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Experience shapes the brain across the life-course: epigenetics, biological embedding and cumulative change

Overview

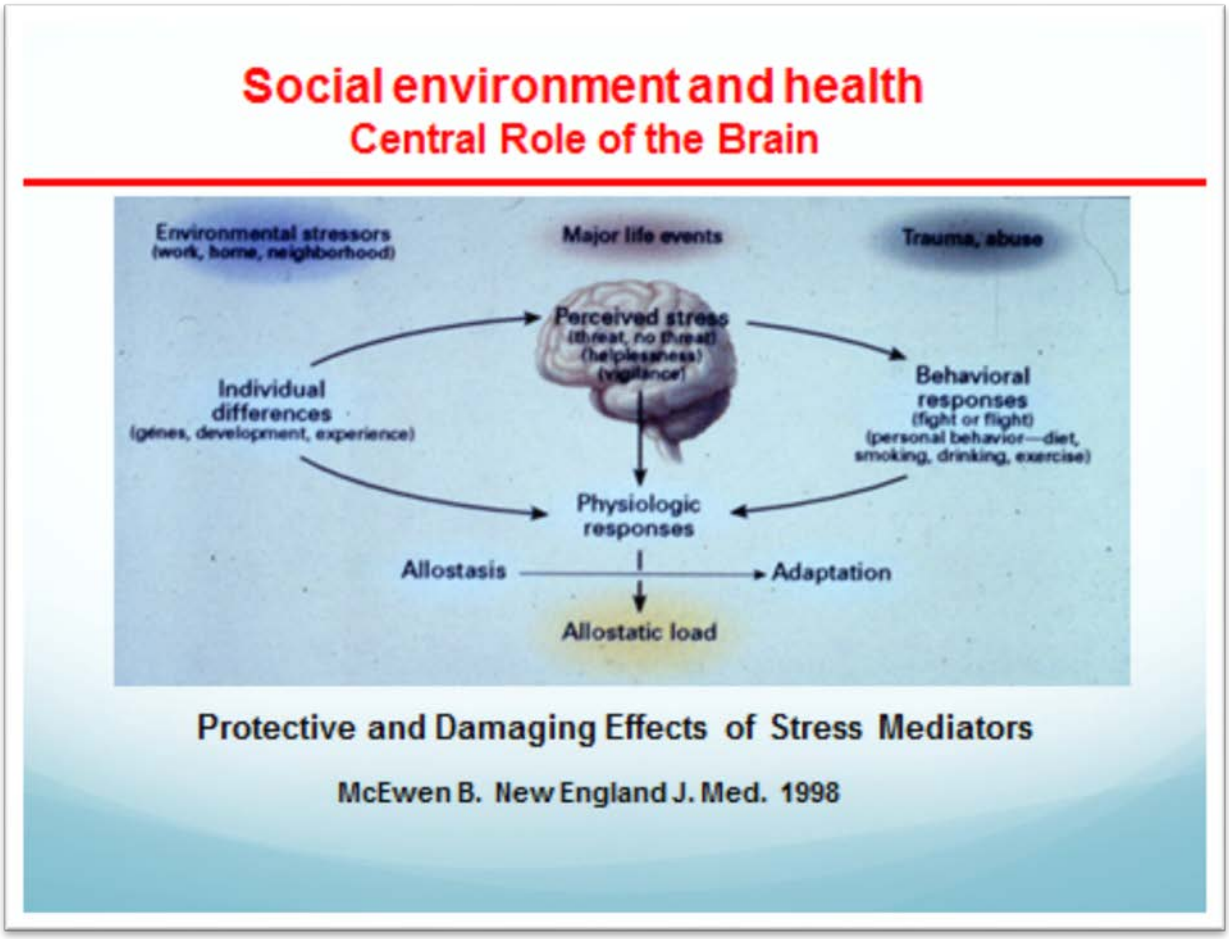
This wide-ranging lecture explored the relationships between conditions and behaviours of everyday life and the biological and psychological pathways through which the stresses of everyday life are related to mortality and morbidity. In addition to looking at these from an individual perspective, the lecture also examined the associations that exist between socioeconomic inequality and health and how these play out over the life-course. A glossary of some key technical terms used is available at the end of this summary.

Summary

Bruce McEwen began describing himself as a neuroendocronologist. As such, he is interested in how the brain and body communicate through hormones, the autonomic nervous system, the immune system, and the metabolic system. So his focus is not only on the brain itself, but how the brain and the body interact with each other.

