Review

Work-Related Stress, Physio-Pathological Mechanisms, and the Influence of Environmental Genetic Factors

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Abstract: Work-related stress is a growing health problem in modern society. The stress response is characterized by numerous neurochemicals, neuroendocrine and immune modifications that involve various neurological systems and circuits, and regulation of the gene expression of the different receptors. In this regard, a lot of research has focused the attention on the role played by the environment in influencing gene expression, which in turn can control the stress response. In particular, genetic factors can moderate the sensitivities of specific types of neural cells or circuits mediating the imprinting of the environment on different biological systems. In this current review, we wish to analyze systematic reviews and recent experimental research on the physio-pathological mechanisms that underline stress-related responses. In particular, we analyze the relationship between genetic and epigenetic factors in the stress response.

Keywords: work-related stress; environment; genetic factors; stress

1. Introduction

In the professional world, alongside specific risk agents responsible for occupational diseases, there are other factors, such as stress conditions, capable of creating non-specific occupational diseases with more or less serious consequences on the biological, physical, psychological, and social level of the individual [1–3]. Stress related to work is one of the most frequent causes of occupational diseases, including cancer. The European Agency for Safety and Health at Work has adopted the following definition for stress: “Work-related stress is experienced when requests from the work environment exceed the individual’s ability to deal with this request”.

Although the importance of stress as a pathogenetic factor of various psychosomatic illnesses has been recognized ever since the first half of the last century, it is only in these last decades that the deepening of knowledge in the fields of neurochemistry, neuroendocrinology, and immunology has allowed us to understand and interpret, in large, the variations of the specific mechanisms that are at the basis of pathologies induced by an excess of adverse stimuli [4,5].

As complex as they may be, the responses to stress in humans are the expression of an integrated and genetically controlled biological program [6,7]. The motivations able to invoke an alarmed reaction are part of the individual’s daily life, and the possibility that the person can reduce or cancel the negative consequences depends on their ability to adapt. Stressors that are completely similar can induce quantitatively and qualitatively different responses in accordance with the personality and the experiences of the individual, their biorhythms, and the characteristics of the stressors. Characteristics such as regularity, predictability, avoidability, duration, and intensity, as well as various environmental
factors such as the light/dark cycle, temperature, humidity, noise, ionization of the atmosphere, and the frequencies of magnetic fields can all influence the stress response in different ways [8–15].

In recent years, within this high-technological progress society, the types of stress to which a subject is exposed are not predominantly of a physical nature. The most frequent stressors to manage and to which subjects are exposed are those of a psychosocial nature, favored by a widespread social organization concentrated on pragmatism and industrialization, and characterized by intense emigration and rapid changes in the socio-economic status of the individual, in addition to a progressive weakening of the family structures and the supports provided by the society [16–19].

In this regard, it seems that the European economic crisis, which began in 2008, could play a prominent role in an individual’s probability of contracting stress-related disease [20–25]. In particular, it has been reported that financial crisis, loss of work, and reductions in salary could significantly increase the frequency of mental health disorders and the consumption of substances of abuse. Furthermore, in times of crisis, health outcomes and the risk of health-related financial hardship may be affected by changes in the resources available for health systems (e.g., financial and human resources, drugs and medical devices, running costs and infrastructure), by changes in living conditions, lifestyles, and consumer behaviors, as well as by changes in social norms and values. On the other hand, several critical studies demonstrated that financial crises seemed to be linked to increased work-related stress, and in some cases, to the development of mental illness [26–34]. An elegant review by Mucci and colleagues [35] analyzed results about the economic crisis and physical health, showing that financial crisis was an important stressor that was able to promote negative effects on the health of workers and the general population.

The homeostatic adaptations to stress are essentially regulated by the central nervous system (CNS), the neuroendocrine system (NES), and the immune system (IS) [1,36–41]. These closely connected systems allow us to perceive, process, and transform the stimuli into messages for the various effector organs. The brain is made up of a series of synaptic connections wired between neurons, comparable to thousands of servers that connect millions and millions of computers. The neuron that transmits the signal releases one or more neurotransmitters and neuromodulators into the synaptic space, and these selectively interact with receptors on the surface of the neuron to which the information is to be transmitted. The interaction triggers a cascade of specific biochemical events that are responsible for the appearance of various biological and behavioral effects. This feature allows the different brain areas to interact synchronously to perform complex tasks. Stress-specific variations are determined in the release of neurotransmitters and neuromodulators that, for a short or long time, will influence the responses of the various organs and behaviors, such as emotional, cognitive, alimentary, and sexual [42–47].

The objective of this qualitative systematic review is to examine and interpret the evidence from different studies on neuroendocrine and genetic factors that underline and predict vulnerability to work-related stress responses.

2. Materials and Methods

The author’s search targeted evidence-based guidelines, evidence-based summaries, systematic reviews, and recent experimental research on the physio-pathological mechanisms that underline stress-related responses. The keywords used were “work-related stress”, or “neuroendocrine stress responses”, or “stress and immune system”, or “cytokine and hypothalamic-pituitary-adrenal (HPA) axis”, or “genetic and epigenetic programming of stress responses”. Through this strategy, we identified more than 1000 papers using two primary sources for identifying relevant information: PubMed and SCOPUS (last accessed via PubMed and SCOPUS on September 2019).

