REVIEW ARTICLE

Ageing and its relationship with psychoneuroimmunology

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ABSTRACT

Senescence of the immune system is a complex phenomenon that is typically seen as a state of immunological dysregulation and is characterised by impairment of various lymphocyte activities. Ageing is a condition linked to numerous societal changes that can cause psychological stress, which is frequently seen to be beyond our control and can, in some situations, result in clinically meaningful depression. A rising interest in the study of the connections between the immune system and the central nervous system (psychoneuroimmunology) has emerged in recent years. Present objective was to compile the most recent research on the intricate relationships between stress, depression, psychoneuroimmunology, and the effects on aged people. This review discussed the effects of ageing on the mental health of the older population and changes to the HPA axis. The focus shifts to the gut-brain axis and neurodegeneration after that. The dietary impacts of ageing are also explored towards the conclusion. The study's findings emphasise the importance of using a multidisciplinary approach to properly comprehend the intricate connections between psychoneuroimmunology, nutrition, and mental health.

KEYWORDS

Ageing, Psychoneuroimmunology, Immunogerontolgy, Nutrition, Gut-brain axis

INTRODUCTION

The average lifespan of people is rising everywhere (Ghosh, J., et al., 2022). The number of people attaining the age of 60 and over on the globe is projected to increase from 0.9 billion (12% of the total population) in 2015 to 2 billion (22% of the total population) by 2050, meaning that the elderly population will have double internationally (2020 Population Division, Department of Economic and Social Affairs, United Nations). In addition, by 2050, it is anticipated that 80% of all elderly people will reside in low and middle-income nations (Health and Aging, 2022). The number of senior citizens in India has sharply increased, and it is predicted that by 2025, that number will reach 158.7 million. Overtaking the population of youngsters under the age of 14, the number of elderly adults would reach roughly 324 million (Vaishnav, LM et al., 2022). Worldwide, 322 million individuals are estimated to be depressed (Friedrich, MJ. 2017). Depression, a frequent mental condition that affects 20% of the senior population and is distinguished by a depressed mood, it is the most prevalent psychiatric disorder among elderly people in India. It is typically misdiagnosed and receives inadequate care. Due to modernization, people now prefer to live in nuclear families, both in rural and urban areas. This leads to loneliness among the elderly and a lack of family and social support, which worsens their already precarious health conditions and makes them an easy target for depression. Depression in the older population is still underreported and given little attention (Pilania, M., et a, 2013). Even though India is launching a lot of elderly-friendly plans and programs (The

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Better India, 2019), it lacks the passion to address the depression issue (Vishwakarma, D., et al., 2013).

Aging may be described as a gradual loss of reserve abilities that are unique to each person. Geriatricians refer to this process as "frailty" since it causes a steady decline in mental and physical abilities as well as a change in functional autonomy and quality of life (Fried et al., 2004). Higher mortality rates and medical issues, including falls, swallowing problems, hospitalizations, and institutionalization, are all linked to frailty. In addition, ageing is the primary risk factor for chronic illnesses (Fried et al., 2004), and in cases of acute illness, senior people are less able to react to a sudden danger while under stress (Ghosh, J., et al 2023). The ability to cope with acute stress depends on reserve capabilities, which are influenced by a variety of variables, including the rate of physiological ageing and the severity of a chronic medical condition. According to Lopez-Otin et al. (2013) and El Assar et al. (2017), these two parameters are highly reliant on genetic background, epigenetic, immunological, biochemical, and environmental factors. According to Bouchon's theory (Campillo, M, et al, 1984), the development of elderly patients depends on reserve capabilities that are influenced by physiological ageing, comorbidities, and acute stress. Although understanding of human immunosenescence has increased over the past several decades, the processes behind how stress affects the immune system in older people remain poorly known. In order to guarantee not only an extended lifetime for the senior population but also, and most significantly, an improvement in its health span, it is necessary to better characterise the actors engaged in resilience capability. The central nervous system (CNS) and the immunological network interact complex bidirectionally in a field of study called psychoneuroimmunology. It takes into account the neuroendocrine modulation of immune functions and the corresponding feedback to the brain. Several investigators demonstrated that the ‘widespread’ immune system is not autonomous. It interacts with the whole organism in bidirectional ways, the ‘language’ for such interactions being hormones, neuropeptides, and cytokines produced by immunocytes, CNS, or endocrine cells. Furthermore, direct innervation of lymphoid tissues has been demonstrated both in animals and in humans, and experimental evidence suggests that ‘specific’ neurotransmitters may modulate the functions of immune cells (Kruszewska, B., et al, 2012). In this light, ‘direct’ effects of acute and chronic stress as well as of affective disorders on immunological functions may be expected. Present review aimed at understanding the relationship between ageing and psychoneuroimmunology. The impact of ageing on the mental health of the elderly population and changes to the HPA axis will be covered in this overview. After that, it will concentrate on neurodegeneration and the gut-brain axis. Finally, the nutritional effects of ageing as well are discussed.

