

# LLLT applications may enhance ASD aspects related to disturbances in the gut microbiome, mitochondrial activity, and neural network function

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## Abstract

Autism Spectrum Disorder constitutes a complex, elaborate, and diverse condition at a developmental, biological, and neurophysiological level. It is recognized primarily by the behavioral manifestations of the individual in communication, social interaction, and by extension in his cognitive development and adaptation to society as a whole. A wide range of studies have linked the pathophysiology of autism to dysfunctional elements in the development and function of mitochondria, cells, neurons, and the gastrointestinal microbiome. Low Light Laser Therapy (LLLT) is an innovative, emerging, non-invasive treatment method. It utilizes low levels of red light/near-infrared light positively affecting biological and pathological processes of the body by enhancing cellular, mitochondrial stimulation, neurogenesis, synaptogenesis, and immune system development, regulating the gut microbiome's function. The retrospective literature review focuses on the possibility of effective use of the method in autism. According to the literature, LLLT does not have many applications in patients with ASD and is still in the early stages of its use in the disorder. However, the results of the studies highlight its therapeutic effect in several areas related to the disease, pointing out that it is a promising therapeutic approach for the evolution of autism in the future.

**Keywords:** Low light laser therapy, Autism, Microbiome, Synaptogenesis-neurogenesis, Mitochondrial function.

## As aplicações de TLBL podem melhorar os aspectos do TEA relacionados a distúrbios no microbioma intestinal, atividade mitocondrial e função da rede neural

### Resumo

O Transtorno do Espectro Autista constitui uma condição complexa, elaborada e diversificada em nível de desenvolvimento, biológico e neurofisiológico. É reconhecida principalmente pelas manifestações comportamentais do indivíduo na comunicação, interação social e, por extensão, em seu desenvolvimento cognitivo e adaptação à sociedade como um todo. Uma ampla gama de estudos ligou a fisiopatologia do autismo a elementos disfuncionais no desenvolvimento e função das mitocôndrias, células, neurônios e do microbioma gastrointestinal. Terapia a laser de baixa luminosidade (TLBL) é um método de tratamento inovador, emergente e não invasivo. Ele utiliza baixos níveis de luz vermelha/luz quase infravermelha (NIR) afetando positivamente os processos biológicos e patológicos do corpo, melhorando a estimulação celular, mitocondrial, neurogênese, sinaptogênese e desenvolvimento do sistema imunológico, regulando a função do microbioma intestinal. A revisão retrospectiva da literatura enfoca a possibilidade de uso efetivo do método no autismo. De acordo com a literatura, a TLBL não tem muitas aplicações em pacientes com TEA e ainda está em estágios iniciais de seu uso no transtorno. No entanto, os resultados dos estudos destacam seu efeito terapêutico em diversas áreas relacionadas à doença, apontando que é uma abordagem terapêutica promissora para a evolução do autismo no futuro.

**Palavras-chave:** Terapia a laser de baixa luminosidade, Autismo, Microbioma, Sinaptogênese-neurogênese, Função mitocondrial.

### 1. Introduction

The therapeutic use of light at the end of the eighteenth century was the cornerstone of its utilization in the medical field when Niels Ryberg Finsen was the first to use red and blue light in the treatment of various human ailments. He demonstrated the bactericidal action and environmental tissue stimulation of the concentrated chemical rays of sunlight. Then in the early 1960s, the discovery of laser technology was prominent in the medical field but was initially treated sparingly due to concerns about its biological effects (Anders et al., 2015).

The laser is a landmark invention of the 20th century. However, at the beginning of its use, it was more of a discovery than a scope-specific invention, as coherent light generation was anticipated to be utilized in communications and research in general. As various types of lasers and new applications emerged, they attracted scientific and public interest (Hecht, 2010).

With regard to neuroscience, photobiomodulation (PBM) is being used more frequently as an alternative non-invasive way of treatment. The scientific community is interested in it since it is a secure, flexible, and functional method. The energy produced by the absorption of photons by the cellular mitochondria, acts as a regulator of organisms in the cellular environment, creating a possibility for treating diseases or ailments (Pan et al., 2023).

PBM, also known as Low Light Laser Therapy (LLLT), uses low-power lasers, where through the absorption of photons intracellularly they positively affect the oxidative state of cells, the effect on the expression of proteins involved in oxidative stress, the inflammation, pain, and neuron growth. Additionally, since LLLT inhibits apoptosis, inflammation, stimulates angiogenesis, and allows neurogenesis and synaptogenesis to some extent, it is recommended as an effective therapeutic process in the nervous system (Ramezani et al., 2021).

Autism is a set of heterogeneous developmental conditions which exhibit difficulties in social communication and unusual patterns of repetitive behaviors and interests (Lai et al., 2014). The degree of challenges faced by children with autism can vary significantly depending on their stage of development, mental capacity, and environmental effects (Syriopoulou-Delli et al., 2021).

In terms of the cause of ASD is a multifactorial phenomenon. Genetic, biological, environmental, and nutritional factors make up the complexity and complexity of the disease's symptoms. Mitochondrial dysfunctions and disturbances in synaptic development and brain neuroplasticity are particularly highlighted (Hamblin, 2022).

Additionally, research on both humans and animals has demonstrated that immunological dysregulation brought on by the gut microbiota is linked to ASD and plays a substantial role in its pathogenesis. As a consequence, is the emergence of neurobehavioral and intestinal dysfunction (Yang et al., 2020). Notably, the imbalance in the levels of metabolites produced by gut bacteria could cause behavioral and neurochemical changes associated with ASD, such as altered neurotransmitters (dopamine, serotonin, and glutamate), mitochondrial dysfunction, intestinal disorders, and increased oxidative stress (Lasheras et al., 2020).

