHN is emerging as a possible mediator of the effect of certain food on cognition and mood. Consequently, modulating AHN by diet could be a target of choice to prevent cognitive decline during ageing, as well as to counteract the effect of stress and prevent depression.

TYPES OF DEPRESSION

Depressive disorders come in different forms. Three more common presentations of clinical depression are major depressive disorder, dysthymic disorder, and bipolar disorder.

1) Major depressive disorder:

This is characterized by a combination of symptoms that interfere with the person’s ability to work, sleep, eat, and enjoy once pleasurable activities. Disabling episodes may occur one or more times over a person’s lifetime.

2) Dysthymia:

It is a chronic, depressive set of symptoms that are not disabling but that prevent the person from feeling good and functioning well. People with dysthymia may also experience major depressive episodes.

3) Bipolar disorder:

This is characterized by cycles of depression and elation, or mania. Mood changes can be dramatic and rapid but are more often gradual. It is often a chronic condition.

Other forms of depressive episodes include Seasonal Affective Disorder, Postpartum Depression, adjustment disorders, and atypical depression.

- **Seasonal Affective Disorder (SAD):** It is a pattern of depressive illness in which symptoms recur every winter. This form of depressive illness often is accompanied by such symptoms as marked decrease in energy, increased need for sleep, and carbohydrate craving.

- **Postpartum depression:** It can be extremely serious for both a mother and the child of the mother. Mild moodiness and sadness are very common after having a baby, but when symptoms are more than mild or last more than a few days, help should be sought.

- **Adjustment disorder with depressed mood:** This is a type of depression that results when something negative happens to a person that depresses him or her. It generally fades as time passes and the person gets over whatever caused the distress.

- **Atypical depression:** A person experiencing depression with atypical features generally has an increased appetite and sleeps more than usual. A person with atypical depression may be able to enjoy pleasurable circumstances despite being unable to seek out such circumstances. This is in contrast to “typical” depression in which decreased appetite, insomnia, and anhedonia (an absence of pleasure in
anything) generally occur. Despite its name, atypical depression may be more common than other
types of depression.

On the basis of aetiological factors, Depression can again be classified in two categories as:

1) Autogenous:
   In which the intrinsic factors like biological, endocrinal mechanisms are main causes.

2) Reactive:
   This occurs due to extrinsic factors like stress, broken relationships, and emotional disturbances.

MANAGEMENT OF DEPRESSION:

1) Medication:
   Drugs like Selective Serotonin Reuptake Inhibitors (SSRIs) and Mono Amino Oxidase (MAO)
   Inhibitors are prescribed to maintain the levels of Serotonin and Norepinephrine at the synapses.

2) Psychotherapy:
   Cognitive Behavior Therapy (CBT) including Behavior Therapy, Group Therapy, Family
   Therapy, etc. are used to improve behavior, relationships and reduce stress.

3) Somatic therapies
   It is widely used particularly in cases of psychotic depression, suicidal tendencies  to have
   immediate effect.
   Electro Convulsive Therapy (ECT)
   Repetitive transcranial magnetic stimulation (rTMS)
   Vagus nerve stimulation (VNS)
   Transcranial direct current stimulation (tDCS)
   Light therapy
   Sleep deprivation therapy
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