IMMUNOGERONTOLOGY

As more and more individuals live longer lives, immune gerontology is becoming a science that is increasingly relevant. Immune senescence has been described as a condition of the immune system that is dysregulated (Pinti, M., et al, 2016). While certain immune systems decline with age and some even improve, many others do not. There are a few things to keep in mind in order to comprehend this better. In general, the planned (intrinsic or genetic) and stochastic (extrinsic) theories of ageing can be combined to form contemporary models of cellular ageing, which attempt to describe immunosenescence (Montecino-Rodriguez, E., et al, 2013). At the cell and molecular biology levels, mechanisms of positive control of T lymphocyte immunosenescence have recently been studied (Liu, Z., et al, 2023). In particular, a membrane hypothesis for cellular ageing has been put forth (da Costa, J. P., et al, 2016): as the cell becomes active from a metabolic point of view, the rigidity of the plasma membrane increases, causing changes in the ratio of saturated to unsaturated fatty acids, the ratio of sphingomyelin to phospholipids, and perturbations in ionic channels (Escribá, P. V., et al, 2008). The elderly may have a more "rigid" cell membrane that affects how hormones or antigens attach to their particular receptors (Fülöp, T., et al, 2007). Other studies contend that changes in the signal transduction pathway from the cell membrane to the nucleus may be the cause of the age-related reduction in lymphocyte activity (Carlson, M. E., et al, 2008). The fact that a significant fraction of healthy aged participants exhibit reactions equivalent to controls suggests that immune system degradation is probably not a 'per se'

hallmark of ageing (López-Otín, C., et al, 2013). Indeed, studies on centenarians (Franceschi, C., et al, 1995) show that while this population does not avoid immunological ageing, some immune responses, such as cytotoxic activities, are maintained at a high degree of effectiveness, perhaps aiding in their "successful ageing. Since immunological variables may play a role in cancer, cardiovascular disease, susceptibility to viral or infectious illnesses, and autoimmune disorders, the senescence of the immune system is therapeutically relevant. In a prospective analysis, reduced T cell function as measured by mitogen-induced proliferation was linked to higher mortality (Bruunsgaard, H., et al, 2000). In older participants without any other symptoms of ill health, delayed hypersensitivity, a skin test that assesses cell-mediated immunity, has been shown to be an excellent predictor of future all-cause death and perhaps cancer mortality (De Martinis, M., et al, 2017). The key features of age-related immunological changes are highlighted and are included in table 1 (Weyand, C. M., et al, 2016)

TABLE-1: IMMUNE ANOMALIES IN THE ELDERLY

Immune parameter	Modification
Thymus hormone production	Decreased
Total lymphocyte Count	Unmodified
T lymphocytes (CD3+)	Unmodified or decreased
T suppressor/cytotoxic (CD8+)	Unmodified or decreased
T lymphocytes (CD4+)	Unmodified
Proliferation of lymphocytes in response to mitogens or antigens	Decreased
Leu7+ cells	Increased
Activity of NK	Increased, unmodified or decreased
Function of macrophage	Unmodified
IL-2 production	Decreased
Exogenous IL-2-induced proliferation	Decreased
IL-2R expression	Unmodified or decreased (low affinity)
Immunoglobulin level	Increased (IgG1, 2, 3, IgA), unmodified (IgG4, IgM)
B lymphocytes	Unmodified or decreased
Function of polymorphonuclear neutrophils	Decreased
cutaneous testing for delayed hypersensitivity	Decreased
IFNs Production	Unmodified or decreased
generation of antibodies against certain foreign antigens	Decreased
Titers of autoantibody	Increased

