ANNUAL REVIEWS

*Annual Review of Clinical Psychology*

# Stress and Psychiatric Disorders: The Role of Mitochondria

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Annu. Rev. Clin. Psychol. 2020. 16:165–86

First published as a Review in Advance on February 24, 2020

The *Annual Review of Clinical Psychology* is online at clinpsy.annualreviews.org

https://doi.org/10.1146/annurev-clinpsy-082719-104030



## Keywords

mitochondria, psychosocial stress, early life adversity, allostatic load

## Abstract

In seeking to understand mental health and disease, it is fundamental to identify the biological substrates that draw together the experiences and physiological processes that underlie observed psychological changes. Mitochondria are subcellular organelles best known for their central role in energetics, producing adenosine triphosphate to power most cellular processes. Converging lines of evidence indicate that mitochondria play a key role in the biological embedding of adversity. Preclinical research documents the effects of stress exposure on mitochondrial structure and function, and recent human research suggests alterations constituting recalibrations, both adaptive and nonadaptive. Current research suggests dynamic relationships among stress exposure, neuroendocrine signaling, inflammation, and mitochondrial function. These complex relationships are implicated in disease risk, and their elucidation may inform prevention and treatment of stress- and trauma-related disorders. We review and evaluate the evidence for mitochondrial dysfunction as a consequence of stress exposure and as a contributing factor to psychiatric disease.

## Contents



## 1. INTRODUCTION

Human experience is marked by a broad range of stressors, adversities, and traumas. These vary by severity, timing, chronicity, and type of exposure. Sources of stress differ over time and according to geographical region, economic status, and a myriad of other variables. As investigators seek to improve understanding of key determinants of early experience, the sequelae of early life adversity are brought into focus—from the scope of broadly defined population health down to the molecular mechanisms underlying the complex interactions of genes and environment. A unifying and critical question underlies the work of the developmental psychologist, the epidemiologist, and the molecular neuroscientist: Why should early experiences shape one's development and health outcomes throughout life (Hartman et al. 2017, Lewis 1997)? In the pursuit of understanding risk, resilience, and opportunities for therapeutic interventions, these lines of investigation convene on the fundamental principle that humans are adaptive—acutely, over the course of a lifetime, and evolutionarily. The human body employs a suite of environmentally responsive biobehavioral processes that promotes survival and that, in an evolutionary context, increases the likelihood of survival across generations.

However, adaptation is a compromise. Responses that are advantageous in certain circumstances can result in maladaptive consequences in other settings. Convincing evidence across various fields of inquiry has reliably demonstrated over the past two decades that adversity in childhood is associated with increased risk of both psychopathology and chronic health problems

throughout the life span (Havranek et al. 2015, Jakubowski et al. 2018, Nanni et al. 2012, Nemeroff 2016). The psychological and biophysical sequelae of stress exposure originate in evolutionary mechanisms designed to enable an individual to respond to an environmental threat. While acutely these processes may be adaptive, in excess, they produce broad systemic physiologic and psychological disruption.

The mitochondrion, well known for its role in cellular energy production, represents a critical nexus of biological, psychological, and social factors that underlie the mechanisms and consequences of the stress response. Psychosocial factors affect biological processes through physiological systems that are highly integrated with mitochondrial functioning. Mitochondria are subcellular organelles with broad functions in energetics, cell signaling, and hormone production. Mitochondrial structure and function are exquisitely responsive to the environment and serve as both targets and mediators of the stress response (Picard & McEwen 2018a,b). As a highly energy-dependent organ, the brain is densely populated by mitochondria (Juster et al. 2016). Thus, there is a profound impact of mitochondrial dysfunction on psychological processes, and increasing evidence demonstrates associations of stress-related mitochondrial dysfunction and psychopathology (Picard et al. 2018b, Trumpff et al. 2019a, Tyrka et al. 2016). Animal models involving experimentally induced defects in mitochondria and stress paradigms produce pathophysiological states that suggest common mechanistic origins underlying these processes. Such processes are found in evidence from studies of the central nervous system (CNS), neuroendocrine system, and immune system and may implicate mitochondrial dysfunction in stress-related disease.

In this selective review, we discuss the role of mitochondria in the stress response and stress-related psychiatric disorders. We begin by introducing mitochondria and the role they may play in the biological embedding of adverse experiences. We then discuss recent evidence that demonstrates the role of mitochondria within the stress response; we focus on the interaction of mitochondria with established endocrine, inflammatory, and epigenetic pathways that underlie stress physiology. These findings are integrated with recent studies suggesting a role for mitochondrial dysfunction in stress-related psychiatric disorders. Finally, we reflect on the limitations of current evidence and look toward future directions to better understand the unique contribution of mitochondria to psychological function and potential for treatment interventions. The literature covered here is not exhaustive but, rather, highlights key findings that characterize the current state of the field with respect to this highly dynamic organelle.

## 2. THE ORIGIN AND PHYSIOLOGICAL FUNCTIONS OF MITOCHONDRIA

Endosymbiosis, from the Greek words for within, together, and living, is the process by which one cell comes to live within another. Mitochondria originated as bacteria, engulfed by an ancestor of the modern mammalian cell about 1.5 billion years ago (Archibald 2015, Sagan 1967). With the exception of red blood cells, every cell of the human body contains hundreds to thousands of these life-sustaining organelles. Mitochondria maintain characteristics of their bacterial origin, including their own genome—the maternally inherited, circular, double-stranded, mitochondrial DNA (mtDNA) (Kasahara & Kato 2018, McFarland et al. 2010). Mitochondria play a critical role in a broad range of functions within the cell and throughout the body, from energetics, epigenetics, and inflammation to hormone synthesis and metabolism (Juster et al. 2016, Picard et al. 2018a, Shaughnessy et al. 2014). They respond dynamically to metabolites and neuroendocrine factors, drive inflammatory processes, and regulate cell division and cell survival. Mitochondria sense, integrate, and signal information about their environments (Picard & McEwen 2018a).

Justifying the appellation "the powerhouse of the cell," mitochondria are the cell's primary site of energy flow. The genes of mtDNA encode for protein complexes that serve as the machinery for supplying cellular energy: the electron transport chain (ETC) and oxidative phosphorylation (Shaughnessy et al. 2014). Through a series of chemical reactions and conversions, the ETC transforms metabolites derived from food and oxygen into an electrochemical gradient (Wallace 2005). This gradient fuels a number of processes within mitochondria, including the synthesis of adenosine triphosphate (ATP), which serves as the energy currency used throughout the cell to power many essential processes of life, from DNA synthesis to neurotransmission and muscle contraction. The electrochemical gradient further supports a number of additional critical functions of the mitochondria, including the transport of ions, proteins, and other molecules as well as the synthesis of steroid hormones (Hoffmann & Spengler 2018, Picard et al. 2018a).

The brain is a highly energy-dependent organ and is densely populated with mitochondria (Magistretti & Allaman 2015). Mitochondria play an important role in brain function (Srivastava et al. 2018), as is evident in inherited mitochondrial disease, a heterogeneous group of disorders caused by mutations in mtDNA and nuclear genes that encode for structural mitochondrial proteins or proteins involved in mitochondrial function. Many of these disorders are characterized by atrophy in cortical, brain stem, and cerebellar brain regions (Gorman et al. 2016) as well as a variety of neurological symptoms, such as changes in vision, deafness, difficulty swallowing, diminished muscle tone, lack of coordination, neuropathy, and seizures (McFarland et al. 2010). Mitochondrial diseases are also associated with affective changes; more than half of individuals with mitochondrial disease express comorbid psychiatric disorders (Kasahara & Kato 2018). Further, mitochondrial dysfunction is found in primary developmental and neuropsychiatric diseases such as autism (Goh et al. 2014), attention-deficit/hyperactivity disorder (Hwang et al. 2017), Alzheimer's disease, and Parkinson's disease (Flannery & Trushina 2019, Yan et al. 2013). Mitochondria also play an important role in neural plasticity (Steib et al. 2014). Thus, mitochondria are integral to brain function, and there are intriguing potential psychiatric implications for mitochondrial dysfunction in the context of stress exposure.

## 3. ALLOSTASIS UNDER THE MICROSCOPE: MITOCHONDRIAL ALLOSTATIC LOAD

### 3.1. Defining Stress

The term stress can describe a number of distinct concepts. Stress may refer to an event, a stressor, or stress exposure. It may describe one's psychological state or the perception of stress, which is subjective. Stress may refer to a characterized set of physiological responses commonly understood to be activated in the setting of environmental challenges. In this review, we use clarifying terms to disambiguate these distinct concepts.

Stressful experiences or exposures encompass a wide variety of environmental demands on the individual. A stress exposure may have the potential for positive outcomes marked by reward, such as a job interview or an exam. In such situations, the stress-related physiological response is activated and deactivated over the time course of a discrete stressor. Acute stress may also occur in the setting of a profoundly negative experience, such as the death of a parent or spouse. In the wake of such events, personal resources and external support may allow the individual to prevail and continue to thrive. In so-called toxic stress, the exposure may be severe or chronic, and an individual's lack of internal or external resources to promote resilience may result in absence of control over the environment. In such circumstances, the physiological and behavioral recalibrations may serve to protect some functions while disadvantaging others. Untethered, maladaptive processes serve to promote physiological dysregulation and pathology (Shonkoff et al. 2009). Chronic, prolonged

exposure to toxic stress imparts disorders of both mental and physical health (Basu et al. 2017, Jakubowski et al. 2018, Rich-Edwards et al. 2010, Wegman & Stetler 2009, Widom et al. 2015).

