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Psychological Stress and Mitochondria: A Systematic Review

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Abstract

Objective—Mitochondria are multifunctional life-sustaining organelles that represent a potential intersection point between psychosocial experiences and biological stress responses. This article provides a systematic review of the effects of psychological stress on mitochondrial structure and function.

Methods—A systematic review of the literature investigating the effects of psychological stress on mitochondrial function was conducted. The review focused on experimentally controlled studies allowing us to draw causal inference about the effect of induced psychological stress on mitochondria.

Results—A total of 23 studies met the inclusion criteria. All studies involved male laboratory animals, and most demonstrated that acute and chronic stressors influenced specific facets of mitochondrial function, particularly within the brain. Nineteen studies showed significant adverse effects of psychological stress on mitochondria and four found increases in function or size after stress. In humans, only six observational studies were available, none with experimental designs, and most only measured biological markers that do not directly reflect mitochondrial function, such as mitochondrial DNA copy number.

Conclusons—Overall, evidence supports the notion that acute and chronic stressors influence various aspects of mitochondrial biology, and that chronic stress exposure can lead to molecular and functional recalibrations among mitochondria. Limitations of current animal and human studies are discussed. Maladaptive mitochondrial changes that characterize this subcellular state of stress are termed mitochondrial allostatic load. Prospective studies with sensitive measures of specific mitochondrial outcomes will be needed to establish the link between psychosocial stressors, emotional states, the resulting neuroendocrine and immune processes, and mitochondrial energetics relevant to mind-body research in humans.

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INTRODUCTION

Mitochondria are subcellular organelles that sustain life through energy transformation and intracellular signaling. They have recently emerged as a key component of the stress response (1–3). However, unlike traditional biomarkers that reflect a specific biological process, mitochondria are complex multifunctional organisms that contain their own genome, reproduce, perform hundreds of biochemical reactions, and can adopt specific functions based on which cells they inhabit. Despite the recent rise of mitochondrial research in modern medicine (4), mitochondrial biology is relatively poorly understood compared with other aspects of cellular biology. Nevertheless, research over the past decade has demonstrated that genetic and biochemical mitochondrial defects cause debilitating multisystemic clinical disorders (5), and animal models have confirmed that changes in mitochondria directly influence systemic metabolic regulation (6), brain function (7), immune activation (8), and even the rate of aging and life-span (9–11).

In relation to stress pathophysiology, research has used various indicators of stress (e.g., psychological distress, social or life stressors, negative emotional states, and psychiatric disorders) and has mostly examined physiological processes centered around three systems: the brain, the endocrine, and the immune systems (12,13). The resulting findings from psychosomatic medicine, psychoneuroimmunology, and psychoneuroendocrinology have demonstrated that psychosocial experiences and life exposures influence subcellular processes including immune activation/suppression (14,15), oncogenic behavior (16), gene expression regulation (17), telomere maintenance (18), and epigenetic processes (19). Emotional states—both adverse (e.g., anxiety and depression) and positive (e.g., happiness and optimism)—are thus suspected to trigger broad-acting biological pathways such as inflammation that meaningfully influence morbidity and mortality (20). But how do external exposures make their way “under the skin” and “into the genome”? Do mitochondria contribute to the transduction of stressful experiences into lasting biological consequences that affect human health and disease?

Recent discoveries provide converging evidence implicating mitochondria at two major levels: as a *target* of stress and as *mediator* of stress pathophysiology. The latter portion of this model proposes that mitochondria underlie systemic recalibrations associated with stress pathophysiology and allostatic load, and consequently, that dysfunctional mitochondria are harbingers of stress-induced molecular and cellular alterations leading to the biological embedding of stress. For a comprehensive discussion of mitochondrial stress transduction and of the links between key concepts in psychosomatic medicine, psychoneuroendocrinology, psychoneuroimmunology, and mitochondria, the reader is referred to the associated article in this issue of *Psychosomatic Medicine* (21). Here, we examine evidence about the first step of this model, namely, whether mitochondria respond

to psychological stress exposure. We first provide a brief introduction of mitochondrial structures and function relevant to stress pathophysiology.

Mitochondrial Structures

Mitochondria exhibit several structural features of their bacterial origin. This includes a double-membrane organization: the inner and outer mitochondrial membranes, which enclose the mitochondrial matrix (Fig. 1). Under stress, mitochondrial can swell and membranes become distended. The mitochondrial matrix contains enzymes of the Kreb's cycle (also known as the tricarboxylic acid (TCA) cycle) and β-oxidation pathway that metabolize ingested energy food substrates, including sugars and fats, respectively (27). Another vestige of bacterial heritage is their circular mitochondrial DNA (mtDNA) (Fig. 2). Mitochondria are the only organelle to contain their own genome. In humans and animals, the mtDNA is uniquely inherited from the mother (30) and harbors single-nucleotide polymorphisms that correlate with ethnicity (31,32). The mtDNA does not have loose ends and thus does not contain telomeres, the DNA-protein complexes that cap the end of chromosomes in the nucleus (33). The mtDNA also lacks introns and is more susceptible to damage in comparison to the nuclear genome (34), which may explain its greater vulnerability to damage with aging, and possibly with chronic stress.

Mitochondrial Functions

The mitochondrial genome is of prime importance because it encodes essential genes for energy production by the respiratory chain. The respiratory chain, also known as the electron transport chain, is located in the tight folds of the inner membrane called "cristae" and contains five multiprotein enzyme complexes—I, II, III, IV, and V (Fig. 1, left). Most of the mitochondrial proteins (>1500) are encoded in the nuclear genome, except for the 13 encoded by the mtDNA (Fig. 2). All mtDNA-encoded proteins are subunits of the respiratory chain complexes I, III, IV, and V. Only complex II (succinate dehydrogenase) is fully encoded by the nuclear genome. The respiratory chain complexes are large enzymes composed of multiple proteins that transport energy in the form of electrons derived from ingested food substrates, initially catabolized by the TCA cycle and β-oxidation. The terminal respiratory chain complex IV (cytochrome *c* oxidase, or COX) combines the transported electrons with breathed oxygen (O_2), which acts as ultimate electron acceptor. The energy harnessed from this process thus establishes the life-sustaining mitochondrial electrochemical gradient ($\Delta\Psi$), akin to a charged battery. Generating the mitochondrial electrochemical gradient is the ultimate reason why living organisms must eat and breathe. The flow of energy through mitochondria distinguishes the living person from the inert body; it enables mitochondrial functions required for life.

