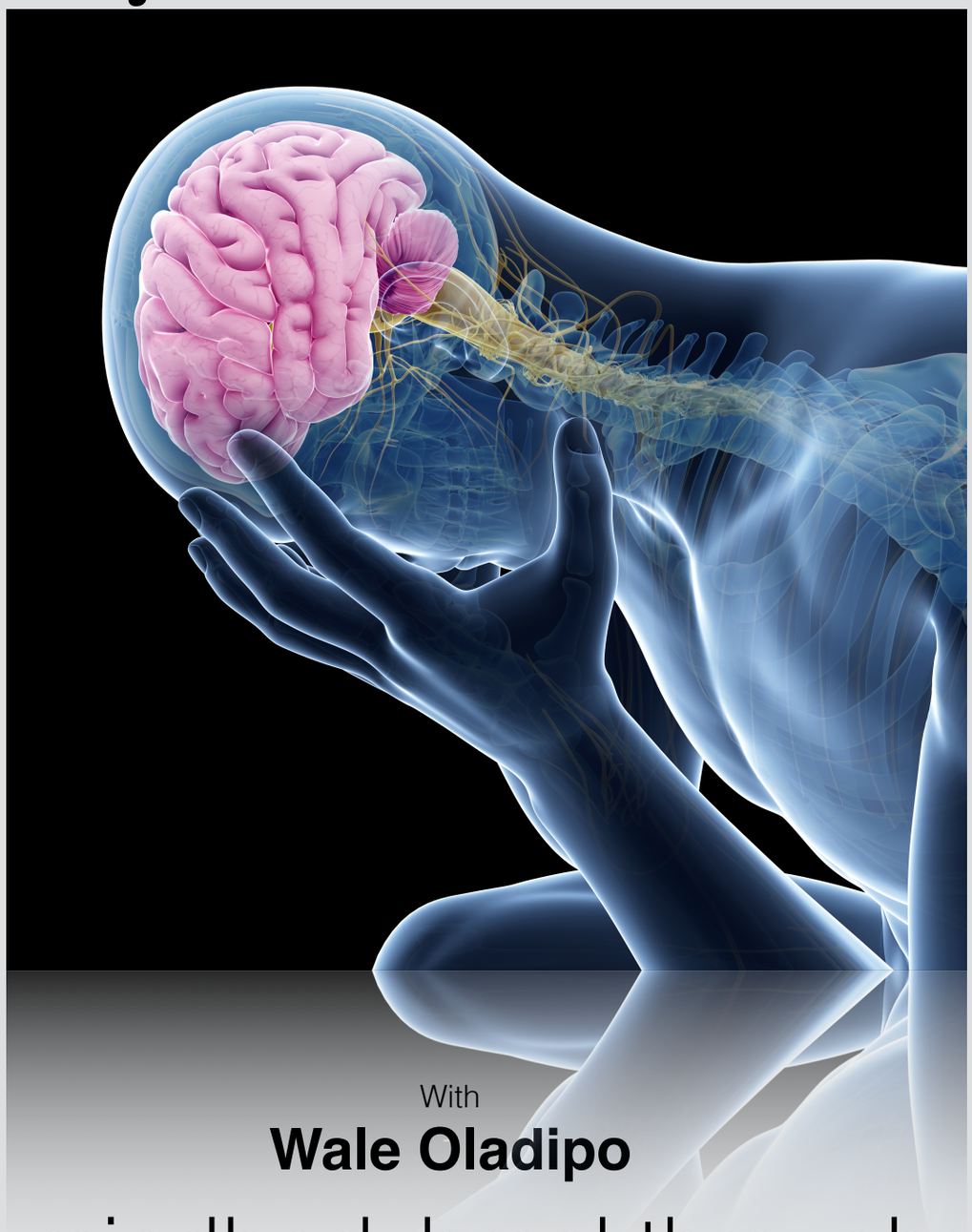
MindBody Breakthrough
Restoring Control, Inspiring Success

Basic Neuroscience Of Major Depressive Disorder (MDD)



With

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Course Outline

- Basic Understanding

- Neurotransmitters & Brain Regions Implicated in MDD

Session 1

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What Is Depression?

Depression, otherwise known as major depressive disorder (MDD) or clinical depression, is a neuro-biochemical condition that has been found to affect key neurotransmitters and regions of the brain involved in emotions, cognition, pleasure and motivation.