### 3.2. Allostasis

Allostasis, a complex collection of physiological functions, allows an organism to adapt and maintain stability in a dynamic environment (McEwen & Stellar 1993, Sterling & Eyer 1988). These biobehavioral responses are coordinated by the CNS and extend throughout the body to optimize functioning according to varying environmental and internal demands. Multiple interwoven systems, from the CNS to the endocrine and immune systems, interact to produce dynamic, physiological changes. In excess, these processes are overextended, leading to maladaptive, pathological functioning (Danese & Lewis 2017, Danese & McEwen 2012).

This review is primarily focused on the psychological sequelae and psychiatric disorders associated with stress and trauma. However, it should be noted that because of the integrated and systemic nature of stress physiology, the pathology associated with adversity involves multiple organ systems and a variety of medical conditions. For example, allostatic processes are evident in the recalibration of cardiovascular functioning to meet the demands of a stressful environment. Sympathetic activation and exposure to glucocorticoids during an acute stressor prompt a brief, well-circumscribed cardiovascular activation with an associated elevation in blood pressure; this response is useful for coping with or fleeing from a stressor. With chronic stress and associated dysregulated glucocorticoid exposure over time, individuals face increased risk of disease through arterial stiffening, coronary artery calcification, or aneurysm (Havranek et al. 2015). The concept of allostasis refers to stress-induced adaptations across a wide range of physiological systems. Pathology represents the end product of adaptive processes that have become dysfunctional in an organism's attempt to adapt to environmental adversity.

Health behaviors represent a major category of risk and resilience factors. They integrate multiple domains of allostasis and represent behavioral responses to external and internal cues. Unhealthy behaviors, such as overeating and substance abuse, can acutely alter negative affective states accompanying a stressor. While these behaviors may initially serve to manage and reduce the apprehension, anxiety, and tension associated with stress exposure, over time, they often exacerbate physiological perturbations and further increase the risk of systemic disease.

### 3.3. Mitochondrial Allostatic Load

Accumulating evidence supports a key role for mitochondria in the physiological response to both acute and chronic stress exposure as well as the biological embedding of adversity in health and psychological functioning. In the setting of acute stress exposure, mitochondria respond dynamically to cues from stress-associated neuroendocrine, metabolic, and inflammatory pathways. With chronic exposure to stress, mitochondria demonstrate both structural and functional dysregulation. As illustrated in **Figure 1**, mitochondrial allostatic load comprises the cumulative adaptive and maladaptive effects of chronic stress exposure on mitochondrial structure and function and the resulting pathological changes across a wide range of bodily systems (Picard et al. 2014a, Picard & McEwen 2018a,b). Distinct from traditional biomarkers of allostatic load, such as lipids and glucose, mitochondria are living organelles; thus, they both shed light on dynamic responses to stressors and pose challenges to sensitive and specific measurement of their responses (Picard & McEwen 2018a). In Sections 4 and 5, we describe the growing understanding of the role of mitochondria in physiological stress—their interaction with primary stress mediators like glucocorticoids, secondary processes including metabolic and inflammatory mechanisms, and tertiary end points—with a focus on psychiatric disease.

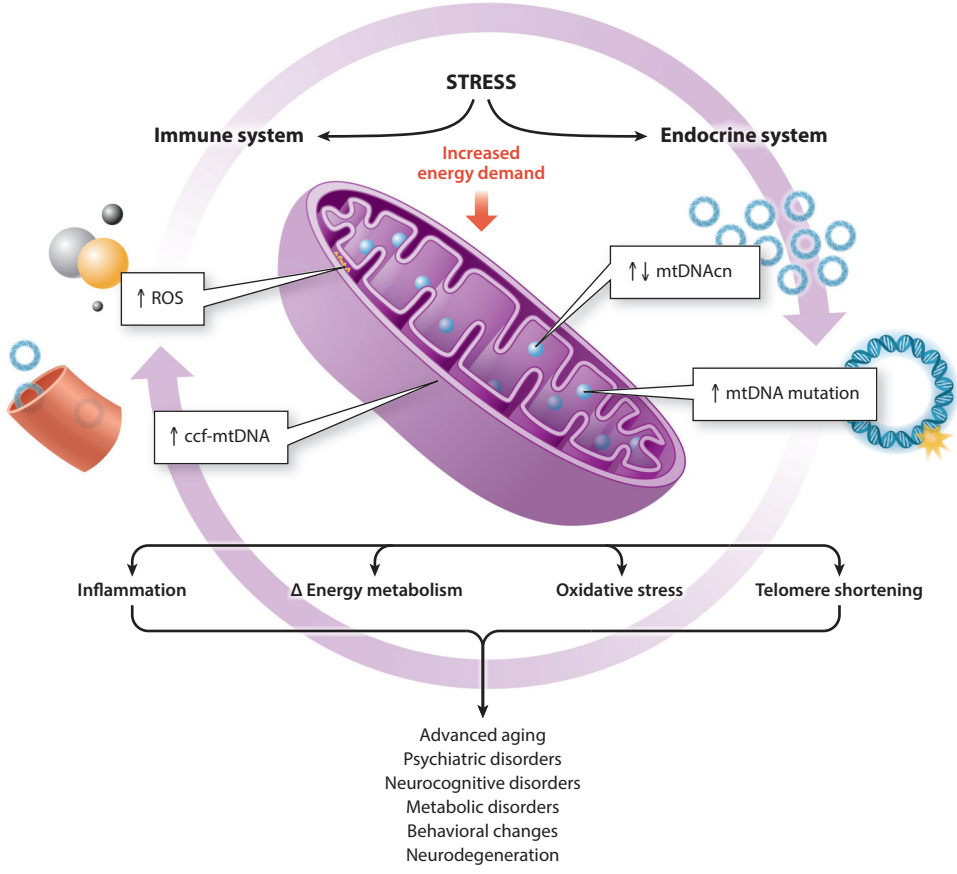


**Figure 1**

Conceptual framework for the interplay of stress exposure and mitochondrial alterations via the inflammatory and endocrine systems, which increases the risk of pathological states in vulnerable populations. Abbreviations: ccf-mtDNA, circulating cell-free mtDNA; mtDNA, mitochondrial DNA; mtDNAcn, mtDNA copy number; ROS, reactive oxygen species.

## 4. STRESS EXPOSURE: ESTABLISHED PATHWAYS AND IMPLICATIONS FOR MITOCHONDRIAL STRUCTURE AND FUNCTION

### 4.1. Stress-Associated Endocrine Pathways

The endocrine pathways underlying the acute stress response are well documented and serve as a foundation for the current understanding of stress physiology. In a threatening experience, the sympathetic–adrenal–medullary (SAM) axis is activated within seconds, and catecholamines, such as adrenaline, are released from the adrenal gland. Within minutes, the hypothalamic–pituitary–adrenal (HPA) axis is stimulated, and corticotropin-releasing factor (CRF) is released. CRF acts on the pituitary gland, precipitating the release of adrenocorticotropic hormone (ACTH). Systemically, ACTH stimulates the production of the glucocorticoid hormone cortisol (Sapolsky et al. 2000). Glucocorticoids serve a number of important functions in the stress response, including negative feedback to the HPA axis, which provides timely suppression of ongoing stress-related

processes. The circulation of glucocorticoids also provides for the mobilization and availability of energy substrates in the form of glucose and lipids, which are critical substrates for mitochondrial function (Hoffmann & Spengler 2018, Picard et al. 2014a, Picard & McEwen 2018a).

The negative feedback mechanism that enables a well-circumscribed response to stress is altered with chronic or repeated stress, resulting in HPA axis dysregulation (Berens et al. 2017). Continued stress exposure drives hyperactivation of this system, leading to elevated levels of circulating cortisol. However, there is evidence that sustained HPA axis hyperactivation eventually results in underresponsive, hypoactive functioning (Bunea et al. 2017, Nemeroff 2016). Differential patterns of dysregulation appear to be mediated in part by the type of stressor, reported age at the time of stress, and chronicity (Khoury et al. 2019).

### 4.2. Stress-Associated Inflammation

The stress response also engages the immune system in a complex manner, alternately activating and suppressing distinct immune functions (Rohleder 2014, Segerstrom & Miller 2004, Steptoe et al. 2007). The interaction of stress exposure and immune response is postulated to be a mechanism that provides optimal inflammatory defense against injury and infection in adverse conditions (Godoy et al. 2018, Marsland et al. 2017). In response to an acute stressor, signaling molecules called cytokines are released. Cytokines are important mediators of the local and systemic inflammatory response to pathogens. They also potentiate the stress response, activating the release of cortisol, which conversely inhibits cytokine production, thus downregulating stress-associated inflammation (Godoy et al. 2018, Marsland et al. 2017).