3. Neuroendocrine Control of the Stress Response

The stress response is characterized by numerous neurochemicals, neuroendocrine and immune modifications that involve various neurological systems and circuits, as well as regulation of the gene
expression of the different receptors. The main brain structures involved in stress responses include the prefrontal cortex, the amygdala, the hippocampal septum system, and the adrenergic nuclei of the brain stem, including the nuclei coeruleus, paravertebral, cuneiform, and the dorsal nucleus of the raphe [41,48–51].

Corticotropic releasing hormone (CRH) and adrenalin (AD) are the main brain mediators that coordinate stress responses. In particular, the CRH response is mediated by two receptors, CRH-R1 and CRH-R2. CRH-R1 receptors are involved in processing sensory information and motor control, while CRH-R2 receptors regulate emotional, affective, and cognitive behavior [52–55]. A typical neuroendocrine stress response involves the immediate release of CRH and vasopressin from the hypothalamus that, by mutual reinforcement, stimulates the pituitary to secrete the adrenocorticotropic hormone (ACTH), which activates the secretion of cortisol (COR) from the adrenal gland [56,57].

The effects of COR are mediated by two subtypes of receptors: The mineralcorticoid receptors (MRs), which are continually occupied by COR during the day and exert a tonic inhibition on the activity of the HPA axis, and the glucocorticoid receptors (GRs), which are activated only when the COR levels are elevated, as happens during stress or the morning peak [58–63]. It has been observed that a down-regulation of the MRs determines a serious deficit of learning and memory, while a down-regulation of the GRs allows individuals to still be able to learn and remember past experiences [39,64–68]. A greater release of glutamic acid also contributes to the negative effects of stressors, such as a reduction in serotonin as well as in the levels of Brain-Derived Neurotrophic Factor (BDNF), a peptide that regulates the proliferation and differentiation of synapses and the survival of neurons, which is expressed in numerous brain structures [69–71]. Increased levels of AD in acute stress facilitate the formation of memories associated with intense emotions, while in chronic stress, elevated COR levels are maintained for a long time with consequent disturbances of emotional, affective, and cognitive behavior [72].

The locus ceruleus is a critical component of the brain’s vigilance system as it controls the subject’s state of alert. A rapid activation of the locus ceruleus–AD system contributes to the processing of somatic adaptation responses to stress, such as increased blood pressure and heart rate, erection pacing, and mydriasis, as well as activation of metabolic processes [73].

The HPA axis and the locus cereuleus–AD system differ in their temporal responses. The locus cereuleus response is fast and runs out quickly, while the HPA axis response starts immediately and lasts longer. There is an increase in the blood levels of CRH and AD through a negative feedback mechanism during post-stress periods, which reduces the production and secretion of CRH and AD. CRH, in addition to controlling the response of the HPA axis, also acts as a neurotransmitter in various extra hypothalamic circuits in order to effectively integrate multiple brain responses to stressors. In addition to activating the alert state and increasing motor reflexes and emotional tone, CRH also influences cognitive processes [1,39,73–75].

4. The Immune System’s Role in the Stress Response

The CNS, peripheral nervous system (PNS), and IS are part of a completely integrated biological circuit, and their signals are used both for the exchange of information between the elements of the same system and for communication between the three systems. The CNS modifies its responses through both self-regulation mechanisms and signals coming from the NES and the IS. The existence of a bidirectional network of communication between the NES and IS causes the body to respond to non-cognitive stimuli, such as those of an infectious, immune, and neoplastic nature. Changes in the responses of the NES and IS due to stress and the genetic characteristics of the subject can also depend on the meaning attributed to the stressors in relation to the subject’s previous experiences and the presence or absence of social support [76–78].

COR and AD, which are released following the activation of the HPA axis and the central sympathetic system, are the main compounds that modulate the IS response [79–81]. After an event of acute stress, there is an increase in the blood levels of AD due to activation of the HPA axis.
which therefore increases the production of specific mediators—the cytokines—by the IS [82–85]. The cytokines are chemical messengers that flag the presence of danger coming from non-cognitive stimuli to the organism. These cross the blood–brain barrier with an active transport mechanism, facilitating the release of CRH and ACTH from the hypothalamus and the hypophysis [86,87]. Once the stress response is over, the elevated blood levels of COR, through a central counter-regulation mechanism, bring the activity of the IS back to the basal levels. If the stress is prolonged, the repeated activation of the HPA axis and of the central adrenergic system induces a persistent increase in the blood levels of COR and AD, which activates the IS and predisposes the subject to numerous types of pathologies [86–89].

5. Role of Genetic and Epigenetic Factors in the Stress Response

Different studies have reported that epigenetics is a risk factor for the onset of stress-related disorders [90,91]. The possibility that environmental work stresses can cause organic pathologies and behavioral disturbances is inversely proportional to their genetic component [92]. Pathologies with a strong genetic component may manifest themselves in response to mild or moderate stressors, while intense and prolonged stressors are required to induce pathologies characterized by a lower genetic determination. Psychiatric disorders such as schizophrenia can be unveiled by stressors of modest intensity, while a depressive syndrome needs severe stimuli to manifest itself, as it has a minor genetic component. As in the case of post-traumatic stress disorder, if the magnitude of the stressful event is particularly high, a mental illness can also arise in subjects with normal and resilient genomes [93,94]. Two possible mechanisms with which genes and the environment can interact are: “Genetic control of sensitivity to the environment” and “genetic control of exposure to the environment”. Genetic control of sensitivity to the environment suggests that genes, at least in part, make individuals more or less vulnerable to the effects of environmental stressors, while genetic control of exposure to the environment implies that genetic factors influence the likelihood of individual selections, such as the necessity to emigrate for work, or exposure to environments with lower risks of stress [95–97].