Depression DSM-5 Diagnostic Criteria

The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either **depressed mood** or **loss of interest or pleasure**.

Depression DSM-5 Diagnostic Criteria

1. Depressed mood most of the day, nearly every day

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.

4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down)

5. Fatigue or loss of energy nearly every day.

6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.

7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.

8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Other MDD Symptoms:

Adults:

- Feelings of profound sadness, tearfulness, emptiness or hopelessness
- Angry outbursts, irritability or frustration, even over small matters
- Sleep disturbances, including insomnia or sleeping too much
- Anxiety, agitation or restlessness
- Fixating on past failures or self-blame
- Trouble making decisions and remembering things
- Unexplained somatic problems, such as back pain, digestive issues or headaches
- Often wanting to stay at home, rather than going out to socialise or doing new things
- Psycho-motor retardation

Teens:

- Irritability, feeling negative and worthless, anger, poor performance, poor attendance at school, feeling misunderstood and extremely sensitive, using recreational drugs or alcohol, eating or sleeping too much, self-harm, loss of interest in normal activities, and avoidance of social interaction.

Younger Children:

- Sadness, irritability, clinginess, worry, aches and pains, being underweight, or refusing to go to school.

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Causes of Depression

Evidence suggests that depression is often caused by the epigenetic interplay between genes and environment (Mullins, N. et al. 2016);

Environmental factors may include:

- Childhood trauma (such as maternal deprivation, insecure attachment, abuse (emotional, psychological, physical or sexual, etc))
- Prenatal or post-natal trauma
- Chronic stress exposure (such as, work-related bulling, loneliness, etc.)

- Multiple traumatic events in adolescent-hood or adulthood

Epigenetic factors may include:

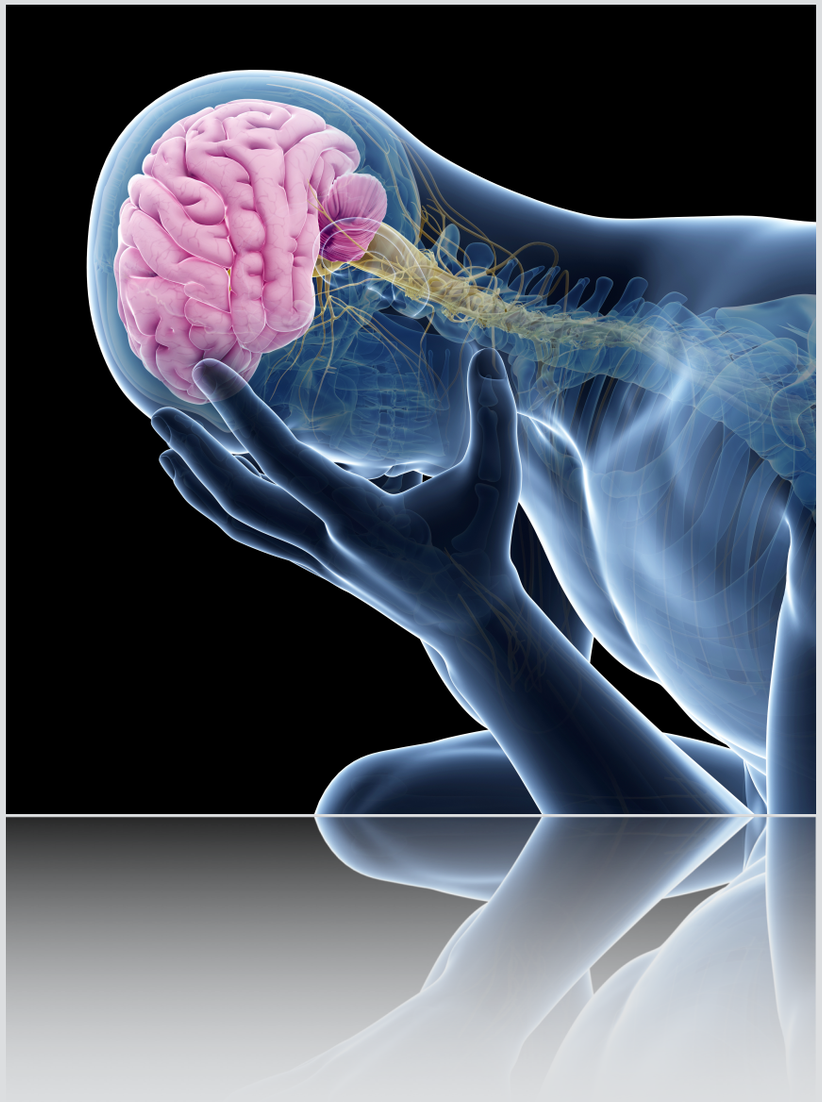
Variations in the gene coding for the serotonin transporter, 5-HTT (Caspi A et al., 2003)