Individuals with chronic stress exposure in childhood demonstrate significant and graded elevations in inflammatory proteins as adults, an association not explained by mediators such as adult stressors or unhealthy behaviors (Baumeister et al. 2016, Danese et al. 2007, Takizawa et al. 2015). Adults with early life stress (ELS) have a greater inflammatory response to acute social stressors compared with those without a history of adversity (Carpenter et al. 2010). Chronic stress may lead to diminished glucocorticoid sensitivity to cytokine production (Meyer & Wirtz 2018). Taken together, this evidence indicates that chronic psychosocial stress leads to elevated risk of inflammation and disease (Meyer & Wirtz 2018).

### 4.3. Stress-Associated Telomere Shortening

A large body of literature also documents that stress exposure alters telomeres, the DNA–protein complexes that cap the ends of chromosomes and confer chromosomal stability. DNA segments are routinely removed from the ends of chromosomes with each cell replication cycle, and telomeres provide a buffer so that critical DNA segments are protected. Telomere shortening beyond a threshold leads to the arrest of the cell cycle, cellular senescence, and possibly DNA damage and cell death. Telomere shortening is associated with aging and with medical and psychiatric disease (Epel & Prather 2018). Telomere attrition is predictive of age-associated diseases, such as heart disease and diabetes. Furthermore, shorter telomeres are found in psychiatric disorders, including major depressive disorder (MDD) and anxiety disorders (Ridout et al. 2018, Wei et al. 2016). Telomeres are responsive to cumulative stress; specifically, exposure to glucocorticoids, inflammation, and oxidative stress is associated with telomere attrition, and this association suggests a possible mechanism linking stress, aging, and disease (Ridout et al. 2016). Over the past decade, a growing body of evidence has demonstrated a robust inverse relationship between telomere length and early adversity (Epel & Prather 2018, Hanssen et al. 2017, Li et al. 2017, Ridout et al. 2018).

## 4.4. Mitochondria at the Intersection of Stress Pathways

The fight-or-flight response to a threat requires energy in the form of ATP to fuel survival behaviors. Energy is also required for the physiological processes that allow the body to adapt and respond to stress challenges. The stress response increases the availability of energy substrates, such as glucose, which is used as fuel by the brain (Magistretti & Allaman 2015). Mitochondria provide the energy that fuels key enzymatic reactions, transcription and translation of genetic material to provide various substrates, release and reuptake of neurotransmitters, the synthesis of hormones, sympathetic activation, behavioral adaptations, and structural changes to tissues and organs (Picard et al. 2018a). Further, steroid hormones such as glucocorticoids are both synthesized and metabolized by mitochondria (Hoffmann & Spengler 2018, Picard et al. 2018a). To meet these high energy demands, mitochondrial activity is activated by the presence of neuroendocrine and metabolic stress mediators, including glucocorticoids and circulating glucose (Du et al. 2009, Picard et al. 2014a, Psarra & Sekeris 2011, Smith et al. 2018, Trumpff et al. 2019a).

In response to acute stress exposure, neuroendocrine pathways stimulate mechanisms and behaviors to modulate use of energy stores, such as modifications in eating behaviors (shifting preference toward calorically dense macronutrients) and rapid mobilization of free fatty acids from central fat stores. Mitochondria are sensitive to these changes in the metabolic milieu, endocrine stressors, and stress mediators. With high levels of glucocorticoid exposure, mitochondria have diminished calcium-buffering capacity, an important function of mitochondria in maintaining the internal environment of the cell. Rapid calcium flux or calcium overload in the cell promotes sensitization to cell death (Du et al. 2009, Picard et al. 2014a, Srivastava et al. 2018). In acute stress, circulating levels of important substrates, such as glucose or lipids, increase to provide the energy needed to respond to a stressor. In the context of hyperglycemia, mitochondria band together, undergoing fusion to promote survival. In conditions of severe or prolonged exposure to stress, these substrates are chronically elevated, and mitochondria become fragmented, increasing the risk of cell death (Hoffmann & Spengler 2018, Meyer et al. 2018, Shutt & McBride 2013). Prolonged fragmentation is associated with further oxidative stress and damage to mtDNA (Liesa & Shirihai 2013). These changes impair the bioenergetic functions of mitochondria and are amplified over time (Picard & McEwen 2018a).

Consistent with their symbiotic origins, mitochondria communicate with other parts of the cell, providing signals about their functional status (Chandel 2015). The mitochondrial response to stress is communicated both locally within the cell and systemically throughout the body. Exposure to stress mediators precipitates mitochondrial release of signaling molecules, which are collectively referred to as mitokines. Mitokines serve as signals that indicate mitochondrial fitness, which is of particular importance in the context of environmental stressors. Mitokines include various mitochondrial metabolites, calcium, and reactive oxygen species (Chandel 2015, Shaughnessy et al. 2014). Reactive oxygen species are generated as by-products of the energy-producing processes within mitochondria; at low levels, reactive oxygen species support a number of key functions in the cell. When elevated, reactive oxygen species overwhelm the cell's antioxidant capacity and promote oxidative stress, which causes cell death and tissue damage (Meyer et al. 2018). As with other mitokines, reactive oxygen species can drive local and systemic pathological processes that involve oxidative stress, inflammation, metabolism, gene expression, and cell senescence (Picard & McEwen 2018a). These signals are particularly important in the nucleus, where the genome is largely under mitochondrial regulation (Picard et al. 2014b). These mechanisms allow mitochondria to influence broad physiological processes throughout the body (Picard & McEwen 2018b).

Another important mitokine is circulating cell-free mtDNA (ccf-mtDNA), which is present in low levels in healthy individuals, abundant in inflammatory disease, and significantly increased in

critically ill hospital patients (Nakahira et al. 2013). ccf-mtDNA is generated by mitochondria in the event of stress, cell damage, or death; it is released into the bloodstream and then circulates freely throughout the body. The immune system recognizes ccf-mtDNA as foreign because of its evolutionary origin as bacteria, and systemic inflammation results (Picard et al. 2014a, Zhang et al. 2010). While acute exposure to psychosocial stress has been associated with decreases in reactive oxygen species, prolonged exposure is associated with mitochondrially derived oxidative stress, which further activates a number of proinflammatory processes, including cytokine release and proinflammatory gene expression (Meyer & Wirtz 2018). Moreover, cytokines appear to stimulate mitochondrial production of glucocorticoids in the immune-mediated propagation of the stress response (Meyer & Wirtz 2018).

Stressors in the environment are translated into biological and physiological changes through adaptation on the cellular level. While mtDNA does not contain telomeres, telomere length on nuclear chromosomes and mitochondrial biogenesis have been linked, including in relation to ELS (Cai et al. 2015a, Tyrka et al. 2016). Increasing evidence suggests complex coregulation of telomere length and mitochondrial function, with mitochondrially derived oxidative stress driving telomere attrition and shorter telomeres leading to mitochondrial dysfunction and cell death (Picard & McEwen 2018a).

## 5. STRESS-INDUCED MITOCHONDRIAL DYSFUNCTION, AGING, AND DISEASE RISK

### 5.1. Mitochondria and Aging

Over the past two decades, there has been tremendous interest in the relationship between stress, molecular mechanisms of aging, and age- and stress-related conditions, including psychiatric disorders, cardiovascular disease, obesity, diabetes, and cancer (Epel & Prather 2018, Lagouge & Larsson 2013). Shortened telomere length, a marker of accelerated cellular aging, has been associated with age-related disease, stress exposure (particularly ELS), and psychiatric disorders, including MDD and anxiety (Cai et al. 2015a, Epel & Prather 2018, Ridout et al. 2018, Tyrka et al. 2016). Mitochondria have been increasingly recognized for their importance in both the stress response and the aging process, with current research focusing on the role of mitochondria in accelerated aging and the development of age-related disease (Han et al. 2019). Aging itself is associated with perturbations in mitochondrial structure and function, including impaired replication, alterations in mtDNA copy number (mtDNAcn), increased reactive oxygen species production, mtDNA mutations, and organelle damage with resulting release of ccf-mtDNA (Bratic & Larsson 2013, Lagouge & Larsson 2013, Picard et al. 2014a). In the setting of chronic stress exposure, these changes may accumulate, accelerating aging and increasing an individual's risk of developing age- and stress-related metabolic conditions, such as cardiovascular disease and diabetes (Picard et al. 2014a, Ridout et al. 2016). For example, increases in ccf-mtDNA levels not only have been shown to predict mortality in patients admitted to medical intensive care units but also have been associated with up to an eightfold increased risk of death within 28 days of admission (Nakahira et al. 2013). Furthermore, considering that age-related conditions such as diabetes, cancer, and cardiovascular disease are accompanied by alterations in homeostatic mechanisms governing energy use and metabolism, it is consistent that mtDNA mutations and mitochondrial dysfunction have been documented to contribute to the onset of these diseases (Wallace 2005).

