 doi:10.20944/preprints202205.0281.v1

Concept Paper

A Molecular Framework for Autistic Experiences: Mitochondrial Allostatic Load as A Mediator between Autism and Psychopathology

Caitlyn Mahony[1] and Colleen O' Ryan [1*]

[1] Molecular & Cell Biology, University of Cape Town, Private Bag, Rondebosch, Cape Town 7700, South Africa; MHNCAI001@myuct.ac.za
*Corresponding author: colleen.oryan@uct.ac.za

Abstract: Molecular research into Autism Spectrum Conditions (ASC) is undergoing an essential shift towards a biopsychosocial framework that is informed by autistic experiences. In this context, research aims are moving away from correcting external autistic behaviors and towards alleviating internal distress. ASC is associated with high rates of depression, suicidality and comorbid psychopathologies, but the underlying mechanisms that mediate this relationship are poorly understood. Here, we integrate emerging psychosocial characterizations of internal autistic experiences within a molecular framework to yield insight into the prevalence of psychopathology in ASC. We demonstrate that recent conceptualizations 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 ELS that contributes to allostatic load, culminating in a pathophysiological state that is experienced as autistic burnout. Autistic burnout is thought to contribute to psychopathology via both psychosocial and neurophysiological mechanisms, but these remain largely unexplored by molecular researchers. Considering recent insights from converging bodies of work 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 metabolism, 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 etiology. Together, this suggests an increased exposure to, and an 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 future research into molecular mechanisms that affect the quality of life and well-being of autistic individuals. Moreover, this framework emphasizes the need for increased access to diagnosis, accommodations, and resources to improve mental health outcomes in autism.

Keywords: autism; autistic burnout; social camouflaging; early life stress; suicidality; psychopathology; mitochondrial allostatic load

1. Introduction

Research into autism spectrum conditions (ASC) operates at the intersection of disparate psychosocial and biomedical disciplines that traditionally work in isolation rather than within cohesive interdisciplinary frameworks. However, the complex and rapidly evolving context of autism research calls for a novel integrative approach. The current conceptualization of ASC, used in both academic and clinical contexts, is based solely on how autism is perceived by external neurotypical observers rather than an understanding of internal autistic experiences (1). Therefore, much of the molecular research into ASC has been rooted in the assumption that effective therapeutic strategies would aim to

 doi:10.20944/preprints202205.0281.v1

decrease autistic behaviors. However, as autism research is increasingly informed by inclusive participatory research practices, the field is moving towards a more comprehensive integration of the biopsychosocial disability model (2,3). This integrative 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 autism research is shifting its focus towards improving quality of life and minimizing internal distress rather than eradicating or correcting autistic behaviors (14).

This paradigm shift is yet to be fully integrated into the molecular and medical fields of autism research, as 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). These limitations are increasingly well-recognized in clinical settings (1), especially with respect to the reliability of autism assessments in females and people of color across varied sociocultural contexts (17–24). Yet, molecular studies require deeply-phenotyped cohorts characterized according to standardized diagnostic criteria in order to accurately distinguish between complex molecular signatures (25). Thus, it has been difficult for molecular researchers to move away from the deficits-based medical model of disability to integrate evolving understandings of autistic experiences into their research questions. In addition, much of molecular research uses limited measurements of behavior and flawed indicators of functioning. The efficacy of an intervention is often measured by a decrease in ASC diagnostic criteria but it is becoming clear that this is not a good indicator of health, well-being or quality of life for autistic individuals. In fact, the chronic suppression of autistic traits contributes to anxiety, depression, burnout, poor quality of life and poor mental health in ASC (26–29). It is now recognized that any therapeutic intervention should focus on improving physical and psychological well-being rather than decreasing ASC-associated behaviors, allowing for the fact that health may look different in autism. Importantly, the relationship 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 biological or behavioral differences may certainly be able to improve quality of life. Still, it should be acknowledged that much of molecular research has aimed to decrease the severity of the autism phenotype without understanding that this is not synonymous with an improved quality of life.

This highlights a weakness in molecular autism research in that it is generally not informed by autistic experiences. Yet, molecular research is essential to provide accurate information about ASC to autistic individuals, their families and peers, clinicians, and the general public. Knowledge about the origins and manifestations of ASC can be used to inform the implementation of effective accommodations in schools and workplaces, as well as to combat the widespread misinformation and stigmatization surrounding autism. Additionally, clinicians and researchers are still grappling with the current diagnostic label that does 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 with evolving understandings of autism in a biopsychosocial framework.

However, an interdisciplinary framework is not only needed drive autism research that is relevant, useful and transformative for the autistic community (3,14). An integrative approach also has the potential to yield novel insights into molecular ASC etiology. It is widely recognized that many promising findings from *in vitro* and *in vivo* molecular studies have failed to translate into reproducible results in human clinical trials (16,30–

 doi:10.20944/preprints202205.0281.v1

34). This is largely attributed to the complex interplay between genetic, epigenetic and environmental mechanisms that contribute to ASC etiology. Furthermore, molecular research is inherently reductionist and grounded in a one-dimensional understanding of ASC that is removed from the internal experience of autism. This could be another prevailing limitation that hinders the translatability of molecular research in a clinical and sociological context (1). As such, an integrative approach is needed to highlight the convergence between different scientific disciplines involved in autism research. Moreover, this approach could provide new insight into the cellular mechanisms at the intersection of environmental stressors and biological processes that directly impact the quality of life and well-being of autistic individuals. In particular, integrating molecular research with recent characterizations of internal autistic experiences could be crucial to understand the high rates of psychopathology and suicidality in ASC.

Here, we incorporate recent conceptualizations of social camouflaging and autistic burnout within a scientific framework based on molecular neuroscience to suggest an increased risk of exposure to, and an underlying molecular susceptibility to, early life stress (ELS) and Chronic Adolescent Stress (CAS) in ASC. Interactions between psychosocial stress, underlying physiology and allostatic load have previously been proposed to influence clinical outcomes in autism (35,36). However, this model remains understudied by molecular researchers and emerging definitions for distinct autistic experiences have not yet been assimilated with recent discoveries pertaining to the biological mechanisms that mediate the response to ELS. This article proposes an integrative framework shaped by autistic experiences that demonstrates how psychosocial and biological factors converge to increase the prevalence of psychopathology in ASC. 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 directly affect the quality of life and well-being of autistic individuals.

2. 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 (37–39). A growing body of literature demonstrates significantly increased rates of generalized anxiety disorder (GAD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), self-harm, and suicidal ideation in ASC (29,40,41). Between 63% (40) and 66% (42) of autistic adults are reported to be at risk of suicide; where suicide attempts are 3-4 times more frequent in ASC (43) and mortality by self-harm and suicide is significantly increased (39). Moreover, the onset of MDD occurs earlier in ASC; it was recently reported that 39% of 10-13 year-olds with autism reached clinically significant thresholds for measures of depression compared to only 6.5% of typically developing children(44). Current research suggests that psychopathology in ASC is associated with social difficulties (41), alexithymia (40), cognitive rigidity (45), loneliness and lack of social support (46) or increased exposure to traumatic experiences (47). 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 etiology (48). Moreover, it has been suggested that underlying biological mechanisms in ASC etiology could mediate a susceptibility to depression and other mood disorders (44,49). Thus, it is critical to understand the internal experiences and physiological mechanisms involved in this relationship in order to identify prevention strategies. Emerging research has begun to characterize a distinct phenomenon known as autistic burnout according to how it is experienced and defined by autistic individuals. This is an understudied, yet integral aspect of the internal experience of autism that could play a central role in distinguishing psychological health from psychopathology.

 doi:10.20944/preprints202205.0281.v1

Recent studies have generated complementary definitions for autistic burnout, which is described as a "*a state of physiological and psychological incapacitation, exhaustion, and distress in every area of life"* (50). This is a recurring condition marked by loss of function, reduced tolerance to stimulus and an increased manifestation of autistic traits (51) that directly impacts "*functioning, mental health, quality of life and well-being"* (52). Autistic burnout is conceptually similar to non-autistic burnout in that both result from chronically operating beyond personal capacity. However, current research emphasizes that autistic burnout is distinct from both clinical depression and non-autistic burnout (50,51) with respect to its causes, manifestations and functional implications (53). Autistic burnout results from "*chronic life stress and a mismatch of expectations and abilities without adequate supports"* (50). 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"* (50). There are three core components of social camouflaging; i) deliberately adopting new social behaviors to make up for social difficulties (compensation) (26,54); ii) consciously suppressing autistic traits in order to appear non-autistic (masking); and iii) implementing strategies to manage internal discomfort invisibly (assimilation) (21). Chronic social camouflaging leads to internal distress, an eroded sense of self, and physical and mental exhaustion (26,55,56) and is associated with psychopathology (28), self-injury (57–59), and a higher risk of lifetime suicidality (29). However, camouflaging also facilitates access to employment, relationships and social acceptance and is an unavoidable prerequisite for independent functioning (27,57).

In fact, 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 independent functioning, which is further exacerbated by the intensified presentation of autistic traits (51). Moreover, the inescapable demand to meet the neurotypical threshold for functionality makes recovery from autistic burnout much more difficult. Autistic burnout is described as "pervasive" (50), "chronic"(52), and "recurring"(51) which most closely aligns with a concept known as habitual burnout, when functional impairments become embedded into daily life (60). Notably, the symptoms of habitual burnout include insomnia, anxiety, behavioral dysregulation, depression, self-doubt, emptiness and isolation (60). The manifestations and functional implications of autistic burnout are thus highly specific to its context (53) and present a significant risk for the development of psychopathology. 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 (51). 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 (50). 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 (50).

Notably, autistic individuals who remain undiagnosed throughout childhood are particularly susceptible to both autistic burnout and psychopathology due to an absence of adequate supports and the chronic suppression of autistic traits. Furthermore, undiagnosed autistic individuals lack an explanation for their differences and challenges and tend to internalize these as personal failings (56,61). 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 (62). This culminates in low self-esteem, a lack of self-worth, and destructive core beliefs that are all risk factors for the development of psychopathology (63). Altogether, this demonstrates how the pervasive lack of awareness and stigma surrounding ASC contributes to autistic burnout (52) and how early diagnosis could play an important role in preventing psychopathology. While the link between ASC and psychopathology is well-established, there is a critical gap in the literature on what

 doi:10.20944/preprints202205.0281.v1

physiological factors lead to autistic burnout, how they differ from, or contribute to the etiology of MDD and crucially, how these could be prevented or treated. Moreover, the molecular mechanisms that mediate the relationship between ASC etiology, autistic burnout and psychopathology are unknown and remain largely unexplored by molecular researchers. However, we propose that converging bodies of work in molecular neuroscience highlight a potentially important connection between early life adversity, allostatic load and psychopathology in ASC.

3. Early life stress, chronic adolescent stress and allostatic load in ASC

There is substantial evidence from both human epidemiological studies and animal models that ELS and CAS increase the risk of psychopathology and suicidality in adulthood (64–70). Notably, the established definitions for ELS and CAS closely mirror those emerging to characterize autistic experiences of childhood and adolescence, which points to the relevance of molecular ELS research in the context of ASC. While it has historically been challenging to reach a consensus for the definition of ELS or CAS, current models agree that stress refers to *"environmental events or chronic conditions that objectively threaten the physical and/or psychological well-being of an individual"* (65), undermine a child's *"sense of safety, stability, and bonding"*(71) and for which "*adequate coping resources are unavailable*" (66). While much of the literature focuses on adverse childhood experiences, adolescence is also a critical period for brain development that is highly sensitive to stress, and CAS is known to contribute to the development of depression, anxiety, and other stress-related psychopathologies (65). Researchers have previously distinguished between good, tolerable stress 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"*(72).

Importantly, cumulative evidence 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 (73), social vulnerability and isolation (74), bullying, discrimination, and ostracism (75), and other forms of victimization (76). Differences with respect to social communication, development, and integration can make it difficult for autistic children to feel a sense of a sense of "safety, stability or bonding" with their families or peers. Moreover, situations that are "tolerable" for neurotypical children are experienced as "toxic" stressors due to distinct neurophysiological differences in autism. Exposure to every-day sensory stimuli is painful, uncontrollable, and thus "personally threatening" due to difficulties with sensory processing. Personal accounts of social camouflaging describe a need *"to exceed what nature has given"* (26) in order to manage both the "*physically assaultive*", "*uncertain, exhausting nature of the social environment"* (77), and the persistent fear of stress, rejection and being misunderstood by peers (78). In this context, autistic children are pushed beyond their capacity just to achieve a degree of social participation; even further resources are expended to camouflage sufficiently to achieve social acceptance. Accordingly, social camouflaging has been conceptualized as the discrepancy between the internal experience of autism and the external presentation of autistic traits (21,79,80), while autistic burnout has been described as "*having all of your internal resources exhausted beyond measure*" (50). Thus, the 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.

Since camouflaging strategies become increasingly complex and intentional from middle childhood, it could be argued that social camouflaging acts as a distinct form of CAS in autism. Middle childhood is a critical period for socialization that is marked by the development of self-concept and an increasing capacity for self-regulation (81). The self-concept tasks of middle childhood culminate in the ability to "*take the self as an object and view it as others do*", internalize expectations for one's own behavior and develop strategies to meet these expectations (81). This enables an autistic child to both identify the

 doi:10.20944/preprints202205.0281.v1

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 underlying biology and sociocultural factors that contribute to socialization. Equally, there are significant differences with respect to an individuals' ability and motivation to mask their autistic traits. This has important implications for the relationship between ASC etiology, chronic stress and psychopathology. What has previously been conceptualized as a more severe autism phenotype – presenting with extreme sensory sensitivities, greater difficulties with self-regulation and social communication or atypical developmental profiles - might be associated with a lower tendency to mask but an increased exposure to early childhood adversity. On the other hand, a greater tendency to mask may be marked by a subclinical phenotype but a greater susceptibility to CAS induced by the chronic suppression of autistic traits, which may explain the increased rates of depression and suicidality in high-masking autistic individuals. This emphasizes that different external presentations of autism are not always reflective of the profound physiological and psychological dysregulation experienced internally. In fact, despite the etiological heterogeneity of ASC, an underlying susceptibility to stress-related pathologies could be a common mechanism responsible for negative clinical outcomes in autism.

Furthermore, the resonance between descriptions of social camouflaging, autistic burnout, and toxic stress serves as 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 (82). Allostatic load provides an integrative model with which to quantify the cumulative impact of biological, psychological and social factors that contribute to pathology (82). In this context, social camouflaging could act as a distinct form of toxic stress that contributes to allostatic load in autism. Autistic burnout may represent a distinct pathophysiological state resulting from allostatic overload, which increases the risk of psychopathology via both physiological and psychosocial mechanisms. In fact, Singletary (2015) previously recognized that autistic children are exposed to significant psychosocial and biological stress during early life and proposed an interaction between ELS, underlying physiology and allostatic overload contributing to ASC etiology (35). Scarpa *et al.* (2021) further proposed that underlying features of ASC etiology also predispose autistic individuals to pathological responses to stress and trauma (36). The recent characterization of unique autistic experiences that closely overlap with the accepted definitions for ELS and CAS points to the need for a more integrative framework to characterize interactions between neurobiology, environmental stressors and allostatic overload in the context of ASC. Notably, the molecular mechanisms that mediate the association between ELS, CAS and psychopathology are also known to contribute to 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.

4. Mitochondrial allostatic load and convergent molecular mechanisms in ELS, ASC, and psychopathology

There are well-characterized neurobiological and psychological aspects of ASC etiology that predispose autistic individuals to stress-related pathologies (36). However, the molecular mechanisms that mediate this susceptibility are complex and poorly understood. While the concept of allostatic load is well-established(83–85), the field has not yet described specific molecular mechanisms that mediate pathological stress responses, nor identified reproducible molecular biomarkers to measure allostatic load(86). The Hypothalamic-Pituitary-Adrenal (HPA) axis has been the focus of stress pathophysiology research in ASC, but the current evidence for HPA axis dysregulation in autism is inconsistent(87). Recently, mitochondrial metabolism has been recognized as a central regulator of the major neuroendocrine and neuroimmune systems involved in allostasis (82). In

 doi:10.20944/preprints202205.0281.v1

particular, emerging research highlights the relevance of mitochondrial allostatic load (MAL) in stress pathophysiology (85). MAL refers to adaptive changes to mitochondrial morphology, dynamics, and function that are observed in response to chronic stress. 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.