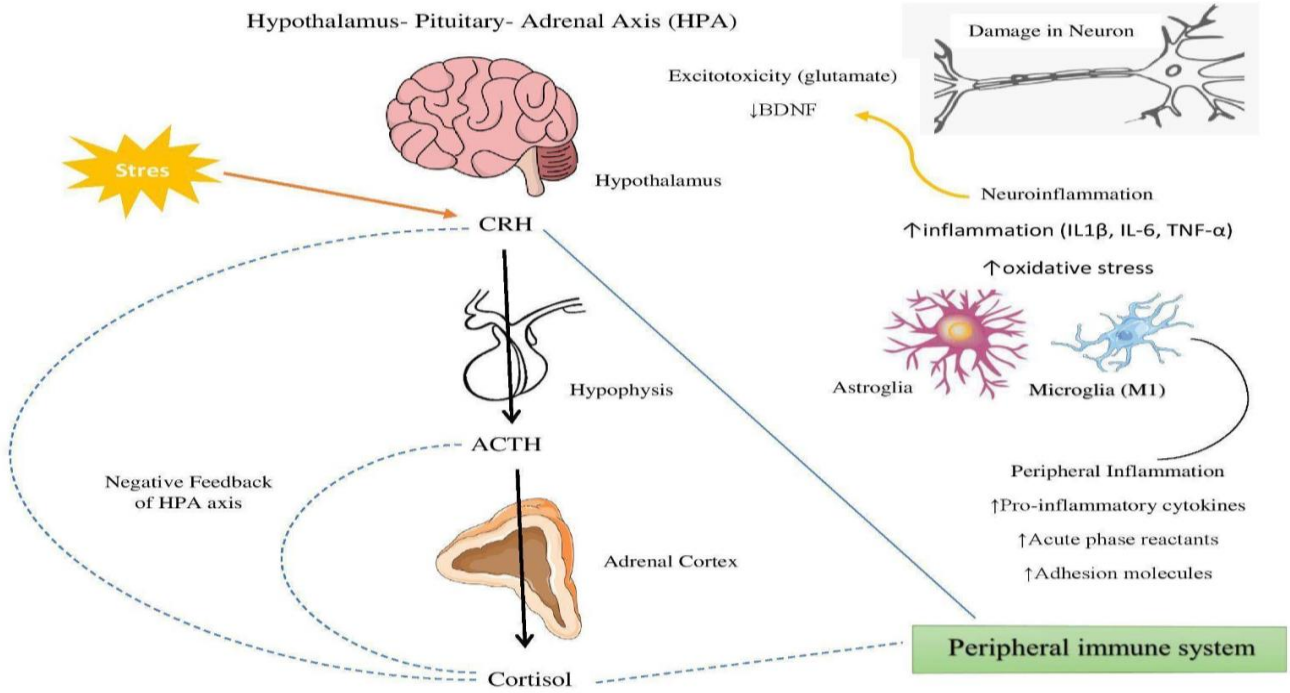
DEPRESSION CAUSED BY AGEING, STRESS, AND THE HPA AXIS:

In a biological sense, ageing results from the build-up of various forms of cellular and molecular damage over time. As a result, one's physical and mental capabilities steadily decline, their chance of being sick rises, and finally they pass away. (Health and Aging, 2022) These modifications are not linear nor constant, and they only obliquely relate to a person's age stated in years. Variety with age is not a coincidence. Aside from biological modifications, ageing is typically associated with other life changes including retirement, relocation to a better house, and the loss of friends and companions. Hearing loss, cataracts and refractive errors, back and neck pain and osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression, and dementia are age-related disorders that are also prevalent in older adults (Health and Aging, 2022). As people age, they become increasingly susceptible to many illnesses at once. The world's population is rapidly getting older. Between 2015 and 2050, the proportion of old people is expected to nearly double, from 12% to 22% (Mental health of older adults, 2017). In absolute terms, it is predicted that the number of people over 60 will increase from 900 million to 2 billion. It's critical to acknowledge the specific physical and mental health problems that older people face. (Mental health of older adults, 2017). The most common mental and neurological conditions in this age group are dementia and depression, which affect around 5% and 7% of the world's senior population, respectively. Depression can cause extreme discomfort and make it difficult to carry out regular tasks. Unipolar depression affects