Other than energy production, mitochondria perform multiple essential functions that influence gene expression within the cell nucleus (Fig. 1, right) and physiological regulation across the organism (21). Notably, mitochondria are the major producers of reactive oxygen species (ROS) within the cell (35,36), which play signaling and other life-sustaining roles at low levels, but can lead to oxidative stress when they overwhelm antioxidant defense mechanisms, possibly playing key role in neurodegenerative processes (37) and in stress pathophysiology.

The energy harnessed from electron transport stored across the inner mitochondrial membrane as *membrane potential* is used to drive multiple distinct functions. One of the first to be discovered was the production of adenosine triphosphate (ATP) (38), which fuels most cellular reactions, including gene expression, chromatin remodeling, ion homeostasis, protein and hormone synthesis, secretion, neurotransmitter release and reuptake, and muscle contraction, to name a few. The metaphor of "mitochondria as powerhouse" has thus dominated the imagination of biologists and the public over the past half-century. The ability of mitochondria to use oxygen at the level of the respiratory chain complexes, referred to as *mitochondrial oxidative capacity*, thus depends on a functional respiratory chain and intact mtDNA. Mitochondrial respiratory capacity can be measured directly in fresh cells by respirometry (39–41), or indirectly from frozen samples by measuring the enzymatic activity of respiratory chain complexes (42). Mitochondrial ATP synthesis can also be directly measured in fresh cells (43).

Quantity Versus Quality

The "quality" or function of mitochondria also varies independently from mitochondrial content and this may influence their responses to stress. For instance, tissues with different metabolic demands contain different types of mitochondria, defined either by their function (44) or by protein composition (45). In neurons, synaptic mitochondria qualitatively differ from mitochondria in the cell body (46)—even if they are from the same cell. Therefore, combining metrics representing both mitochondrial function and content provides a fuller picture of mitochondrial recalibrations. Stress exposure may also independently influence mitochondrial content and function, which may have markedly different effects on cellular and organismal health. This underscores the empirical value to assess in parallel both mitochondrial content or function outcomes to enable an accurate interpretation of stress-induced mitochondrial recalibrations.

Here we present a systematic review evaluating experimental studies of the effects of induced psychological stress on mitochondrial structures and functions.

METHODS

The study selection process for this systematic review was based on PRISMA guidelines (47). Search terms included the following: "mitochondri*" (e.g., mitochondion, mitochondria, and mitochondrial), stress* (e.g., stress, stressful, and stressor), and psycholog* (e.g., psychology and psychological). Date limits were from 1960 to January 1, 2017. Only studies in English or French were included. In categorizing reasons for rejection, in cases where multiple criteria were not met "review" had precedence over "not psychological stress," which had precedence over "not mitochondrial function," which had precedence over other categories (Fig. 3).

Only studies directly measuring at least one aspect of mitochondrial *function* (e.g., respiration, respiratory chain enzymatic activity, and ROS production), or electron microscopy studies *quantifying* changes in mitochondrial morphology or structure, were included. Studies reporting single molecular markers that only provide indirect information on mitochondrial function were not included. Similarly, only studies of psychological stress

were retained, whereas studies of physical of metabolic stressors such as food or water restriction were not included. Social isolation studies, which differ in several ways from traditional acute and chronic stress paradigms, were not included in this review, although two reports have also suggested effects on mitochondrial function (48,49).

Notably, after screening titles and abstracts, 22 articles listing “mitochondrial function” as a main outcome in the abstract did not actually assess functional measures and were therefore excluded. These articles, some of which are discussed hereinafter in the section “Additional Findings In Animal Studies,” assessed protein markers, gene expression, or other molecular markers (e.g., metabolites and apoptotic cell death). After exclusion of ineligible studies, 23 articles were retained and included in this systematic review.

RESULTS

Table 1 summarizes data for each study including species, stressor, and main outcome measures. There were no human study with induced psychosocial stress monitoring mitochondrial function, so all studies included are in animal models. Rats were most often studied (58% of studies), followed by the mouse (38%) and one study in gerbils. The stressors most frequently used was chronic restraint stress (e.g., 21 consecutive days of physical restraint, 2 hours per day; 38%), followed by chronic unpredictable stress (e.g., 40 consecutive days with alternating novel environmental exposures on each day; 33%) and acute restraint stress (e.g., a single bout of physical restraint lasting 30–120 minutes; 21%). Other stressors included noise exposure and cage overcrowding. The most studied organs were the brain (67%), the heart (13%), and other specialized tissues (e.g., testes and gut; 21%). Only one study examined more than one tissue, precluding robust conclusions about whether induced stress has organ-specific effects. In 46% of studies, mitochondrial function and integrity were most often measured via respiratory chain enzymatic activity, which can be assessed on frozen tissues (73). Other outcomes included oxygen consumption (33%), quantitative electron microscopy (29%), membrane potential (13%), ATP synthesis (13%), and ROS production (8%). Mitochondrial DNA copy number, which is not a measure of mitochondrial function, was measured in 9% of studies. This distribution of outcome measures reflects in part the technical aspects of mitochondrial studies. Enzymatic activities can measured on frozen tissues, whereas other functional measurements require fresh tissues and are therefore more difficult to implement. This also illustrates the multifunctional nature of mitochondria and the need to empirically assess multiple aspects of their function to define the impact of stress on mitochondrial behavior or phenotype.

Four main themes emerge from this body of work. First, chronic stress induced through a form of psychosocial stressor decreases mitochondrial energy production capacity and alters mitochondrial morphology. This manifested at multiple levels, in respiratory chain enzymatic activity of various complexes, in the rate or oxygen consumption (i.e., respiration) measured directly from fresh tissues or isolated mitochondria, in mitochondrial membrane potential, or in mitochondrial content (Table 1).

Second, acute and chronic stressors have different and in some cases opposite effects on mitochondrial functions. Acute stress may damage mitochondrial structure within hours and

enhance certain aspects of their function. Several studies investigating mitochondrial morphology and ultrastructure by electron microscopy reported acute mitochondrial damage with stress (53,55,57,70,74), whereas other showed increased size of mitochondria with chronic stress (63), possibly reflecting an increase in biogenesis. Although some studies reported gross disruption in mitochondria indicative of dysfunction and pathological swelling, the lack of quantitative analysis of mitochondrial shape and morphology precludes conclusions regarding the effects of stress on mitochondrial shape. Differential effects on mtDNA copy number (mtDNAcn) have also been reported. One study found 50% to 60% decreased mtDNAcn in various brain regions after chronic unpredictable stress (61), whereas another study revealed increased mtDNAcn in peripheral tissues after chronic restraint stress (52). The liver, in particular, showed the highest change after 4 weeks of stress, with a doubling of mtDNAcn (75). The increase in mtDNAcn is in keeping with compensatory up-regulation of biogenesis and greater mtDNA replication in response to energy deficiency when the mtDNA is mutated (76,77). Antioxidant enzymes may also be up-regulated acutely, likely as an adaptive response, but then decrease with chronic restraint stress (78,79). Overall, these data are consistent with an inverted U-shaped relationship linking the *duration* of psychosocial stress with mitochondrial changes, and mitochondrial allostatic load (MAL) more generally (21).