4.1. Mitochondrial allostatic load

A growing body of research suggests that mitochondrial dysfunction is involved in the relationship between ELS and psychopathology. Clinical studies show that ELS is associated with indicators of oxidative stress, including decreased levels of glutathione peroxidase and an increase in superoxide dismutase, protein carbonylation, and total reactive antioxidant potential (88). In line with this, several preclinical models for ELS show an increase in protein carbonylation and a decrease in superoxide dismutase and catalase activity in brain tissue (89) and increased reactive oxygen species (ROS), mitochondrial glutathione, and cytochrome c release in cardiac tissue (90). Ruigrok et al., (2021) recently showed that ELS led to impaired ETC activity in the hypothalamus and altered the expression of genes involved in mitochondrial fission and antioxidant defense in the hippocampus, leading to cognitive impairments(91). Moreover, a recent systematic review presented consistent evidence for reduced mitochondrial energy production capacity and electron chain (ETC) complex activity, altered mitochondrial morphology and changes in mitochondrial DNA (mtDNA) copy number in animal models for chronic stress (92). Notably, the duration and type of stress, as well as underlying genetic differences significantly affect how mitochondrial function is altered in response to stress(92). Conversely, experimentally disrupting mitochondrial function has been shown to alter the physiological and behavioral consequences of psychological stress(82).

Similarly, extensive evidence suggests a role for mitochondrial dysfunction in the etiology of MDD, which has recently been comprehensively reviewed (85,93–98). 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 (95,99). Numerous independent studies have reported increased oxidative stress and altered ETC activity (100) and decreased levels of antioxidants and antioxidant enzymes (101) in the brain tissue of patients with MDD. Of note, Karabatsiakis *et al.* (2014) reported significantly impaired mitochondrial respiration in patients with MDD which correlated significantly with the severity of depressive symptoms (102). Preclinical studies also consistently demonstrate an increase in ROS and a decrease in ATP and glutathione in models for depression (95). Importantly, many pre-clinical models for MDD are induced by exposure to forms of ELS, and such models consistently implicate mitochondrial mechanisms in the subsequent development of depressive behaviors (98). *In vivo* models have shown that mitochondrial ETC complex activity is disrupted in brain tissue following maternal deprivation (103), chronic restraint stress (104), acute restraint stress(105), social isolation (106), chronic mild stress (107) and chronic unpredictable stress (108). Moreover, several transcriptomic profiling studies have reported significant dysregulation of mitochondrial genes involved in lipid metabolism, oxidative phosphorylation (OXPHOS) and glucose homeostasis in animal models for chronic and acute stress (96,109–111). Thus, both human epidemiological studies and animal models suggest a role for mitochondrial dysfunction in the development of MDD after ELS. In fact, Allen, Caruncho and Kalynchuk, (2021) recently reviewed the central role of MAL in the development of psychopathology following ELS, highlighting how mitochondrial dysfunction contributes to the symptoms of MDD and emphasizing the utility of targeting mitochondrial function to develop novel pharmacological treatments (85).

 doi:10.20944/preprints202205.0281.v1

The role played by MAL in the response to ELS is particularly relevant in the context of autism, given that mitochondrial dysfunction is also a well-established component of ASC etiology. A 1998 review of ASC clinical data first demonstrated decreased glucose uptake and ATP synthesis in the cortex, as well as lactic acidosis, carnitine deficiency and elevated urine levels of Krebs cycle metabolites (112). Since then, multiple lines of evidence have emerged to support a role for mitochondrial dysfunction in ASC, which have been well described in recent reviews (113–119). Of note, clinical studies have reported altered mtDNA copy numbers and deletions (116,120–123), as well as mtDNA mutations (124,125), mitochondrial ETC defects (120,122,126) and altered plasma levels of lactate, pyruvate, alanine, creatine kinase, glutathione-S-transferase and caspase 7 (124,127). 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 complex 1,3 and 4 (128), while disruptions to mitochondrial bioenergetics, dynamics and morphology were observed in ASC-derived fibroblasts (129,130). Moreover, multiple independent transcriptomic studies have reported down-regulated expression of genes involved in mitochondrial respiration in ASC brain tissue (131–134), while ASC transcriptomic, proteomic and DNA methylation functional enrichment signatures consistently converge on mitochondrial OXPHOS (135). Furthermore, increased oxidative stress is a well-documented aspect of ASC etiology, and several recent reviews have described the cumulative evidence for altered glutathione metabolism, lipid peroxidation, protein oxidation, DNA oxidation and antioxidant enzyme activity in ASC (136–141). Therefore, there is substantial evidence for altered mitochondrial metabolism in ASC, which may serve as a molecular susceptibility to the pathophysiological consequences of ELS. In line with this, emerging research highlights mitochondria as essential modulators of both the neuroendocrine and neuroimmune components of allostasis.

4.2. MAL and the HPA axis: interdependent mechanisms in stress-related psychopathology

The HPA axis is the major neuroendocrine system that initiates the stress response and plays a central role in coordinating molecular components of allostatic load (65). Children are particularly vulnerable to HPA disruption during periods of higher HPA axis plasticity. These periods occur between 0-5yrs old and during adolescence; thus, HPA signaling is a key mediator of pathological responses to ELS (66,142) and CAS (65). Recent systematic reviews have demonstrated that HPA axis dysregulation plays an important role in mood disorders, suicidal behavior(143), and in mediating the relationship between ELS and major depression(144). Transcriptomic studies in brain tissue indicate that HPA axis signaling is involved in the development of MDD following ELS exposure (64,145). This is reflected by altered cortisol and catecholamine responses in individuals with a history of ELS who develop PTSD, depression and suicidality(146). Finally, recent work in animal models has demonstrated distinct alterations to HPA axis signaling, stress reactivity, and cognitive and emotional functioning in response to both ELS (64) and CAS (147).

Importantly, there is a growing body of literature demonstrating a bidirectional interaction between the HPA axis and mitochondrial metabolism (65). Mitochondria are directly responsible for the synthesis of stress-responsive progestogens, mineralocorticoids, androgens, estrogens and glucocorticoids (GCs) like cortisol and corticosterone (148). Moreover, mitochondrial metabolism not only regulates, but is also modulated by, GC signaling(82,149); this is comprehensively reviewed by Kokkinopoulou and Moutsatsou (2021) (150). GCs are released in response to HPA axis activation and can cross the blood–brain barrier to act on GC receptors (GRs) and regulate genes involved in neurogenesis, neuroplasticity, and neurotransmission (151). *In vitro* studies have demonstrated that GCs improve mitochondrial oxidation, membrane potential, and calcium buffering capacity at physiological levels, while supraphysiological levels impair mitochondrial function (152). More recent work shows that chronic GC treatment reduces the activity of specific mitochondrial ETC complexes and increases mitochondrial ROS production and mitochondrial fragmentation (153–155). GCs can influence mitochondrial metabolism by regulating

 doi:10.20944/preprints202205.0281.v1

the expression of relevant genes via GC response elements (GREs) in the nucleus and potentially via the three known GREs in mtDNA to influence the expression of mitochondrial genes (150,156,157). In particular, GCs have been shown to increase the expression of peroxisome proliferator-activated receptor gamma coactivator-1 alpha, mitochondrial transcription factor A, and nuclear respiratory factors 1 and 2 which are central transcriptional regulators of mitochondrial biogenesis (149,157,158). Notably, animal models have shown that both chronic stress and corticosterone treatment increase mtDNA copy number (159), and conversely, that mtDNA genetic variants can alter corticosterone production and HPA signaling (160,161). Moreover, human epidemiological studies have shown that mtDNA copy number is elevated in people with a history of ELS (162), and in major depression (159) and recent work has demonstrated that the positive relationship between ELS and mtDNA copy number was mediated by differential methylation of the GR (N3RC1) (162). Altogether, this highlights a mechanistic relationship between HPA axis activation and mitochondrial biogenesis, dynamics and function that points an intersection between MAL and well-established stress-responsive processes involved in psychopathology.

Thus, both mitochondrial function and GC signaling are independently implicated in the response to ELS and the development of MDD. Moreover, recent data indicate that these mechanisms are interdependent, which may reveal a novel molecular susceptibility to ELS that has been overlooked in the context of ASC (87). Several candidate autism risk genes are known to increase the risk of developing mental illness after exposure to ELS (82,163–166) but the associated mechanisms are unclear. Although much research has investigated a role for stress-responsive HPA axis signaling in the relationship between autism and psychopathology, this has yielded inconsistent results. Several studies have reported HPA hyperactivation (167–170) and increased stress reactivity (171) in ASC, but these findings lack intra- and inter-individual reproducibility (167). Many studies assess HPA function using single end-point measurements of salivary cortisol, but these cannot reflect complex interactions between biological signaling processes and genetic architecture with sufficient resolution. More targeted molecular studies have shown disruptions to GR expression in ASC brain tissue (172); while genetic polymorphisms in the GR co-chaperone FKBP Prolyl Isomerase 5 (FKBP5) were associated with serum cortisol levels in ASC (173) and moderated the relationship between autistic traits and social anxiety (174). However, a recent review reported conflicting evidence for HPA dysregulation, and its association with psychopathology, in ASC (44). Thus, the relationship between HPA axis signaling and psychopathology in autism is complex and likely mediated by pleiotropic biological factors that contribute to an increased susceptibility to HPA axis dysregulation (175). In this context, the emerging relationship between mitochondrial metabolism and HPA axis stress-response signaling highlights mitochondrial dysfunction as a common biological signature that is consistently observed in idiopathic ASC and could act as a novel susceptibility to stress-related psychopathology.

4.3. The neuroimmune system: a molecular mediator 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. A dysregulation of neuroimmune homeostasis is well-documented in human clinical studies of neuropathology and is observed in response to ELS (66,176,180) and in several psychopathologies (181–183). In fact, it has been proposed that the neuroendocrineimmune network is a central molecular mediator between the psyche, psychosocial stress and psychopathology (185). Accordingly, preclinical models have demonstrated that chronic stress consistently induces microglial activation and proinflammatory cytokine signaling in key brain regions involved in psychiatric disorders (176). This disrupts microglial proliferation and phagocytic capacity, leading to impaired neuronal development and functional deficits in cognitive performance, memory, reward processing, and processing of social stimuli (177). Furthermore, recent animal studies showed that ELS-induced

 doi:10.20944/preprints202205.0281.v1

depressive behaviors were associated with neuroinflammation (89) and aberrant microglial activity (178), while CAS was also shown to increase hippocampal immune reactivity (179). Notably, there is also extensive evidence for neuroinflammation and gliosis in ASC (140,184–189), including reports of elevated inflammatory cytokines in ASC blood and post-mortem brain tissue, as well as immunohistochemistry, positron emission tomography and morphological data that demonstrates glial over-proliferation and over-activation in ASC (190–195). A seminal transcriptomic study in 2011 reported significant differential expression of genes involved in inflammation, astrocyte function and microglia activation in ASC brain tissue (196) and the glial fibrillary acidic protein (GFAP) was shown to be overexpressed at both the mRNA and protein levels in ASD post-mortem brain tissue (197). Post-mortem studies have also reported a significant upregulation of microglial-specific genes (194), increased microglial density (192,198) and excessive microglial activation (193,199) in ASC brain tissue and two recent systematic reviews have found consistent evidence for dysregulated microglial morphology, organization and activation in autism (188,200). Neuroimmune signaling therefore denotes another mechanistic overlap between ASC neurophysiology and the pathophysiological response to ELS.

In fact, the neuroimmune system also serves as an intermediary between MAL and the HPA axis on a molecular level. Mitochondrial metabolism is a central modulator of glial cell phenotypes and neuroinflammatory state (82) while the bidirectional relationship between inflammatory and GC signaling has been well-documented in the context of MDD and other psychopathologies (201,202). Glial functions are controlled by tightly regulated interactions between microglia, astrocytes, oligodendrocytes and neurons, which are closely coupled to glial metabolism(203). Importantly, glial phenotypes are dynamic, shift in response to different stimuli and can be either neuroprotective or neurotoxic (204). The transition to an inflammatory phenotype under pathogenic conditions is known as reactive gliosis, which is characterized by transcriptional, biochemical, metabolic and morphological remodeling (205). This has distinct implications for the metabolism, physiology and function of different glial cell types (206–211), each of which are implicated in specific aspects of ASD etiology (184,188,212–215). In particular, the tight coupling of mitochondrial metabolism and microglial activation is highly relevant in the context of ELS and ASC. Microglia are the only glial cells present in the early embryonic brain (216) that play an essential role in the regulation of phagocytosis, synaptic pruning, neurogenesis, neuronal excitability, synaptic activity and axonal myelination (211,217–219), all of which are thought to be dysregulated in autism (184,220,221).

Mitochondrial dysfunction can induce microglial activation via both extrinsic and intrinsic mechanisms. Mitochondrial dysfunction in surrounding tissue leads to the release of damage-associated molecular patterns (DAMPs) that bind to microglial receptors (117), Moreover, microglial activation is marked by intrinsic metabolic reprogramming, and different microglial phenotypes are associated with distinct metabolic pathways (218). While resting microglia rely primarily on OXPHOS (222), the shift towards the inflammatory M1 phenotype is driven by a decrease in mitochondrial respiration and an upregulation of glycolysis that enhances flux through the pentose phosphate pathway and increases lactate production to meet increased cellular energy demands (204). Recent work has demonstrated that mitochondrial metabolism directly regulates microglial activation (223,224) and that disrupting mitochondrial function has profound implications for microglial inflammatory state (217,218,224,225). *In vitro* models have shown that inhibiting mitochondrial ETC activity (226) or increasing mitochondrial fragmentation (218) induces microglial activation and pro-inflammatory cytokine signaling which could be mitigated by inhibiting mitochondrial fission (227) or normalizing mitochondrial membrane potential and ROS (218). On the other hand, mitochondrial stress impaired the transition to the anti-inflammatory M2 phenotype (228). Thus, mitochondrial dysfunction exacerbates the proinflammatory M1 phenotype leading to the release of neurotoxic inflammatory cytokines and oxidative stress (229). Conversely, exposure to changing cytokine stimuli has been shown to alter microglial metabolic state. Inflammatory stimuli were found to induce a metabolic switch from OXPHOS to glycolysis in cultured microglia (230),

 doi:10.20944/preprints202205.0281.v1

marked by increased lactate production and decreased OXPHOS, mitochondrial oxygen consumption and ATP synthesis (231,232). This metabolic shift correlated with increased production of proinflammatory cytokines (233) and nitric oxide (230), highlighting the close coupling of mitochondrial metabolism, microglial phenotypes and neuroinflammation.

Stress-sensitive neuroendocrine mediators including both catecholamines and GCs are also known to modulate immune system responses (82) by suppressing leukocyte trafficking and activation, as well as inflammatory cytokine production (202). Conversely, inflammatory cytokines modulate GC signaling by decreasing GR expression, altering GR phosphorylation or disrupting GR nuclear translocation and DNA binding (234). Cytokine-stimulated immune cells can also mediate HPA axis activation by inducing CRH production in the hypothalamus, leading to the secretion of adrenocorticotropic hormone (ACTH) and cortisol by the pituitary gland and adrenal cortex respectively (158). Of particular relevance, interleukin 6 (IL6) has been shown to activate HPA axis signaling and stimulate GC secretion in animal models and conversely, cortisol is known to inhibit the peripheral production of IL6) (158). IL6 is one of the most consistently upregulated inflammatory markers associated with ELS (180), MDD (183) and ASC (235) and recent preclinical studies have demonstrated that neuroimmune and HPA neuroendocrine interactions may mediate the neuroinflammatory response to ELS. ELS was shown to increase GR promoter methylation and decrease GR expression, which was associated with upregulated proinflammatory cytokine signaling (158). Similarly, chronic stress was shown to disrupt GR signaling on a transcriptomic level, while increasing microglial activation (236). Considering that GR signaling regulates mtDNA gene expression and mitochondrial functions - and that the mitochondria are central to immune modulation - it has been proposed that HPA-immune signaling could be mediated by mitochondrial mechanisms (82). Notably, several recent studies demonstrated that ELS induces sex-specific changes in both mitochondrial metabolism and markers of neuroinflammation (237–239), which supports a role for MAL in mediating the neuroinflammatory stress responses that lead to psychopathology. Altogether, this points to a tightly coupled interplay between mitochondrial metabolism, neuroimmune and neuroendocrine signaling that underlies the established relationship between ELS, MAL, and psychopathology. This discussion has highlighted that both mitochondrial dysfunction and neuroinflammation are well-established hallmarks of ASC etiology that each play central roles in modulating the HPA axis stress response. Thus, these molecular signatures could serve as an underlying susceptibility to ELS that may contribute to the high rates of psychopathology in autism.

