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EDITED BY  
Jeffrey C. Glennon,  
University College Dublin, Ireland

REVIEWED BY  
Shiro Suda,  
Jichi Medical University, Japan  
Lane Strathearn,  
The University of Iowa, United States

\*CORRESPONDENCE  
Colleen O’Ryan  
colleen.oryan@uct.ac.za

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# A molecular framework for autistic experiences: Mitochondrial allostatic load as a mediator between autism and psychopathology

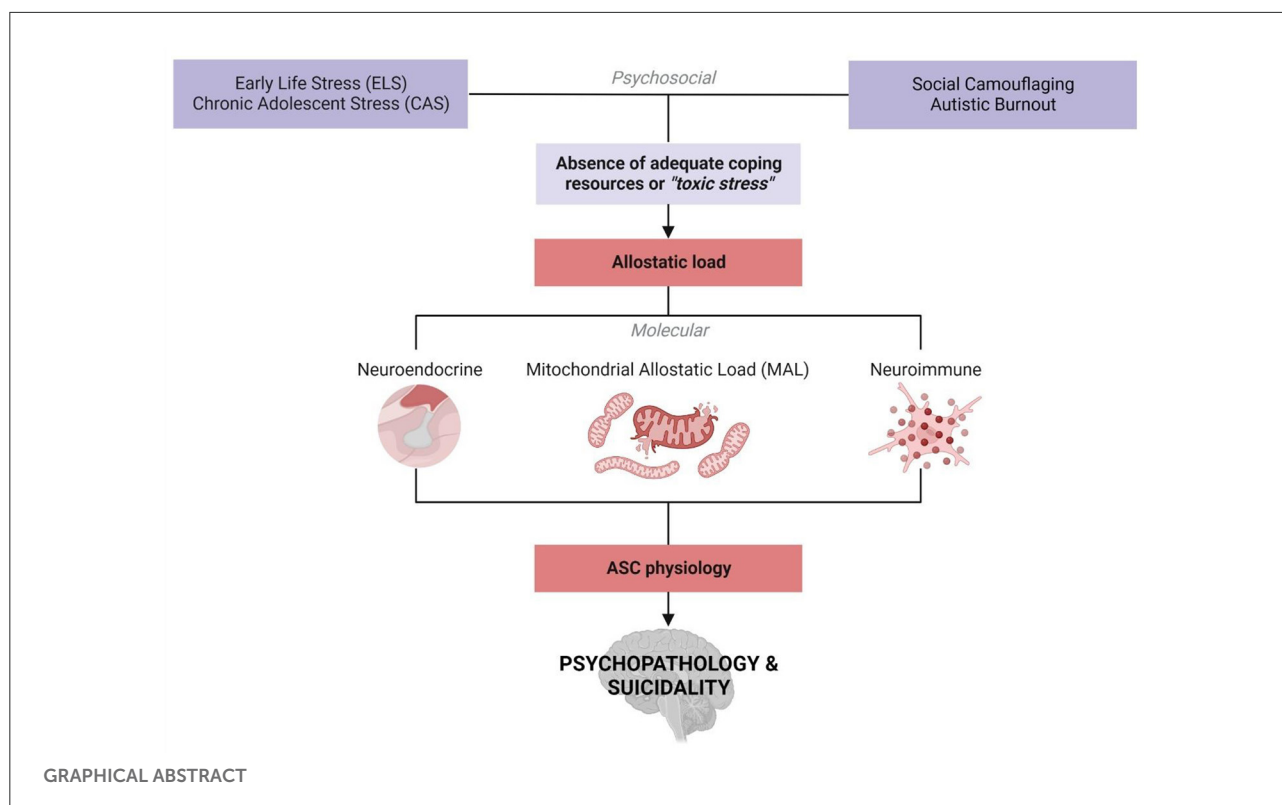
Caitlyn Mahony and Colleen O’Ryan\*

Department of Molecular and Cell Biology, University of Cape Town, Cape Town, South Africa

Molecular autism research is evolving toward a biopsychosocial framework that is more informed by autistic experiences. In this context, research aims are moving away from correcting external autistic behaviors and toward alleviating internal distress. Autism Spectrum Conditions (ASCs) are associated with high rates of depression, suicidality and other comorbid psychopathologies, but this relationship is poorly understood. Here, we integrate emerging characterizations of internal autistic experiences within a molecular framework to yield insight into the prevalence of psychopathology in ASC. We demonstrate that descriptions of social camouflaging and autistic burnout resonate closely with the accepted definitions for early life stress (ELS) and chronic adolescent stress (CAS). We propose that social camouflaging could be considered a distinct form of CAS that contributes to allostatic overload, culminating in a pathophysiological state that is experienced as autistic burnout. Autistic burnout is thought to contribute to psychopathology *via* psychological and physiological mechanisms, but these remain largely unexplored by molecular researchers. Building on converging fields in molecular neuroscience, we discuss the substantial evidence implicating mitochondrial dysfunction in ASC to propose a novel role for mitochondrial allostatic load in the relationship between autism and psychopathology. An interplay between mitochondrial, neuroimmune and neuroendocrine signaling is increasingly implicated in stress-related psychopathologies, and these molecular players are also associated with neurodevelopmental, neurophysiological and neurochemical aspects of ASC. Together, this suggests an increased exposure and underlying molecular susceptibility to ELS that increases the risk of psychopathology in ASC. This article describes an integrative framework shaped by autistic experiences that highlights novel avenues for molecular research into mechanisms that directly affect the quality of life and wellbeing of autistic individuals. Moreover, this framework emphasizes the need for increased access to diagnoses, accommodations, and resources to improve mental health outcomes in autism.

## KEYWORDS

autism (ASD), autistic burnout, social camouflaging, psychopathology, suicidality, early life stress (ELS), chronic adolescent stress (CAS), mitochondrial allostatic load



## Introduction

Research into autism spectrum conditions (ASCs) spans disparate psychosocial and biomedical disciplines that traditionally work in isolation. However, the complex and rapidly evolving sociological context of autism research calls for a more integrative approach. Psychosocial and clinical conceptualizations of ASC fundamentally define the parameters of molecular autism research. Therefore, it is essential to integrate evolving understandings of autistic experiences within a molecular framework. Historically, ASC has been defined by the external perceptions of neurotypical observers rather than an understanding of internal autistic experiences (1). This has manifested as an over-reliance on the medical model of disability in autism research, which was often rooted in the pathologization of ASC-associated behaviors. With the increasing incorporation of inclusive participatory research practices, the field is progressing toward a more comprehensive integration of the biopsychosocial disability model (2, 3). This interdisciplinary model recognizes that while the biological (4–7) and behavioral (8–11) differences associated with ASC present challenges to independent functioning, the inability to function within a societal framework that accommodates only one neurotype is not indicative of an underlying biological deficit (12, 13). Congruent with this, psychosocial research is shifting its focus to improving quality of life and minimizing

internal distress, rather than eradicating or correcting autistic behaviors (14).

However, this paradigm shift is yet to be fully integrated into the medical and molecular fields of autism research, since these disciplines require unambiguous definitions of disease, reductionist animal and cell culture models, and highly specific questions with limited scope. The challenges of biomedical research are already compounded by the etiological heterogeneity of ASC (15, 16) and the limitations of its conceptualization in diagnostic texts (1, 17). These limitations are increasingly well-recognized in clinical settings, especially with respect to the questionable reliability of autism assessments in females and people of color across varied sociocultural settings (18–25). Yet, molecular studies require deeply-phenotyped cohorts characterized according to standardized diagnostic criteria in order to accurately distinguish between complex molecular signatures (26). In this context, an over-reliance on an antiquated deficits-based disability model is often unavoidable. Moreover, biomedical research often relies on limited measurements of behavior and flawed indicators of functioning. The efficacy of an intervention is frequently measured by a decrease in ASC diagnostic criteria, but it is becoming clear that this is not a good indicator of health, wellbeing or quality of life for autistic individuals. In fact, the chronic suppression of autistic traits contributes to anxiety, depression, burnout, a diminished quality of life and

poor mental health in ASC (27–30). It is now recognized that therapeutic interventions should prioritize physical and psychological wellbeing, which may indeed manifest differently in different neurotypes. Of course, the association between internal distress and the external presentation of autistic behaviors will reflect the variability that is inherent to all facets of ASC etiology. Molecular interventions that target behavioral or biological differences may potentially improve health or wellbeing. Still, it should be acknowledged that much biomedical research has sought to decrease the “autism phenotype” without recognizing that this is not synonymous with an enhanced quality of life.

Nevertheless, molecular research has demonstrated potential to be relevant, useful and transformative for the autistic community. Genetic insight into the heritability of ASC has been instrumental in improving access to early diagnoses, and shifting blame away from caregivers or autistic individuals themselves for their differences. Moreover, an understanding of molecular ASC etiology has been used to mitigate common comorbidities that reduce quality of life. For example, molecular therapies have been developed to treat tumors and epilepsy in individuals with a monogenic form of autism called tuberous sclerosis (31). Concurrently, clinicians are still struggling with existing diagnostic guidelines that do not easily distinguish between ASC and co-morbidities, or reflect the heterogeneity in autism presentations, internal lived experiences or underlying biological processes. In conjunction with other psychosocial models, molecular research could be a useful tool to improve the resolution, specificity and utility of diagnostic labels. Ultimately, this could lead to a better understanding of individual autism presentations, their specific challenges, and relevant accommodations. Therefore, it is essential that molecular researchers grapple with the task of integrating the rigor of scientific experimental design and evolving understandings of autism within a biopsychosocial framework.

Importantly, an interdisciplinary approach could also yield novel mechanistic insights into molecular ASC etiology. Many promising findings from *in vitro* and *in vivo* molecular studies have failed to translate into reproducible results in human clinical trials (16, 32–36). This has largely been attributed to the complex interplay among genetic, epigenetic and environmental mechanisms in ASC. However, molecular research is also inherently reductionist and grounded in a one-dimensional understanding of ASC that is removed from the internal experience of autism. This could be a prevailing limitation that hinders the translatability of molecular research in a clinical and sociological context (1). Consequently, an integrative approach is needed to highlight the convergence between different scientific disciplines involved in autism research. In particular, this approach could provide crucial insight into the cellular mechanisms at the intersection of environmental stressors and biological processes that directly impact quality of life.