7% of older adults in general and accounts for 5.7% of years lived with disabilities (YLDs). (Mental health of older adults, 2017). Depression may lead to eating habits that promote obesity, or, on the other side, it may cause a significant loss of appetite and exhaustion, which may occasionally lead to the condition known as elderly anorexia. In older people who are sad, memory loss and insomnia are more prevalent. (Mental health of older adults, 2017). Additionally, they react more slowly than usual, which raises the hazards associated with actions like driving, taking care of oneself, and other tasks that need whole concentration. (How to prevent depression as you age, 2022). Depression is both underdiagnosed and undertreated in situations that provide basic healthcare. Because symptoms often co-occur with other problems that older people experience, they are usually disregarded and mistreated. (How to prevent depression as you age, 2022)

Chronic stress works as a catalyst for anxiety and depression by altering the hypothalamic-pituitary-adrenal (HPA) axis and immune system (Stephens and Wand 2012). There is experimental and clinical proof that the elevated levels of pro-inflammatory cytokines and glucocorticoids that are present in both depression and persistently stressful situations contribute to the behavioural abnormalities connected to depression. (Felgerand and Lotrich, 2013). Any environmental disturbance, internal or external, that affects homeostasis can be referred to as stress. This term underlines the range of responses an individual may have to a stressful experience. The hypothalamus, pituitary, and adrenal glands are part of the feedback loop that makes up the HPA axis. The regulation of the axis is also significantly influenced by the hippocampus, amygdala, bed nucleus of the stria terminalis (BNST), and paraventricular nuclei (PVN) (Bomholt, S. F., et al, 2004). An emotional or physical stressor causes the HPA axis to become active. Two hormones released by the brain, arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH), induce the pituitary to create more adrenocorticotropin hormone (ACTH) (Bomholt, S. F., et al, 2004). The corticotropin-releasing factor (CRF), also known as CRH, a 41-amino acid peptide distributed throughout the central nervous system, is the primary regulator of the mammalian stress response. CRH interacts with pituitary ACTH-secreting receptors (Figure 1). The blood carries ACTH to the adrenal cortex, where it interacts with receptors on adrenocortical cells to trigger cortisol secretion (Bomholt, S. F., et al, 2004). The adrenal glucocorticoid stress hormone that is released in humans and other animals is called cortisol. Corticosterone is a hormone that is produced by several other species, including rats. The majority of cortisol that is circulating in the body is protein-bound to CBG (Baumeister, D., et al, 2008). Only "free" or unbound cortisol can attach to receptors. At least two different intracellular receptor types are involved in cortisol's binding. (Baumeister, D., et al, 2008). Type I or mineralocorticoid receptors are the first to bind cortisol and often do so before type II or glucocorticoid receptors. Type I receptors have the highest affinity for cortisol. These cortisol binding properties set them apart from other synthetic corticosteroids like prednisone and dexamethasone (DEX), which virtually exclusively attach to the type II receptor. (Bomholt, S. F., et al, 2004). Cortisol sends a signal to the pituitary and hypothalamus that is negative, ending the loop. The HPA axis is subject to at least two different types of detrimental feedback (Bomholt, S. F., et al, 2004). The first is cortisol's negative feedback to the pituitary, which depends on the amount of cortisol present. A second mechanism known as rapid feedback involves interactions with receptors in the hypothalamus and hippocampus and is reliant on the pace of change in cortisol concentration rather than its absolute concentration. It is obvious that people with MDD frequently have abnormalities of the HPA axis. According to research, depression can recur and have negative consequences on the brain and other organs (Cowen, P. J, 2010).

FIGURE-1- THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS (WALKER, J. J., ET AL, 2010)



GUT MICROBIOTA, THE MICROBIOTA-GUT-BRAIN AXIS, AND NEURODEGENERATION

The human gut, which has 200–300 m^2 of mucosa, is the "secret garden" of 10 trillion different symbionts, or the "microbiota," which is made up of 50 bacterial phyla and around 100–1000 bacterial species (Qin, Raes et al., 2010). Microbiota are 10 times more prevalent in the human body than somatic and germ line cells. The "microbiome," which is 150 times bigger than the human genome, is the term for the aggregate genes of the microbiota. 150–170 different bacterial species are found in the average individual; they thrive in the warm, nutrient-rich environment of the gut and perform structural, metabolic, and defense functions (Bäckhed, F., Roswall, 2015). The human gut microbiota is made up of a variety of microorganisms, including bacteria, viruses, parasites, and eukaryotes. (Lozupone, 2012) Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria are the seven divisions of bacteria that thrive most in the gut milieu. (Bäckhed, et al, 2005). The Bacteroidetes and Firmicutes make up more than 90% of the total population of these seven divisions. The genera of Bacteroides and Prevotella include the majority of the species that make up the phylum Bacteroidetes. (Lagier, et al, 2016). It has been suggested that the relative predominance of these species, known as enterotypes, is substantially determined by food. (Lagier, et al, 2016)

