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Maternal inflammation during pregnancy and offspring brain development: the role of mitochondria

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Abstract

The association between maternal immune activation (MIA) during pregnancy and risk for offspring neuropsychiatric disorders has been increasingly recognized over the past several years. Among the mechanistic pathways that have been described through which maternal inflammation during pregnancy may affect fetal brain development, the role of mitochondria has received little attention. In the current review the role of mitochondria as a potential mediator of the association between MIA during pregnancy and offspring brain development and risk for psychiatric disorders will be proposed. As a basis for this postulation convergent evidence is presented supporting the obligatory role of mitochondria in brain development, the role of mitochondria as mediators and initiators of inflammatory processes, and evidence of mitochondrial dysfunction in pre-clinical MIA exposure models and human neurodevelopmental disorders. Elucidating the role of mitochondria as a potential mediator of MIA-induced alterations in brain development and neurodevelopmental disease risk may not only provide new insight into the pathophysiology of

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mental health disorders that have their origins in exposure to infection/immune activation during pregnancy but may also offer new therapeutic targets.

Keywords

Maternal immune activation; neurodevelopment; brain; mitochondria; bioenergetic function; oxidative stress

I. Introduction: MIA, mitochondria and brain development

Maternal immune activation (MIA) during pregnancy constitutes a well-established risk factor for offspring neuropsychiatric disorders. A convergent body of epidemiological, preclinical, and prospective observational research supports the embryonic/fetal period of brain development as being particularly susceptible to disorganizing influences. Inflammatory mediators play a key role for both healthy as well as abnormal brain development during the intrauterine period of life, at which time the developing embryo/fetus responds to 'suboptimal' conditions by producing structural and functional changes in cells, tissues and systems that modulate susceptibility for many complex common disorders (*i.e.*, the concept of fetal, or developmental, programming of health and disease risk). Several mechanistic pathways have been described through which maternal inflammation during pregnancy may affect fetal brain development either via direct mechanisms of action like pro-inflammatory cytokine-induced intracellular signaling pathways (1) or indirectly via effects such as priming microglial functioning (2). Mitochondria, which are sensitive to immune alterations, are fundamentally important to many of these processes and others, and thus may mediate some of the inflammatory-related influences on brain development. Furthermore, there is a large body of clinical epidemiological studies that demonstrate the presence of mitochondrial dysfunction in the context of neurodevelopmental disorders, for which maternal infection/immune activation during pregnancy is an established risk factor (see section 3.3 for more details). However, the specific importance of mitochondria in the association between MIA during pregnancy and offspring neurodevelopment has received little attention to date. In this review, we first discuss plasticity of the developing brain and the mitochondrial biology system during fetal life and describe the specific role mitochondria play in all aspects of brain development. We then review literature in support of maternal inflammation during pregnancy altering mitochondrial biology and of mitochondrial biology acting as a potential mediator of the association between MIA during pregnancy and altered offspring brain development and risk for psychiatric disorders. While the evidence in the current review for supporting mitochondrial dysfunction as a mediator of the association between MIA and offspring risk for neurodevelopmental disorders stems from preclinical models inducing MIA by *acute infections*, we note that mitochondrial dysfunction likely also plays an important role in the association between offspring neurodevelopmental disorders and chronic maternal inflammation during pregnancy, which is common in the context of highly prevalent maternal conditions/circumstance like obesity, stress, as well as exposure to environmental toxins (3).We conclude by articulating current knowledge gaps and future research directions.

2. The developing brain: role of mitochondria

Before we discuss how MIA may affect brain development via mitochondrial function (in section 3), in this section we first provide a basic overview of fundamental brain developmental processes and of key aspects of mitochondrial structure and function and then describe the role of mitochondrial function in brain development.

2.1. Overview of human brain development

Comprehensive in-depth descriptions of embryonic and fetal brain development have been provided elsewhere (4, 5)(ref (6) for subcortical development) and are beyond the scope of the current paper, but an overview of the temporal sequence of critical developmental steps is provided here and discussed further in section 2.3. Developmental neurogenesis is the critical process by which neural stem cells (NSCs) differentiate into the distinct cell types that constitute a functioning neural circuitry. This process starts with NSCs in the neural tube expanding their pool via symmetrical division. NSC division then becomes asymmetric, allowing for the generation of a copy of the original NSC and a neural progenitor cell (NPC), that will primarily differentiate into a neuron, or into a glia cell (astrocyte, microglia, or oligodendrocyte) (7–9). While NSCs continue to divide within the ventricular zone, NPCs begin a process of migration in the formation of the cortex (4). The first cells arriving in the cortical plate will form layer VI while later-born cells form progressively more superficial layers (10, 11). After migrating to their final destination, neurons begin to form synaptic connections within the developing brain with rapid acceleration in the third trimester (12). Around mid-gestation, gliogenesis and the process of myelination begins, allowing for more efficient cell-to-cell communication (13). *Ex-utero* synaptogenesis, myelination, and pruning are dominant developmental processes in early postnatal life and perpetuate until at least early adulthood (4).

2.2. Overview of the mitochondrial biology system

Mitochondria are multifunctional double-membrane organelles that regulate several fundamental cellular processes, including the production of over 90% of cellular energy. Through oxidative phosphorylation (OXPHOS), mitochondria oxidize the food we eat, with the air we breathe, to generate cellular energy in the form of ATP (adenosine triphosphate). Through OXPHOS, mitochondria shuttle electrons through the four respiratory complexes (Complex I-IV) of the electron transport chain to generate a proton gradient across the inner mitochondrial membrane (mitochondrial membrane potential (MMP)) that powers the production of ATP. Measurement of any of these collective steps, is referred to as mitochondrial bioenergetic function. Early embryonic and fetal development, especially of the brain, is an energy demanding process (14), and thus, mitochondrial health and the capacity to meet the bioenergetic demands of the cell, place mitochondria central to this process of early development.

Beyond this essential and well-established bioenergetic function, mitochondria are increasingly viewed as *active* regulators of signal transduction in numerous pathways (15), serving an important role in cellular signaling, regulating cell proliferation, differentiation and apoptosis, primarily through the modulation of Ca^{2+} homeostasis,

metabolite availability, cellular redox, and production of reactive oxygen species (ROS) (16–18). While ROS at low levels is now considered a standard signaling molecule (17, 19), when mitochondrial function is impaired, damaging elevations of ROS levels can occur (20), which places mitochondria at the center of cellular production and regulation of oxidative stress (21, 22). Importantly, there is increasing understanding that these layered aspects of mitochondrial function and signaling regulate cell specification in early development, such that mitochondrial activity is a necessary requirement for differentiation in embryonic and neuronal stem cells (as will be discussed below) (23, 24). Furthermore, mitochondria serve as a site of production for various metabolic substrates (25–27) essential for rapid cellular proliferation during embryonic and fetal development.

These many and multi-faceted aspects of mitochondrial function are closely tied to the dynamic form and structure of mitochondria, and to the spatial interaction of these organelles with each other and with other intracellular structures. The approximately 10^2-10^3 mitochondria per cell form dynamic branched networks, and when two or more mitochondrion combine, this is known as fusion, whereas their separation is known as fission (28, 29). These opposing processes (*i.e.,* fission/fusion dynamics) are carefully balanced, serving an important regulatory role in bioenergetic function (30). Furthermore, mitochondrial fission can be used to isolate poorly functioning or damaged mitochondrial components for destruction (mitophagy), and this mitophagy is carefully balanced by the generation of new mitochondria (mitochondrial biogenesis) (31). Mitochondria maintain normal functions through such mitochondrial quality control measures (*i.e.,* mitophagy/biogenesis), and this controlled regulation of mitochondrial content (or cellular density) is necessary to maintain mitochondrial health and to meet the energy demands of the cell. Appropriate mitochondrial density is not only critical at the cellular level, but the spatial distribution and subcellular density of mitochondria within the cell is critical too. The multiple mitochondria per cell are not evenly distributed and are recruited, for example, to energy or calcium demanding subcellular compartments, such as the presynaptic terminal in neurons (32). Perturbations in mitochondrial movement and recruitment to specific sites of the cell can lead to subcellular ATP depletion and interfere with the mitochondrial Ca^{2+} signaling particularly important for neuronal development (discussed further below).

Mitochondria are maternally inherited bacterial endosymbionts, that accordingly, contain their own genome (*i.e.,* mtDNA) that is unique from nuclear DNA (33). The health (*i.e.,* quantity and quality) of mtDNA is critical to success in the earliest stages of development, as levels of mtDNA and ATP production are tied to rates of fertilization and implantation (34, 35), as well as placental and fetal growth (36). mtDNA does not contain histones or telomeres and is located in close proximity to the OXPHOS machinery that produce ROS. As a result mtDNA is more susceptible than nuclear DNA to damage (37–39), and demonstrates a higher intrinsic mutation rate (40). Notably, the mtDNA in oxygen demanding tissues, such as the brain, demonstrate even higher levels of mtDNA damage, of which the immature/developing brain is particularly susceptible, due to its poorly developed scavenging systems and high availability of iron for the catalytic formation of free radicals (41). The accumulation of mtDNA defects impairs mitochondrial bioenergetic function, and such changes are generally stable and amplified over time (42). Thus, prenatal exposures that impact mtDNA quality (*e.g.,* deletion and mutation) provides a plausible mechanism by

which phenotypes of mitochondrial dysfunction may persist over time and confer long term effects on health and disease risk.

We have recently reviewed the evidence to support the developmental plasticity of mitochondrial biology (43), and herein argue that because mitochondria play a fundamental role in all aspects of cellular function in early development, any perturbation to the system, for example, in the context of MIA, will have long-term downstream effects. Thus, in addition to MIA-induced alterations in mitochondrial function during critical processes of brain development having long lasting consequences on its integrity (as reviewed below) programmed alterations in mitochondrial function by prenatal environmental conditions, like inflammation, have the potential to affect functioning of the brain and disease susceptibility across the lifespan (Figure 1).