The ontogenesis of the brain, from the first fetal outline to complete development, is characterized by a series of histological and biochemical changes induced by the continuous interaction of genes with the environment. In particular, CRH plays a decisive role in the maturation of the HPA axis, as it can regulate the development of neuronal circuits and connections aimed at stress responses. CRH also interacts with the neurons that synthesize serotonin, GABA, and BDNF, which have trophic effects on the brain during the early periods of ontogeny [98–100].

There is vast literature that demonstrates how the quality of the environment has a deep impact on the development of different brain circuits. Most of the knowledge of the early effects of stress on humans comes from retrospective studies of children whose mothers suffered psychological stress during pregnancy. These children showed delayed motor development, reduced attention, excessive reactivity and aggression, mood disturbances, irresponsible social behavior, and in adulthood they became more vulnerable to anxiety and depression disorders, and encountered a greater risk of taking drugs. It has been suggested that these behavioral disorders are mediated, at least in part, by the excessive activation of the mother’s HPA axis. According to these observations, experimental animal studies have shown that intense and persistent prenatal stress induces, from the first days of birth, a dysfunction of the HPA axis with an increase in the release of CRH, ACTH, and cortisol in the young ones, as well as an accentuated response of the sympathetic autonomic system. These effects are accompanied by a loss of neurons and receptors in the brain areas that control stress responses and correlate with an increase in emotionality, depression, minor social interaction, and cognitive impairment [101,102].

In recent years, epigenome studies have shown that modifications in the regulation of gene expression are transferable from one generation to another through the parent’s sperm. “It has been demonstrated that sperm is not meant to only transport 23 chromosomes, but it also carries an epigenetic cargo consisting of methylated DNA, non-coding RNAs, protamines, and histones which
are critical for fertilization and programming early embryonic development. While observing multiple animal studies, it resulted that paternal stress before conception was associated with changes in sires’ sperm miRNAs (small molecules that have the function of silencing and degrading specific messenger RNAs, preventing their translation into proteins), decreased HPA axis responses following an acute stressor in the child, and increased expression of glucocorticoid-responsive genes in the brain of the child” [103–106].

There is limited epidemiological data on the effects of human paternal preconception exposure on children’s health. However, in a series of recent studies of human epidemiology among adults born to mothers and father with Holocaust post-traumatic stress disorders (PTSD), this condition was associated with an increased risk of PTSD, lower levels of urinary cortisol, increased glucocorticoid sensitivity, and lower methylation of the GRs gene in the child [107].

6. Conclusions

In the professional work environment, together with specific risks responsible for occupational diseases, there are non-specific psychosocial and environmental risks that can determine different organic and behavioral disorders. The homeostatic adaptations to stress are regulated by the CNS, NES, and IS, which constitute an integrated biological circuit under the control of genes. COR and the AD, released after the activation of the HPA axis and the central sympathetic system, are the main factors that modulate the stress response. Pathologies with a strong genetic component can be triggered by mild stressors, while those with a modest genetic component require more severe stressors. Brain ontogenesis is characterized by continuous neurobiological changes induced by a persistent interaction of genes with the environment. Retrospective studies in the human field have shown that psychological stress during pregnancy determines emotional, affective, cognitive, and social behavior disorders in the child that correlate with a dysfunction of the HPA axis and with an increased response of the sympathetic autonomic system.

Recent experimental research on epigenomes has shown that modifications in the regulation of gene expressions are transferable through the parent’s sperm to the child. In particular, animal studies have shown that paternal stress before conception induces modifications in the miRNAs of the sperm to the child which determine a dysfunction of the HPA axis associated with various behavioral disorders. These recent studies demonstrate how, when both parents have the knowledge of the negative consequences of psychosocial stress on the health of their child, it is essential to be able to implement a correct lifestyle before and after conception. Undoubtedly, a decisive contribution to this knowledge must be given by all social figures who are required to guarantee the health and well-being of the worker.

This qualitative systematic review [108] provides further information about the roles played by homeostatic adaptations to stress that are responsible for the appearances of various biological and behavioral effects. Furthermore, our review, by focusing on the involvement of epigenetic factors as risks for the onset of stress-related disorders, provides new avenues of research regarding the mechanisms with which genes and the environment interact and predispose individuals to the onset of stress-related illness.

Taken together, these observations highlight the demand for further investigations that are able to identify and characterize the specific neuroendocrine and genetic factors that subtend and predict vulnerability to the work-related stress response.

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References

1. McEwen, B.S. Protective and damaging effects of stress mediators: Central role of the brain Dialogues. Clin. Neurosci. 2006, 8, 367–381.