The mother contributes the bulk of the infant's microbiota before birth, and it continues to grow through feeding and interaction with the outside world. New research suggests that colonisation of the infant's gut may begin in pregnancy with the placenta. Over the following two to three years, the infant's microbiota rapidly changes to match that of an adult, with its composition being impacted by things like delivery method (vaginal birth vs. caesarean section), source of nutrition (breast milk vs. formula), region, and antibiotic exposure. (Dominguez-Bello, et al 2010). These years have come to be seen as a vulnerable time because disruptions may have long-lasting effects on development, particularly brain development, and they may also predispose a person to subsequent disease. The microbiota is assumed to remain stable throughout childhood, adolescence, and adulthood before changing further in later life (Dominguez-Bello, et al 2010).

The identification of the typical microbiota of older people is crucial since several neurological illnesses affect the elderly. Diet may have a significant role in the age-related changes in the microbiota of the elderly; if insufficient, it can result in a decrease in microbial diversity, a condition that has been connected to inflammation (or "inflammaging") in the elderly. Research on the hormone signalling of the gastrointestinal endocrine system in neurons and brain cells gave rise to the notion of a gut-brain axis in 1980 (Track, 1980). The gut-brain axis is influenced by the microbiome, and this idea has been strengthened and broadened over the years (Carabotti et al., 2015; Hsiao et al., 2013; Margolis et al., 2021). Today, the phrase "brain-gut-microbiota" describes more than just the axis; it also refers to the brain-gut-microbiota system in hosts and interactions between the central nervous system (CNS), endocrine chemical signal system, immune regulation, microbiota and metabolic effects, and barrier functions in the brain and gut. In order to sustain a person's state of health, these elements must be coordinated (Foster and McVey Neufeld, 2013; Lynch and Pedersen, 2016; Maiuolo et al., 2021; Margolis et al., 2021). Numerous illnesses, including mental health conditions like depression, may develop if there is an imbalance in the brain-gut-microbiota axis (Foster and McVey Neufeld, 2013; Lynch and Pedersen, 2016; Maiuolo et al., 2021; Margolis et al., 2021). We now have a better knowledge of how the gut microbiota affects mental health, including depression, thanks to studies showing that it communicates with the central nervous system (CNS) through a variety of pathways (Foster and McVey Neufeld, 2013; Morais et al., 2021). In the brain-gut-microbiota system, neural signal networks such as the spinal nerves, vagus nerves, and enteric nervous system (ENS) are crucial and quick response pathways. The ENS, sometimes referred to as the "brain in the gut" or "second brain," regulates the environment both within and outside of the gut (Margolis et al., 2021; Niesler et al., 2021). According to Margolis et al., the intricate control of the ENS plays a variety of roles in modifying microbial composition, metabolites associated to the microbiota, neurotransmitter and immunological signaling, and intestinal barrier protection. Thus, the brain-gut-microbiota axis network includes signals from different sources as well as bidirectional communication between the CNS and ENS. Numerous studies have shown that the vagal pathway is the most direct route for microbial signals to go to the brain. On the one hand, the vagus nerve controls eating behaviour, including gastrointestinal motility and secretory processes (Pavlov and Tracey, 2012). Contrarily, the vagus nerve plays a role in the body's inflammatory responses in the stomach, the brain, and other organs (Pavlov and Tracey, 2012).

The vagus nerve senses inflammatory cytokines via its afferent and efferent arms, which then integrate afferent signalling into the brain. It also performs an output function by regulating immune activation and inhibiting pro-inflammatory cytokine release from the gut or other organs by the efferent arm, which helps to produce the inflammatory reflex (Pavlov and Tracey, 2012). Additionally, it has been suggested that acetylcholine receptors and their ligands play a critical role in the immune system by regulating the cholinergic anti-inflammatory pathway via the vagus nerve (Bonaz et al., 2018; Pavlov and Tracey, 2012).