Here, we integrate recent characterizations of internal autistic experiences within a molecular framework to yield insight into psychopathology and suicidality in ASC. Interactions between psychosocial stress, ASC physiology and allostatic load have previously been proposed to influence clinical outcomes in autism (37–39). Singletary (37) proposed that autistic children are exposed to significant stress that could disrupt social and cognitive development during the early post-natal period. Thus, he suggested that interactions between early life stress (ELS), underlying physiology and allostatic overload may contribute to ASC presentations (37). More recently, Scarpa et al. (38) developed a biosocial vulnerability model which suggests that ASC neurophysiology mediates a predisposition to pathological trauma responses. However, this model remains understudied by molecular researchers.

In this article, we assimilate the emerging definitions for social camouflaging and autistic burnout with recent insights into the biological mechanisms that mediate the stress response. Previous authors focused on the relationship between ELS and the manifestation of autistic traits. However, we consider the putative role of ELS in mediating the relationship between ASC and psychopathology from a molecular perspective. Consequently, we propose an increased risk of exposure to, and an underlying molecular susceptibility to, ELS and Chronic Adolescent Stress (CAS) in ASC. Both ELS and CAS are known to contribute to psychopathology and a molecular interplay between mitochondrial allostatic load (MAL), the Hypothalamic-Pituitary-Adrenal (HPA) axis, and neuroinflammation is increasingly implicated in this association (40). Notably, mitochondrial dysfunction and neuroinflammation are widely documented molecular signatures in ASC, and each are known to regulate HPA axis signaling. Moreover, these signaling pathways converge on neurodevelopmental, neurophysiological and neurochemical processes that are disrupted in response to ELS and may be involved in the etiology of both ASC and psychopathology. This article describes an integrative framework shaped by autistic experiences that demonstrates how psychosocial and biological factors converge to increase the risk of psychopathology. This framework emphasizes the need to improve access to diagnoses, accommodations, and resources to mitigate poor mental health outcomes in autism. Moreover, this highlights novel avenues for future research into molecular mechanisms that affect the health and wellbeing of autistic individuals.

## Psychopathology and suicidality in ASC: The role of social camouflaging and autistic burnout

ASC is associated with a high prevalence of comorbid psychopathologies that substantially impair functioning and decrease quality of life (41–43). In particular, the rates of

generalized anxiety disorder (GAD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), self-harm, and suicidal ideation are significantly increased in ASC (30, 44, 45). It was recently reported that autistic children between 10 and 13 years old were six times more likely to reach clinically significant thresholds for measures of depression (46), indicating an earlier onset of MDD in ASC. Moreover, three measures of suicidality are more than twice as high in autistic individuals compared to the general population—including the rates of suicide risk, suicide attempts, and mortality by self-harm and suicide (43, 44, 47, 48). Compounding this, there are unique challenges associated with the assessment of suicidal ideation and suicide risk given that alexithymia and communication difficulties are core components of ASC (49). The high prevalence of psychopathology in autism is currently attributed to social difficulties, alexithymia, cognitive rigidity, loneliness, a lack of social support and increased exposure to traumatic experiences (44, 45, 50, 51). In addition, it has been suggested that underlying genetic (52) and neurological (38, 46, 53) mechanisms in ASC etiology could mediate a susceptibility to depression and other mood disorders. Thus, it is critical to understand the internal experiences and physiological mechanisms that mediate the relationship between ASC and psychopathology.

Emerging research has begun to characterize the distinct phenomena known as autistic burnout and social camouflaging, based on the lived experiences of autistic individuals. Importantly, this nascent research has intrinsic limitations in that it does not yet represent the diversity of experiences across the autism spectrum (29). Ongoing research is still defining, operationalizing, and empirically validating the afore-mentioned constructs in a clinical and research context (54–58). Nevertheless, considering some internal experiences of ASC may yield valuable insights beyond the inferences based solely on observable behaviors. Moreover, autistic burnout and social camouflaging are both understudied, yet integral aspects of the internal experience of autism that could play a central role in distinguishing psychological health from psychopathology.

While the field is still refining a consensus definition for autistic burnout, complementary working definitions are converging on similar experiences. Autistic burnout has been described as “*a state of physiological and psychological incapacitation, exhaustion, and distress in every area of life*” (59) marked by loss of function, reduced tolerance to stimulus and an increased manifestation of autistic traits (60). This condition results from “*a mismatch of expectations and abilities without adequate supports*” (59) and directly impacts “*mental health, quality of life and well-being*” (61). Autistic burnout is conceptually similar to non-autistic burnout in that it results from chronically operating beyond personal capacity. However, autistic burnout is distinct with respect to its causes, manifestations and functional implications (62).

The main contributor to autistic burnout is social camouflaging, defined as “*the need to suppress autistic traits or*

*disability... in order to meet family, social, vocational, or other mainstream expectations*” (59). While several different tools are emerging to quantitatively measure social camouflaging (55, 56, 58), current models agree on the presence of three core components: (i) deliberately adopting new social behaviors to make up for social difficulties (compensation); (ii) consciously suppressing autistic traits in order to appear non-autistic (masking); and (iii) implementing strategies to manage internal discomfort invisibly (assimilation) (22, 27, 58). Chronic social camouflaging leads to internal distress, an eroded sense of self, and physical and mental exhaustion (27, 63, 64) and is associated with psychopathology (29), self-injury (65–67), and a higher risk of lifetime suicidality (30).

However, camouflaging also facilitates access to employment, relationships and social acceptance and is an unavoidable prerequisite for independent functioning (28, 65). Thus, autistic individuals are required to exert substantial effort to perform typically “autonomic” aspects of everyday life. Consequently, autistic burnout is characterized by an inability to maintain basic levels of functioning, which is further exacerbated by the intensified presentation of autistic traits (60). Moreover, the inescapable demand to meet the neurotypical threshold for functionality makes recovery from autistic burnout considerably more difficult. Autistic burnout is “pervasive” (59), “chronic” (60), and “recurring” (61); this most closely aligns with a concept known as habitual burnout (68) which describes a state of functional impairment that has become embedded into daily life. Notably, the symptoms of habitual burnout include insomnia, anxiety, behavioral dysregulation, depression, self-doubt, emptiness and isolation (68). The characteristics and consequences of autistic burnout are thus highly specific to its context and present a significant risk for the development of psychopathology (62).

Importantly, autistic burnout is also distinct from clinical depression, despite some superficial similarities. Both MDD and autistic burnout are associated with chronic fatigue, cognitive incapacitation, and suicidal ideation; however, the anhedonia and existential hopelessness that characterizes MDD is not always a defining feature of autistic burnout (60). While depression is described as a lack of *motivation* to participate in life, autistic burnout is experienced as a lack of *capacity* to do so (59). Nevertheless, autistic burnout can lead to the subsequent development of MDD and vice versa. Moreover, the struggle to survive in a constant state of burnout can seem objectively irrational, while the fundamental logistics of living become a physiological impossibility. Thus, autistic burnout represents a distinct, independent and fundamentally different path to suicidal ideation even in the absence of clinical psychopathology (59).

Notably, the interplay between social camouflaging, autistic burnout, and psychopathology is exacerbated in autistic individuals who remain undiagnosed throughout childhood due to an absence of adequate supports and the chronic

suppression of autistic traits. Furthermore, undiagnosed autistic individuals lack an explanation for their differences or challenges and tend to internalize these as personal failings (64, 69). A pervasive experience among late-diagnosed autistic individuals is a lifelong sense of “inherent wrongness”, alienation, and a deep sense of shame about who they are (70). This culminates in low self-esteem, a lack of self-worth, and destructive core beliefs that are all risk factors for psychopathology (71). This emphasizes how the lack of awareness and stigma surrounding ASC contributes to autistic burnout and how early diagnosis could play an important role in preventing psychopathology (61). While the link between ASC and psychopathology is well-established, there is a critical gap in the literature on what physiological mechanisms lead to autistic burnout, how they differ from, or contribute to psychopathology, and crucially, how these could be prevented. However, recent progress in molecular neuroscience may reveal an important connection between early life adversity, allostatic load and psychopathology in ASC.

## Early life stress, chronic adolescent stress, and allostatic load in ASC

There is substantial evidence from both epidemiological and preclinical studies that ELS and CAS increase the risk of psychopathology and suicidality in adulthood (72–79). Notably, the established definitions for ELS and CAS closely mirror those emerging for autistic experiences of childhood and adolescence. While it has historically been challenging to derive a universally accepted definition for ELS or CAS, current models agree that stress refers to “*environmental events or chronic conditions that objectively threaten the physical and/or psychological wellbeing of an individual*” (73), undermine a child’s “*sense of safety, stability, and bonding*” (80) and for which “*adequate coping resources are unavailable*” (74). Much of the literature focuses on adverse childhood experiences, as ELS during infancy (0–2 yrs old) is thought to disrupt critical periods of post-natal brain development leading to impairments in cognition, language processing, social capacity, and behavioral and emotional regulation (81). However, adolescence is also a critical period for brain development that is highly sensitive to stress. In fact, CAS is known to contribute to the development of depression, anxiety, and other stress-related psychopathologies (73). Researchers have previously distinguished between good, tolerable, and toxic stress; these differentially induce adaptation, resilience or pathology, respectively. Here, the defining feature of toxic stress is “*a lack of internal resources or external support systems, resulting in chronic physiological dysregulation*” (82).

Importantly, the literature suggests that autism is associated with a significantly increased exposure to toxic stress in childhood and adolescence. Children with ASC are statistically more likely to experience early adversity (83), social vulnerability and isolation (84), bullying, discrimination, and ostracism

(85), and other forms of victimization (86). Differences with respect to social communication, development and integration can make it difficult for autistic children to feel a sense of “safety and stability” among their peers. Moreover, situations that are “tolerable” for neurotypical children are experienced as “toxic” stressors due to distinct neurophysiological differences in autism. Exposure to everyday sensory stimuli is painful, uncontrollable, and “personally threatening” due to difficulties with sensory processing. Thus, autistic children are pushed beyond their capacity just to achieve a degree of social participation, and even further resources are expended to achieve social acceptance. Personal accounts of social camouflaging describe attempts to manage both the “*physically assaultive*”, “*uncertain, exhausting nature of the social environment*” (87), and the persistent fear of stress, rejection and being misunderstood by peers (88). Social camouflaging has been conceptualized as the discrepancy between the internal experience of autism and the external presentation of autistic traits (22, 56, 58), and is experienced as a need “*to exceed what nature has given*” (27); similarly, autistic burnout has been described as “*having all of your internal resources exhausted beyond measure*” (59). This literature consistently points to a mismatch between external demands and internal capacity, and clearly demonstrates an absence of “adequate coping resources” which is consistent with the accepted definitions for toxic stress.