Given the heterogeneity of ASD in terms of symptoms and the causes that cause it, science has been turning more and more in recent years to alternative forms of treatment for the optimal treatment of the phenomenon. Consequently, it is appropriate to investigate the relatively emerging therapeutic approach of LLLT in autism, considering that it is a non-invasive procedure, without the use of drugs and with non-existent or minimal-mild side effects. Therefore, the present study explores applications of LLLT in autism and focuses on potential improvements involving mitochondrial, and synaptic function, as well as the gut microbiome, domains that appear to be under-functioning in ASD. It aims to highlight the method as a promising complementary or dominant, depending on the case, treatment of the disease, as it can work beneficially in various fields of autism pathology, thus improving the overall clinical picture.

## **2. Materials and Methods**

The current research was conducted in selected databases such as Google Scholar, PubMed, and Research Gate by conducting a literature review. The above method is considered efficient for describing a topic and related concepts and theories (Aromataris & Pearson, 2014). The authors chose narrative review because it allows flexible management of knowledge gained resulting from using a wide range of information sources (Byrne, 2016).

The next set of keywords provided the basis for the search and source identification: low-light laser therapy, autism, microbiome, synaptogenesis-neurogenesis, and mitochondrial function. The continuation of the study was followed by the categorization of the resources, according to the content of the thematic sections of the article. Finally, the research procedure was finished, with the writing of the study, which included the discussion of the results and the drawing of conclusions as a final stage. The timeframe of dates associated with the narrative review ranged between 2010 and 2023, with a particular focus on the years 2015-2023, due to the approach of the topic regarding contemporary concerns. Eligibility criteria of the sources were considered their publication in reputable international scientific publications, and their necessity and usefulness in the conceptual understanding and processing of the individual research topics. In addition, the purpose, objectives of the articles, and the

documentation of their results were assessed, compared to the content of the present study. While sources that were unrelated to the employment of low-power lasers did not aid in the comprehension and precise interpretation of the data disregarded.

The conduct of the research focused on the search for the existence of positive consequences in dysfunctional sections of ASD, through the application of LLLT. We specifically investigated if using low-power lasers can enhance and improve gut dysbiosis, mitochondria, and the development of the brain's neuronal network, thereby influencing how autism develops over time.

### **3. Conceptual background**

#### *3.1. Autism Spectrum Disorder (ASD)*

According to estimates, the prevalence of ASD is rising rapidly worldwide, reflecting approximately 1% of the world's population. It is a complicated neurodevelopmental disorder with several genetic and epigenetic risk factors, and its unclear diagnosis makes its treatment difficult (Abirami et al., 2020).

The clinical picture of ASD varies significantly depending on the presence of comorbidity (ADHD, fragile X syndrome, intellectual disability, anxiety in various forms, depression, defiant or aggressive behavior, bipolar disorder, inflammatory bowel disease, epilepsy, Tourette syndrome, tic disorders), and the current environmental requirements. The initial signs include problems with joint attention, eye contact, a decreased desire for social communication, altered response to sensory stimuli, and a lack of social play imitation. Autism-related cognitive deficiencies might vary, but remarkable performance in some areas is frequently seen (Sharma et al., 2018; Lord et al., 2018).

The wide range of abilities and levels of functioning in autism spectrum disorder includes weakness in cognitive skills, functional language skills, involvement in self-injury, limited adaptive living skills, and high intelligence with impaired social skills (Maximo et al., 2014).

In light of the involvement of interacting cognitive and social functions in the development of ASD, a holistic intervention approach to children with autism is necessary while covering weaknesses in different areas of development. Essentially, an effective intervention should combine a variety of actions in multiple settings. (Bamicha & Drigas, 2022b; Predescu et al., 2018). The use of alternative forms of treatment for deficits in ASD is preferred, as far as possible, since a medication's administration causes side effects and focuses on symptom therapy (Ntaountaki et al., 2019; Stathopoulou et al., 2019; Bamicha & Drigas, 2022b).

#### *3.2. Low Light Laser Therapy (LLLT)*

In 1900, Max Planck introduced the photon theoretical approach when he discovered that light energy emitted by a heated body is transferred and absorbed in specific amounts of energy called quanta, which are related to the frequency of the radiation (Azadgoli & Baker, 2016). Subsequently, the first conceptual structural position for the laser was made by Einstein in 1917, referring to the relationship between radiation and energy, pointing out that photons could stimulate the emission of identical photons from excited atoms (Hecht, 2010).

Several years later, in 1967, Endre Mester observed that laser light at low doses could induce hair growth at an accelerated rate and healing of excision wounds in mice. As a consequence of the research came the exploitation of the specialized field of phototherapy that uses low-intensity light for clinical treatment with stimulatory and inhibitory effects, depending on the light parameters used (Anders et al., 2015; Hamilton et al., 2022). The abbreviation "laser" stands for light amplification by stimulated emission of radiation (de Sousa, 2016).

Various names for Photobiomodulation include low-level laser (light) therapy, low-intensity laser therapy, low-reactive laser therapy, cold laser, non-thermal laser, soft laser, biostimulation laser, and Photobiomodulation laser, or even more, light-emitting diode therapy and organic light-emitting diode therapy (de Sousa, 2016).

Photobiomodulation (PBM) uses light from the visible and near-infrared part of the spectrum at a relatively low power density without causing tissue heating or burning. While it often uses a laser as a light source, it does not act thermally or ablatively. Specifically, photons stimulate chemical changes within cells, creating beneficial biological responses, such as neuroprotective responses, increase in metabolism, blood flow, and neurogenesis (Hennessy & Hamblin, 2017).