It is widely accepted that stress contributes to the pathophysiology of depression and that resilience is mediated by adaptive changes in a number of circuits, including BDNF, pro-inflammatory cytokines, and the spleen (Hashimoto, 2019; Zhang et al., 2021). According to studies, certain rodents are resistant to learned helplessness (LH) and chronic social defeat stress (CSDS). In comparison to control and CSDS susceptible mice, our team found that CSDS robust mice had greater amounts of Bifidobacterium (Yang et al., 2017a). Additionally, compared to vehicle treatment, oral administration of Bifidobacterium significantly enhanced the number of mice resistive to CSDS, indicating that Bifidobacterium provides resistance to CSDS (Yang et al., 2017a). We also noted that LH susceptible rats had significantly higher relative abundances of the genera Lactobacillus, Clostridium cluster III, and Anaerofustis than control and LH resilient rats did, as well as lower levels of acetic and propionic acids in their faeces than control and LH resilient rats did (Zhang et al., 2019a). The brain-gut-microbiota axis may be critical in the development of depression-like phenotypes, according to growing evidence from preclinical research (Martin, C. R., et al, 2018). Stress-induced depression-like behaviours in rodents have been

shown to be accompanied by abnormal levels of gut microbiota-related SCFAs, as well as other metabolites like alanine, isoleucine, L-threonine, serine, and tyrosine, which may be connected to altered levels of 5-HT in the brain and depressive-like phenotypes (Chang, L., et al, 2022). In contrast to healthy controls, patients with depression have abnormal gut microbiota composition, which further supports the idea that the brain-gut-microbiota axis plays a role in depression (Jiang et al., 2015; Naseribafrouei et al., 2014). One such study also discovered that Faecalibacterium was connected to clinician-related depression scale scores and that gut microbiota dysbiosis in depressed patients was related to lower BDNF levels, both of which contributed to the severity of depressive symptoms (Jiang et al., 2015). Machine learning targeting single nucleotide, precise amplicon sequence variations in patients' gut microbiomes revealed in a recent study that the gut microbiota DNA contributes to the depression phenotype in differentiating depressed patients from controls (Young, R. B., et al, 2021). In-depth research on depressed individuals used a multilayer omics viewpoint to explore how changes to the gut microbiome and metabolomics affect gut ecology and contribute to the pathophysiology of depression (Yang et al., 2020a).

Is inflammasome a crucial point of convergence for stress and nutritional dysregulation in nutritional psychoneuroimmunology?

Due to significant advancements in the prevention, postponement, or treatment of several illnesses often associated with ageing, life expectancy is steadily rising. But more research is still needed to understand the underlying causes of the many comorbidities that arise with ageing. (Lunenfeld, B., et al., 2013). On the one hand, ageing severely weakens the immune system; it is characterised by a variety of alterations in hematopoiesis, adaptive, and innate systems, as well as an environment that is pro-inflammatory (Fali, T., et al., 2018). On the other hand, stressful situations (acute or long-term) can affect the immune system by causing the release of hormones, which are likewise changed as we age. In light of several extrinsic and intrinsic elements, psychoneuroimmunology is now showing that older people do not respond to stress equally when they are experiencing acute medical issues. These factors could make it more difficult for elderly people to build a powerful immune response. (McEwen, B. S. 2000)