2. Uchida, S.; Hara, K.; Kobayashi, A.; Otsuki, K.; Yamagata, H.; Hobara, T.; Suzuki, T.; Miyata, N.; Watanabe, Y. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 2011, 69, 359–372. [CrossRef] [PubMed]

3. Landolt, K.; Maruff, P.; Horan, B.; Kingsley, M.; Kinsella, G.; O’Halloran, P.D.; Hale, M.W.; Wright, B.J. Chronic work stress and decreased vagal tone impairs decision making and reaction time in jockeys. Psychoneuroendocrinology 2017, 84, 151–158. [CrossRef] [PubMed]

4. Ostroumova, O.D.; Kochetkov, A.I. Worksite hypertension as a model of stress-induced arterial hypertension. Ter Arkh. 2018, 90, 123–132. [CrossRef]

5. Bergomi, M.; Modenese, A.; Ferretti, E.; Ferrari, A.; Licitra, G.; Vivoli, R.; Gobba, F.; Aggazzotti, G. Work-related stress and role of personality in a sample of Italian bus drivers. Work 2017, 57, 433–440. [CrossRef]

6. Hettema, J.M.; Neale, M.C.; Kendler, K.S. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am. J. Psychiatry 2011, 158, 1568–1578. [CrossRef]

7. Smoller, J.W. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Psychoneuroendocrinology 2016, 41, 297–319. [CrossRef]

8. Selye, H. The general adaptation syndrome and the diseases of adaptation. J. Allergy 1946, 17, 231–247. [CrossRef]

9. Selye, H. Stress and the general adaptation syndrome. Br. Med. J. 1950, 1, 1383–1392. [CrossRef]

10. Kalmbach, D.A.; Pillai, V.; Chen, P.; Arnedt, J.T.; Drake, C.L. Shift work disorder, depression, and anxiety in the transition to rotating shifts: The role of sleep reactivity. Sleep Med. 2015, 16, 1532–1538. [CrossRef]

11. Cannizzaro, E.; Cannizzaro, C.; Plescia, F.; Martorana, D.; Moscadini, S.; Coco, D.L. Effects of shift work on cardiovascular activity, serum cortisol and white blood cell count in a group of Italian fishermen. EMB J. 2012, 109–113. [CrossRef]

12. Cannizzaro, E.; Cannizzaro, C.; Martorana, D.; Moscadini, S.; Coco, D.L. Exposure to ototoxic agents and hearing loss: A review of current knowledge. Hear. Balance Commun. 2014, 12, 166–175. [CrossRef]

13. Consales, C.; Cirotti, C.; Filomeni, G.; Panatta, M.; Butera, A.; Merla, C.; Lopresto, V.; Pinto, R.; Marino, C.; Benassi, B. Fifty-Hertz Magnetic Field Affects the Epigenetic Modulation of the miR-34b/c in Neuronal Cells. Mol. Neurobiol. 2018, 55, 5698–5714. [CrossRef]

14. Walker, E.D.; Brammer, A.; Cherniack, M.G.; Laden, F.; Cavallari, J.M. Cardiovascular and stress responses to short-term noise exposures—A panel study in healthy males. Environ. Res. 2016, 150, 391–397. [CrossRef]

15. Ritsher, J.E.B.; Warner, V.; Johnson, J.G.; Dohenwend, B.P. Inter-generational longitudinal study of social class and depression: A test of social causation and social selection models. Br. J. Psychiatry 2001, 178, s84–s90. [CrossRef]

16. Kavikondala, S.; Stewart, S.M.; Ni, M.Y.; Chan, B.H.; Lee, P.H.; Li, K.K.; McDowell, I.; Johnston, J.M.; Chan, S.S.; Lam, T.H.; et al. Structure and validity of Family Harmony Scale: An instrument for measuring harmony. Psychol. Assess. 2015. [CrossRef]

17. Pesonen, A.K.; Räikkönen, K.; Heinonen, K.; Kajantie, E.; Forsén, T.; Eriksson, J.G. Depressive symptoms in adults separated from their parents as children: A natural experiment during World War II. Am. J. Epidemiol. 2007, 166, 1126–1133. [CrossRef]

18. Ni, M.Y.; Jiang, C.; Cheng, K.K.; Zhang, W.; Gilman, S.E.; Lam, T.H.; Leung, G.M.; Schooling, C.M. Stress across the life course and depression in a rapidly developing population: The Guangzhou Biobank Cohort Study. Int. J. Geriatr. Psychiatry 2016, 31, 629–637. [CrossRef]

19. Gili, M.; Roca, M.; Basu, S.; McKee, M.; Stuckler, D. The mental health risks of economic crisis in Spain: Evidence from primary care centres, 2006 and 2010. Eur. J. Public Health 2013, 23, 103–108. [CrossRef]
21. Katikireddi, S.V.; Niedzwiedz, C.L.; Popham, F. Trends in population mental health before and after the 2008 recession: A repeat cross-sectional analysis of the 1991–2010 Health Surveys of England. BMJ Open 2012, 2, e001790. [CrossRef] [PubMed]

22. Evans-Lacko, S.; Knapp, M.; McCrone, P.; Thornicroft, G.; Mojtahai, R. The mental health consequences of the recession: Economic hardship and employment of people with mental health problems in 27 European countries. PLoS ONE 2013, 8, e69792. [CrossRef] [PubMed]

23. Suhreke, M.; Stuckler, D. Will the recession be bad for our health? It depends. Soc. Sci. Med. 2012, 75, 647–653. [CrossRef] [PubMed]

24. Reeves, A.; McKee, M.; Stuckler, D. Economic suicides in the Great Recession in Europe and North America. Br. J. Psychiatry 2014, 205, 246–247. [CrossRef]

25. Ballacchino, A.; Salvago, P.; Cannizzaro, E.; Costanzo, R.; Di Marzo, M.; Ferrara, S.; LaMattina, E.; Messina, G.; Mucia, M.; Mulè, A.; et al. Association between sleep-disordered breathing and hearing disorders: Clinical observation in Sicilian patients. Acta Med. Mediterr. 2015, 31, 607–614.