Third, because parts of the respiratory chain are encoded by mtDNA and other components are not, comparing them allows us to discern functional changes that could arise form mtDNA defects and those arising from other mechanisms, such as changes in biogenesis or regulatory molecular modifications of various proteins. Among the respiratory chain complexes, complex IV (COX), which is encoded by the mtDNA, was the most frequently affected. Studies, mostly conducted with the brain, reported changes in COX activity ranging from 0 to 80% decreased specific COX activity. Unlike other enzymes, no study found increase in COX activity from stress. However, one study found selective decrease in complex I and complex II (succinate dehydrogenase), but not in COX (62).

Fourth, certain factors can influence mitochondrial vulnerability to stress. One study did not find significant alterations of mitochondria function in normal mice, but observed a significant decrease in COX activity in transgenic mice (lacking the *Malpar1* gene) (54). Such observation suggests that genetic factors can sensitize or confer a predisposition of mitochondria to the effects of psychological stress. Although not the direct focus of this review, several studies also included an intervention arm where animals either exercised or received specific small-molecule compounds acutely or chronically before stress exposure. As indicated in Table 1 (see results marked with "[ ]"), certain compounds including antioxidants conferred protection against stress-induced mitochondrial dysfunction (64,65,67,68), indicating the existence of stress-sensitizing and stress-buffering factors (i.e., moderators) for the effects of induced stress on mitochondria.

Additional Findings in Animal Studies

This section discusses some studies that did not meet the criteria for inclusion in the present systematic review of the literature because they did not directly measure mitochondrial function, but nevertheless provided strong complimentary indirect evidence that stress alters

some aspect of mitochondrial energetics. For example, some studies described herein evaluated specific molecular components of mitochondria (e.g., proteins inside mitochondria), which, although they do not represent function, may reflect some form of molecular recalibration and could constitute the molecular basis for functional defects observed in functional studies. In this section we discuss examples of these complimentary outcomes, which when assessed in parallel with functional outcomes will reinforce the interpretation of future studies.

Some studies analyzed stress biomarkers in rats exposed to chronic mild unpredictable stress using *metabolomics*. Metabolomics allows for the unbiased detection of hundreds to thousands of metabolites, many of which are directly or indirectly derived from mitochondrial metabolism (80). One study in particular showed circulating metabolic profiles in response to induced stress that are suggestive of altered energy metabolism implicating mitochondrial respiratory chain dysfunction (81). Mice with different anxious-like behavior (e.g., avoidance of open spaces) also have different metabolomic signatures in the brain and blood (82). Interestingly, parallel work in humans has also related various emotional states (e.g., depressive symptoms) to certain metabolomic profiles, such as amino acids, using cross-sectional research designs (20,83).

Other studies have performed detailed analyses of the ensemble of proteins contained in mitochondria using *proteomics*, finding widespread changes in the protein composition of brain mitochondria under stress (84). The mitochondrial proteome also differs between mice with low- versus high-anxiety–like behaviors (85), suggesting that different mitochondrial phenotypes in the brain may be at the origin of anxious traits and social behavior (86) and influence physiological stress responses (87), as discussed previously.

At the gene level, *transcriptomics* has been used to reveal that restraint stress alters gene expression widely in the hippocampus (88), but also of mtDNA-encoded genes (87,89). The stressor duration may also have varying effects. In rats, acute stress induces down-regulation of several mtDNA genes, whereas chronic stress causes opposite effects on certain mtDNA transcripts that compose of respiratory chain complex I (89). These changes seem to depend on glucocorticoids and may involve epigenetic changes in mtDNA methylation (89), consistent with the effect of the glucocorticoid receptor (GR) on mtDNA. Accordingly, cortisol treatment of isolated mitochondria enhances respiratory chain efficiency (energy produced per oxygen consumed) and increases complex I–driven respiration, which is partially encoded by the mtDNA, in a mechanism that requires mitochondrial gene expression and protein synthesis (90). In contrast, cortisol does not seem to have an effect on complex II (90), which is entirely encoded by the nuclear DNA, suggesting that glucocorticoids acutely and chronically alter mitochondrial respiratory chain function directly by acting on the mtDNA.

Additional Findings Based on Human Studies

This systematic review yielded six articles reporting mitochondrial function or molecular marker of mitochondrial health in humans exposed to different life stressors. Because of the lack of experimental manipulation of emotional states, which precludes definitive conclusions regarding the directional and causal effects of psychological distress on

mitochondria, none of the human studies could be included in the systematic review. Nevertheless, these data form the basis of a new field and deserve discussion here, in the context of evidence presented previously. Table 2 summarizes available human observational studies linking self-reported or interview-based measures of psychosocial stressors and psychological distress, including psychopathology, to some aspects of mitochondrial biology.

One study found higher mtDNAcn in whole blood from American individuals who had endured either parental loss or childhood maltreatment (adverse childhood experiences, or ACEs) and with psychopathology including major depression, depressive disorders, anxiety disorders, and substance abuse disorders compared with controls without ACE (94). Another study measured whole-blood mtDNA in Chinese women with clinical levels of depressive symptoms, and also found higher mtDNAcn (52) and higher levels of mtDNA mutations (i.e., heteroplasmy) compared with women without depression (75). However, these studies are confounded by the use of whole blood (95,96) (see discussion of limitations hereinafter) and the cross-sectional study design, which cannot tease apart directionality or causality. Whether psychological symptoms (e.g., anhedonia and sadness in major depression) cause changes in mtDNA, or whether changes in mtDNA reflect an underlying pathophysiological state that contributes to psychological symptoms (i.e., reverse causation), remains to be determined.

Another study measured mitochondrial respiration and cellular mitochondrial content in frozen leukocytes of women retrospectively reporting ACEs (91). Using the Childhood Trauma Questionnaire, women were categorized as having “none,” “low/moderate,” or “severe” childhood maltreatment load based on the sum of their ACE frequency. This study found that compared with those who reported no maltreatment load, women with a severe load had blood leukocytes consuming more oxygen under basal (unstimulated) conditions. This result could reflect the combined product of energy demand by the cell and endogenous mitochondrial function, suggesting that early life trauma may reprogram cellular energetics (91). However, it does not specifically reflect mitochondrial dysfunction. Mitochondrial *content*, assed by citrate synthase (CS) activity, was also similar between individuals with varying levels of childhood trauma and controls. Notably, this research revealed that certain mitochondrial respiratory parameters were correlated with systemic inflammatory markers. Thus, these findings hint at two possibilities: either that stress-induced inflammation influences cell energetics, or that experiencing such psychosocial stressors (and potentially the emotional responses associated with these experiences) causes alterations in cellular or mitochondrial energetics, which in turn induce inflammation. The second possibility is consistent with *in vitro* work and mitochondrial stress transduction leading to biological embedding of life exposures (21), but further work is needed to establish the directionality of these effects.

