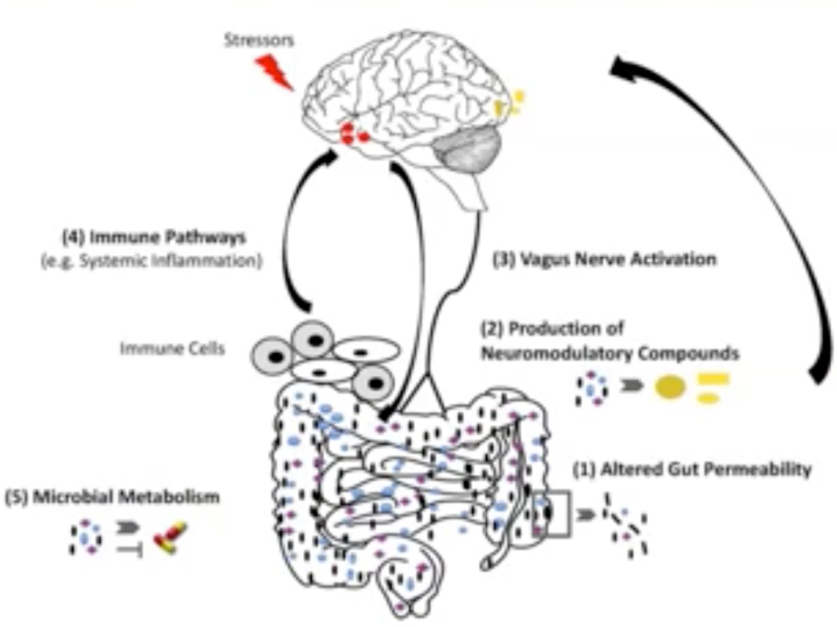
Week 1b – Stress & the Brain:

Gut-brain interactions:

→ **Peripheral serotonin:** cells in the gut produce large quantities of serotonin, which may have a signalling effect on the brain.
→ **Immune system:** an intestinal microbiome can prompt immune cells to produce cytokines that can influence neurophysiology.
→ **Bacterial molecules:** microbes produce metabolites such as butyrate, which can alter the activity of cells in the blood-brain barrier.
→ The '**microbiome'** technically refers to the combined *genetic* material of the microbiota.
→ The **'microbiota'** refers to the trillions of *bacteria* and other *microorganisms* that live in the gut.
→ The adult microbiome contains > 100x more genes than the human genome.
→ It now appears the microbiota impacts the brain, behaviour & cognitive function. For example, shy mice become more adventurous after receiving a gut microbiota transplant from social/active mice.
→ The gut microbiota modulates development and homeostasis of the CNS through immune, circulatory and neural pathways. The CNS impacts the gut via neural and endocrine response.



→ **Risk factors for gut microbiota dysbiosis include:**
- Genetics – HLA DR15*1501
- Low levels of sunlight exposure/low vitamin D
- EBV+/mononucleosis
- Tobacco smoke
- Obesity
- Shift work

→ **This is a bi-directional, reciprocal, integrated system.** Microbiota dysbiosis can lead to disease developing, but also the development of disease can lead to more dysbiosis.

→ **Activation of the immune** system occurs due to the illness triggering gut dysbiosis, which leads to systemic inflammation which triggers the immune system, which in turn leads to cytokines infiltrating into the brain. This triggers a series of temporary behavioural, cognitive, and emotional changes aimed at conserving the body's function (including fever, sleep, depressed mood, hyperalgesia (increased pain sensation), loss of interest in usual activities, anorexia (reduced appetite), decreased social interaction, impaired concentration).

Sickness behaviour:

→ **Sickness behaviour** is believed to be triggered by cytokines released by the body in response to infection, and travel to the brain.

→ **Cytokines** are a group of small proteins important in cell signalling. They are released by cells, and influence the behaviour of other cells.

→ Cytokines are too big to pass through the blood-brain barrier, so are believed to enter the brain indirectly or trigger new cytokines to be released within the brain.

→ In experiments volunteers were injected/infected with the common cold, and showed impaired performance on visual detection, hand-eye coordination & general cognitive tasks.

→ People with more severe illness had negative mood, fatigue, memory and attentional deficits. More accidents are found to occur at work when employees are sick.

→ Sickness behaviour is thought to be an organized strategy evolved to conserve energy and improve the fight against infection. Some have suggested that *excessive* sickness behaviour (and cytokine release) may lead to neuropsychiatric syndromes such as fatigues syndromes and major depression. The theory is based mainly on overlapping syndromes and is still speculative.

→ Cytokine release can also trigger the 'stress response', and stress can be linked to changes in immune function.

→ Research suggests that kissing may allow the transfer of hormones such as testosterone (to increase arousal) and oxytocin, whilst others suggest it is a show of trust and close bond (and may be territorial in nature).

Stress:

→ Is a response to a *perceived* aversive or threatening situation.

→ Associated with feelings of being overloaded, wound-up, tight, tense and worried.