Low-Level Light Therapy (LLLT) belongs to light-based therapeutic interventions. Photobiomodulation, the procedure for absorbing low-energy red/near-infrared light energy, enhances mitochondrial ATP production, signaling, and cell function, limiting oxidative stress. It has to do with how much power the laser light's target captures, and the subsequent biochemical consequences of the process (Glass, 2021).

Tissue and laser qualities will affect how well a laser will work on a tissue sample. Regarding the tissue, parameters

such as its structure, water content, thermal conductivity, heat capacity, density, and ability to absorb, disperse or reflect the emitted energy are decisive for the result. In addition, laser power, density, energy content, and wavelength affect treatment performance (Azadgoli & Baker, 2016).

Several studies highlight the potential applications of Photobiomodulation in disorders ranging from neurotrauma and neurodegeneration to neuropsychiatric disorders, making it a novel potential treatment strategy for neurological diseases (Pan et al., 2023).

Photobiomodulation's application can have therapeutic effects on several disorders and ailments, as shown schematically in Figure 1.

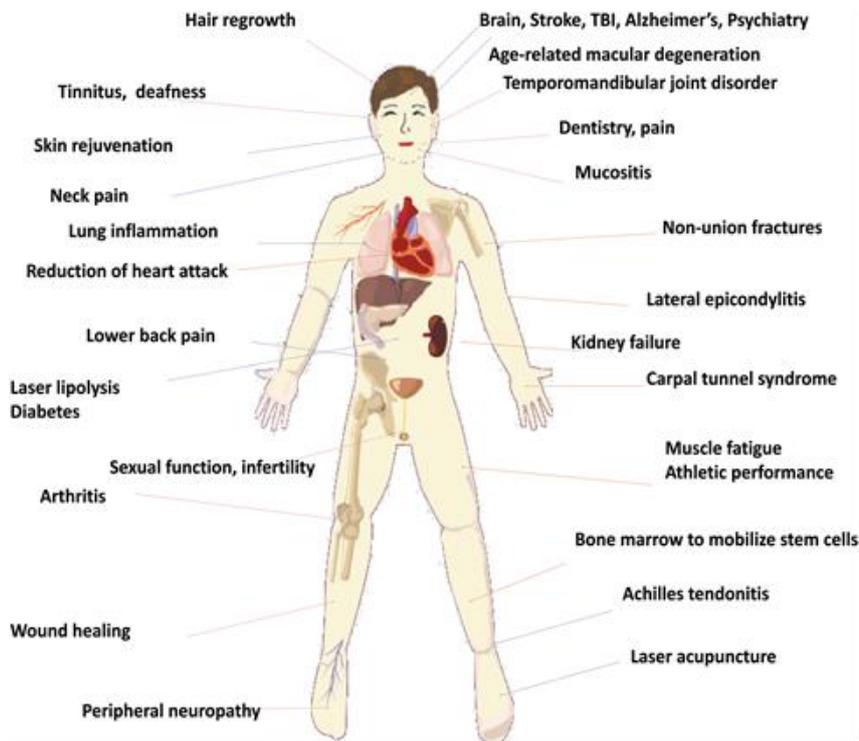


Figure 1. Harnessing Photobiomodulation has a beneficial impact on human health. Source: Liebert et al. (2019).

Several of the positive effects of PBM in the treatment of different diseases and conditions are captured by the authors Liebert et al., 2019, in the image up top. A few of them are wound healing, orthopedic conditions, cardiovascular diseases, neurological and intestinal disorders, and dental cases. Aside from that, Photobiomodulation's use promotes anti-aging, pain relief, skin regeneration, and healing

#### 4. Dysfunctional sections in ASD

##### 4.1 Mitochondrial activity in ASD

The neurodevelopmental disease known as autism spectrum disorder (ASD) is characterized by restricted behavioral patterns and challenges with the growth of social interaction and communication. Identifying a cellular process that underlies cognitive, behavioral, and developmental abnormalities has been a significant challenge for researchers (Wen & Yao, 2021).

Several studies using peripheral biomarkers have linked oxidative stress, mitochondrial dysfunction, and immune system dysfunction in individuals with ASD. In addition, it has been observed that physiological abnormalities affect peripheral organs, directly affecting brain function, with implications for processing speech, hearing, memory, behavior, sensory perception, and motor coordination (Rossignol & Frye, 2014).

Research reveals an atypical mitochondrial function in children with ASD, resulting in fatigue, seizures, gastrointestinal disturbances, endocrine abnormalities, muscle weakness, and limited growth. Consequently, mitochondria are an influential therapeutic target for the autism spectrum, aiming to improve several symptoms (Frye, 2020a).

Mitochondria are organelles of the cell that are involved in essential cellular and physiological functions. They contribute to cellular energy metabolism, lipid and steroid metabolism, calcium signaling regulation, free radical production, and apoptosis (Hollis et al., 2017).

Mitochondria play a dominant role in energy production for most cells, cell growth, and cell apoptosis. The brain requires plenty of energy for efficient operation, so mitochondrial dysfunction significantly affects it. Indirect effects of its limited function are felt in the immune system, causing a reduced number of immune cells and in the gastrointestinal tract, leading to dysregulation and malfunction of enterocytes as a side effect (Moradi et al., 2021).

Notable is the connection between oxidative stress and mitochondrial dysfunction. Specifically, oxidative stress causes dysfunctional mitochondria, disrupting the levels of reactive oxygen species (ROS) that are a by-product of normal mitochondrial function. ROS is of utmost significance in cell signaling (cell signaling) and homeostasis, not but, if their levels are not kept low, they become harmful to the body because they oxidize and limit cell function. However, different factors can boost ROS or impair mitochondrial activity (Rose et al., 2018).