Almost all illnesses are negatively impacted by a dysregulated nutritional and/or metabolic status (Whitaker, R. M., et al., 2016), which can also cause a patient who is otherwise stable to deteriorate into a confused or demented condition (Nifli, A. P., 2018). Correlational research suggests that a wide variety of meals may have an effect on how the brain functions (Marx, W., et al., 2017), but there are few clear routes that outline how nutrients mechanically control behavior Stress is often detrimental to health, whether it be physical, mental, or emotional. (Razzoli, M., et al., 2018). Because most rodent-based research uses inbred strains of mice that often live in standardized microcommunities that intrinsically limit genetic and epigenetic diversity, rodent models are particularly good at uncovering the effects of stress. Given the regularity of the induced responses, the research on behavior and nutritional status is so intrinsically simplified. Generally speaking, nutritional stress occurs when a species experiences hunger (Reineke, L. C., et al. 2018). However, this one-sided approach seems to undervalue the beneficial effects of fasting (Brandhorst, S., et al., 2015) as well as the stressful impacts of overeating (He, L., et al., 2018). Stress and nutrition are inextricably related since they frequently alter food intake. However, it is strikingly unclear whether this metaphorical quid pro quo is adaptive or maladaptive. Even the adage "feed a cold, starve a fever" is a puzzling scientific puzzle that is still being investigated over 500 years after it is said to have been invented. (Smith, J. 2015). Elucidating brain-based pathways shared by food intake and stress may likely help in the mechanistic understanding of some of our most challenging to treat health concerns, particularly mental illness and addiction, because eating behaviour is essential to organismal survival. As a result, the revelation that what is consumed might affect the immune system in relation to the inflammasome (Finucane, O. M., et al., 2015) creates a crucial hub for the communication between nutrients and the brain.

NUTRITIONAL EFFECTS ON AGEING

Ageing and nutrition have a complicated relationship since it might be difficult to determine what influences what. Nutritional therapies can only postpone natural ageing, not

reverse it. The pathological, physiological, social, and psychological conditions of humans change as they age. The elderly's diet has a significant impact on their overall health and the ageing process (Shepherd A, 2009). In this population, the prevalence of malnutrition is cumulative and is linked to deteriorating functional status, impaired muscle function, decreased bone mass, immune dysfunction, anaemia, impaired cognitive function, poor wound healing, sluggish post-operative recovery, higher hospital readmission rates, and mortality. Older adults are frequently left to care for themselves to preserve their health as a result of shifting socioeconomic situations, which may make it more difficult to maintain a healthy dietary status. Due to developmental programming, nutritional decisions continue to be very important throughout life, having a significant impact on the individual's general health and welfare as well as perhaps future generations. For life, health, and successful reproduction, all healthy individuals require the same fundamental nutrients, including carbohydrates, necessary amino acids, essential fatty acids, and as many as 28 vitamins and minerals. However, when a person moves from one period of life to the next, the levels of essential nutrients alter. Contrary to the elderly, young children require a larger calorie intake proportional to body size to support physical and mental growth (Shepherd A, 2009; Shepherd A. A, part 2, 2008; Shepherd A. A, part 1, 2008)

Despite its complexity, there is a bidirectional correlation between nutrition and ageing, meaning that both factors influence one another (Table 2). Both cross-sectional and longitudinal studies (Roseboom, T., et al, 2006) have shown that there is an overall reduction in nutritional status with ageing. In nations with poor economies, low literacy rates, and little nutritional knowledge, this age-related fall in nutritional status may be more pronounced. Day-to-day variations in energy intake (20–25%) and expenditure (10%) (Goran, M. I., et al, 1993) imply significant daily variations in energy balance. When compared to youth, the energy balance in old age is much worse, indicating that the control of energy intake in old age is severely reduced (Goran, M. I., et al, 1993). Additionally, a number of previous animal experiments (Goran, M. I., et al, 1993) showed that as people age, their ability to regulate their food consumption declines. Due to a variety of physical, physiological, and social factors (Rolls, B. J., et al, 1995), ageing is frequently linked with reduced appetite and early satiety. According to several studies, older participants who had fasted or had an experimentally induced negative energy balance reported abnormally low hunger levels (Rolls, B. J., et al, 1995; Goran, M. I., et al, 1993). Age-related changes in glucose homeostasis may be a factor in altered appetite and satiety. In both rats and people, blood glucose has long been theorised to be the catalyst for hunger signals (Blundell J. E, 1998). Additionally, it has been demonstrated that delayed gastric emptying generally leads to enhanced fullness and decreased appetite (Blundell J. E, 1998)

TABLE 2: LIST OF THE NUTRIENTS THAT INFLUENCE AGEING

Nutrients	Age related effects	Key References
Protein	A diet heavy in carbohydrates and low in protein is linked to a long lifespan. A high consumption of animal protein increases the risk of urothelial cell cancer, whereas a high intake of plant protein decreases the risk.	(Allen, N. E., et al, 2013)
Fats	In general, a high-fat diet (HFD) is linked to higher mortality and a rise in the prevalence of several metabolic illnesses, such as type II diabetes and cardiovascular issues. Diets rich in natural unsaturated fatty acids lower blood pressure, improve insulin sensitivity, and lower the risks of cardiovascular and metabolic diseases. Diets rich in unsaturated fatty acids lead to decreased blood levels of harmful low-density lipoproteins and increased levels of protective high-density lipoproteins.	(Honda, Y., et al, 2010; Carey, J. R., et al, 2008; Solon-Biet., et al, 2014)

