Feature Review

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Adding fuel to the fire: the impact of stress on the ageing brain

Jack A. Prenderville[1], Paul J. Kennedy[1], Timothy G. Dinan[1,2], and John F. Cryan[1,3]

[1] Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland
[2] Department of Psychiatry, University College Cork, Cork, Ireland
[3] Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

Both ageing and chronic stress are associated with altered brain plasticity, dysregulation of the immune system, and an increased risk of developing brain disorders; all of which have consequences for cognitive and emotional processing. Here we examine the similarities between behavioural changes during ageing and stress altered behaviours (anxiety, depressive-like behaviour, cognition, and sociability) in rodents and humans. The molecular mechanisms hypothesised to mediate age-related changes in brain function including dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, dysregulation of neurotransmission and neurotrophic factor signalling, increased inflammatory state, genetic and epigenetic changes, oxidative stress, metabolic changes, and changes in the microbiota–gut–brain axis are discussed. Finally, we explore how the already stressed aged brain psychologically and physiologically responds to external stressors.

Introduction

In 1951, Sir Peter Medawar delivered his inaugural lecture to University College London entitled *An Unsolved Problem of Biology* [1]. The 'problem' to which Medawar was referring to and challenging researchers to solve was biological ageing. During this lecture, Medawar noted that ageing is often accompanied by a 'decline of bodily faculties and sensibilities and energies', a phenomenon which he coined 'senescence'. In the years since this ground-breaking lecture, significant progress has been made in identifying the mechanisms and consequences of senescence yet many aspects remain poorly understood; and, with the global 60 years+ age group growing faster than any other age group, it is becoming increasingly important to continue to delineate biological ageing in order to cope with this rapidly changing population demographic. Understanding the complex functional changes that occur during ageing of the mammalian brain is proving difficult – brain ageing is accompanied by diffuse and often dramatic physiological changes and, as a consequence of this, the emergence of a distinct behavioural phenotype [2]. Additionally, homeostatic capacity is compromised during ageing rendering the body increasingly susceptible to challenges that pose a threat to its internal environment. One challenge that poses a threat to the young healthy brain and can prove particularly detrimental for the aged brain is chronic or traumatic stressful life events.

This review will explore how ageing affects behaviours known to be modulated by stress, including anxiety, depression, cognition, and social behaviour, in addition to examining the stress-related molecular mechanisms that may influence these behavioural changes. Finally, we will outline how the stress response (see Glossary) is altered with age and what potential impact this may have on an already declining brain function.

Stress: brain and behaviour

Short-term acute stress constitutes an adaptive response and is an important feature of an organism's ability to respond to stimuli in its external environment and thus plays a crucial role in maintaining one of the main characteristics of life. However, chronic stress is predominantly maladaptive, with many pernicious consequences for both brain and behaviour [3]. The major physiological response to stress in humans and rodents is activation of the HPA axis culminating in a release of glucocorticoid hormones from the adrenal glands (cortisol in humans and corticosterone in rodents). Glucocorticoid receptors are ubiquitously expressed and thus stress can lead to a range of biological

Glossary

Cortisol awakening response: the sharp increase (approximately 50%) of cortisol that occurs within 20–30 minutes of awakening from sleep.
Gut microbiota: all microorganisms residing within the gastrointestinal tract.
Inflamm-ageing: the progressive increase in proinflammatory status during ageing.
Immunosenescence: the gradual decline in immune system function as a result of chronic activation across the lifetime.
Metabolic syndrome: a constellation of symptoms including increased adiposity, glucose dysregulation, dyslipidaemia, and elevated blood pressure.
Microbiome: the combined genetic material of all microorganisms in a microbiota.
Microbiota–gut–brain axis: the multiple bidirectional systems through which the gut microbiota and brain communicate, encompassing neural (vagus nerve), hormonal (HPA axis), and immune pathways.
Senescence: biological ageing accompanied by functional deterioration.
Stress response: the physiological response to a real or perceived external threat or stressor involving hormonal and metabolic processes.
Theory of mind (ToM): the human ability to attribute mental states such as desires, beliefs, intentions, and emotions to themselves and others. ToM provides humans with the capacity to anticipate the behaviour of others and use deceptive, empathetic, and cooperative strategies in their social environment.

Corresponding author: Cryan, J.F. (j.cryan@ucc.ie).
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effects such as immune modulation and energy metabolism [4]. Subsequent deactivation of the HPA axis occurs via a negative feedback loop, where cortisol/corticosterone released from the adrenal glands acts on glucocorticoid and mineralocorticoid receptors at the level of the pituitary, the hypothalamus, and higher cognitive regions including the hippocampus, amygdala, and prefrontal cortex (PFC), to inhibit further cortisol release [5]. Studies in adult animals have established that prolonged activation of the HPA axis due to chronic stress induces adrenal gland hypertrophy, basal hypersecretion of corticosterone [6], impaired negative feedback of the HPA axis coupled to decreased hippocampal glucocorticoid receptor expression [7], and neuronal dendritic atrophy in several brain regions including the hippocampus [8].