2.3. Obligatory role for mitochondrial function in brain development

2.3.1. In neurogenesis—Stem cells possess the dual capacity to either self-renew or commit to a specific cell type via differentiation and proliferation. Increasingly, mitochondrial bioenergetic function and fission/fusion dynamics are being recognized as essential regulators of each of these processes. With respect to stem cell renewal capacity, the crucial role of fission/fusion dynamics has been demonstrated via manipulation of fission (mitofusin-1 & −2 (MFN1/2)) and fusion proteins (dynaminrelated protein 1(DRP1)) in uncommitted mouse cells (44). Specifically, loss of MFN1/2 resulted in a drastic inability to form neurospheres, while DRP1 increased neurosphere yield (44). Furthermore, loss of the fusion protein (optic atrophy 1 (OPA1)) resulted in decreased primary and secondary neurospheres (44).

Both mitochondrial biogenesis and bioenergetics regulate fate decisions of NPCs to either proliferation or differentiation. Differentiated NSCs are characterized by low mitochondrial and mtDNA content, and the switch from glycolytic metabolism to mitochondrial OXPHOS, controls the shift from NSC proliferation to NSC differentiation into NPCs and subsequent cell types(45–48). Preclinical murine studies demonstrate that mitochondrial bioenergetics are necessary for NPC differentiation and proliferation. Specifically, a one-day treatment of rotenone, a mitochondrial Complex I inhibitor, on cell cultures derived from mouse pups (postnatal day 5) can reduce NPC proliferation and differentiation, while a long-term rotenone treatment fully inhibits NPC proliferation and differentiation (49, 50). Moreover, genetically induced mitochondrial dysfunction (*i.e.*, by ablating mitochondrial Complex II gene), leads to impaired differentiation of glia-like central NSCs into neurons and oligodendrocytes (but not into astrocytes), leading to brain atrophy and early death (51).

Besides the described metabolic changes in the scope of neurogenesis, mitochondria also change their morphology and dynamics depending on the state of the developing cell(52, 53). While the mitochondrion appears rather simple in mouse NSCs (*i.e.*, round containing little cristae), during differentiation, it becomes a complex tubular network of elongated cristae-rich mitochondria with a dense matrix (54–58). Empirical studies in this context point to the pivotal role of the mitochondrial fission protein DRP1 in mitochondrial dynamics during neurogenesis. More specifically, while a knock-down of DRP1 was found to lead to an impairment of mitochondrial fission promoting NSC differentiation in human

pluripotent stem cells, an overexpression of active DRP1 mutant was found to enhance pluripotency (59, 60).

Neuronal migration, a highly energetic process, is also critically dependent on mitochondrial dynamics and bioenergetics. For example, the genetic disruption of OXPHOS in mice, lacking ANT1 (adenine nucleotide transferase 1), a protein encoding an inner mitochondrial membrane protein that transports ADP (adenosine diphosphate) into mitochondria and ATP from mitochondria to the cytosol, has been related to alterations of interneuron migration. These data suggest that interneuron polarity during migration is particularly sensitive to disruptions in mitochondrial bioenergetics, and that OXPHOS is required for normal migration of interneurons from the basal forebrain to the neocortex (61). Other mouse models show that, under basal conditions, autophagy levels are correlated with the bioenergetic requirements of cells and that decreases in ATP/ADP levels – due to abnormalities in OXPHOS – during the migratory phase lead to the entry of cells into the stationary phase and to the induction of autophagy (62). Hence, these findings point to the critical contribution of the integrity of OXPHOS to the dynamic regulation of the pace and periodicity of neuronal migration.

2.3.2. In glial cell development—In the process of gliogenesis, NSCs differentiate into non-neuronal glial cell-types including astrocytes, oligodendrocytes, and microglia. With respect to astrocytes during development, mitochondria play a role in regulating astrocyte maturation and subsequent synapse formation (63). Specifically, recent evidence has demonstrated that conditional deletion of the metabolic regulator PGC-1α (peroxisome proliferator-activated receptor gamma co-activator 1α) controls the mitochondrial biogenesis in developing astrocytes, and compromises the proliferation and maturation of astrocytes with a subsequent effect on the number and function of excitatory synapses in mice (63).

The importance of mitochondrial functioning in the context of oligodendrocyte development is evident from studies using developing human oligodendroglial cells differentially exposed to rotenone, inhibiting bioenergetic function (64). Specifically, in vitro, differentiated oligodendroglial cells have been observed to be uniquely sensitive (*e.g.*, viability and ATP synthesis) to rotenone exposure relative to undifferentiated cells (64), thus demonstrating the fundamental importance of mitochondrial function in oligodendrocyte development. Because oligodendrocytes are the myelinating cells of the central nervous system, their health is of consequence to myelination in humans both perinatally (65) and well into at least late childhood (66, 67) with long-term effects for efficiency of neural signal transduction.

Yolk-sac derived microglia enter the developing brain primarily before the formation of the blood-brain barrier. After migration into the brain in this early gestational period, they are believed to self-sustain through adulthood where they form the basis of the immune response in the central nervous system (68). While the specific role for mitochondria in the proliferation and migration of microglial cells is not yet entirely clear, xenographic transfer of hamster mitochondria into embryonic ischemic cortical rat neurons has been shown to transiently increase the proliferation of microglia (69).

2.3.3. In the development of the blood-brain barrier (BBB)—The BBB is a semipermeable border composed of endothelial cells restricting solutes from entry into the extracellular space surrounding the central nervous system. The integrity of the BBB can be indirectly tied to mitochondria as microglia and astrocytes (discussed above) underlie its formation (70). Further evidence supports the direct relevance of mitochondria to the BBB. Specifically in preclinical models, endothelial cells found within the BBB are enriched for mitochondria, containing twice the mitochondrial content relative to endothelial cells in other tissues (71), and recent experimental evidence in mature rodents supports a causal role of impaired mitochondrial function in the degradation of the BBB integrity (72).

2.3.4. In axonal development—The development of axonal projections that originate in the cell body and extend to target neurons is essential to the formation of circuits underlying human behavior (73). Axonal growth is a highly energetic and mitochondrial-dependent process as evidenced by the spatiotemporal distribution of mitochondria during extension. For example, in actively growing chick and rodent axons, there is a marked increase in subcellular mitochondrial density in the far distal regions adjacent to the growth cone (74), with additional clusters found in branch points (75). Further, when axonal reorganization occurs (*e.g.*, in the case of physical restriction or destruction) via depolymerization of the actin filaments, mitochondrial distribution changes in response by favoring more proximally growing axons that represent better candidates for eventual connection to target neurons. This energetic prioritization has been further demonstrated via alternating branch growth in rat hippocampal neurons where mitochondrial transport into newly formed axons occurs after the nascent axon has elongated past the length of other minor processes extending out from the cell body (76).

In addition to singular neuron to neuron connections, the functional mapping between neuronal networks is further facilitated by axonal branching, where collateral branches extend out from the singular axon to form a dense network of terminal arbors (77) with multiple endpoint targets. Several recent studies have highlighted the critical role mitochondria play in the branching process. For example, branching sites are largely dependent on the density, positioning, and functioning of stalled mitochondria (*i.e.*, those exhibiting neither anterograde or retrograde transport) along the axon. Specifically, it has been demonstrated that the mitochondria-associated microtubule binding protein syntaphilin is necessary for axonal branching in mouse models, suggesting a direct link between mitochondria immobilization, mitochondrial spatiotemporal density and branch formation (78). Collectively, this then supports the fundamental importance of mitochondria in providing sufficient ATP for axonal growth, and further, because redistribution of resources is only necessary in the case of limitation, it suggests that axonal extension and branching may be a rate limited process susceptible to mitochondrial dysfunction. For a more complete review of the role of mitochondria in axonal development, please see Smith *et al.* (79).

2.3.5. In synaptogenesis—Following the processes of neural proliferation, differentiation, migration, and finally axonal formation, synapses are assembled for establishing interneuronal communication (synaptogenesis) (80). It stands to reason, then, that because processes upstream of synapse formation are mitochondria dependent

(see above sections), synaptogenesis is indirectly mitochondria-dependent. In addition to this indirect role, there is evidence of a specific direct role for mitochondria in the formation of synaptic connections. In one study of embryonic (day18) rodent hippocampal neurons manipulated using dynamin-like GTPases (DRP1 and OPA1) to reduce dendritic mitochondria content, Li *et al.* (2004) conclude that mitochondria are an essential and limiting factor for synaptogenesis based on observed correlations between the intra-neuronal spatial distribution of mitochondria and synapse plasticity (81). Furthermore, Stavsky *et al.* (2021) observed that when deleting NCLX (the mitochondrial sodium calcium lithium exchanger (82)) in mice and culturing hippocampal neurons from newborn pups (postnatal day 0–2), neuronal mitochondria demonstrated basal calcium overload, membrane depolarization, and reduced calcium influx and efflux (83). In addition, the authors observed reduced calcium transients in the presynaptic terminals that led to a lower probability of neurotransmitter release and weaker synaptic transmission (83). Finally, a model of growth retardation involving placental mass reduction has been shown to decrease the density of synapses and increase subcellular mitochondrial density in the visual cortex of offspring fetal sheep (gestation day 140) (84). The authors posit that the observed increase in mitochondrial density (*e.g.*, increased aerobic efficiency) is a compensation mechanism to counteract reductions in synaptogenesis (84), thus suggesting a rate limited role of mitochondria in the formation of synapses.