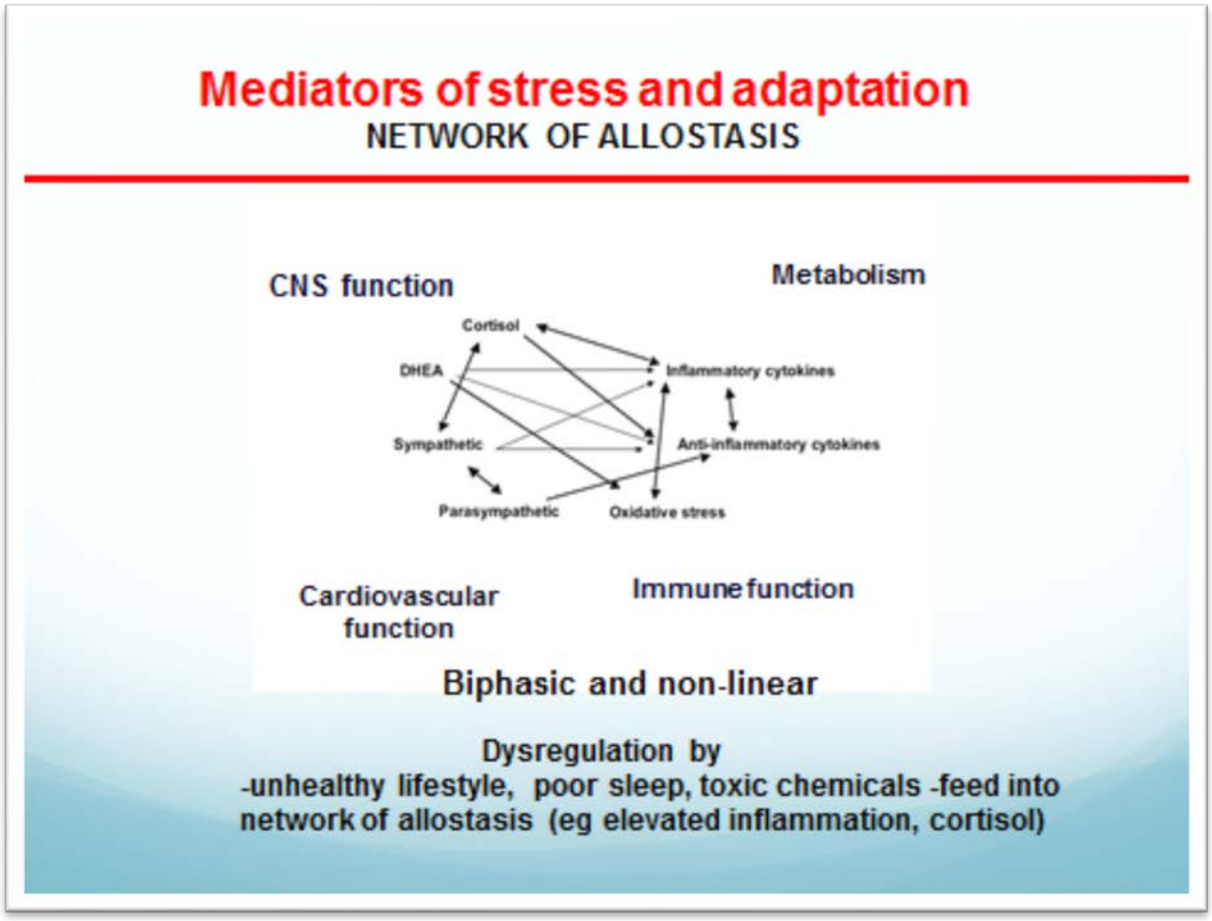
This interest extends to how the social environment and other contexts affect the brain and, through the brain, the rest of the body. This is related to health and disease through the life-course. During his talk, he introduced the concepts of epigenetics and biological embedding which help to explain how environmental factors regulate the expression of genes and affect brain and body function. He suggested that the pioneering work of Marmot in the Whitehall study had shown that this effect is not simply one of extremes. Rather there is an almost linear gradient linking income, education, health, and mortality. This also helped to explain how well individuals respond to stress.

How does this effect “get under your skin”? He offered a simplified model of this complex process. This is shown in the slide below.