4.4. From MAL to neurophysiology, neurochemistry, and behavior: a mechanistic perspective

A role for MAL in the relationship between autism and psychopathology is supported by the mounting evidence that points to mitochondrial metabolism as a key regulator of neurodevelopment, neurophysiology and neurochemistry. In fact, mitochondria modulate distinct neurological processes that are disrupted in response to ELS and involved in the etiology of both ASC and psychopathology. ELS has been shown to dysregulate the proliferation, differentiation and survival of neuronal stem cells (NSCs) (64), culminating in disruptions to synaptogenesis, synaptic pruning, long-term potentiation, and the balance between excitatory and inhibitory synapses (146). ELS-induced disruptions to neurodevelopment, synaptogenesis, synaptic plasticity and myelination are thought to contribute to the cognitive and behavioral differences observed later in life (240). Extensive synaptic remodeling also occurs during adolescence and CAS has been shown to alter neuroplasticity with implications for psychology and behavior throughout adulthood (65). These neurophysiological differences have previously been attributed to HPA axis signaling, as GCs are known to modulate NSC fate and neurogenesis via interactions with the brain-derived neurotrophic factor (BDNF), phosphoinositide 3-kinase (PI3K)/Akt, hedgehog, and Wnt pathways (241,242). However, just as the concept of MAL has become

 doi:10.20944/preprints202205.0281.v1

increasingly well-established in stress research, mitochondria are also emerging as central players in the regulation of neurogenesis and NSC self-renewal (243–245).

Neuronal differentiation is closely tied to metabolic state, which is coupled to, and regulated by, mTOR signaling and this relationship plays an important role in mediating the metabolic shift that is required to facilitate neurogenesis (246–248). Notably, both mTOR signaling (246,249–251) and mitochondrial function (252–257) are essential for synaptic signaling, function and plasticity. Wang et al., (2020) recently showed that ELS impaired synaptic plasticity by inhibiting mTOR signaling in the mouse hippocampus, resulting in increased anxiety-like behavior and cognitive impairments (258) while Sanchez et al., (2022) also demonstrated that ELS induced hyperactivation of the mTOR complex and reduced oxidative metabolic capacity in the amygdala (259). This suggests that the mTOR-dependent modulation of NSC metabolic state contributes to the neurophysiological, cognitive and behavioral changes induced by ELS. As an important regulator of microglial activation, mitochondrial metabolism also modulates both neuronal apoptosis and synaptic pruning during neurodevelopment; moreover microglial metabolism is essential to regulate myelin processing in the adult brain(207). Mitochondrial dysfunction is known to disrupt myelination by decreasing the myelinating potential of oligodendrocytes, increasing oxidative damage and disrupting neuronal fatty acid metabolism (260). Myelin is used as an alternative energy source if glycolysis is inhibited (207) and the physiological turnover of myelin is dependent on microglial phagocytic efficiency. In fact, microglial dysfunction has been shown to precede major myelin breakdown in hereditary demyelinating disorders(211). These data are highly relevant in the context of ASC which is also characterized by disruptions to mTOR signaling (251,261,262), synaptic pruning(200,263) and myelination (214) leading to cortical hyperconnectivity and the resultant behavioral phenotypes (219,264). Thus, the mitochondrial modulation of neurodevelopment, synaptogenesis and myelination manifests in neurophysiological features that are consistently associated with ELS and are well-established components of ASC etiology.

In addition, both ELS and ASC are marked by disruptions to neurotransmission and neuroendocrinology. Preclinical models have demonstrated that both ELS and CAS disrupt glutamatergic and GABAergic neurotransmission, leading to impaired social recognition, decreased social interest, reduced cognitive function, cognitive inflexibility and increased anxiety-like behaviors (265–268). ELS has also been shown to disrupt both serotonin and dopamine signaling in animal models (238). Several preclinical models have shown that ELS alters the mRNA expression of dopamine receptors, the density of dopamine transporters and the rate of dopamine metabolism and turnover in brain tissue (269). Moreover, a meta-analysis of rodent studies found robust associations between ELS exposure and specific dopamine metabolites in the striatum (270). Similarly, Adjimann, Argañaraz and Soiza-Reilly, (2021) recently summarized the current evidence from animal models suggesting that serotonin plays a central role in the development of psychopathology in response to ELS (271). These data are supported by human cohort studies which have shown that ELS alters glutamate/glutamine cycling (272), dopaminergic neurotransmitter responses(273,274) and serotonin transporter binding (275) in patients who presented with MDD, while serotonin receptor genetic polymorphisms have been shown to mediate the effect of ELS on the subsequent development of depression (276). CAS also alters neuroendocrinology on several fronts and has been shown to induce glutamatergic excitotoxicity and decrease levels of serotonin, basal dopamine and norepinephrine (65). Notably, an unbalanced excitatory-to-inhibitory synaptic signaling ratio (163,166,277) and disruptions to glutamatergic (166,215,278–282), serotonergic (283–287) and dopaminergic (163,165,288) neurotransmission are well-established aspects of ASC neurochemistry that are associated with distinct aspects of ASC etiology. Glutamatergic excitotoxicity is thought to contribute to to anxiety, perseveration, restlessness, migraines, tics and motor stereotypies, social interaction and social memory, and language and cognitive impairments (282). Disruptions to serotonin signaling are linked to altered social cognition, facial recognition, emotion processing and communication (286) while dopamine signaling is associated with disruptions to sleep, mood and attention (163,165,288).

 doi:10.20944/preprints202205.0281.v1

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 dysregulation of glutamatergic and GABAergic signaling contributes to the etiology of anxiety disorders (328–331), PTSD (332), eating disorders(333–335), OCD (336) and substance use disorders (SUDs) (337,338). The serotonergic, dopaminergic and noradrenergic systems are implicated in MDD, anxiety and SUDs (339–341) while serotonin is also associated with mood disorders, aggression, anti-social conduct, OCD, stress disorders and ADHD (342–344) and dopamine is thought to play a role in eating disorders (345,346), executive dysfunction and behavioral inhibition (347,348). Moreover, well-documented interactions between neurotransmitter, neuroimmune and neuroendocrine pathways play a central role in modulating suicide risk after ELS exposure (143). Glutamate is involved in both driving HPA responses and limiting HPA overactivation (318–320) and conversely, GC signaling is known to modulate glutamatergic synapse plasticity and excitability (321). Serotonergic neurotransmission excites CRH neurons in the amygdala (183) and acts as an important regulator of GR signaling in the PFC after exposure to acute stress(322). On the other hand, animal models show that corticosteroids decrease serotonin receptor binding densities (323,324) and this relationship is implicated as a mediator of suicide risk following ELS (276). Finally, GCs also activate the mesolimbic dopamine pathway (325,326) 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 (327).

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. Separate reviews have comprehensively described the close coupling of mitochondrial function with glutamatergic (289–291), serotonergic (292–294) and dopaminergic (295–299) neurotransmission, although this remains understudied in the context of MAL and psychopathology. Firstly, glutamatergic neurotransmission is tightly coupled to neuronal and astrocytic metabolism (300,301). Glutamate functions as a substrate for both the mitochondrial TCA cycle and the transulfuration pathway, thereby fueling OXPHOS and antioxidant synthesis to promote mitochondrial function and mitigate against oxidative stress (290,301–304). 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 (305). Dopamine autooxidation is also regulated by intracellular redox state, and an accumulation of oxidative dopamine metabolites can lead to mitochondrial membrane depolarization (306) and decreased ETC activity and ATP synthesis (298). Moreover, dopamine 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 (297). 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 towards glycolysis in glial cells upregulates the production of lactate and serine, which potentiates glutamatergic excitotoxicity and neuroinflammation (215,307).

Similarly, a reciprocal relationship between mitochondrial function and the two branches of tryptophan metabolism modulates the synthesis of serotonin, melatonin, and kynurenine (KYN) metabolites (308). Serotonin positively regulates mitochondrial biogenesis, oxidative capacity and ATP synthesis (294,309) while serotonin deficiency disrupts amino acid and lipid metabolism, TCA cycling, OXPHOS and antioxidant activity (310,311). Serotonin also functions as a precursor to melatonin, which regulates mitochondrial OXPHOS, redox homeostasis and inflammatory responses(312). Moreover, melatonin regulates the expression of the rate limiting enzymes involved in serotonin synthesis and catabolism (313), thereby modulating 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

 doi:10.20944/preprints202205.0281.v1

regulated by interactions between glial cells and neurons. The KYN metabolites kynurenic acid (KYNA) and quinolinic acid (QUIN) inhibit and activate glutamate receptors respectively (112) and flux in the QUIN branch of the KYN pathway that alters *de novo* NAD+ synthesis also modulates metabolic and oxidative state (314). Mitochondrial dysfunction shifts the KYN pathway towards QUIN production by increasing the demand for NAD+ (315); conversely, QUIN contributes to mitochondrial dysfunction by increasing cytoplasmic calcium concentration and superoxide production in microglia (316). A pathogenic shift towards a reactive glial phenotype under inflammatory conditions upregulates microglial tryptophan import, which both decreases local tryptophan availability for serotonin synthesis and further increases the production of QUIN in microglia (316). Moreover, QUIN upregulates glutamatergic neurotransmission and inhibits glutamate uptake from the synaptic cleft, thereby promoting excitotoxicity(317). Altogether, this demonstrates that a disruption of the relationship between mitochondrial function and the glutamatergic, serotonergic and dopaminergic neurotransmitter cycles increases oxidative stress and shifts glial metabolism towards glycolysis, thereby contributing to gliosis, excitotoxicity and neuroinflammation (215,297,317).

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 both 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 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; and thus represents a crucial target for future molecular research that aims to improve the quality of life of autistic individuals.

5. 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 more cohesive understanding of pathological stress responses (349). 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 argument put forward 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 ASC (Figure 1). This framework integrates emerging literature that is foregrounding autistic experiences with the molecular model for allostatic load that has been developed to quantify the cumulative impact of biological and psychosocial stress (82). This framework proposes 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.

Autistic children are more likely to be exposed to early childhood adversity, psychosocial stress and experiences that threaten their safety or well-being, while also having inadequate internal resources to cope with these stressors. Moreover, the recent characterization of concepts like social camouflaging and autistic burnout in academic literature has highlighted that autistic children are exposed to chronic and distinct forms of stress throughout adolescence that often go unrecognized. During middle childhood, children with ASC are increasingly required to suppress autistic traits in order to meet social and academic expectations, although the extent to which each individual is motivated or able to meet these expectations is mediated by a complex interplay between underlying physiology and sociocultural factors that contribute to socialization. Chronic social camouflaging creates an increasing mismatch between internal capacity and external expectations, culminating in autistic burnout. Importantly, both social camouflaging and autistic

 doi:10.20944/preprints202205.0281.v1

burnout are known to contribute to the development of psychopathology and suicidality in ASC but 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 are known to mediate the relationship between ELS, CAS and psychopathology revolve around interdependent signaling between mitochondrial metabolism, inflammatory immune responses and stress-responsive GC 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 are known to play an essential role in the regulation of neurodevelopment by facilitating the metabolic shift towards OXPHOS that is required for neuronal differentiation. Mitochondria also modulate microglial activation, which is essential 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 in the adult brain. The stress-responsive 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 review has highlighted how these molecular mechanisms are implicated in the neurophysiology and neurochemistry of autism and contribute to the development of psychopathology following ELS.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 May 2022 doi:10.20944/preprints202205.0281.v1

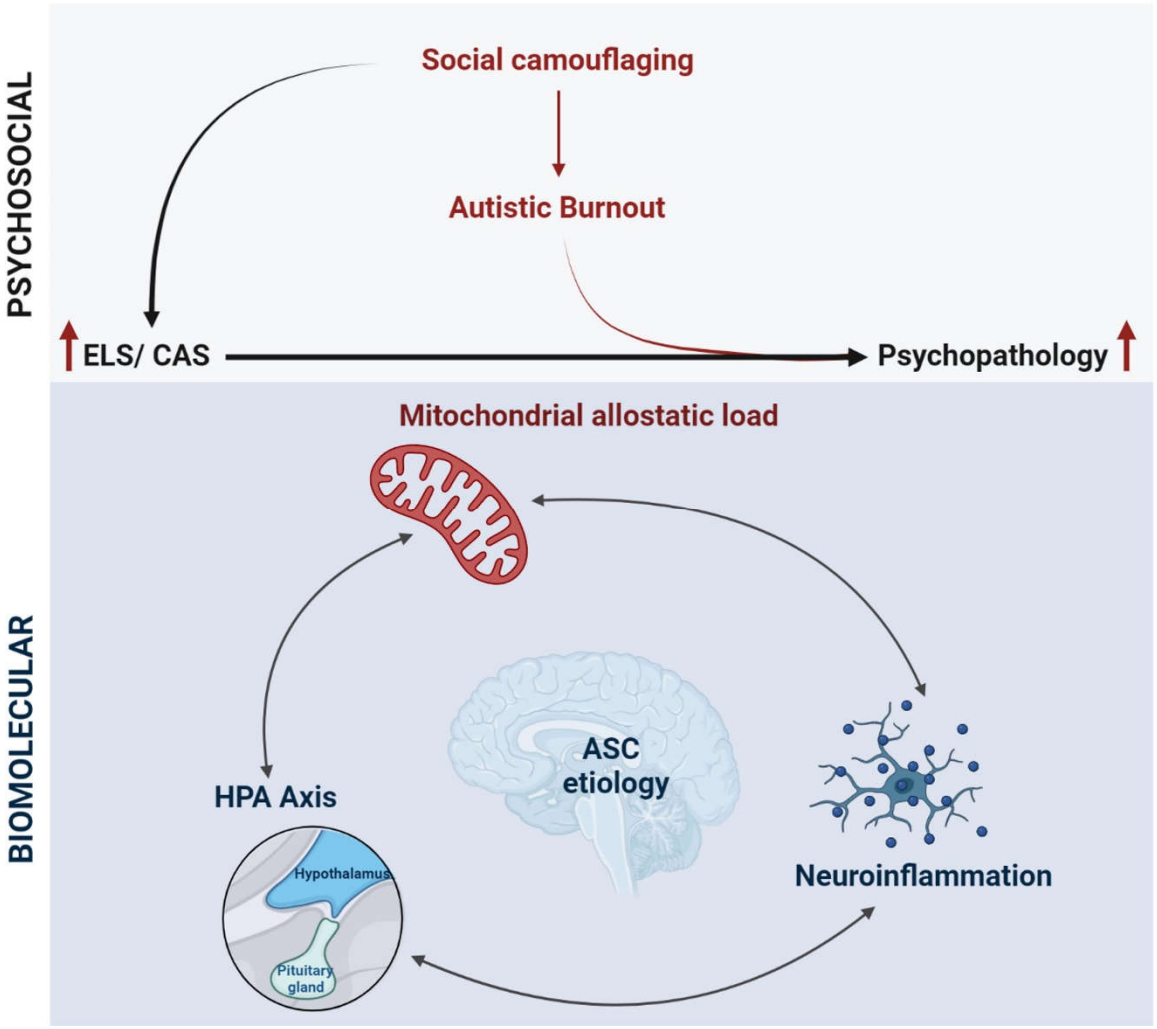

Figure 1. An integrative biopsychosocial vulnerability framework for the development of psychopathology in ASC. There is a well-established relationship between exposure to early life stress (ELS) or chronic adolescent stress (CAS) and the development of psychopathology(68–70,350). Autism is associated with both a significantly increased risk of exposure to ELS(35,36) and high rates of psychopathology and suicidality (29,39,40,43). Emerging characterizations of internal autistic experiences including social camouflaging (21,55,56) and autistic burnout (50–52) overlap closely with established definitions for ELS (65,66) and lead to increased levels of anxiety, depression, self-injury and suicidality in ASC (28,29,57,58). 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) (85) plays a central role in the development of psychopathology following ELS by disrupting a tightly coupled signaling network between neuroimmune (66,176,180,181,183) and neuroendocrine signaling (65,66,142). Separate reviews have comprehensively described the tightly regulated biochemical relationships between mitochondrial dysfunction and gliosis (204,218,223,351); mitochondrial metabolism and HPA axis signaling (82,149,150); and the HPA axis and inflammatory immune response pathways (201,202). ASC etiology is characterized by mitochondrial dysfunction (117–119), gliosis and neuroinflammation (184–189,200) and a complex signature of HPA axis dysregulation (44,175). 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 (211,219,243,245,289,294,297). 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.

Considering both the increased risk of exposure to, and underlying vulnerability to, ELS in autism emphasizes how psychosocial and biological factors converge to increase

 doi:10.20944/preprints202205.0281.v1

the risk of psychopathology. This interplay could act as a potential mechanism that contributes to the high rates of depression and suicidality in autistic adults and may reveal a biological signature that underlies autistic burnout. Autistic burnout, depression and suicidality are factors that directly impair health, well-being and function for people with autism and 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, further investigating an underlying susceptibility to ELS could inform research into novel molecular interventions. Targeted therapeutic strategies might be able to protect children with ASC from the development of psychopathology, facilitate recovery from autistic burnout, or identify diagnostic tools to differentiate autistic burnout from clinical depression. Ultimately, this highlights the utility of molecular research that considers autistic experiences in order to progress towards findings that could tangibly improve the quality of life for autistic individuals.