The relationship between psychiatric conditions and cellular aging is important to consider as mental illness has negative associations with physical health, including increased risk of premature

death and earlier onset of age-related chronic medical conditions (Viron & Stern 2010). Further, coping with a psychiatric condition can be an inherent source of chronic stress, which may predispose patients to poorer health outcomes. In addition, individuals with psychiatric conditions are more likely to engage in adverse health behaviors, including alcohol and substance use and poor dietary choices (Kilian et al. 2006), furthering metabolic risk. In the following sections, we outline the role that mitochondria play in these pathologic processes and how they may mediate the relationship between stress and poor health outcomes.

## 5.2. Stress and the Brain

In the brain, corticolimbic networks are designed to detect and adapt to environmental threats through coordination of the stress response. A perceived threat selectively activates brain regions that contribute to a coordinated biobehavioral response. The prefrontal cortex provides the overarching executive function of the brain, controlling cognition, learning, memory, and impulse control (Tottenham & Galván 2016). In the context of stress exposure, prefrontal inhibitory control over the amygdala is released, triggering a cascade of autonomic and neuroendocrine mechanisms via the sympathetic nervous system and the HPA axis, respectively (Bunea et al. 2017, Godoy et al. 2018). The amygdala applies emotional valence, drives fear conditioning, and has downstream output to the SAM and neuroendocrine regulatory systems (Berens et al. 2017). The hippocampus provides for memory, cognition, and negative feedback to the HPA axis (Juster et al. 2016, McEwen 2007).

Early adversity can have a significant impact on these neural networks as they grow and mature during childhood, adolescence, and adulthood. In addition to the psychological, social, and emotional responses to traumatic experiences, the effects of extreme and chronic stress on corticolimbic brain circuitry may result in enduring difficulties with emotion regulation, fear learning, and executive function. Extreme or chronic early stress has been linked to abnormalities in cognitive functions regulated by the prefrontal cortex, including attention, impulsivity, and executive functioning (Danese & McEwen 2012). Individuals with a history of significant adversity often have difficulty with emotion regulation, including hypervigilance, anxiety, anger, and compromised behavioral control (Tottenham & Galván 2016).

There is substantial evidence in support of volumetric brain changes secondary to stress exposure. Reductions in prefrontal gray matter has been observed in children and adults with a history of ELS (McEwen & Morrison 2013). Adults with ELS also demonstrate reduced hippocampal volume (Lupien et al. 2018). Both increases and decreases in amygdala volume have been detected; however, the direction of these changes is likely moderated by the type of exposure as well as its timing (Berens et al. 2017). Several potential mechanisms for these changes have been proposed; of particular note is the neurotoxicity hypothesis, whereby mediators, such as glucocorticoids, disrupt growth, maturation, and survival of neurons (Lupien et al. 2018). Multiple other stress mediators have been identified as potentially neurotoxic in development, including cytokines, excitatory amino acids, endogenous opioids, brain-derived neurotrophic factor (Berens et al. 2017, Zimmermann et al. 2019), telomere shortening, and mitochondrial dysfunction (Epel & Prather 2018).

## 5.3. Mitochondria and the Brain: Stress-Induced Alterations

The mitochondrion has been identified as a potential mechanism by which activation of the stress response system induces changes in brain morphology, development, and capabilities. In a dysregulated stress response system, mitochondria produce increased reactive oxygen species, which overwhelm the antioxidant capacity of the cells and can result in mtDNA mutations (Lagouge &

Larsson 2013). The resulting oxidative stress has been postulated to play a role in the pathogenesis of neuropsychiatric disorders, particularly depression and dementia. It is suggested that in such disease processes, the accumulation of reactive oxygen species and mtDNA mutations, among other abnormalities, causes impaired cell functioning and replication, which lead to apoptosis and neuronal atrophy (Forlenza & Miller 2006; Irie et al. 2001, 2003; Maes et al. 2009; Yan et al. 2013). This proposed mechanism has been supported by animal models wherein stress exposure, either by corticosterone or immobilization, generated impaired mitochondrial functioning within the cortex, hypothalamus, and hippocampus (Gong et al. 2011, Madrigal et al. 2001) along with depressive and anxiety-like behaviors (Yang et al. 2016). Furthermore, alterations to mitochondrial proteins and functioning via the oxidative phosphorylation pathway within hippocampal synapses have been observed in rodent models of stress-induced depression (Xie et al. 2018). These findings indicate that mitochondria may play a critical role in neuronal integrity and synaptic transmission, thus contributing to the development of stress-related disease.

### 5.4. Primary Mitochondrial Disease, the Brain, and Behavior

Stress is not the only pathway by which the brain is influenced by mitochondrial aberrations. For example, individuals with primary mitochondrial disorders have appreciable hyperintensities within the basal ganglia, cerebellum, and brain stem along with atrophy in the cerebellum and cerebrum and white matter leukoencephalopathy (Bricout et al. 2014, Friedman et al. 2010). Furthermore, animal models reveal that mtDNA mutations influence brain development, leading to appreciable malformations in the hippocampus and cerebrum (Ross et al. 2013), and that mitochondrial dysfunction is associated with neurodegeneration in the amygdala and hippocampus (Romero-Granados et al. 2011). Structural changes in these brain regions are involved in the stress response and have been observed in neuropsychiatric conditions, including anxiety, depression (Epel & Prather 2018), posttraumatic stress disorder (PTSD) (Gurvits et al. 1996), Parkinson's disease, and Alzheimer's disease (Weintraub et al. 2012).

Alterations to mtDNA and mitochondrial function have also been associated with behavioral and psychiatric symptoms. In humans, mitochondrial disorders are often associated with psychiatric disorders, including schizophrenia, bipolar disorder, and depression (Rosebush et al. 2017, Shao et al. 2008). This link has been further supported by data from animal models. For example, rodents with mtDNA mutations have been shown to develop alterations in circadian rhythms, consistent with the manic phase of bipolar disorder, that were exacerbated by antidepressants and alleviated by lithium treatment (Kasahara et al. 2006). Manipulation of mitochondrial functioning in rodents also has been shown to generate alterations in anxious social behaviors (Hollis et al. 2015). Specifically, mitochondrial dysfunction resulted in altered brain metabolism and produced anxiety-like behaviors with detrimental effects on social standing, whereas augmented mitochondrial functioning resulted in improved social standing in high-anxiety rodents (Hollis et al. 2015). In another rodent study, impaired mitochondrial activity interfered with learning acquisition and memory consolidation during maze tasks designed to test hippocampal and amygdala functioning (Romero-Granados et al. 2011).

### 5.5. The Role of Mitochondria in Neuropsychiatric Conditions

Mitochondrial impairments and alterations have been observed in individuals diagnosed with primary neuropsychiatric conditions. Positron emission tomography (PET) scans are a useful tool for monitoring cellular metabolism and have been employed in these populations to index mitochondrial performance. PET imaging has revealed reduced metabolic rates in the brains of patients

with schizophrenia (Mitelman et al. 2018), MDD (Su et al. 2014), and bipolar disorder, particularly in the depressive phase (Shao et al. 2008). Furthermore, deficits in the components of the mitochondrial ETC have been associated with the pathogenesis of neuropsychiatric diseases, including Alzheimer's and Parkinson's diseases, MDD, schizophrenia, and bipolar disorder, with the strongest evidence in neurodegenerative disorders (Holper et al. 2019).

Mitochondrial involvement in neuropsychiatric disease states can also be evaluated using peripheral molecular biomarkers—namely, mtDNAcn, a marker of mitochondrial biogenesis, and ccf-mtDNA, a potential indicator of mitochondrial stress. There is evidence of increased mtDNAcn and mtDNA deletions within the neurons of patients with Parkinson's disease (Bury et al. 2017) as well as increased mtDNA deletions and oxidative damage in the brains of those with Alzheimer's disease (Corral-Debrinski el al. 1994, Wang et al. 2005). Additional research has demonstrated a similar relationship between elevated mtDNAcn in peripheral blood cells and autism spectrum disorders (Chen et al. 2015, Yoo et al. 2017) and has suggested that mitochondrial dysfunction may underlie a subtype of autism (Goh et al. 2014).

Our group examined leukocyte mtDNAcn in 290 healthy unmedicated adults with and without a history of ELS, including childhood maltreatment and parental loss, as well as with and without a lifetime history of depressive, anxiety, and substance use disorders. We observed that both ELS and lifetime psychopathology were independently associated with elevations of mtDNAcn and shorter leukocyte telomere length (Tyrka et al. 2016). Furthermore, in the largest study to date, Cai et al. (2015a) studied 11,670 Chinese women with and without recurrent MDD and found that higher salivary mtDNAcn and shorter telomere length were associated with MDD. These authors also observed higher mtDNAcn in depressed patients versus controls in two additional smaller samples (Cai et al. 2015a). Moreover, other investigations have reported higher leukocyte mtDNA levels in adults with MDD (Tsujii et al. 2019) and suicide (Otsuka et al. 2017). However, some studies have found no difference in salivary or leukocyte mtDNAcn (He et al. 2014, Tymofiyeva et al. 2018, Verhoeven et al. 2018) or a decrease of mtDNAcn in older adults with MDD (Kim et al. 2011). Another recent study found no difference in mtDNAcn between a small number of depressed patients and healthy controls; however, mtDNAcn was negatively correlated with severity of depression, and blood cells from depressed patients had impairments in repair and degradation of mtDNA in response to oxidative stress (Czarny et al. 2019). These biomarkers have also been examined in other psychiatric disorders. There is evidence for an association between higher mtDNAcn and lifetime anxiety disorders as well as substance use disorders (Tyrka et al. 2016), mixed depression, anxiety- and stress-related disorders (Wang et al. 2017), and anxiety symptoms in adolescents (Tymofiyeva et al. 2018). However, one study found lower mtDNAcn in the granulocytes of male combat veterans with PTSD compared with those without PTSD (Bersani et al. 2016). Findings are mixed for bipolar disorder, with evidence of decreased mtDNAcn (Tsujii et al. 2019, Wang et al. 2017, Yamaki et al. 2018), increased mtDNAcn (Fries et al. 2017), or no significant difference in comparison with controls (de Sousa et al. 2014, Yamaki et al. 2018).