Mitochondria function effectively, differentiating their morphology inside the cells by maintaining homeostasis with fusion and fission processes. Fusion allows mitochondria to rescue damaged mitochondria, while fission facilitates the separation of mitochondria with weakened mitochondrial DNA (mtDNA), keeping only healthy mitochondria inside the cell (Son & Han, 2018). Mitochondrial dynamics, the balance between the processes of mitochondrial fusion and fission, constitutes a quality control mechanism of mitochondrial function. For example, excessive mitochondrial fission that can be caused by oxidative stress contributes to mitochondrial dysfunction (Yang et al., 2020).

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#### *4.2 Atypical connectivity patterns in ASD*

The traits of autism include mitochondrial dysfunction and oxidative stress, localized to the cortex, hippocampus, and cerebellum. Increased lipid peroxidation, elevated amounts of reactive oxygen species, aberrant calcium homeostasis, and neurotransmitter imbalance are signs of neuronal dysfunction. In addition, the functional connectivity disorder in the brain of individuals with autism affects areas related to language, personality, task switching, social interaction development, self-control, planning, working memory, and in a broader sense, executive function (Hamilton et al., 2022).

The ability of the brain to create functional connections thereby defines brain plasticity and structural changes in response to resulting internal and external environmental changes (Hamblin, 2019).

Synapses are specialized asymmetric connections of cells that make up the communication units of the brain. ASD is usually diagnosed before turning three, a period characterized by intense synaptogenesis. Studies identify a synaptic dysfunction in autism created by gene mutations and environmental factors, most of the time causing functional and cognitive impairments. Therefore, the pathogenesis of ASD is attributed, to some extent, to the existence of synaptic abnormalities involving synaptogenesis, synaptic plasticity, and neurotransmitter function (Guang et al., 2018).

For humans to perform higher-order activities, the cooperation of different neural networks involving memory, executive system, and emotional and default function is required (Mitrofanis & Henderson, 2020).

The default mode network is activated when the person is in a state of calm, and rest, and is focused on internal thoughts such as recalling memories, envisioning the future, and mind wandering, without engaging in any mental work (Raichle, 2015).

While the cause of autism has not been determined, postmortem imaging studies of people with ASD point to abnormalities in the arrangement, and organization of neuronal material, which is a widely accepted explanation for the complex neurodevelopmental disorder (Bitsika & Sharpley, 2023). The results of electroencephalograms and fMRI studies highlighted dysfunctions in the connectivity of neural networks, specifically in the default mode network. The network's restrictions described above, related to introspective awareness and mind wandering, have been attributed to social-cognitive deficits in autism (Pallanti et al., 2022).

Previous studies estimate impaired microglia function in ASD patients. Microglia, the cells of the brain's immune system, play a significant role in regulating synaptic formation, removing unnecessary synaptic connections. Additionally, they release chemicals such as glutamate and ATP, facilitating synaptic activity. Research reports that the maturation of microglia is structurally and functionally influenced by gut microbes (Moradi, et al., 2021).

Additionally, microglia and astrocytes support synaptic function and plasticity in the brain while maintaining homeostasis in the body (Matta et al., 2019). In particular, microglia develop two-way communication with the brain

environment in the prenatal and postnatal period, which can influence the development of neurons and synaptic contacts, nonetheless, neurons can also have an impact on the phenotypic characteristics of microglia (Carroll et al., 2021). Several studies in the brains of postmortem ASD patients show increased microglia and astroglial activation in the cerebellum and cerebral cortex, along with increased levels of proinflammatory cytokines in the cerebrospinal fluid and brain regions cortical. In addition, dysfunctional connectivity is observed in the brain's regions related to social-communicative functioning (Vuong & Hsiao, 2017).

When reactive oxygen species (ROS) production rises, and the body can't counteract its effects by producing enough antioxidants, oxidative stress, which is evident in ASD, ensues. Because of this, ROS can be damaging to the body, especially when they are present at high levels over an extended period (Hennessy & Hamblin, 2017). In addition, mitochondrial dysfunction has been associated with the accumulation of ROS within cells, as they react to oxidative stress when a relatively low ROS environment is present. But, when this becomes detrimental to the organism, it is the dominant cause of neuroinflammation and damage to the astrocyte-neuron junction leading to ASD (Bjørklund et al., 2020; Pangrazzi et al., 2020).

Postmortem studies in ASD patients showed cerebellar dysfunction with reduced Purkinje cell numbers, reduced GABAergic function, and increased levels of oxidative stress, associated with the cerebellum. Autism symptoms that lack language, social interaction, and sensorimotor skills seem to be related to cerebellar problems (Khongrum & Wattanathorn, 2017).

Studies in mouse animal models of ASD report that gene mutations associated with neuroplasticity can cause cellular hypo-plasticity or hyper-plasticity with consequences for cognition and behavior. Additionally, it is reported that an excitation-inhibition imbalance in brain function and a deficit in inhibitory neurotransmission are fundamental factors in the development of neuroplasticity, affecting the manifestation of cognitive, social, and behavioral performance in individuals with autism (Desarkar et al., 2015).

Specifically, abnormal GABAergic and glutamatergic neurotransmission in specific brain regions is associated with inhibition-excitation imbalance in ASD, impacting symptomatology. In addition, frontal brain networks show the most prolonged development compared to other brain regions, suggesting the possible dependence of plasticity on experiences. The results of these processes are reflected as a consequence of the individual's overall growth (Carroll et al., 2021).

