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Autism Spectrum Disorders: The Mitochondria Connection

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Abstract: Autism spectrum disorders (ASD) are considered neurodevelopmental disorders characterized by restricted patterns of behavior and difficulties with communication and social interaction. Cumulative evidence suggests ASD have a wide range of co-occurring multisystemic conditions beyond the primary diagnosis. However, the etiology of ASD still eludes us. Finding a key cellular process responsible for the cognitive features, specific behaviors, and abnormalities in multiple systems presents major challenges to researchers. Mitochondria are multifaceted organelles involved in many cellular functions. The relationship between mitochondria and ASD has been studied for many years. Mitochondria may play a crucial role in ASD pathophysiology. By reviewing the connections between mitochondria and ASD from genes, pathways, biological activities, and clinical manifestations, we hope to provide clues for future studies that elucidate the biological basis of ASD symptoms and behaviors.

Keywords: autism; cell signaling; energy metabolism; information processing; mitochondria

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INTRODUCTION

Autism, or autism spectrum disorders (ASD), is a developmental disorder diagnosed as early as 18 months. Signs of ASD often develop during the ages 2 and 3. According to the Centers for Disease Control, about 1 in 54 children was identified with ASD in the United States in 2016 (1). The diagnosis of ASD is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) autism diagnostic criteria. There are three severity levels of ASD: level 1 "requiring support," level 2 "requiring substantial support," and level 3 "requiring very substantial support." Autism is a chronic condition that could last years or be lifelong. Currently, there is no proven cure for ASD, but there are treatments that can help with symptoms. The cause of ASD is unclear. There are no pathognomonic biological features identified that are responsible for the heterogeneity of ASD. It is believed that there are multiple causes of ASD, including many genetic and environmental factors. So far, more than a thousand genes have been identified to be related to ASD at different levels of involvement. Environmental factors include prenatal exposure to toxins, prenatal stress, prenatal trace metal dyshomeostasis, maternal metabolic conditions, and maternal immune system disorders among others (2). The complexity of ASD poses major challenges to research.

Mitochondria are double-membrane-bound organelles existing in most cells of eukaryotes. They are called the "powerhouse of the cell" as they produce most of the energy cells need. They convert the energy from chemical fuels (such as pyruvate from glucose, fatty acids from fats, and amino acids) and generate adenosine triphosphate (ATP), which is the chemical energy currency of the cells. The process is called oxidative phosphorylation, and it is conducted by electron transport chain (ETC) complexes (Complex I, II, III, and IV) and ATP synthase (Complex V) (3). Besides energy conversion, mitochondria are also in the center of cellular information processing, such as signaling, cellular differentiation, cell death, and growth. They control calcium homeostasis and regulate calcium signaling, which is vital to many cellular activities (4, 5). A group of proteins functioning in mitochondria determine if a cell will undergo apoptosis (programmed cell death) or proliferation (3). The number of mitochondria in different types of cells varies. Normally, the more energy a type of cell needs, the more mitochondria they have. For example, the heart muscle cells have the most mitochondria as they have a high energy demand. Each mitochondrion has its own genome, different from the genome in the cell nucleus. The human mitochondrial genome has 37 genes, 13 of which encode 13 proteins involved in the oxidative phosphorylation process. Thus, mitochondrial DNA (mtDNA) encoded proteins affect the cellular energy metabolism directly. In humans, mtDNA is mostly maternally inherited. In rare cases, mtDNA can be from both parents (6).

There is mounting evidence supporting the idea that mitochondria play an important role in ASD pathophysiology. For example, mtDNA mutations and mitochondrial functional disturbances were higher in individuals with ASD than in the general population. Mitochondria disorders and ASD share a lot of common clinical manifestations. ASD-related genes are enriched in the pathways that function in/around mitochondria. Elucidating the biological mechanisms of the mitochondria-ASD connection may help researchers solve the ASD etiology puzzle.

MITOCHONDRIAL DYSFUNCTION IN ASD

As early as 1985, lactic acidosis, a common feature of mitochondrial disease, was observed in ASD (7). An exploratory population-based, case-control study found that 8 out of 10 autistic children had higher plasma pyruvate levels, indicating mitochondrial dysfunction. It also found mtDNA over-replications in 5 out of 10 cases and mtDNA deletions in 2 cases (8). A genetic study found that 10 out of 60 ASD individuals had mtDNA deletions (9). A cohort study found mtDNA haplogroup variation is a risk factor for ASD (10). Further, postmortem studies found lower expression levels of mitochondrial ETC complexes in the cerebellum and the frontal and temporal regions of the brain (11) and compromised mitochondrial function in the temporal lobe of individuals with ASD (12). Defects in skeletal muscle ETC complexes were also identified in individuals with ASD in several studies (13). A brain-imaging study found that a mitochondrial biomarker, lactate, was significantly higher in autistic brains (14). A meta-analysis of 68 publications found that the prevalence of mitochondrial disease in ASD was 5%, while it was 0.01% in the general population. Additionally, levels of mitochondrial markers such as lactate, pyruvate, carnitine, and ubiquinone were significantly different between ASD and controls (15). Autistic regression is also linked to mitochondrial disease (16). Collectively, mitochondria abnormalities were observed in both the brain and the body in individuals with ASD.

MITOCHONDRIAL DYSFUNCTION/DISEASES AND ASD HAVE COMMON CLINICAL MANIFESTATIONS

Studies found that ASD and mitochondrial disease have overlapping clinical features (17). If mitochondria were not functioning properly, it could cause multisystem disorders affecting more than one type of cell or organs. As mitochondria are the "powerhouse of the cell", those that require high energy to function well, such as heart, brain, muscles, and gastrointestinal tract, tend to be affected most with mitochondrial dysfunction/diseases. Symptoms and severity can vary greatly amongst individuals as they depend on which body part is affected and the ratio of healthy/defective mitochondria in the cells. Some of the symptoms include developmental delay or disability, seizures, strokes, vision impairment, hearing impairment, language impairment, slow growth, fatigue, movement disorders, diabetes, heart/liver/kidney conditions, respiratory conditions, gastrointestinal (GI) conditions, and cancer (3).