Epigenetics he described as the study of the ways in which DNA and the environment interact to moderate or express ('switch on/off') genetic responses – but without altering the gene structure. One such process is DNA methylation, which mediates the extent of response to factors such as stress, the environment and so on. Prof McEwen cited data from a study of identical twins that showed while in early life methylation patterns are the same for identical twins, over the life-course this response comes to be affected by life experience and is therefore different in identical twins. This type of interaction between gene and environment he said was cumulative over the life cycle and helps to determine the phenotype of an individual.

Stress and the response to it is an important factor in how this plays out. The way in which the brain and body interact to mediate response to stress, is described as allostatic load. Response to acute stress is mediated by a network of factors summarised in the slide below.



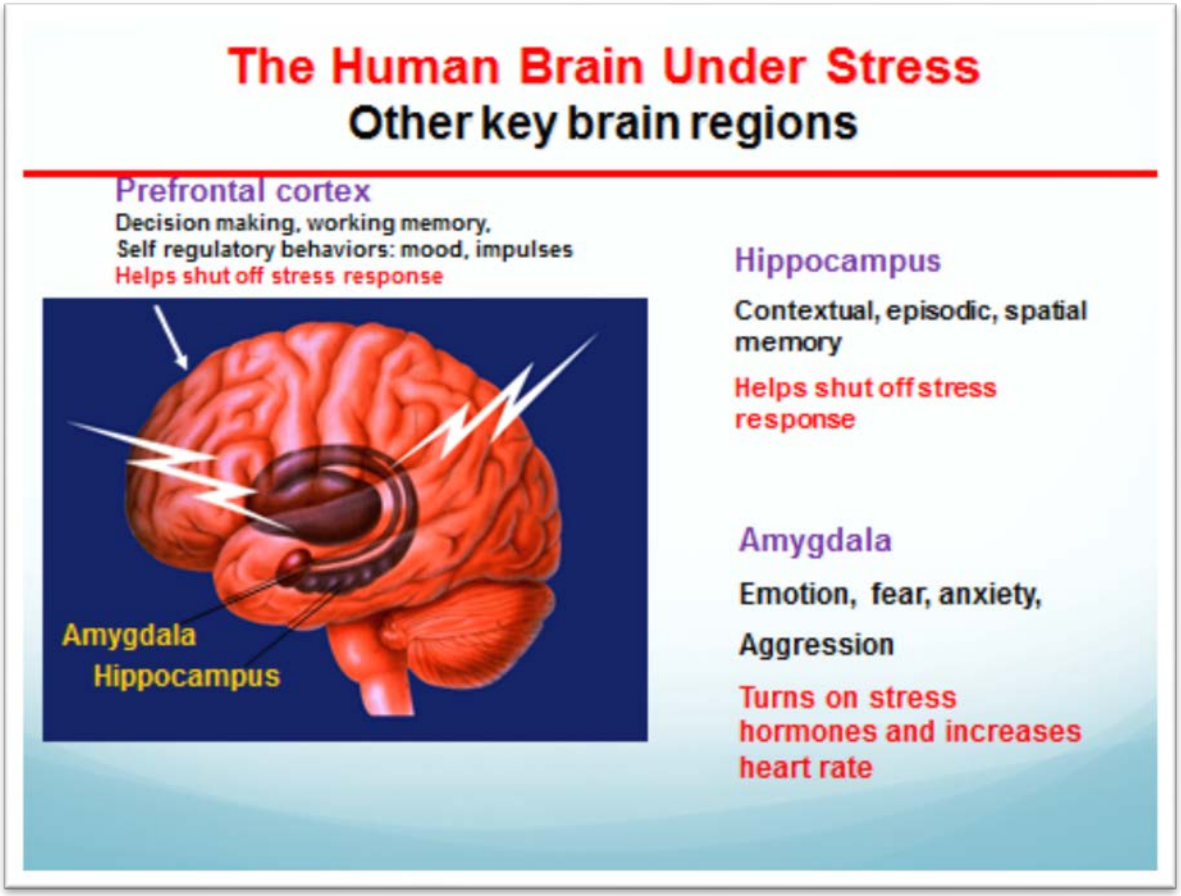
Prof McEwen distinguished between three types of stress:

Positive stress arising from the exhilaration of a challenge for which there is a satisfying outcome. This gives a sense of mastery and control and generates self-esteem.

Tolerable stress which arises from adverse life events in a context of good emotional and social support. Getting through these also generates a sense of mastery, control, and self-esteem.