We propose that social camouflaging could act as a distinct form of CAS in autism. Camouflaging strategies become increasingly complex and intentional from middle childhood, which is a critical period for socialization marked by the development of self-concept and an increasing capacity for self-regulation (89). The self-concept tasks of middle childhood culminate in the ability to internalize expectations for one’s own behavior and develop strategies to meet these expectations (89). This enables an autistic child to both identify the need to suppress autistic traits and develop enough self-regulation to implement camouflaging as a replacement for natural behaviors. The extent to which these tasks are completed will vary widely across the autism spectrum depending on differences in both ASC presentations and sociocultural factors that contribute to socialization. Equally, there are significant differences with respect to an individual’s ability and motivation to mask their autistic traits.

This has important implications for the relationship between ASC, chronic stress and psychopathology. Individuals with more extreme sensory sensitivities, greater difficulties with self-regulation and communication, or atypical developmental profiles may be highly vulnerable to increased early life adversity. Yet, this might also facilitate earlier diagnosis, access to accommodations, and a reduced motivation or tendency to engage in chronic camouflaging. Conversely, many individuals with a greater tendency to mask may present with a “subclinical” autism phenotype, but a significant susceptibility to CAS induced by the chronic suppression of autistic traits. It is worth



reiterating that social camouflaging refers to internal efforts that are, by definition, removed from external presentations. High levels of masking do not correlate with any particular expression of autism and cannot be inferred based on the nature or degree of observable autistic traits. Rather, this emphasizes that different external autism presentations are not always reflective of the profound physiological and psychological dysregulation experienced internally. Despite the heterogeneity of ASC, an underlying susceptibility to stress-related pathologies could be a common mechanism responsible for negative clinical outcomes in this context.

The resonance between internal experiences of autism and established models for toxic stress provides a point of convergence between psychosocial and molecular research into ASC. From a molecular standpoint, ELS and CAS are thought to contribute to allostatic load, which describes the pathophysiological consequences of chronic stress on the metabolic, endocrine and immune systems required for homeostasis (40). Allostatic load provides an integrative model to quantify the cumulative impact of biological, psychological and social factors that contribute to pathology (40). In this context, social camouflaging could serve as a unique form of toxic stress that increases allostatic load in autism. Autistic burnout may represent a distinct pathophysiological state resulting from allostatic overload, culminating in neurological and psychological dysregulation that leads to psychopathology. Previous work has described how allostatic load may interact with behavioral, psychosocial and physiological aspects of ASC (37–39, 90); however, this model remains poorly characterized from a molecular perspective. Notably, the molecular mechanisms that mediate the association between ELS, CAS and psychopathology are also involved in ASC etiology. This could signify an underlying molecular susceptibility to ELS that may yield mechanistic insight into the relationship between autistic burnout, psychopathology and suicidality.

## Mitochondrial allostatic load and convergent molecular mechanisms

The concept of allostatic load is well-established (91–93), but the specific molecular mechanisms that mediate pathological stress responses remain poorly characterized (94). The HPA axis has traditionally been the focus of stress pathophysiology research in ASC; however, the evidence for HPA axis dysregulation in autism is inconsistent (95). Recently, mitochondrial metabolism has been recognized as a central regulator of the major neuroendocrine and neuroimmune systems involved in allostasis (40). Emerging evidence highlights the particular relevance of mitochondrial allostatic load (MAL), which describes adaptive changes to mitochondrial morphology, dynamics, and function in response to chronic stress (93). Notably, mitochondrial dysfunction is a biological signature

that is not only consistently observed in idiopathic ASC, but also independently implicated in ELS and psychopathology. Thus, MAL could serve as a central molecular mechanism involved in the development of psychological disorders in autistic individuals.

## Mitochondrial allostatic load

A preliminary but growing body of evidence suggests that mitochondrial dysfunction is involved in the relationship between ELS and psychopathology (96–98). Clinical studies have shown that ELS increases mitochondrial respiratory activity (99, 100), mitochondrial DNA (mtDNA) copy number (101, 102), and circulating cell-free mtDNA (103, 104), all of which indicate a dysregulation of mitochondrial function. Epidemiological studies also demonstrate that ELS disrupts typical indicators of redox homeostasis, including reactive oxygen species (ROS), antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase, and total reactive antioxidant potential (105, 106). This is reflected in animal models for ELS showing decreased SOD and increased protein carbonylation, ROS and glutathione (107, 108). Preclinical studies further demonstrated that ELS impairs mitochondrial electron transport chain (ETC) activity in the hypothalamus and dysregulates mitochondrial fission and antioxidant defense genes in the hippocampus, leading to cognitive impairments (109). Moreover, a recent systematic review presented consistent evidence for reduced mitochondrial energy production capacity and ETC complex activity, altered mitochondrial morphology and changes in mtDNA copy number in animal models for chronic stress (110). Notably, the duration and type of stress, as well as underlying genetic differences significantly affect how stress alters mitochondrial function (110). Conversely, experimentally disrupting mitochondrial function alters the physiological and behavioral consequences of psychological stress (40).

Similarly, mitochondrial dysfunction has been widely implicated in the pathogenesis of MDD; this has recently been comprehensively reviewed (93, 111–117). Mood disorders are frequently reported in patients with mtDNA mutations and up to half of patients with primary mitochondrial diseases present with MDD. Conversely, depression is associated with elevated mtDNA deletions, aberrant mtDNA copy number and oxidative mtDNA damage (113, 118, 119). Independent studies have reported increased oxidative stress and altered ETC activity (120) and decreased levels of antioxidants and antioxidant enzymes (121) in the brain tissue of patients with depression. Of note, Karabatsiakos et al. (122) reported significantly impaired mitochondrial metabolism in individuals with MDD, which correlated significantly with the severity of depressive symptoms. Pre-clinical studies also demonstrate an increase in ROS and a decrease in ATP and glutathione in models for depression (113). Importantly, many pre-clinical

models for MDD are induced by ELS, and consistently implicate mitochondrial mechanisms in the subsequent development of depressive behaviors (116). For example, *in vivo* models for MDD have shown that mitochondrial ETC complex activity is disrupted in brain tissue following maternal deprivation, social isolation, restraint stress, mild stress, and unpredictable stress (123–128). Moreover, several transcriptomic studies have reported significant dysregulation of mitochondrial genes involved in lipid metabolism, oxidative phosphorylation (OXPHOS) and glucose homeostasis in preclinical models for chronic and acute stress (114, 129–131). Thus, both epidemiological studies and animal models support a role for mitochondrial dysfunction in the relationship between ELS and MDD. Indeed, a recent review describes the central role of MAL in the symptoms of MDD and emphasizes the utility of targeting mitochondrial function to develop novel pharmacological treatments (93).

Mitochondrial dysfunction is also a widely-studied molecular signature associated with ASC; thus, the interplay between ELS and MAL is particularly relevant in this context. A seminal 1998 review of ASC clinical data demonstrated decreased cortical glucose uptake and ATP synthesis, as well as plasma lactic acidosis, carnitine deficiency and elevated urinary Krebs cycle metabolites (132). Subsequently, multiple lines of evidence have emerged to support a role for mitochondrial dysfunction in ASC and these are well-described in recent reviews (133–139). Noteworthy, clinical studies have reported altered mtDNA copy numbers and deletions (136, 140–143), mtDNA mutations (144, 145), mitochondrial ETC deficits (140, 142, 146) and altered plasma levels of lactate, pyruvate, alanine, creatine kinase, glutathione-S-transferase and caspase 7 (144, 147). Recent studies in ASC-derived lymphoblastoid cell lines (LCLs) showed significantly increased mitochondrial respiration and mitochondrial membrane potential as well as elevated activities of ETC complexes (148), while disruptions to mitochondrial bioenergetics, dynamics and morphology were observed in ASC-derived fibroblasts (149, 150). This is supported by independent transcriptomic studies that have reported reduced expression of mitochondrial respiration genes in ASC brain tissue (151–154). In fact, ASC transcriptomic, proteomic and DNA methylation functional enrichment signatures consistently converge on mitochondrial OXPHOS (155). Furthermore, increased oxidative stress is well-documented in ASC, with recent reviews discussing the cumulative evidence for altered glutathione metabolism, lipid peroxidation, protein oxidation, DNA oxidation and antioxidant enzyme activity in ASC (156–161). Thus, there is substantial evidence for altered mitochondrial metabolism in ASC, which could serve as a molecular susceptibility to the pathological consequences of MAL.

Notably, the relationship between MAL and ELS has only recently emerged, and the limitations of the current state of knowledge have been comprehensively evaluated (97). The field

is still developing quantitative cell-specific techniques and more integrative computational approaches to better characterize the complex and dynamic role of mitochondria in psychopathology and disease. Only recently have clinical studies explored indices of MAL, and these studies may be confounded by genetic and environmental factors that affect mitochondrial function (96). Nevertheless, the evolving field of mitochondrial psychobiology (97) represents a novel avenue for future research to explore a role for MAL in ASC clinical outcomes. Moreover, mitochondria are mechanistically implicated as essential modulators of both the neuroendocrine and neuroimmune components of allostasis (40, 96), each of which are thought to play a role in ASC.

## MAL and the HPA axis in stress-related psychopathology

The HPA axis is the major neuroendocrine system involved in initiating the stress response and coordinating the molecular components of allostatic load (73). Children are particularly vulnerable to HPA disruption during early childhood and adolescence, which are periods marked by higher HPA axis plasticity. Thus, HPA signaling is a key mediator of pathological responses to ELS and CAS (73, 81). A recent systematic review has demonstrated an established role for HPA axis dysregulation in mood disorders, suicidal behavior, and the relationship between ELS and major depression (162). Transcriptomic studies in brain tissue suggest that HPA axis signaling is involved in the development of MDD following ELS (72, 163). Furthermore, disruptions to cortisol and catecholamine signaling have been reported in individuals with a history of ELS who develop PTSD, depression and suicidality (164). Recent work in animal models has also shown distinct perturbations to HPA axis signaling, stress reactivity, and cognitive and emotional functioning in response to both ELS and CAS (165).