26. Karanikolos, M.; Mladovsky, P.; Cylus, J.; Thomson, S.; Basu, S.; Stuckler, D.; Mackenbach, J.P.; McKee, M. Economic crisis in workplace: The impact of fear the crisis on mental health. Work 2015, 51, 135–142. [CrossRef]

27. Lopez Bernal, J.A.; Gasparrini, A.; Artundo, C.M.; McKee, M. The effect of the late 2000s financial crisis on suicides in Spain: An interrupted time-series analysis. Eur. J. Public Health 2013, 23, 732–736. [CrossRef]

28. Barr, B.; Taylor-Robinson, D.; Scott-Samuel, A.; McKee, M.; Stuckler, D. Suicides associated with the 2008–10 economic recession in England: Time trend analysis. BMJ 2012, 345, e5142. [CrossRef]

29. Giorgi, G.; Arcangeli, G.; Mucci, N.; Cupelli, V. Economic stress in workplace: The impact of fear the crisis on mental health. Work 2015, 51, 135–142. [CrossRef]

30. Giorgi, G.; Arcangeli, G.; Mucci, N.; Cupelli, V.; Gioffrè, P.A.; Rosati, M.V.; Tomei, F.; Tomei, G.; Breso-Esteve, E.; Arcangeli, G. Work-related stress assessment in a population of Italian workers. The stress Questionnaire. Sci. Total Environ. 2015, 502, 673–679. [CrossRef]

31. Mucci, N.; Giorgi, G.; Fiz Perez, J.; Iavicoli, I.; Arcangeli, G. Predictors of trauma in bank employee robbery victims. Neuropsychiatr. Dis. Treat. 2015, 2015, 2605–2612. [CrossRef] [PubMed]

32. Mucci, N.; Giorgi, G.; Cupelli, V.; Arcangeli, G. Future health care workers mental health problems and correlates. World Appl. Sci. J. 2014, 30, 710–715.

33. Giorgi, G.; Leon-Perez, J.M.; Cupelli, V.; Mucci, N.; Arcangeli, G. Do I just look stressed or am I stressed? Work-related stress in a sample of Italian employees. Ind. Health 2014, 52, 43–53. [CrossRef]

34. Parmar, D.; Stavropoulou, C.; Ioannidi, J.P.A. Health outcomes during the 2008 financial crisis in Europe: Systematic literature review. BMJ 2016, 354, i4588. [CrossRef] [PubMed]

35. Mucci, N.; Giorgi, G.; Roncaioli, M.; Fiz Perez, J.; Arcangeli, G. The correlation between stress and economic crisis: A systematic review. Neuropsychiatr. Dis. Treat. 2016, 12, 983–993. [CrossRef] [PubMed]

36. Ketchesin, K.D.; Stinnett, G.S.; Seasholtz, A.F. Corticotropin-releasing hormone-binding protein and stress: From invertebrates to humans. Stress 2017, 20, 449–464. [CrossRef] [PubMed]

37. Miller, D.B.; O’Callaghan, J.P. Neuroendocrine aspects of the response to stress. Metabolism 2002, 51, 5–10. [CrossRef] [PubMed]

38. McEwen, B.S.; Stellar, E. Stress and the individual. Mechanisms leading to disease. Arch. Intern. Med. 1993, 153, 2093–2101. [CrossRef]

39. Sapolsky, R.M.; Romero, L.M.; Munck, A.U. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 2000, 21, 55–89.

40. Vitlic, A.; Lord, J.M.; Phillips, A.C. Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system. AGE 2014, 36, 9631. [CrossRef]

41. McEwen, B.S. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol. Rev. 2007, 87, 873–904. [CrossRef] [PubMed]

42. Chrousos, G.P.; Gold, P.W. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 1992, 267, 1244–1252. [CrossRef] [PubMed]

43. Martines, F.; Salvago, P.; Ferrara, S.; Messina, G.; Mucia, M.; Plescia, F.; Sireci, F. Factors influencing the development of otitis media among Sicilian children affected by upper respiratory tract infections. Braz. J. Otorhinolaryngol. 2016, 82, 215–222. [CrossRef] [PubMed]

