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ADAPTING TO STRESS: UNDERSTANDING THE NEUROBIOLOGY OF RESILIENCE

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ABSTRACT

There is significant variation in the way individuals react and respond to extreme stress and adversity. While some individuals develop psychiatric conditions such as Post-Traumatic Stress Disorder (PTSD) or Major Depressive Disorder (MDD), others, recover from stressful

experiences without displaying significant symptoms of psychological ill-health, demonstrating stress-resilience. To understand why some individuals exhibit characteristics of a resilient profile, the interplay between neurochemical, genetic and epigenetic processes over time needs to be explained. In this review, we examine the hormones, neuropeptides, neurotransmitters and neural circuits associated with resilience and vulnerability to stress-related disorders. We debate how this increasing body of knowledge could also be useful in the creation of a stress-resilient profile. Additionally, identification of the underlying neurobiological components related to resilience may offer a contribution to improved approaches toward the prevention and treatment of stress-related disorders.

INTRODUCTION

Stress can be defined as a physiological and psychological reaction of the body toward an event or situation, commonly termed a stressor. The given stressor can be perceived broadly as either challenging or threatening¹⁻³. Challenges that are perceived as exhilarating, while at the same time being manageable, are normally classified as positive and beneficial to the individual, leading to accomplishment. However, threatening experiences, which are perceived as irritating or imposing significant danger, may result in short-term or long-term physiological and psychological ill health^{4,5}.

The brain is the central organ responsible for the stress response. It processes perceptual information for potential threats and initiates a response. Secondly, it regulates the physiological and/or psychological responses that can either be adaptive or damaging to the individual⁴. Furthermore, the brain is responsible for establishing a two-way communication between itself and the immune and cardiovascular systems via endocrine and neural mechanisms during the stress response^{4,6}.

The adaptive physiological response to acute stress comprises a process known as allostasis. This process performs the function of maintaining the internal viability of the organism amid changing environmental conditions⁷⁻⁹. In the short term, this is achieved by physiological changes in the Autonomic Nervous System (ANS) through the Sympathetic Nervous System (SNS), Hypothalamic-Pituitary-Adrenal (HPA) Axis hormones, cytokines and a number of other systems^{10,11}.

A physiological response to environmental stressors is of evolutionary advantage as a function of the acute stress response, more commonly known as the “fight-or-flight”

mechanism¹². However, if recovery is not accompanied by an adequate homeostatic response, the initial response could ultimately result in harmful after effects¹³. The prevailing effects of stress have been conceptualised as the allostatic load, which represents the physiological and psychological consequences of repeated chronic exposure to heightened neuroendocrine responses. In turn, the cumulative effect of these responses can result in psychopathological conditions such as Post-Traumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD), among others^{14,15}.

By examining how humans and animals adapt to highly aversive environments, researchers have recently identified some of the neural, neurochemical, genetic and epigenetic components that may characterize vulnerability, and conversely resilience, in individual responses¹⁶⁻¹⁸. This paper assesses the role of these factors in relation to individuals who appear to show resilience in the face of extreme or repeated traumatic stressors. This review had three main objectives. First, understand the dynamic concept of stress and resilience and what differentiates a resilient from a non-resilient individual; second, identify the neurochemicals, genetic and epigenetic mechanisms hypothesised as a basis of resilience or vulnerability to a stress-related disorder; third, to understand whether the ability to cope with high levels of stress are inborn, inherited and/or acquired through specific training (e.g. through a stress inoculation process) or some combination of the above. A comprehensive review of the current research and introduction to the physical processes associated with resilience is of interest and importance to the medical community.

The literature search was conducted between February 2014 and June 2014. Relevant studies published in peer-reviewed journals were identified through electronic searches on PubMed,

Web of Science, Embase, PsycINFO databases. Key search terms to identify title and/or abstract included words such as: “stress” OR “resilience” OR “adaptation” OR “allostasis” OR “allostatic load” OR “PTSD” OR “depression” *combined with* “physiology” OR “psychopathology” OR “neurochemistry” OR “neuropeptide” OR “neurotransmitters” OR “hormones” OR “neurobiological factors” OR “endocrine system” OR “sympathetic nervous system” OR “hypothalamic-pituitary-adrenal axis” OR “central nervous system” OR “genes” OR “genetic” OR “genetic variation” OR “epigenetic” OR “psychiatric disorders” OR “toxic”.

UNDERSTANDING RESILIENCE TO STRESS

Concept of Resilience

Resilience is the dynamic process through which an individual can adaptively overcome a stressful and/or traumatic event(s), while maintaining relatively normal physical and psychological function over time¹⁹⁻²¹. Additionally, resilience is referred to as a two-dimensional construct. This implies that when an individual has been subject to a stressor (such as exposure to a life-threatening event), the experience has led to a positive adjustment. As such, this bi-dimensional construct implies two evaluations. The first is about the significance of risk or adversity associated with negative life conditions, and the second is about how a positive “adaptation” is displayed through behaviour on social competence or success at that specific life stage²². In this context, individuals classified as stress resilient are normally defined as exhibiting an enhanced capacity of avoiding deleterious physiological and psychological consequences as a result of exposure to extreme stress, which could otherwise result in serious stress-related psychiatric disorders, such as PTSD or MDD^{16,20}. It is important to mention that resilience is not

conceptualised as the absence of a diagnosable psychiatric condition but rather a constructive adaptation to adversity and traumatic experience^{19,22}.

The characterization of resilience is still difficult to conceptualise and operationalize, as it represents many forms of successful adaptive biological, behavioural and cognitive responses to traumatic events^{21,23}. As individuals exhibit a pattern of recuperation from life-threatening experiences, researchers have sometimes used the concept of resilience inappropriately. For example, other adaptive responses to traumatic experiences such as recovery from trauma can also be observed. The concept of recovery from trauma, indicates a trajectory in which normal functioning temporarily gives way to a disruption through the manifestation of significant psychiatric symptoms for a period of several months, followed by a slow but yet significant recovery over months to levels of functioning prior to trauma^{19,24}. Therefore, while both these responses are similar in the long-term, only the resilient ones exhibit a stable trajectory of healthy functioning over time^{19,24}. In this review, we will only characterize the biological stress responses known to be linked with resilient phenotypes and how their enhanced neurobiological response is processed.