Author Contributions: CM reviewed the relevant literature, developed the conceptual framework and wrote the paper. COR refined the conceptual framework, wrote the paper, and coordinated project supervision, administration and acquisition of funding.

Funding: This work was supported by the University of Cape Town and the National Research Foundation, South Africa (CPRR 180508327125).

Conflicts 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.

References

1. Whiteley P, Carr K, Shattock P. Research, Clinical, and Sociological Aspects of Autism. Frontiers in Psychiatry. 2021 Apr 29;12:560.
2. Milton DEM. Autistic expertise: A critical reflection on the production of knowledge in autism studies. Autism. 2014 Oct 1;18(7):794–802.
3. Fletcher-Watson S, Adams J, Brook K, Charman T, Crane L, Cusack J, et al. Making the future together: Shaping autism research through meaningful participation. Autism. 2019 May 1;23(4):943–53.
4. Brkić D, Ng-Cordell E, O'Brien S, Scerif G, Astle D, Baker K. Gene functional networks and autism spectrum characteristics in young people with intellectual disability: a dimensional phenotyping study. Molecular Autism. 2020 Dec 11;11(1):98.
5. Quesnel-Vallières M, Weatheritt RJ, Cordes SP, Blencowe BJ. Autism spectrum disorder: insights into convergent mechanisms from transcriptomics. Vol. 20, Nature Reviews Genetics. Nature Publishing Group; 2019. p. 51–63.
6. Wiśniowiecka-Kowalnik B, Nowakowska BA. Genetics and epigenetics of autism spectrum disorder—current evidence in the field. Vol. 60, Journal of Applied Genetics. Springer Verlag; 2019. p. 37–47.
7. Zhang XC, Shu LQ, Zhao X Sen, Li XK. Autism spectrum disorders: autistic phenotypes and complicated mechanisms. Vol. 15, World Journal of Pediatrics. Institute of Pediatrics of Zhejiang University; 2019. p. 17–25.
8. Charman T, Jones CRG, Pickles A, Simonoff E, Baird G, Happé F. Defining the cognitive phenotype of autism. Brain Research. 2011 Mar 22;1380:10–21.
9. Berry K, Russell K, Frost K. Restricted and Repetitive Behaviors in Autism Spectrum Disorder: a Review of Associated Features and Presentation Across Clinical Populations. Current Developmental Disorders Reports. 2018 Jun 1;5(2):108–15.
10. Magiati I, Tay XW, Howlin P. Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: A systematic review of longitudinal follow-up studies in adulthood. Clinical Psychology Review. 2014 Feb 1;34(1):73–86.
11. Tager-Flusberg H, Joseph RM. Identifying neurocognitive phenotypes in autism. Philosophical Transactions of the Royal Society of London Series B: Biological Sciences. 2003 Feb 28;358(1430):303–14.
12. Doyle N. Neurodiversity at work: a biopsychosocial model and the impact on working adults. British Medical Bulletin. 2020 Sep 1;135(1):108.
13. Bölte S, De Schipper E, Robison JE, Wong VCN, Selb M, Singhal N, et al. Classification of functioning and impairment: The development of ICF core sets for autism spectrum disorder. Autism Research. 2014;7(1):167–72.
14. Leadbitter K, Buckle KL, Ellis C, Dekker M. Autistic Self-Advocacy and the Neurodiversity Movement: Implications for Autism Early Intervention Research and Practice. Frontiers in Psychology. 2021 Apr 12;12:782.
15. Mesleh AG, Abdulla SA, El-Agnaf O. Paving the Way toward Personalized Medicine: Current Advances and Challenges in Multi-OMICS Approach in Autism Spectrum Disorder for Biomarkers Discovery and Patient Stratification. J Pers Med. 2021 Jan 13;11(1):41.
16. McCracken JT, Anagnostou E, Arango C, Dawson G, Farchione T, Mantua V, et al. Drug development for Autism Spectrum Disorder (ASD): Progress, challenges, and future directions. European Neuropsychopharmacology. 2021 Jul 1;48:3–31.

17. Divan G, Bhavnani S, Leadbitter K, Ellis C, Dasgupta J, Abubakar A, et al. Annual Research Review: Achieving universal health coverage for young children with autism spectrum disorder in low- and middle-income countries: a review of reviews. Journal of Child Psychology and Psychiatry. 2021 May 1;62(5):514–35.
18. Donohue MR, Childs AW, Richards M, Robins DL. Race influences parent report of concerns about symptoms of autism spectrum disorder. Autism. 2019 Jan 1;23(1):100–11.
19. Durkin MS, Maenner MJ, Baio J, Christensen D, Daniels J, Fitzgerald R, et al. Autism Spectrum Disorder Among US Children (2002-2010): Socioeconomic, Racial, and Ethnic Disparities. Am J Public Health. 2017 Nov 1;107(11):1818–26.
20. Fombonne E, Zuckerman KE. Clinical Profiles of Black and White Children Referred for Autism Diagnosis. Journal of Autism and Developmental Disorders 2021. 2021 Apr 19;1–11.
21. Hull L, Petrides K V., Mandy W. The Female Autism Phenotype and Camouflaging: a Narrative Review. Review Journal of Autism and Developmental Disorders. 2020 Dec 1;7(4):306–17.
22. Lockwood Estrin G, Milner V, Spain D, Happé F, Colvert E. Barriers to Autism Spectrum Disorder Diagnosis for Young Women and Girls: a Systematic Review. Review Journal of Autism and Developmental Disorders. 2020 Oct 29;1–17.
23. Mandell DS, Wiggins LD, Carpenter LA, Daniels J, DiGuiseppi C, Durkin MS, et al. Racial/Ethnic Disparities in the Identification of Children With Autism Spectrum Disorders. American Journal of Public Health. 2009 Mar 1;99(3):493.
24. Yingling ME, Hock RM, Bell BA. Time-Lag Between Diagnosis of Autism Spectrum Disorder and Onset of Publicly-Funded Early Intensive Behavioral Intervention: Do Race-Ethnicity and Neighborhood Matter? J Autism Dev Disord. 2018 Feb 1;48(2):561–71.
25. Scahill L, Lord C. Subject Selection and Characterization in Clinical Trials in Children with Autism. CNS Spectrums. 2004;9(1):22–32.
26. Hull L, Petrides K V., Allison C, Smith P, Baron-Cohen S, Lai MC, et al. "Putting on My Best Normal": Social Camouflaging in Adults with Autism Spectrum Conditions. Journal of Autism and Developmental Disorders. 2017 Aug 1;47(8):2519–34.
27. Cage E, Troxell-Whitman Z. Understanding the Reasons, Contexts and Costs of Camouflaging for Autistic Adults. Journal of Autism and Developmental Disorders. 2019 May 15;49(5):1899–911.
28. Cook J, Hull L, Crane L, Mandy W. Camouflaging in autism: A systematic review. Clinical Psychology Review. 2021 Nov 1;89:102080.
29. Cassidy SA, Gould K, Townsend E, Pelton M, Robertson AE, Rodgers J. Is Camouflaging Autistic Traits Associated with Suicidal Thoughts and Behaviours? Expanding the Interpersonal Psychological Theory of Suicide in an Undergraduate Student Sample. Journal of Autism and Developmental Disorders. 2020 Oct 1;50(10):3638–48.
30. Young N, Findling RL. An update on pharmacotherapy for autism spectrum disorder in children and adolescents. Current Opinion in Psychiatry. 2015 Mar 6;28(2):91–101.
31. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger JI, Hallmayer JF. Autism genetics: opportunities and challenges for clinical translation. Nature Reviews Genetics 2017 18:6. 2017 Mar 6;18(6):362–76.
32. Jeste SS, Geschwind DH. Clinical trials for neurodevelopmental disorders: At a therapeutic frontier. Science Translational Medicine. 2016 Jan 13;8(321).
33. Loth E, Murphy DG, Spooren W. Defining precision medicine approaches to autism spectrum disorders: Concepts and challenges. Frontiers in Psychiatry. 2016 Nov 29;7(NOV):188.
34. Sestan N, State MW. Lost in Translation: Traversing the Complex Path from Genomics to Therapeutics in Autism Spectrum Disorder. Neuron. 2018 Oct 24;100(2):406–23.
35. Singletary WM. An integrative model of autism spectrum disorder: ASD as a neurobiological disorder of experienced environmental deprivation, early life stress and allostatic overload. Vol. 17, Neuropsychoanalysis. Routledge; 2015. p. 81–119.
36. Scarpa A, Swain DM, Factor RS, Dahiya A V., Bertollo JR. Enhancing Flexibility: A Biosocial Model for Resilience to Adversity in Youth With Autism. SAGE Open. 2021 Aug 5;11(3).
37. Etyemez S, Saleh A, Hamilton JE, Koshy AJ, Abraham JE, Selek S. Higher prevalence of mood disorders in admitted patients with autism. Neurology, Psychiatry and Brain Research. 2020 Sep 1;37:87–90.
38. Smith IC, White SW. Socio-emotional determinants of depressive symptoms in adolescents and adults with autism spectrum disorder: A systematic review: https://doi.org/101177/1362361320908101. 2020 Mar 19;24(4):995–1010.
39. Oakley B, Loth E, Murphy DG. Autism and mood disorders. Vol. 33, International Review of Psychiatry. Taylor & Francis; 2021. p. 280–99.
40. Costa AP, Loor C, Steffgen G. Suicidality in adults with autism spectrum disorder: The role of depressive symptomatology, alexithymia, and antidepressants. Journal of Autism and Developmental Disorders. 2020 Mar 14;50(10):3585–97.
41. Dow D, Morgan L, Hooker JL, Michaels MS, Joiner TE, Woods J, et al. Anxiety, Depression, and the Interpersonal Theory of Suicide in a Community Sample of Adults with Autism Spectrum Disorder. https://doi.org/101080/1381111820191678537. 2019;25(2):297–314.
42. Cassidy S, Bradley P, Robinson J, Allison C, McHugh M, Baron-Cohen S. Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study. The Lancet Psychiatry. 2014 Jul 1;1(2):142–7.
43. Kõlves K, Fitzgerald C, Nordentoft M, Wood SJ, Erlangsen A. Assessment of Suicidal Behaviors Among Individuals With Autism Spectrum Disorder in Denmark. JAMA Network Open. 2021 Jan 4;4(1):e2033565–e2033565.

44. Muscatello RA, Andujar J, Taylor JL, Corbett BA. Exploring Key Physiological System Profiles at Rest and the Association with Depressive Symptoms in Autism Spectrum Disorder. Journal of Autism and Developmental Disorders. 2020 Apr 30;51(1):15–29.
45. South M, Beck JS, Lundwall R, Christensen M, Cutrer EA, Gabrielsen TP, et al. Unrelenting Depression and Suicidality in Women with Autistic Traits. Journal of Autism and Developmental Disorders. 2020 Oct 1;50(10):3606–19.
46. Hedley D, Uljarević M, Foley KR, Richdale A, Trollor J. Risk and protective factors underlying depression and suicidal ideation in Autism Spectrum Disorder. Depression and Anxiety. 2018 Jul 1;35(7):648–57.
47. Haruvi-Lamdan N, Horesh D, Golan O. PTSD and autism spectrum disorder: Co-morbidity, gaps in research, and potential shared mechanisms. Psychological Trauma: Theory, Research, Practice, and Policy. 2018 May 1;10(3):290–9.
48. Howe SJ, Hewitt K, Baraskewich J, Cassidy S, McMorris CA. Suicidality Among Children and Youth With and Without Autism Spectrum Disorder: A Systematic Review of Existing Risk Assessment Tools. Journal of Autism and Developmental Disorders. 2020 Oct 1;50(10):3462–76.
49. Unruh KE, Bodfish JW, Gotham KO. Adults with Autism and Adults with Depression Show Similar Attentional Biases to Social-Affective Images. Journal of Autism and Developmental Disorders. 2020 Jul 1;50(7):2336–47.
50. Raymaker DM, Teo AR, Steckler NA, Lentz B, Scharer M, Santos AD, et al. "Having All of Your Internal Resources Exhausted Beyond Measure and Being Left with No Clean-Up Crew": Defining Autistic Burnout. https://home.liebertpub.com/aut. 2020 Jun 10;2(2):132–43.
51. Higgins JM, Arnold SRC, Weise J, Pellicano E, Trollor JN. Defining autistic burnout through experts by lived experience: Grounded Delphi method investigating #AutisticBurnout. Autism. 2021 Nov 1;25(8):2356–69.
52. Mantzalas J, Richdale AL, Adikari A, Lowe J, Dissanayake C. What Is Autistic Burnout? A Thematic Analysis of Posts on Two Online Platforms. Autism in Adulthood. 2021 Sep 20;
53. Mantzalas J, Richdale AL, Dissanayake C. A conceptual model of risk and protective factors for autistic burnout. Autism Research. 2022 Apr 13;
54. Livingston LA, Shah P, Happé F. Compensatory strategies below the behavioural surface in autism: a qualitative study. The Lancet Psychiatry. 2019 Sep 1;6(9):766–77.
55. Bradley L, Shaw R, Baron-Cohen S, Cassidy S. Autistic Adults' Experiences of Camouflaging and Its Perceived Impact on Mental Health. Autism in Adulthood. 2021 Dec 1;3(4):320–9.
56. Leedham A, Thompson AR, Smith R, Freeth M. 'I was exhausted trying to figure it out': The experiences of females receiving an autism diagnosis in middle to late adulthood. Autism. 2020 Jan 1;24(1):135–46.
57. Tubío-Fungueiriño M, Cruz S, Sampaio A, Carracedo A, Fernández-Prieto M. Social Camouflaging in Females with Autism Spectrum Disorder: A Systematic Review. Journal of Autism and Developmental Disorders. 2021 Jul 1;51(7):2190–9.
58. Kim SY, Lecavalier L. Depression in young autistic people: A scoping review. Research in Autism Spectrum Disorders. 2021 Oct 1;88:101841.
59. Hull L, Levy L, Lai MC, Petrides K V., Baron-Cohen S, Allison C, et al. Is social camouflaging associated with anxiety and depression in autistic adults? Molecular Autism. 2021 Dec 1;12(1):1–13.
60. Montero-Marín J, García-Campayo J, Mera DM, Del Hoyo YL. A new definition of burnout syndrome based on Farber's proposal. Journal of Occupational Medicine and Toxicology. 2009 Nov 30;4(1):1–17.
61. Lilley R, Lawson W, Hall G, Mahony J, Clapham H, Heyworth M, et al. "A way to be me": Autobiographical reflections of autistic adults diagnosed in mid-to-late adulthood. Autism. 2021 Oct 22;13623613211050694.
62. Stagg SD, Belcher H. Living with autism without knowing: receiving a diagnosis in later life. http://mc.manuscriptcentral.com/HPBM. 2019 Jan 1;7(1):348–61.
63. van der Cruijsen R, Boyer BE. Explicit and implicit self-esteem in youth with autism spectrum disorders. Autism. 2021 Feb 1;25(2):349–60.
64. Malinovskaya NA, Morgun A V., Lopatina OL, Panina YA, Volkova V V., Gasymly EL, et al. Early Life Stress: Consequences for the Development of the Brain. Neuroscience and Behavioral Physiology 2018 48:2. 2018 Feb 9;48(2):233–50.
65. Sheth C, McGlade E, Yurgelun-Todd D. Chronic Stress in Adolescents and Its Neurobiological and Psychopathological Consequences: An RDoC Perspective. Chronic Stress. 2017 Jun 18;1.
66. Fogelman N, Canli T. Early life stress, physiology, and genetics: A review. Frontiers in Psychology. 2019;10(JULY):1668.
67. Lähdepuro A, Savolainen K, Lahti-Pulkkinen M, Eriksson JG, Lahti J, Tuovinen S, et al. The Impact of Early Life Stress on Anxiety Symptoms in Late Adulthood. Scientific Reports 2019 9:1. 2019 Mar 13;9(1):1–13.
68. LeMoult J, Humphreys KL, Tracy A, Hoffmeister JA, Ip E, Gotlib IH. Meta-analysis: Exposure to Early Life Stress and Risk for Depression in Childhood and Adolescence. Journal of the American Academy of Child & Adolescent Psychiatry. 2020 Jul 1;59(7):842–55.
69. Sahle BW, Reavley NJ, Li W, Morgan AJ, Yap MBH, Reupert A, et al. The association between adverse childhood experiences and common mental disorders and suicidality: an umbrella review of systematic reviews and meta-analyses. European Child and Adolescent Psychiatry. 2021 Feb 27;1:1–11.
70. Su YY, D'Arcy C, Li M, O'Donnell KJ, Caron J, Meaney MJ, et al. Specific and cumulative lifetime stressors in the aetiology of major depression: A longitudinal community-based population study. Epidemiology and Psychiatric Sciences. 2022 Jan 26;31:e3.
71. Jones CM, Merrick MT, Houry DE. Identifying and Preventing Adverse Childhood Experiences: Implications for Clinical Practice. JAMA. 2020 Jan 7;323(1):25–6.