Like mitochondrial disorders, ASD manifests differently in different individuals, hence the term "spectrum". It also comes with a large number of comorbid medical conditions. However, what causes the diverse variations remains unclear. The core symptoms of ASD are social and communication difficulties along with stereotypic and repetitive behaviors. In addition, individuals with ASD may experience inappropriate social interaction, restricted interests, learning disability, intellectual disability, language impairments and developmental delay. Autism is considered a primary central nervous system (CNS) disorder. The comorbid

neurological conditions of ASD include attention deficit hyperactivity disorder (ADHD), epilepsy, seizure, and sleep disorders (18, 19). However, as more and more non-neurological features were observed, our view of ASD has shifted to a spectrum disorder that affects multiple physiological systems. These multisystem conditions include GI conditions (20), cardiac conditions, respiratory conditions, asthma, low blood pressure and prediabetes (21), immune dysregulation (22), and metabolic dysfunction (23). A study reported that 86.9% of autistic individuals were at risk for motor impairment (24). Low muscle tone is also observed in individuals with ASD (25).

Comparing the clinical features of mitochondrial dysfunction and ASD, we see that both disorders have various symptoms in type and severity, affecting multiple systems. However, the common clinical features are primarily neurological, cardiac, or muscle-related, all of which are intensive energy usage systems.

ENERGY CONVERSION

Cells rely on mitochondria to convert food into ATP to function. Mitochondria consist of an outer and an inner membrane separated by an intermembrane space, the cristae formed by the infoldings of the inner membrane, and the matrix, which is the space within the inner membrane. ATP is generated at the inner membrane by oxidative phosphorylation involving ETC complex I-IV and ATP synthase. The ETC complexes pump the protons (H^+) from the matrix into the intermembrane space and create an electrochemical gradient, using the energy released by the electron transfer from NADH and FADH2, which are produced in the tricarboxylic acid (TCA) cycle in the matrix. The ATP synthase releases the protons back into the matrix while using the proton flow as the energy source to produce ATP. This process requires the mitochondrial membrane to be intact to maintain the proton gradient. Otherwise, the energy production will stop, and the cell will die. This process is oxygen-dependent and is known as aerobic respiration. It requires oxygen to receive electrons from NADH and FADH2, allowing more electrons to be passed along, thus maintaining the proton pumping.

Several studies found decreased ETC complex expression levels or activities in different regions of the brain in autistic individuals (26). In addition, brain and body energy metabolism disturbances were found in ASD in several studies, with or without mtDNA mutations (16). Thus, there is a link between energy metabolism and ASD, especially in the brain.

Information processing and signal transmission are the main functions of the brain, which are energy-intensive. A single neuron uses approximately 4.7 billion ATPs per second in a resting brain (27). For adults in a resting state, the brain uses about 20% of all the body's energy (28). Studies found that brain energy use was highest in child development—as high as 66% of the body's resting metabolism (29, 30). One would imagine that lack of energy, especially during brain development, would radically affect the function of the brain. This makes us wonder if the root cause of energy metabolism disturbances in ASD is due to the malfunction of mitochondria during brain development. The number of abnormal mitochondria the cells have, and the types of cells affected could explain the multisystemic autistic traits and different levels of severity.

INFORMATION PROCESSING

It was suggested that ASD are disorders of neural information processing, and that multiple causal factors affect the developing brain and shift the way the brain process information, thus altering cognition and behavior (31). Studies found that individuals with ASD had a reduction or constraint in information processing, and it was correlated with social and communication challenges (32, 33). Mitochondria play a central role in information processing. They control calcium homeostasis and are involved in all kinds of important cell signaling. They are also the key players in apoptosis.

Calcium homeostasis and calcium signaling

Mitochondria take up calcium ions (Ca^{2+}) through the inner membrane into the matrix and store them there. The calcium accumulation is driven by the membrane potential from the electrochemical proton gradient generated by ETC. The mitochondrial outer membrane is permeable to Ca^{2+}. On the inner membrane, there is mitochondrial calcium uniporter (MCU) that can accumulate calcium rapidly. The Na^{+}-Ca^{2+} exchangers mediate the release of Ca^{2+} back to the cytosol. The ability to uptake, store (up to 20-fold more calcium than cytosol), and release the Ca^{2+} make mitochondria an intracellular calcium buffer (4, 5).

Being the calcium stores inside the cells, mitochondria sense and regulate cellular calcium signaling. The relationship between mitochondria and calcium is a two-way road; calcium also regulates mitochondrial dynamics and functionality. In addition, calcium is a regulator in the TCA cycle and plays a role in apoptosis (34). Thus, calcium signaling regulates numerous cellular processes, including cellular motility, muscle contraction, neuron excitability, gene transcription, cell proliferation, cell differentiation, and apoptosis, among others (35). Calcium signaling abnormalities were linked to hypertension, heart disease, diabetes, manic depression, and Alzheimer's disease (36).

Genes that encode voltage-gated calcium channels (such as *CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1E, CACNA1F, CACNA1G, CACNA1H*, and *CACNA1I*) were identified to be associated with ASD (37). In addition, intracellular calcium dysregulation has been studied in ASD, and a hub role was suggested for calcium signaling in the pathophysiology (38–40).

It is suggested that the mitochondrial calcium flux (influx and efflux) is necessary for neurotransmission (41). Synapses are essential for the neurotransmission between neurons and other cells. A synapse is a junction between two nerve cells that allow them pass signals. Mutations in genes associated with synaptic structure and function such as *TSC1, TSC2, NF1, SHANK3, CHD10, NLGN3, NLGN2*, and *NRXN1* have been found in ASD (42, 43). Therefore, synaptic dysfunction is considered a contributor to ASD pathophysiology. Both genetic and environmental factors can cause synaptic dysfunction (43), which leads to cognitive impairments. Neurotransmitter imbalance is also observed in ASD (44). Altered levels of Gamma-aminobutyric acid (GABA), glutamate, and serotonin (5-hydroxytryptamine, 5-HT) were found in ASD. In addition, dopaminergic signaling pathway alterations were reported in the autistic brain. Magnetic resonance imaging (MRI)

studies showed a significant reduction of N-acetyl aspartate (NAA) in the brain of individuals with ASD. Altered plasma levels of oxytocin have also been found in autistic individuals (45).