3. Inflammation and mitochondrial function: focus on the intrauterine period

As reviewed above, virtually all aspects of brain development are ultimately mitochondria-dependent. To support the premise that mitochondria mediate aspects of MIA-induced effects on the developing brain, the following section provides evidence of altered offspring mitochondrial structure and function in the context of MIA.

3.1. Immune mediators and mitochondrial function

A growing body of research suggests that mitochondria act as central hubs in the regulation of innate immunity and inflammatory responses (85), and are thus acutely sensitive to inflammatory processes. For example, *in vitro* exposure to inflammatory molecules has been linked to overall cellular reductions in mitochondrial bioenergetics (86–91), increased intracellular ROS (88, 92, 93), increased mitochondrial fragmentation/fission (94, 95), and decreases in mtDNA content (96, 97). These inflammation-induced changes in mitochondria have been observed *in vitro* in neural and glial cells (86–88, 90, 91, 98), and through *in vivo* injection of the endotoxin lipopolysaccahride directly into the brain compartment (99). In addition, immune cell activation and quiescence is coupled with mitochondrial function and content (100, 101), and lipopolysaccahride administration has been shown to repurpose lymphocyte mitochondria from ATP synthesis to ROS production (102), further potentiating a pro-inflammatory state. Importantly, this process has specifically been demonstrated in microglia, with mitochondrial structure (fission/fusion dynamics) thought to play a central role in the process (86, 87). Moreover, perhaps due to mitochondria's bacterial origins, molecules originating from mitochondria itself (*i.e.*, ATP, mtDNA, mROS) act as danger-associated molecular patterns in the intra- and extra-cellular environment,

responsible for the activation of Nodlike receptor family, pyrin domain containing 3 (NLRP3) inflammasome and subsequent *amplification* of inflammatory responses (103–106). Thus, mitochondrial function is not only sensitive to inflammatory stimuli, but the release of mitochondrial molecules in response to inflammation or cellular stress can directly induce neuroinflammation, akin to a positive feedback loop. In this context, mitochondria are not only a potential target and mediator of MIA-dependent effects on the developing brain, but may participate in a self-reinforcing cellular stress response cycle, such as is discussed in the cellular danger response model (107). This interrelationship between mitochondria and inflammation is evident across the lifespan, but is particularly consequential during the sensitive window of embryological/fetal brain development.

3.2. Mitochondrial dysfunction as a mediator of preclinical MIA-related effects on the developing brain

Mitochondria are developmentally plastic (43), their structure and function are altered by inflammatory stimuli (reviewed above), and we propose herein that they are a likely mediator underlying the impact of MIA exposure on offspring neurodevelopmental. We conducted a review of empirical studies in which MIA was induced during pregnancy and mitochondria-relevant measures were obtained in either neuronal or glial cells/tissue of the offspring. Our review identified 12 published preclinical (primarily murine) studies (Table 1) (108–119) providing evidence for MIA-induced changes in offspring brain mitochondrial structure/morphology (111, 114, 115), mitochondrial content/density (111), indirect (112, 113, 116) and direct measures of mitochondrial bioenergetic function (electron transport chain enzymatic activity (110, 114), MMP (114, 117)), and oxidative stress levels (108, 109, 114, 115, 118, 119). Further, unbiased/untargeted proteomics analysis suggested that the top two significant pathways differentiating the brain of MIAexposed offspring relative to controls were specific to mitochondrial bioenergetic activity (i.e., OXPHOS, tricyclic acid cycle) (116). Importantly in the majority of reviewed studies (108–117), these MIA-induced changes in mitochondria in the brain paralleled changes in brain integrity (e.g., synaptosomal structure (110)) and behavior (*e.g.*, altered inhibitory behavior (115, 117), social behavior (109, 110, 115), sensorimotor coordination (110)).

Two recent studies strengthening the empirical support for an association between preclinical MIA and offspring brain mitochondrial dysfunction are of particular relevance. The first, employed multiple layered measures of mitochondrial structure and function in the hippocampus of adolescent offspring born to dams exposed to lipopolysaccahride during pregnancy (gestation day 9.5) to demonstrate a comprehensive decrease in gene expression, protein level and enzymatic activity specific to mitochondrial electron transport chain Complex I, that also corresponded with a holistic decrease in bioenergetic function, measured by MMP (114). Furthermore, this study demonstrated mitochondrial specific increases in oxidative stress (mROS) and decreases in mitochondrial specific antioxidant levels, which is consistent with the increase in oxidative stress reported across all studies that assessed MIA-induced oxidative damage (108, 109, 114, 115, 118, 119). Previous work has highlighted ROS as a mediator of fetal neurodevelopmental programming (120, 121), and we bring the focus here to mitochondria, as the primary source of ROS, particularly in response to inflammatory insults (88). The second study presents the first empirical

evidence to inform more directly on the cause-effect-relationship between MIA-dependent programming of mitochondrial dysfunction and behavior. Specifically, Robiscek *et al.* (2018) demonstrate decreased mitochondrial bioenergetic function (measured by MMP) in cortical neurons in MIA-exposed rats which parallel behavioral deficits (117). Interestingly, both of these features are rescued by postnatal mitochondrial therapy via intracranial injections of isolated active normal mitochondria (117). The promise of mitochondrial therapy is further supported by the successful treatment of human neurons derived from schizophrenic patients using isolated active normal mitochondria (117), which normalized cellular oxygen consumption and MMP to the levels observed in neurons from control patients. Similarly, Naviaux *et al.* (2013) had previously employed a postnatal therapy in MIA-exposed offspring that targets the extracellular release of mitochondrial molecules (*i.e.*, mitokines), and was able to rescue cerebral mitochondrial function and core social deficits (110). The same mitokine therapy was employed in a recent human phase I/II randomized control trial in children with autism, and improved scores on the Autism Diagnostic Observation Schedule (122). The efficacy of such mitochondrial targeted treatments supports the premise that mitochondrial activity is sufficient to induce, and potentially rescue, neurodevelopmental disorders.

3.3. Mitochondrial dysfunction in the context of human neurodevelopmental disorders

Further support for the role of mitochondrial function as a potential mediator of the association between MIA during pregnancy and mental health risk comes from clinical epidemiological studies that suggest a relationship between mitochondrial dysfunction and neurodevelopmental disorders, for which maternal infection/immune activation during pregnancy is an established risk factor. Brain mitochondrial dysfunction has been reported in autism spectrum disorder (123–125), attention deficit hyperactivity disorder (126), and schizophrenia (127, 128). Specifically, patients differed from healthy controls in mitochondrial density/localization (124, 126–128), bioenergetic function (123, 125, 126), fission/fusion dynamics (125), and structure/morphology (126, 128). Furthermore, inherited mtDNA mutations are associated with increased risk for neurodevelopmental disorders (129–133), which supports the premise that mitochondrial dysfunction may be a cause rather than a secondary consequence of these disorders. Moreover, in preclinical murine models where mitochondrial *specific* defects can be induced through mutations or overexpression, and temporality can be established, mild mitochondrial dysfunction has proven sufficient to cause autism spectrum disorder (134), schizophrenia (135, 136), and broad neurodevelopmental disorder (137) phenotypes. Thus, there is empirical evidence supporting a *causal* role for the integrity of mitochondrial structure and function in early brain development. Because mitochondria regulate and are regulated by inflammatory processes, there is furthermore a basis for concluding a causal role of mitochondria in MIA-induced changes in brain development and risk for neurodevelopmental disorders.

4. Conclusions and future directions

Convergent evidence supporting the obligatory role of mitochondria in brain development and the role of mitochondria as mediators and initiators of inflammatory processes, as well as evidence of mitochondrial dysfunction in pre-clinical MIA exposure models and

human neurodevelopmental disorders, suggests that mitochondria play a pivotal role in MIA-induced alterations in brain development.

While the conceptual model presented here is supported by empirical evidence, we address below two major limitations (*i.e.*, knowledge gaps) presenting opportunities for future research. First, preclinical studies demonstrate that mitochondrial dysfunction is induced by MIA, and parallels MIA-induced changes in brain development and behavior; however, evidence to support clear cause-and-effect of mitochondrial function in this pathway is still limited (110, 117). Further empirical evidence is needed to support which aspects of mitochondrial function are sufficient *and* necessary for MIA-induced alterations in neurodevelopment, with parallel evidence that these aspects can be mitigated by mitochondrial targeted therapies. Novel insights from such studies could lead to potential therapeutic targets, that may be applied prenatally, or even postnatally while the brain retains a high degree of neuroplasticity, as has successfully been done in first pioneer studies (110, 117). Second, confirmatory analyses in humans are necessary to demonstrate the generalization of the consequences of MIA exposures during pregnancy for offspring mitochondrial function, generally and *specifically in the brain*. Human studies in *living* patients have been limited to accessible peripheral tissues that serve as a proxy to mitochondrial function in the brain (methods reviewed in (138)), yet we highlight some methodological advances for areas of potential future clinical research. Specifically, novel non-invasive indirect measurement (magnetic resonance and positron emission tomography imaging) of mitochondrial bioenergetic function (139, 140) and mROS production (141) in the brain have been demonstrated in pre-clinical animal models and are potential tools for future *in-vivo* research in human studies. Furthermore, recent advances in induced pluripotent stem cell and umbilical mesenchymal stem cells (uMSCs) research would allow for collection of non-invasive tissues at birth (*e.g.*, umbilical cord) and/or early in life (*e.g.*, hair follicles) with demonstrated potential for differentiation to neuronal cell-lineages (142–144). Such tissues could be utilized for 2D and 3D differentiation research studies of the central nervous system under varying inflammatory conditions, and in particular, progress in using human primary cell cultures to generate more complex 3D brain organoids (144) now allows for improved *ex-vivo* modeling of inflammation-induced mitochondrial deficits in the developing brain and to examine treatment options.