44. Ortolani, D.; Garcia, M.C.; Melo-Thomas, L.; Spadari-Bratfisch, R.C. Stress-induced endocrine response and anxiety: The effects of comfort food in rats. Stress 2014, 17, 211–218. [CrossRef]
45. Cannizzaro, C.; Plescia, F.; Martire, M.; Gagliano, M.; Cannizzaro, G.; Mantia, G.; Cannizzaro, E. Single, intense prenatal stress decreases emotionality and enhances learning performance in the adolescent rat offspring: Interaction with a brief, daily maternal separation. *Behav. Brain Res.* 2006, 169, 128–136. [CrossRef]
46. Martines, F.; Sireci, F.; Cannizzaro, E.; Costanzo, R.; Martines, E.; Mucia, M.; Plescia, F.; Salvago, P. Clinical observations and risk factors for tinnitus in a Sicilian cohort. *Eur. Arch. Otorhinolaryngol.* 2015, 272, 2719–2729. [CrossRef]
47. Eskildsen, A.; Fentz, H.N.; Andersen, L.P.; Pedersen, A.D.; Kristensen, S.B.; Andersen, J.H. Perceived stress, disturbed sleep, and cognitive impairments in patients with work-related stress complaints: A longitudinal study. *Stress* 2017, 20, 371–378. [CrossRef]
48. Bains, J.S.; Cusulin, J.I.W.; Inoue, W. Stress-related synaptic plasticity in the hypothalamus. *Nat. Rev. Neurosci.* 2015, 16, 377–388. [CrossRef]
49. Ulrich-Lai, Y.M.; Herman, J.P. Neural regulation of endocrine and autonomic stress responses. *Nat. Rev. Neurosci.* 2009, 10, 397–409. [CrossRef]
50. Russo, S.J.; Nestler, E.J. The brain reward circuitry in mood disorders. *Nat. Rev. Neurosci.* 2013, 14, 609–625. [CrossRef]
51. Godoy, L.D.; Rossignoli, M.T.; Delfino-Pereira, P.; Garcia-Cairasco, N.; de Lima Umeoka, E.H. A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. *Front. Behav. Neurosci.* 2018, 12, 127. [CrossRef] [PubMed]
52. Gyires, K.; Feher, A. Stress, Neuropeptides and Gastric Mucosa. *Curr. Pharm. Des.* 2017, 23, 3928–3940. [CrossRef] [PubMed]
53. Klenerova, V.; Kvetnansky, R.; Hynie, S. The Effect of Acute and Repeated Stress on CRH-R1 and CRH-R2 mRNA Expression in Pituitaries of Wild Type and CRH Knock-Out Mice. *Cell Mol. Neurobiol.* 2018, 38, 163–169. [CrossRef] [PubMed]
54. Contarino, A.; Dellu, F.; Koob, G.F.; Smith, G.W.; Lee, K.F.; Vale, W.W.; Gold, L.H. Dissociation of locomotor activation and suppression of food intake induced by CRF in CRF1-deficient mice. *Endocrinology* 2000, 141, 2698–2702. [CrossRef]
55. Bale, T.L.; Contarino, A.; Smith, G.W.; Chan, R.; Gold, L.H.; Sawchenko, P.E.; Koob, G.F.; Vale, W.W.; Lee, K.F. Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. *Nat. Genet.* 2002, 24, 410–414. [CrossRef]
56. Cannizzaro, C.; La Barbera, M.; Plescia, F.; Cacace, S.; Tringali, G. Ethanol modulates corticotropin releasing hormone release from the rat hypothalamus: Does acetaldehyde play a role? *Alcohol. Clin. Exp. Res.* 2010, 34, 588–593. [CrossRef] [PubMed]
57. Zelena, D.; Pintér, O.; Balázsfi, D.G.; Langnaese, K.; Richter, K.; Landgraf, R.; Makara, G.B.; Engelmann, M. Vasopressin signaling at brain level controls stress hormone release: The vasopressin-deficient Brattleboro rat as a model. *Amino Acids* 2015, 47, 2245–2253. [CrossRef]
58. Reul, J.M.; de Kloet, E.R. Two receptor systems for corticosterone in rat brain: Microdistribution and differential occupation. *Endocrinology* 1985, 117, 2505–2511. [CrossRef]
59. Reul, J.M.; de Kloet, E.R. Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vitro autoradiography and computerized image analysis. *J. Steroid Biochem.* 1986, 24, 269–272. [CrossRef]
60. De Kloet, E.R.; Sibug, R.M.; Helmerhorst, F.M.; Schmidt, M. Stress, genes and the mechanism of programming the brain for later life. *Neurosci. Biobehav. Rev.* 2005, 29, 271–281. [CrossRef]
61. De Kloet, E.R.; Sarabdjitsingh, R.A. Everything has rhythm: Focus on glucocorticoid pulsatility. *Endocrinology* 2008, 149, 3241–3243. [CrossRef] [PubMed]
62. Joëls, M.; Pasricha, N.; Karst, H. The interplay between rapid and slow corticosteroid actions in brain. *Eur. J. Pharmacol.* 2013, 719, 44–52. [CrossRef] [PubMed]
63. Young, E.A.; Abelson, J.; Lightman, S.L. Cortisol pulsatility and its role in stress regulation and health. *Front. Neuroendocriniol.* 2004, 25, 69–76. [CrossRef] [PubMed]
64. Zhe, D.; Fang, H.; Yuxiu, S. Expressions of hippocampal mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) in the single-prolonged stress-rats. *Acta Histochem. ET Cytochem.* 2008, 41, 89–95. [CrossRef]
65. McEwen, B.S.; Sapolsky, R.M. Stress and cognitive function. *Curr. Opin. Neurobiol.* 1995, 5, 205–216. [CrossRef]
66. Lupien, S.J.; Lepage, M. Stress, memory, and the hippocampus: can’t live with it, can’t live without it. *Behav. Brain Res.* 2001, 127, 137–158. [CrossRef]
67. Donley, M.P.; Schulkin, J.; Rosen, J.B. Glucocorticoid receptor antagonism in the basolateral amygdala and ventral hippocampus interferes with long-term memory of contextual fear. *Behav. Brain Res.* **2005**, *164*, 197–205. [CrossRef]