NEUROCHEMICAL, GENETIC, EPIGENETIC FACTORS IN STRESS RESILIENCE

Neurochemical Factors in Stress Resilience

A significant number of neurochemicals (such as neuropeptides, hormones and neurotransmitters) are involved in the acute psychobiological response to stress. These neurochemicals have been investigated in relation to stress resilience, and conversely, to the risk of psychopathology^{10,16}. According to several studies, these neurochemicals have been shown to be significantly altered by stress and to perform an important functional interaction in the brain,

by mediating the neural circuits and molecular pathways relevant to cognitive functioning, fear conditioning, regulation of reward and social behaviour^{10,17}. So far, some of the neurochemical components linked to stress resilience include constituents of the SNS, for example norepinephrine (NE) and neuropeptide-Y (NPY) or galanin, from the HPA Axis, corticotropin-releasing hormone (CRH), cortisol, dehydroepiandrosterone (DHEA), and from other systems including the dopaminergic, serotonergic systems, brain-derived neurotrophic factor (BDNF), or neurosteroidogenic enzymes^{10,18,25}.

- Sympathetic Nervous System (SNS)

Under circumstances of potential danger, the human and animal SNS will release neurochemical components such as epinephrine, the hormone responsible for the fight-or-flight response, and NE in order to protect the organism from the perceived threat. However, danger response varies from one individual to the other, and therefore stress responses can vary significantly^{12,26}.

In cases where individuals exhibit an unusual hyper-sensitive SNS response to stress, they can be subject to a higher risk of chronic anxiety, intrusive memories, fear, hypervigilance, and in some cases be diagnosed as having PTSD²⁷. It is also recognised that the maintenance of an SNS response within a certain level of activation, not so high to result in psychiatric symptoms though, has been observed in highly resilient individual^{28,29}.

- Norepinephrine (NE)

NE is a catecholamine present within cells of the Central (CNS) and Peripheral Nervous System (PNS) and is known to work as a neurotransmitter during the stress response²⁷. NE is particularly noted for its function in cognitive alertness and vigilant concentration in individuals under

stress²⁷. Under stressful circumstances, the organism will release NE from the brainstem nuclei and locus coeruleus. In turn NE modulates the fight-or-flight response along with epinephrine by immediately increasing its heart rate, pressing the liberation of glucose from energy stores and so increasing blood stream to skeletal muscle and brain oxygen supply³⁰. A higher activation of the NE system is known for inhibiting functions in the prefrontal cortex, and therefore promoting instinctual responses over more complex cognitive responses³⁰.

Clinical evidence suggests that abnormal regulation of brain NE systems is observed in patients with PTSD, through symptoms such as re-experiencing, hyperarousal, tachycardia, increased diastolic blood pressure, and diaphoresis²⁷. However, studies that evaluated the blockade of β -adrenergic receptors in the amygdala were thought to ameliorate the development of aversive memories in human and animal studies^{13,31}. Thus, based on these findings, some authors suggest that a reduced responsiveness of NE could be linked with resilience to stress¹⁷.

- Neuropeptide-Y (NPY)

NPY is a 36-amino acid neuropeptide highly expressed in the mammalian brain and known to act as a neurotransmitter. It is produced in several areas of the brain, such as the hypothalamus, and is believed to have several important functions, including reducing anxiety, stress, pain perception, circadian rhythms and lowering blood pressure^{27,32}. Normally, NPY is released with NE when the SNS is highly activated. One of its main functions, is to restrain the ongoing release of NE and to prevent SNS overshoots^{27,32}. Numerous studies have proved the valuable function of NPY in mediating resilience and vulnerability to stress in both animals and humans^{29,32-34}. For example, studies with small rodents presenting PTSD-like behaviour exhibit a significant down-regulation of NPY in various areas of the brain, particularly the hippocampus

and amygdala. Additionally, centrally administered NPY doses in these small rodents showed a reverse in these negative behaviours (such as lower predator-scent stress)³⁵. Studies conducted on military personnel participating in particularly stressful training, known as Survival, Evasion, Resistance and Escape (SERE), compared highly resilient members of the US Special Forces with their regular infantry counterparts. The Special Forces participants were shown to produce higher concentrations of NPY and exhibit an enhanced physical and psychological performance, followed by a reduced vulnerability to stress-induced anxiety and dissociation. These robust increases of NE in the US Special Forces personnel were followed by similar robust increases in the levels of NPY^{29,34}.

In support, of the importance of NPY as a mediating factor in the stress response, one study compared a healthy civilian control group to a group of military veterans diagnosed as having PTSD. The study comprised a rest stage and a stress stage, the findings revealed that the veteran group displayed lower levels of NPY in each phase³⁶. Studies of veterans who suffered from PTSD showed that they exhibited a significant increase in NE levels which was not positively accompanied by a significant increase in their NPY levels. It is hypothesised that this maintained symptoms of anxiety, hyper-vigilance and intrusive combat-related memories^{27,36}. Additionally, other clinical studies have also shown that decreased concentrations of NPY in plasma and cerebrospinal fluid (CSF) were observed in individuals with PTSD and MDD^{37,38}.

In view of the current evidence, NPY can be seen as a novel molecular therapeutic target aimed to ameliorate and/or treat symptoms of PTSD. Indeed, a recent study examining the properties of intranasal NPY in a single prolonged stress animal model of PTSD showed reducing anxiety-like behaviours, particularly when administered before the stress task³⁹. In term

of human studies, we are only aware of one approved by the US National Institutes of Health (NIH) to investigate the safety and efficacy of intranasal NPY administration to individuals suffering from PTSD. At the time of writing this review the study was in the recruitment phase and as such results were not available for inclusion⁴⁰.