In summary, we argue that mitochondrial function is a promising mechanism through which maternal immune activation/inflammation during pregnancy, can impact the risk for neurodevelopmental and psychiatric disorders. Elucidating the role of mitochondria as a mediator of MIA-induced alterations in brain development and neurodevelopmental disease risk may not only provide new insight into the pathophysiology of mental health disorders, but may also offer new therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Jonakait GM (2007): The effects of maternal inflammation on neuronal development: possible mechanisms. Int J Dev Neurosci 25(7): 415–25. [PubMed: 17949937]
2. Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, et al. (2014): Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol 10(11): 643–60. [PubMed: 25311587]
3. Bilbo SD, Block CL, Bolton JL, Hanamsagar R, and Tran PK (2018): Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. Exp Neurol 299(Pt A): 241–251. [PubMed: 28698032]
4. Stiles J and Jernigan TL (2010): The basics of brain development. Neuropsychol Rev 20(4): 327–48. [PubMed: 21042938]
5. Silbereis JC, Pochareddy S, Zhu Y, Li M, and Sestan N (2016): The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. Neuron 89(2): 248–68. [PubMed: 26796689]
6. Meng H, Zhang Z, Geng H, Lin X, Feng L, Teng G, et al. (2012): Development of the subcortical brain structures in the second trimester: assessment with 7.0-T MRI. Neuroradiology 54(10): 1153–9. [PubMed: 22811291]
7. McConnell SK (1995): Constructing the cerebral cortex: neurogenesis and fate determination. Neuron 15(4): 761–8. [PubMed: 7576626]
8. Paridaen JT and Huttner WB (2014): Neurogenesis during development of the vertebrate central nervous system. EMBO Rep 15(4): 351–64. [PubMed: 24639559]
9. Rao MS and Mayer-Proschel M (1997): Glial-restricted precursors are derived from multipotent neuroepithelial stem cells. Dev Biol 188(1): 48–63. [PubMed: 9245511]
10. Kriegstein AR and Noctor SC (2004): Patterns of neuronal migration in the embryonic cortex. Trends Neurosci 27(7): 392–9. [PubMed: 15219738]
11. ten Donkelaar HJ, Yamada S, Shiota K, and van der Vliet T (2014): Overview of the Development of the Human Brain and Spinal Cord, in Clinical Neuroembryology: Development and Developmental Disorders of the Human Central Nervous System. Springer Berlin Heidelberg: Berlin, Heidelberg. pp 152.
12. Bourgeois JP (1997): Synaptogenesis, heterochrony and epigenesis in the mammalian neocortex. Acta Paediatr Suppl 422: 27–33. [PubMed: 9298788]
13. Abraham H, Vincze A, Jewgenow I, Veszpremi B, Kravjak A, Gomori E, et al. (2010): Myelination in the human hippocampal formation from midgestation to adulthood. Int J Dev Neurosci 28(5): 401–10. [PubMed: 20417266]
14. Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, Hof PR, et al. (2014): Metabolic costs and evolutionary implications of human brain development. Proc Natl Acad Sci U S A 111(36): 13010–5. [PubMed: 25157149]
15. Chandel NS (2014): Mitochondria as signaling organelles. BMC Biol 12: 34. [PubMed: 24884669]
16. Kasahara A and Scorrano L (2014): Mitochondria: from cell death executioners to regulators of cell differentiation. Trends Cell Biol 24(12): 761–70. [PubMed: 25189346]
17. D'Autreaux B and Toledano MB (2007): ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis. Nat Rev Mol Cell Biol 8(10): 813–24. [PubMed: 17848967]
18. Aon MA, Cortassa S, Juhaszova M, and Sollott SJ (2016): Mitochondrial health, the epigenome and healthspan. Clin Sci (Lond) 130(15): 1285–305. [PubMed: 27358026]
19. Pourova J, Kottova M, Voprsalova M, and Pour M (2010): Reactive oxygen and nitrogen species in normal physiological processes. Acta Physiol (Oxf) 198(1): 15–35. [PubMed: 19732041]

20. Pitkanen S and Robinson BH (1996): Mitochondrial complex I deficiency leads to increased production of superoxide radicals and induction of superoxide dismutase. J Clin Invest 98(2): 345–51. [PubMed: 8755643]
21. Hill BG, Benavides GA, Lancaster JR Jr., Ballinger S, Dell'Italia L, Jianhua Z, et al. (2012): Integration of cellular bioenergetics with mitochondrial quality control and autophagy. Biol Chem 393(12): 14851512.
22. Shokolenko I, Venediktova N, Bochkareva A, Wilson GL, and Alexeyev MF (2009): Oxidative stress induces degradation of mitochondrial DNA. Nucleic Acids Res 37(8): 2539–48. [PubMed: 19264794]
23. Mandal S, Lindgren AG, Srivastava AS, Clark AT, and Banerjee U (2011): Mitochondrial function controls proliferation and early differentiation potential of embryonic stem cells. Stem Cells 29(3): 486–95. [PubMed: 21425411]
24. Pereira SL, Graos M, Rodrigues AS, Anjo SI, Carvalho RA, Oliveira PJ, et al. (2013): Inhibition of mitochondrial complex III blocks neuronal differentiation and maintains embryonic stem cell pluripotency. PLoS One 8(12): e82095. [PubMed: 24312632]
25. Papadopoulos V and Miller WL (2012): Role of mitochondria in steroidogenesis. Best Pract Res Clin Endocrinol Metab 26(6): 771–90. [PubMed: 23168279]
26. Cheng Z and Ristow M (2013): Mitochondria and metabolic homeostasis. Antioxid Redox Signal 19(3): 240–2. [PubMed: 23432475]
27. Ahn CS and Metallo CM (2015): Mitochondria as biosynthetic factories for cancer proliferation. Cancer Metab 3(1): 1. [PubMed: 25621173]
28. Frederick RL and Shaw JM (2007): Moving mitochondria: establishing distribution of an essential organelle. Traffic 8(12): 1668–75. [PubMed: 17944806]
29. Boldogh IR and Pon LA (2007): Mitochondria on the move. Trends Cell Biol 17(10): 502–10. [PubMed: 17804238]
30. Westermann B (2012): Bioenergetic role of mitochondrial fusion and fission. Biochim Biophys Acta 1817(10): 1833–8. [PubMed: 22409868]
31. Hux VJ, Roberts JM, and Okun ML (2017): Allostatic load in early pregnancy is associated with poor sleep quality. Sleep Med 33: 85–90. [PubMed: 28449913]
32. Billups B and Forsythe ID (2002): Presynaptic mitochondrial calcium sequestration influences transmission at mammalian central synapses. J Neurosci 22(14): 5840–7. [PubMed: 12122046]
33. Lane N (2017): Serial endosymbiosis or singular event at the origin of eukaryotes? J Theor Biol 434: 58–67. [PubMed: 28501637]
34. Van Blerkom J, Davis PW, and Lee J (1995): ATP content of human oocytes and developmental potential and outcome after in-vitro fertilization and embryo transfer. Hum Reprod 10(2): 415–24. [PubMed: 7769073]
35. Santos TA, El Shourbagy S, and St John JC (2006): Mitochondrial content reflects oocyte variability and fertilization outcome. Fertil Steril 85(3): 584–91. [PubMed: 16500323]
36. Wakefield SL, Lane M, and Mitchell M (2011): Impaired mitochondrial function in the preimplantation embryo perturbs fetal and placental development in the mouse. Biol Reprod 84(3): 572–80. [PubMed: 21076083]
37. Yakes FM and Van Houten B (1997): Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. Proc Natl Acad Sci U S A 94(2): 514–9. [PubMed: 9012815]
38. Furda A, Santos JH, Meyer JN, and Van Houten B (2014): Quantitative PCR-based measurement of nuclear and mitochondrial DNA damage and repair in mammalian cells. Methods Mol Biol 1105: 419–37. [PubMed: 24623245]
39. Van Houten B, Woshner V, and Santos JH (2006): Role of mitochondrial DNA in toxic responses to oxidative stress. DNA Repair (Amst) 5(2): 145–52. [PubMed: 15878696]
40. Sato A, Endo H, Umetsu K, Sone H, Yanagisawa Y, Saigusa A, et al. (2003): Polymorphism, heteroplasmy, mitochondrial fusion and diabetes. Biosci Rep 23(5–6): 313–37. [PubMed: 15074546]
41. Blomgren K and Hagberg H (2006): Free radicals, mitochondria, and hypoxia-ischemia in the developing brain. Free Radic Biol Med 40(3): 388–97. [PubMed: 16443153]