In addition, the dysfunction of the neurotransmitter system that many individuals with autism experience affects neuronal cell differentiation, synaptogenesis, and, by extension, neuroplasticity of the brain. It is due to the relationship between neurotransmitters and the cerebellum, cortical organization, general brain development, and synaptic remodeling. Consequently, deficits in the performance of neurotransmitters such as serotonin, dopamine, noradrenaline, GABA, glutamate, neuropeptides, and subsequent receptor-mediated signaling pathways and gene regulation have been linked to the developmental course of ASD (Abirami et al., 2020).

#### *4.3 Gut microbiome alterations in ASD*

The gut microbiota is now commonly acknowledged to be closely concerning health and disease (Liebert et al., 2019). The connection of autism with changes in the gastrointestinal microbiome is considered characteristic, affecting brain networks and connectivity and the development of social behaviors. Communication occurs between the gut and the brain via the stretched vagus nerve, which produces this (Hamilton et al., 2022).

According to the findings of studies, an altered microbial composition of the gut is observed in people with ASD. In particular, many children with autism present with gastrointestinal problems such as irritable bowel, indigestion, abdominal pain, and dysbiosis of the intestinal mucosa that result from microbial imbalance. A microbiome is a set of microorganisms (bacteria, fungi, viruses, archaea and protozoa) that colonize various parts of the body, such as the skin, eyes, respiratory tract, and intestine (Alharthi, et al., 2022).

Given the growing evidence that gut microbiota populations may support certain neurobehavioral disorders, this term has since been linked and expanded to the gut-microbiome (microbiota)-brain axis (Rosenfeld, 2015). Findings from different studies correlate the onset of ASD symptoms with gut microbiota and neurotransmitter levels. At the same time, they indicate the importance of intervention in the functioning of neurotransmitters, which can limit the behavioral difficulties of people with autism. Various neuroactive compounds that inhibit or activate central neurons are produced by the intestinal microflora, such as serotonin, GABA, dopamine (DA), and histamine (Garcia-Gutierrez et al., 2020).

The balanced microbial composition of the gut contributes positively to human health. It is pointed out that the gastrointestinal tract is an organ that produces numerous metabolites and neuroactive substances. Consequently, it can affect the child's developmental course on the central nervous system (CNS) and the enteric nervous system (ENS), which constitute the gut-brain microbe axis. This is achieved through the communication pathway and

interaction of gut flora with the brain (Alharthi, et al., 2022).

Above all, through neurological, immunological, and endocrine mechanisms, the gut microbiota regulates CNS functions. Consequently, numerous neuroactive compounds generated by the microbiome, including aminobutyric acid, catecholamines, and cytokines, communicate with the central nervous system (CNS) through the vagus nerve and endocrine system (Yang, et al., 2020).

Carabotti et al. (2015) describe a two-way interaction of the central and enteric nervous systems, the so-called gut-brain axis (GBA), that allows the connection of cognitive and emotional centers of the brain with peripheral intestinal functions. It is a two-way communication that connects the emotional and cognitive centers of the brain with peripheral intestinal functions. Communication is achieved through signaling from the gut microbiota to the brain and from the brain to the gut microbiota through neural, endocrine, immunological, and chemical links

## **5. LLLT usage in ASD**

In recent years, therapeutic interventions for children with ASD have turned to different forms of support to eliminate the side effects of medication. Some of them are special diets, vitamin supplements, yoga, acupuncture, music therapy, the therapeutic approach of sensory integration, the use of digital-supportive technology, etc. (Brondino et al., 2015; Sideraki & Drigas, 2021; Pergantis & Drigas, 2023a,b). Moreover, it is widely recognized that the use of ICT is a significant area of study and an effective tool for the diagnosis and treatment of ASD, addressing severe deficiencies in several sectors (Marchi et al., 2018; Bakola et al., 2019; Syriopoulou-Delli & Gkiolnta, 2020; Stathopoulou et al., 2019; Chaidi & Drigas, 2020; Drigas & Sideraki, 2021).

Combining alternative and conventional therapies is beneficial in many cases of autism by reducing or alleviating symptoms (Sharma et al., 2018). Considering the positive effects of PBM on synaptogenesis, neurogenesis, mitochondrial function, and gut microbiome regulation, it might be incorporated into alternative ASD interventions (Hamblin, 2022).

### *5.1 The basic purpose of the therapy approach - Positive results*

Photobiomodulation (PBM), also known as low-level light therapy (LLLT), involves the use of light in the red (600–670 nm) and near-infrared (NIR) light (800–1100 nm) spectrum in relatively low power density (Lee, Ding, & Chan, 2022). Due to its limited potency depending on the target tissue, its usage does not raise the temperature of the tissue being treated and, as a result, does not substantially alter the gross tissue structure. One of the most significant chromophores is cytochrome c oxidase, which absorbs light in the near-infrared region (de Freitas & Hamblin, 2016b).

PBM is a non-invasive treatment that promotes energy production, reducing oxidative stress, and inflammation. Moreover, it gives rise to advantages to mitochondrial function and behaviors affected by it, notably when used in neurological illnesses. Consequently, it is a promising therapy approach for brain disorders (Yang, et al., 2020; Hamblin, 2022).

Furthermore, it enhances blood flow, increases mitochondrial function, and promotes tissue mending and oxygenation. In addition, it reduces swelling, lessens inflammation, protects against apoptosis, regulating the level of microglial activation. Additionally, it improves brain function by stimulating neurogenesis and enhancing synaptogenesis. It has been demonstrated to improve regional cerebral blood flow and tissue oxygenation in healthy human volunteers (both children and adults), having positive effects on memory, mood, and cognition (Hamblin, 2018).