The proportion of total variance in a trait due to genetic variation (the heritability) for MDD has been estimated from twin studies at 37%. (Sullivan, P.F. et al., 2000)

This suggests that while genetic factors play a significant role, MDD cannot be considered a genetic disorder, as two-thirds of the factors involved are not explained by genetic variability. (Kennedy, S.H. & Gorwood, P., 2012)

Session 2

The Biochemistry Of Depression



Neurotransmitters Implicated in Depression

Neurotransmitters are chemical messengers that transmit signals across a synapse from one neurone to another. MDD is linked to the dysregulation of the three major neurotransmitters. Too little or too much of these neurotransmitters or their receptors have been implicated in MDD. (Kandel. E et al., 1991; Blier, P., 2013)

- Serotonin (happiness, feel good chemical)

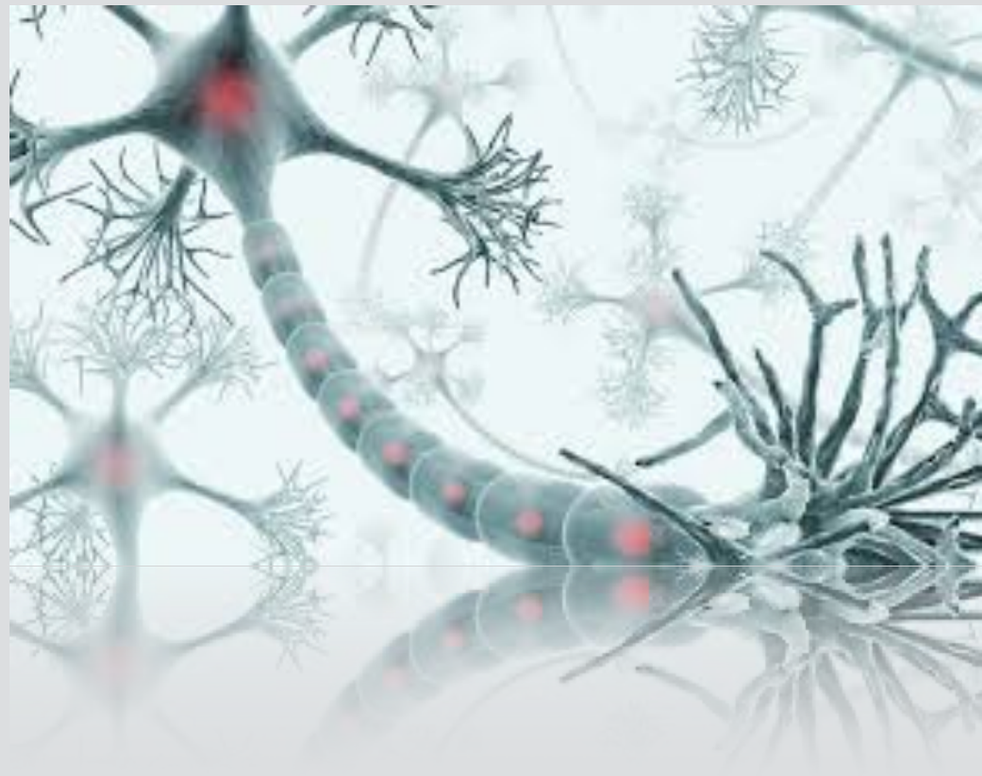
Uncontrollable obsession to sadness, gloom and despair

- Dopamine (motivation, rewards, pleasure)

Dysfunction of the pleasure pathway (anhedonia)

- Norepinephrine (Noradrenaline) (stress response)