42. Picard M, Vincent AE, and Turnbull DM (2016): Expanding Our Understanding of mtDNA Deletions. Cell Metab 24(1): 3–4. [PubMed: 27411002]
43. Gyllenhammer LE, Entringer S, Buss C, and Wadhwa PD (2020): Developmental programming of mitochondrial biology: a conceptual framework and review. Proc Biol Sci 287(1926): 20192713. [PubMed: 32345161]
44. Khacho M, Clark A, Svoboda DS, Azzi J, MacLaurin JG, Meghaizel C, et al. (2016): Mitochondrial Dynamics Impacts Stem Cell Identity and Fate Decisions by Regulating a Nuclear Transcriptional Program. Cell Stem Cell 19(2): 232–247. [PubMed: 27237737]
45. Chen CT, Hsu SH, and Wei YH (2010): Upregulation of mitochondrial function and antioxidant defense in the differentiation of stem cells. Biochim Biophys Acta 1800(3): 257–63. [PubMed: 19747960]
46. Facucho-Oliveira JM, Alderson J, Spikings EC, Egginton S, and St John JC (2007): Mitochondrial DNA replication during differentiation of murine embryonic stem cells. J Cell Sci 120(Pt 22): 4025–34. [PubMed: 17971411]
47. Folmes CD and Terzic A (2014): Metabolic determinants of embryonic development and stem cell fate. Reprod Fertil Dev 27(1): 82–8. [PubMed: 25472047]
48. O'Brien LC, Keeney PM, and Bennett JP Jr. (2015): Differentiation of Human Neural Stem Cells into Motor Neurons Stimulates Mitochondrial Biogenesis and Decreases Glycolytic Flux. Stem Cells Dev 24(17): 1984–94. [PubMed: 25892363]
49. Park K-Y and Kim Man S (2018): Inhibition of Proliferation and Neurogenesis of Mouse Subventricular Zone Neural Stem Cells by a Mitochondrial Inhibitor Rotenone. Journal of Life Science 28(12): 1397–1405.
50. Park K-Y and Kim Man S (2019): Effects of Transient Treatment with Rotenone, a Mitochondrial Inhibitor, on Mouse Subventricular Zone Neural Stem Cells. Journal of Life Science 29(12): 1329–1336.
51. Diaz-Castro B, Pardal R, Garcia-Flores P, Sobrino V, Duran R, Piruat JI, et al. (2015): Resistance of glia-like central and peripheral neural stem cells to genetically induced mitochondrial dysfunction-differential effects on neurogenesis. EMBO Rep 16(11): 1511–9. [PubMed: 26392570]
52. Wang L, Zhang T, Wang L, Cai Y, Zhong X, He X, et al. (2017): Fatty acid synthesis is critical for stem cell pluripotency via promoting mitochondrial fission. EMBO J 36(10): 1330–1347. [PubMed: 28377463]
53. Wilkerson DC and Sankar U (2011): Mitochondria: a sulfhydryl oxidase and fission GTPase connect mitochondrial dynamics with pluripotency in embryonic stem cells. Int J Biochem Cell Biol 43(9): 1252–6. [PubMed: 21605695]
54. Bukowiecki R, Adjaye J, and Prigione A (2014): Mitochondrial function in pluripotent stem cells and cellular reprogramming. Gerontology 60(2): 174–82. [PubMed: 24281332]
55. Folmes CD, Nelson TJ, Martinez-Fernandez A, Arrell DK, Lindor JZ, Dzeja PP, et al. (2011): Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metab 14(2): 264–71. [PubMed: 21803296]
56. Mils V, Bosch S, Roy J, Bel-Vialar S, Belenguer P, Pituello F, et al. (2015): Mitochondrial reshaping accompanies neural differentiation in the developing spinal cord. PLoS One 10(5): e0128130. [PubMed: 26020522]
57. Prieto J, Leon M, Ponsoda X, Garcia-Garcia F, Bort R, Serna E, et al. (2016): Dysfunctional mitochondrial fission impairs cell reprogramming. Cell Cycle 15(23): 3240–3250. [PubMed: 27753531]
58. Prieto J, Leon M, Ponsoda X, Sendra R, Bort R, Ferrer-Lorente R, et al. (2016): Early ERK1/2 activation promotes DRP1-dependent mitochondrial fission necessary for cell reprogramming. Nat Commun 7: 11124. [PubMed: 27030341]
59. Son G and Han J (2018): Roles of mitochondria in neuronal development. BMB Rep 51(11): 549–556. [PubMed: 30269744]
60. Hoque A, Sivakumaran P, Bond ST, Ling NXY, Kong AM, Scott JW, et al. (2018): Mitochondrial fission protein Drp1 inhibition promotes cardiac mesodermal differentiation of human pluripotent stem cells. Cell Death Discov 4: 39. [PubMed: 29531836]

61. Lin-Hendel EG, McManus MJ, Wallace DC, Anderson SA, and Golden JA (2016): Differential Mitochondrial Requirements for Radially and Non-radially Migrating Cortical Neurons: Implications for Mitochondrial Disorders. Cell Rep 15(2): 229–37. [PubMed: 27050514]
62. Bressan C, Pecora A, Gagnon D, Snapyan M, Labrecque S, De Koninck P, et al. (2020): The dynamic interplay between ATP/ADP levels and autophagy sustain neuronal migration in vivo. Elife 9.
63. Zehnder T, Petrelli F, Romanos J, De Oliveira Figueiredo EC, Lewis TL Jr., Deglon N, et al. (2021): Mitochondrial biogenesis in developing astrocytes regulates astrocyte maturation and synapse formation. Cell Rep 35(2): 108952. [PubMed: 33852851]
64. Schoenfeld R, Wong A, Silva J, Li M, Itoh A, Horiuchi M, et al. (2010): Oligodendroglial differentiation induces mitochondrial genes and inhibition of mitochondrial function represses oligodendroglial differentiation. Mitochondrion 10(2): 143–50. [PubMed: 20005986]
65. Tolcos M, Petratos S, Hirst JJ, Wong F, Spencer SJ, Azhan A, et al. (2017): Blocked, delayed, or obstructed: What causes poor white matter development in intrauterine growth restricted infants? Prog Neurobiol 154: 62–77. [PubMed: 28392287]
66. Baumann N and Pham-Dinh D (2001): Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiol Rev 81(2): 871–927. [PubMed: 11274346]
67. Miller DJ, Duka T, Stimpson CD, Schapiro SJ, Baze WB, McArthur MJ, et al. (2012): Prolonged myelination in human neocortical evolution. Proc Natl Acad Sci U S A 109(41): 16480–5. [PubMed: 23012402]
68. Tan YL, Yuan Y, and Tian L (2020): Microglial regional heterogeneity and its role in the brain. Mol Psychiatry 25(2): 351–367. [PubMed: 31772305]
69. Huang PJ, Kuo CC, Lee HC, Shen CI, Cheng FC, Wu SF, et al. (2016): Transferring Xenogenic Mitochondria Provides Neural Protection Against Ischemic Stress in Ischemic Rat Brains. Cell Transplant 25(5): 913–27. [PubMed: 26555763]
70. Saili KS, Zurlinden TJ, Schwab AJ, Silvin A, Baker NC, Hunter ES 3rd, et al. (2017): Blood-brain barrier development: Systems modeling and predictive toxicology. Birth Defects Res 109(20): 1680–1710. [PubMed: 29251840]
71. Oldendorf WH, Cornford ME, and Brown WJ (1977): The large apparent work capability of the blood-brain barrier: a study of the mitochondrial content of capillary endothelial cells in brain and other tissues of the rat. Ann Neurol 1(5): 409–17. [PubMed: 617259]
72. Doll DN, Hu H, Sun J, Lewis SE, Simpkins JW, and Ren X (2015): Mitochondrial crisis in cerebrovascular endothelial cells opens the blood-brain barrier. Stroke 46(6): 1681–9. [PubMed: 25922503]
73. Ye X, Qiu Y, Gao Y, Wan D, and Zhu H (2019): A Subtle Network Mediating Axon Guidance: Intrinsic Dynamic Structure of Growth Cone, Attractive and Repulsive Molecular Cues, and the Intermediate Role of Signaling Pathways. Neural Plast 2019: 1719829. [PubMed: 31097955]
74. Morris RL and Hollenbeck PJ (1993): The regulation of bidirectional mitochondrial transport is coordinated with axonal outgrowth. J Cell Sci 104 (Pt 3): 917–27. [PubMed: 8314882]
75. Dedov VN, Armati PJ, and Roufogalis BD (2000): Three-dimensional organisation of mitochondrial clusters in regenerating dorsal root ganglion (DRG) neurons from neonatal rats: evidence for mobile mitochondrial pools. J Peripher Nerv Syst 5(1): 3–10. [PubMed: 10780677]
76. Ruthel G and Hollenbeck PJ (2003): Response of mitochondrial traffic to axon determination and differential branch growth. J Neurosci 23(24): 8618–24. [PubMed: 13679431]
77. Kalil K and Dent EW (2014): Branch management: mechanisms of axon branching in the developing vertebrate CNS. Nat Rev Neurosci 15(1): 7–18. [PubMed: 24356070]
78. Courchet J, Lewis TL Jr., Lee S, Courchet V, Liou DY, Aizawa S, et al. (2013): Terminal axon branching is regulated by the LKB1-NUAK1 kinase pathway via presynaptic mitochondrial capture. Cell 153(7): 1510–25. [PubMed: 23791179]
79. Smith GM and Gallo G (2018): The role of mitochondria in axon development and regeneration. Dev Neurobiol 78(3): 221–237. [PubMed: 29030922]
80. Tau GZ and Peterson BS (2010): Normal development of brain circuits. Neuropsychopharmacology 35(1): 147–68. [PubMed: 19794405]