Variability in these findings could be due to differences in sample characteristics, such as severity and chronicity of the psychiatric disorder, the presence of other medical conditions, and medication use. Another potential source of this variability is the cell or tissue source of the mtDNA as some studies have examined blood (which has a mixture of cell types) and others have sampled saliva (which contains a mixture of blood and oral cells). However, the largest study to date found that the cellular composition of saliva differed only slightly for cases and controls and did not explain the differences in mtDNA (Cai et al. 2015b). It is important to note that whole blood samples, and possibly saliva, contain mtDNA that comprises intracellular as well as ccf-mtDNA; thus, studies of mtDNAcn in whole blood cannot distinguish between these effects. Recent work

also documents a robust increase in ccf-mtDNA in response to psychosocial stress in healthy adults (Hummel et al. 2018, Trumpff et al. 2019a), and there is evidence that this increase may be due to stress-induced glucocorticoid signaling (Trumpff et al. 2019a). A recent study examined both ccf-mtDNA and intracellular mtDNA from peripheral blood mononuclear cells (PBMCs) and found that compared with healthy controls, depressed patients had elevations in ccf-mtDNA but not PBMC mtDNAcn (Lindqvist et al. 2018). In another study, ccf-mtDNA was elevated in individuals after a suicide attempt compared with nonsuicidal controls (Lindqvist et al. 2016). Furthermore, ccf-mtDNA was positively correlated with cortisol in the dexamethasone suppression test—a finding that linked impaired HPA axis function to cellular or mitochondrial damage (Lindqvist et al. 2016).

## 5.6. Stress and Neuropsychopathology: Mitochondrial Involvement

Considering that stress and trauma are major risk factors for psychopathology, that stress exposure activates systems known to be pathogenic for a variety of disorders, and that mitochondria play a prominent role in coordinating these responses, mitochondria may provide the biological link between psychosocial stress and psychiatric outcomes. This concept is supported by the preclinical work discussed above demonstrating that both stress-induced mitochondrial abnormalities and experimentally induced mitochondrial dysfunction produce behavioral changes that resemble psychiatric symptoms. As discussed above, recent studies have begun to examine mitochondrial indices in humans with psychiatric conditions; only two of those studies have assessed the role of stress exposure (Cai et al. 2015a, Tyrka et al. 2016).

In our group's study of healthy, unmedicated adults, childhood adversity, including moderate-severe maltreatment on the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994) and/or childhood parental loss (death or desertion identified via interview), was linked to elevated mtDNAcn, even among those with no lifetime psychiatric disorder (Tyrka et al. 2016). This effect was not accounted for by measures of subclinical psychiatric symptoms, recent perceived stress, or resilience. The effect for those with both early stress and lifetime psychiatric disorders was greater than for those with early stress alone, but not surprisingly, the burden of early adversity was also greater in the former group. Conversely, lifetime depressive, anxiety, and substance use disorders were also associated with elevations in mtDNAcn, even in the absence of early adversity, and this finding was not explained by recent perceived stress or symptom burden. Thus, early adversity and lifetime psychiatric conditions were each uniquely linked to mtDNAcn, possibly because of shared neuroendocrine, inflammatory, or oxidative stress mechanisms.

Our group also recently reported similar findings in a sample of 256 maltreated and comparison preschool-aged children (Ridout et al. 2019). Maltreatment, as well as other measures of adversity, was a significant positive predictor of salivary mtDNAcn. Furthermore, elevations in mtDNAcn were associated with the presence of internalizing behaviors consistent with symptoms of anxiety and depression.

In their large study of Chinese women with and without recurrent MDD, Cai et al. (2015a) reported that higher mtDNAcn and shorter telomere length were seen with both a measure of 16 lifetime traumatic events as well as an abbreviated measure of childhood sexual abuse, and the maltreatment effects were stronger with increasingly severe abuse. However, the association of these stress measures and the molecular measures was conditional on the presence of MDD. Furthermore, in contrast to the study by our group (Tyrka et al. 2016), there was no significant effect of the measured stress exposures among non-MDD controls. Conversely, MDD had associations with higher mtDNAcn and shorter telomere length that were independent of the stress measures.

Cai et al. (2015a) also examined an animal stress model and found that 4 weeks of stress exposure resulted in increased mtDNAcn and reduced telomere length in blood and saliva. The increases in mtDNAcn at 4 weeks were associated with impaired mitochondrial function in the liver and were at least partially resolved after 4 more weeks without stress exposure. Further experiments revealed that administration of the glucocorticoid corticosterone was sufficient to induce changes to mtDNAcn and telomere length after 4 weeks, suggesting a mechanism for these molecular signatures via the HPA axis (Cai et al. 2015a). The authors hypothesized that the extent and persistence of molecular changes due to adversity may be influenced by individual genetic or additional unmeasured environmental factors and that those with depressive manifestations may have larger or longer-lasting effects. In a related study, a greater mtDNA mutation load was seen with depressed participants compared with controls, and at least one of these mutations was associated with the amount of mtDNA (Cai et al. 2015b). The authors used animal models to demonstrate that this increase in mutation burden could be generated from stress exposure, thus drawing together changes in mitochondrial genomic sequence and copy number with the stress response (Cai et al. 2015b).

Most work assessing mitochondria in humans has examined mtDNA, which is easily and reliably isolated and measured from frozen tissue. Alterations in mtDNAcn are thought to reflect mitochondrial biogenesis, and increases may occur in response to impairments in mitochondrial function (Giordano et al. 2014). However, mtDNAcn is an indirect measure, and variability in associations with psychiatric conditions may reflect a variety of underlying processes affecting mtDNAcn. Picard et al. (2016) developed the Mitochondrial Health Index (MHI), which integrates measures of both mitochondrial mass (how many mitochondria or their volume) and mitochondrial enzymatic activity (reflecting mitochondrial function) to represent the overall functional capacity of mitochondria. In a sample of 91 mothers, approximately half of whom were experiencing chronic stress in the form of caring for a child with autism, both stress exposure and mood were related to MHI, with lower MHI in individuals with more perceived stress and higher MHI associated with positive mood. There was no significant relationship between the individual components of the MHI and caregiving status; thus, the MHI may be a valuable composite measure of mitochondrial functional capacity.

It is also possible to directly measure mitochondrial functional capacity, but because reliable measurement of mitochondrial activity requires live, intact cells, it is not methodologically feasible for certain studies (van der Windt et al. 2016). Although there are concerns regarding mitochondrial viability from frozen tissue, some investigations have analyzed mitochondrial functioning using cryogenically preserved cells. In a study of 30 women with variable levels of childhood maltreatment as measured by the CTQ, Boeck et al. (2016) found that maltreatment was linked to greater reactive oxygen species production, oxidative stress, and mitochondrial oxygen consumption in a dose-dependent fashion, and reactive oxygen species and mitochondrial activity were associated with the release of inflammatory cytokines.

The literature described above highlights how chronic or severe psychosocial stressors can alter biological processes that accelerate cellular aging and potentially increase disease risk through mitochondrial mechanisms. It is also important to acknowledge that age-related, neurological, and psychiatric illnesses can be inherent sources of stress and thus may affect mitochondrial function independent of other sources of adversity. Moreover, mitochondrial dysfunction occurs through inborn genetic errors and disease states that are unrelated to psychosocial stressors. Meaningful early progress has begun to characterize the role of mitochondria in adversity, the aging process, and the pathophysiology of stress- and age-related disease processes. There is increasing awareness of the function of mitochondria in disease pathogenesis, but there is still more progress to be made.

In Section 6, we describe the limitations of current evidence and provide suggestions for future directions.

## 6. CURRENT LIMITATIONS AND FUTURE DIRECTIONS

Accumulating evidence from animal models and recent human studies has identified the mitochondrion as a critical intersection point for psychosocial factors and stress physiology. Despite improved understanding of the wide-ranging roles of this organelle in regulating key stress-related processes, many questions remain. The mechanisms that underlie these processes are highly complex, in part because of their dynamic integration with neuroendocrine, inflammatory, and epigenetic systems—all of which are influenced to varying degrees by genetic, environmental, and developmental factors. As illustrated in **Figure 1**, the relationship between stress, mitochondria, and psychiatric disorders is nonlinear, with bidirectional interaction among multiple interwoven physiological systems. Very few human studies have been conducted thus far, and the results are mixed, highlighting the limitations to our current understanding and encouraging careful consideration by investigators moving forward.