Nutrients	Age related effects	Key References
	Inflammatory reactions brought on by dietary trans-fats (unsaturated fatty acids with trans-isomers) raise the chance of developing cardiovascular and metabolic illnesses. Dietary lipids may have an impact on mammalian health and longevity by changing the compositions of body fat and cell membranes. Arachidonic acids, which are omega (x)-6 PUFAs, trigger apoptosis in cancer cells.	
Carbohydrates	Consuming more glucose makes you age faster Human cells grown in culture age more quickly when there are high glucose concentrations in the medium. Trehalose, pyruvate, malate, fumarate, and N acetylglucosamine (GlcNAc), among other carbohydrates or carbohydrates' metabolites, have been proven to lengthen C. elegans' lifespans. Age-related disorders, such as diabetes and heart problems, can be prevented by following a low-carbohydrate diet	(Lee, H. J., et al, 2014; Schulz, T. J., et al, Schulz, T. J, 2007, Schlotterer, A., et al, 2009)
Vitamins and Minerals	Rotifers, nematodes, and fruit flies live substantially longer when given vitamin E/tocopherol [297-315] The bean beetle lives longer when given more vitamin C/ascorbic acid, a well-known antioxidant. Maculatus Callosobruchus Numerous vitamin B family members also extend the lives of flies, Zucker fatty rats, and C. elegans; nevertheless, a mega-dose of vitamins and minerals modestly raises the death rate in humans. Mineral antioxidant selenium (Se) drastically lowers DNA deterioration and prolongs the replicative life of cultured adrenocortical cells.	(Solon-Biet., et al, 2014; Hornsby and Harris, 1987; Preuss, H. G., et al, 2011, Choudhury, S. R., et al 2022)

A reliable substitute indication of the physiological operation of different organs is the basal metabolic rate (BMR). BMR decreases with ageing as a result of age-related physiological changes in the organ system that cause negative changes in energy expenditure. Thermic energy, overall energy expenditure, and amount of physical activity also decrease. Additionally, the energy expenditure's reactivity to the energy imbalance has decreased (Melanson, K. J., et al, 1997). A landmark study by Keys et al. (Keys, A., et al, 1973) found that BMR decreased by as much as 1-2% every decade as people aged. In this approach, the results (Keys, A., et al, 1973) may be used to anticipate a decrease in BMR of roughly 400 kJ/day over the life span stage of 20 to 70 years of age. The fundamental cause of the age-related decline in BMR may be age-related changes in body composition (Melanson, K. J., et al, 1997). Basal or resting energy expenditure, diet-induced thermogenesis, and energy used during exercise make up daily energy expenditure (Keys, A., et al, 1973). With ageing, all components might undergo changes. First off, although per kg fat-free mass is either maintained or just slightly reduced when lean mass declines, BMR in proportion to body weight declines. Second, there is less diet-induced thermogenesis with decreased food intake. Third, activity declines, especially with impairment. Despite the age-related fall in energy intake, these modifications lead to a favourable energy balance in middle age and the above-described alterations in body composition. Finally, when people become older and develop anorexia, their energy balance turns negative, and their BMI and fat mass decrease. Similarly, a decline in BMR may also be linked to anorexia and weight loss brought on by chronic illness. The immune system is impacted by these changes.

CONCLUSION

Here, we explored the connections between psychological stress, depressive symptoms, and immunological processes, paying particular attention to those elements relevant to ageing.

Although the clinical significance of these interactions has yet to be determined, the high prevalence of autoimmune, infectious, and neoplastic illnesses in the elderly implies that attention should be paid to psychoneuroimmune interactions in this population. Future study on psychoneuroimmunology and ageing requires further in-depth analysis, particularly a multidisciplinary approach to completely comprehend the complicated interaction between psychoneuroimmunology, food, and mental health.

AUTHORS CONTRIBUTION

All authors have contributed equally.

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