In rodents, chronic stress can induce alterations in several neurotransmitter systems [9] and influence immune system function, particularly in relation to oxidative stress [10] and inflammatory cytokine expression [11]. In addition, chronic stress disturbs normal communication along the microbiota–brain–gut axis and alters the composition of the gut microbiota [12]. The behavioural ramifications of repeated stress exposure, which may be as a consequence of some or all of these cellular changes, include increased anxiety- and depressive-like behaviour [13], reduced social behaviour [14], and cognitive impairments [15].

Although there are inherent difficulties in determining causal relationships in human studies, they largely reflect rodent studies by indicating that chronic stress in adulthood may lead to HPA axis dysfunction [16], heightened immune activity [17], altered grey matter volume in several brain regions including the hippocampus [18], and cognitive impairment [19]. The role of chronic or pathological stressors in the pathophysiology of depressive [5] and anxiety disorders [20] is well recognised. Impaired social functioning [21] and social–cognitive deficits [22] are common in depressed individuals, which provide some indication that chronic stress may impact social–cognitive processes. However, there is currently a paucity of data on the impact of chronic stress on social–cognitive function in healthy adults. Finally, chronic stress is considered a key factor in the pathophysiology of brain–gut axis disorders such as irritable bowel syndrome in which an altered composition of the gut microbiota is thought to underlie many aspects of symptomatology [23].

In summary, chronic stress has multiple effects on brain and behaviour and, as will be outlined, many of these effects are also observed during ageing.

Advancing age alters actions

Ageing angst

Anxiety behaviours have been widely investigated following stressful situations and to a lesser extent in ageing. Data from rodent studies suggest that ageing (Box 1 and Table I therein) is generally accompanied by increased anxiety-like behaviour. However, strain and sex can be important variables in the expression of this type of behaviour (Table 1) and it should be highlighted that the reproductive history of female animals can determine the expression of age-related anxiety-like behaviour [24].

Box 1. How old is old?

According to the United Nations (UN) [148], ';By 2050, the number of older persons in the world will exceed the number of young for the first time in history.' A daunting statistic, but what exactly does it mean? What is 'young' and how old is 'older'? In the case of this particular report, the authors (the UN) define 'older persons' as >60 years, while 'young' is defined as <15 years. Despite these definitions, science lacks a gold standard protocol for segregating age groups and the chronological age of 'young', 'middle-aged', and 'aged' subjects in studies is often arbitrarily defined and prone to inter-study variation.

Mammalian lifespan can be loosely divided into five stages: infancy, adolescence, adulthood, middle-age, and old-age, based on a variety of physiological and psychological parameters. The precise age of transition between these periods is heavily debated and can also vary from person to person. In rodents, the early periods in the lifespan appear to be the most well defined – infancy in rodents is considered to span from birth to weaning (postnatal day 21); adolescence is generally thought to be the period between weaning and adulthood (postnatal day 60) [149]. However, the 'young control' or 'adult' reference group in murine studies is usually 3–6 months of age and the 2–3 month period (sometimes referred to as 'young adulthood') is usually reserved as a transition period between adolescence and adulthood as rate of development is still high. Similarly, the early stages of life in humans are the best defined – infancy/childhood: 0–9 years; adolescence: 10–19 years [according to the World Health Organisation (WHO)]. A major limitation of ageing research is the inter-study variation of age groups and, therefore, considering the age ranges utilised in the literature and the recommendations by Flurkey and colleagues [150], we propose that approximate chronological ages be used in defining the stage of ageing in human and murine studies (Table I).

Table I. New recommended age ranges to define life stages

Stage	Human (years)	Rat/mouse (months)
Infancy/childhood	0–9	0–21 (days)
Adolescence	10–19	22–59 (days)
Adulthood	20–30	2–6
Late adulthood	31–37	7–9
Middle age	38–47	10–15
Late middle age	48–59	16–19
Old age	60+	20+

In elderly adults, as with younger populations, anxiety disorders late in life are more common in females [25]. In clinical samples, the prevalence of anxiety disorders in elderly adults is considerably higher than younger persons, with a global estimate of 15% [26]. However, in community samples of healthy elderly adults, anxiety disorders are no more prevalent than during mid-life as determined by current diagnostic criteria [27]. Increased anxiety in clinical samples, in the absence of neurological disorders, may be the result of physical decline as demonstrated by a study suggesting that progression towards frailty is predictive of developing clinically relevant anxiety problems [28].

Ageing abjection

Although not as extensively studied as anxiety-like behaviour, the majority of studies in rodents suggest that ageing is associated with an increase in depressive-like behaviour, however, as with anxiety, species, strain, and sex differences are apparent (Table 1).

Depression in humans may also be subject to age-related change but is influenced by a variety of environmental