Importantly, a bidirectional relationship is emerging between the HPA axis and mitochondrial metabolism (Figure 1). Stress-responsive glucocorticoids (GCs) like cortisol and corticosterone (166) are released in response to HPA axis activation and act on GC receptors (GRs) to regulate genes involved in neurogenesis, neuroplasticity, and neurotransmission (167). Mitochondria are directly responsible for the synthesis of GCs *via* cytochrome P450 enzymes that are coupled to mitochondrial redox state (168). Mitochondrial metabolism not only regulates, but is also modulated by, GC signaling (40, 102); this relationship is mediated by both genomic and non-genomic mechanisms that have been comprehensively reviewed (169–176). At physiological levels, short-term GC exposure improves mitochondrial oxidation, membrane potential and calcium buffering, while chronic GC treatment reduces the activity of specific mitochondrial ETC complexes, increases mitochondrial

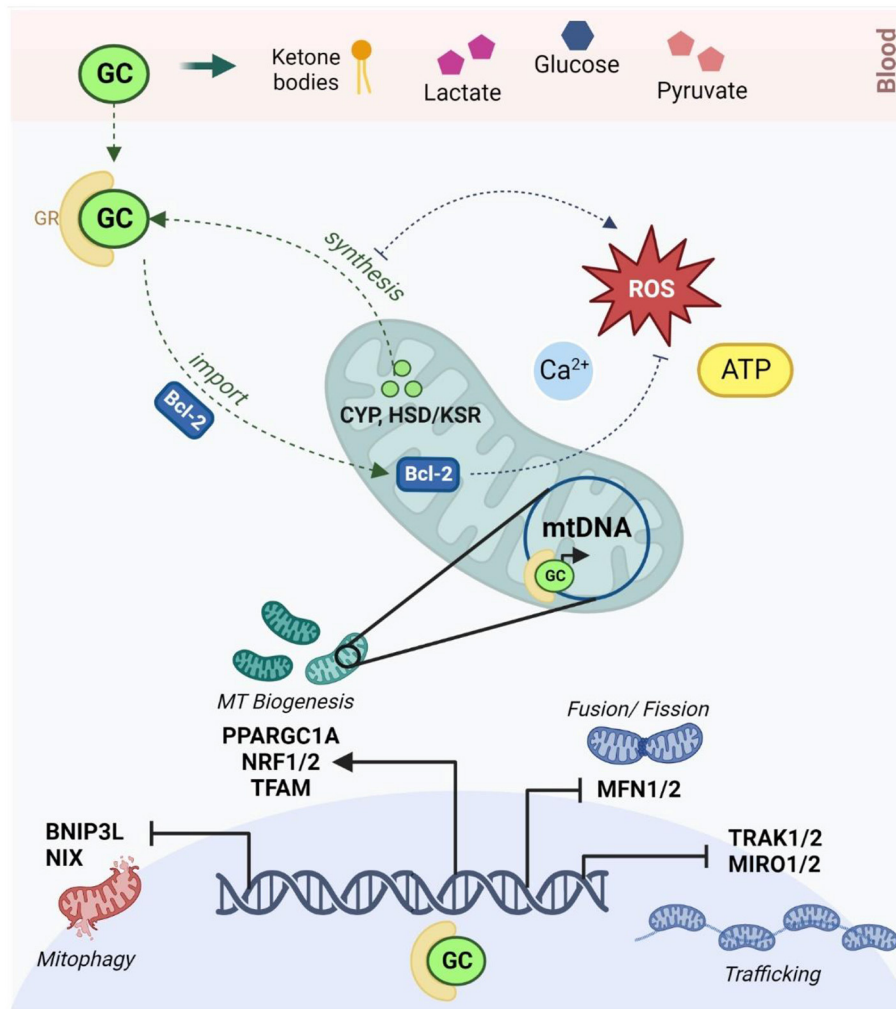


FIGURE 1

The reciprocal relationship between glucocorticoid signaling and mitochondrial allostasis (created with BioRender.com). HPA activation in response to chronic stress leads to the release of GCs which diffuse through the blood-brain barrier to activate GRs in neurons. GCs alter circulating levels of key energetic substrates including ketone bodies, glucose, lactate and pyruvate, which modulates mtFAO, glycolysis and OXPHOS. Activated GRs act *via* Bcl-2 and other non-genomic mechanisms to modulate membrane potential, calcium buffering, ATP production and redox homeostasis in the mitochondria. Activated GRs also bind to glucocorticoid response elements in both nuclear and mitochondrial DNA to moderate the transcription of key genes involved in the regulation of mitochondrial trafficking (TRAK1/2, MIRO1/2), morphology (MFN1/2), biogenesis (PPARGC1A, TFAM, NRF1/2) and mitophagy (BNIP3, NIX). Conversely, mitochondria are responsible for the synthesis of GCs *via* the CYP540 and HSD/KSR enzymes. GC synthesis increases mitochondrial ROS, and conversely, oxidative stress is known to inhibit steroidogenesis. HPA, hypothalamic-pituitary-adrenal; GCs, glucocorticoids; GRs, glucocorticoid receptors; mtFAO, mitochondrial fatty acid oxidation; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; MFN1/2, mitofusin 1 and 2; TRAK1/2, Trafficking Kinesin Protein 1/2; MIRO 1/2, Mitochondrial Rho GTPase; BNIP3, Bcl2 Interacting Protein 3; NIX, BNIP3-like; PPARGC1A, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; TFAM, mitochondrial transcription factor A; NRF1/2, NRF1/2 nuclear respiratory factors 1 and 2; CYP, cytochrome P450; HSD/KSR, hydroxysteroid dehydrogenase/ketosteroid reductase.

ROS production, and upregulates mitochondrial fragmentation (175, 177–180). Moreover, GCs affect the availability and turnover of key energetic substrates in the brain, including pyruvate, glucose, lactate and ketone bodies which regulate mitochondrial OXPHOS, glycolysis and fatty acid oxidation, respectively (169). GCs also modulate mitochondrial dynamics by regulating the expression of relevant genes *via* GC response

elements (GREs) in both nuclear and mtDNA (172–174). GCs have been shown to downregulate the transcription of the genes involved in mitochondrial fusion, trafficking and clearance (170, 180) and increase the expression of several central transcriptional regulators of mitochondrial biogenesis (102, 174, 181). Notably, animal models have shown that both chronic stress and corticosterone treatment increase mtDNA



copy number (119), and conversely, that mtDNA genetic variants can alter corticosterone production and HPA signaling (182, 183). Additionally, epidemiological studies have shown that mtDNA copy number is elevated in people with a history of ELS (184) and in major depression (119), while recent work demonstrated that the relationship between ELS and mtDNA copy number was mediated by differential methylation of the GR (184). Thus, both mitochondrial function and GC signaling are independently implicated in the response to ELS and MDD and recent findings suggest that these mechanisms are interdependent.

Interestingly, this may reveal a novel molecular susceptibility to ELS that has been overlooked in the context of ASC. Although much research has investigated a role for HPA signaling in the relationship between autism and psychopathology, this has yielded inconsistent results. There is a large body of evidence suggesting global disruptions to cortisol signaling in autism (95, 185–193) and independent studies have reported HPA hyperactivation (185, 188, 194, 195) and increased stress reactivity (186, 196) in ASC. A relationship between elevated evening cortisol and psychopathology in ASC has been proposed (194); altered cortisol responses were associated with GAD and social anxiety in boys with ASC (197, 198), while the cortisol awakening response was reported to correlate with depression and suicidal ideation in autistic girls (199). Moreover, targeted molecular studies have found disruptions to GR expression in ASC brain tissue (200), while genetic polymorphisms in the GR chaperone were associated with serum cortisol levels (201) and moderated the relationship between autistic traits and social anxiety (202). However, several reviews have summarized the conflicting evidence for HPA dysregulation, and its association with psychopathology, in ASC (46, 95, 185–187, 203). These authors emphasize that current findings lack intra- and inter-individual reproducibility, while numerous studies report no significant differences in cortisol levels, rhythms, variability or responsivity in ASC. Of note, Muscatello et al. (46) found no relationship between HPA activation, depression and anxiety in autistic children; instead reporting a complex multi-systemic relationship between HPA signaling and psychopathology. Yet, many studies assess HPA function using end-point measurements of salivary cortisol, which cannot always reflect complex interactions between biological signaling processes and genetic architecture with sufficient resolution. The existing literature suggests some role for the HPA axis in ASC etiology; however, the relationship between HPA axis signaling and psychopathology in autism is multifaceted and likely mediated by pleiotropic biological factors that contribute to an increased susceptibility to HPA axis dysregulation (46). In this context, the emerging relationship between mitochondrial metabolism and HPA signaling highlights mitochondrial dysfunction as a common biological signature that could act as a novel susceptibility to stress-related psychopathology in ASC.

## The neuroimmune system: A link between MAL and the HPA stress response

The neuroimmune system is the second established component of allostatic load that works in concert with HPA neuroendocrine signaling to modulate the stress response. Neuroimmune dysregulation is well-documented in clinical studies of neuropathology and is observed in response to ELS (74, 204, 205), and neurodevelopmental (206) and psychological (207–209) disorders. In fact, Bottaccioli et al. (210) proposed that the “neuroendocrine-immune” network is a central molecular mediator between psychosocial stress and the psyche. Accordingly, preclinical models have demonstrated that chronic stress consistently induces microglial activation and proinflammatory cytokine signaling in key brain regions involved in psychiatric disorders (205). Moreover, recent animal studies showed that ELS-induced depressive behaviors were associated with neuroinflammation (108, 211, 212) and aberrant microglial activity (213), while CAS was also shown to increase hippocampal immune reactivity (214). Furthermore, disruptions to microglial phagocytosis impaired neuronal development, cognitive performance, memory, reward processing, and processing of social stimuli (215). Notably, there is also extensive evidence for neuroinflammation in ASC (160, 216–221). Inflammatory cytokines are reported to be elevated in ASC blood and post-mortem brain tissue, while immunohistochemistry, positron emission tomography and morphological data demonstrates glial over-proliferation and over-activation in ASC (222–227). Transcriptomic studies have shown that genes involved in inflammation, astrocyte function and microglial activation were significantly dysregulated in ASC brain tissue (228), including the glial-specific marker GFAP which was overexpressed at both the mRNA and protein levels (229). Post-mortem studies also found a significant upregulation of microglial-specific genes (226), increased microglial density (224, 230) and excessive microglial activation (225, 231) in ASC brain tissue, while two recent systematic reviews report consistent evidence for disrupted microglial morphology, organization and activation in autism (220, 232). Although the precise nature of neuroimmune dysregulation is context-specific and pleiotropic in both ASC and ELS (204, 233), these data reveal an interesting mechanistic overlap between ASC neurology and stress-related psychopathology.