One study evaluated the levels of circulating cell-free mtDNA (ccf-mtDNA) in plasma from individuals after nonviolent suicide attempt, an acute stressful event presumably preceded by psychological distress, compared with individuals who did not engage in suicidal behaviors (92). Suicide attempters had strikingly elevated (Cohen $d = 2.6$) level of ccf-mtDNA compared with controls, possibly reflecting MAL. Because ccf-mtDNA lies outside the

cells, circulating in the liquid fraction of blood, it does not contribute to tissue energy production capacity and therefore does not represent mitochondrial function. Current evidence suggests that ccf-mtDNA is a general sign of physiological stress particularly induced by injury and associated with inflammation (21,97). It will therefore be interesting to understand the link between psychological stress, the neuroendocrine and cellular factors that lead to mtDNA release, and both their immediate and long-term physiological effects.

Another study targeted caregiver women who care for a child with autism spectrum disorder, which is a psychopathology that fosters elevated levels of psychological distress in the caregivers given its detrimental impact in various life domains of the child (e.g., persistent deficits in social communication, stereotyped or repetitive behaviors and interests). The authors measured respiratory chain maximal enzymatic activities, mitochondrial content, respiratory chain protein abundance, and mtDNAcn in isolated mixed blood cells (93). Although mitochondrial content was unaltered, mitochondrial respiratory chain activity per mitochondrion–indexed as mitochondrial health–was significantly lower in caregivers compared with controls, with the largest group difference effect size being for COX (which is mtDNA-encoded). This result is similar to findings in animal models which, collectively, implicate mtDNA-encoded components that may decrease the overall energy production capacity of mitochondria in blood cells exposed to chronic stressors. Of relevance to the psycho-somatic model, this study found that morning and evening mood on days preceding blood draw accounted for 12% to 15% of the variance in the mitochondrial health index (MHI) on subsequent days, but not the reverse, suggesting that mitochondria respond to proximal emotional states. Accordingly, lower positive mood was a significant mediator of the effect between the chronic life stressor (i.e., caregiving of a child with autism spectrum disorder versus controls) and poorer mitochondrial health (93), potentially indicating a directional effect of acute psychological states on mitochondrial function.

Overall, there are very few studies in human subjects and most did not directly assess mitochondrial function. Nevertheless, the preliminary data available thus far support a potential association of psychosocial stressors and psychological distress with some aspects of mitochondrial function, but limitations in design and methodology encourage caution in interpreting these results.

DISCUSSION

Studies meeting the inclusion criteria for this systematic review collectively demonstrate four main points. First, chronic stress paradigms cause significant effects on mitochondrial energy production capacity and mitochondrial morphology. Second, acute and chronic stress may have different and possibly opposite effects on mitochondrial functions. Third, specific elements of mitochondrial function may be differentially affected by stress, such as mtDNA-encoded complex IV (COX). Fourth, behavioral, genetic, and dietary factors may influence mitochondrial vulnerability to stress. Collectively, available evidence supports the hypothesis that psychological stress causes MAL and calls for the need for more research investigating this question particularly in humans.

Evidence from metabolomic, proteomic, and transcriptomic studies also suggest additional layers of regulation by which stressful experiences may alter mitochondrial components among rodents. Although these metabolites, protein composition, and gene expression outcomes do not reflect the functionality of mitochondria, when assessed in parallel with functional outcomes, they will help explain and refine our understanding of the mechanisms by which stress influences mitochondrial function and health. In addition, whereas functional changes should be regarded as primary indicators of MAL (21), stress-induced molecular changes within mitochondria may also reflect compensatory mechanisms or recalibrations that contribute to long-term changes in mitochondrial function and to the accumulation of MAL.

Limitations of Animal Studies

Albeit informative, the reviewed animal studies include some major limitations. a) The lack of direct measurement of mitochondrial content to normalize activity metrics makes it impossible to distinguish between overall decrease in mitochondrial content and decreased function or “quality” of individual organelles. This would be resolved by measuring in parallel both markers of mitochondrial content and function in future work. b) Another limitation is the improper methodology to measure mitochondrial membrane potential, which could be improved by the use of ratiometric dyes, and also controlling for mitochondrial content. c) Within each study, analyses were conducted mostly in only one tissue, not enabling to determine the general versus tissue-specific effects of induced stress. d) The studies using prolonged stressors (e.g., restraint for >8 hours) do not always specify whether such duration prevented normal feeding/drinking, which could either counteract or further exaggerate some effects of stress on mitochondrial functions. e) Restraint stress paradigms commonly used could be construed as a “physical” stressor, and consequently, the mitochondrial changes reported may reflect physical rather than psychological stress. It is also apparent that stress induction paradigms and methodologies are not uniform across laboratories, which could contribute to discrepancies in the effects of stress on mitochondrial outcomes outlined in this systematic review. This is also true of assays used to characterize mitochondrial functions, because specific methods favored and available vary from one laboratory to another. Only few studies, apart from those assessing respiratory chain enzymatic activity in brain showing consistent overall decrease maximal enzymatic activity, have been replicated and have provided a satisfactory level of confirmation.

Perhaps the most notable and ubiquitous limitation of existing studies reviewed here is the exclusive use of male animals. This is largely explained by the common assumption in preclinical research that compared with male rodents without an estrous cycle, animal-to-animal variability is greater, and the data therefore are more “messy,” in females. However, this assumption is largely incorrect in regard to behavioral, metabolic, hormonal, and morphological traits (98). However, this still pervasive bias remains a significant obstacle to generalizability and to our ability to translate these data into human research (99). Given substantial sex differences in mitochondrial biology and their responses to perturbations (100) stress-related mitochondrial studies will benefit from equal inclusion of both sexes.