72. Picard M, McEwen BS, Epel ES, Sandi C. An energetic view of stress: Focus on mitochondria. Frontiers in Neuroendocrinology. 2018 Apr 1;49:72–85.
73. Kuenzel E, Seguin D, Nicolson R, Duerden EG. Early adversity and positive parenting: Association with cognitive outcomes in children with autism spectrum disorder. Autism Research. 2021;
74. Griffiths S, Allison C, Kenny R, Holt R, Smith P, Baron-Cohen S. The Vulnerability Experiences Quotient (VEQ): A Study of Vulnerability, Mental Health and Life Satisfaction in Autistic Adults. Autism Research. 2019 Oct 1;12(10):1516–28.
75. Schroeder JH, Cappadocia MC, Bebko JM, Pepler DJ, Weiss JA. Shedding light on a pervasive problem: A review of research on bullying experiences among children with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2014 Jan 25;44(7):1520–34.
76. Trundle G, Jones KA, Ropar D, Egan V. Prevalence of Victimisation in Autistic Individuals: A Systematic Review and Meta-Analysis: https://doi.org/101177/15248380221093689. 2022 May 6;152483802210936.
77. Tierney S, Burns J, Kilbey E. Looking behind the mask: Social coping strategies of girls on the autistic spectrum. Research in Autism Spectrum Disorders. 2016 Mar 1;23:73–83.
78. Cage E, Di Monaco J, Newell V. Experiences of Autism Acceptance and Mental Health in Autistic Adults. J Autism Dev Disord. 2018 Feb 1;48(2):473–84.
79. Lai MC, Lombardo M V., Ruigrok ANV, Chakrabarti B, Auyeung B, Szatmari P, et al. Quantifying and exploring camouflaging in men and women with autism. Autism. 2017 Aug 1;21(6):690.
80. Livingston LA, Happé F. Conceptualising compensation in neurodevelopmental disorders: Reflections from autism spectrum disorder. Neurosci Biobehav Rev. 2017 Sep 1;80:729–42.
81. Children NRC (US) P to R the S of BR on SA, Collins WA. Self-Understanding And Self-Regulation In Middle Childhood. 1984;
82. Picard M, McEwen BS. Psychological Stress and Mitochondria: A Conceptual Framework. Psychosom Med. 2018 Feb 1;80(2):126.
83. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neuroscience & Biobehavioral Reviews. 2010 Sep 1;35(1):2–16.
84. McEwen CA. Connecting the biology of stress, allostatic load and epigenetics to social structures and processes. Neurobiology of Stress. 2022 Jan 4;100426.
85. Allen J, Caruncho HJ, Kalynchuk LE. Severe life stress, mitochondrial dysfunction, and depressive behavior: A pathophysiological and therapeutic perspective. Mitochondrion. 2021 Jan 1;56:111–7.
86. Guidi J, Lucente M, Sonino N, Fava GA. Allostatic Load and Its Impact on Health: A Systematic Review. Psychotherapy and Psychosomatics. 2021 Jan 1;90(1):11–27.
87. Taylor JL, Corbett BA. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. Psychoneuroendocrinology. 2014 Nov 1;49(1):207–28.
88. do Prado CH, Grassi-Oliveira R, Wieck A, Zaparte A, Filho LD, da Silva Morrone M, et al. The impact of childhood maltreatment on redox state: Relationship with oxidative damage and antioxidant defenses in adolescents with no psychiatric disorder. Neuroscience Letters. 2016 Mar 23;617:173–7.
89. Réus GZ, Fernandes GC, de Moura AB, Silva RH, Darabas AC, de Souza TG, et al. Early life experience contributes to the developmental programming of depressive-like behaviour, neuroinflammation and oxidative stress. Journal of Psychiatric Research. 2017 Dec 1;95:196–207.
90. Sahafi E, Peeri M, Hosseini MJ, Azarbyjani MA. Cardiac oxidative stress following maternal separation stress was mitigated following adolescent voluntary exercise in adult male rat. Physiology & Behavior. 2018 Jan 1;183:39–45.
91. Ruigrok SR, Yim K, Emmerzaal TL, Geenen B, Stöberl N, den Blaauwen JL, et al. Effects of early-life stress on peripheral and central mitochondria in male mice across ages. Psychoneuroendocrinology. 2021 Oct 1;132:105346.
92. Picard M, McEwen BS. Psychological Stress and Mitochondria: A Systematic Review. Psychosom Med. 2018 Feb 1;80(2):141.
93. Tobe EH. Mitochondrial dysfunction, oxidative stress, and major depressive disorder. Neuropsychiatric Disease and Treatment. 2013 Apr 25;9:567.
94. Bansal Y, Kuhad A. Mitochondrial Dysfunction in Depression. Current Neuropharmacology. 2016 Jun 27;14(6):610–8.
95. Allen J, Romay-Tallon R, Brymer KJ, Caruncho HJ, Kalynchuk LE. Mitochondria and mood: Mitochondrial dysfunction as a key player in the manifestation of depression. Frontiers in Neuroscience. 2018 Jun 6;12(JUN):386.
96. Xie X, Shen Q, Yu C, Xiao Q, Zhou J, Xiong Z, et al. Depression-like behaviors are accompanied by disrupted mitochondrial energy metabolism in chronic corticosterone-induced mice. The Journal of Steroid Biochemistry and Molecular Biology. 2020 Jun 1;200:105607.
97. Głombik K, Budziszewska B, Basta-Kaim A. Mitochondria-targeting therapeutic strategies in the treatment of depression. Mitochondrion. 2021 May 1;58:169–78.
98. Kolar D, Kleteckova L, Brozka H, Vales K. Mini-review: Brain energy metabolism and its role in animal models of depression, bipolar disorder, schizophrenia and autism. Neuroscience Letters. 2021 Aug 24;760:136003.
99. Chung JK, Lee SY, Park M, Joo EJ, Kim SA. Investigation of mitochondrial DNA copy number in patients with major depressive disorder. Psychiatry Research. 2019 Dec 1;282.
100. Ben-Shachar D, Karry R. Neuroanatomical Pattern of Mitochondrial Complex I Pathology Varies between Schizophrenia, Bipolar Disorder and Major Depression. PLOS ONE. 2008 Nov 7;3(11):e3676.

101. Anderson G. Linking the biological underpinnings of depression: Role of mitochondria interactions with melatonin, inflammation, sirtuins, tryptophan catabolites, DNA repair and oxidative and nitrosative stress, with consequences for classification and cognition. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018 Jan 3;80:255–66.
102. Karabatsiakis A, Böck C, Salinas-Manrique J, Kolassa S, Calzia E, Dietrich DE, et al. Mitochondrial respiration in peripheral blood mononuclear cells correlates with depressive subsymptoms and severity of major depression. Translational Psychiatry 2014 4:6. 2014 Jun 10;4(6):e397–e397.
103. Zugno AI, Pacheco FD, Budni J, de Oliveira MB, Canever L, Heylmann AS, et al. Maternal deprivation disrupts mitochondrial energy homeostasis in the brain of rats subjected to ketamine-induced schizophrenia. Metabolic Brain Disease. 2015 Aug 1;30(4):1043–53.
104. Kambe Y, Miyata A. Potential involvement of the mitochondrial unfolded protein response in depressive-like symptoms in mice. Neuroscience Letters. 2015 Feb 19;588:166–71.
105. Martín-Aragón S, Villar Á, Benedí J. Age-dependent effects of esculetin on mood-related behavior and cognition from stressed mice are associated with restoring brain antioxidant status. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2016 Feb 4;65:1–16.
106. Sonei N, Amiri S, Jafarian I, Anoush M, Rahimi-Balaei M, Bergen H, et al. Mitochondrial dysfunction bridges negative affective disorders and cardiomyopathy in socially isolated rats: Pros and cons of fluoxetine. http://dx.doi.org/103109/156229752016114921 8. 2016 Jan 2;18(1):39–53.
107. Ortmann CF, Réus GZ, Ignácio ZM, Abelaira HM, Titus SE, de Carvalho P, et al. Enriched Flavonoid Fraction from Cecropia pachystachya Trécul Leaves Exerts Antidepressant-like Behavior and Protects Brain Against Oxidative Stress in Rats Subjected to Chronic Mild Stress. Neurotoxicity Research. 2016 May 1;29(4):469–83.
108. Rinwa P, Kumar A. Piperine potentiates the protective effects of curcumin against chronic unpredictable stress-induced cognitive impairment and oxidative damage in mice. Brain Research. 2012 Dec 7;1488:38–50.
109. Nollet M, Hicks H, McCarthy AP, Wu H, Möller-Levet CS, Laing EE, et al. REM sleep's unique associations with corticosterone regulation, apoptotic pathways, and behavior in chronic stress in mice. Proc Natl Acad Sci U S A. 2019 Feb 12;116(7):2733–42.
110. Bagot RCC, Cates HMM, Purushothaman I, Lorsch ZSS, Walker DMM, Wang J, et al. Circuit-wide Transcriptional Profiling Reveals Brain Region-Specific Gene Networks Regulating Depression Susceptibility. Neuron. 2016 Jun 1;90(5):969–83.
111. von Ziegler LM, Floriou-Servou A, Waag R, Das Gupta RR, Sturman O, Gapp K, et al. Multiomic profiling of the acute stress response in the mouse hippocampus. Nature Communications 2022 13:1. 2022 Apr 5;13(1):1–20.
112. Lombard J. Autism: a mitochondrial disorder? Medical Hypotheses. 1998 Jun;50(6):497–500.
113. Siddiqui MF, Elwell C, Johnson MH. Mitochondrial Dysfunction in Autism Spectrum Disorders. Autism-Open Access. 2016;6(4).
114. Griffiths KK, Levy RJ. Evidence of Mitochondrial Dysfunction in Autism: Biochemical Links, Genetic-Based Associations, and Non-Energy-Related Mechanisms. Oxid Med Cell Longev. 2017;2017:4314025.
115. Rose S, Niyazov DM, Rossignol DA, Goldenthal M, Kahler SG, Frye RE. Clinical and Molecular Characteristics of Mitochondrial Dysfunction in Autism Spectrum Disorder. Vol. 22, Molecular Diagnosis and Therapy. Springer International Publishing; 2018. p. 571–93.
116. Varga NÁ, Pentelényi K, Balicza P, Gézsi A, Reményi V, Hársfalvi V, et al. Mitochondrial dysfunction and autism: Comprehensive genetic analyses of children with autism and mtDNA deletion. Behavioral and Brain Functions. 2018;
117. Castora FJ. Mitochondrial function and abnormalities implicated in the pathogenesis of ASD. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2019 Jun 8;92:83–108.
118. Citrigno L, Muglia M, Qualtieri A, Spadafora P, Cavalcanti F, Pioggia G, et al. The Mitochondrial Dysfunction Hypothesis in Autism Spectrum Disorders: Current Status and Future Perspectives. International Journal of Molecular Sciences [Internet]. 2020 Aug 12 [cited 2020 Sep 4];21(16):5785. Available from: https://www.mdpi.com/1422-0067/21/16/5785
119. Frye RE. Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and Targeted Treatments. Vol. 35, Seminars in Pediatric Neurology. W.B. Saunders; 2020. p. 100829.
120. Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, et al. Mitochondrial dysfunction in autism. JAMA - Journal of the American Medical Association. 2010 Dec 1;304(21):2389–96.
121. Valiente-Pallejà A, Torrell H, Muntané G, Cortés MJ, Martínez-Leal R, Abasolo N, et al. Genetic and clinical evidence of mitochondrial dysfunction in autism spectrum disorder and intellectual disability. Human Molecular Genetics. 2018 Mar 1;27(5):891–900.
122. Gu F, Chauhan V, Kaur K, Brown WT, LaFauci G, Wegiel J, et al. Alterations in mitochondrial DNA copy number and the activities of electron transport chain complexes and pyruvate dehydrogenase in the frontal cortex from subjects with autism. Transl Psychiatry. 2013 Sep 3;3(9).
123. Chen S, Li Z, He Y, Zhang F, Li H, Liao Y, et al. Elevated mitochondrial DNA copy number in peripheral blood cells is associated with childhood autism. BMC Psychiatry. 2015 Dec 12;15(1):50.
124. Weissman JR, Kelley RI, Bauman ML, Cohen BH, Murray KF, Mitchell RL, et al. Mitochondrial disease in autism spectrum disorder patients: A cohort analysis. PLoS ONE. 2008;
125. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Molecular Psychiatry. 2012 Mar 25;17(3):290–314.
126. Tang G, Gutierrez Rios P, Kuo SH, Akman HO, Rosoklija G, Tanji K, et al. Mitochondrial abnormalities in temporal lobe of autistic brain. Neurobiology of Disease. 2013 Jun 1;54:349–61.

127. Khemakhem AM, Frye RE, El-Ansary A, Al-Ayadhi L, Bacha A Ben. Novel biomarkers of metabolic dysfunction is autism spectrum disorder: potential for biological diagnostic markers. Metabolic Brain Disease. 2017 Dec 1;32(6):1983–97.
128. Hassan H, Zakaria F, Makpol S, Karim NA. A Link between Mitochondrial Dysregulation and Idiopathic Autism Spectrum Disorder (ASD): Alterations in Mitochondrial Respiratory Capacity and Membrane Potential. Current Issues in Molecular Biology. 2021 Dec 16;43(3):2238–52.
129. Pecorelli A, Ferrara F, Messano N, Cordone V, Schiavone ML, Cervellati F, et al. Alterations of mitochondrial bioenergetics, dynamics, and morphology support the theory of oxidative damage involvement in autism spectrum disorder. FASEB Journal. 2020 Apr 4;34(5):6521–38.
130. Frye RE, Lionnard L, Singh I, Karim MA, Chajra H, Frechet M, et al. Mitochondrial morphology is associated with respiratory chain uncoupling in autism spectrum disorder. Translational Psychiatry. 2021 Dec 13;11(1):527.
131. Ginsberg MR, Rubin RA, Falcone T, Ting AH, Natowicz MR. Brain Transcriptional and Epigenetic Associations with Autism. PLoS ONE. 2012 Sep 12;7(9).
132. Zeidán-Chuliá F, de Oliveira BHN, Salmina AB, Casanova MF, Gelain DP, Noda M, et al. Altered expression of Alzheimer's disease-related genes in the cerebellum of autistic patients: a model for disrupted brain connectome and therapy. Cell Death Dis. 2014 May 22;5(5):e1250–e1250.
133. Aldosary M, Al-Bakheet A, Al-Dhalaan H, Almass R, Alsagob M, Al-Younes B, et al. Rett Syndrome, a Neurodevelopmental Disorder, Whole-Transcriptome, and Mitochondrial Genome Multiomics Analyses Identify Novel Variations and Disease Pathways. OMICS: A Journal of Integrative Biology. 2020 Mar 1;24(3):160–71.
134. Forés-Martos J, Catalá-López F, Sánchez-Valle J, Ibáñez K, Tejero H, Palma-Gudiel H, et al. Transcriptomic metaanalyses of autistic brains reveals shared gene expression and biological pathway abnormalities with cancer. Molecular Autism. 2019 Apr 8;10(1):17.
135. Mahony C, O'ryan C. Convergent canonical pathways in autism spectrum disorder from proteomic, transcriptomic and DNA methylation data [Internet]. Vol. 22, International Journal of Molecular Sciences. 2021. p. 10757. Available from: https://www.mdpi.com/1422-0067/22/19/10757
136. Bjørklund G, Meguid NA, El-Bana MA, Tinkov AA, Saad K, Dadar M, et al. Oxidative Stress in Autism Spectrum Disorder. Molecular Neurobiology. 2020 May 1;57(5):2314–32.
137. Hu T, Dong Y, He C, Zhao M, He Q. The Gut Microbiota and Oxidative Stress in Autism Spectrum Disorders (ASD). Oxidative Medicine and Cellular Longevity. 2020;2020.
138. Chen L, Shi XJ, Liu H, Mao X, Gui LN, Wang H, et al. Oxidative stress marker aberrations in children with autism spectrum disorder: a systematic review and meta-analysis of 87 studies (N =9109). Translational Psychiatry 2021 11:1. 2021 Jan 5;11(1):1–10.
139. Manivasagam T, Arunadevi S, Essa MM, SaravanaBabu C, Borah A, Thenmozhi AJ, et al. Role of Oxidative Stress and Antioxidants in Autism. Advances in Neurobiology. 2020;24:193–206.
140. Pangrazzi L, Balasco L, Bozzi Y. Oxidative Stress and Immune System Dysfunction in Autism Spectrum Disorders. International Journal of Molecular Sciences 2020, Vol 21, Page 3293. 2020 May 6;21(9):3293.
141. Thorsen M. Oxidative stress, metabolic and mitochondrial abnormalities associated with autism spectrum disorder. In: Progress in Molecular Biology and Translational Science [Internet]. Elsevier B.V.; 2020 [cited 2020 Sep 29]. p. 331–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1877117320300624
142. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental trajectories of early life stress and trauma: A narrative review on neurobiological aspects beyond stress system dysregulation. Frontiers in Psychiatry. 2019;10(MAR):118.
143. Berardelli I, Serafini G, Cortese N, Fiaschè F, O'connor RC, Pompili M. The Involvement of Hypothalamus–Pituitary–Adrenal (HPA) Axis in Suicide Risk. Brain Sciences 2020, Vol 10, Page 653. 2020 Sep 21;10(9):653.
144. Ceruso A, Martínez-Cengotitabengoa M, Peters-Corbett A, Diaz-Gutierrez MJ, Martínez-Cengotitabengoa M. Alterations of the HPA Axis Observed in Patients with Major Depressive Disorder and Their Relation to Early Life Stress: A Systematic Review. Neuropsychobiology. 2020 Nov 1;79(6):417–27.
145. Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science [Internet]. 2018 [cited 2019 Jun 5];359(6376):693. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29439242
146. Pervanidou P, Chrousos GP. Early-Life Stress: From Neuroendocrine Mechanisms to Stress-Related Disorders. Hormone Research in Paediatrics [Internet]. 2018 Jul 1 [cited 2021 Nov 12];89(5):372–9. Available from: https://www.karger.com/Article/FullText/488468
147. Cotella EM, Morano RL, Wulsin AC, Martelle SM, Lemen P, Fitzgerald M, et al. Lasting Impact of Chronic Adolescent Stress and Glucocorticoid Receptor Selective Modulation in Male and Female Rats. Psychoneuroendocrinology. 2020 Feb 1;112:104490.
148. Midzak A, Papadopoulos V. Adrenal mitochondria and steroidogenesis: From individual proteins to functional protein assemblies. Frontiers in Endocrinology. 2016 Jul 29;7(JUL):106.
149. Ridout KK, Khan M, Ridout SJ. Adverse Childhood Experiences Run Deep: Toxic Early Life Stress, Telomeres, and Mitochondrial DNA Copy Number, the Biological Markers of Cumulative Stress. BioEssays. 2018 Sep 1;40(9):1800077.
150. Kokkinopoulou I, Moutsatsou P. Mitochondrial Glucocorticoid Receptors and Their Actions. International Journal of Molecular Sciences 2021, Vol 22, Page 6054. 2021 Jun 3;22(11):6054.
151. Finsterwald C, Alberini CM. Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: from adaptive responses to psychopathologies. Neurobiol Learn Mem. 2014;0:17.

152. Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, Falke C, et al. Dynamic regulation of mitochondrial function by glucocorticoids. Proc Natl Acad Sci U S A. 2009 Mar 3;106(9):3543–8.
153. He Y, Zhang L, Zhu Z, Xiao A, Yu H, Gan X. Blockade of cyclophilin D rescues dexamethasone-induced oxidative stress in gingival tissue. PLOS ONE. 2017 Mar 1;12(3):e0173270.
154. Tome ME, Lee K, Jaramillo MC, Briehl MM. Mitochondria are the primary source of the H 2O 2 signal for glucocorticoid-induced apoptosis of lymphoma cells. Experimental and Therapeutic Medicine. 2012 Aug 1;4(2):237–42.
155. Picard M, Juster RP, McEwen BS. Mitochondrial allostatic load puts the "gluc" back in glucocorticoids. Nature Reviews Endocrinology. 2014 May 25;10(5):303–10.
156. Lapp HE, Bartlett AA, Hunter RG. Stress and glucocorticoid receptor regulation of mitochondrial gene expression. Journal of Molecular Endocrinology. 2019 Feb 1;62(2):R121–8.
157. Lee SR, Kim HK, Song IS, Youm J, Dizon LA, Jeong SH, et al. Glucocorticoids and their receptors: Insights into specific roles in mitochondria. Progress in Biophysics and Molecular Biology. 2013;112(1–2):44–54.
158. Dempster KS, O'Leary DD, MacNeil AJ, Hodges GJ, Wade TJ. Linking the hemodynamic consequences of adverse childhood experiences to an altered HPA axis and acute stress response. Brain, Behavior, and Immunity. 2021;93:254–63.
159. Cai N, Chang S, Li Y, Li Q, Hu J, Liang J, et al. Molecular signatures of major depression. Current Biology. 2015 May 4;25(9):1146–56.
160. Picard M, McManus MJ, Gray JD, Nasca C, Moffat C, Kopinski PK, et al. Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress. Proc Natl Acad Sci U S A. 2015 Dec 1;112(48):E6614–23.
161. Gimsa U, Kanitz E, Otten W, Ibrahim SM. Behavior and stress reactivity in mouse strains with mitochondrial DNA variations. Ann N Y Acad Sci. 2009;1153:131–8.
162. Ridout KK, Coe JL, Parade SH, Marsit CJ, Kao HT, Porton B, et al. Molecular markers of neuroendocrine function and mitochondrial biogenesis associated with early life stress. Psychoneuroendocrinology. 2020 Jun 1;116:104632.
163. Marotta R, Risoleo MC, Messina G, Parisi L, Carotenuto M, Vetri L, et al. The Neurochemistry of Autism. Brain Sciences. 2020 Mar 13;10(3):1–18.
164. Nakamura K, Sekine Y, Ouchi Y, Tsujii M, Yoshikawa E, Futatsubashi M, et al. Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. Archives of General Psychiatry. 2010 Jan 1;67(1):59–68.
165. DiCarlo GE, Aguilar JI, Matthies HJG, Harrison FE, Bundschuh KE, West A, et al. Autism-linked dopamine transporter mutation alters striatal dopamine neurotransmission and dopamine-dependent behaviors. Journal of Clinical Investigation. 2019 Aug 1;129(8):3407–19.
166. Essa MM, Braidy N, Vijayan KR, Subash S, Guillemin GJ. Excitotoxicity in the pathogenesis of autism. Vol. 23, Neurotoxicity Research. Springer; 2013. p. 393–400.
167. Tordjman S, Anderson GM, Kermarrec S, Bonnot O, Geoffray MM, Brailly-Tabard S, et al. Altered circadian patterns of salivary cortisol in low-functioning children and adolescents with autism. Psychoneuroendocrinology. 2014 Dec 1;50:227–45.
168. Muscatello RA, Corbett BA. Comparing the effects of age, pubertal development, and symptom profile on cortisol rhythm in children and adolescents with autism spectrum disorder. Autism Research. 2018 Jan 1;11(1):110–20.
169. Tomarken AJ, Han GT, Corbett BA. Temporal patterns, heterogeneity, and stability of diurnal cortisol rhythms in children with autism spectrum disorder. Psychoneuroendocrinology. 2015 Dec 1;62:217–26.
170. Ogawa S, Lee YA, Yamaguchi Y, Shibata Y, Goto Y. Associations of acute and chronic stress hormones with cognitive functions in autism spectrum disorder. Neuroscience. 2017 Feb 20;343:229–39.
171. Spratt EG, Nicholas JS, Brady KT, Carpenter LA, Hatcher CR, Meekins KA, et al. Enhanced cortisol response to stress in children in autism. Journal of Autism and Developmental Disorders. 2012 Jan 22;42(1):75–81.
172. Patel N, Crider A, Pandya CD, Ahmed AO, Pillai A. Altered mRNA Levels of Glucocorticoid Receptor, Mineralocorticoid Receptor, and Co-Chaperones (FKBP5 and PTGES3) in the Middle Frontal Gyrus of Autism Spectrum Disorder Subjects. Molecular Neurobiology. 2016 May 26;53(4):2090–9.
173. Bozkurt H, Çim A, Şimşek Ş, Şahin S. Association between the rs1360780 polymorphism in FKBP5 gene and serum cortisol levels in children with autism spectrum disorder. 2021;
174. Yang T, Liu J, Zhang Y, Zhang Q, Shangguan L, Li Z, et al. Coping style predicts sense of security and mediates the relationship between autistic traits and social anxiety: Moderation by a polymorphism of the FKBP5 gene. Behavioural Brain Research. 2021 Apr 23;404:113142.
175. Wong ASK, Burns S, Woodruff E. Examining the impact of social stressor stimuli in eliciting physiological reactivity in children and adolescents with autism spectrum disorder: A systematic review and meta-analysis protocol. 2021;
176. Dutcher EG, Pama EAC, Lynall ME, Khan S, Clatworthy MR, Robbins TW, et al. Early-life stress and inflammation: A systematic review of a key experimental approach in rodents. Brain Neurosci Adv. 2020 Dec 28;4:2398212820978049.
177. Catale C, Gironda S, Iacono L Lo, Carola V. Microglial Function in the Effects of Early-Life Stress on Brain and Behavioral Development. Journal of Clinical Medicine 2020, Vol 9, Page 468. 2020 Feb 8;9(2):468.
178. Cao P, Chen C, Liu A, Shan Q, Zhu X, Jia C, et al. Early-life inflammation promotes depressive symptoms in adolescence via microglial engulfment of dendritic spines. Neuron. 2021 Aug 18;109(16):2573-2589.e9.
179. Bekhbat M, Howell PA, Rowson SA, Kelly SD, Tansey MG, Neigh GN. Chronic adolescent stress sex-specifically alters central and peripheral neuro-immune reactivity in rats. Brain, Behavior, and Immunity. 2019 Feb 1;76:248–57.

180. Brown M, Worrell C, Pariante CM. Inflammation and early life stress: An updated review of childhood trauma and inflammatory markers in adulthood. Pharmacology Biochemistry and Behavior. 2021 Dec 1;211:173291.
181. Lurie DI. An Integrative Approach to Neuroinflammation in Psychiatric disorders and Neuropathic Pain. J Exp Neurosci. 2018 Aug 13;12:1179069518793639.
182. Furtado M, Katzman MA. Examining the role of neuroinflammation in major depression. Psychiatry Research. 2015 Sep 30;229(1–2):27–36.
183. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, et al. Neuroinflammation and depression: A review. European Journal of Neuroscience. 2021 Jan 1;53(1):151–71.
184. Petrelli F, Pucci L, Bezzi P. Astrocytes and microglia and their potential link with autism spectrum disorders. Frontiers in Cellular Neuroscience. 2016 Feb 12;10(FEB).
185. Gładysz D, Krzywdzińska A, Hozyasz KK. Immune Abnormalities in Autism Spectrum Disorder—Could They Hold Promise for Causative Treatment? Vol. 55, Molecular Neurobiology. Humana Press Inc.; 2018. p. 6387–435.
186. Mekori-Domachevsky E, Segal-Gavish H, Gross R. Neuroinflammation and neuroprotection in schizophrenia and autism spectrum disorder. In: Neuroprotection in Autism, Schizophrenia and Alzheimer's disease. Elsevier; 2019. p. 101–22.
187. Liao X, Liu Y, Fu X, Li Y. Postmortem Studies of Neuroinflammation in Autism Spectrum Disorder: a Systematic Review [Internet]. Vol. 57, Molecular Neurobiology. Springer; 2020 [cited 2021 Feb 14]. p. 3424–38. Available from: https://doi.org/10.1007/s12035-020-01976-5
188. Liao X, Yang J, Wang H, Li Y. Microglia mediated neuroinflammation in autism spectrum disorder. Journal of Psychiatric Research [Internet]. 2020 Nov 1 [cited 2021 Feb 14];130:167–76. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022395620308785
189. Liao X, Li Y. Nuclear Factor Kappa B in Autism Spectrum Disorder: A Systematic Review. Vol. 159, Pharmacological Research. Academic Press; 2020. p. 104918.
190. Fatemi SH, Folsom TD, Reutiman TJ, Lee S. Expression of astrocytic markers aquaporin 4 and connexin 43 is altered in brains of subjects with autism. Synapse. 2008 Jul;62(7):501.
191. Wegiel J, Kuchna I, Nowicki K, Imaki H, Wegiel J, Marchi E, et al. The neuropathology of autism: Defects of neurogenesis and neuronal migration, and dysplastic changes. Acta Neuropathologica. 2010 Jun;119(6):755–70.
192. Tetreault NA, Hakeem AY, Jiang S, Williams BA, Allman E, Wold BJ, et al. Microglia in the cerebral cortex in autism. Journal of Autism and Developmental Disorders. 2012 Dec 31;42(12):2569–84.
193. Suzuki K, Sugihara G, Ouchi Y, Nakamura K, Futatsubashi M, Takebayashi K, et al. Microglial Activation in Young Adults With Autism Spectrum Disorder. JAMA Psychiatry. 2013 Jan 1;70(1):49–58.
194. Edmonson C, Ziats MN, Rennert OM. Altered glial marker expression in autistic post-mortem prefrontal cortex and cerebellum. Molecular Autism. 2014 Jan 10;5(1):3.
195. Gupta S, Ellis SE, Ashar FN, Moes A, Bader JS, Zhan J, et al. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nature Communications 2014 5:1. 2014 Dec 10;5(1):1–8.
196. Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature. 2011 Jun;474(7351).
197. Laurence JA, Fatemi SH. Glial fibrillary acidic protein is elevated in superior frontal, parietal and cerebellar cortices of autistic subjects. Cerebellum. 2005;4(3):206–10.
198. Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J, et al. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. Biol Psychiatry. 2010 Aug 15;68(4):368–76.
199. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Annals of Neurology. 2005 Jan 1;57(1):67–81.
200. Fetit R, Hillary RF, Price DJ, Lawrie SM. The neuropathology of autism: A systematic review of post-mortem studies of autism and related disorders. Neuroscience & Biobehavioral Reviews. 2021 Oct 1;129:35–62.
201. Pace TWW, Miller AH. Cytokines and Glucocorticoid Receptor Signaling: Relevance to Major Depression. Ann N Y Acad Sci. 2009;1179:86.
202. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Vol. 107, Neuron. Cell Press; 2020. p. 234–56.
203. Bronzuoli MR, Facchinetti R, Ingrassia D, Sarvadio M, Schiavi S, Steardo L, et al. Neuroglia in the autistic brain: evidence from a preclinical model. Molecular Autism. 2018 Dec 27;9(1):1–17.
204. Afridi R, Kim JH, Rahman MH, Suk K. Metabolic Regulation of Glial Phenotypes: Implications in Neuron–Glia Interactions and Neurological Disorders. Frontiers in Cellular Neuroscience. 2020 Feb 11;14:20.
205. Moulson AJ, Squair JW, Franklin RJM, Tetzlaff W, Assinck P. Diversity of Reactive Astrogliosis in CNS Pathology: Heterogeneity or Plasticity? Frontiers in Cellular Neuroscience. 2021 Jul 26;15:284.
206. Saab AS, Tzvetavona ID, Trevisiol A, Baltan S, Dibaj P, Kusch K, et al. Oligodendroglial NMDA Receptors Regulate Glucose Import and Axonal Energy Metabolism. Neuron. 2016 Jul 6;91(1):119–32.
207. Poitelon Y, Kopec AM, Belin S. Myelin Fat Facts: An Overview of Lipids and Fatty Acid Metabolism. Cells. 2020 Mar 27;9(4):812.
208. Babetto E, Wong KM, Beirowski B. A glycolytic shift in Schwann cells supports injured axons. Nature Neuroscience. 2020 Aug 17;1–14.
209. Liddelow SA, Marsh SE, Stevens B. Microglia and Astrocytes in Disease: Dynamic Duo or Partners in Crime? Trends in Immunology. 2020 Sep 1;41(9):820–35.