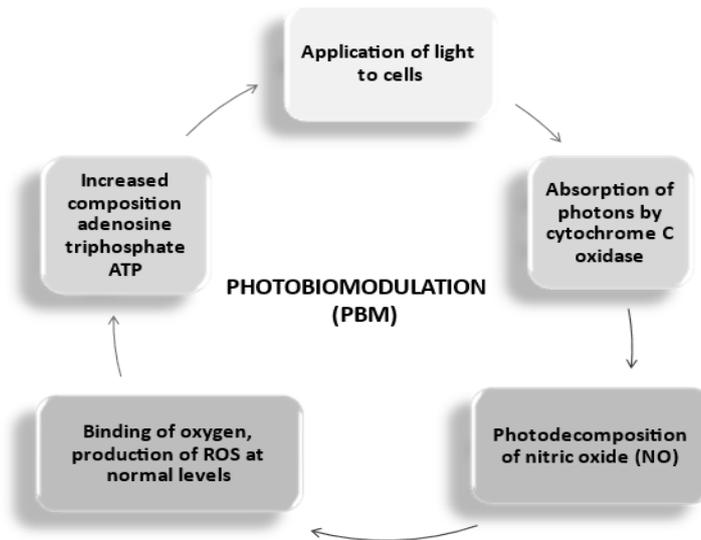


Figure 2. gives prominence to essential processes activated as low-power laser light acts upon cells. Source: Authors.

Authors Bamicha and Salapata in their present study, according to the data from various research (de Freitas & Hamblin, 2016b; Zein et al., 2018; Wong-Riley & Liang, 2019; Liebert et al., 2019; Mitrofanis & Henderson, 2020; Pallanti et al. 2022) created Figure 2., which illustrates key processes as red and near-infrared (NIR) light acts on cells. When light is applied to cells, mitochondria are the initial sites of light absorption, and cytochrome C oxidase (CCO) acts as a photoreceptor. Photon absorption then activates a set of reactions known as cell signaling pathways that cause nitric oxide (NO) breakdown, ROS production, and increased ATP synthesis. It appears that brain cells with fewer mitochondria respond more favorably to low light levels.

### 5.2 LLLT utilization in ASD

Leisman et al. (2018) investigated the effectiveness of low-level laser therapy in improving irritability (aggression, tantrums, self-injurious behavior) of 40 children and adolescents with autism aged 5-17 years. The experimental group consisted of 21 kids and received eight 5-minute treatments with red laser light to the temporal regions and the skull base. The remaining 19 children formed the control group that was given a placebo (laser). The intervention lasted four weeks and involved two weekly treatments separated by three to four days. The study's results revealed that, in contrast to the children who received a placebo, children with ASD signs of irritability have improved.

Remarkably, the intervention's results remained consistent and increased over time. Specifically, Machado et al. (2019) studied the effectiveness of using low-level laser therapy (LLLT) in the study of Leisman et al. (2018), 6 months after its completion, finding maintenance of improvement. They even point out that photobiomodulation can significantly regulate brain-derived neurotrophic factor (BDNF) is closely related to dendrite development, neuroplasticity, and brain connectivity.

Machado et al. (2020) noted that continuing from their earlier research, the treatment can result in maintenance and an increase in symptom improvement 12 months following its administration. Suggesting that accomplished when LLLT gradually puts together and rearranges brain networks' structural and functional connections, which correspond to the symptoms of autism.

Then follows Figure 3. which illustrates some of the core abnormalities in brain structure and function associated with ASD.

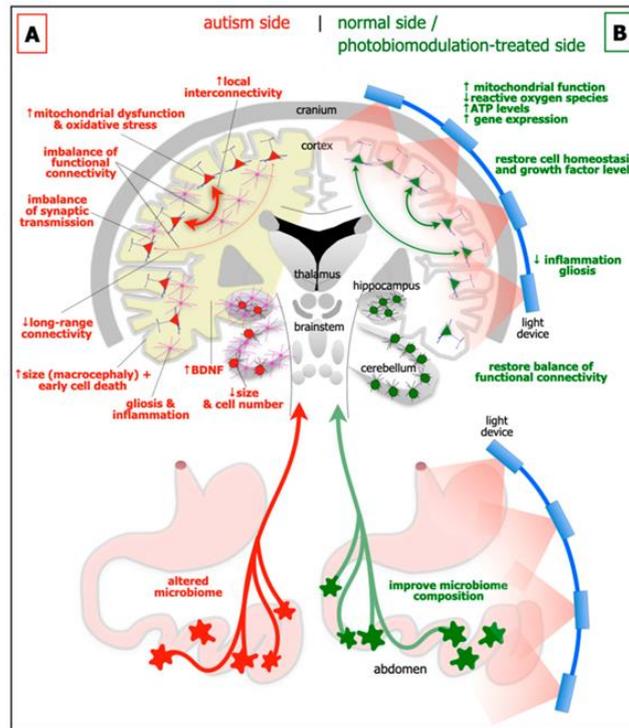


Figure 3. Fundamental deficits in autism are amenable to improvement through photobiomodulation. Source: Hamilton et al. (2022)

Using the previously mentioned Figure 3, Hamilton et al. (2022) highlight the principal deviations observed in autism captured in A - left side, while in B - right part following photobiomodulation therapy, the alterations are visible. Therefore, the A - left side includes the altered microbiome in the gastrointestinal tract, a decrease in the size of the cerebellum and the number of cerebellar cells, an increase in brain neurotrophic factor (BDNF) levels, gliosis and inflammation in the brain, macrocephaly, a decrease in activity connectivity, synaptic imbalance in the brain, functional connectivity imbalance, dysfunction and oxidative stress in the brain and an increase in local connectivity in the cortex. While, through PBM therapeutic intervention the mentioned changes can be enhanced and improved on the B-right side.