While animal models have provided critical insight into the mitochondrial response to acute and chronic stress exposure and can identify behaviors similar to those seen with psychiatric conditions, human studies are necessary to understand the complex cognitive and affective phenotypes observed in stress-associated psychiatric disorders. Clinical studies have assessed mitochondrial function in response to stressors of varying nature, chronicity, and reported age of stress exposure. As with any human study, there are complexities associated with measuring and disentangling sources of variance. Whereas animal models allow for strict control of genetic and environmental factors as well as experimental designs that isolate causal factors and directly measure outcomes, human studies inherently present the opportunity for interference by a vast number of potential confounders—some of which may serve as critical moderators or mediators of disease risk. Participants have individual genetic predispositions, unique personal experiences, and varying degrees of resilience and coping. They have distinct patterns of health-influencing behaviors (some of which may be clandestine), potential recent stressors, substance histories, and underlying medical problems that may meaningfully contribute to mitochondrial functioning. Medications (e.g., antidepressants) appear to alter energy metabolism and may affect mitochondrial processes (Adzic et al. 2016). This broad variability makes it difficult to precisely measure the relationship of stress exposure and mitochondrial function in human samples. Intensive measurement, or control of a broad range of exposures, behaviors, and health conditions, is costly and generally only possible in smaller studies, which may have limited generalizability. However, when these factors go unmeasured, error is increased and effect sizes are diminished.

Measures of mitochondrial mass and function are limited by the lack of universal procedures for a number of laboratory processes, such as storing and collecting samples from these living, metabolically active organelles. The methodological choices made by investigators may substantially affect their findings. While freezing samples allows for analytes to be run en masse, it may also increase the likelihood of degradation of the sample, resulting in modified biological activity of the sample (Han et al. 2019). This is particularly an issue for studies of mitochondrial functional capacity, whereas mtDNA is more stable. Furthermore, there is a tremendous amount of variation in tissue sampling, including in vitro versus in vivo studies, cells from blood versus saliva, tissues from living versus postmortem samples, and cells from human versus animal sources. As with other examinations of peripheral markers of biological processes relevant to stress and disease risk, the inclusion of whole blood or saliva containing mixed cell populations raises cellular heterogeneity as a possible confounder (Han et al. 2019).

Although research on the role of mitochondria in the biological response to adversity, trauma, and psychopathology is at a relatively early stage, most of the complexities discussed above apply to the preceding decades of research on the biological embedding of stress exposure and the molecular mechanisms and sequelae of psychiatric conditions. The state of the field has also opened the door to a wide variety of additional questions, including the role of biological sex, which influences mitochondrial function (Klinge 2017, Trumpff et al. 2019b). Other questions concern how reversible these mitochondrial changes are and the role of treatment, via psychotherapy, other behavioral approaches, or psychotropic medications, in helping to reverse these changes or stem their effects.

In this review, we have discussed emerging evidence indicating that chronic stress generates maladaptive alterations in mitochondria, which contribute to allostatic processes, ultimately promoting aging and disease. Together with the extensive body of literature on early adversity, these findings collectively highlight the critical value of early screening and intervention for childhood maltreatment. Preliminary assessments of the impact of early intervention reveal that trauma-informed treatments may help to reverse physiological effects of childhood adversity (Slopen et al. 2014). The research reviewed here provides a foundation from which to expand our understanding of risk and resilience and identify therapeutic interventions targeting these biological mechanisms. Further studies are needed that seek to elucidate how mitochondria contribute to neuronal circuits that regulate specific behaviors, vulnerability, and resilience to stress exposure. Continued efforts across relevant fields should be focused on translating this emerging area of research into clinical applications that improve the health outcomes of vulnerable patient populations.

### SUMMARY POINTS

1. Mitochondria play a key role in the physiologic stress response through dynamic interactions with stress-associated neuroendocrine, metabolic, and inflammatory pathways.
2. Recent clinical evidence suggests that mitochondria are involved in the pathological processes underlying several psychiatric disorders.
3. Animal studies and emerging clinical evidence indicate that exposure to chronic or severe stressors can alter mitochondrial DNA and mitochondrial function; this process may confer risk of psychiatric and other health conditions.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

## ACKNOWLEDGMENTS

We would like to thank Mauricio Mazzariol for graphic design of **Figure 1**. T.E.D. and E.M.O. received support from R25 MH101076, and A.R.T.'s time was supported by NIH grants MH101107 and HD086487.

## LITERATURE CITED

Adzic M, Brkic Z, Bulajic S, Mitic M, Radojcic MB. 2016. Antidepressant action on mitochondrial dysfunction in psychiatric disorders. *Drug Dev. Res.* 77:400–6

Archibald JM. 2015. Endosymbiosis and eukaryotic cell evolution. *Curr. Biol.* 25:R911–21
Basu A, McLaughlin KA, Misra S, Koenen KC. 2017. Childhood maltreatment and health impact: the examples of cardiovascular disease and type 2 diabetes mellitus in adults. *Clin. Psychol.* 24:125–39
Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol. Psychiatry* 21:642–49
Berens AE, Jensen SKG, Nelson CA 3rd. 2017. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Med.* 15:135
Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, et al. 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am. J. Psychiatry* 151:1132–36
Bersani FS, Morley C, Lindqvist D, Epel ES, Picard M, et al. 2016. Mitochondrial DNA copy number is reduced in male combat veterans with PTSD. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 64:10–17
Boeck C, Koenig AM, Schury K, Geiger ML, Karabatsiakis A, et al. 2016. Inflammation in adult women with a history of child maltreatment: the involvement of mitochondrial alterations and oxidative stress. *Mitochondrion* 30:197–207
Bratic A, Larsson NG. 2013. The role of mitochondria in aging. *J. Clin. Investig.* 123:951–57
Bricout M, Grevent D, Lebre AS, Rio M, Desguerre I, et al. 2014. Brain imaging in mitochondrial respiratory chain deficiency: combination of brain MRI features as a useful tool for genotype/phenotype correlations. *J. Med. Genet.* 51:429–35
Bunea IM, Szentagotai-Tatar A, Miu AC. 2017. Early-life adversity and cortisol response to social stress: a meta-analysis. *Transl. Psychiatry* 7:1274
Bury AG, Pyle A, Elson JL, Greaves L, Morris CM, et al. 2017. Mitochondrial DNA changes in pedunculopontine cholinergic neurons in Parkinson disease. *Ann. Neurol.* 82:1016–21
Cai N, Chang S, Li Y, Li Q, Hu J, et al. 2015a. Molecular signatures of major depression. *Curr. Biol.* 25:1146–56
Cai N, Li Y, Chang S, Liang J, Lin C, et al. 2015b. Genetic control over mtDNA and its relationship to major depressive disorder. *Curr. Biol.* 25:3170–77
Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. 2010. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology* 35:2617–23
Chandel NS. 2015. Evolution of mitochondria as signaling organelles. *Cell Metab.* 22:204–6
Chen S, Li Z, He Y, Zhang F, Li H, et al. 2015. Elevated mitochondrial DNA copy number in peripheral blood cells is associated with childhood autism. *BMC Psychiatry* 15:50
Corral-Debrinski M, Horton T, Lott MT, Shoffner JM, McKee AC, et al. 1994. Marked changes in mitochondrial DNA deletion levels in Alzheimer brains. *Genomics* 23:471–76
Czarny P, Wigner P, Strycharz J, Swiderska E, Synowiec E, et al. 2019. Mitochondrial DNA copy number, damage, repair and degradation in depressive disorder. *World J. Biol. Psychiatry.* **https://doi.org/10.1080/15622975.2019.1588993**
Danese A, Lewis SJ. 2017. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? *Neuropsychopharmacology* 42:99–114
Danese A, McEwen BS. 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol. Behav.* 106:29–39
Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. 2007. Childhood maltreatment predicts adult inflammation in a life-course study. *PNAS* 104:1319–24
de Sousa RT, Uno M, Zanetti MV, Shinjo SM, Busatto GF, et al. 2014. Leukocyte mitochondrial DNA copy number in bipolar disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 48:32–35
Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, et al. 2009. Dynamic regulation of mitochondrial function by glucocorticoids. *PNAS* 106:3543–48
Epel ES, Prather AA. 2018. Stress, telomeres, and psychopathology: toward a deeper understanding of a triad of early aging. *Annu. Rev. Clin. Psychol.* 14:371–97
Flannery PJ, Trushina E. 2019. Mitochondrial dynamics and transport in Alzheimer's disease. *Mol. Cell Neurosci.* 98:109–20

Forlenza MJ, Miller GE. 2006. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. *Psychosom. Med.* 68(1):1–7

Friedman SD, Shaw DW, Ishak G, Gropman AL, Saneto RP. 2010. The use of neuroimaging in the diagnosis of mitochondrial disease. *Dev. Disabil. Res. Rev.* 16:129–35

Fries GR, Bauer IE, Scaini G, Wu MJ, Kazimi IF, et al. 2017. Accelerated epigenetic aging and mitochondrial DNA copy number in bipolar disorder. *Transl. Psychiatry* 7:1283