Signaling pathways

Mitochondria are a signaling platform. They are involved in many important cell signaling pathways that regulate a wide range of cellular activities. These pathways include, among others, calcium-dependent mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)-Akt, mammalian target of rapamycin (mTOR), wingless-int (Wnt), Ras, AMP-activated protein kinase (AMPK), and insulin signaling pathways (46). These pathways have complex and diverse cellular functions, such as cell proliferation, differentiation, migration, cytoskeletal dynamism, growth, survival, cell cycle regulation, transcription, translation, metabolism, immune response, autophagy, protein synthesis, and many more. Many of these signaling pathways were found to be associated with ASD. ASD-related genes function in Ras/MAPK/PI3K/Akt/mTOR signaling and insulin signaling pathways have been observed (46, 47). A study using pathway network analysis identified MAPK signaling pathway and calcium signaling pathway, specifically their integrated part, "calcium-PRC (protein kinase C)-Ras-Raf-MAPK/ERK," as a hub and a major contributor to ASD pathophysiology (38). Mutations in the PI3K-Akt-mTOR pathway were found in individuals with ASD (48). Dysregulated IGF-1/PI3K/AKT/mTOR signaling was suggested to be associated with ASD (49). Altered Wnt signaling (50) and Ras-MAPK signaling (51) are also linked to ASD.

Oxidative stress and inflammation

Mitochondria regulate reactive oxygen species (ROS) generation and elimination. ROS are highly reactive chemical molecules containing oxygen formed from oxidative phosphorylation due to the electron receptivity of O_2. ROS can cause damage to DNA, RNA, proteins, and lipids as they oxidize these cellular components. Cells have a protective mechanism—a variety of antioxidant enzymes to eliminate the ROS to avoid oxygen toxicity and damage to the cell structures. However, if there is a dramatic increase of the ROS level, or the elimination is inefficient, either of which could disrupt the ROS balance and cause harm to the cells—known as oxidative stress (3). At normal levels, some ROS function as redox (reduction-oxidation reaction) messengers in cell signaling. Thus, oxidative stress not only will damage cell components but also disrupt ROS-dependent cell signaling. Long-term oxidative stress could trigger chronic inflammation and lead to many medical conditions.

Oxidative stress, inflammation, and immune system dysfunction have been studied in ASD for a long time. Higher rates of mitochondrial hydrogen peroxide production were observed in individuals with ASD (8). Elevated levels of lipid peroxidation markers, decreased levels of serum antioxidants, and altered activities of antioxidant enzymes, all of which indicating oxidative stress, have been found in ASD (52). Increased plasma levels of pro-inflammation cytokines, higher expression of neuroinflammation markers in postmortem brain samples, and cytokine/chemokine imbalance were detected in ASD (53). These findings suggest immune system dysfunction is associated with ASD.

Apoptosis

Apoptosis is a cellular process that allows cells to die in a programmed fashion, which is a highly regulated process. For example, if the cells were damaged beyond repair, they undergo apoptosis. Apoptosis is also a necessary process during development, including neural development. There are two major pathways, the intrinsic pathway (the initial signals come from inside the cells) and the extrinsic pathway (the initial signals come from outside of the cells – from other cells) that start the apoptosis. Both pathways induce cell death by activating caspases, leading to the caspase cascade, a chain reaction of protein degradation. The intrinsic pathway is also called the mitochondrial pathway, as mitochondria are essential to the process.

The B-cell lymphoma 2 (Bcl-2) family of proteins consist of anti-apoptotic proteins (e.g., Bcl-2, Bcl-XL) and pro-apoptotic proteins (e.g., Bax, Bak). In healthy cells, the anti-apoptotic proteins inhibit the action of pro-apoptotic proteins by binding to them. However, during apoptosis, anti-apoptotic proteins no longer block the pro-apoptotic proteins, which will promote mitochondrial outer membrane permeabilization and lead to the activation of caspases (3, 54).

Apoptosis is vital for brain development, and abnormal apoptosis is found in ASD (55). Postmortem studies found the expression level of Bcl-2 protein was significantly reduced by 34–51% in different regions of the brain, and while the Bcl-2 was decreased, p53, caspase-3, and cathepsin D were significantly increased (56–61). A study examining lymphoblasts from the blood of autistic individuals found decreased expression of Bcl-2 by 32% and increased expression of cathepsin D by three times (62). The samples in these studies were mostly from children and adolescents. The decrease of anti-apoptotic protein and increase of pro-apoptotic proteins suggest excessive apoptosis in the brain of autistic individuals at an early age. Altered brain growth was observed in ASD: studies reported abnormal overgrowth during the first two years, followed by slow or arrested growth (63). Excessive apoptosis may be the major contributor of the abnormally slow brain growth.

The information processing theory in psychology describes how we process—perceive, analyze, manipulate, use, store, and recall—the information we receive, rather than simply responding to stimulus. As children grow, their cognitive ability to process and respond to the information they receive improves. The core symptoms of ASD are social interaction and communication difficulties. Individuals on the spectrum may have difficulty identifying and processing the feelings/emotions of others. This seems like the brain is wired differently in the information processing part during development. As discussed above, mitochondrial functions are associated with ASD in many ways in the information processing perspective. However, there is a long way from the clinical features to the underlying biological mechanism, and many blanks between cellular information processing and human behaviors need to be filled.

NON-CODING RNA POSSIBILITIES

Non-coding RNAs (ncRNAs) are RNAs that are not translated into proteins. Types of ncRNA include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small RNAs, long ncRNAs (lncRNAs), and circular RNAs (CircRNAs). For a long time, ncRNAs

have been ignored as they were thought to be non-functional. However, growing evidence suggests otherwise. ncRNAs are emerging as important regulators of various cellular processes such as epigenetic regulation and gene expression regulation. They also are associated with multiple disorders, including neurological disorders, cardiovascular diseases, and cancer (64).

A number of ncRNAs have been identified to be associated with ASD. Hundreds of lncRNAs are reported to be expressed differently in ASD, in the blood, and the brain. Some of them are involved in the regulation of *BDNF* and *SHANK2,* which are ASD-related genes, and some of them regulate genes that regulate synaptic density and structure (65). microRNAs (miRNAs), such as miR-132, miR-23a, miR-93, miR-106b, miR-146b, and miRNA-148b, were found expressed differently in the blood and brain of ASD individuals (66).