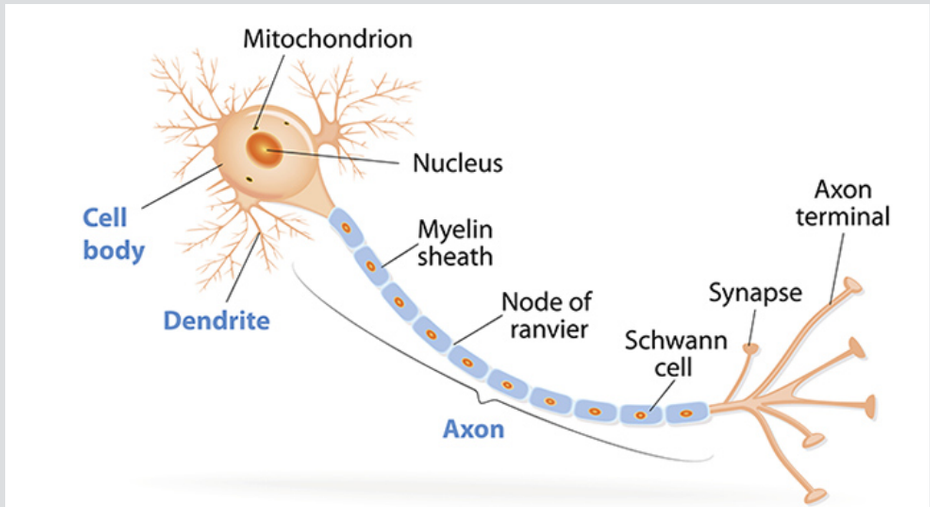
Psychomotor retardation (slowing down of mind and body movement)

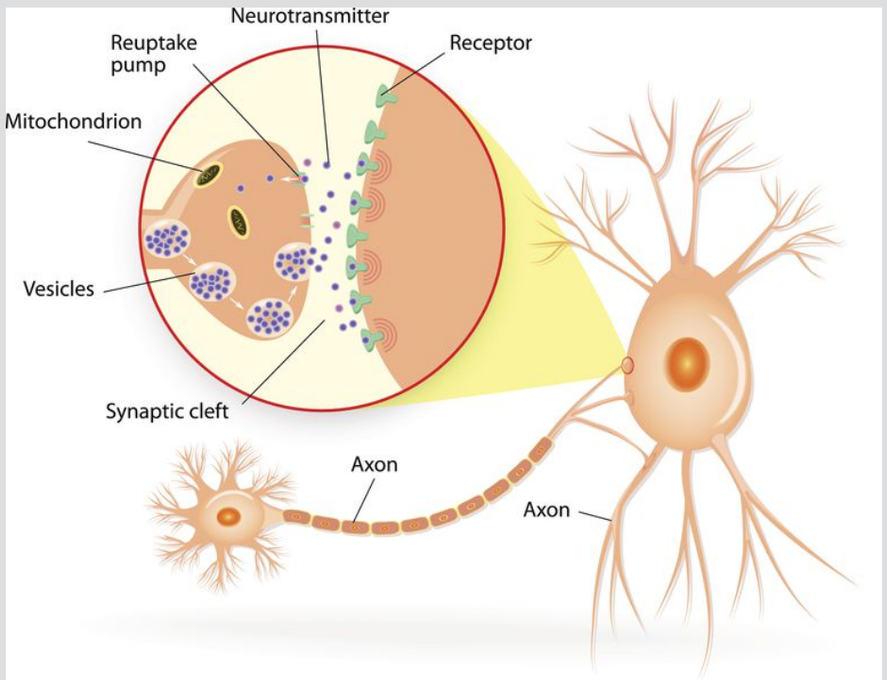


Serotonin & Major Depression

Much of the modern depression research has focussed on the role of serotonin in the onset of MDD. (Albert, P.R. & Benkelfat, C., 2013)

- The serotonin hypothesis of depression suggests that a reduction in neurotransmitter serotonin leads to increased predisposition to depression.
- Once serotonin is released in the pre-synaptic axon terminal and binds to post-synaptic dendrites receptors, it is then taken back up by pre-synaptic receptors (auto-receptors) and repackaged for future use. Or it can be degraded in the synapses and the debris flushed out through the CSF-blood-urine pathways (This is carried out by MAOA transporters).
- Over the years, scientific papers have offered more confusion than clarity as whether depression is caused by too much serotonin or too little. The best evidence suggests that most antidepressant medications works not just on serotonin but also on dopamine and norepinephrine (including SSRIs, tricyclics and MAO inhibitors, St John's Wort), adding to the overall confusion.