81. Li Z, Okamoto K, Hayashi Y, and Sheng M (2004): The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 119(6): 873–87. [PubMed: 15607982]
82. Boyman L, Williams GS, Khananshvili D, Sekler I, and Lederer WJ (2013): NCLX: the mitochondrial sodium calcium exchanger. J Mol Cell Cardiol 59: 205–13. [PubMed: 23538132]
83. Stavsky A, Stoler O, Kostic M, Katoshevsky T, Assali EA, Savic I, et al. (2021): Aberrant activity of mitochondrial NCLX is linked to impaired synaptic transmission and is associated with mental retardation. Commun Biol 4(1): 666. [PubMed: 34079053]
84. Bisignano M and Rees S (1988): The effects of intrauterine growth retardation on synaptogenesis and mitochondrial formation in the cerebral and cerebellar cortices of fetal sheep. Int J Dev Neurosci 6(5): 453–60. [PubMed: 3202003]
85. Mohanty A, Tiwari-Pandey R, and Pandey NR (2019): Mitochondria: the indispensable players in innate immunity and guardians of the inflammatory response. J Cell Commun Signal 13(3): 303–318. [PubMed: 30719617]
86. Nair S, Sobotka KS, Joshi P, Gressens P, Fleiss B, Thornton C, et al. (2019): Lipopolysaccharide-induced alteration of mitochondrial morphology induces a metabolic shift in microglia modulating the inflammatory response in vitro and in vivo. Glia 67(6): 1047–1061. [PubMed: 30637805]
87. Voloboueva LA, Emery JF, Sun X, and Giffard RG (2013): Inflammatory response of microglial BV-2 cells includes a glycolytic shift and is modulated by mitochondrial glucose-regulated protein 75/mortalin. FEBS Lett 587(6): 756–62. [PubMed: 23395614]
88. Park J, Min JS, Kim B, Chae UB, Yun JW, Choi MS, et al. (2015): Mitochondrial ROS govern the LPSinduced pro-inflammatory response in microglia cells by regulating MAPK and NF-kappaB pathways. Neurosci Lett 584: 191–6. [PubMed: 25459294]
89. Zell R, Geck P, Werdan K, and Boekstegers P (1997): TNF-alpha and IL-1 alpha inhibit both pyruvate dehydrogenase activity and mitochondrial function in cardiomyocytes: evidence for primary impairment of mitochondrial function. Mol Cell Biochem 177(1–2): 61–7. [PubMed: 9450646]
90. Doll DN, Rellick SL, Barr TL, Ren X, and Simpkins JW (2015): Rapid mitochondrial dysfunction mediates TNF-alpha-induced neurotoxicity. J Neurochem 132(4): 443–51. [PubMed: 25492727]
91. Haileselassie B, Joshi AU, Minhas PS, Mukherjee R, Andreasson KI, and Mochly-Rosen D (2020): Mitochondrial dysfunction mediated through dynamin-related protein 1 (Drp1) propagates impairment in blood brain barrier in septic encephalopathy. J Neuroinflammation 17(1): 36. [PubMed: 31987040]
92. Chen XH, Zhao YP, Xue M, Ji CB, Gao CL, Zhu JG, et al. (2010): TNF-alpha induces mitochondrial dysfunction in 3T3-L1 adipocytes. Mol Cell Endocrinol 328(1–2): 63–9. [PubMed: 20667497]
93. Ji C, Chen X, Gao C, Jiao L, Wang J, Xu G, et al. (2011): IL-6 induces lipolysis and mitochondrial dysfunction, but does not affect insulin-mediated glucose transport in 3T3-L1 adipocytes. J Bioenerg Biomembr 43(4): 367–75. [PubMed: 21732177]
94. Gao F, Reynolds MB, Passalacqua KD, Sexton JZ, Abuaita BH, and O'Riordan MXD (2020): The Mitochondrial Fission Regulator DRP1 Controls Post-Transcriptional Regulation of TNF-alpha. Front Cell Infect Microbiol 10: 593805. [PubMed: 33520735]
95. Yu W, Wang X, Zhao J, Liu R, Liu J, Wang Z, et al. (2020): Stat2-Drp1 mediated mitochondrial mass increase is necessary for pro-inflammatory differentiation of macrophages. Redox Biol 37: 101761. [PubMed: 33080440]
96. Suematsu N, Tsutsui H, Wen J, Kang D, Ikeuchi M, Ide T, et al. (2003): Oxidative stress mediates tumor necrosis factor-alpha-induced mitochondrial DNA damage and dysfunction in cardiac myocytes. Circulation 107(10): 1418–23. [PubMed: 12642364]
97. Vadrot N, Ghanem S, Braut F, Gavrilescu L, Pilard N, Mansouri A, et al. (2012): Mitochondrial DNA maintenance is regulated in human hepatoma cells by glycogen synthase kinase 3beta and p53 in response to tumor necrosis factor alpha. PLoS One 7(7): e40879. [PubMed: 22911714]
98. Katoh M, Wu B, Nguyen HB, Thai TQ, Yamasaki R, Lu H, et al. (2017): Polymorphic regulation of mitochondrial fission and fusion modifies phenotypes of microglia in neuroinflammation. Sci Rep 7(1): 4942. [PubMed: 28694451]

99. Hunter RL, Dragicevic N, Seifert K, Choi DY, Liu M, Kim HC, et al. (2007): Inflammation induces mitochondrial dysfunction and dopaminergic neurodegeneration in the nigrostriatal system. J Neurochem 100(5): 1375–86. [PubMed: 17254027]
100. Pearce EL, Poffenberger MC, Chang CH, and Jones RG (2013): Fueling immunity: insights into metabolism and lymphocyte function. Science 342(6155): 1242454. [PubMed: 24115444]
101. Pearce EL and Pearce EJ (2013): Metabolic pathways in immune cell activation and quiescence. Immunity 38(4): 633–43. [PubMed: 23601682]
102. Mills EL, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, et al. (2016): Succinate Dehydrogenase Supports Metabolic Repurposing of Mitochondria to Drive Inflammatory Macrophages. Cell 167(2): 457–470 e13. [PubMed: 27667687]
103. Jo EK, Kim JK, Shin DM, and Sasakawa C (2016): Molecular mechanisms regulating NLRP3 inflammasome activation. Cell Mol Immunol 13(2): 148–59. [PubMed: 26549800]
104. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. (2012): Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 36(3): 401–14. [PubMed: 22342844]
105. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. (2010): Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 464(7285): 104–7. [PubMed: 20203610]
106. Collins LV, Hajizadeh S, Holme E, Jonsson IM, and Tarkowski A (2004): Endogenously oxidized mitochondrial DNA induces in vivo and in vitro inflammatory responses. J Leukoc Biol 75(6): 9951000.
107. Naviaux RK (2018): Antipurinergic therapy for autism-An in-depth review. Mitochondrion 43: 1–15. [PubMed: 29253638]
108. Zhu Y, Carvey PM, and Ling Z (2007): Altered glutathione homeostasis in animals prenatally exposed to lipopolysaccharide. Neurochem Int 50(4): 671–80. [PubMed: 17291629]
109. Swanepoel T, Moller M, and Harvey BH (2018): N-acetyl cysteine reverses bio-behavioural changes induced by prenatal inflammation, adolescent methamphetamine exposure and combined challenges. Psychopharmacology (Berl) 235(1): 351–368. [PubMed: 29116368]
110. Naviaux RK, Zolkipli Z, Wang L, Nakayama T, Naviaux JC, Le TP, et al. (2013): Antipurinergic therapy corrects the autism-like features in the poly(IC) mouse model. PLoS One 8(3): e57380. [PubMed: 23516405]
111. Doehner J, Genoud C, Imhof C, Krstic D, and Knuesel I (2012): Extrusion of misfolded and aggregated proteins--a protective strategy of aging neurons? Eur J Neurosci 35(12): 1938–50. [PubMed: 22708604]
112. Anderson A, Genaro-Mattos TC, Allen LB, Koczok K, Korade Z, and Mirnics K (2021): Interaction of maternal immune activation and genetic interneuronal inhibition. Brain Res 1759: 147370. [PubMed: 33600830]
113. Gyorffy BA, Gulyassy P, Gellen B, Volgyi K, Madarasi D, Kis V, et al. (2016): Widespread alterations in the synaptic proteome of the adolescent cerebral cortex following prenatal immune activation in rats. Brain Behav Immun 56: 289–309. [PubMed: 27058163]
114. Cieslik M, Gassowska-Dobrowolska M, Zawadzka A, Frontczak-Baniewicz M, Gewartowska M, Dominiak A, et al. (2020): The Synaptic Dysregulation in Adolescent Rats Exposed to Maternal Immune Activation. Front Mol Neurosci 13: 555290. [PubMed: 33519375]
115. Cieslik M, Gassowska-Dobrowolska M, Jesko H, Czapski GA, Wilkaniec A, Zawadzka A, et al. (2020): Maternal Immune Activation Induces Neuroinflammation and Cortical Synaptic Deficits in the Adolescent Rat Offspring. Int J Mol Sci 21(11).
116. Farrelly L, Focking M, Piontkewitz Y, Dicker P, English J, Wynne K, et al. (2015): Maternal immune activation induces changes in myelin and metabolic proteins, some of which can be prevented with risperidone in adolescence. Dev Neurosci 37(1): 43–55. [PubMed: 25592202]
117. Robicsek O, Ene HM, Karry R, Ytzhaki O, Asor E, McPhie D, et al. (2018): Isolated Mitochondria Transfer Improves Neuronal Differentiation of Schizophrenia-Derived Induced Pluripotent Stem Cells and Rescues Deficits in a Rat Model of the Disorder. Schizophr Bull 44(2): 432–442. [PubMed: 28586483]