So far as we know, besides the nucleus, mitochondria are the only organelles that have their own genome (mtDNA) and their own machinery to synthesis RNA and proteins. According to MitoCarta3.0 (67), there are 1136 human genes encoding proteins localized in mitochondria. mtDNA has 37 genes encoding 22 tRNAs, 2 rRNAs, 13 proteins which are some of the subunits of the ETC and ATP synthase (68). The rest of the proteins in the mitochondria are encoded by nuclear DNA (nDNA) and imported from the cytoplasm. Due to this unique mitochondrial genetic system, there is intense crosstalk between mitochondria and nucleus, which is mediated by many factors, including ncRNA (69). It is reported that mitochondria produce their own lncRNAs and miRNAs, and there is also crosstalk between mitochondria ncRNAs and nuclear ncRNAs (70). Mitochondria ncRNAs are reported to be linked to mitochondrial disease. ncRNAs regulate mitochondria function in all aspects, including the TCA cycle, oxidative phosphorylation, fatty acid/amino acid/nucleotide metabolism, mitochondrial transport and dynamics, and ROS production (71). Therefore, it is not surprising that ncRNAs were associated with mitochondria-related diseases, including neurodegenerative diseases, heart disease, diabetes, and cancer (70, 71).

Little is known regarding the relationship between ncRNA, ASD, and mitochondria. However, as discussed above, given that ncRNAs are involved in numerous mitochondrial activities, it is highly possible that ncRNAs regulating mitochondria function and mitochondria-nucleus crosstalk would be involved in ASD. Although adding a new dimension to the already complex network between mitochondria and ASD, it is worth exploring the roles of ncRNAs in this relationship to understand the whole picture of the mitochondria-ASD connections and to help develop new RNA and/or gene therapies for the condition.

MACHINE LEARNING TOOLS FOR FUTURE STUDIES AND THERAPEUTIC TREATMENT DEVELOPMENT

There are growing interests in applying machine learning techniques in ASD research, specifically in the diagnostic process of ASD (72–76). Machine learning could also help researchers classifying ASD traits (77). The main applications include the classification of ASD using behavioral data, neuroimaging data, developmental data, genetic data, and electronic health records. A related topic is

identifying essential features, such as neuroimaging biomarkers and genes associated with ASD, which benefit classification accuracy and improve the understanding of the disorder. In these tasks, supervised learning methods, which train the models using the labeled historical data, are preferred. The methods adopted in the literature include support vector machine, decision trees, random forest, linear discriminant analysis, logistic regression, k-nearest neighbors, least absolute shrinkage and selection operator regression, elastic net, and so on. Different types of neural networks were also implemented, including feedforward neural networks, convolutional neural networks, long short-term memory, etc. Theoretically, any classification algorithms applied to pattern recognition can also be implemented to ASD diagnosis. Some researchers have also studied unsupervised learning to detect ASD by using clustering analysis (78, 79). This type of technique is typically useful when there is a lack of labeled data. Without the labeled data from the knowledge already known, there is a chance to explore new possibilities and find new clues that researchers might otherwise ignore. Compared to supervised classification, the studies on ASD diagnosis based on clustering are relatively few. Another related research field is ASD text mining, which aims to extract knowledge from existing ASD research or social network data through machine learning.

However, despite that machine learning offers promising solutions for ASD diagnosis and is becoming complementary to the clinician-led diagnostic processes, its performance largely depends on the amount and quality of the historical data for model training. In many cases, machine learning simply represents "the same biases, conceptual flaws, and practical weaknesses evident in existing diagnostic processes" of the historical data generated (80). Therefore, the application in clinical settings is still limited and in development.

Besides helping diagnosis, machine learning is also applied in analyzing large gene data, specifically at the genome scale, given that genetics has been one of the most extensively studied areas in ASD research. According to AutDB (a modular database for autism research), an evolving database integrating different kinds of genetic data generated by research studies, 1241 genes are currently associated with ASD (81). Numerous approaches were developed to help find new ASD risk genes and validate/evaluate their association to ASD (79, 82, 83).

Machine learning tools are also used to help identify ASD blood biomarkers by performing the proteomic analysis (84), which is usually a complex and time-consuming task without a powerful analyzing tool. Machine learning-based decision-making tools are also used to screen and discover new treatments/drugs to treat neuropsychiatric disorders by analyzing the different biomarkers (genetic and biochemical) and molecules to chemical reactions. This approach could also help identify the best treatment for each patient by analyzing the treatment response from each patient, so-called precision medicine (85).

There is growing interest in applying graph machine learning (GML) in biomedicine research as GML is a valuable tool to mine graph-structure data, model functional relationships amongst genes, proteins, and other molecules using multiple datasets. Deep neural networks, specifically graph neural networks (GNNs), are used for analyzing graph-structure data. GNNs update the features of nodes in a network from the information of the neighboring nodes (86). In ASD research, GNNs are mostly used in brain fMRI (functional MRI) data to characterize the brain changes in ASD and look for fMRI biomarkers (87–90).

To the best of our knowledge, there is no research focusing on exploring the connections between mitochondria-related biological features and ASD with the help of machine learning. With accumulating evidence putting the mitochondria under the spotlight, a machine learning-based approach that analyzes the complex multisystemic connections between mitochondria and ASD could be fruitful in finding the biological mechanism of ASD and develop a new strategy for treatment. As Randolph-Gips and Srinivasan proposed (78), a systems model involving time scales (as ASD are developmental disorders) is very much needed for ASD research which includes the parameters such as genetics, biochemical markers from lab tests, symptoms and severity, treatments, and treatment outcomes. Deep learning modeling algorithms could be a game-changer as they provide great analyzing power to the playground in gene/protein interactions and disease modeling.

CONCLUSION

Extensive research has been done regarding the ASD-mitochondria connections. New investigations are in progress and novel findings are being discovered. What we discussed here is only a small portion of the enormous research results. This review is focused on the two main functions of mitochondria—energy conversion and information processing—and their connections to ASD from genetics to clinical manifestations. The core symptoms and multisystemic comorbid conditions of ASD gathering around the energy-intensive systems suggesting an energy problem with ASD. This idea is supported by the mtDNA abnormalities, decreased expression levels and activities of ETC complexes, and energy metabolism disturbances found in individuals with ASD.