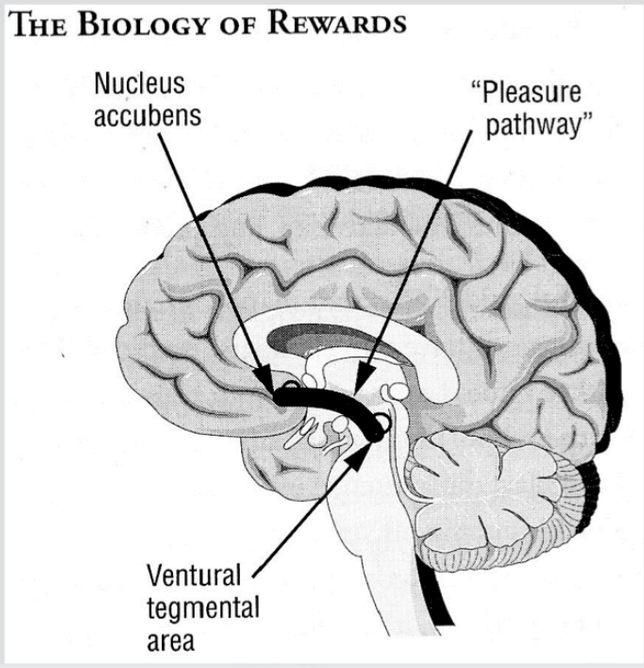




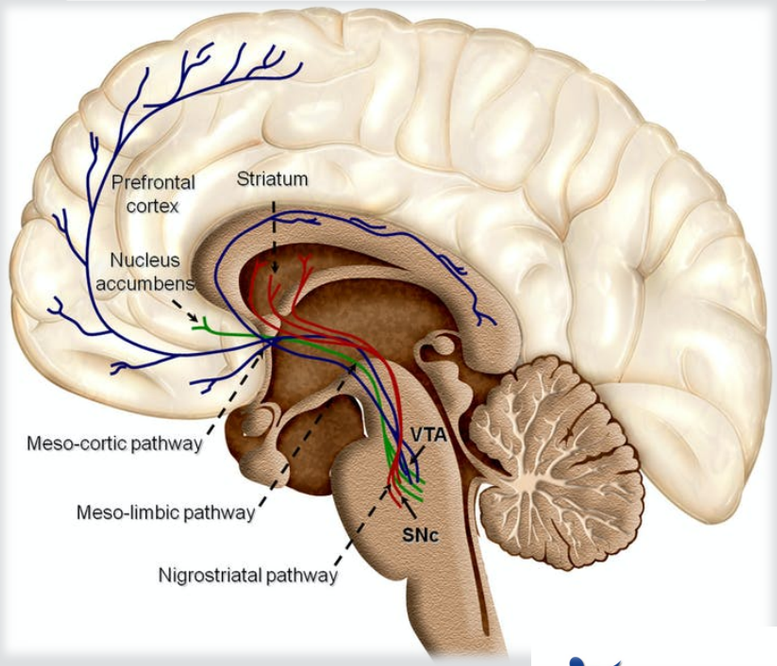
Dopamine & Major Depression

- Dopamine is known as the neurotransmitter involved in pleasure signalling in the pleasure pathway (mesolimbic pathway) in the brain. Dreyer. J.L. (2010). Anhedonia (inability to feel pleasure) is considered a core feature of major depressive disorder, and the dopamine system plays a pivotal role in the hedonic deficits in a depressed brain.

- A hypothesis implicating dopamine in depression was first proposed in the 1970s (Randrup et al. 1975). Further results from studies in depression, Parkinson's disease, and animal models of depression suggest a deficiency of dopamine in major depressive disorder. (Kapur S. & Mann J.J., 1991)



- The pleasure pathway is made up of various specific brain regions, like the ventral tegmental area (VTA), which spreads neuronal connections to other areas involved in the process; nucleus accumbens, the striatum, the anterior cingulate cortex, the hippocampus, the amygdala, and the cerebral cortex.