- Galanin

Galanin is a 30-amino acid neuropeptide existent in humans and encoded by the GAL gene, which is extensively expressed in the brain, and is known to have a significant effect in the SNS response. While the functional role of galanin is still vastly unknown, this neuropeptide appears to have some neuroprotective activity in the PNS and in the promotion of neurogenesis^{41,42}. Galanin is known to have an effect on the cardiovascular and sleep regulation, anxiety response, learning skills, memory and pain response control⁴³. Further to this, galanin is also known to be an inhibitory hyperpolarizing neuropeptide, alike NPY⁴⁴.

A significant high percentage, approximately 80%, of noradrenergic neurons located in the locus coeruleus (situated in the nucleus of the pons) are involved in the physiological response to stress and panic and co-express galanin^{10,45}. Galanin is normally released when NE is highly activated. Consequently, its activity reduces the firing action of the locus coeruleus^{45,46}. In rodent behavioural studies, centrally administered galanin has been known to modulate anxiety-like behaviours and when injected directly into the central nucleus of the amygdala, it was shown to block the negative effects of stress^{47,48}. These findings suggest that the noradrenergic response to stress leads to the release of galanin into the central nucleus of the amygdala as a protection against the anxiogenic effects of NE¹⁰. Conversely, researchers that studied knockout mice galanin receptors found that these animals showed increased anxiety-like behaviour, leading to

an augmented vulnerability to anxiety and isolation¹¹. According to these findings, the response to stress noradrenergic response may be contingent on a balance established between NE, NPY and galanin transmission¹⁰.

Novel approaches to evaluate the enhanced therapeutic characteristics of galanin are currently underway. For example, a study which evaluated small rodents exposed to different sets of experiences and stress tasks, revealed that both physical exercise and galanin therapy rodent groups exhibit decreased anxiety-like behaviours, while the group of rodents deprived of exercise exhibit increased anxiety-like behaviours. According to the authors, both physical exercise and galanin therapy groups demonstrated increased levels of galanin⁴⁹.

- Hypothalamic-Pituitary-Adrenal (HPA) Axis

A complex set of brain interactions between the hypothalamus, the pituitary gland and the adrenal gland, known as HPA Axis, play a crucial role in the human and animal stress response^{25,50-52}. Under an immediate threatening or stressful event, the hypothalamus releases a peptide hormone and neurotransmitter known as CRH into the hypothalamic-hypophyseal portal system (the connection between the hypothalamus and anterior pituitary) to mediate its stress response. The hypothalamic-hypophyseal portal system will then carry out the CRH into the anterior lobe of the pituitary where it will stimulate the production of another polypeptide tropic hormone known as adrenocorticotrophic hormone (ACTH). In turn, the ACTH hormone stimulates the synthesis of two steroid hormones, cortisol and DHEA into their stress response⁵². In several human and animal studies, resilience has been associated with the brain's ability to moderate stress-induced increases in CRH and cortisol. This operation occurs through an

elaborate negative feedback system which involves an optimal functioning and equilibrium of mineralocorticoid and glucocorticoid receptors^{53,54}.

- Corticotropin-Releasing Hormone (CRH)

CRH is a 41-amino acid peptide hormone and neurotransmitter encoded by the CRH gene and is known to play an important role in the acute stress response. Particularly in increased arousal, motor activity and reduced reward expectations and activated fear behaviours⁵⁵. CRH acts via the two receptors (CRH-1 and CRH-2), which are normally secreted by the paraventricular nucleus (PVN) of the hypothalamus in response to stress⁵⁶. Studies that evaluated different concentration levels found that increased CRH concentrations have been associated with PTSD, MDD and symptoms of fear and anxiety⁵⁷⁻⁵⁹. Conversely, those individuals who displayed reduced CRH concentrations were normally found to be resilient individuals¹⁰.

CRH-1 and CRH-2 receptors are spread in the different areas of the brain. CRH-1 receptor is normally found in the hippocampus, basolateral amygdala and neocortex, while CRH-2 receptor is normally found in the dorsal raphe, medial and cortical nuclei of the amygdala and lateral septum⁶⁰. The CRH-1 signaling is known to play a role in the anxiogenic circuit and leads to anxiety-like responses, while the CRH-2 controls the effects of CRH-1 signaling, and can either be anxiogenic or anxiolytic⁶¹⁻⁶³. In rodent studies where they exhibited a deficiency in the CRH-1 receptor, the animals displayed a reduced anxiety-like behaviour and a diminished stress response. However, animals that exhibited a deficiency in the CRH-2 receptor showed augmented anxiety like-behaviours and were hypersensitive to stress⁶⁴⁻⁶⁶. According to these findings, the triggering of the CRH-1 receptors are potentially linked with anxiety-like responses, while the triggering of the CRH-2 receptors are potentially linked with anxiolytic-like responses.

Though evidence exists highlighting the properties of CRH in animals, until now it has not been possible to examine the CRH-1 and CRH-2 receptors in humans¹⁰.

- Cortisol

Cortisol is a glucocorticoid that is part of the class of the steroid hormones produced by the zona fasciculata of the adrenal cortex. Its primary function is to mobilize and replenish energy stores⁶⁷. Cortisol is also known to perform an important role in the stress response by way of significant increases in vigilance, increased arousal, consolidation of memory and selective attention⁶⁸. While cortisol has an important regulatory effect on the amygdala, hippocampus and prefrontal cortex, the prolonged exposure to high levels of cortisol in the organism proved to have significant toxic effects, particularly in the neurodegeneration of the hippocampus, resulting in memory and learning deficits⁶⁷. Studies that included cortisol supplementation in healthy individuals revealed that the repeated administration of cortisol led to significant cognitive impairments, similar to those observed in patients diagnosed with depression⁶⁹. It is also well documented that excessively low and high cortisol levels have been found in individuals with a PTSD diagnosis⁷⁰. Recent findings suggest that in order to modulate the negative effects of cortisol, DHEA (which is also secreted with cortisol) serves a protective role, and is associated with resilience¹⁶.