### 5.3 Use of transcranial photobiomodulation (tPBM) in ASD

Sharma et al. (2018) report that the connectivity dysfunction seen in ASD affects behavioral dysregulation, specifically crucial social cognition networks related to the ability to interpret, empathize with, and respond to others. Mostly when the brain fails to connect and interpret incoming social information from different sensory pathways, as occurs when deficits Theory of Mind arise. In light of this is the disruption of social relations with effects on the evolution of the cognitive and metacognitive mechanism (Sharma et al., 2018; Bamicha & Drigas, 2022a; Bamicha & Drigas, 2022b; Bamicha & Drigas, 2023a; Bamicha & Drigas, 2023b).

Maintaining a person's social connection with others is of fundamental importance since it affects their day-to-day lives, the accomplishment of their needs, and, in general, their survival. The use of non-invasive brain stimulation is a particularly beneficial approach to social plasticity's growth in individuals with developmental disorders such as autism (Boggio et al., 2015).

The latest studies report growing interest in the potential of non-invasive brain stimulation in neurodevelopmental disorders. It is apparently due to the positive effect it provides on the regulation of the neuroplasticity of the brain and the promotion of the social-emotional and cognitive mechanisms of the individual (Pallanti et al., 2022). Non-Invasive Brain Stimulation (NIBS) techniques are widely used in healthy adults both to enhance them socially-emotionally, behaviorally, and cognitively, as well as to enrich the study of the functioning of brain mechanisms. In addition, they apply to cases of neuropsychic or psychiatric rehabilitation and control the brain's neuroplasticity. The specific methods are considered serviceable in the recovery and restoration of sensorimotor, executive functions, attention, and memory, along with dealing with deficits in social knowledge and behavior (Finişguerra et al., 2019).

One of the methods of PBM is transcranial Photobiomodulation (tPBM), or Transcranial Low-Level Laser Therapy

(tLLLT), which involves a transcranial, non-invasive delivery of low-level light. During the progression of the process, photon absorption is realized in the mitochondria and ion channels in the cells, resulting in the activation of signaling processes and the increased expression of protective genes (Hennessy & Hamblin, 2017).

It first involves the penetration of light into the skin and skull, and then the light is absorbed by the brain tissue through specific chromophores, such as water, oxyhemoglobin (HbO<sub>2</sub>), deoxyhemoglobin (Hb), myoglobin, melanin, cytochromes and flavins such as water, oxyhemoglobin (HbO<sub>2</sub>), deoxyhemoglobin (Hb), myoglobin, melanin, cytochromes, and flavin (Pallanti et al., 2022; de la Torre, 2017). The process consists of placing one or more light sources in one or more areas of the head, aiming to stimulate a specific part of the brain, depending on the disease or disorder being treated. The light can come from a laser or a light-emitting diode (LED) and can be pulsed or continuous (Hennessy & Hamblin, 2017).

Research by Barrett and Gonzalez-Lima (2013) is the first study in healthy humans to show that transcranial red-to-near-infrared (rNIR) laser stimulation improves emotional and cognitive functions (attention, memory, mood) of the brain related to the frontal cortex. LLLT might thus prove beneficial for enhancing neuropsychological issues when used as a treatment for cognitive and emotional brain disorders.

Similar results have been shown in healthy young people and seniors, describing positive effects on their cognitive mechanism after PBM application. Specifically, cognitive skills activated in the frontal lobe were enhanced focusing on working memory, cognitive flexibility, sustained attention, inhibitory ability, executive function in general, and rule-based learning (Rojas, & Gonzalez-Lima, 2016; Lee et al., 2022; Cheung et al., 2023).

A late study by Naeser et al. (2020) on men with chronic stroke reports the positive effects of photobiomodulation. In particular, the appliance of red to near-infrared light ( $\lambda = 600\text{--}1000$  nm) to body tissues via transcranial application affects the functional connectivity of intrinsic neural networks, such as the default mode network. More generally, it improves the functional interaction of the default mode network with the executive mechanism networks, promoting balance between them and, by extension, cognitive development.

The study's findings described above could be promising for autism as well. Essentially the research of Pallanti et al. (2022) indicates that there are shortcomings with the connectivity of neural networks, especially in the default mode network of individuals with autism, and the cognitive and social difficulties that result.

According to the study by Ceranoglu et al. (2022), as reported at the Conference of The BRAIN Foundation (Pleasanton, CA, USA) Nanda & Frye 2023, transcranial photobiomodulation (tPBM) was used in 10 subjects with ASD aged 18 to 59 years. The application of the method had a duration of 8 weeks. It harnessed a specific wavelength of near-infrared light that penetrated brain tissue, stimulating mitochondria, and causing increased cellular metabolism and gene transcription. The results of the research were positive, as an improvement in social awareness-communication, social motivation, and restricted/repetitive behaviors was observed. Remarkably, side effects were mild and transient.

Similar results were reported in the study by Pallanti et al. (2022), where 21 kids and teens with ASD (5 to 15 years old) received transcranial photobiomodulation. Following the parents' completion of the required training, two stimulation devices—alpha and gamma—were employed and delivered at home. The alpha stimulator delivered 810 nm near-infrared light pulsing at 10 Hz via the transcranial LED clusters mounted on the helmet. 10 Hz is associated with alpha brain waves produced by the brain during meditation and relaxation states. While the gamma excitation device had a light pulse frequency of 40 Hz and an output of 810 nm near-infrared light. The frequency of gamma stimulation simulates the gamma neural waves associated with increased cognitive activities. The treatment lasted six months and was administered five days a week. Children in each 20-minute session engaged in stimulating activities (such as drawing, coloring, reading, playing, or doing homework). The benefits of the rehabilitation technique were apparent in the improvement of sleep quality, responsiveness, and behavioral and cognitive stiffness, as well as the enhancement of attention and responsiveness.