Limitations of Human Studies and Opportunities for Future Research

Existing human studies underscore five main limitations and point the way toward more robust research. The first limitation is the use of single molecular mitochondrial markers, which do not directly reflect mitochondrial function. Certain mitochondrial outcomes such as mtDNAcn, do not directly reflect mitochondrial function. In the absence of functional measures, the physiological meaning of increases and decreases of mtDNAcn is unclear and impossible to conclusively interpret. This is especially true in cases where mtDNAcn is measured from whole blood, which is composed of several different immune and nonimmune cell types with different mtDNA levels. Moving forward, dynamic measures of mitochondrial *function* could be assessed in parallel with molecular markers of mitochondrial content. Metrics of function and content could also be combined into indices of MHI that may be more sensitive and precise than individual markers alone (93). Improving the sensitivity of mitochondrial outcomes will provide more robust evidence into the link of psychosocial stressors and emotional states with mitochondria.

The second and related limitation is the use of mixed blood cell populations. Blood immune cell composition changes dynamically with various stress indicators (95,96) and undergo substantial circadian (i.e., across the day) oscillations (101). This is relevant because each immune cell type contains different amount of mitochondria that exhibit qualitatively different functions (102). Thus, the relative abundance of different leukocytes subpopulations could substantially alter mitochondrial measures without any real change in mitochondrial function in any cell type. For example, a small change in the proportion of platelets, an enucleated cell type that contributes to coagulation, artificially alters apparent mtDNAcn when measured in whole blood or in peripheral blood mononuclear cells contaminated with platelets (103,104). Future studies would be strengthened by the isolation of specific leukocyte populations. When it is not possible to sort different cell types, avoiding platelet contamination in peripheral blood mononuclear cells (PBMCs), with appropriate platelet depletion steps, would improve the interpretability of mitochondrial function data.

A third limitation of human studies is the exclusive use of blood-derived immune cells. Mitochondria are present in all tissue types, and stress-induced mitochondrial dysfunction could be tissue-specific. Some psychosocial stressors and emotional states may preferentially affect brain mitochondria (contributing to neurological disorders and cognitive decline), whereas others may affect liver and heart mitochondria (contributing to metabolic disorders). Other than blood, biopsies of other tissues are amenable to mitochondrial assessments, including buccal and urinary epithelial cells, as well as fat and skeletal muscle, among others. Certain immune cell subtypes (e.g., monocytes versus granulocytes and memory versus effector lymphocytes) may also be differentially affected. Although studies in leukocytes can be informative of mitochondrial health in immune cells themselves, studies incorporating measures across different accessible tissues and cell types will be insightful to understand the broader relevance—both diagnostic and prognostic—of mitochondrial function and mtDNAcn.

A fourth limitation relates to the retrospective and cross-sectional design of human studies. In comparison to experimental studies such as those reviewed previously where stress

exposure is manipulated by experimenters, all human studies so far have compared groups that differ in the experience of psychosocial stressors (e.g., exposure or not to early life stress) or in the levels of psychological distress (e.g., presence versus absence of psychiatric disorders). Such designs limit conclusions about causality and cannot rule out the contribution of potential covariates (e.g., exercise, sleep, and nutrition). Longitudinal and prospective study designs with comprehensive assessment of potential covariates such as physical activity, as well as studies monitoring emotional stress with repeated measures of mitochondrial function, are needed to establish the directionality of effects linking psychosocial stressors, the resulting emotional responses, and mitochondrial functions in humans.

Finally, the fifth limitation noted is the unequal representation of sex in current studies. Contrary to animal studies that exclusively included males, human studies have predominantly included women (see Table 2). Because of known sexual dimorphism in mitochondrial functions (101), research with balanced sex (and gender) composition will be needed to achieve a complete picture of mitochondrial recalibrations in men and women. In addition, so far, human studies have only concentrated on young adults or middle-aged individuals. Considering both sex and age in future research will enable building a more accurate and generalizable understanding of the role of mitochondrial dysfunction in stress pathophysiology in the population and across the life-span. We next discuss processes within mitochondria that may contribute to resilience and possibly explain the effects of stress-buffering interventions on mitochondrial health and downstream stress biomarkers.

Stress-Buffering Interventions: A Role for Mitochondria?

As discussed previously, mitochondrial oxidative stress is an indicator of MAL that contributes to stress pathophysiology (reviewed in Ref. (105)). The corollary is that mitochondrial antioxidant capacity should buffer against the effects of chronic stress. Although the major source of ROS and oxidative stress within cells is generally mitochondria (35), oxidative damage from stress could be of mitochondrial or of other origin. In line with the idea that mitochondrial oxidative stress contributes to cellular dysregulation, enhancing mitochondrial antioxidant capacity by experimentally overexpressing antioxidant enzymes in mouse mitochondria was previously shown to increase resilience to metabolic stress (106,107) and even increase life-span in mice (108). Likewise, oral administration of a mitochondria-targeted antioxidant decreased anxiety-like behavior in inbred mice selected for high-anxious traits (109). A similar effect was observed for depressive-like behaviors with the administration of the mitochondrial metabolite acetyl-L-carnitine (110,111). Similarly, chronic mild stress induces depression-like behavior in normal mice, which is counteracted by the induction of mitochondrial biogenesis in skeletal muscle via the overexpression of peroxisome proliferator–activated receptor-γ co-activator 1α (PGC-1α) (112). Similarly, low sociability usually associated with peripubertal stress is reverted by brain injection of resveratrol, a compound that stimulates mitochondrial biogenesis (113). This body of evidence indirectly supports a role of mitochondrial oxidative stress and mitochondrial function in stress pathophysiology.

However, it remains to be established whether the pathophysiology associated with chronic stress can be prevented or mitigated by mitochondria-targeted interventions, and whether this could be applied in humans. Certain behaviors like physical activity and exercise may have biological stress–buffering effects in humans (114,115). Interestingly, exercise increases several markers of mitochondrial content and function both in humans and in rodents (61,116,117). Furthermore, in one study where stressed sedentary animals experienced a decrease in respiratory chain enzymatic activities, animals trained with treadmill running showed the expected increase in mitochondrial content and function, and in parallel exhibited partial to complete protection against the stress-induced decreases in mitochondrial function and mtDNAcn (61). In humans, acute exercise before a series of mental arithmetic challenges along with social evaluative threat has also been shown to modulate hypothalamic-pituitary-adrenal (HPA) axis reactivity as well as hippocampal and prefrontal cortex activation (118). Because exercise acutely changes mitochondrial function and chronically increases in mitochondrial content and function in various organs, it is possible that the stress-buffering effects of exercise in humans could be mediated by changes of mitochondrial function. This possibility remains to be empirically evaluated.