118. Al-Amin MM, Alam T, Hasan SM, Hasan AT, and Quddus AH (2016): Prenatal maternal lipopolysaccharide administration leads to age- and region-specific oxidative stress in the early developmental stage in offspring. Neuroscience 318: 84–93. [PubMed: 26774051]
119. Briscoe T, Duncan J, Cock M, Choo J, Rice G, Harding R, et al. (2006): Activation of NF-kappaB transcription factor in the preterm ovine brain and placenta after acute LPS exposure. J Neurosci Res 83(4): 567–74. [PubMed: 16435393]
120. Buss C (2021): Maternal oxidative stress during pregnancy and offspring neurodevelopment. Brain Behav Immun 93: 6–7. [PubMed: 33454300]
121. Cattane N, Richetto J, and Cattaneo A (2020): Prenatal exposure to environmental insults and enhanced risk of developing Schizophrenia and Autism Spectrum Disorder: focus on biological pathways and epigenetic mechanisms. Neurosci Biobehav Rev 117: 253–278. [PubMed: 29981347]
122. Naviaux RK, Curtis B, Li K, Naviaux JC, Bright AT, Reiner GE, et al. (2017): Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial. Ann Clin Transl Neurol 4(7): 491–505. [PubMed: 28695149]
123. Rose S, Niyazov DM, Rossignol DA, Goldenthal M, Kahler SG, and Frye RE (2018): Clinical and Molecular Characteristics of Mitochondrial Dysfunction in Autism Spectrum Disorder. Molecular diagnosis & therapy 22(5): 571–593. [PubMed: 30039193]
124. Minshew NJ, Goldstein G, Dombrowski SM, Panchalingam K, and Pettegrew JW (1993): A preliminary 31P MRS study of autism: evidence for undersynthesis and increased degradation of brain membranes. Biol Psychiatry 33(11–12): 762–73. [PubMed: 8373914]
125. Tang G, Gutierrez Rios P, Kuo SH, Akman HO, Rosoklija G, Tanji K, et al. (2013): Mitochondrial abnormalities in temporal lobe of autistic brain. Neurobiol Dis 54: 349–61. [PubMed: 23333625]
126. Nguyen Nguyen HT, Kato H, Sato H, Yamaza H, Sakai Y, Ohga S, et al. (2019): Positive effect of exogenous brain-derived neurotrophic factor on impaired neurite development and mitochondrial function in dopaminergic neurons derived from dental pulp stem cells from children with attention deficit hyperactivity disorder. Biochem Biophys Res Commun 513(4): 1048–1054. [PubMed: 31010680]
127. Roberts RC (2017): Postmortem studies on mitochondria in schizophrenia. Schizophrenia research 187: 17–25. [PubMed: 28189530]
128. Eltokhi A, Santuy A, Merchan-Perez A, and Sprengel R (2020): Glutamatergic Dysfunction and Synaptic Ultrastructural Alterations in Schizophrenia and Autism Spectrum Disorder: Evidence from Human and Rodent Studies. International journal of molecular sciences 22(1): 59.
129. Pons R, Andreu AL, Checcarelli N, Vila MR, Engelstad K, Sue CM, et al. (2004): Mitochondrial DNA abnormalities and autistic spectrum disorders. J Pediatr 144(1): 81–5. [PubMed: 14722523]
130. Patowary A, Nesbitt R, Archer M, Bernier R, and Brkanac Z (2017): Next Generation Sequencing Mitochondrial DNA Analysis in Autism Spectrum Disorder. Autism Res 10(8): 1338–1343. [PubMed: 28419775]
131. Ichikawa T, Arai M, Miyashita M, Arai M, Obata N, Nohara I, et al. (2012): Schizophrenia: maternal inheritance and heteroplasmy of mtDNA mutations. Mol Genet Metab 105(1): 103–9. [PubMed: 22030097]
132. Graf WD, Marin-Garcia J, Gao HG, Pizzo S, Naviaux RK, Markusic D, et al. (2000): Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation. J Child Neurol 15(6): 357–61. [PubMed: 10868777]
133. Napoli E, Song G, Panoutsopoulos A, Riyadh MA, Kaushik G, Halmai J, et al. (2018): Beyond autophagy: a novel role for autism-linked Wdfy3 in brain mitophagy. Sci Rep 8(1): 11348. [PubMed: 30054502]
134. Yardeni T, Cristancho AG, McCoy AJ, Schaefer PM, McManus MJ, Marsh ED, et al. (2021): An mtDNA mutant mouse demonstrates that mitochondrial deficiency can result in autism endophenotypes. Proc Natl Acad Sci U S A 118(6).
135. Pletnikov MV, Ayhan Y, Nikolskaia O, Xu Y, Ovanesov MV, Huang H, et al. (2008): Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. 13(2): 173–186.

136. Uzuneser TC, Speidel J, Kogias G, Wang AL, de Souza Silva MA, Huston JP, et al. (2019): Disruptedin-Schizophrenia 1 (DISC1) Overexpression and Juvenile Immune Activation Cause Sex-Specific Schizophrenia-Related Psychopathology in Rats. Front Psychiatry 10: 222. [PubMed: 31057438]

137. Fernandez A, Meechan DW, Karpinski BA, Paronett EM, Bryan CA, Rutz HL, et al. (2019): Mitochondrial Dysfunction Leads to Cortical Under-Connectivity and Cognitive Impairment. Neuron 102(6): 1127–1142 e3. [PubMed: 31079872]

138. Picard M, Trumpff C, and Burelle Y (2019): Mitochondrial Psychobiology: Foundations and Applications. Curr Opin Behav Sci 28: 142–151. [PubMed: 32637466]

139. Tsukada H, Nishiyama S, Fukumoto D, Kanazawa M, and Harada N (2014): Novel PET probes 18F-BCPP-EF and 18F-BCPP-BF for mitochondrial complex I: a PET study in comparison with 18F-BMS-747158–02 in rat brain. J Nucl Med 55(3): 473–80. [PubMed: 24470629]

140. Tsukada H, Ohba H, Kanazawa M, Kakiuchi T, and Harada N (2014): Evaluation of 18F-BCPP-EF for mitochondrial complex 1 imaging in the brain of conscious monkeys using PET. Eur J Nucl Med Mol Imaging 41(4): 755–63. [PubMed: 24258008]

141. Zhelev Z, Bakalova R, Aoki I, Lazarova D, and Saga T (2013): Imaging of superoxide generation in the dopaminergic area of the brain in Parkinson's disease, using mito-TEMPO. ACS Chem Neurosci 4(11): 1439–45. [PubMed: 24024751]

142. Re S, Dogan AA, Ben-Shachar D, Berger G, Werling AM, Walitza S, et al. (2018): Improved Generation of Induced Pluripotent Stem Cells From Hair Derived Keratinocytes - A Tool to Study Neurodevelopmental Disorders as ADHD. Front Cell Neurosci 12: 321. [PubMed: 30319360]

143. Fu YS, Cheng YC, Lin MY, Cheng H, Chu PM, Chou SC, et al. (2006): Conversion of human umbilical cord mesenchymal stem cells in Wharton's jelly to dopaminergic neurons in vitro: potential therapeutic application for Parkinsonism. Stem Cells 24(1): 115–24. [PubMed: 16099997]

144. Chen S, Zhang W, Wang JM, Duan HT, Kong JH, Wang YX, et al. (2016): Differentiation of isolated human umbilical cord mesenchymal stem cells into neural stem cells. Int J Ophthalmol 9(1): 41–7. [PubMed: 26949608]

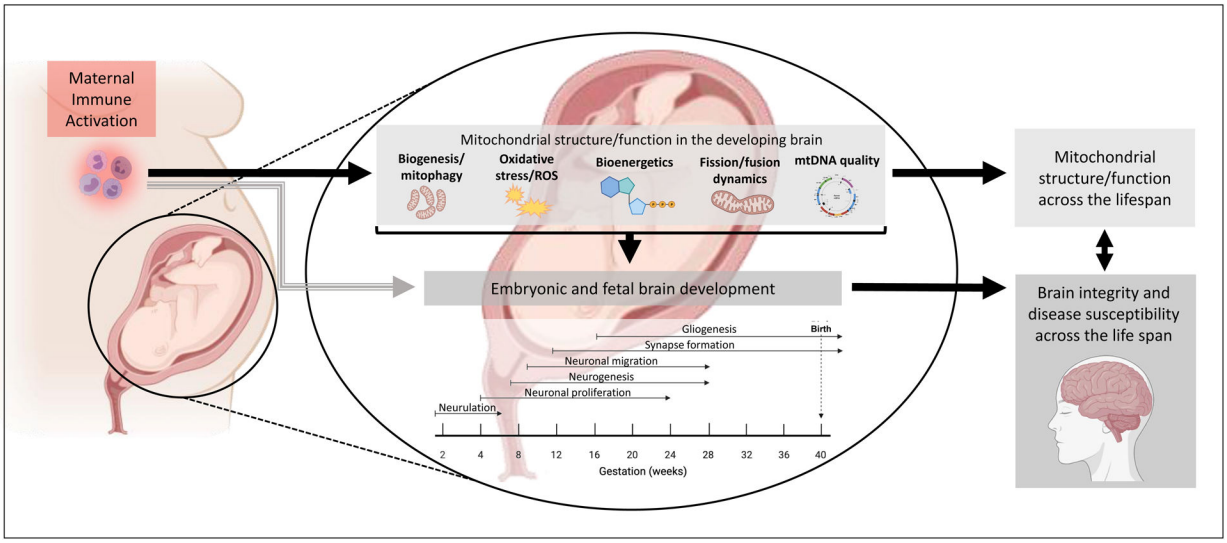

Figure 1: Conceptual Figure

Note. ROS=Reactive Oxygen Species, mtDNA=mitochondrial DNA.

Maternal immune activation (MIA) can alter aspects of offspring mitochondrial structure and function including mitochondrial biogenesis/mitophagy, oxidative stress/ROS production, bioenergetic function, fission/fusion dynamics, and mtDNA quality. *Mitochondrial biogenesis and mitophagy* refer to the coordinated control of mitochondrial content, either through the generation of new mitochondria (mitochondrial biogenesis) or the controlled destruction/regulated turnover of mitochondria (mitophagy). *Mitochondrial oxidative stress/ROS production* refer to an imbalance between free radical production (mitochondrial derived) and antioxidant control of these species, which may result in damaged proteins, lipids, DNA, etc. *Bioenergetic function* refers to mitochondrial capacity to meet the energetic needs (*e.g.*, ATP) of the cell or subcellular compartment. Mitochondria organelles form a dynamic reticulated network, and the subsections of this network can separate from and fuse with each other, referred to as *fission/fusion dynamics*. Specifically, *fusion* involves the tethering of two adjacent mitochondria followed by merging, of the inner and outer mitochondrial membranes, whereas *fission* is the opposing process of fragmentation of a mitochondrial network into two or more mitochondria. Finally, *mtDNA quality* refers to the level and phenotypic impact (burden) of mtDNA mutations and deletions within an individual mitochondrion or across mitochondria in a cell or tissue. As all of these aspects of mitochondrial function are crucially involved in neurodevelopmental processes, these MIA-induced alterations can affect neurodevelopment at different stages. Moreover, alterations in mitochondrial structure/function due to MIA may be programmed and, hence, can persist over the life span. Thus, in addition to the effects of MIA-induced alterations in mitochondrial function on the developing brain, these mitochondrial alterations may continue to exert long-term effects on the brain (and other systems) over the lifespan of the individual.