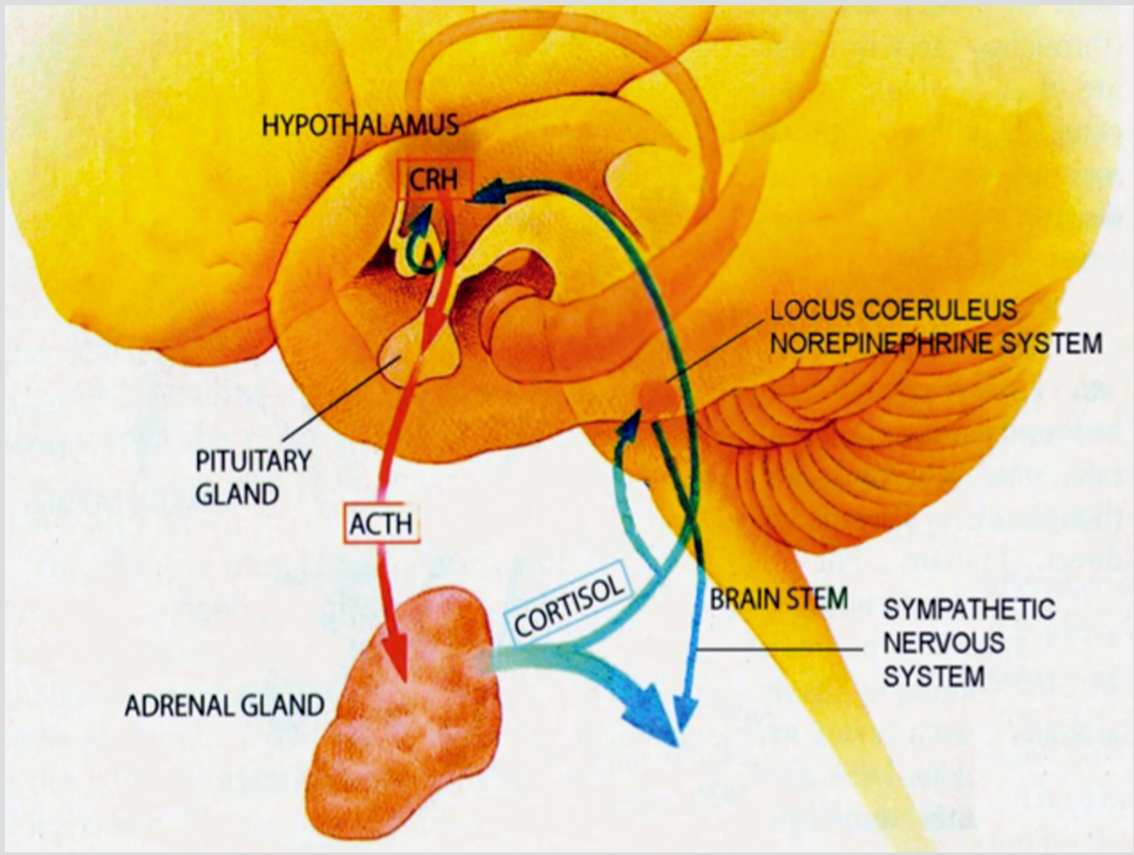
- In the learned-helplessness model (LH) of depression, the dysregulation of the dopamine system has been implicated in the inability of individuals with depression to engage positive behavioural/avoidance responses necessary to escape avoidable stressors. (Kram et al., 2002)

Norepinephrine & Major Depression

- Norepinephrine (LC) is the primary neurotransmitter for the sympathetic nervous system (e.g. alertness, arousal and energy mobilisation). It is a critical modulator of neural circuits involved in learning and memory, mood, sleep, appetite, and neuroendocrine function. (Hagena, H. et al. 2016)

- Norepinephrine is synthesised in the locus coeruleus. The neurones in the locus coeruleus projects diffusely throughout the brain, increasing their baseline levels of activation. (Hansen, N. 2017)

- In MDD, studies have supported a defect in the norepinephrine regulation, explaining the psychomotor retardation symptoms commonly found in major depression (Xiaojun, S. & Gang Z., 2020)