- Dehydroepiandrosterone (DHEA) and DHEA Sulfate Ester (DHEA-S)

DHEA and DHEA-S are two endogenous hormones secreted by the adrenal cortex, and are known to be the most abundant circulating steroid hormones present in humans⁷¹⁻⁷³. While their precise mechanisms of action are not completely understood, some studies suggest that DHEA

and its derivative sulfate ester might serve in a variety of physiological aspects in the organism. These include control of fatness, mineral metabolism, sexual functioning, anti-inflammatory and antioxidant effects⁷¹⁻⁷³. Further studies also hypothesize that DHEA may exert a protective response against stress^{71,72}.

Several military studies highlighted the beneficial properties of DHEA and DHEA-S in supporting a protective role. A number of studies were conducted on healthy military personnel undergoing the SERE training school or the Combat Diver Qualification Course (CDQC). The results showed that soldiers who performed better under acute stress had a higher increased of DHEA or higher DHEA-to-cortisol ratio in the blood. These soldiers also showed a superior physical and psychological performance and reported fewer symptoms of dissociation⁷¹⁻⁷³. A further innovative study provided endogenous DHEA supplementation in a randomized, controlled, double-blind field study. They used a treatment versus control group, within a group of soldiers undergoing SERE training. The study focused on higher salivary concentrations of DHEA and DHEA-S as a result of DHEA treatment, none of the group differences resulted in a superior performance or in a reduction of dissociative symptoms⁷⁴. In general, DHEA administration studies with humans have failed to show any evidence of improved neurocognitive performance on their outcomes^{75,76}. However, there has been a double blind, placebo-controlled trial study which found improved mood and memory recollections after DHEA treatment in a sample of healthy young men. Though, individuals in this latest study were not exposed to any form of stress task⁷⁷.

Nevertheless, studies evaluating these two steroid hormones reported that a reduced concentration of DHEA ratio-to-cortisol can be translated into a higher risk of experiencing

chronic fatigue syndrome, anxiety, anorexia nervosa, depression, schizophrenia and PTSD⁷¹. Yet, this pattern of findings has not been observed thoroughly in all PTSD studies, which in relation to each other show conflicting results^{78,79}.

- Dopaminergic System, Dopamine

Dopamine is a hormone and neurotransmitter implicated in various neural functions including attention, motivational behaviour and motor control. Dopamine is also known to play an important role in the stress response⁸⁰. Stress inhibits the release of dopamine in the nucleus accumbens, an area mainly associated with the reward pathway, and activates the release of dopamine in the medial prefrontal cortex, an area associated in complex cognitive behaviour, personality expression, decision making and moderating social behaviour¹⁰. A further study evaluated lesions of dopamine neurons in the medial prefrontal cortex, the results suggested that reduced prefrontal cortical dopamine levels lead to the maintenance of the fear response, an outcome normally observed in individuals with PTSD⁸¹. Conversely, studies that identified high levels of dopamine release in the medial prefrontal cortex resulted in cognitive impairment. Thus, the data suggests that there is an optimal range for stress-induced increases in dopamine, released in the medial prefrontal cortex, that may facilitate advantageous behavioural responses. There has, until now, been little research concerning the function of dopamine in stress-related disorders¹⁰.

- Serotonergic System, Serotonin

Serotonin is a monoamine neurotransmitter present in the Central Nervous System (CNS). It is known to have an effect on the regulation of appetite, sleep, feelings of wellbeing and happiness. Serotonin is also known for its effects on mood and anxiety. The acute stress response is linked

with the augmented serotonin turnover in different areas of the brain, particularly in the lateral hypothalamus, amygdala, prefrontal cortex and nucleus accumbens^{18,30,82}. The liberation of serotonin in the brain is known to have both anxiolytic and anxiogenic effects, and this outcome is mediated by which part of the forebrain and receptors are stimulated. For example, stimulation of the serotonin 2A receptor results in anxiogenic effects, while the stimulation of the serotonin 1A are anxiolytic and potentially associated with adaptive reactions to stressful occurrences^{83,84}. Two additional serotonin receptors, particularly the serotonin 1B and 2C receptors, have also been studied and though to be associated with adaptive reactions to stressful circumstances³⁰.

- Brain-Derived Neurotropic Factor (BDNF)

BDNF is a protein encoded by the BDNF gene and is part of the neurotrophin family of growth factors^{85,86}. This neurotropic factor works in specific neurons of the CNS and PNS, and is known for supporting the survival of existing neurons, by stimulating the growth and differentiation of new neurons and synapses^{87,88}. BDNF is expressed in several regions of the brain such as the amygdala, prefrontal cortex, hippocampus and basal forebrain, and is implied in anxiety and mood disorders¹⁸.

Numerous studies have reported that a down-regulation of BDNF in the hippocampus has been observed in small rodents exposed to various types of stressors and in depressed patients who successfully committed suicide^{89,90}. According to some authors, hippocampal BDNF expression may have a significant influence in both stress resilience and risk of psychiatric problems¹⁸. BDNF acts through the BDNF-tyrosine kinase B (BDNF-TrkB) receptor. According to some human and animal studies that evaluated the BDNF-TrkB pathway, this receptor was related with PTSD symptomatology⁹¹. Conversely, those studies which administered antidepressants found

an increase in BDNF-TrkB receptors in the hippocampus and prefrontal cortex and a potential role to hippocampal neurogenesis⁹². However, this evidence was not observed in all BDNF-TrkB studies¹⁸.

- Neurosteroidogenic Enzymes, Allopregnanolone (ALLO)

ALLO is a cholesterol-derived neuroactive steroid present in the CNS that is synthesized from progesterone, a steroid hormone, in a two-step pathway, by action of the 5 α -reductase and 3 α -hydroxysteroid dehydrogenase enzymes, both steroidogenic enzymes^{93,94}. In particular, certain 3 α -reduced metabolites of progesterone such as ALLO are potent positive allosteric modulators of the Gama-Aminobutyric Acid (GABA_A) receptor, particularly known for being the chief inhibitory neurotransmitter in the vertebrate CNS^{93,94}.