68. Khakṣari, M.; Rashidy-Pour, A.; Vafaei, A.A. Central mineralocorticoid receptors are indispensable for corticosterone-induced impairment of memory retrieval in rats. *Neuroscience* **2007**, *149*, 729–738. [CrossRef]

69. Lowery-Gionta, E.G.; Crowley, N.A.; Bukalo, O.; Silverstein, S.; Holmes, A.; Kash, T.L. Chronic stress dysregulates amygdalar output to the prefrontal cortex. *Psychoneuroendocrinology* **2018**, *139*, 68–75. [CrossRef]

70. Zaletel, I.; Filipović, D.; Puškaš, N. Hippocampal BDNF in physiological conditions and social isolation. *Rev. Neurosci.* **2017**, *28*, 673–692. [CrossRef]

71. Jeanneteau, F.; Borie, A.; Chao, M.; Garabedian, M. Bridging the gap between BDNF and glucocorticoid effects on brain networks. *Psychoneuroendocrinology* **2018**. [CrossRef]

72. Osborne, D.M.; Pearson-Leary, J.; McNay, E.C. The neuroenergetics of stress hormones in the hippocampus and implications for memory. *Front. Neurosci.* **2015**, *9*, 164. [CrossRef] [PubMed]

73. Winklewski, P.J.; Radkowski, M.; Wszedybyl-Winklewska, M.; Demkow, U. Stress Response, Brain Noradrenergic System and Cognition. *Adv. Exp. Med. Biol.* **2017**, *980*, 67–74. [PubMed]

74. Wong, D.L.; Tai, T.C.; Wong-Faull, D.C.; Claycomb, R.; Meloni, E.G.; Myers, K.M.; Carlezen, W.A., Jr.; Kvetnansky, R. Epinephrine: A short- and long-term regulator of stress and development of illness: A potential new role for epinephrine in stress. *Cell Mol. Neurobiol.* **2012**, *32*, 737–748. [CrossRef]

75. Womble, J.R.; Larson, D.F.; Copeland, J.G.; Brown, B.R.; Haddox, M.K.; Russell, D.H. Adrenal medulla denervation prevents stress-induced epinephrine plasma elevation and cardiac hypertrophy. *Life Sci.* **1980**, *27*, 2417–2420. [CrossRef]

76. Sorrells, S.F.; Sapolsky, R.M. An inflammatory review of glucocorticoid actions in the CNS. *Brain Behav. Immun.* **2007**, *21*, 259–272. [CrossRef]

77. Panerai, A.E.; Sacerdote, P.; Bianchi, M.; Manfredi, B. Intermittent but not continuous inescapable footshock stressand intracerebroventricular interleukin-1 similarly affect immunocytes and immunocyte b-endorphin concentrations in the rat. *Int. J. Clin. Pharmacol. Res.* **1997**, *17*, 115–116.

78. Moynihan, J.A. Mechanisms of stress-induced modulation of immunity. *Brain Behav. Immun.* **2003**, *17*, S11–S16. [CrossRef]

79. Borges, S.; Gayer-Anderson, C.; Mondelli, V. A systematic review of the activity of the hypothalamic-pituitary-adrenal axis in first episode psychosis. *Psychoneuroendocrinology* **2013**, *38*, 603–611. [CrossRef]

80. Wolf, O.T. Stress and memory in humans: Twelve years of progress? *Brain Res.* **2009**, *1293*, 142–154. [CrossRef]

81. Aguilera, G. HPA axis responsiveness to stress: Implications for healthy aging. *Exp. Gerontol.* **2011**, *46*, 90–95. [CrossRef] [PubMed]

82. Al-Noori, S.; Cimpan, A.; Maltzer, Z.; Kaiyala, K.J.; Ramsay, D.S. Plasma corticosterone, epinephrine, and norepinephrine levels increase during administration of nitrous oxide in rats. *Stress* **2018**, *21*, 274–278. [CrossRef] [PubMed]

83. Aguilera, G. HPA axis responsiveness to stress: Implications for healthy aging. *Exp. Gerontol.* **2011**, *46*, 90–95. [CrossRef] [PubMed]

84. Flak, J.N.; Myers, B.; Solomon, M.B.; McIlfveen, J.M.; Krause, E.G.; Herman, J.P. Role of paraventricular nucleus-projecting norepinephrine/epinephrine neurons in acute and chronic stress. *Eur. J. Neurosci.* **2014**, *39*, 1903–1911. [CrossRef] [PubMed]

85. Smith, S.M.; Vale, W.W. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin. Neurosci.* **2006**, *8*, 383–395.

86. Gadde-Michalska, A.; Tadeusz, J.; Rachwalska, P.; Bugajski, J. Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems. *Pharmacol. Rep.* **2013**, *65*, 1655–1662. [CrossRef]