The neuroimmune system also acts as an intermediary between MAL and the HPA axis on a molecular level. Firstly, mitochondrial metabolism is a central modulator of glial cell phenotypes and neuroinflammatory state (40). Glial functions are controlled by tightly regulated interactions between microglia, astrocytes, oligodendrocytes and neurons, which are closely coupled to glial metabolism (234). Glial phenotypes are dynamic, shift in response to different stimuli and can be

either neuroprotective or neurotoxic (235). The transition to an inflammatory phenotype is known as reactive gliosis, which is characterized by transcriptional, biochemical, metabolic and morphological re-modeling (236). This has distinct implications for the metabolism, physiology and function of different glial cell types (237–242). While microglia, astrocytes and oligodendrocytes are each implicated in specific aspects of ASC neurology (216, 220, 243–246), microglial phenotypes are particularly relevant in the context of neurodevelopment. Microglia are the only glial cells present in the early embryonic brain (247) that play an essential role in the regulation of neurogenesis, synaptic activity and axonal myelination (242, 248–250), all of which are dysregulated in autism (216, 251, 252). Moreover, a cohesive body of work from animal models suggests that microglia are centrally involved in the neurological and behavioral consequences of ELS (253).

Importantly, mitochondrial dysfunction can induce microglial activation *via* both extrinsic and intrinsic mechanisms (Figure 2) (235, 254). Mitochondrial dysfunction in surrounding brain tissue leads to the release of damage-associated molecular patterns (DAMPs) that bind to microglial receptors and induce pro-inflammatory pathways (137). Moreover, microglial activation is marked by intrinsic metabolic reprogramming, and different microglial phenotypes are associated with distinct metabolic pathways (249). While resting microglia rely primarily on OXPHOS (255), the shift toward the inflammatory M1 phenotype is driven by a decrease in mitochondrial respiration and an upregulation of glycolysis. The latter enhances flux through the pentose phosphate pathway and increases lactate production to meet increased cellular energy demands (235). Recent work has demonstrated that mitochondrial metabolism directly regulates microglial activation (256, 257) and that disrupting mitochondrial function has profound implications for microglial inflammatory state (248, 249, 257, 258). *In vitro* studies have shown that inhibiting mitochondrial ETC activity (259) or increasing mitochondrial fragmentation (249) induces microglial activation and pro-inflammatory cytokine signaling; this could be mitigated by targeting mitochondrial fission (260), membrane potential, or ROS (249). Concurrently, mitochondrial stress impairs the transition to the anti-inflammatory M2 phenotype (261), which exacerbates neuroinflammation and oxidative stress (262). Conversely, different cytokine stimuli are known to alter microglial metabolic state. Inflammatory stimuli were found to induce a metabolic switch from OXPHOS to glycolysis in microglia *in vitro* (263), marked by increased lactate production and decreased OXPHOS, oxygen consumption and ATP production (264, 265). This metabolic shift correlated with increased production of proinflammatory cytokines (266) and nitric oxide (263), demonstrating a proinflammatory feedback loop driven by metabolic reprogramming. Ultimately, this highlights an intrinsic coupling between the neuroimmune and mitochondrial mechanisms implicated in allostatic load.

Stress-responsive neuroendocrine mediators are also known to modulate immune responses (40), and the bidirectional relationship between inflammatory- and GC- signaling has been well-documented in the context of psychopathology (106, 209, 267–270). GRs mediate anti-inflammatory effects *via* the transcriptional transrepression of pro-inflammatory genes such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and the activation of anti-inflammatory genes like annexin 1 (171, 268, 270). GRs also regulate key pathways involved in cell proliferation and differentiation to inhibit immune cell activation and inflammatory cytokine production. On the other hand, GCs have been shown to upregulate pro-inflammatory pathways *via* toll-like receptors, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) or the NLRP3 inflammasome (209). Conversely, inflammatory cytokines modulate GC signaling by disrupting GR expression, phosphorylation and nuclear translocation (271). Cytokine-stimulated immune cells can also promote HPA axis activation and GC signaling by upregulating the production of corticotrophin-releasing hormone (CRH) in the hypothalamus (181). Of particular relevance, animal models have demonstrated an antagonistic relationship between HPA activity and interleukin 6 (IL-6), which is one of the most consistently upregulated inflammatory markers associated with ELS (204), MDD (209) and ASC (272) that has also been widely implicated in psychological disorders (273). Markedly, recent preclinical studies suggest that neuroimmune-HPA interactions facilitate the neuroinflammatory response to stress. ELS was shown to increase GR promoter methylation and decrease GR expression, which was associated with upregulated proinflammatory NF- $\kappa$ B signaling (274). Similarly, CAS led to a significant transcriptional dysregulation of GR signaling, increased NF- $\kappa$ B signaling and excessive microglial activation in female rats (275).

Given that GR signaling regulates mitochondrial function, and that mitochondria are central to immune modulation, it has been proposed that HPA-immune interactions could be mediated by mitochondrial mechanisms (40, 171, 276). Mitochondria co-ordinate several of the inflammatory pathways at the interface between HPA and immune signaling, including NF- $\kappa$ B, IL-6, and inflammasome signaling (99). The GC-dependent NF- $\kappa$ B and MAPK signaling pathways are also intrinsically coupled to central regulators of mitochondrial biogenesis and homeostasis, including PPARGC1A (277). Moreover, GCs have been shown to upregulate the secretion of cell-free mtDNA *in vitro*, which in turn, serves as a potent activator of inflammatory signaling (103). Congruent with this, recent data demonstrate that ELS concurrently impairs mitochondrial function and increases neuroinflammation in animal models (278). Additionally, clinical studies report a significant correlation between mitochondrial respiration, oxidative stress and the production of pro-inflammatory cytokines, including IL-6, following ELS (99). Collectively, this reveals a tightly coupled interplay between mitochondrial