Energy is required for all cellular processes, including information processing and signal transmission. On the other hand, cell signaling also regulates energy production. The interplay of energy and information is the fundamental element of cellular activities. Many of the mitochondria-related signaling pathways that are important to brain functions are found defective in ASD. These pathways also function in multiple systems and are related to immune system dysfunction and metabolic conditions other than ASD. Mitochondria are essential to apoptosis which is vital to brain development. Differently expressed apoptosis-related proteins localized on the mitochondrial membrane were observed in the autistic brain, indicating excessive apoptosis of brain cells during development. This is consistent with altered brain growth that was observed in children with ASD.

Emerging studies regarding ncRNA and ASD, and ncRNA and mitochondria, provide clues for a new dimension to the mitochondria-ASD connections, which also add a new layer of complexity to the already complicated network.

Though there is mounting evidence regarding ASD and mitochondria, putting the pieces together and drawing a complete picture of their connections require more biological mechanisms to be deciphered. The complexity of both mitochondria and ASD, and the extremely complex network between them pose major challenges to researchers. A systems model using new techniques such as machine learning could very much help with the task. Integrating data mining

and machine learning with existing research results from multiple disciplines could help elucidating the biological mechanisms underlying the clinical features. It could also help find new interventions and develop personalized healthcare for ASD. Once developed, the model could be applied to other complex medical conditions beyond ASD as mitochondria are involved in many medical conditions.

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REFERENCES

1. Maenner MJ. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. MMWR Surveill Summ. 2020 [cited 2021 May 21];69.
2. Grabrucker AM. Environmental Factors in Autism. Front Psychiatry. 2013 [cited 2021 May 22];3. https://doi.org/10.3389/fpsyt.2012.00118
3. Wen Y. Maxwell's demon at work: Mitochondria, the organelles that convert information into energy? Chronic Dis Transl Med. 2018;4(2):135–8. https://doi.org/10.1016/j.cdtm.2018.05.002
4. Giorgi C, Marchi S, Pinton P. The machineries, regulation and cellular functions of mitochondrial calcium. Nat Rev Mol Cell Biol. 2018;19(11):713–30. https://doi.org/10.1038/s41580-018-0052-8
5. Rizzuto R, De Stefani D, Raffaello A, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. Nat Rev Mol Cell Biol. 2012;13(9):566–78. https://doi.org/10.1038/nrm3412
6. Luo S, Valencia CA, Zhang J, Lee N-C, Slone J, Gui B, et al. Biparental Inheritance of Mitochondrial DNA in Humans. Proc Natl Acad Sci USA. 2018;115(51):13039–44. https://doi.org/10.1073/pnas.1810946115
7. Coleman M, Blass JP. Autism and lactic acidosis. J Autism Dev Disord. 1985;15(1):1–8. https://doi.org/10.1007/BF01837894
8. Giulivi C, Zhang Y-F, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, et al. Mitochondrial Dysfunction in Autism. JAMA J Am Med Assoc. 2010;304(21):2389. https://doi.org/10.1001/jama.2010.1706
9. 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. Behav Brain Funct. 2018;14(1):4. https://doi.org/10.1186/s12993-018-0135-x
10. Chalkia D, Singh LN, Leipzig J, Lvova M, Derbeneva O, Lakatos A, et al. Association Between Mitochondrial DNA Haplogroup Variation and Autism Spectrum Disorders. JAMA Psychiatry. 2017;74(11):1161–8. https://doi.org/10.1001/jamapsychiatry.2017.2604
11. Chauhan A, Gu F, Essa MM, Wegiel J, Kaur K, Brown WT, et al. Brain region-specific deficit in mitochondrial electron transport chain complexes in children with autism. J Neurochem. 2011;117(2):209–20. https://doi.org/10.1111/j.1471-4159.2011.07189.x
12. Tang G, Rios PG, Kuo S-H, Akman HO, Rosoklija G, Tanji K, et al. Mitochondrial abnormalities in temporal lobe of autistic brain. Neurobiol Dis. 2013;54:349–61. https://doi.org/10.1016/j.nbd.2013.01.006