Toxic stress is associated with a lack of sense of control. It is associated with poor social and emotional support. Those affected by it often have compromised brain architecture due to early life experiences. The presence of a particular human genotype, which can be referred to as being context sensitive, can make this worse.

How does toxic stress arise? Prof McEwen showed a slide (see below) which concentrated on three brain areas important in the development of resilience in the face of stress.



The prefrontal cortex is key in decision-making, self-regulation of behaviours, mood and so on. It helps in closing off the stress response.

The hippocampus is important in assessing context, recall, and spatial memory. It helps in closing down the stress response.

The amygdala regulates emotions like fear, anxiety, and aggression. It promotes the stress hormone response.

Over the past 20 years or so, it has been revealed that the human brain is 'plastic' and can remodel itself in relation to experience including stressful experience. This can involve the generation and depletion of synaptic and dendritic connections and their ability to carry chemicals which mediate responses, including stress responses. The stress hormone cortisol acts primarily through these to activate gene expression. Glucocorticoids can also penetrate deep into receptor cells in the hippocampus, and when activity is associated with toxic stress it can cause connections to degenerate, limiting the extent to which stress response can be mediated.

During acute stress, there is an increase in extracellular glutamate, which helps to mediate the stress response. When stress becomes chronic, this glutamate generation is not appropriately stemmed. In acute stress glutamate seems to help development of new brain connections, but in chronic stress, glutamate overflow contributes to depression and many neurodegenerative diseases.

In summarising this part of his lecture, Prof McEwen stated that stress played an important role in synaptic transmission enhancement and appropriate suppression of response. This increases the long-term potential of the brain and contributes to self-preservation, learning, and memory. It also contributes to the adaptive plasticity of the brain and mediates dendritic remodelling of the brain, and helps in moderating the potential damage from events like stroke or seizures or head trauma. However, there is a question of balance. Increasing frequency, duration, and intensity of stress can become chronic stress in which the stimulating and suppressive aspects of the stress response become unbalanced, and become destabilising and damaging rather than protective.

The human brain under stress

Prof McEwen then turned his attention to the hippocampus, the prefrontal cortex, and the amygdala under stress.

The hippocampus atrophies in major depression, type 2 diabetes, post-traumatic stress disorder (PTSD), and Cushing's disease. Chronic stress, chronic jet lag, lack of exercise, obesity, and chronic inflammation also cause it to atrophy.

The hippocampus increases in size with regular exercise, intense learning, and anti-depressive treatment.

Prof McEwen showed a short video clip, (included with his slides on the resources page) which illustrated the point. A child is crying, increasing stress. The child receives attention from a concerned adult and the stress subsides. He called this 'serve and return'. If the child's cry goes unnoticed, its reactions are quite different with associated effects on brain development. These helpful or unhelpful responses lead to different kinds of biological embedding through the operation of context-sensitive alleles, which can lead to epigenetic and transgenerational modifications via both DNA and behaviour.

In exploring this further, he explained that monoamine oxidase and serotonin transporter genes influence vulnerability to life stress in causing depression. Research has shown there are variants of these two genes, one of which increases the risk of childhood abuse being transmitted down the generations. However, in order for these effects to be seen there has to be abuse in the person's life. Rather than thinking about these variants as good or bad, he suggested a resilience analogy – the dandelion and the orchid – the latter of which is more susceptible to changes in its environment. If you have the context sensitive (orchid) version of the gene you are more vulnerable to early life abuse and neglect but if abuse is not present, you may do even better than with the non-context sensitive (dandelion) version. He then cited research on the child response to parental conflict, which indicated that a child is less affected by such conflict if it has low serotonin transporter gene reactivity. The research also indicated that high sensitivity to abuse in childhood is related to adult experience of abuse.

Considering developmental issues for children further, Prof McEwen identified three areas of study: low socioeconomic status, chaos in the home, and 'risky families'.

Low socioeconomic status tends to be associated with poorer language skills, poorer executive function, and learning ability.

Research shows that chaos in the home is associated with greater helplessness and distress, poor self-regulatory behaviour; obesity, elevated blood pressure, and cardiovascular reactivity.

Risky families (described as being cold, unsupportive or neglectful), have not been so extensively studied, but seem to have a similar effect. Research shows that childhood abuse is associated with increased DNA methylation in the human brain and altered brain structure in young suicide victims.