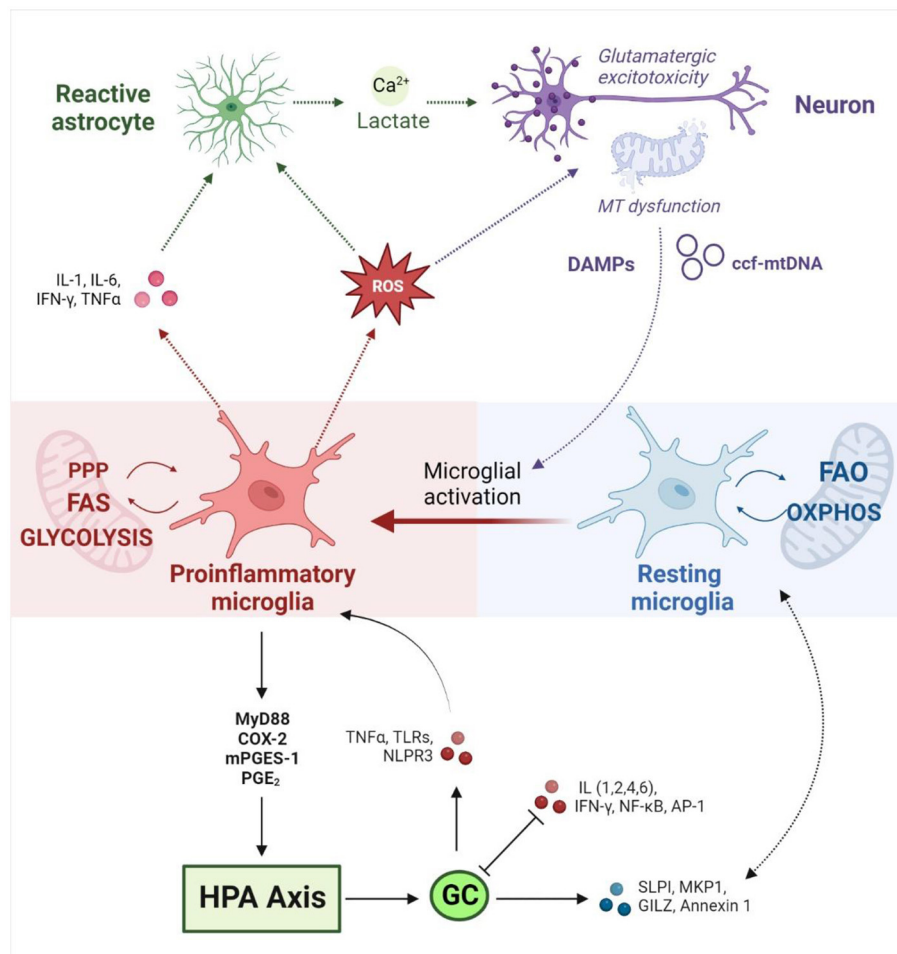


FIGURE 2

Neuroimmune responses at the interface between mitochondrial metabolism and the HPA axis (created with BioRender.com). Neuroimmune homeostasis is maintained by a tightly regulated interplay between dynamic glial phenotypes. Microglial activation toward a pro-inflammatory state is driven by intrinsic metabolic reprogramming away from OXPHOS and FAO toward glycolysis, FAS and the PPP. Conversely, microglial metabolic profile directly influences inflammatory state. Activated microglia release pro-inflammatory cytokines and ROS, which in turn activates neighboring astrocytes and induces mitochondrial dysfunction in neurons. Reactive astrocytes release lactate and calcium, which upregulates glutamatergic neurotransmission and culminates in an excitotoxic loop that drives further inflammation and oxidative stress. Damaged mitochondria in neurons induce the release of DAMPs and ccf-mtDNA which induce pro-inflammatory signaling in microglia. Inflammatory stimuli drive hypothalamic CRH production via MyD88, COX-2, mPEGS-1 and PGE2. HPA activation leads to the release of GCs which mediate inflammatory signaling on several fronts. GCs promote anti-inflammatory responses via SLP1, MKP-1, GILZ and Annexin 1, while downregulating pro-inflammatory signaling by IL-1, 2, 4 and 6, NF-κB, IFN-γ, and AP1. GCs have also been shown to upregulate inflammatory pathways via TLRs, TNF-α and the NLRP3 inflammasome. Conversely, pro-inflammatory cytokines interfere with GC signaling by disrupting GR expression, phosphorylation and nuclear translocation. MT, mitochondrial; HPA, hypothalamic-pituitary-adrenal; OXPHOS, oxidative phosphorylation; FAO, fatty acid oxidation; FAS, fatty acid synthesis; PPP, pentose phosphate pathway; ROS, reactive oxygen species; DAMPs, Damage Associated Molecular Patterns; ccf-mtDNA, circulating cell-free mitochondrial DNA; GCs, glucocorticoids; CRH, corticotrophin-releasing hormone; MyD88, Myeloid differentiation primary response 88; COX-2, Prostaglandin-endoperoxide synthase 2; mPEGS-1, microsomal prostaglandin E synthase; PGE2, prostaglandin E2; SLP1, secretory leukocyte protease inhibitor; MKP-1, mitogen-activated protein kinase phosphatase-1; GILZ, glucocorticoid-induced leucine zipper protein; IL, Interleukin; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; IFN-γ, Interferon gamma; AP-1, activator protein 1; TLRs, toll-like receptors; TNF-α, tumor necrosis factor α; NLRP3, NLR family pyrin domain containing 3.

metabolism, neuroimmune and neuroendocrine signaling that underlies the established relationship between ELS, MAL and psychopathology. This discussion has highlighted evidence implicating each of these molecular stress signatures in

ASC (Table 1), emphasizing how mitochondrial dysfunction plays a central role in modulating the neuroimmune and neuroendocrine stress responses that contribute to allostatic load. Undoubtedly, further work is required to fully elucidate

TABLE 1 Molecular components of allostatic load implicated in ASC.

| Component of allostatic load | Evidence of dysregulation in ASC  | Original reports                 | Meta analyses and reviews             |
|------------------------------|---|----------------------------------|---------------------------------------|
| Mitochondrial                | <p>Transcriptomic, proteomic and epigenomic mitochondrial signatures</p> <p>Mitochondrial DNA copy number, deletions and mutations</p> <p>Altered electron transport chain function, mitochondrial membrane potential, bioenergetics, dynamics and morphology</p> <p>Increased lactic acidosis and Krebs cycle metabolites, decreased carnitine and altered pyruvate, alanine, creatine kinase, glutathione-S-transferase and caspase 7 in plasma</p> <p>Decreased glucose uptake, ATP synthesis &amp; transcription of OXPHOS genes in brain tissue</p> <p>Dysregulated glutathione metabolism, lipid peroxidation, protein oxidation, DNA oxidation and antioxidant enzyme activity</p> | (136, 140, 142–144, 146–153)     | (132–135, 137–139, 141, 145, 154–161) |
| Neuroendocrine               | <p>Global disruptions to cortisol signaling</p> <p>Hypothalamic–pituitary–adrenal (HPA) hyperactivation and increased stress reactivity</p> <p>Disrupted glucocorticoid receptor (GR) expression in brain tissue</p> <p>Mutations in GR cochaperone associated with serum cortisol and social anxiety</p> <p>Cortisol awakening response, evening cortisol and signaling between the HPA and autonomic nervous system correlated with psychopathology, anxiety, depression and suicidal ideation</p>  | (46, 185, 188, 193–196, 199–202) | (46, 95, 186, 187, 191, 192)          |
| Neuroimmune                  | <p>Elevated inflammatory cytokines in blood and brain tissue</p> <p>Reactive gliosis, increased microglial density and activation and disrupted microglial morphology and organization</p> <p>Dysregulated transcription of genes involved in inflammation, astrocyte function and microglial activation and significant upregulation of microglial-specific genes</p>  | (222–230)                        | (160, 216–221, 232)                   |

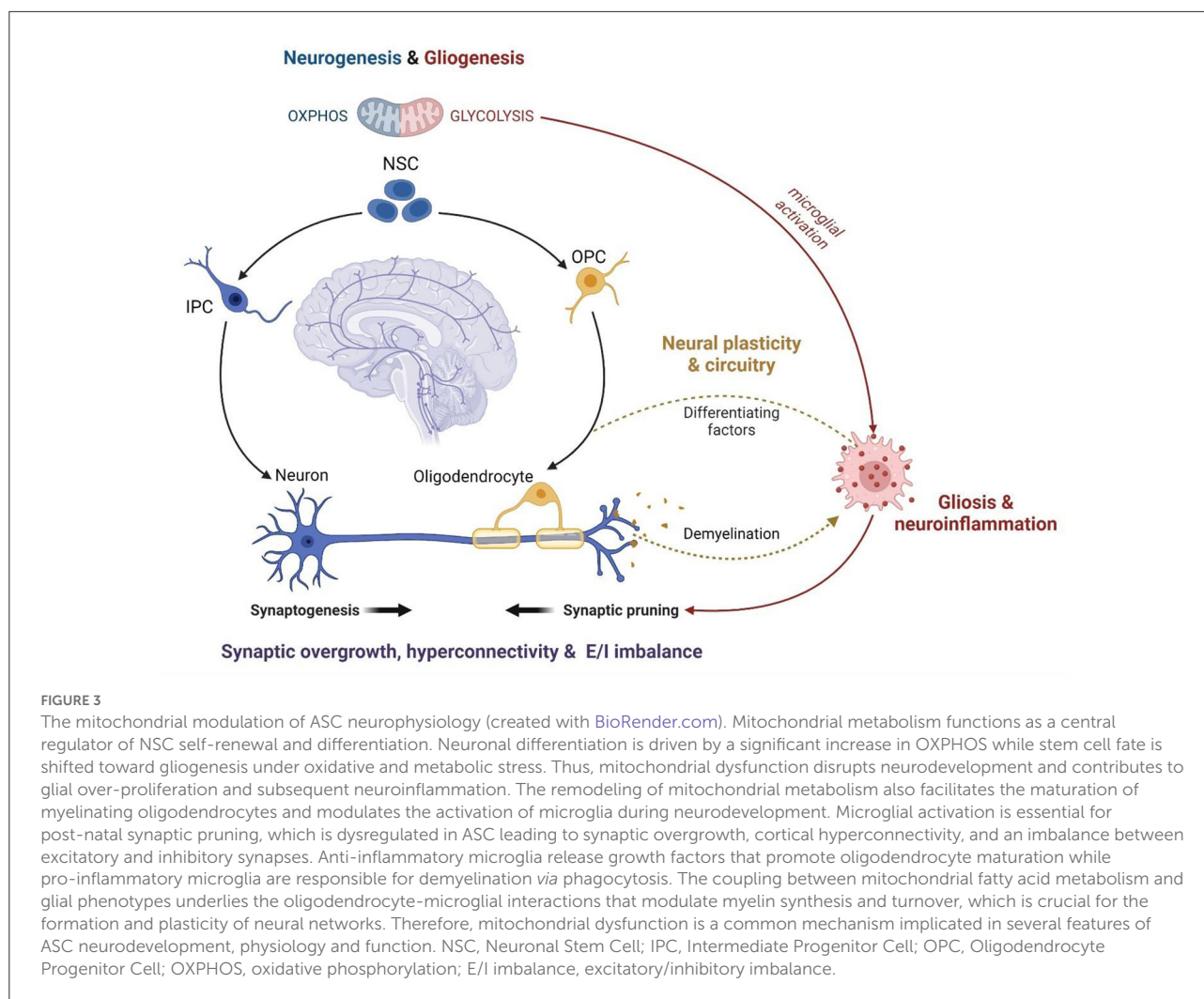
the molecular relationships between the HPA axis, MAL and neuroinflammation, and to better characterize how these mechanisms contribute to clinical aspects of ASC. Nevertheless, this model points to a molecular signature that could serve as an underlying susceptibility to ELS, and may contribute to the high rates of psychopathology and suicidality in ASC.

## From MAL to neurophysiology, neurochemistry, and behavior: A mechanistic perspective

A role for MAL in the relationship between autism and psychopathology is supported by mounting evidence that mitochondria are centrally involved in neurodevelopment, neurophysiology and neurochemistry. In fact, mitochondria are known to modulate distinct neurological processes that are

disrupted in response to ELS and involved in the etiology of ASC. ELS alters the proliferation, differentiation and survival of neuronal stem cells (NSCs), culminating in disruptions to synaptogenesis, synaptic pruning, and neurotransmission (72, 164). Extensive synaptic remodeling also occurs during adolescence, and CAS is known to disrupt synaptic plasticity and myelination with long-term implications for psychology, cognition and behavior (73, 279). These neurophysiological differences have largely been attributed to signaling between the HPA axis, GCs and neurogenic factors (e.g., Brain-derived neurotrophic factor and Wnt) (233, 234). However, just as the concept of MAL is becoming increasingly established in stress research, mitochondria are also emerging as central regulators of neurodevelopment and physiology (Figure 3).

The balance between NSC self-renewal and neuro-, oligo- and astrogenesis is closely tied to metabolic state. Neurogenesis requires a metabolic shift from glycolysis to OXPHOS while oxidative and metabolic stress drive stem cell fate



toward gliogenesis (280–283). Moreover, distinct alterations to mitochondrial morphology and function are observed during the maturation of myelinating oligodendrocytes (284, 285). Metabolic state is coupled to, and regulated by, mTOR signaling, and each are essential for synaptic signaling, function and plasticity (286–295). In fact, preclinical data suggest that ELS impairs neuronal metabolism and synaptic plasticity *via* mTOR-dependent mechanisms (296, 297). The interplay between mitochondrial metabolism and microglial activation is also essential to regulate neuronal apoptosis, synaptic pruning and myelination during neurodevelopment (238, 242, 298). Synaptogenesis is tightly regulated to shape neural circuitry and connectivity (243, 299) while myelin processing is vital for the activity, synchronization and dynamics of neural networks (300). Notably, disruptions to mTOR signaling (289, 301, 302), synaptic pruning (232, 303) and myelination (245) are hallmarks of ASC that contribute to cortical hyperconnectivity and the resultant behavioral phenotypes (250, 299). Thus,

the mitochondrial modulation of neuronal development, plasticity and circuitry converges on shared neurophysiological mechanisms in ELS and ASC.