CONCLUSIONS

Results from this systematic review highlight the need for more interdisciplinary research to map the links between the mind (psyche), mitochondria (mito), and the body (soma). Establishing the effects of psychosocial stress on mitochondria in humans will require the development and application of robust and comprehensive assessments of mitochondrial recalibrations among specific cell types. Moreover, in humans, stressors can vary in their nature (e.g., discrimination, violence, social isolation, job strain/loss, caregiving, and bereavement), can be of changing duration (e.g., acute and chronic), may elicit a wide range of emotional responses (e.g., anxiety, depression, anger, and helplessness) with diverse levels of intensity (e.g., mild, moderate, or severe symptoms), and can occur at different stages of the life-span (early childhood, midlife, or in elderly). Mitochondrial responses to stressors are also likely not linear (21). It will therefore be equally important to operationalize and distinguish between different life stressors and the resulting individualized experiences, and to assess important covariates that can independently influence mitochondrial content or function. Prospective and longitudinal studies combining these variables will be particularly valuable.

Building from established models where psychosomatic processes are known to operate, incorporating mitochondrial measures in study designs should accelerate the progression of our understanding around the interaction of mitochondria with the broad-acting brain-immune-endocrine processes that affect health outcomes. This joining of disciplines under a shared “psycho-mito-somatic” framework, as discussed in the joint article in this issue of *Psychosomatic Medicine* (21), should simultaneously promote a more holistic understanding of the processes that precipitate dysregulation and disease within the organism, and of the mechanisms that enable healthy individuals to successfully adapt to life challenges.

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Glossary

ACE	adverse childhood experiences
ATP	adenosine triphosphate
ccf-mtDNA	circulating cell-free mtDNA
Complex I	mitochondrial NADH dehydrogenase
COX	cytochrome c oxidase, also complex IV
CS	citrate synthase
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenal
IL-6	Interleukin 6
MAL	mitochondrial allostatic load
mtDNA	mitochondrial DNA
mtDNAcn	mtDNA copy number
Nf-kB	nuclear factor kappa B
PGC-1α	peroxisome proliferator activated receptor gamma co-activator 1 alpha
ROS	reactive oxygen species
ROS	reactive oxygen species
SDH	succinate dehydrogenase, also complex II

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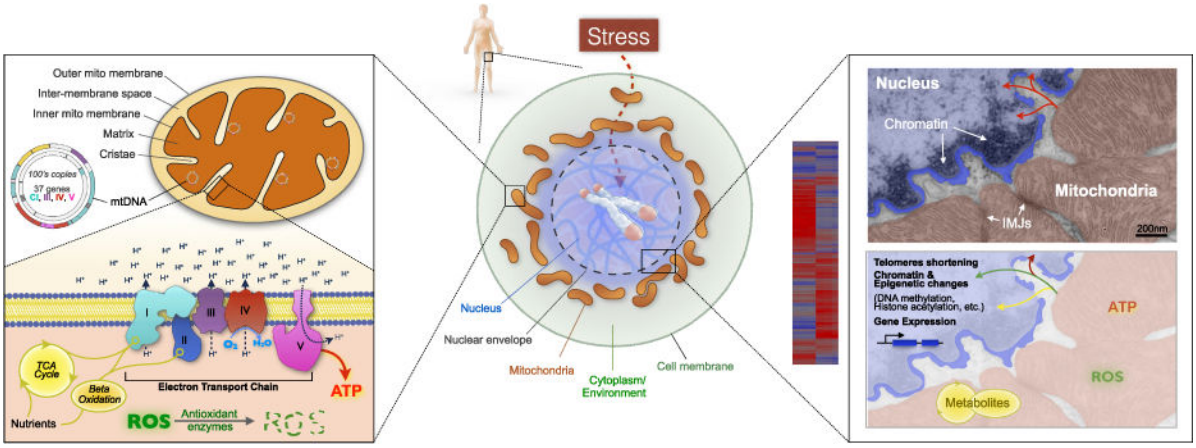

FIGURE 1.

Mitochondrial structures, functions, and their positioning within the cell. (Center) Psychosomatic medicine research aims to understand how psychosocial and behavioral exposures including stress influence biological and physiological processes across the organism, including those inside the cell nucleus where genes are transcriptionally and epigenetically regulated. Mitochondria are positioned in the cell cytoplasm at the interface between psychosocial and behavioral factors and the cell nucleus. (Left) Detailed cartoon of mitochondrial structures, including the electron transport chain (respiratory chain) illustrating the flow of energy from nutrients to the pumping of protons (H^+) to generate membrane potential, in part used to synthesize ATP, the energy currency of the cell. This process generates ROS, which are detoxified by specific mitochondrial antioxidant enzymes. (Right) Magnification of the mito-nuclear interface in a pseudo-colored electron micrograph showing the physical proximity between the chromatin in the nucleus and mitochondria (22). Mitochondria also communicate with each other via IMJs, nanotunnels, and other mechanisms (23). Signals derived from mitochondrial metabolism interact with other biochemical factors to coordinate gene expression and telomere maintenance via transcriptional and epigenetic mechanisms (24–26). ROS = reactive oxygen species; IMJs = intermitochondrial junctions; mtDNA = mitochondrial DNA; TCA = tricarboxylic acid; ATP = adenosine triphosphate. Color image is available only in online version (www.psychosomaticmedicine.org).

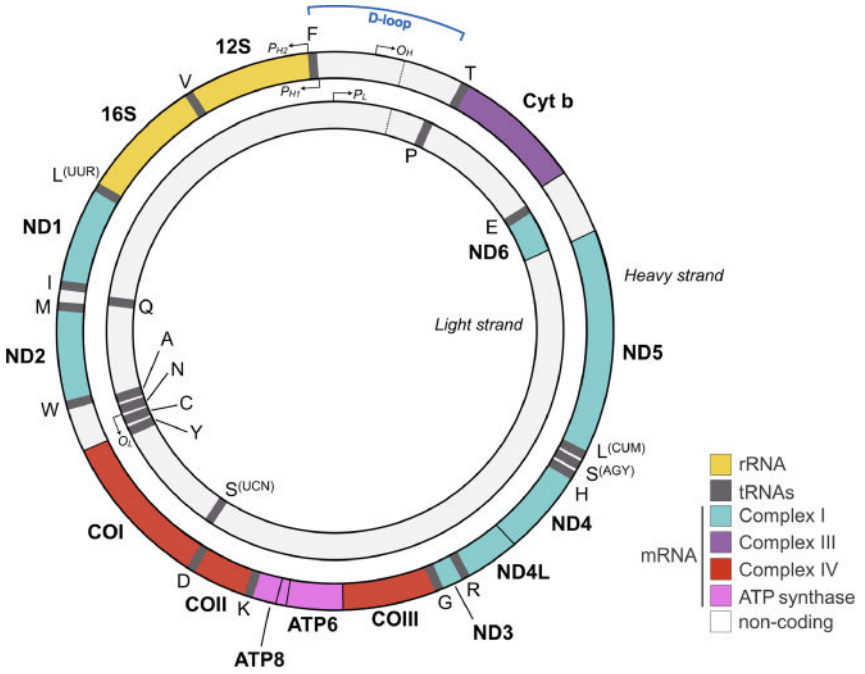

FIGURE 2.