Stress increases ALLO levels in the brain to concentrations that can activate the GABA_A receptors, and according to several studies ALLO might have potential pharmacological properties, particularly anticonvulsant and anxiolytic actions^{94,95}. New hypothesis concerning the putative anxiolytic and antidepressant properties of ALLO involve the role of stress in the HPA Axis dysregulation^{95,96}. Acute stress produces an increase in ALLO levels which negatively modulates the stress-induced HPA Axis activation, thus aiding the recovery of physiological homeostasis after a stressful stimuli^{97,98}. For example, in a study of small rodents, forced-swimming stress induced a time-dependent increase in the amount of ALLO and progesterone, both in the plasma and in brain areas such as cerebral cortex, hypothalamus and plasma by producing protection against the damaging effects of stressors⁹⁷. Nevertheless, other studies investigating chronic stress response, highlight a significant reduction in the ALLO concentration levels. This suggests that chronic stress may alter ALLO synthesis and lead to a

dysregulation in the HPA Axis⁹⁸. In a recent study of small rodents, chronic stress was associated with a significant reduction in endogenous ALLO levels and an increased risk of anxiety-like behaviours and depression⁹⁸. The exogenous administration of ALLO from the onset of isolation-induced chronic stress and a period of chronic stress was able to reduce the occurrence of anxiety-like behaviours and depression, and regulate the HPA Axis dysfunction⁹⁵. Based on these findings, it appears that ALLO is a key regulator of physiological functions and potentially important variable in resilience.

Early Genetic Factors in Stress Resilience

Genetics is the process of trait inheritance through the sharing of molecular structure and function of genes, gene behaviour and distribution, variation and change among similar or related organisms⁹⁹. Genetic factors play a very significant function in the determination of an individual's response to stress and therefore regulate their risk or resilience to a psychiatric condition^{17,18}. Indeed, studies developed with identical twins have projected an overall heritability rate of 32% to 38% in PTSD cases¹⁰⁰. Some studies considering individuals Deoxyribonucleic Acid (DNA) genetic make-up and their particular history of exposure to environmental stressors found that stress regulation response could be significantly affected by genetically modified differences in reactivity of the SNS, of the CNS through the HPA Axis, the noradrenergic and dopaminergic system, the serotonergic system, and the BDNF^{17,18,100}. We should mention here that this area is still largely unexplained and particularly unknown¹⁰¹.

- Sympathetic Nervous System (SNS) Related Genes

Regulation of the SNS can also be affected by genetic factors. Demonstrating the fundamental role of SNS reactivity, is a study that evaluated the genetically modified variation of

SNS activity in a group of healthy individuals, found that a polymorphism in the alpha adrenergic-2 receptor gene appears to be considerably linked with their autonomic hyper-responsiveness¹⁰². Further, another study found that during stress exposure, NPY levels were disturbed by polymorphism in the gene encoding of the NPY molecule¹⁰³. This suggests that the association between the noradrenergic system (NE) and stressor might be mediated by different alpha-2 adrenergic receptors subtypes. Consequently, when researchers evaluated the effects of mice knocked out by the alpha-2A adrenergic receptor, their findings suggested this receptor displayed stress-protective functions. Opposing these findings other studies have shown the alpha-2C adrenergic receptor was involved in stress susceptibility^{101,104}.

The SNS response to stress may also be disturbed by changes in the NPY-gene^{17,18}. Supporting this evidence, a study found that two NPY haplotypes have been associated with increased vulnerability to anxiety symptoms after experiencing severe adversity during youth¹⁰⁵. Another study evaluated the effects of NPY genetic expression on emotions and stress resilience and revealed that the presence of lower haplotype-driven NPY expression was predictive of diminished resilience, assessed by the presence of a higher emotional-induced activation of the amygdala in the brain¹⁰⁶. Still, the long term variant of the NPY encoding gene was related to a reduced PTSD susceptibility and negative emotional states in depression^{106,107}.

- Hypothalamic-Pituitary-Adrenal (HPA) Axis-Related Genes

Changes in genes that control HPA Axis reactivity appear to contribute significantly to modifications in biologically-based stress response systems and influence resilience or vulnerability to psychiatric conditions^{100,108}. Polymorphisms (mutation in the genotype) and haplotypes (combination of DNA sequences) in two key genes of the HPA Axis include the

corticotropin-releasing-hormone receptor 1 gene (CRHR1 gene) and the FK506-binding protein 5 gene (FKBP5), both potentially known for interacting with early life trauma (childhood maltreatment or abuse) and predictive of later life stress-related psychiatric conditions¹⁰⁸. A significant number of studies have examined CRHR1 gene variation in PTSD and MDD in individuals exposed to life-threatening circumstances. For example, the genetic marker spanning the CRHR1 receptor gene rs110402 has been associated with cortisol levels and the developing of depression in adult males who experienced trauma during their childhood¹⁰⁹. Other studies found protective effects of the CRHR1 TAT haplotype rs7209436, rs110402, rs242924 genetic markers in adults who have been victims of childhood maltreatment¹¹⁰. Concerning the FKBP5 gene, studies have shown the involvement of this gene in the modulation of the glucocorticoid receptor activity and signaling, and predicted the severity of the onset of depression and PTSD symptoms in adult with childhood trauma^{111,112}.

- Noradrenergic and Dopaminergic Genes System

Another polymorphism that has been associated with vulnerability to a psychiatric condition is found in the gene that codes Catechol-O-Methyltransferase (COMT), an enzyme degraded in the noradrenergic and dopaminergic systems¹¹³. The COMT Val158Met polymorphism has been studied in relation to stress and psychiatric disorders, suggesting an association with cases of PTSD¹¹³. For example, in a human study evaluating traumatic load, diagnosis of PTSD and COMT Val158Met polymorphism, results showed that a gene environment interaction among the human COMT Val158 Met polymorphism and the magnitude of traumatic events experienced increased the risk of developing PTSD¹¹⁴. Another study was developed with a sample of Vietnam and Gulf War veterans who experienced significant

amounts of operational stress. Its findings also suggested that COMT Val158Met polymorphism moderated the effect of PTSD-related processes on right anterior cingulate cortex volume¹¹⁵.