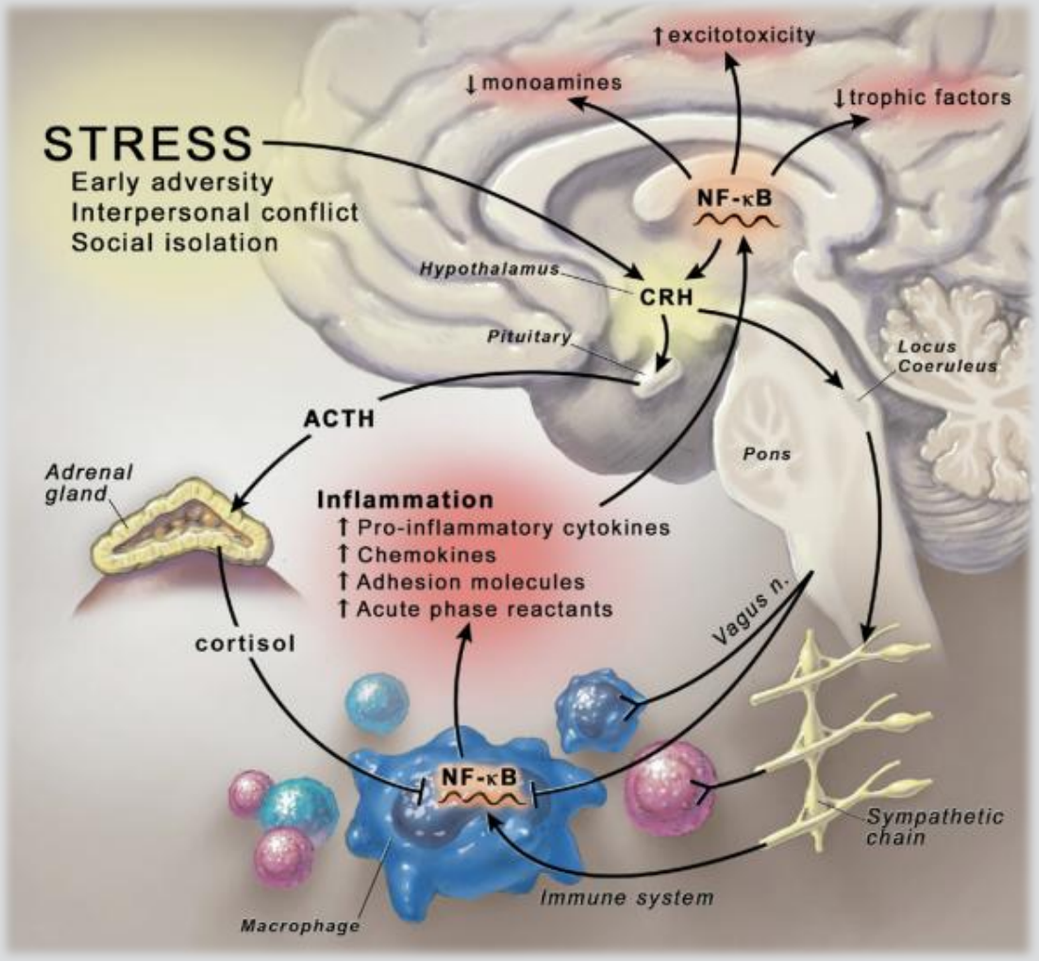


Stress, Inflammation & Depression

- Psychosocial stress (e.g. trauma or chronic stress exposure) activates the inflammatory response both in the central and peripheral nervous system. For example, healthy volunteers exposed to stressors such as public speaking and mental arithmetic stressor were found to exhibit significant increases in cytokines (such as NF-κB and Interleukin-6 (IL-6), C-reactive protein (CRP)) (Bierhaus, A., et al., 2003)

- Cytokines (inflammation) stimulate the activation of sympathetic nervous system (fight/flight response) and the HPA axis, leading to the release of CRH, ACTH and cortisol. (Pace, T.W. et al., 2006)

- Childhood maltreatments predict adult inflammation. Increased inflammation is found to be a hall-mark of early life stress; in that childhood trauma has been associated with increased CRH levels in the blood. (Danese, A. et al., 2007)
- The parasympathetic nervous system (PNS), our rest and digest response, plays a significant role in controlling inflammation. For example, studies have shown that stimulation of efferent vagus nerve fibres inhibit cytokine pro-inflammatory responses. (Pavlov, V.A. et al., 2005)



NF-κB, nuclear factor kappa B (inflammation signalling molecule)

Q&A Session

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"There are no constraints on the human mind, no walls around the human spirit, no barriers to our progress except those we ourselves erect."

—Ronald Reagan, 40th U.S President