13. Griffiths KK, Levy RJ. Evidence of Mitochondrial Dysfunction in Autism: Biochemical Links, Genetic-Based Associations, and Non-Energy-Related Mechanisms. Oxid Med Cell Longev [Internet]. 2017 [cited 2021 May 21];2017. https://doi.org/10.1155/2017/4314025
14. Goh S, Dong Z, Zhang Y, DiMauro S, Peterson BS. Brain imaging evidence that mitochondrial dysfunction is a neurobiological subtype of Autism Spectrum Disorder. JAMA Psychiatry. 2014;71(6):665–71. https://doi.org/10.1001/jamapsychiatry.2014.179
15. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012;17(3):290–314. https://doi.org/10.1038/mp.2010.136
16. Chauhan A, Gu F, Chauhan V. Mitochondrial respiratory chain defects in autism and other neurodevelopmental disorders. J Pediatr Biochem. 2012;2(4):213–23. https://doi.org/10.1055/s-0036-1586418
17. Frye RE, Rossignol DA. Mitochondrial dysfunction can connect the diverse medical symptoms associated with autism spectrum disorders. Pediatr Res. 2011;69(5 Pt 2):41R-47R. https://doi.org/10.1203/PDR.0b013e318212f16b
18. Mannion A, Leader G. Comorbidity in autism spectrum disorder: A literature review. Res Autism Spectr Disord. 2013;7(12):1595–616. https://doi.org/10.1016/j.rasd.2013.09.006
19. Doshi-Velez F, Ge Y, Kohane I. Comorbidity Clusters in Autism Spectrum Disorders: An Electronic Health Record Time-Series Analysis. Pediatrics. 2014;133(1):e54–63. https://doi.org/10.1542/peds.2013-0819
20. Hsiao EY. Gastrointestinal Issues in Autism Spectrum Disorder. Harv Rev Psychiatry. 2014;22(2):104–11. https://doi.org/10.1097/HRP.0000000000000029
21. Weir E, Allison C, Warrier V, Baron-Cohen S. Increased prevalence of non-communicable physical health conditions among autistic adults. Autism. 2021;25(3):681–94. https://doi.org/10.1177/1362361320953652
22. Hsiao EY. Immune dysregulation in autism spectrum disorder. Int Rev Neurobiol. 2013;113:269–302. https://doi.org/10.1016/B978-0-12-418700-9.00009-5
23. Cheng N, Rho JM, Masino SA. Metabolic Dysfunction Underlying Autism Spectrum Disorder and Potential Treatment Approaches. Front Mol Neurosci [Internet]. 2017 Feb 21 [cited 2021 May 21];10. https://doi.org/10.3389/fnmol.2017.00034
24. Bhat AN. Is Motor Impairment in Autism Spectrum Disorder Distinct From Developmental Coordination Disorder? A Report From the SPARK Study. Phys Ther. 2020;100(4):633–44. https://doi.org/10.1093/ptj/pzz190
25. Serdarevic F, Ghassabian A, van Batenburg-Eddes T, White T, Blanken LME, Jaddoe VWV, et al. Infant Muscle Tone and Childhood Autistic Traits. Autism Res Off J Int Soc Autism Res. 2017;10(5):757–68. https://doi.org/10.1002/aur.1739
26. Siddiqui MF, Elwell C, Johnson MH. Mitochondrial Dysfunction in Autism Spectrum Disorders. Autism-Open Access [Internet]. 2016 Sep 27 [cited 2021 May 12];6(5). https://doi.org/10.4172/2165-7890.1000190
27. Zhu X-H, Qiao H, Du F, Xiong Q, Liu X, Zhang X, et al. Quantitative imaging of energy expenditure in human brain. NeuroImage. 2012;60(4):2107–17. https://doi.org/10.1016/j.neuroimage.2012.02.013
28. Raichle ME, Gusnard DA. Appraising the brain's energy budget. Proc Natl Acad Sci USA. 2002;99(16):10237–9. https://doi.org/10.1073/pnas.172399499
29. Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, Hof PR, et al. Metabolic costs and evolutionary implications of human brain development. Proc Natl Acad Sci USA. 2014;111(36):13010–5. https://doi.org/10.1073/pnas.1323099111
30. Kuzawa CW, Blair C. A hypothesis linking the energy demand of the brain to obesity risk. Proc Natl Acad Sci USA 2019;116(27):13266–75. https://doi.org/10.1073/pnas.1816908116
31. Belmonte MK, Cook EH, Anderson GM, Rubenstein JLR, Greenough WT, Beckel-Mitchener A, et al. Autism as a disorder of neural information processing: directions for research and targets for therapy. Mol Psychiatry. 2004;9(7):646–63. https://doi.org/10.1038/sj.mp.4001499
32. Williams DL, Goldstein G, Minshew NJ. Neuropsychologic functioning in children with autism: further evidence for disordered complex information-processing. Child Neuropsychol J Norm Abnorm Dev Child Adolesc. 2006;12(4–5):279–98. https://doi.org/10.1080/09297040600681190

33. Haigh SM, Walsh JA, Mazefsky CA, Minshew NJ, Eack SM. Processing Speed is Impaired in Adults with Autism Spectrum Disorder, and Relates to Social Communication Abilities. J Autism Dev Disord. 2018;48(8):2653–62. https://doi.org/10.1007/s10803-018-3515-z
34. Duchen MR. Mitochondria and calcium: from cell signalling to cell death. J Physiol. 2000;529(Pt 1): 57–68. https://doi.org/10.1111/j.1469-7793.2000.00057.x
35. Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signalling. Nat Rev Mol Cell Biol. 2000;1(1):11–21. https://doi.org/10.1038/35036035
36. Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol. 2003;4(7):517–29. https://doi.org/10.1038/nrm1155
37. Liao X, Li Y. Genetic associations between voltage-gated calcium channels and autism spectrum disorder: a systematic review. Mol Brain. 2020;13(1):96. https://doi.org/10.1186/s13041-020-00634-0
38. Wen Y, Alshikho MJ, Herbert MR. Pathway Network Analyses for Autism Reveal Multisystem Involvement, Major Overlaps with Other Diseases and Convergence upon MAPK and Calcium Signaling. PLOS ONE. 2016;11(4):e0153329. https://doi.org/10.1371/journal.pone.0153329
39. Schmunk G, Nguyen RL, Ferguson DL, Kumar K, Parker I, Gargus JJ. High-throughput screen detects calcium signaling dysfunction in typical sporadic autism spectrum disorder. Sci Rep [Internet]. 2017 Feb 1 [cited 2021 May 27];7. https://doi.org/10.1038/srep40740
40. Nguyen RL, Medvedeva YV, Ayyagari TE, Schmunk G, Gargus JJ. Intracellular calcium dysregulation in autism spectrum disorder: An analysis of converging organelle signaling pathways. Biochim Biophys Acta BBA - Mol Cell Res. 2018;1865(11, Part B):1718–32. https://doi.org/10.1016/j.bbamcr.2018.08.003
41. Hollenbeck PJ. Mitochondria and Neurotransmission: Evacuating the Synapse. Neuron. 2005;47(3):331–3. https://doi.org/10.1016/j.neuron.2005.07.017
42. Zoghbi HY, Bear MF. Synaptic Dysfunction in Neurodevelopmental Disorders Associated with Autism and Intellectual Disabilities. Cold Spring Harb Perspect Biol [Internet]. 2012 Mar [cited 2021 May 29]; 4(3). https://doi.org/10.1101/cshperspect.a009886
43. Guang S, Pang N, Deng X, Yang L, He F, Wu L, et al. Synaptopathology Involved in Autism Spectrum Disorder. Front Cell Neurosci [Internet]. 2018 [cited 2021 May 29];12. https://doi.org/10.3389/fncel.2018.00470
44. Gao R, Penzes P. Common Mechanisms of Excitatory and Inhibitory Imbalance in Schizophrenia and Autism Spectrum Disorders. Curr Mol Med. 2015;15(2):146–67. https://doi.org/10.2174/1566524015666150303003028
45. Marotta R, Risoleo MC, Messina G, Parisi L, Carotenuto M, Vetri L, et al. The Neurochemistry of Autism. Brain Sci [Internet]. 2020 Mar 13 [cited 2021 May 29];10(3). https://doi.org/10.3390/brainsci10030163
46. Wen Y, Herbert MR. Connecting the dots: Overlaps between autism and cancer suggest possible common mechanisms regarding signaling pathways related to metabolic alterations. Med Hypotheses. 2017;103:118–23. https://doi.org/10.1016/j.mehy.2017.05.004
47. Stern M. Insulin Signaling and Autism. Front Endocrinol [Internet]. 2011 Oct 14 [cited 2021 May 28];2. https://doi.org/10.3389/fendo.2011.00054
48. Yeung KS, Tso WWY, Ip JJK, Mak CCY, Leung GKC, Tsang MHY, et al. Identification of mutations in the PI3K-AKT-mTOR signalling pathway in patients with macrocephaly and developmental delay and/or autism. Mol Autism. 2017;8(1):66. https://doi.org/10.1186/s13229-017-0182-4
49. Chen J, Alberts I, Li X. Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in autism spectrum disorders. Int J Dev Neurosci. 2014;35:35–41. https://doi.org/10.1016/j.ijdevneu.2014.03.006
50. Kumar S, Reynolds K, Ji Y, Gu R, Rai S, Zhou CJ. Impaired neurodevelopmental pathways in autism spectrum disorder: a review of signaling mechanisms and crosstalk. J Neurodev Disord. 2019;11(1):10. https://doi.org/10.1186/s11689-019-9268-y
51. Adviento B, Corbin IL, Widjaja F, Desachy G, Enrique N, Rosser T, et al. Autism traits in the RASopathies. J Med Genet. 2014;51(1):10–20. https://doi.org/10.1136/jmedgenet-2013-101951
52. Chauhan A, Chauhan V. Oxidative stress in autism. Pathophysiol Off J Int Soc Pathophysiol. 2006;13(3):171–81. https://doi.org/10.1016/j.pathophys.2006.05.007