Polymorphisms in the dopaminergic receptor genes have also been associated in the risk of developing depression and PTSD. According to a study that evaluated the Dopamine Transporter gene polymorphism (DAT1), the results suggest that this gene contributed significantly to a susceptibility to PTSD in those individuals with a previous history of trauma¹¹⁶. Additionally, studies that evaluated the Dopamine receptor gene D2 polymorphism (DRD2) suggest that determined DRD2 signaling explained part of personality traits related to emotion processing as well as individuals variability in specific brain responses to emotionally relevant inputs¹¹⁷. Another study that evaluated the Dopamine receptor gene D4 polymorphism (DRD4) showed that this polymorphism influenced vulnerability to stress and trauma and a significant higher risk of developing a case of PTSD¹¹⁸.

- Serotonergic Gene System

Several studies assessing the polymorphic trait characteristics of the serotonin transporter gene, through the effects of gene multiplied by environment interactions, have promoted advances in the area of stress-related disorders¹⁸. For example, in studies that evaluated the interaction between stress and the polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR), results showed the presence of the shorter allele of 5-HTTLPR linked with an increased risk for depression and PTSD^{119,120}. Conversely, human studies evaluating the presence of the long allele of the 5-HTTLPR found a positive association with self-reported emotional resilience¹²¹.

- Brain-Derived Neurotropic Factor (BDNF) Genes

Recent scientific evidence suggests that BDNF Val66Met polymorphism may be potentially linked with the modulation of the stress reactivity in humans^{122,123}. For example, a study that evaluated the BDNF Val66Met polymorphism in a group of healthy university students, found that the BDNF Val66Met carriers were more susceptible for anxiety symptoms and exhibited an increased cortisol stress response in face of stressful events¹²³. Two further studies also identified an association between this polymorphic gene and cases of depression and anxiety. A clinical study found that depressed patients with the BDNF Val66 Met polymorphism exhibited higher rates of chronic MDD¹²⁴. Another study found that the BDNF Val66Met polymorphism interacted with early life stress to predict anxiety and depression¹²⁵.

Most of the evidence gathered in this area does not support a positive association between BDNF Val66Met polymorphism and stress-related disorders, particularly MDD and/or PTSD^{126,127}. For example a meta-analysis which evaluated the association between BDNF Val66Met polymorphism and depressed (MDD) individuals, did not find an association between these two variables¹²⁶. Another meta-analysis which evaluated the same polymorphism with anxiety disorders also did not find an association between the variables¹²⁸. A further meta-analysis did not find an association with PTSD¹²⁷.

Epigenetic Factors in Stress Resilience

Epigenetics corresponds to the functional alterations in the chromatin structure that trigger long-lasting modifications in gene expression without creating changes in the DNA sequence^{129,130}. These functional alterations help to regulate the phenotype and gene expression of an individual using mechanisms such as DNA methylation and histone methylation and acetylation, among others^{17,18}. Recent research with monozygotic twin studies have determined

that during the lifetime of these individuals, there is a meaningful and profound accumulation of epigenetic differences that could be explained by distinctive life development events and/or stressful experiences¹³¹. In fact, various studies have shown that hardship and adversity experienced during youth can result in persistent epigenetic marks in the genome that alter gene expression and induce both neural and behavioural changes across adulthood¹³². These epigenetic modifications are known to be implicated in social and maternal behaviour, learning and memory deficits, depression and PTSD symptomatology^{129,130}. Recent advances in our understanding of the epigenetics of the regulation of stress focuses on at least two distinct aspects of stress-induced epigenetic pathology or resilience. This is through mechanisms such as DNA methylation or histone methylation, and/or acetylation^{129,130}. Although there has been recent progress toward understanding the epigenetic regulation of stress and how such mechanisms contribute to susceptibility and resilience to stress-related disorders, careful interpretation is required as this area remains largely unexplained¹²⁹.

- DNA Methylation

DNA methylation is a biochemical process known for altering the expression of genes in cells when cells divide and differentiate. It is also known to be factor in the neural development of the organism and is potentially linked to psychiatric disorders¹³⁰. A series of studies have already linked the biochemical process of DNA methylation to psychiatric conditions^{129,130}. Post-mortem studies of suicide victims with a history of childhood abuse found that increased DNA methylation of a specific exon 1₇ glucocorticoid receptor (NR3C1) gene expression promoter in the hippocampus decreased hippocampal GR expression. This in comparison with other postmortem victims of sudden or accidental death without history of childhood abuse¹³³. Another

human study aimed to compare the expression of DNA methyltransferase (DNMT) messenger Ribonucleic Acid (mRNA) between individuals who committed suicide and had a MDD diagnosis with individuals who died suddenly as a result of other causes other than suicide. The first ones had significant alterations in the DNMT gene transcripts expression in brain areas including the frontopolar cortex, amygdala and the paraventricular nucleus of the hippocampus¹³⁴. Thus, this study shown that DNMT-3B expression was augmented in areas like the frontopolar cortex, previously known to be linked with an increase in DNA methylation of the γ -aminobutyric acid (GABA)(A) receptor alpha-1 subunit promoter region^{18,134}. Additionally, another study aimed to evaluate the effect of gene expression and PTSD-associated methylation in 33 candidate genes. Their findings suggested that higher DNA methylation of Mannosidase Alpha Class 2C Member 1 (MAN2C1) shown to relate with higher exposure to potentially traumatic situations and predictive of PTSD¹³⁵. Nevertheless, the precise role of MAN2C1 in the stress response remains unclear¹³⁶.