Adapted from Nutton et al. 2011, created with BioRender.com.

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Table 1:

Summary of preclinical MIA prenatal exposure studies

First Author	Year	Animal Model	MIA Protocol	Mitochondrial Effects in the Brain	Brain/Behavior Phenotypes
Briscoe, T. (123)	2006	Ovine	Prenatal exposure: Gestational day (GD) 95 intravenous bolus dose of lipopolysaccharide (LPS; 1μg/kg) vs. control (saline) directly to fetus (catheter); MIA validation: Direct fetal exposure via catheter, with demonstrated rise in cytokines.	↑*oxidative stress* in the parietal, temporal, occipital, and thalamus-basal ganglia regions (measured by ↑lipid peroxide production and 8-Isoprostane) and in the placenta	
Zhu, Y. (112)	2007	Sprague-Dawley rats	Prenatal exposure: GD 10.5 intraperitoneal (i.p). injection of LPS (10,000 endotoxin units/kg) vs. control (saline); Postnatal exposure (in separate animals without prenatal exposure): 4 months post-natal acute supranigral injection of LPS (10μg/4μl in saline) vs. control (saline); MIA validation: Not described.	↑*oxidative stress* in the midbrain (measured by ↓ glutathione (GSH) and ↑ in oxidized GSH and lipid peroxide production) [in both prenatal and postnatal LPS exposure groups]	Brain: ↓DA neuron count in the substantia nigra
Doehner, J. (115)	2012	C57BL/6J mice	Prenatal exposure: GD17 intravenous injection of Poly(I:C) (5mg/kg) vs. control (saline); MIA validation: Not described.	↑*mito density/content* in reelin-positive granules in the hippocampus	Brain: ↑size and number of reelin-immunoreactive deposits (accumulation of aggregation-prone proteins and peptides)-associated with neuritic swellings
Naviaux, R.K. (114)	2013	C57BL/6J mice	2 Prenatal exposure groups: *1)* Single dose i.p. injection of Poly(I:C) on GD12.5 (2 mg/kg); *2)* Double dose i.p. injection of Poly(I:C) on GD12.5 (3 mg/kg) & GD17.4 (1.5 mg/kg); all vs. control group (saline) [all results are reported as 2 groups combined]; Postnatal Therapy: 6 weeks postpartum received weekly suramin injection; MIA validation: Not described.	↑*mito bioenergetic function* in the cerebrum (measured by ↑ complex I and IV activity; no change in Complex II, III activity or complex protein levels) [induced by Poly(I:C) and corrected by APT therapy] No change in *mito density/content* (measured by citrate synthase)	Behavior: ↓social preference, ↓sensorimotor coordination; Brain: ↓cerebellar purkinje cell, ultrastructural synaptic dysmorphology, ERK1/2 and CAMKII signal transduction abnormalities. [All are induced by Poly(I:C) and rescued by APT treatment]
Farrelly, L. (120)	2015	Wistar rats	Prenatal exposure: G15 intravenous injection of Poly(I:C) (4 mg/kg) vs. control (saline); Postnatal Therapy: Postnatal Day (PND) 34–47 i.p. daily injection of risperidone (0.045 mg/kg) vs. control (saline); MIA validation: Not described.	↑ *mito bioenergetic proteins* in the prefrontal cortex (PFC) (measured in unbiased proteomics: top 2 significantly different pathways were related to primarily ↑mitochondrial OXPHOS and tricarboxylic acid cycle (TCA cycle) proteins) [induced by Poly(I:C) with some reversed by risperidone treatment]	Brain: Measured 7 myelin and myelin-related proteins in the PFC, 2 were altered by Poly(I:C) (measured in hypothesis driven proteomics analysis- isoform 3 of myelin basic protein and rhombex 29 were altered by Poly(I:C)).
Al-Amin, M.M. (122)	2016	Swiss albino mice	Prenatal exposure: GD 16 i.p. injection of LPS (50 μg/kg) vs. control (water); MIA validation: Not described.	↑ *oxidative stress* that is age and brain region specific (measured on PND 1- ↑ GSH level, ↓ superoxide dismutase activity; PND 7- ↑advanced oxidation of protein product level; PND 14- ↑lipid peroxidation (MDA) and activity of catalase; PND 21- ONLY ↑MDA remains (across all brain regions measured: hippocampus and cerebellum, cortex)	
Györffy, B.A. (117)	2016	Wistar rats	Prenatal exposure: GD 13.5 i.p. injection of LPS (20 μg/kg) vs. control (saline); MIA validation: Demonstrated rise in rectal temperature of dams 3hrs post LPS injection.	Altered proteins in energy homeostasis/carbohydrate metabolism (proxy for *mito bioenergetic function)* Altered proteins in *oxidative stress*	Brain: Altered proteins in neurite outgrowth/cytoskeleton and synaptic vesicle exo- and endocytosis.

First Author	Year	Animal Model	MIA Protocol	Mitochondrial Effects in the Brain	Brain/Behavior Phenotypes
Swanepoel, T. (113)	2018	Sprague-Dawley rats	Prenatal exposure: GD15–16 subcutaneous injection of LPS (100 μg/kg) vs. control (saline); Postnatal challenge & therapy: Postnatal day (PND) 35–50 methamphetamine (MA) with N-acetyl cysteine (NAC) treatment vs control PND 51–64; MIA validation: Not described.	↑ *oxidative stress* in the frontal cortical and striatum (measured by ↑MDA, marker of lipid peroxidation) and ↑in plasma ROS [in both prenatal LPS exposure and LPS + 2nd hit postnatal MA exposure groups; All reversed by NAC therapy]	Behavior: ↑social withdrawal, ↓recognition memory, deficit in prepulse inhibition [induced by LPS and LPS+MA; reversed by (mostly) NAC]; Brain: ↑frontal cortical dopamine and noradrenaline [induced by LPS and LPS+MA; reversed by NAC]
Robicsek, O. (121)	2018	Wistar rats (*in-vivo model*); see manuscript for *in-vitro* model	Prenatal exposure: GD15, injected into the tail vein with poly-I:C (4 mg/kg/ml) vs. control (saline); Postnatal therapy: PNDs 34–46 isolated active normal mitochondria (IAN-MIT) (100 μg/4.5μl), injected into the medial prefrontal cortex; MIA validation: Not described.	↓*mito bioenergetic function* in frontal cortex neurons (measured by mitochondrial membrane potential (MMP)) [induced by Poly(I:C) and rescued by IAN-MIT therapy] No change in mitochondrial distribution and network connectivity	Behavior: Latent inhibition was absent in Poly(I:C) exposed mice, but was rescued by IAN-MIT postnatal therapy.
Cieślik, M. (119)	2020	Wistar rats	Prenatal exposure: GD9.5 i.p. injection of LPS (100 μg/kg) vs. control (saline); MIA validation: Demonstrated maternal sickness behavior up to 24hrs post LPS injection.	Altered *mitochondrial structure/morphology* in cerebral cortex (measured by ultrastructural changes (cristae blurring)) ↑ *oxidative stress* in the cerebral cortex (measured by ↑12-lipoxygenase and cyclooxygenase-2 mRNA levels, ↑DCF fluorescence (to quantify ROS), ↑oxidized GSH (GSSG),↓GSH/GSSG ratio)	Behavior: ↑ heterogeneity in intensity of play behavior, ↓social interaction (no change in locomotor and exploratory activity, anxiety-related behavior); Brain: ↓Formation and turnover of synaptic vesicles (protein levels), disturbed synaptic membranes & changed myelin (via ultrastructural measurement)
Anderson, A. (116)	2021	Wild type (WT) rats (see manuscript for transgenic models)	Prenatal exposure: GD12.5 i.p. injection of Poly(I:C) (100 μL/10g) vs. control (saline) [Poly(I:C) exposure given to WT and transgenic mice- only WT discussed here]; MIA validation: Not described, but cite previous studies conducted by lab with demonstrated cytokine rise.	Altered energy metabolism and acylcarnitine species in the neocortex (authors argue proxy for *mitochondrial metabolism)*	
Cieślik, M. (118)	2021	Wistar rats	Prenatal exposure: GD9.5 i.p. injection of LPS (100 μg/kg) vs. control (saline); MIA validation: Demonstrated maternal sickness behavior up to 24hrs post LPS injection.	↓*mito bioenergetic function* in the hippocampus (measured by ↓ gene expression for Complex I (mt-Nd1) and Complex IV (mt-Co1), ↓protein level for ND1 (CI), ↓ CI enzyme activity (no change CIV), and ↓ MMP) Altered *mitochondrial structure/morphology* in the hippocampus (measured by ultrastructural changes of synaptic mitochondria (“swollen” mitochondria) ↑*oxidative stress* in the hippocampus (measured by ↓reduced/oxidized glutathione ratio (indicates enhanced generation of ROS); ↓ total GSH; ↑oxidized DCF (proxy for ROS); ↓mito antioxidant enzymes(Sod1 and Sod2))	Brain:↑size of synaptic cleft (no change in size and # of synaptic vesicles (SVs)), ultrastructural changes in synapses (↓packing density of SVs in the presynaptic area, blurred and thickened structure of the synaptic cleft), altered synaptic proteins