53. Pangrazzi L, Balasco L, Bozzi Y. Oxidative Stress and Immune System Dysfunction in Autism Spectrum Disorders. Int J Mol Sci [Internet]. 2020 May 6 [cited 2021 May 28];21(9). https://doi.org/10.3390/ijms21093293
54. Wang C, Youle RJ. The Role of Mitochondria in Apoptosis. Annu Rev Genet. 2009;43:95–118. https://doi.org/10.1146/annurev-genet-102108-134850
55. Wei H, Alberts I, Li X. The apoptotic perspective of autism. Int J Dev Neurosci. 2014;36(1):13–8. https://doi.org/10.1016/j.ijdevneu.2014.04.004
56. Fatemi SH, Halt AR, Stary JM, Realmuto GM, Jalali-Mousavi M. Reduction in anti-apoptotic protein Bcl-2 in autistic cerebellum. Neuroreport. 2001;12(5):929–33. https://doi.org/10.1097/00001756-200104170-00013
57. Fatemi SH, Stary JM, Halt AR, Realmuto GR. Dysregulation of Reelin and Bcl-2 proteins in autistic cerebellum. J Autism Dev Disord. 2001;31(6):529–35. https://doi.org/10.1023/A:1013234708757
58. Fatemi SH, Halt AR. Altered levels of Bcl2 and p53 proteins in parietal cortex reflect deranged apoptotic regulation in autism. Synap N Y N. 2001;42(4):281–4. https://doi.org/10.1002/syn.10002
59. Araghi-Niknam M, Fatemi SH. Levels of Bcl-2 and P53 are altered in superior frontal and cerebellar cortices of autistic subjects. Cell Mol Neurobiol. 2003;23(6):945–52. https://doi.org/10.1023/B:CEMN.0000005322.27203.73
60. Sheikh AM, Malik M, Wen G, Chauhan A, Chauhan V, Gong C-X, et al. BDNF-Akt-Bcl2 antiapoptotic signaling pathway is compromised in the brain of autistic subjects. J Neurosci Res. 2010;88(12):2641–7. https://doi.org/10.1002/jnr.22416
61. Sheikh AM, Li X, Wen G, Tauqeer Z, Brown WT, Malik M. Cathepsin D and apoptosis related proteins are elevated in the brain of autistic subjects. Neuroscience. 2010;165(2):363–70. https://doi.org/10.1016/j.neuroscience.2009.10.035
62. Malik M, Sheikh AM, Wen G, Spivack W, Brown WT, Li X. Expression of inflammatory cytokines, Bcl2 and cathepsin D are altered in lymphoblasts of autistic subjects. Immunobiology. 2011;216(1):80–5. https://doi.org/10.1016/j.imbio.2010.03.001
63. Courchesne E. Brain development in autism: early overgrowth followed by premature arrest of growth. Ment Retard Dev Disabil Res Rev. 2004;10(2):106–11. https://doi.org/10.1002/mrdd.20020
64. Esteller M. Non-coding RNAs in human disease. Nat Rev Genet. 2011;12(12):861–74. https://doi.org/10.1038/nrg3074
65. Tang J, Yu Y, Yang W. Long noncoding RNA and its contribution to autism spectrum disorders. CNS Neurosci Ther. 2017;23(8):645–56. https://doi.org/10.1111/cns.12710
66. Zhang S-F, Gao J, Liu C-M. The Role of Non-Coding RNAs in Neurodevelopmental Disorders. Front Genet [Internet]. 2019 [cited 2021 May 30];10. https://doi.org/10.3389/fgene.2019.01033
67. Rath S, Sharma R, Gupta R, Ast T, Chan C, Durham TJ, et al. MitoCarta3.0: an updated mitochondrial proteome now with sub-organelle localization and pathway annotations. Nucleic Acids Res. 2021;49(D1):D1541–7. https://doi.org/10.1093/nar/gkaa1011
68. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med. 2003;348(26):2656–68. https://doi.org/10.1056/NEJMra022567
69. Dong Y, Yoshitomi T, Hu J-F, Cui J. Long noncoding RNAs coordinate functions between mitochondria and the nucleus. Epigenetics Chromatin. 2017;10(1):41. https://doi.org/10.1186/s13072-017-0149-x
70. Cavalcante GC, Magalhães L, Ribeiro-dos-Santos Â, Vidal AF. Mitochondrial Epigenetics: Non-Coding RNAs as a Novel Layer of Complexity. Int J Mol Sci [Internet]. 2020 Mar 6 [cited 2021 May 30];21(5). https://doi.org/10.3390/ijms21051838
71. Gusic M, Prokisch H. ncRNAs: New Players in Mitochondrial Health and Disease? Front Genet [Internet]. 2020 [cited 2021 May 30];11. https://doi.org/10.3389/fgene.2020.00095
72. Hyde KK, Novack MN, LaHaye N, Parlett-Pelleriti C, Anden R, Dixon DR, et al. Applications of Supervised Machine Learning in Autism Spectrum Disorder Research: a Review. Rev J Autism Dev Disord. 2019;6(2):128–46. https://doi.org/10.1007/s40489-019-00158-x
73. Song D-Y, Kim SY, Bong G, Kim JM, Yoo HJ. The Use of Artificial Intelligence in Screening and Diagnosis of Autism Spectrum Disorder: A Literature Review. J Korean Acad Child Adolesc Psychiatry. 2019;30(4):145–52. https://doi.org/10.5765/jkacap.190027