In addition, disruptions to neurotransmitter signaling and neuroendocrinology are implicated in both ELS and ASC. Preclinical studies have shown that chronic stress disrupts glutamate- (304–307), serotonin- (308) and dopamine- (309–312) signaling, leading to increased anxiety-like behaviors and impairments in social recognition, social interest and cognitive flexibility. These data are supported by human cohort studies showing that ELS disrupts dopaminergic responses to psychosocial stress (313, 314), and alters glutamate/glutamine cycling (315) and serotonin transporter binding (316) in patients with MDD. In fact, genetic mutations in the serotonin receptor have been shown to mediate the effect of ELS on the subsequent rates of depression and suicidality (317). CAS also alters neuroendocrinology on several fronts, by inducing glutamatergic excitotoxicity and decreasing levels of serotonin,



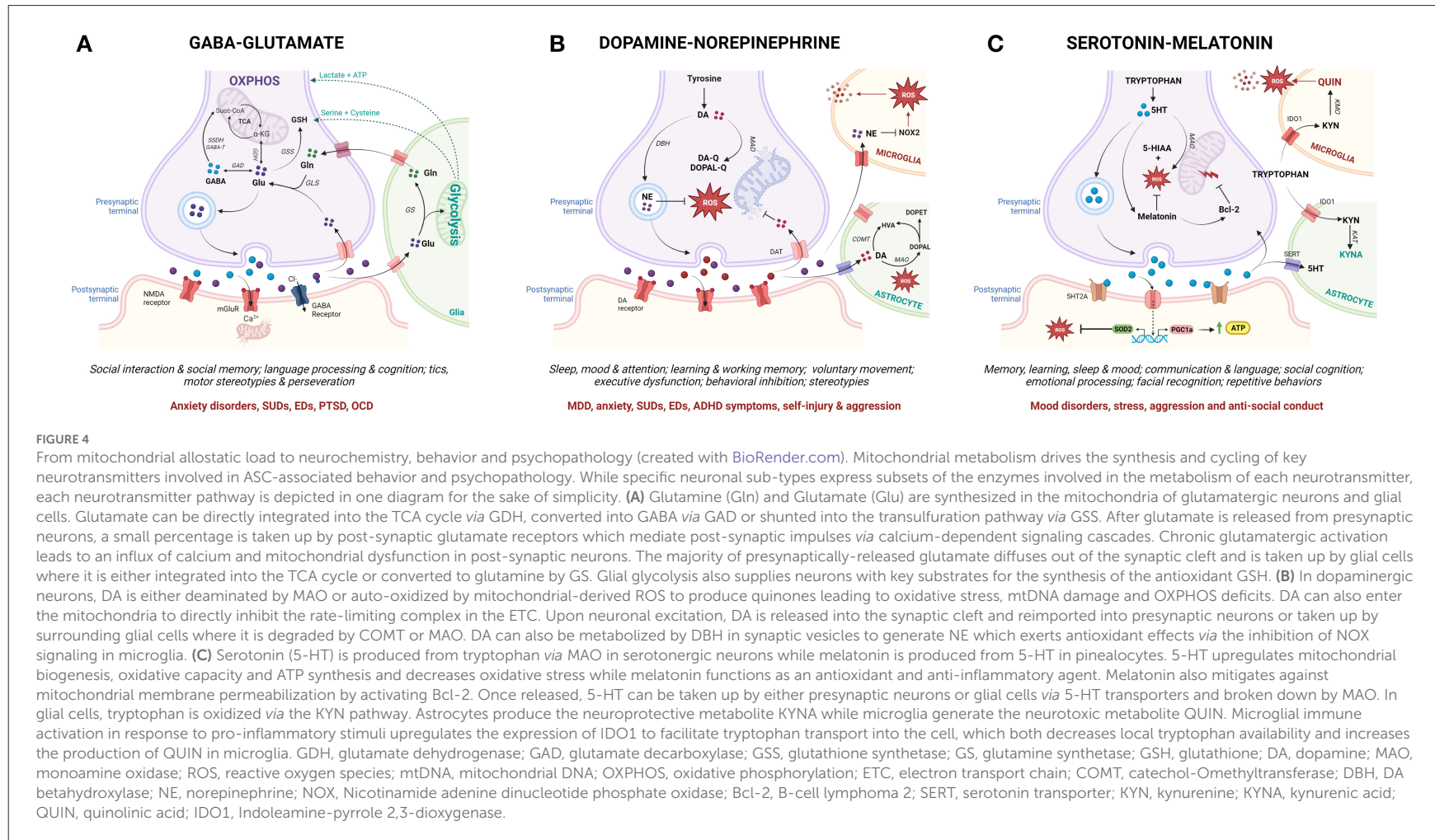
dopamine and norepinephrine (73). Notably, an unbalanced excitatory-to-inhibitory synaptic signaling ratio (318–320) and disruptions to glutamatergic (246, 320–325), serotonergic (326–330) and dopaminergic (319, 331, 332) neurotransmission are well-established aspects of ASC neurochemistry that are associated with distinct aspects of ASC etiology. Glutamatergic excitotoxicity is thought to contribute to anxiety, perseveration, motor stereotypies, and differences in language, social memory and cognition (325). Serotonin signaling is linked to altered social cognition, facial recognition, emotion processing and communication (329) while dopamine signaling is associated with disruptions to sleep, mood and attention in ASC (319, 331, 332).

This underlying neuroendocrinological dysregulation is not only associated with core facets of ASC etiology, but also has direct functional implications for stress-related psychopathology. A disruption of glutamatergic and GABAergic signaling contributes to the etiology of anxiety disorders (333–336), PTSD (337), eating disorders (338–340), OCD (341) and substance use disorders (SUDs) (342, 343). The serotonergic, dopaminergic and noradrenergic systems are implicated in MDD, anxiety and SUDs (344–346) while serotonin is also associated with mood disorders, stress, aggression and anti-social conduct (347–349), and dopamine is thought to play a role in eating disorders (350, 351), executive dysfunction and behavioral inhibition (352, 353). Moreover, well-documented interactions between neurotransmitter, neuroimmune and neuroendocrine pathways play a central role in modulating suicide risk after ELS exposure (354). Glutamate is involved in both driving HPA responses and limiting HPA overactivation (355–357), and conversely, GC signaling is known to modulate glutamatergic synapse plasticity and excitability (358). Serotonergic neurotransmission excites CRH-producing neurons in the amygdala (209) and acts as an important regulator of GR signaling in the pre-frontal cortex after exposure to acute stress (359). On the other hand, animal models show that corticosteroids decrease serotonin receptor binding densities (360, 361) and this relationship is implicated as a mediator of suicidality following ELS (317). Finally, GCs also activate the mesolimbic dopamine pathway (362, 363) by upregulating the rate-limiting step of dopamine synthesis, downregulating dopamine degradation, clearance and synaptic uptake, or by acting directly on GRs in dopamine-receptive neurons (364).

Crucially, MAL functions as a mechanistic link between the molecular, neurochemical and behavioral aspects of ASC that have been highlighted here as potential contributors to psychopathology (Figure 4). Numerous reviews have comprehensively described the close coupling of mitochondrial function with glutamatergic (365–367), serotonergic (368–370) and dopaminergic (371–375) neurotransmission, although this relationship remains understudied in the context of MAL and psychopathology. Glutamatergic neurotransmission is tightly

coupled to neuronal and astrocytic metabolism, and glutamate functions as a substrate for both the mitochondrial citric acid cycle and the transsulfuration pathway (Figure 4A) (376, 377). In this way, glutamate fuels OXPHOS and antioxidant synthesis to promote mitochondrial function and combat oxidative stress (366, 377–380). Thus, mitochondrial metabolism is essential for glutamate-glutamine cycling, and cytoplasmic glutamate levels are regulated by mitochondrial TCA cycle flux as well as intracellular redox homeostasis (381). Dopamine (DA) auto-oxidation is also regulated by intracellular redox state (Figure 4B), and an accumulation of oxidative dopamine metabolites leads to mitochondrial membrane depolarization, decreased ETC activity and impaired ATP synthesis (374). Moreover, DA can also be directly taken up by mitochondria where it reversibly inhibits the first ETC complex, leading to oxidative stress and impaired mitochondrial energy production (373). On the other hand, DA functions as a precursor to norepinephrine (NE) which protects mitochondrial function by preventing membrane depolarization, and has both anti-inflammatory and anti-oxidant properties (382). Conversely, mitochondrial dysfunction can disrupt both glutamatergic and dopaminergic neurotransmitter signaling; TCA cycle anaplerosis diverts glutamate away from glutamine recycling, while oxidative stress promotes the generation of oxidative dopamine derivatives. Notably, the consequent shift toward glycolysis in glial cells upregulates pro-inflammatory signaling and increases the production of lactate and serine, which potentiates glutamatergic excitotoxicity (246, 383).