The human mitochondrial genome (mtDNA). The mtDNA contains 16,569 nucleotides and encodes 37 canonical genes, including 2 rRNA and 22 tRNA required for protein synthesis. Encoded proteins constitute part of the respiratory chain and include seven subunits of complex I, one subunit of complex III, three subunits of complex IV, and two subunits of complex V. Other mtDNA-encoded mRNA transcripts giving rise to secreted mitokines have also been described (28). The mtDNA is composed of light (inner circle) and heavy (outer circle) mtDNA strands. The mtDNA is replicated from two origins of replication on the light and heavy strands termed O_L and O_H, respectively. mtDNA gene expression is initiated from promoters on the heavy strand (P_{H1} and P_{H2}) and on the light strand (P_L). The glucocorticoid receptor and other transcription factors interact with the mtDNA near the D-loop (29). Ethnic differences exist in mtDNA sequence (31,32). Note that colors for each gene are matched to the respiratory chain complexes, of which they encode a subunit in Figure 1. mtDNA = mitochondrial DNA; rRNA = ribosomal RNA; tRNA = transfer RNA; mRNA = messenger RNA; ATP = adenosine triphosphate. Color image is available only in online version (www.psychosomaticmedicine.org).

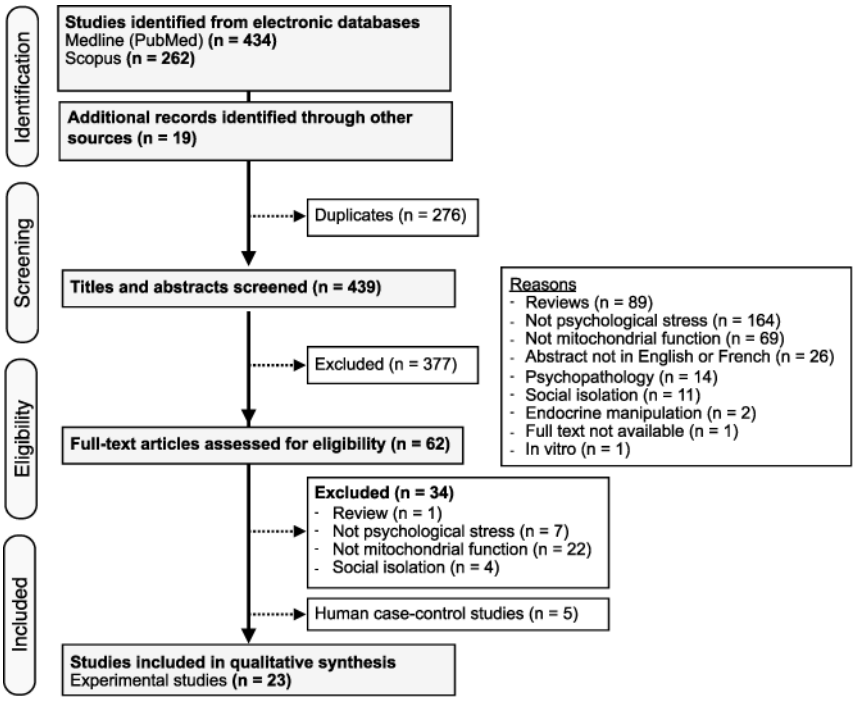

FIGURE 3.
Flow diagram for study selection in the systematic review. See “Methods” for details.

TABLE 1

Results From the Systematic Review of Experimental Studies Evaluating the Effects of Induced Psychological Stress on Mitochondrial Structure and Function

Author	Year	Reference	Species	Sex	Stressor	Tissue	Mito Outcome	Result
Andric et al.	2013	(50)	Rat	♂	ARS (2 h), CRS (2 d, 10 d)	Testes, Leydig cells	Respiration, ΔΨm	↓ Respiration, ↓ ΔΨm
Batandier et al.	2014	(51)	Rat	♂	ARS (0.5 h)	Brain, forebrain	Respiration, RC activity, ROS production, PTP sensitivity	↓ CI-driven respiration, ↓ CI activity, ⟷ ROS production, ↓ PTP sensitivity (apoptotic resistance)
Cai et al.	2015	(52)	Mouse	♂	CUS	Liver, saliva, hippocampus, skeletal muscle, ovary	Respiration (liver only), mtDNAcn	↓ increase in respiration (State 3/State 2), ↑ mtDNAcn
Gak et al.	2015	(53)	Rat	♂	ARS (2 h) CRS (2 d, 10 d)	Testes, Leidig cells	ΔΨm, EM	↓ ΔΨm at 1 and 2 d, mito swelling, ↑ mitochondrial content at 10 d
García-Fernández et al.	2012	(54)	Mouse	♂	CRS (21 d)	Brain, hippocampus	RC enzyme activity, MnSOD activity	⟷ COX activity in normal mice, [↓ in malpar1 KO (>60%)]
Gesi et al.	2002	(55)	Rat	♂	Noise (6, 12 h)	Cardiomyocytes, right atrium, and ventricle	EM	20%–30% of swollen mitochondria (additional data in Gesi et al. 2002)
Gong et al.	2011	(56)	Mouse	♂	CUS	Brain, hippocampus, prefrontal cortex, hypothalamus	Respiration, ΔΨm, EM	↓ Maximal respiration, ↓ ΔΨm, mito swelling
Heinzeller	1985	(57)	Gerbil	♂	Aggression	Brain, pineal gland	EM	↓ Mito size with night stress, not day stress
Kambe and Miyata	2015	(58)	Mouse	♂	CRS (14 d)	Brain, forebrain	Respiration	↓ CI-driven respiration (State 3, 250 μMADP), ⟷ leak respiration (State 4)
Li et al.	2012	(59)	Mouse	♂	ARS (18 h)	Spleen lymphocytes	ΔΨm, Cyt *c* release	↓ ΔΨm, ↑ cyt c release, ↑ apoptosis
Liu et al.	2004	(60)	Rat	♂	CRS (21 d)	Heart, ventricle	Respiration, ATP synthesis	↓ Coupling efficiency (10%–20%), ↓ ATP synthase activity (50%), ↓ ATP
Liu and Zhou	2012	(61)	Rat	♂	CUS (40 d)	Brain, cortex, hippocampus, striatum	RC enzyme activity, ROS production, mtDNAcn	↑ ROS production, ↓ CI, CIV activity (30%–40%), ↓ mito content (30%), ↓ mtDNAcn (50%–60%) [protection by exercise]
Madrigal et al.	2001	(62)	Rat	♂	CRS (7, 14, 21 d)	Brain, forebrain	RC enzyme activity, respiration, ATP synthesis	↓ CI, CII activity (50%–70%), ⟷ CIV activity ⟷ respiration, ⟷ ATP synthesis
Magarinos et al.	1997	(63)	Rat	♂	ARS (6 h), CRS (21 d)	Brain, dorsal hippocampus, mossy fibers	EM	↑ Mitochondrial size (CRS), ⟷ with ARS
Martin-Aragon et al.	2016	(64)	Mouse	♂	CRS (4 d)	Brain, cortex	RC enzyme activity	↓ CIV activity (30%–50%) [protection by esculetin]
Ortmann et al.	2016	(65)	Rat	♂	CUS (40 d)	Brain, multiple regions	RC enzyme activity	↑ CI, CII,CIII (20%–100%); ⟷ CIV activity (modified by flavanoid)
Rezin et al.	2008	(66)	Rat	♂	CUS (40 d)	Brain, multiple regions	RC enzyme activity	↓ CI, CIII, CIV activity (30%–50%) in cerebellum and cortex only, ⟷ CII