74. Lee SH, Maenner MJ, Heilig CM. A comparison of machine learning algorithms for the surveillance of autism spectrum disorder. PLoS ONE [Internet]. 2019 Sep 25 [cited 2021 May 31];14(9). https://doi.org/10.1371/journal.pone.0222907
75. Rahman MM, Usman OL, Muniyandi RC, Sahran S, Mohamed S, Razak RA. A Review of Machine Learning Methods of Feature Selection and Classification for Autism Spectrum Disorder. Brain Sci. 2020;10(12). https://doi.org/10.3390/brainsci10120949
76. Hosseinzadeh M, Koohpayehzadeh J, Bali AO, Rad FA, Souri A, Mazaherinezhad A, et al. A review on diagnostic autism spectrum disorder approaches based on the Internet of Things and Machine Learning. J Supercomput. 2021;77(3):2590–608. https://doi.org/10.1007/s11227-020-03357-0
77. Omar KS, Mondal P, Khan NS, Rizvi MdRK, Islam MN. A Machine Learning Approach to Predict Autism Spectrum Disorder. In: 2019 International Conference on Electrical, Computer and Communication Engineering (ECCE). 2019. p. 1–6. https://doi.org/10.1109/ECACE.2019.8679454
78. Randolph-Gips M, Srinivasan P. Modeling autism: a systems biology approach. J Clin Bioinforma. 2012;2(1):17. https://doi.org/10.1186/2043-9113-2-17
79. Oh DH, Kim IB, Kim SH, Ahn DH. Predicting Autism Spectrum Disorder Using Blood-based Gene Expression Signatures and Machine Learning. Clin Psychopharmacol Neurosci. 2017;15(1):47–52. https://doi.org/10.9758/cpn.2017.15.1.47
80. Erden YJ, Hummerstone H, Rainey S. Automating autism assessment: What AI can bring to the diagnostic process. J Eval Clin Pract. 2021;27(3):485–90. https://doi.org/10.1111/jep.13527
81. Basu SN, Kollu R, Banerjee-Basu S. AutDB: a gene reference resource for autism research. Nucleic Acids Res. 2009;37(suppl_1):D832–6. https://doi.org/10.1093/nar/gkn835
82. Lin Y, Afshar S, Rajadhyaksha AM, Potash JB, Han S. A Machine Learning Approach to Predicting Autism Risk Genes: Validation of Known Genes and Discovery of New Candidates. Front Genet [Internet]. 2020 [cited 2021 May 31];11. https://doi.org/10.3389/fgene.2020.500064
83. Zhou J, Park CY, Theesfeld CL, Wong AK, Yuan Y, Scheckel C, et al. Whole-genome deep-learning analysis identifies contribution of noncoding mutations to autism risk. Nat Genet. 2019;51(6):973–80. https://doi.org/10.1038/s41588-019-0420-0
84. Hewitson L, Mathews JA, Devlin M, Schutte C, Lee J, German DC. Blood biomarker discovery for autism spectrum disorder: A proteomic analysis. PLOS ONE. 2021;16(2):e0246581. https://doi.org/10.1371/journal.pone.0246581
85. Zilocchi M, Broderick K, Phanse S, Aly KA, Babu M. Mitochondria under the spotlight: On the implications of mitochondrial dysfunction and its connectivity to neuropsychiatric disorders. Comput Struct Biotechnol J. 2020;18:2535–46. https://doi.org/10.1016/j.csbj.2020.09.008
86. Gaudelet T, Day B, Jamasb AR, Soman J, Regep C, Liu G, et al. Utilising Graph Machine Learning within Drug Discovery and Development. ArXiv201205716 Cs Q-Bio [Internet]. 2021 Feb 10 [cited 2021 May 31]; https://doi.org/10.1093/bib/bbab159
87. Zhou Y, Yu F, Duong T. Multiparametric MRI Characterization and Prediction in Autism Spectrum Disorder Using Graph Theory and Machine Learning. PLOS ONE. 2014;9(6):e90405. https://doi.org/10.1371/journal.pone.0090405
88. Li X, Dvornek NC, Zhou Y, Zhuang J, Ventola P, Duncan JS. Graph Neural Network for Interpreting Task-fMRI Biomarkers. In: Shen D, Liu T, Peters TM, Staib LH, Essert C, Zhou S, et al., editors. Medical Image Computing and Computer Assisted Intervention - MICCAI 2019. Cham: Springer International Publishing; 2019. p. 485–93. https://doi.org/10.1007/978-3-030-32254-0_54
89. Li X, Dvornek NC, Zhuang J, Ventola P, Duncan J. Graph embedding using Infomax for ASD classification and brain functional difference detection. In: Medical Imaging 2020: Biomedical Applications in Molecular, Structural, and Functional Imaging [Internet]. https://doi.org/10.1117/12.2549451
90. Li X, Zhou Y, Dvornek NC, Zhang M, Zhuang J, Ventola P, et al. Pooling Regularized Graph Neural Network for fMRI Biomarker Analysis. ArXiv200714589 Cs Stat [Internet]. 2020 Jul 29 [cited 2021 May 31];