- Histone Methylation and Acetylation

Histone Methylation is a biochemical process through which a methyl group is shifted into amino acids of histone protein in chromosomes¹³². As a mechanism, histone methylation is linked with stimulation of the neural pathways and potentially for its function in learning and long-term memory¹³⁷. Scientific studies have already showed that female rats have different behavioural patterns of interaction with their offspring. While some mother rats exhibit increased levels of nurturing behaviours (such as nursing, licking, grooming), others do not¹³⁸. These different nurturing behaviours have a significant impact, where offspring of high-nurturing

mothers are known for exhibiting less fearfulness, anxiety, reduced corticosterone responses to stress, increased central benzodiazepine receptor density in the amygdala and locus coeruleus and higher quantities of glucocorticoid receptors (GR) gene promoter in the hippocampus^{138,139}. Interestingly, superior hippocampal GR expressions in the offspring are thought to be mediated by the transcription factor Nerve Growth Factor-Inducible protein A (NGFI-A)¹³⁹. For example, in a study where offspring rats received low levels of nurturing care from their mothers exhibited an augmented methylation of the GR gene promoter at the NGFI-A binding site in the hippocampus¹³⁹. Thus, lower levels of GR expression in the hippocampus led to several traits in adulthood, including higher levels of corticosterone (both before and after stress exposure), and higher levels of anxiety-like behaviours. Thus, these differences observed in methylation appear the first weeks of life and continue into their adulthood¹³⁹.

Histone Acetylation is the biochemical process by which the lysine for the histone core is acetylated as part of gene regulation¹⁴⁰. According to some rodent studies, histone acetylation has been observed in several regions of the hippocampus after exposure to acute stress, which could potentially lead to its role in memory formation and stress response¹³². Scientific evidence that histone acetylation could have a significant role in depression was found through studies showing that the intracerebral and systemic administration of several Histone Deacetylase Inhibitors (HDACi) either alone or combined with antidepressants, where results showed, in a variety of animal models, improved antidepressant responses¹³². Another animal study revealed that histone acetylation (H3K14ac) is briefly reduced and then augmented in the nucleus accumbens (a central region of the limbic system) after chronic social defeat stress, where this action was reflected by a decrease in Histone Deacetylase 2 (HDAC2). Supporting this evidence,

another study also found similar effects in the nucleus accumbens of depressed humans who have been evaluated postmortem¹⁴¹. They highlight that histone acetylation has an important function in the development of stress and depression^{141,142}. Additionally, another study supported the impact of histone acetylation in animal models by providing evidence that overexpression of dominant negative HDAC2 in the nucleus accumbens resulted in antidepressant-like behaviours, compared to controls. However, an overexpression of a similar version of the HDAC2 (strongly related with chromatin) in small rodents was linked with more depression-like behaviours¹³². Though, animal studies with the Histone Deacetylase 5 (HDAC5) suggest a protective effect in the nucleus accumbens. For example, a study with small rodents subjected to chronic social defeat stress, exhibited a reduction in the HDAC5 expression while chronic antidepressant treatment led to an increased HDAC5 expression. Thus, lacking of HDAC5 expression increased depressive-like behaviours when compared with controls¹⁴³.

DEVELOPMENTAL FACTORS AND STRESS RESILIENCE OVER THE LIFE CYCLE

The accrued scientific evidence also suggests that environmental stress over the life cycle can be extremely important in explaining an individual's risk to a stress-related psychiatric injury, and conversely, stress resilience^{144,145}. Human and animal studies suggest that severe stressful experiences during early life can negatively affect the development of stress response system and cause long-lasting ill-health^{109,145-147}. Strong, frequent and prolonged activation of the stress response system during childhood has been labelled toxic stress (e.g. physical/emotional abuse, chronic neglect, constant exposure to violence). This can disturb the normal development of the brain and other systems and increase the risk of stress-related disorders in adulthood. Thus, the higher number of stressful and/or adverse experiences encountered in childhood the

higher risk of these individuals to develop cognitive, emotional and development problems¹⁴⁸. In fact, studies that evaluated parental neglect and abusive behaviour toward children during the early weeks of life found fewer stress management skills, lower self-independence and higher levels of anxiety and stress. This was reflected in increased HPA Axis and CNS activity when the same individuals were subjected to stressors in later life¹⁴⁷. Additionally, these early life stressor experiences led to hyper-functioning of NE system, reduction in the hippocampal volume, and amygdala responsiveness to negative facial expressions^{149,150}.

Research in human and animal models suggest that certain factors can play an exceptionally important role in determining whether an early traumatic experience can result in vulnerability or resilience to a psychiatric disorder. One of the factors known to play an important role in these circumstances is the degree of control that an individual has over the stressor. Another factor is the possibility of changing the situation^{11,18}. It is already known that when individuals are led to believe that they are unable to change stressful circumstances, “learned helplessness” occurs¹⁵¹. Learned helplessness is a mental state where an individual, after experiencing ongoing adverse stimuli considered painful or unpleasant, becomes incapable and/or unwilling to avoid consequent encounters with the given stimuli. Even if there is the possibility of avoiding it, because they have learnt by experience that the stressor cannot be controlled or avoided¹⁵². This has been confirmed through a classic study involving dogs exposed to erratic shocks¹⁵¹. In studies with animals subjected to shocks that could be avoided by behavioural modification, learned helplessness seemed not to occur¹⁵³. Thus, evidence indicates that individuals may learn resilience through experience and hardship, in particular by developing qualities that facilitate appropriate coping strategies, adaptation and recovery from stress¹⁰¹. Studies also suggest that it

may be possible to inoculate individuals against the negative effects of exposure to high levels of stress^{154,155}. This concept, termed “stress inoculation”, happens when an individual acquires an adaptive stress response to the negative effects of following stressors. Stress inoculation is thus seen as a form of immunity against similar stressors which might occur in the future, essentially being analogous to vaccine induced immunity against disease¹⁵⁶.

Particularly animal studies tends to support the stress-inoculation concept and shows that early-life exposure to stressful events may protect against some of future negative effects of stress¹⁰⁰. One study evaluated the contribution of early-stressors in the emotional stability of small rodents. The researchers randomly exposed a group of infant rats to intermittent foot shocks, sufficient to elicit evasive movements, as a stress task, alongside a control group that did not experience shock. When they subjected the same two groups of rodents to a new stressful situation, those that had been intermittently subjected to stress displayed an enhanced coping response and a lower emotional response^{157,158}.