Author	Year	Reference	Species	Sex	Stressor	Tissue	Mito Outcome	Result
Rinwa and Kumar	2012	(67)	Mouse	♂	CUS (28 d)	Brain, whole	RC enzyme activity	↓ CI, CII, CIII, CIV activity (50%–80%) [protection by curcumin and piperine]
Rinwa and Kumar	2014	(68)	Mouse	♂	CUS (28 d)	Brain, hippocampus	RC enzyme activity	↓ CI, CII activity (70%–80%) [partial protection by L-NAME and Ginsen]
Seo et al.	2011	(69)	Mouse	♂	CRS (16 d)	Brain, hippocampus	RC enzyme activity	↓ CIV, ⟷ CI,CII,CS
Soldani et al.	1997	(70)	Rat	♂	Noise (1, 6, 12 h)	Heart, ventricles	EM	Swelling (10%–20%), vacuolization, loss of cristae integrity
Vicario et al.	2012	(71)	Rat	♂	Crowding (15 d) and Rec (1 h–30 d)	Intestinal mucosa	RC enzyme activity + CS, RC protein levels	During recovery ⟷ CII and CIV, ↓ CS (↑ CII/CS and CIV/CS ratios); stress ↓ COXI protein abundance [↑ by CRF]
Wen et al.	2014	(72)	Rat	♂	CUS (28 d)	Brain, raphe nucleus	Respiration, ATP synthesis, SOD and GPX activity	↑ Respiratory control ratio, ↑ ATP synthesis, ↑ SOD and GPX activity [exercise prevented these effects]

ARS = acute restraint (immobilization) stress; CRS = chronic restraint (immobilization) stress; ΔΨm = mitochondrial membrane potential; RC = respiratory chain, also electron transport chain; ROS = reactive oxygen species; PTP = mitochondrial permeability transition pore; CI = respiratory chain complex I, NADH dehydrogenase; CUS = chronic unpredictable stress, also known as chronic mild stress; mtDNAcn = mitochondrial DNA copy number; EM = electron microscopy; MnSOD = manganese superoxide dismutase; COX = cytochrome *c* oxidase; KO = knockout; = ADP = adenosine diphosphate; Cyt *c* = mitochondrial cytochrome *c*; ATP = adenosine triphosphate; CIV = respiratory chain complex IV, COX; CII = respiratory chain complex II, succinate dehydrogenase; CIII = respiratory chain complex III; L-NAME = N-nitroarginine methyl ester; CS = citrate synthase; COXI = cytochrome *c* oxidase, subunit 1; Rec = recovery; CRF = corticotropin releasing factor; SOD = superoxide dismutase; GPX = glutathione peroxidase.

State 2/4 respiration represents oxygen consumption in the absence of ADP (mitochondria not making ATP); State 3 respiration represents oxygen consumption in the presence of ADP (mitochondria actively making ATP); ↑, increase; ↓, decrease; ⟷, unchanged. Items in Results maked by [ ] are interventions/moderators shown to modify the effect of stress on mitochondrial outcomes.

TABLE 2

Studies Investigating the Association of Psychosocial Stressors and Emotional States With Mitochondria in Humans

Author	Year	Reference	Sex	Stressor	Assessment	Tissue	Mito Outcome	Result
Boeck et al.[a]	2016	(91)	♀	ACE (severity)	Self-report	PBMCs (frozen)	Cellular respiration	Higher cellular respiration in women with severe CTQ scores, positively correlated with inflammatory markers IL-1β, IL-6, and TNFα
Cai et al.	2015	(52)	♀	ACE, SLE, PD (yes, no)	SCID, self-report	Whole blood	mtDNAcn	Higher mtDNAcn with life history of depression and childhood trauma
Cai et al.	2015	(75)	♀	ACE, SLE, PD (yes, no)	SCID, self-report	Whole blood	mtDNA mutations	Higher mtDNA heteroplasmy (mutation load) in depressed individuals versus controls
Lindqvist et al.	2016	(92)	♀,♂	Suicide attempt (yes, no)	SCID	Plasma	ccf-mtDNA	Elevated levels of ccf-mtDNA in suicide attempters versus controls
Picard et al.[a]	2018	(93)	♀	Caregiving status (yes, no), daily mood (positive, negative)	SCID, self-report	PBMCs	RC enzyme activity and protein, mtDNAcn	Lower MHI in caregivers versus controls, highest effect size for CIV, mediated by positive mood; no difference in mtDNAcn or mitochondrial content
Tyrka et al.	2015	(94)	♀,♂	ACE, PD (yes, no)	SCID, self-report	Whole blood	mtDNAcn	Higher mtDNAcn with both psychopathology (mixed types) and childhood trauma

ACE = adverse childhood experiences (includes trauma measured by the CTQ and other early life stressors); PBMCs = peripheral blood mononuclear cells; CTQ = Childhood Trauma Questionnaire; IL-1β = interleukin 1β; IL-6 = interleukin 6; TNFα = tumor necrosis factor α; SLE = stressful life events; PD = psychiatric disorders (includes anxiety, major depression, bipolar, posttraumatic stress, and substance abuse); SCID = Structured Clinical Interview for DSM-III/IV; mtDNAcn = mitochondrial DNA copy number; ccf-mtDNA = circulating cell-free mitochondrial DNA; RC = respiratory chain, also electron transport chain; MHI = mitochondrial health index; CIV = respiratory chain complex IV, cytochrome *c* oxidase.

[a]Denotes studies reporting functional mitochondrial outcomes.