210. Loving BA, Bruce KD. Lipid and Lipoprotein Metabolism in Microglia. Frontiers in Physiology. 2020 Apr 28;0:393.
211. Chausse B, Kakimoto PA, Kann O. Microglia and lipids: how metabolism controls brain innate immunity. Seminars in Cell & Developmental Biology. 2021 Apr 1;112:137–44.
212. Arcuri C, Mecca C, Bianchi R, Giambanco I, Donato R. The Pathophysiological Role of Microglia in Dynamic Surveillance, Phagocytosis and Structural Remodeling of the Developing CNS. Frontiers in Molecular Neuroscience. 2017 Jun 19;10.
213. Zeidán-Chuliá F, Salmina AB, Malinovskaya NA, Noda M, Verkhratsky A, Moreira JCF. The glial perspective of autism spectrum disorders. Neuroscience & Biobehavioral Reviews. 2014 Jan 1;38:160–72.
214. Galvez-Contreras AY, Zarate-Lopez D, Torres-Chavez AL, Gonzalez-Perez O. Role of Oligodendrocytes and Myelin in the Pathophysiology of Autism Spectrum Disorder. Brain Sciences 2020, Vol 10, Page 951. 2020 Dec 8;10(12):951.
215. Strunecka A, Blaylock R, Patocka J, Strunecky O. Immunoexcitotoxicity as the central mechanism of etiopathology and treatment of autism spectrum disorders: A possible role of fluoride and aluminum. Surgical Neurology International. 2018;9(1):74.
216. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, et al. Microglia Sculpt Postnatal Neural Circuits in an Activity and Complement-Dependent Manner. Neuron. 2012 May 24;74(4):691–705.
217. Bernier LP, York EM, MacVicar BA. Immunometabolism in the Brain: How Metabolism Shapes Microglial Function. Trends in Neurosciences. 2020 Nov 1;43(11):854–69.
218. Lauro C, Limatola C. Metabolic Reprograming of Microglia in the Regulation of the Innate Inflammatory Response. Frontiers in Immunology. 2020 Mar 20;0:493.
219. Zengeler KE, Lukens JR. Innate immunity at the crossroads of healthy brain maturation and neurodevelopmental disorders. Nature Reviews Immunology 2021 21:7. 2021 Jan 21;21(7):454–68.
220. Clarke LE, Barres BA. Emerging roles of astrocytes in neural circuit development. Vol. 14, Nature Reviews Neuroscience. NIH Public Access; 2013. p. 311–21.
221. Sahlender DA, Savtchouk I, Volterra A. What do we know about gliotransmitter release from astrocytes? Vol. 369, Philosophical Transactions of the Royal Society B: Biological Sciences. Royal Society of London; 2014.
222. Pellerin L, Pellegri G, Bittar PG, Charnay Y, Bouras C, Martin JL, et al. Evidence Supporting the Existence of an Activity-Dependent Astrocyte-Neuron Lactate Shuttle. Developmental Neuroscience. 1998 Oct;20(4–5):291–9.
223. Harry GJ, Childers G, Giridharan S, Hernandes IL. An association between mitochondria and microglia effector function: what do we think we know? Neuroimmunology and Neuroinflammation. 2020 Jun 16;7(2):150–65.
224. Fairley LH, Wong JH, Barron AM. Mitochondrial Regulation of Microglial Immunometabolism in Alzheimer's Disease. Frontiers in Immunology. 2021 Feb 25;12.
225. Rose J, Brian C, Woods J, Pappa A, Panayiotidis MI, Powers R, et al. Mitochondrial dysfunction in glial cells: Implications for neuronal homeostasis and survival. Toxicology. 2017 Nov 1;391:109–15.
226. Ye J, Jiang Z, Chen X, Liu M, Li J, Liu N. Electron transport chain inhibitors induce microglia activation through enhancing mitochondrial reactive oxygen species production. Experimental Cell Research. 2016 Jan 15;340(2):315–26.
227. Park J, Choi H, Min JS, Park SJ, Kim JH, Park HJ, et al. Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. Journal of Neurochemistry. 2013 Oct 1;127(2):221–32.
228. Ferger AI, Campanelli L, Reimer V, Muth KN, Merdian I, Ludolph AC, et al. Effects of mitochondrial dysfunction on the immunological properties of microglia. Journal of Neuroinflammation. 2010 Aug 11;7(1):1–10.
229. Tang Y, Le W. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. Mol Neurobiol. 2016 Mar 1;53(2):1181–94.
230. Gimeno-Bayón J, López-López A, Rodríguez MJ, Mahy N. Glucose pathways adaptation supports acquisition of activated microglia phenotype. Journal of Neuroscience Research. 2014 Jun 1;92(6):723–31.
231. Voloboueva LA, Lee SW, Emery JF, Palmer TD, Giffard RG. Mitochondrial protection attenuates inflammation-induced impairment of neurogenesis in vitro and in vivo. Journal of Neuroscience. 2010 Sep 15;30(37):12242–51.
232. Lively S, Schlichter LC. Microglia responses to pro-inflammatory stimuli (LPS, IFNγ+TNFα) and reprogramming by resolving cytokines (IL-4, IL-10). Frontiers in Cellular Neuroscience. 2018 Jul 24;12.
233. Freemerman AJ, Johnson AR, Sacks GN, Milner JJ, Kirk EL, Troester MA, et al. Metabolic reprogramming of macrophages: Glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype. Journal of Biological Chemistry. 2014 Mar 14;289(11):7884–96.
234. Ahmad MH, Rizvi MA, Fatima M, Mondal AC. Pathophysiological implications of neuroinflammation mediated HPA axis dysregulation in the prognosis of cancer and depression. Molecular and Cellular Endocrinology. 2021 Jan 15;520:111093.
235. Heidari A, Rostam-Abadi Y, Rezaei N. The immune system and autism spectrum disorder: association and therapeutic challenges. 2021;
236. Bekhbat M, Mukhara D, Dozmorov MG, Stansfield JC, Benusa SD, Hyer MM, et al. Adolescent stress sensitizes the adult neuroimmune transcriptome and leads to sex-specific microglial and behavioral phenotypes. Neuropsychopharmacology 2021 46:5. 2021 Feb 8;46(5):949–58.
237. Zhu Y, Klomparens EA, Guo S, Geng X. Neuroinflammation caused by mental stress: the effect of chronic restraint stress and acute repeated social defeat stress in mice. Neurological Research. 2019 Aug 3;41(8):762–9.
238. González-Pardo H, Arias JL, Gómez-Lázaro E, Taboada IL, Conejo NM. Sex-Specific Effects of Early Life Stress on Brain Mitochondrial Function, Monoamine Levels and Neuroinflammation. Brain Sciences 2020, Vol 10, Page 447. 2020 Jul 14;10(7):447.

239. Eidson LN, deSousa Rodrigues ME, Johnson MA, Barnum CJ, Duke BJ, Yang Y, et al. Chronic psychological stress during adolescence induces sex-dependent adulthood inflammation, increased adiposity, and abnormal behaviors that are ameliorated by selective inhibition of soluble tumor necrosis factor with XPro1595. Brain, Behavior, and Immunity. 2019 Oct 1;81:305–16.
240. Oginga FO, Magwai T, Shangase KB, Xulu KR, Mpofana T. Early Life Stress and Brain Plasticity: From Alterations of Brain Morphology to Development of Psychopathology. NeuroSci 2022, Vol 3, Pages 104-110. 2022 Feb 3;3(1):104–10.
241. Numakawa T, Odaka H, Adachi N. Actions of Brain-Derived Neurotrophic Factor and Glucocorticoid Stress in Neurogenesis. International Journal of Molecular Sciences 2017, Vol 18, Page 2312. 2017 Nov 2;18(11):2312.
242. Odaka H, Adachi N, Numakawa T. Impact of glucocorticoid on neurogenesis. Neural Regeneration Research. 2017 Jul 1;12(7):1028.
243. Maffezzini C, Calvo-Garrido J, Wredenberg A, Freyer C. Metabolic regulation of neurodifferentiation in the adult brain. Cellular and Molecular Life Sciences [Internet]. 2020 Jan 7 [cited 2020 Jan 28]; Available from: http://link.springer.com/10.1007/s00018-019-03430-9
244. Khacho M, Harris R, Slack RS. Mitochondria as central regulators of neural stem cell fate and cognitive function. Nature Reviews Neuroscience [Internet]. 2019 Jan 21 [cited 2019 Sep 23];20(1):34–48. Available from: http://www.nature.com/articles/s41583-018-0091-3
245. Iwata R, Vanderhaeghen P. Regulatory roles of mitochondria and metabolism in neurogenesis. Current Opinion in Neurobiology. 2021 Aug 1;69:231–40.
246. Licausi F, Hartman NW. Role of mTOR complexes in neurogenesis. Vol. 19, International Journal of Molecular Sciences. MDPI AG; 2018.
247. Beckervordersandforth R. Mitochondrial Metabolism-Mediated Regulation of Adult Neurogenesis. Brain Plasticity. 2017 Jul 11;3(1):73–87.
248. Wullschleger S, Loewith R, Hall MN. TOR Signaling in Growth and Metabolism. Cell. 2006 Feb 10;124(3):471–84.
249. Tang G, Gudsnuk K, Kuo SH, Cotrina ML, Rosoklija G, Sosunov A, et al. Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits. Neuron. 2014 Sep 3;83(5):1131–43.
250. Trifonova EA, Khlebodarova TM, Gruntenko NE. Molecular mechanisms of autism as a form of synaptic dysfunction. Russian Journal of Genetics: Applied Research. 2017 Dec 1;7(8):869–77.
251. Pagani M, Barsotti N, Bertero A, Trakoshis S, Ulysse L, Locarno A, et al. mTOR-related synaptic pathology causes autism spectrum disorder-associated functional hyperconnectivity. Nature Communications 2021 12:1. 2021 Oct 19;12(1):1–15.
252. Guo L, Tian J, Du H. Mitochondrial Dysfunction and Synaptic Transmission Failure in Alzheimer's Disease. J Alzheimers Dis. 2017;57(4):1071–86.
253. Cai Q, Tammineni P. Mitochondrial Aspects of Synaptic Dysfunction in Alzheimer's Disease. J Alzheimers Dis. 2017;57(4):1087–103.
254. Du H, Guo L, Yan SS. Synaptic mitochondrial pathology in Alzheimer's disease. Antioxid Redox Signal. 2012 Jun 15;16(12):1467–75.
255. Li J, Spletter ML, Johnson DA, Wright LS, Svendsen CN, Johnson JA. Rotenone-induced caspase 9/3-independent and -dependent cell death in undifferentiated and differentiated human neural stem cells. Journal of Neurochemistry. 2005 Feb;92(3):462–76.
256. Mendoza E, Miranda-Barrientos JA, Vázquez-Roque RA, Morales-Herrera E, Ruelas A, De la Rosa G, et al. In vivo mitochondrial inhibition alters corticostriatal synaptic function and the modulatory effects of neurotrophins. Neuroscience. 2014 Nov 7;280:156–70.
257. Yu Q, Du F, Douglas JT, Yu H, Yan SS, Yan SF. Mitochondrial Dysfunction Triggers Synaptic Deficits via Activation of p38 MAP Kinase Signaling in Differentiated Alzheimer's Disease Trans-Mitochondrial Cybrid Cells. Journal of Alzheimer's Disease. 2017 Jan 1;59(1):223–39.
258. Wang A, Zou X, Wu J, Ma Q, Yuan N, Ding F, et al. Early-Life Stress Alters Synaptic Plasticity and mTOR Signaling: Correlation With Anxiety-Like and Cognition-Related Behavior. Frontiers in Genetics. 2020 Dec 14;11.
259. Martín-Sánchez A, González-Pardo H, Alegre-Zurano L, Castro-Zavala A, López-Taboada I, Valverde O, et al. Early-life stress induces emotional and molecular alterations in female mice that are partially reversed by cannabidiol. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2022 Apr 20;115:110508.
260. Tracey TJ, Steyn FJ, Wolvetang EJ, Ngo ST. Neuronal Lipid Metabolism: Multiple Pathways Driving Functional Outcomes in Health and Disease. Frontiers in Molecular Neuroscience. 2018 Jan 23;11.
261. Ganesan H, Balasubramanian V, Iyer M, Venugopal A, Subramaniam MD, Cho SGG, et al. mTOR signalling pathway - A root cause for idiopathic autism? BMB Reports. 2019 Jul 31;52(7).
262. Boksha IS, Prokhorova TA, Tereshkina EB, Savushkina OK, Burbaeva GSh. Protein Phosphorylation Signaling Cascades in Autism: The Role of mTOR Pathway. Biochemistry (Moscow) 2021 86:5. 2021 May 20;86(5):577–96.
263. Carroll L, Braeutigam S, Dawes JM, Krsnik Z, Kostovic I, Coutinho E, et al. Autism Spectrum Disorders: Multiple Routes to, and Multiple Consequences of, Abnormal Synaptic Function and Connectivity. Neuroscientist. 2021 Feb 1;27(1):10–29.
264. Cowan M, Petri WA, Jr. Microglia: Immune Regulators of Neurodevelopment. Frontiers in Immunology. 2018 Nov 7;9(NOV):2576.
265. Ohta K ichi, Suzuki S, Warita K, Sumitani K, Tenkumo C, Ozawa T, et al. The effects of early life stress on the excitatory/inhibitory balance of the medial prefrontal cortex. Behavioural Brain Research. 2020 Feb 3;379:112306.

266. Hyer MM, Shaw GA, Goswamee P, Dyer SK, Burns CM, Soriano E, et al. Chronic adolescent stress causes sustained impairment of cognitive flexibility and hippocampal synaptic strength in female rats. Neurobiology of Stress. 2021 May 1;14:100303.
267. Deutschmann AU, Kirkland JM, Briand LA. Adolescent social isolation induced alterations in nucleus accumbens glutamate signalling. Addiction Biology. 2021;e13077.
268. Xu H, Wang J, Jing H, Ellenbroek B, Shao F, Wang W. mPFC GABAergic transmission mediated the role of BDNF signaling in cognitive impairment but not anxiety induced by adolescent social stress. Neuropharmacology. 2021 Feb 15;184:108412.
269. Oswald LM, Dunn KE, Seminowicz DA, Storr CL. Early Life Stress and Risks for Opioid Misuse: Review of Data Supporting Neurobiological Underpinnings. Journal of Personalized Medicine 2021, Vol 11, Page 315. 2021 Apr 19;11(4):315.
270. Bonapersona V, Joëls M, Sarabdjitsingh RA. Effects of early life stress on biochemical indicators of the dopaminergic system: A 3 level meta-analysis of rodent studies. Neuroscience & Biobehavioral Reviews. 2018 Dec 1;95:1–16.
271. Adjimann TS, Argañaraz C V., Soiza-Reilly M. Serotonin-related rodent models of early-life exposure relevant for neurodevelopmental vulnerability to psychiatric disorders. Translational Psychiatry 2021 11:1. 2021 May 11;11(1):1–23.
272. Averill LA, Abdallah CG, Fenton LR, Fasula MK, Jiang L, Rothman DL, et al. Early life stress and glutamate neurotransmission in major depressive disorder. European Neuropsychopharmacology. 2020 Jun 1;35:71–80.
273. Oswald LM, Wand GS, Kuwabara H, Wong DF, Zhu S, Brasic JR. History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. Psychopharmacology (Berl). 2014 Jan 22;231(12):2417–33.
274. Pruessner JC, Champagne F, Meaney MJ, Dagher A. Dopamine Release in Response to a Psychological Stress in Humans and Its Relationship to Early Life Maternal Care: A Positron Emission Tomography Study Using [11C]Raclopride. Journal of Neuroscience. 2004 Mar 17;24(11):2825–31.
275. Underwood MD, Kassir SA, Bakalian MJ, Galfalvy H, Dwork AJ, Mann JJ, et al. Serotonin receptors and suicide, major depression, alcohol use disorder and reported early life adversity. Translational Psychiatry 2018 8:1. 2018 Dec 14;8(1):1–15.
276. Pompili M, Serafini G, Innamorati M, Möller-Leimkühler AM, Giupponi G, Girardi P, et al. The hypothalamic-pituitary-adrenal axis and serotonin abnormalities: a selective overview for the implications of suicide prevention. European Archives of Psychiatry and Clinical Neuroscience 2010 260:8. 2010 Feb 20;260(8):583–600.
277. Lee EJ, Choi SY, Kim E. NMDA receptor dysfunction in autism spectrum disorders. Current Opinion in Pharmacology Feb 1, 2015 p. 8–13.
278. Vieira MM, Jeong J, Roche KW. The role of NMDA receptor and neuroligin rare variants in synaptic dysfunction underlying neurodevelopmental disorders. Current Opinion in Neurobiology. 2021 Aug 1;69:93–104.
279. Yang P, Chang CL. Glutamate-mediated signaling and autism spectrum disorders: emerging treatment targets. Curr Pharm Des. 2014 Sep 16;20(32):5186–93.
280. Zheng Z, Zhu T, Qu Y, Mu D. Blood Glutamate Levels in Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. PLOS ONE. 2016 Jul 1;11(7):e0158688.
281. Bjørklund G, Tinkov AA, Hosnedlová B, Kizek R, Ajsuvakova OP, Chirumbolo S, et al. The role of glutathione redox imbalance in autism spectrum disorder: A review. Free Radical Biology and Medicine [Internet]. 2020 Nov 20 [cited 2020 Dec 7];160:149–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0891584920311539
282. Kawada K, Kuramoto N, Mimori S. Possibility that the Onset of Autism Spectrum Disorder is Induced by Failure of the Glutamine-Glutamate Cycle. Current Molecular Pharmacology. 2020 Mar 19;13.
283. László A, Horváth E, Eck E, Fekete M. Serum serotonin, lactate and pyruvate levels in infantile autistic children. Clin Chim Acta. 1994;229(1–2):205–7.
284. Pagan C, Delorme R, Callebert J, Goubran-Botros H, Amsellem F, Drouot X, et al. The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectrum disorders. Transl Psychiatry. 2014 Jan 1;4(11).
285. Aaron E, Montgomery A, Ren X, Guter S, Anderson G, Carneiro AMD, et al. Whole Blood Serotonin Levels and Platelet 5-HT 2A Binding in Autism Spectrum Disorder. J Autism Dev Disord. 2019;49(6).
286. Muller CL, Anacker AMJ, Veenstra-VanderWeele J. The serotonin system in autism spectrum disorder: From biomarker to animal models. Neuroscience. 2016;321:24–41.
287. Daly E, D. Tricklebank M, Wichers R. Neurodevelopmental roles and the serotonin hypothesis of autism spectrum disorder. In: The Serotonin System. Elsevier; 2019. p. 23–44.
288. Pavăl D. A Dopamine Hypothesis of Autism Spectrum Disorder. Developmental Neuroscience. 2017 Sep 1;39(5):355–60.
289. Cavalcanti-de-Albuquerque JP, de-Souza-Ferreira E, de Carvalho DP, Galina A. Coupling of GABA Metabolism to Mitochondrial Glucose Phosphorylation. Neurochemical Research. 2021 Oct 8;1–11.
290. Aldana BI, Zhang Y, Jensen P, Chandrasekaran A, Christensen SK, Nielsen TT, et al. Glutamate-glutamine homeostasis is perturbed in neurons and astrocytes derived from patient iPSC models of frontotemporal dementia. Molecular Brain. 2020 Sep 14;13(1):125.
291. Johnson SC, Kayser EB, Bornstein R, Stokes J, Bitto A, Park KY, et al. Regional metabolic signatures in the Ndufs4(KO) mouse brain implicate defective glutamate/α-ketoglutarate metabolism in mitochondrial disease. Molecular Genetics and Metabolism. 2020 Jun 1;130(2):118–32.
292. Gardner A, Boles RG. Beyond the serotonin hypothesis: Mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2011 Apr 29;35(3):730–43.
293. de la Fuente C, Burke DG, Eaton S, Heales SJR. Inhibition of neuronal mitochondrial complex I or lysosomal glucocerebrosidase is associated with increased dopamine and serotonin turnover. Neurochemistry International. 2017 Oct 1;109:94–100.