Similarly, a reciprocal relationship between mitochondrial function and the two branches of tryptophan metabolism modulates the synthesis of serotonin, melatonin, and kynurenine (KYN) metabolites (Figure 4C) (384). Serotonin positively regulates mitochondrial biogenesis, oxidative capacity and ATP synthesis (370, 385) while serotonin deficiency disrupts amino acid and lipid metabolism, oxidative respiration and antioxidant activity (386, 387). Serotonin functions as a precursor to melatonin, which regulates mitochondrial OXPHOS, redox homeostasis and inflammatory responses (388). Moreover, melatonin modulates the expression of the rate-limiting enzymes involved in serotonin synthesis and catabolism (389), thereby controlling the balance between the serotonin and KYN branches of the tryptophan catabolic pathway. Importantly, the KYN pathway functions as a key mediator between neuroendocrinology and neuroinflammation that is tightly regulated by interactions between glial cells and neurons. The KYN metabolites kynurenic acid (KYNA) and quinolinic acid (QUIN), respectively, activate and inhibit glutamate receptors (132). Additionally, flux in the QUIN branch of the KYN pathway that alters *de novo* NAD<sup>+</sup> synthesis also modulates metabolic and oxidative state (390). Mitochondrial dysfunction shifts the KYN pathway toward QUIN production by increasing the demand for



NAD<sup>+</sup> (391); conversely, QUIN contributes to mitochondrial dysfunction by increasing cytoplasmic calcium concentration and superoxide production in microglia (392). A pathogenic shift toward an inflammatory microglial phenotype upregulates tryptophan import, decreasing local tryptophan availability for serotonin synthesis and further increasing the rate of QUIN production (392). Moreover, QUIN upregulates glutamatergic neurotransmission and inhibits glutamate uptake from the synaptic cleft, thereby promoting excitotoxicity (393). Altogether, a disruption of the relationship between mitochondrial function and the glutamatergic, serotonergic and dopaminergic neurotransmitter cycles increases oxidative stress and shifts glial metabolism toward glycolysis, thereby contributing to gliosis, excitotoxicity and neuroinflammation (246, 373, 393).

Thus, these neurotransmitter systems are intrinsically coupled to, and mediators of, the relationship between mitochondrial dysfunction, neuroinflammation and HPA axis signaling that is implicated in ELS and ASC. This discussion highlights that MAL plays a central role in the link between molecular stress signatures and neurophysiological- and neurochemical- mechanisms that lead to psychopathology. Moreover, these mechanisms are known to contribute to distinct neurological and behavioral aspects of ASC etiology and could function as an underlying susceptibility to allostatic load. This provides a preliminary conceptual framework for a molecular signature that may underly autistic burnout, mediate the relationship between social camouflaging and suicidality, or predispose autistic individuals to psychopathology. The interactions between environmental, psychological, physiological and molecular processes involved in ASC are notably understudied and the hypothesis proposed here remains to be further investigated. However, this model does illustrate the necessity for an interdisciplinary framework in molecular autism research. Moreover, our hypothesis describes a mechanistic interplay between MAL, HPA and neuroimmune signaling that could be an important target for future research toward improving quality of life in ASC.

## Conclusion: An integrative biopsychosocial framework for psychopathology in ASC

Molecular research into ELS is increasingly integrating various paradigms from disparate scientific disciplines in order to develop a cohesive understanding of pathological stress responses (394). While ELS research is distinctly and fundamentally separate from autism research, this discussion has highlighted the utility of such an integrative framework to shape molecular research into ASC. The hypothesis presented in this article builds on separate bodies of work, that are well-documented in their respective fields, to propose a

framework for the development of psychopathology in autism (Figure 5). This framework integrates emerging literature that is foregrounding autistic experiences with the molecular model for allostatic load that quantifies the cumulative impact of biological and psychosocial stress (40). We propose that ASC is associated with both an increased exposure to, and an underlying molecular susceptibility to, ELS that contributes to allostatic overload and the subsequent development of psychopathology.

There is substantial evidence that autistic children are more likely to be exposed to ELS and psychosocial stress, while also having inadequate internal resources to cope with these stressors. The recent characterization of concepts like social camouflaging and autistic burnout further highlights that autistic children are exposed to chronic and distinct forms of stress throughout adolescence that often go unrecognized. Chronic social camouflaging creates an increasing mismatch between internal capacity and external expectations, culminating in autistic burnout. Importantly, both social camouflaging and autistic burnout are known to contribute to the development of psychopathology and suicidality in ASC. However, the physiological mechanisms that are involved in these phenomena, or their relationship to each other, remain unknown and largely unexplored by molecular researchers.

The molecular mechanisms that mediate the relationship between ELS, CAS and psychopathology revolve around interdependent signaling between mitochondrial metabolism, inflammatory immune responses and stress-responsive HPA signaling. MAL is emerging as a central modulator of the neurophysiological processes that are disrupted by ELS and contribute to psychopathology. Notably, mitochondrial dysfunction is an underlying component of ASC physiology that is sensitive to GC signaling and plays a central role in regulating HPA axis and innate immune responses. Mitochondria function as essential regulators of neurodevelopment by facilitating the metabolic shift toward OXPHOS that is required for neuronal differentiation. Mitochondria also modulate microglial activation, which is necessary for synaptogenesis and synaptic pruning during neurodevelopment. Moreover, the relationship between mitochondrial metabolism and microglial activation regulates myelin turnover, neuronal function, redox homeostasis and glial inflammatory state throughout childhood and adolescence. The HPA axis is intrinsically coupled to both mitochondrial metabolism and inflammatory signaling, and this relationship is consistently shown to be disrupted by ELS and altered in psychopathology. Notably, the serotonergic, dopaminergic and glutamatergic neurotransmitter systems that are directly involved in many psychological disorders are closely coupled to mitochondrial metabolism, modulated by the HPA axis and represent independent mechanisms that contribute to gliosis and excitotoxicity. This article has highlighted how these molecular mechanisms are

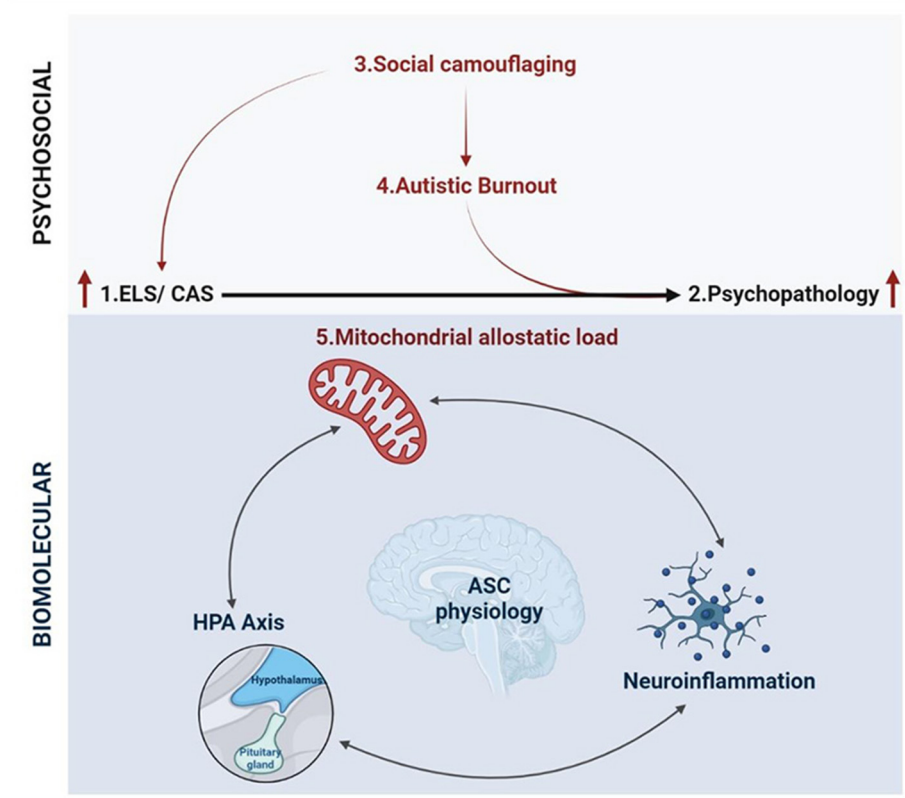


FIGURE 5

An integrative biopsychosocial vulnerability framework for the development of psychopathology in ASC (created with BioRender.com). There is a well-established relationship between exposure to early life stress (ELS) or chronic adolescent stress (CAS) and the development of psychopathology. Autism is associated with both a significantly increased risk of exposure to ELS and high rates of psychopathology and suicidality. Emerging characterizations of internal autistic experiences including social camouflaging and autistic burnout overlap closely with established definitions for ELS and lead to increased levels of anxiety, depression, self-injury and suicidality in ASC. Thus, the development of psychopathology in autism may be mediated by an increased exposure to toxic stressors culminating in allostatic overload. Molecular stress research has demonstrated that mitochondrial allostatic load (MAL) plays a central role in psychopathology following ELS by disrupting a closely coupled network between neuroimmune and neuroendocrine signaling. Cellular neuroscience has comprehensively characterized the tightly regulated biochemical relationships between (i) mitochondrial dysfunction and neuroinflammation, (ii) mitochondrial metabolism and the HPA axis, and (iii) inflammatory- and HPA-signaling. Notably, ASC etiology is also characterized by mitochondrial dysfunction, gliosis and neuroinflammation, and a complex signature of HPA axis dysregulation. Moreover, this three-way molecular interplay converges on the regulation of key neurodevelopmental processes implicated in the response to ELS and psychopathology that are also associated with distinct neurophysiological, neurochemical and behavioral aspects of ASC etiology. Collectively, this could point to a molecular vulnerability to the development of psychopathology in ASC, highlighting how psychosocial and biological factors converge to increase the risk of psychopathology and suicidality.

implicated in the neurophysiology and neurochemistry of autism and contribute to the development of psychopathology following ELS.

Considering both the increased risk of exposure and underlying vulnerability to ELS in autism emphasizes how psychosocial and biological factors converge to increase the risk of psychopathology. This interplay could act as a novel mechanism that contributes to the high rates of depression and suicidality in autistic individuals and may reveal a biological signature that underlies autistic burnout. Autistic burnout, depression and suicidality are factors that directly impair health and wellbeing for people with

autism. Much of the literature highlights the importance of improved access to accommodations, earlier diagnosis and decreased stigmatization of autistic traits in mitigating psychopathology in ASC. In addition, our framework proposes that investigating an underlying susceptibility to ELS could inform research into novel molecular interventions. Targeted therapeutic strategies could potentially protect autistic children from the development of psychopathology, facilitate recovery from autistic burnout, or identify diagnostic tools to differentiate autistic burnout from clinical depression. In particular, this framework highlights the potential to harness recent advances in mitochondrial psychobiology to

better characterize the molecular determinants of mental health in autism. Ultimately, this highlights the utility of molecular research that foregrounds autistic experiences to work toward strategies that tangibly improve the quality of life of autistic individuals.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

CM reviewed the relevant literature, developed the conceptual framework, and wrote the paper. CO’R refined the conceptual framework, wrote the paper, coordinated project supervision, and administration and acquisition of funding. Both authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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