Adverse childhood experiences (ACEs) were found at all socioeconomic levels, and tend to have lasting epigenetic effects on brain architecture such as the relative volumes of the hippocampus, the prefrontal cortex and the amygdala, and the extent of the dendritic networks.

In summarising this section on development and the hippocampus, Prof McEwen suggested that it is smaller in those with early life abuse, is related to low self-esteem, and higher risk of PTSD.

Turning to developmental effects on the amygdala, adverse circumstances of fear and anxiety, especially in early life, cause the amygdala to be enlarged and more active. This is associated with more impetuous response to stress, and with depression and anxiety disorders.

Finally, the prefrontal cortex tends to be underdeveloped in those who experience chaotic home life and early life abuse. This impairs decision-making, mood, self-regulation, and working memory.

The balance of these structures and functions were important in characterising life-course development potential. For example:

Prenatal – maternal stress and response is associated with obesity and the germ line.
Early postnatal – biological embedding can be adverse and/or positive.
Adolescence – mediation of fear, learning, and decision-making.
Young adults – lifestyle and health behaviours are affected.
Ageing – same as young adults + generative possibilities, meaning and purpose, plasticity.

Prof McEwen suggested it might help to think of the executive functions of the brain as akin to an air-traffic control system. This group of skills helps us to focus on multiple streams of information at the same time, while making plans and setting goals and revising and resetting as necessary. This function is a key biological foundation for many aspects of life.

Finally, Prof McEwen asked what can be done to ensure healthy development? He suggested that a balanced approach to multiple intelligences starting with the earliest years would lay a good foundation. Supportive relationships with adults inside and outside the home would help. Developing highly specialised, sensitive interventions as early as possible for children and families experiencing adversity would help. He thought that the nurse family partnership (www.nursefamilypartnership.org) was a good model of what can be done. He also said that prevention reduces human misery and provides a huge return on investment for society. For example, adult disease prevention begins with the reduction of toxic stress in early life, and early childhood programmes have an impact across many areas of life (http://developingchild.harvard.edu/).

He suggested there were three main types of activity that open windows of plasticity and change brain structure and function. These were regular physical activity, mindfulness-based stress reduction, and integrated social support.

The adult human brain shows plasticity and we are only beginning to understand its potential.

Glossary of Terms used by Bruce McEwen in his GCPH lecture April 21 2015

While it is not strictly necessary to know all of the terms used in this summary, readers may find it useful to have a definition of key terminology.

Adrenal glands: glands which are situated just above the kidneys in mammals. Chiefly responsible for the release of stress hormones, including the glucocorticoids.

Allele: is one of a number of alternative forms of the same gene; existing at a single point, or *locus* of a chromosome.

Allostasis: is the process of achieving stability, or homeostasis, through physiological or behavioural change.

Allostatic load: the wear and tear on the body which grows over time when the individual is exposed to repeated or chronic stress.

Autonomic nervous system: a control system that acts largely unconsciously and regulates bodily functions such as the heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. This system is the primary mechanism in control of the fight-or-flight response and the freeze-and-dissociate response.

Biological embedding: the process by which experience gets 'under the skin' and alters human **biology** and development. Systematic differences in experience, in different social environments, lead to different **biological** and developmental outcomes.

Brain plasticity: the notion that the architecture of the brain can be remodelled due to changes in the environment and by experiences, including stressful experiences.

Corticotrophin-releasing factor (CRF): a hormone released by the hypothalamus in response to stress, which in turn activates multiple features of the stress response, including the release of glucocorticoids throughout the body as well as noradrenaline in the brain.

Cortisol: is a steroid hormone, in the glucocorticoid class of hormones, and is produced in humans within the adrenal gland. It is released in response to stress and low blood glucose.

Cytokines: any of several regulatory proteins that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response.

Cytosine: one of the four basic building blocks (nucleotides) of DNA; often represented by the letter C. The other three DNA nucleotides being adenine (A), thymine (T), and guanine (G).

Dendrites: the branching 'arms' of a neuron or nerve cell, that conduct impulses along the cell. A single neuron may possess many dendrites.

Dendritic remodelling: the capacity of dendrites to adapt in response to changes in the environment and neuronal activity. This occurs during normal development of the nervous system, as well as in response to illness or injury in adults.