Giordano C, Iommarini L, Giordano L, Maresca A, Pisano A, et al. 2014. Efficient mitochondrial biogenesis drives incomplete penetrance in Leber's hereditary optic neuropathy. *Brain* 137:335–53

Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH. 2018. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. *Front. Behav. Neurosci.* 12:127

Goh S, Dong Z, Zhang Y, DiMauro S, Peterson BS. 2014. Mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder: evidence from brain imaging. *JAMA Psychiatry* 71:665–71

Gong Y, Chai Y, Ding JH, Sun XL, Hu G. 2011. Chronic mild stress damages mitochondrial ultrastructure and function in mouse brain. *Neurosci. Lett.* 488:76–80

Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, et al. 2016. Mitochondrial diseases. *Nat. Rev. Dis. Primers* 2:16080

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, et al. 1996. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol. Psychiatry* 40:1091–99

Han LKM, Verhoeven JE, Tyrka AR, Penninx B, Wolkowitz OM, et al. 2019. Accelerating research on biological aging and mental health: current challenges and future directions. *Psychoneuroendocrinology* 106:293–311

Hanssen LM, Schutte NS, Malouff JM, Epel ES. 2017. The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis. *Health Psychol. Res.* 5:6378

Hartman S, Li Z, Nettle D, Belsky J. 2017. External-environmental and internal-health early life predictors of adolescent development. *Dev. Psychopathol.* 29:1839–49

Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, et al. 2015. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 132:873–98

He Y, Tang J, Li Z, Li H, Liao Y, et al. 2014. Leukocyte mitochondrial DNA copy number in blood is not associated with major depressive disorder in young adults. *PLOS ONE* 9:e96869

Hoffmann A, Spengler D. 2018. The mitochondrion as potential interface in early-life stress brain programming. *Front. Behav. Neurosci.* 12:306

Hollis F, van der Kooij MA, Zanoletti O, Lozano L, Canto C, Sandi C. 2015. Mitochondrial function in the brain links anxiety with social subordination. *PNAS* 112:15486–91

Holper L, Ben-Shachar D, Mann JJ. 2019. Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease, and Parkinson disease. *Neuropsychopharmacology* 44:837–49

Hummel EM, Hessas E, Muller S, Beiter T, Fisch M, et al. 2018. Cell-free DNA release under psychosocial and physical stress conditions. *Transl. Psychiatry* 8:236

Hwang IW, Hong JH, Kwon BN, Kim HJ, Lee NR, et al. 2017. Association of mitochondrial DNA 10398 A/G polymorphism with attention deficit and hyperactivity disorder in Korean children. *Gene* 630:8–12

Irie M, Asami S, Ikeda M, Kasai H. 2003. Depressive state relates to female oxidative DNA damage via neutrophil activation. *Biochem. Biophys. Res. Commun.* 311:1014–18

Irie M, Asami S, Nagata S, Ikeda M, Miyata M, Kasai H. 2001. Psychosocial factors as a potential trigger of oxidative DNA damage in human leukocytes. *Jpn. J. Cancer Res.* 92:367–76

Jakubowski KP, Cundiff JM, Matthews KA. 2018. Cumulative childhood adversity and adult cardiometabolic disease: a meta-analysis. *Health Psychol.* 37:701–15

Juster RP, Russell JJ, Almeida D, Picard M. 2016. Allostatic load and comorbidities: a mitochondrial, epigenetic, and evolutionary perspective. *Dev. Psychopathol.* 28:1117–46

Kasahara T, Kato T. 2018. What can mitochondrial DNA analysis tell us about mood disorders? *Biol. Psychiatry* 83:731–38

Kasahara T, Kubota M, Miyauchi T, Noda Y, Mouri A, et al. 2006. Mice with neuron-specific accumulation of mitochondrial DNA mutations show mood disorder-like phenotypes. *Mol. Psychiatry* 11:577–93

Khoury JE, Bosquet Enlow M, Plamondon A, Lyons-Ruth K. 2019. The association between adversity and hair cortisol levels in humans: a meta-analysis. *Psychoneuroendocrinology* 103:104–17

Kilian R, Becker T, Kruger K, Schmid S, Frasch K. 2006. Health behavior in psychiatric in-patients compared with a German general population sample. *Acta Psychiatr. Scand.* 114:242–48

Kim MY, Lee JW, Kang HC, Kim E, Lee DC. 2011. Leukocyte mitochondrial DNA (mtDNA) content is associated with depression in old women. *Arch. Gerontol. Geriatr.* 53:e218–21

Klinge CM. 2017. Estrogens regulate life and death in mitochondria. *J. Bioenerg. Biomembr.* 49:307–24

Lagouge M, Larsson NG. 2013. The role of mitochondrial DNA mutations and free radicals in disease and ageing. *J. Intern. Med.* 273:529–43

Lewis M. 1997. *Altering Fate: Why the Past Does Not Predict the Future*. New York: Guilford

Li Z, He Y, Wang D, Tang J, Chen X. 2017. Association between childhood trauma and accelerated telomere erosion in adulthood: a meta-analytic study. *J. Psychiatr. Res.* 93:64–71

Liesa M, Shirihai OS. 2013. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. *Cell Metab.* 17:491–506

Lindqvist D, Fernström J, Grudet C, Ljunggren L, Traskman-Bendz L, et al. 2016. Increased plasma levels of circulating cell-free mitochondrial DNA in suicide attempters: associations with HPA-axis hyperactivity. *Transl. Psychiatry* 6:e971

Lindqvist D, Wolkowitz OM, Picard M, Ohlsson L, Bersani FS, et al. 2018. Circulating cell-free mitochondrial DNA, but not leukocyte mitochondrial DNA copy number, is elevated in major depressive disorder. *Neuropsychopharmacology* 43:1557–64

Lupien SJ, Juster RP, Raymond C, Marin MF. 2018. The effects of chronic stress on the human brain: from neurotoxicity, to vulnerability, to opportunity. *Front. Neuroendocrinol.* 49:91–105

Madrigal JL, Olivenza R, Moro MA, Lizasoain I, Lorenzo P, et al. 2001. Glutathione depletion, lipid peroxidation and mitochondrial dysfunction are induced by chronic stress in rat brain. *Neuropsychopharmacology* 24:420–29

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. 2009. Increased 8-hydroxy-deoxyguanosine, a marker of oxidative damage to DNA, in major depression and myalgic encephalomyelitis / chronic fatigue syndrome. *Neuro Endocrinol. Lett.* 30:715–22

Magistretti PJ, Allaman I. 2015. A cellular perspective on brain energy metabolism and functional imaging. *Neuron* 86:883–901

Marsland AL, Walsh C, Lockwood K, John-Henderson NA. 2017. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. *Brain Behav. Immun.* 64:208–19

McEwen BS. 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol. Rev.* 87:873–904

McEwen BS, Morrison JH. 2013. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron* 79:16–29

McEwen BS, Stellar E. 1993. Stress and the individual. Mechanisms leading to disease. *Arch. Intern. Med.* 153:2093–101

McFarland R, Taylor RW, Turnbull DM. 2010. A neurological perspective on mitochondrial disease. *Lancet Neurol.* 9:829–40

Meyer A, Laverny G, Bernardi L, Charles AL, Alsaleh G, et al. 2018. Mitochondria: an organelle of bacterial origin controlling inflammation. *Front. Immunol.* 9:536

Meyer T, Wirtz PH. 2018. Mechanisms of mitochondrial redox signaling in psychosocial stress-responsive systems: new insights into an old story. *Antioxid. Redox Signal.* 28:760–72

Mitelman SA, Bralet MC, Mehmet Haznedar M, Hollander E, Shihabuddin L, et al. 2018. Positron emission tomography assessment of cerebral glucose metabolic rates in autism spectrum disorder and schizophrenia. *Brain Imaging Behav.* 12:532–46

Nakahira K, Kyung SY, Rogers AJ, Gazourian L, Youn S, et al. 2013. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. *PLOS Med.* 10:e1001577

Nanni V, Uher R, Danese A. 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am. J. Psychiatry* 169:141–51

Nemeroff CB. 2016. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron* 89:892–909

Otsuka I, Izumi T, Boku S, Kimura A, Zhang Y, et al. 2017. Aberrant telomere length and mitochondrial DNA copy number in suicide completers. *Sci. Rep.* 7:3176

Picard M, Juster RP, McEwen BS. 2014a. Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. *Nat. Rev. Endocrinol.* 10:303–10

Picard M, McEwen BS. 2018a. Psychological stress and mitochondria: a conceptual framework. *Psychosom. Med.* 80:126–40

Picard M, McEwen BS. 2018b. Psychological stress and mitochondria: a systematic review. *Psychosom. Med.* 80:141–53

Picard M, McEwen BS, Epel ES, Sandi C. 2018a. An energetic view of stress: focus on mitochondria. *Front. Neuroendocrinol.* 49:72–85

Picard M, Prather AA, Puterman E, Cuillerier A, Coccia M, et al. 2018b. A mitochondrial health index sensitive to mood and caregiving stress. *Biol. Psychiatry* 84:9–17

Picard M, Wallace DC, Burelle Y. 2016. The rise of mitochondria in medicine. *Mitochondrion* 30:105–16