→ Stress can be positive – exciting, motivating, improving alertness & performance. But stress can also be harmful for health & function.

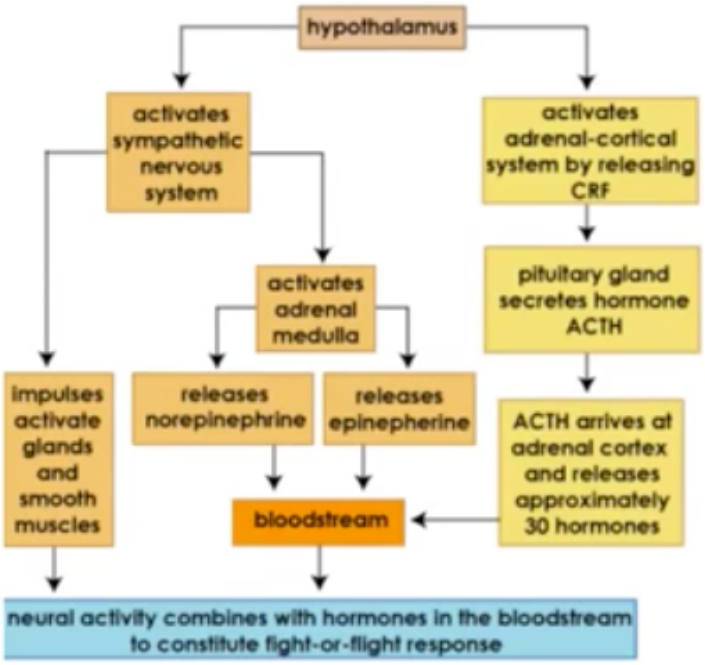
→ A critical component of a stress experience is the real or perceived lack of control over the stressor.

→ Thrill seekers are often attracted to 'calculate risks' with some, but *not* total control of the risk. 'Threat' of bad events without control is enough. Complete lack of control is generally experienced very negatively.

→ **Acute stress:** represents a *single* event that leads to increased 'flight or fight' response raising levels of arousal.
→ **Episodic acute stress:** *repeated* (but *independent*) acute stress (e.g. life chaos, excessive worry about normal events).
→ **Chronic stress:** seemingly endless & uncontrollable stress (e.g. violent or dysfunctional family, living in a warzone, repeated exposure to trauma, severe financial hardship).

Acute stress:

→ There are two main stress systems in the acute stress response, both mediated by the hypothalamus.
→ The hypothalamus activates the HPA system (cortisol) and sympathetic nervous system (noradrenaline/adrenaline).



→ Fight or flight response begins with rapid detection of threat in the amygdala, which activates the hypothalamus (HPA axis pathway) which in turns activates the pituitary gland via the release of corticotrophin-releasing hormone (CRH). This activates the adrenal cortex (adrenal gland), which then releases cortisol and adrenaline (which increase HR, blow flow, metabolism). The hypothalamus also activates the sympathetic NS (sympathetico-adrenal-medullary pathway), which activates the adrenal medulla which releases adrenaline & noradrenaline (and also activates glands and smooth muscles).
→ Optimal performance requires a balance between stress. Function is impaired with too little or too much stress (inverted U).
  - Moderate levels of stress lead to aroused & optimal functioning of the prefrontal cortex (PFC). This allows for cognitive flexibility, responsive attention, good decision making, and a top-down regulation of thoughts,

actions and emotional responses. With mild levels of stress, the PFC inhibits the amygdala.
    - High stress increases arousal further, overwhelming/impairing the function of the prefrontal cortex & releasing/increasing the influence of emotional responses, habitual action & bodies arousal response. With extreme stress, the PFC is inhibited and the amygdala dominates.

→ Acute uncontrollable stress can weaken the PFC mediated inhibitory control, leading to increased substance abuse (*Sinha & Li*).

→ Acute stress can increase amygdala response to increase memory consolidation of stressful events (*Cahill & McGaugh, Roozendaal*).

→ Acute stress can enhance the fear conditioning function of the amygdala (Rodriguez).

Chronic stress:

→ Chronic stress is associated with the following long-term changes within the brain:
    - Amygdala (important in mood): increase in the number and strength of neural connections. Increased amygdala behavioural function, activity, aggression & emotional memory.
    - Hippocampus (important for memory & storage): reduced number & strength of neural connections (more cell death & less neurogenesis). Reduced hippocampal volume, activity & behavioural function. Reduced episodic & declarative memory.
    - Prefrontal cortex (important in executive function): reduced number & strength of neural connections. Reduced PFC behavioural function, reduced PFC volume & reduced PFC activity. Reductions in working memory & fear extinction.

→ Exposure to chronic stressors causes chemical changes in the brain that impair higher cognitive functions whilst strengthening 'primitive' brain reactions. People become more emotionally reactive with impaired rational thinking.

→ Stress also increases sensitivity to stress. Impaired emotional & memory function may reduce flexible emotional processing and reduce separation between memories, causing overgeneralization and less capacity to cope with new real or potential stressful events.