DNA methylation: this involves the addition of a methyl group (a carbon atom bonded to three hydrogen atoms, represented as $-CH_3$) to a cytosine on a DNA sequence. This commonly has the effect of blocking or reducing gene expression. In the case of stress, it prevents the activation of glucocorticoid receptors, which are needed for an appropriate response to stress.

Endocrine system: a group of glands that secrete hormones which regulate the body's internal state including metabolism, growth and development, reproduction, sleep and mood.

Epigenetic: any functional change in the genome that does not involve an alteration of DNA sequence, e.g. protein complexes binding to the DNA which serve to switch genes 'on' or 'off'. For more information see: www.pbs.org/wgbh/nova/body/epigenetics.html

Gene expression: the process by which information from a gene is used in the synthesis of a functional gene product, such as a protein.

Genotype: this is the part of the genetic makeup of an individual which determines a specific characteristic (phenotype) of that individual.

Germ line: the bodily cells such as sperm and eggs that pass on their genetic material to the offspring.

Glucocorticoid receptors: proteins responsible for sensing the presence of glucocorticoids; regulating genes which control development, metabolism, and stress responses.

Glucocorticoid: a class of steroid hormones, the active presence of which reflects a response to stress or the circadian rhythm.

Glutamate: an important neurotransmitter which plays the principal role in neural activation.

Homeostasis: the property of a system in which variables are regulated so that internal conditions remain stable and relatively constant. It is a process that maintains the stability of the human body's internal environment in response to changes in external conditions.

Hypothalamic Pituitary Adrenal axis (HPA): a system that includes the hypothalamus, the pituitary gland, and the adrenal glands, which control reactions to stress and regulates many body functions including the processing of fats and glucose.

Hypothalamus: a small part of the brain which among other functions links the endocrine system to the nervous system through the pituitary gland and is therefore important in stress responses.

Immune system: the system within an organism that protects against disease. It is made up of many biological structures and processes.

Metabolic rate: the amount of energy expenditure per unit time required for functioning vital organs: illness, environmental factors, and stress levels affect metabolic rate.

Metabolic system: all the chemical reactions that occur in a living organism.

Monoamine oxidase (MAO): this is an enzyme. MAO dysfunction (too much or too little MAO activity) is thought to be responsible for a number of psychiatric and neurological disorders. For example, unusually high or low levels of MAO in the body have been associated with schizophrenia and depression.

Neural Growth Factor Inducible (NGFI-A): a specific transcription factor, which binds to that part the genome sequence, which produces the glucocorticoid receptor, associated with the stress response. When activated by maternal stimulation at high levels it displaces a methyl group and allows the glucocorticoid receptor to be read, thus more effectively regulating the stress response.

Neural: referring to the nervous system, a network of *neurons* or nerve cells that specialise in co-ordinating actions and passing signals from one part of the body to another.

Neurotransmitter: chemicals that communicate information throughout our brain and body. They relay signals across synapses, or gaps between nerve cells (or neurons).

Noradrenaline: a hormone and neurotransmitter. As a stress hormone, it affects parts of the brain such as the amygdala where attention and responses are controlled. It also underlies the fight-or-flight response.

Parasympathetic nervous system: part of the autonomic nervous system responsible for the ‘rest and digest’ responses. Has a complementary function to the sympathetic system.

Phenotype: a particular individual characteristic which results from the expression of an organism's genes as well as the influence of environmental factors, and the interactions between the two.

Pituitary gland: a major endocrine gland attached to the base of the brain that is important in controlling growth and development and the functioning of the other endocrine glands.

Serotonin: a neurotransmitter involved in regulating cyclic body processes, contributing to wellbeing and happiness, and maintaining mood balance.

Sympathetic nervous system: part of the autonomic nervous system responsible for the 'fight or flight' response. Has a complementary function to the parasympathetic nervous system.

Synapse: a junction between two nerve cells, consisting of a minute gap across which impulses pass by diffusion of a neurotransmitter.

Synaptic transmission: the passing of signals from one neuron to another across the synapse by means of chemicals known as neurotransmitters.

T3: an abbreviation for tri-iodothyronine: the most powerful thyroid hormone affecting almost every bodily process, including body temperature, growth, and heart rate.

Transcription factor: a protein which binds to specific DNA sequences and thereby controls transcription and the first stage of gene expression.

Transcription: the process by which particular DNA sequences are 'read': the first stage in gene expression. The DNA sequence, or gene, is read and a strand of messenger RNA is produced, which can then be used to produce the protein that is coded for by the DNA sequence.