Picard M, Zhang J, Hancock S, Derbeneva O, Golhar R, et al. 2014b. Progressive increase in mtDNA 3243A>G heteroplasmy causes abrupt transcriptional reprogramming. *PNAS* 111:E4033–42

Psarra AM, Sekeris CE. 2011. Glucocorticoids induce mitochondrial gene transcription in HepG2 cells: role of the mitochondrial glucocorticoid receptor. *Biochim. Biophys. Acta Mol. Cell Res.* 1813:1814–21

Rich-Edwards JW, Spiegelman D, Lividoti Hibert EN, Jun HJ, Todd TJ, et al. 2010. Abuse in childhood and adolescence as a predictor of type 2 diabetes in adult women. *Am. J. Prev. Med.* 39:529–36

Ridout KK, Carpenter LL, Tyrka AR. 2016. The cellular sequelae of early stress: focus on aging and mitochondria. *Neuropsychopharmacology* 41:388–89

Ridout KK, Khan M, Ridout SJ. 2018. Adverse childhood experiences run deep: toxic early life stress, telomeres, and mitochondrial DNA copy number, the biological markers of cumulative stress. *BioEssays* 40:e1800077

Ridout KK, Parade SH, Kao HT, Magnan S, Seifer R, et al. 2019. Childhood maltreatment, behavioral adjustment, and molecular markers of cellular aging in preschool-aged children: a cohort study. *Psychoneuroendocrinology* 107:261–69

Rohleder N. 2014. Stimulation of systemic low-grade inflammation by psychosocial stress. *Psychosom. Med.* 76:181–89

Romero-Granados R, Fontan-Lozano A, Aguilar-Montilla FJ, Carrion AM. 2011. Postnatal proteasome inhibition induces neurodegeneration and cognitive deficiencies in adult mice: a new model of neurodevelopment syndrome. *PLOS ONE* 6:e28927

Rosebush PI, Anglin RE, Rasmussen S, Mazurek MF. 2017. Mental illness in patients with inherited mitochondrial disorders. *Schizophr. Res.* 187:33–37

Ross JM, Stewart JB, Hagstrom E, Brene S, Mourier A, et al. 2013. Germline mitochondrial DNA mutations aggravate ageing and can impair brain development. *Nature* 501:412–15

Sagan L. 1967. On the origin of mitosing cells. *J. Theor. Biol.* 14:255–74

Sapolsky RM, Romero LM, Munck AU. 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr. Rev.* 21:55–89

Segerstrom SC, Miller GE. 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol. Bull.* 130:601–30

Shao L, Martin MV, Watson SJ, Schatzberg A, Akil H, et al. 2008. Mitochondrial involvement in psychiatric disorders. *Ann. Med.* 40:281–95

Shaughnessy DT, McAllister K, Worth L, Haugen AC, Meyer JN, et al. 2014. Mitochondria, energetics, epigenetics, and cellular responses to stress. *Environ. Health Perspect.* 122:1271–78

Shonkoff JP, Boyce WT, McEwen BS. 2009. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA* 301:2252–59

Shutt TE, McBride HM. 2013. Staying cool in difficult times: mitochondrial dynamics, quality control and the stress response. *Biochim. Biophys. Acta Mol. Cell Res.* 1833:417–24

Slopen N, Koenen KC, Kubzansky LD. 2014. Cumulative adversity in childhood and emergent risk factors for long-term health. *J. Pediatr.* 164:631–38.e1–2

Smith RL, Soeters MR, Wust RCI, Houtkooper RH. 2018. Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. *Endocr. Rev.* 39:489–517

Srivastava R, Faust T, Ramos A, Ishizuka K, Sawa A. 2018. Dynamic changes of the mitochondria in psychiatric illnesses: new mechanistic insights from human neuronal models. *Biol. Psychiatry* 83:751–60

Steib K, Schaffner I, Jagasia R, Ebert B, Lie DC. 2014. Mitochondria modify exercise-induced development of stem cell-derived neurons in the adult brain. *J. Neurosci.* 34:6624–33

Steptoe A, Hamer M, Chida Y. 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav. Immun.* 21:901–12

Sterling P, Eyer J. 1988. Allostasis: a new paradigm to explain arousal pathology. In *Handbook of Life Stress, Cognition, and Health*, ed. S Fisher, J Reason, pp. 629–49. Chichester, UK: Wiley

Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. 2014. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. *BMC Psychiatry* 14:321

Takizawa R, Danese A, Maughan B, Arseneault L. 2015. Bullying victimization in childhood predicts inflammation and obesity at mid-life: a five-decade birth cohort study. *Psychol. Med.* 45:2705–15

Tottenham N, Galván A. 2016. Stress and the adolescent brain: amygdala-prefrontal cortex circuitry and ventral striatum as developmental targets. *Neurosci. Biobehav. Rev.* 70:217–27

Trumpff C, Marsland AL, Basualto-Alarcon C, Martin JL, Carroll JE, et al. 2019a. Acute psychological stress increases serum circulating cell-free mitochondrial DNA. *Psychoneuroendocrinology* 106:268–76

Trumpff C, Marsland AL, Sloan RP, Kaufman BA, Picard M. 2019b. Predictors of ccf-mtDNA reactivity to acute psychological stress identified using machine learning classifiers: a proof-of-concept. *Psychoneuroendocrinology* 107:82–92

Tsujii N, Otsuka I, Okazaki S, Yanagi M, Numata S, et al. 2019. Mitochondrial DNA copy number raises the potential of left frontopolar hemodynamic response as a diagnostic marker for distinguishing bipolar disorder from major depressive disorder. *Front. Psychiatry* 10:312

Tymofiyeva O, Henje Blom E, Ho TC, Connolly CG, Lindqvist D, et al. 2018. High levels of mitochondrial DNA are associated with adolescent brain structural hypoconnectivity and increased anxiety but not depression. *J. Affect. Disord.* 232:283–90

Tyrka AR, Parade SH, Price LH, Kao HT, Porton B, et al. 2016. Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. *Biol. Psychiatry* 79:78–86

van der Windt GJ, Chang CH, Pearce EL. 2016. Measuring bioenergetics in T cells using a seahorse extracellular flux analyzer. *Curr. Protoc. Immunol.* 113:316B1–B14

Verhoeven JE, Revesz D, Picard M, Epel EE, Wolkowitz OM, et al. 2018. Depression, telomeres and mitochondrial DNA: between- and within-person associations from a 10-year longitudinal study. *Mol. Psychiatry* 23:850–57

Viron MJ, Stern TA. 2010. The impact of serious mental illness on health and healthcare. *Psychosomatics* 51:458–65

Wallace DC. 2005. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annu. Rev. Genet.* 39:359–407

Wang J, Xiong S, Xie C, Markesbery WR, Lovell MA. 2005. Increased oxidative damage in nuclear and mitochondrial DNA in Alzheimer's disease. *J. Neurochem.* 93:953–62

Wang X, Sundquist K, Rastkhani H, Palmer K, Memon AA, Sundquist J. 2017. Association of mitochondrial DNA in peripheral blood with depression, anxiety and stress- and adjustment disorders in primary health care patients. *Eur. Neuropsychopharmacol.* 27:751–58

Wegman HL, Stetler C. 2009. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. *Psychosom. Med.* 71:805–12

Wei YB, Martinsson L, Liu JJ, Forsell Y, Schalling M, et al. 2016. hTERT genetic variation in depression. *J. Affect. Disord.* 189:62–69

Weintraub D, Dietz N, Duda JE, Wolk DA, Doshi J, et al. 2012. Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. *Brain* 135:170–80

Widom CS, Horan J, Brzustowicz L. 2015. Childhood maltreatment predicts allostatic load in adulthood. *Child Abuse Negl.* 47:59–69

Xie H, Huang H, Tang M, Wu Y, Huang R, et al. 2018. iTRAQ-based quantitative proteomics suggests synaptic mitochondrial dysfunction in the hippocampus of rats susceptible to chronic mild stress. *Neurochem. Res.* 43:2372–83

Yamaki N, Otsuka I, Numata S, Yanagi M, Mouri K, et al. 2018. Mitochondrial DNA copy number of peripheral blood in bipolar disorder: the present study and a meta-analysis. *Psychiatry Res.* 269:115–17

Yan MH, Wang X, Zhu X. 2013. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic. Biol. Med.* 62:90–101

Yang N, Ren Z, Zheng J, Feng L, Li D, et al. 2016. 5-(4-hydroxy-3-dimethoxybenzylidene)-rhodanine (RD-1)-improved mitochondrial function prevents anxiety- and depressive-like states induced by chronic corticosterone injections in mice. *Neuropharmacology* 105:587–93

Yoo HJ, Park M, Kim SA. 2017. Difference in mitochondrial DNA copy number in peripheral blood cells between probands with autism spectrum disorders and their unaffected siblings. *World J. Biol. Psychiatry* 18:151–56

Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, et al. 2010. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464:104–7

Zimmermann KS, Richardson R, Baker KD. 2019. Maturational changes in prefrontal and amygdala circuits in adolescence: implications for understanding fear inhibition during a vulnerable period of development. *Brain Sci.* 9(3):65