87. Mohn, C.E.; Fernandez-Solari, J.; De Laurentiis, A.; Bornstein, S.R.; Ehrhart-Bornstein, M.; Rettori, V. Adrenal glandrespones to lipopolysaccharide after stress and ethanoladministration in male rats. *Stress* **2011**, *14*, 216–226. [CrossRef]

88. Deak, T.; Bordner, K.A.; McElderry, N.K.; Barnum, C.J.; Blandino, P., Jr; Deak, M.M.; Tammarielo, S.P. Stress-induced increases in hypothalamic IL-1: A systematic analysis of multiple stressor paradigms. *Brain Res. Bull.* **2005**, *64*, 541–556. [CrossRef]
91. Bielawski, T.; Misiak, B.; Moustafa, A.; Frydecka, D. Epigenetic mechanisms, trauma, and psychopathology: Targeting chromatin remodeling complexes. *Rev. Neurosci.* 2019, 30, 595–604. [CrossRef] [PubMed]

92. Polli, A.; Ickmans, K.; Godderis, L.; Nijs, J. When Environment Meets Genes: A Clinical Review of the Epigenetics of Pain, Psychological Factors, and Physical Activity. *Arch. Phys. Med. Rehabil.* 2019, 100, 1153–1161. [CrossRef] [PubMed]

93. Jenkins, T.G.; Carrell, D.T. The sperm epigenome and potential implications for the developing embryo. *Int. J. Environ. Res. Public Health* 2019, 16, 4031, 10 of 10. [CrossRef] [PubMed]

94. Wolf, E.J.; Maniates, H.; Nugent, N.; Maihofer, A.X.; Armstrong, D.; Ratanatharathorn, A.; Ashley-Koch, A.E.; Garrett, M.; Kimbrel, N.A.; Lori, A.; et al. Traumatic stress and accelerated DNA methylation age: A meta-analysis. *Psychoneuroendocrinology* 2018, 92, 123–134. [CrossRef] [PubMed]

95. Van Os, J.; Kenis, G.; Rutten, B.P. The environment and schizophrenia. *Nature* 2010, 468, 203–212. [CrossRef] [PubMed]

96. Moreau, J.L.M.; Kesteven, S.; Martin, E.M.M.A.; Lau, K.S.; Yam, M.X.; O’Reilly, V.; Del Monte-Nieto, G.; Baldini, A.; Feneley, M.P.; Moon, A.M.; et al. Gene-environment interaction impacts on heart development and embryo survival. *Development* 2019, 146. [CrossRef] [PubMed]

97. Hunter, D.J. Gene-environment interactions in human diseases. *Nat. Rev. Genet.* 2005, 6, 287–289. [CrossRef] [PubMed]

98. Weinstock, M. Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neurosci. Biobehav. Rev.* 1997, 21, 1–10. [CrossRef]

99. Bosch, O.J.; Müsch, W.; Bredewold, R.; Slattery, D.A.; Neumann, I.D. Prenatal stress increases HPA axis activity and impairs maternal care in lactating female offspring: Implications for postpartum mood disorder. *Psychoneuroendocrinology* 2007, 32, 267–278. [CrossRef] [PubMed]

100. Zagron, G.; Weinstock, M. Maternal adrenal hormone secretion mediates behavioural alterations induced by prenatal stress in male and female rats. *Behav. Brain Res.* 2006, 175, 323–328. [CrossRef]

101. Fagiolini, M.; Jensen, C.L.; Champagne, F.A. Epigenetic influences on brain development and plasticity. *Curr. Opin. Neurobiol.* 2009, 19, 207–212. [CrossRef] [PubMed]

102. Sale, A.; Berardi, N.; Maffei, L. Environment and brain plasticity: Towards an endogenous pharmacotheraphy. *Physiol. Rev.* 2014, 94, 189–234. [CrossRef] [PubMed]

103. Jenkins, T.G.; Carrell, D.T. The sperm epigenome and potential implications for the developing embryo. *Reproduction* 2012, 143, 727–734. [CrossRef] [PubMed]

104. Braun, J.M.; Messerlian, C.; Hauser, R. Fathers Matter: Why It’s Time to Consider the Impact of Paternal Environmental Exposures on Children’s Health. *Curr. Epidemiol. Rep.* 2017, 4, 46–55. [CrossRef] [PubMed]

105. Van den Bergh, B.R.; Van Calster, B.; Smits, T.; Van Huffel, S.; Lagae, L. Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. *Psychoneuroendocrinology* 2008, 33, 536–545.

106. Rodgers, A.B.; Morgan, C.P.; Bronson, S.L.; Revello, S.; Bale, T.L. Paternal stress exposure alters sperm microRNA content and reprograms offspring HPA stress axis regulation. *J. Neurosci.* 2013, 33, 9003–9012. [CrossRef] [PubMed]

107. Yehuda, R.; Daskalakis, N.P.; Lehrner, A.; Desarnaud, F.; Bader, H.N.; Makotkine, I.; Flory, J.D.; Bierer, L.M.; Meaney, M.J. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. *Am. J. Psychiatry.* 2014, 171, 872–880. [CrossRef] [PubMed]

108. Grant, M.J.; Booth, A. A typology of reviews: An analysis of 14 review types and associated methodologies. *Health Inf. Libr. J.* 2009, 26, 91–108. [CrossRef] [PubMed]

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