294. Fanibunda SE, Deb S, Maniyadath B, Tiwari P, Ghai U, Gupta S, et al. Serotonin regulates mitochondrial biogenesis and function in rodent cortical neurons via the 5-HT2A receptor and SIRT1–PGC-1α axis. Proc Natl Acad Sci U S A. 2019 May 28;166(22):11028–37.
295. Sterky FH, Hoffman AF, Milenkovic D, Bao B, Paganelli A, Edgar D, et al. Altered dopamine metabolism and increased vulnerability to MPTP in mice with partial deficiency of mitochondrial complex I in dopamine neurons. Human Molecular Genetics. 2012 Mar 1;21(5):1078–89.
296. Panes J, Wendt A, Ramirez-Molina O, Castro P, Fuentealba J. Deciphering the role of PGC-1 in neurological disorders: From mitochondrial dysfunction to synaptic failure. Vol. 17, Neural Regeneration Research. Wolters Kluwer -- Medknow Publications; 2022. p. 237–45.
297. Ben-Shachar D. The bimodal mechanism of interaction between dopamine and mitochondria as reflected in Parkinson's disease and in schizophrenia. Journal of Neural Transmission. 2020;127(2):159–68.
298. Brenner-Lavie H, Klein E, Zuk R, Gazawi H, Ljubuncic P, Ben-Shachar D. Dopamine modulates mitochondrial function in viable SH-SY5Y cells possibly via its interaction with complex I: Relevance to dopamine pathology in schizophrenia. Biochimica et Biophysica Acta - Bioenergetics. 2008 Feb 1;1777(2):173–85.
299. Burbulla LF, Song P, Mazzulli JR, Zampese E, Wong YC, Jeon S, et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science (1979). 2017 Sep 22;357(6357):1255–61.
300. Patel AB, De Graaf RA, Mason GF, Kanamatsu T, Rothman DL, Shulman RG, et al. Glutamatergic neurotransmission and neuronal glucose oxidation are coupled during intense neuronal activation. Journal of Cerebral Blood Flow and Metabolism. 2004 Sep 20;24(9):972–85.
301. Sonnay S, Poirot J, Just N, Clerc AC, Gruetter R, Rainer G, et al. Astrocytic and neuronal oxidative metabolism are coupled to the rate of glutamate–glutamine cycle in the tree shrew visual cortex. Glia. 2018 Mar 1;66(3):477–91.
302. Robinson MB, Lee ML, DaSilva S. Glutamate Transporters and Mitochondria: Signaling, Co-compartmentalization, Functional Coupling, and Future Directions. Neurochemical Research. 2020 Mar 1;45(3):526–40.
303. Kiemes A, Davies C, Kempton MJ, Lukow PB, Bennallick C, Stone JM, et al. GABA, Glutamate and Neural Activity: A Systematic Review With Meta-Analysis of Multimodal 1H-MRS-fMRI Studies. Frontiers in Psychiatry. 2021 Mar 8;12:255.
304. McKenna MC. The glutamate-glutamine cycle is not stoichiometric: Fates of glutamate in brain. Journal of Neuroscience Research. 2007 Nov 15;85(15):3347–58.
305. Day PE, Matata B, Elahic M. Re-Visiting Glutamate Toxicity: Implications of Monosodium Glutamate Consumption on Glutamate Metabolism and Metabolic Syndrome. Journal of Endocrinology and Diabetes Mellitus. 2015 Apr 10;3(1):20–31.
306. Lakshminarayanan R, Madhavi S, Sim CPC. Oxidative Polymerization of Dopamine: A High-Definition Multifunctional Coatings for Electrospun Nanofibers - An Overview. In: Dopamine - Health and Disease. InTech; 2018.
307. Mosienko V, Teschemacher AG, Kasparov S. Is L-lactate a novel signaling molecule in the brain? Vol. 35, Journal of Cerebral Blood Flow and Metabolism. Nature Publishing Group; 2015. p. 1069–75.
308. Michelhaugh SK, Guastella AR, Mittal S. Overview of the Kynurenine Pathway of Tryptophan Metabolism. Targeting the Broadly Pathogenic Kynurenine Pathway. 2015 Jan 1;3–9.
309. Scholpa NE, Lynn MK, Corum D, Boger HA, Schnellmann RG. 5-HT1F receptor-mediated mitochondrial biogenesis for the treatment of Parkinson's disease. British Journal of Pharmacology. 2018 Jan 1;175(2):348–58.
310. Weng R, Shen S, Burton C, Yang L, Nie H, Tian Y, et al. Lipidomic profiling of tryptophan hydroxylase 2 knockout mice reveals novel lipid biomarkers associated with serotonin deficiency. Anal Bioanal Chem. 2016 Apr 1;408(11):2963–73.
311. Weng R, Shen S, Tian Y, Burton C, Xu X, Liu Y, et al. Metabolomics Approach Reveals Integrated Metabolic Network Associated with Serotonin Deficiency. Scientific Reports 2015 5:1. 2015 Jul 8;5(1):1–13.
312. Molina-Carballo A, Jerez-Calero AE, Muñoz-Hoyos A. Possible Protective Role of Melatonin in Pediatric Infectious Diseases and Neurodevelopmental Pathologies. Journal of Child Science. 2020 Jan 23;10(01):e104–9.
313. Li Y, Hu N, Yang D, Oxenkrug G, Yang Q. Regulating the balance between the kynurenine and serotonin pathways of tryptophan metabolism. The FEBS Journal. 2017 Mar 1;284(6):948–66.
314. Xie N, Zhang L, Gao W, Huang C, Huber PE, Zhou X, et al. NAD+ metabolism: pathophysiologic mechanisms and therapeutic potential. Signal Transduction and Targeted Therapy 2020 5:1. 2020 Oct 7;5(1):1–37.
315. Szalardy L, Klivenyi P, Zadori D, Fulop F, Toldi J, Vecsei L. Mitochondrial Disturbances, Tryptophan Metabolites and Neurodegeneration: Medicinal Chemistry Aspects. Current Medicinal Chemistry. 2012;19(13):1899–920.
316. Castro-Portuguez R, Sutphin GL. Kynurenine pathway, NAD+ synthesis, and mitochondrial function: Targeting tryptophan metabolism to promote longevity and healthspan. Experimental Gerontology. 2020 Apr 1;132:110841.
317. Savino R, Carotenuto M, Polito AN, Di Noia S, Albenzio M, Scarinci A, et al. Analyzing the Potential Biological Determinants of Autism Spectrum Disorder: From Neuroinflammation to the Kynurenine Pathway. Brain Sciences 2020, Vol 10, Page 631. 2020 Sep 11;10(9):631.
318. EVANSON NK, HERMAN JP. Role of Paraventricular Nucleus Glutamate Signaling in Regulation of HPA Axis Stress Responses. Interdisciplinary Information Sciences. 2015;21(3):253–60.
319. Mathew SJ, Coplan JD, Smith ELP, Schoepp DD, Rosenblum LA, Gorman JM. Glutamate—Hypothalamic-Pituitary-Adrenal Axis Interactions: Implications for Mood and Anxiety Disorders. CNS Spectrums. 2001;6(7):555–64.
320. Herman JP, Mueller NK, Figueiredo H. Role of GABA and Glutamate Circuitry in Hypothalamo-Pituitary-Adrenocortical Stress Integration. Ann N Y Acad Sci. 2004 Jun 1;1018(1):35–45.

321. Gulyaeva N V. Glucocorticoid Regulation of the Glutamatergic Synapse: Mechanisms of Stress-Dependent Neuroplasticity. Journal of Evolutionary Biochemistry and Physiology 2021 57:3. 2021 Jul 1;57(3):564–76.
322. Sbrini G, Brivio P, Peeva PM, Todiras M, Bader M, Alenina N, et al. The Absence of Serotonin in the Brain Alters Acute Stress Responsiveness by Interfering With the Genomic Function of the Glucocorticoid Receptors. Frontiers in Cellular Neuroscience. 2020 Jun 1;14:128.
323. Grino M, Guillaume V, Caslanas E, Boudouresque F, Conte-Devolx B, Oliver C. Effect of passive immunization against corticotropin-releasing factor (CRF) on the postadrenalectomy changes of CRF binding sites in the rat anterior pituitary gland. Neuroendocrinology. 1987;45(6):492–7.
324. López JF, Chalmers DT, Little KY, Watson SJ. Regulation of serotonin(1A), glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: Implications for the neurobiology of depression. Biological Psychiatry. 1998 Apr 15;43(8):547–73.
325. Oswald LM, Wong DF, McCaul M, Zhou Y, Kuwabara H, Choi L, et al. Relationships Among Ventral Striatal Dopamine Release, Cortisol Secretion, and Subjective Responses to Amphetamine. Neuropsychopharmacology 2005 30:4. 2005 Feb 9;30(4):821–32.
326. DeRosse P, Barber AD. Overlapping Neurobiological Substrates for Early-Life Stress and Resilience to Psychosis. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2021 Feb 1;6(2):144–53.
327. Lopez SA, Flagel SB. A proposed role for glucocorticoids in mediating dopamine-dependent cue-reward learning. https://doi.org/101080/1025389020201768240. 2020;24(2):154–67.
328. Bandelow B, Bandelow B. Current and Novel Psychopharmacological Drugs for Anxiety Disorders. Advances in Experimental Medicine and Biology. 2020;1191:347–65.
329. Wierońska JM, Stachowicz K, Nowak G, Pilc A. The Loss of Glutamate-GABA Harmony in Anxiety Disorders. Anxiety Disorders. 2011 Aug 1;
330. Ramos-Prats A, Kölldorfer J, Paolo E, Zeidler M, Schmid G, Ferraguti F. An appraisal of the influence of the metabotropic glutamate 5 (mglu5) receptor on sociability and anxiety. Frontiers in Molecular Neuroscience. 2019 Feb 12;12:30.
331. Dogra S, Conn PJ. Targeting metabotropic glutamate receptors for the treatment of depression and other stress-related disorders. Neuropharmacology. 2021 Sep 15;196:108687.
332. Murray SL, Holton KF. Post-traumatic stress disorder may set the neurobiological stage for eating disorders: A focus on glutamatergic dysfunction. Appetite. 2021 Dec 1;167:105599.
333. Mihov Y, Treyer V, Akkus F, Toman E, Milos G, Ametamey SM, et al. Metabotropic glutamate receptor 5 in bulimia nervosa. Scientific Reports 2020 10:1. 2020 Apr 14;10(1):1–10.
334. Oliveira TPD, Gonçalves BDC, Oliveira BS, de Oliveira ACP, Reis HJ, Ferreira CN, et al. Negative Modulation of the Metabotropic Glutamate Receptor Type 5 as a Potential Therapeutic Strategy in Obesity and Binge-Like Eating Behavior. Frontiers in Neuroscience. 2021;15(February):1–13.
335. Hermens DF, Simcock G, Dutton M, Bouças AP, Can AT, Lilley C, et al. Anorexia nervosa, zinc deficiency and the glutamate system: The ketamine option. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2020 Jul 13;101:109921.
336. Karthik S, Sharma LP, Narayanaswamy JC. Investigating the Role of Glutamate in Obsessive-Compulsive Disorder: Current Perspectives. Neuropsychiatric Disease and Treatment. 2020;16:1003.
337. Martinotti G, Chiappini S, Pettorruso M, Mosca A, Miuli A, Di Carlo F, et al. Therapeutic Potentials of Ketamine and Esketamine in Obsessive–Compulsive Disorder (OCD), Substance Use Disorders (SUD) and Eating Disorders (ED): A Review of the Current Literature. Brain Sciences 2021, Vol 11, Page 856. 2021 Jun 27;11(7):856.
338. Roberts-Wolfe D, Kalivas P. Glutamate Transporter GLT-1 as a Therapeutic Target for Substance Use Disorders. CNS & Neurological Disorders - Drug Targets. 2015;14(6):745–56.
339. Liu Y, Zhao J, Guo W. Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. Frontiers in Psychology. 2018 Nov 21;9(NOV):2201.
340. Daut RA, Fonken LK. Circadian regulation of depression: A role for serotonin. Frontiers in Neuroendocrinology. 2019 Jul 1;54:100746.
341. Belujon P, Grace AA. Dopamine System Dysregulation in Major Depressive Disorders. International Journal of Neuropsychopharmacology. 2017 Dec 1;20(12):1036–46.
342. Floris G, Cadeddu R, Bortolato M. The effects of serotonin degradation on psychopathology: role of monoamine oxidase. Handbook of Behavioral Neuroscience. 2020 Jan 1;31:267–78.
343. Gosmann NP, De Abreu Costa M, De Barros Jaeger M, Motta LS, Frozi J, Spanemberg L, et al. Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive, and stress disorders: A 3-level network meta-analysis. PLOS Medicine. 2021 Jun 1;18(6):e1003664.
344. Hou Y wei, Xiong P, Gu X, Huang X, Wang M, Wu J. Association of Serotonin Receptors with Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta-analysis. Current Medical Science 2018 38:3. 2018 Jun 22;38(3):538–51.
345. Mills JG, Thomas SJ, Larkin TA, Deng C. Overeating and food addiction in Major Depressive Disorder: Links to peripheral dopamine. Appetite. 2020 May 1;148:104586.
346. Beeler JA, Burghardt NS. Commentary on Vulnerability and Resilience to Activity-Based Anorexia and the Role of Dopamine. J Exp Neurol. 2021 Mar;2(1):21.
347. Gunther KE, Pérez-Edgar K. Dopaminergic associations between behavioral inhibition, executive functioning, and anxiety in development. Developmental Review. 2021 Jun 1;60:100966.
348. Inozemtseva O, Mejía Núñez E. Executive Dysfunction Associated with Substance Abuse. Dysexecutive Syndromes. 2019;123–42.

 doi:10.20944/preprints202205.0281.v1

349. Sigfusdottir ID, Kristjansson AL, Thorlindsson T, Allegrante JP. Stress and adolescent well-being: the need for an interdisciplinary framework. Health Promotion International. 2017 Dec 1;32(6):1081–90.
350. Targum SD, Nemeroff CB. The Effect of Early Life Stress on Adult Psychiatric Disorders. Innovations in Clinical Neuroscience. 2019 Jan 1;16(1–2):35.
351. Rahman MH, Suk K. Mitochondrial Dynamics and Bioenergetic Alteration During Inflammatory Activation of Astrocytes. Vol. 12, Frontiers in Aging Neuroscience. Frontiers Media S.A.; 2020. p. 459.