DISCUSSION

The neural mechanisms that underlie resilience to stress are extremely complex, involving the interaction of neurobiological, genetic and epigenetic components, together with the environment^{10,16,17}. Whilst genetic factors interact with neurobiological and epigenetic factors thereby affecting the biological characteristics and regulation of neurochemical receptors, environmental factors produce epigenetic alterations in individuals, influencing resilience to stress or risk of a psychiatric condition¹⁶⁻¹⁸. While not part of this review, other factors such as

personality, temperament, physical fitness and social support also play a pivotal role in resilience.

Our growing understanding of resilience leads us to consider how we could establish a resilient profile by examining the complexity of interacting factors. We first noted that a significant number of neurochemical elements (such as NPY, DHEA, CRH, galanin, ALLO) have been linked to the acute stress response and can be associated with resilience to stress^{10,11,45,94}. Each specific pathway and neurochemical element conveyed some protection or promoted resilience when facing stress. However, none of these neurobiological effects was highly significant as inconsistencies were reported with regard to neuro-protective effects.

As some researchers have highlighted, the neurobiological concept of resilience cannot be regarded as the interaction of a single neurochemical element but rather the interaction of multiple neurochemical elements within a complex network of cells in the human brain^{45,159}. In fact, a study that evaluated the negative cumulative effects of multiple physiological dysregulations showed that, when considering any of the biological markers individually, a decline in health status was not found to have any predictive value. Instead, when all markers were considered, they predicted an accentuated cognitive decline and a change in cardiovascular activity^{5,45}. If a similar model were applied to stress-resilient individuals, by combining neurochemistry and its known components to confer protection and including high-levels of NPY, galanin, DHEA, ALLO and the low levels of CRH activation, we may come closer to identifying a neurobiological profile of stress-resilient individuals⁴⁵. The same strategy may also be observed of genetic and epigenetic traits.

Further complication arises in relating neurobiological processes to psychological states under the overarching concept of resilience. For example a particular neurochemical may be found to be co-present with psychological symptoms of stress or resilience however this co-presence may not be sufficient to establish direction of causation. Meaning its presence may conceivably be a cause or conversely a response to intrusive symptomology. Indeed the relation that holds between the neurobiology and psychology of resilience represents a significant obstacle that will need to be addressed in future research.

This review focuses on the underlying neurochemical and physiological processes associated with resilience. As such we did not include literature concerning the important psychological factors and character traits related to the subject. However, it should be noted that active coping strategies, humour, hardiness and extraversion can promote resilience through fostering feelings of mastery, commitment and competence as well as the ability to help others through bonding. Importantly, the propensity of resilient individuals to express positive emotions, in relation to negative events, enables them to control their anxiety and fears¹⁰¹. A significant number of studies have also indicated positive social support has an important factor in maintaining physical and psychological wellbeing. These studies found that higher levels of social support are able to reduce and/or attenuate the impact of PTSD and/or MDD^{159,160}. Additionally, there is an emerging literature which also suggests that a positive social support environment can moderate individual environmental and genetic vulnerabilities and increase their resilience¹⁶¹.

Furthermore, encountering and overcoming stress-inducing situations may have a beneficial effect on the life cycle, in particular over one's perception of control and sense of

stress mastery. However, as different individuals have different stress thresholds, a stressor that may promote resilience in one individual could result in increased vulnerability in another individual. The line between learned helplessness and stress inoculation is a fine one because of the variability of individuals in their biological, psychological and social competences¹⁶.

Choosing to focus on the neurobiological domain for signs of resilience, entailed a neglecting of the psychological and social domains. As we understand them, the neurobiological, genetic, epigenetic and environmental signs of resilience are akin to variables¹⁶². In better understanding these variables and the relation they stand in to each other we will begin to see a more complete picture of the neurobiology of resilience emerge. As research continues, facilitated by advancing technology, our understanding will continue to deepen. In turn this will enable the creation of more comprehensive profile of a stress resilient individual.

The notion of a stress resilient profile will be of use to those who operate in high stress environments. First, in relation to the successful completion of the given task and secondly in relation to the individual's post-task physical and psychological wellbeing. Initial steps in this area have been taken in studies investigating members of the US and Belgian Special Forces Units^{29,163-166}. The UK is yet to conduct resilience related neurobiological research within its military population, this, despite having a tradition of epidemiological research in military mental health¹⁶⁷.

While understanding in the neurobiological domain is advancing, this review has shown that the mechanism of resilience in concert with the psychological domain requires further research. For example, the concept of stress inoculation, mentioned above, presupposes a

psychological or cognitive process in understanding and adaption to the life stressor. In this sense resilience is learnt.

The concept of a neurobiological stress-resilient profile begs the question as to whether one can be created by supplementation. Supplementation may conceivably be used prophylactically as an inoculation against stress and the prevention or mediation of intrusive symptomatology. Interestingly, a number of studies have isolated hormones related to resilience, an example being increased levels of DHEA measured in individuals who demonstrated greater physical and psychological performance under stress. However a further human study showed DHEA supplementation did not manifest in any observable advantage. Whilst neurobiological insights into a resilient profile are being gained the creation of one remains at the moment elusive, without recourse to the psychological domain.

The benefits of improved neurochemistry on psychological performance through prophylactic supplementation is a topic of fascination and one that will continue to be explored. As it is however we should remain aware of an example from history which illustrates this area of research also has the potential to be mishandled with negative consequence when applied¹⁶⁸. The use of prophylactic drugs that target the CNS may reduce fatigue and enhance psychological resilience, however it can also interfere with the individual's moral judgement and mood¹⁶⁸.

In conclusion, the promotion of resilience and prevention of psychopathology are of fundamental concern to the medical community. Moving forward and building on the important insights gained from the current research, an interdisciplinary approach combining neurobiological, genetic, epigenetic and personality traits, as well community and group interactions, may work to facilitate the development of a stress-resilient profile. This in turn

would be significant step toward the prevention and treatment of stress-related psychiatric conditions such as PTSD or MDD.

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