Additionally, 8-week clinical trials of PBM and specifically transcranial LED therapy in adults with ASD at Massachusetts General Hospital report on the safety, tolerability, and efficacy of the treatment. Also, a similar study was performed on children (2–6 years old) twice a week (15 minutes each) for eight weeks, highlighting a significant improvement in the Child Autism Rating Scale in the experimental group compared to the placebo group. Specifically, in children was used an 850nm LED headband pulsed at 40Hz (Hamblin, 2022).

#### *5.4 Usage of laser acupuncture in ASD*

One of the complementary and alternative medicine (CAM) treatments is acupuncture. Acupuncture-related therapies include the non-invasive stimulation of acupuncture points with moxibustion and manual pressure (tuina), lasers, TENS machines, and similar devices (Saunders & Berry, 2020).

Acupuncture is closely associated with Traditional Chinese Medicine. In recent years it has been increasingly

incorporated into pediatric health care, having also been widely used for autism spectrum disorder (ASD). In addition to the traditional use of needle acupuncture, other acupuncture practices have developed. One of these methods is laser acupuncture, the stimulation of standard acupuncture points with low-intensity, non-thermal laser radiation (Yang, et al., 2015).

The success of laser acupuncture is related to understanding the properties of the skin since it is a parameter that prevents the transmission of light. Skin thickness, age, pigmentation, and regional collagen fiber anisotropy alter significantly the effects of light in the tissue. However, it could work adjunctively in various therapeutic approaches (de Freitas & Hamblin, 2016a; Chon et al., 2019).

According to research, oxidative stress plays a fundamental role in the pathophysiology of autism, and laser acupuncture at Shenmen (HT7) can improve oxidative status in many neurological disorders. The study by Khongrum and Wattanathorn (2015) assessed the effect of laser acupuncture at HT7 on behavioral disturbances and oxidative stress status in the cortex, striatum, and hippocampus in rats with evidence of autism. The study's findings indicate that improving oxidative state lowered symptoms resembling autism. Therefore, it could be a potential, non-invasive strategy to repair brain damage and reduce autism-like behaviors.

In a subsequent study, Khongrum and Wattanathorn (2017) observed that laser acupuncture at the HT7 acupoint improves oxidative stress status and inflammation, the amelioration of which restricts Purkinje cell loss and reduction of GABAergic function in the cerebellum in mice with autism. Essentially, increasing Purkinje cells in the cerebellum through this method can improve behavior associated with autism.

Laser acupuncture is a form of acupuncture that, compared to manual acupuncture cure simplifies application with precise "dose" measurements and is painless and non-invasive. It is safe for children and has been used for many years in medicine to treat some of the symptoms of ASD linked to speech and social interaction issues. An illustrative example is the clinical trial by Surapaty et al. (2020), which used verum laser acupuncture and a placebo, administered 3 times per week for 18 treatment sessions, in 46 children aged 2-6 years. The results of the research showed improvements in both speech (comprehension, expression) and social interactions (increased eye contact, reduced stereotypic behaviors) of individuals on the autism spectrum, compared to the placebo control group.

In their study, Knyazkova et al. (2020) investigated the recording of laser acupuncture through electroencephalogram, of the application of laser acupuncture in a child with ASD. Specifically, they chose three acupuncture points (GV20, LI4, P6) to relieve headaches and reduce anxiety, using a red semiconductor laser diode with a wavelength of 650 nm. The study involved two brothers aged 8 and 10, the latter of whom had autism. According to the EEG, the results showed increased brain activity in the child with autism after using the laser, compared to the child of typical development, also observing a change in behavior and an anxiety reduction.

## **6. Discussion**

Photobiomodulation has been shown, in animal model diseases and in humans, to affect neuronal function and improvement, inflammation levels, and microbiome composition. It is a safe, non-invasive method with little or no evidence of side effects or toxicity to the body's cells. Autism is characterized by an altered microbiome in the gastrointestinal tract, synaptic imbalance in the brain, functional connectivity dysfunction, and oxidative stress. In particular, LLLT appears to have a beneficial effect on several ASD dysfunctions and could be a promising method of treating the disorder (Hamilton et al., 2022).

Moreover, PBM affects several biological and pathological processes, regulating cellular function, enhancing mitochondrial stimulation, and improving the gut microbiome (Liebert et al., 2023). Given that it does not involve invasive procedures or drug administration and that LEDs are accepted as safe by the US Food and Drug Administration (FDA), it is significant that it does not manifest any side effects (Hamblin, 2022).

The LLLT method could be a significant tool in controlling cognitive deficits. Considering the appropriate wavelength, duration, dose, flow, and power density could deliver in each case (de la Torre, 2017). Additionally, photobiomodulation of the brain that has a photonic effect on cytochrome-c-oxidase (CCO) has been found to enhance cognitive procedure, due to increased cerebrovascular oxygenation of the prefrontal cortex (Holmes et al., 2019). It is made clear that the improvement of cerebral metabolic function, the stimulation of neurogenesis and synaptogenesis, the regulation of neurotransmitter function, but also the provision of neuroprotection through anti-inflammatory and antioxidant biological signaling constitute some primary, beneficial influences of brain PBM treatment (Salehpour et al., 2018; Hamblin, 2016).

The cause of ASD is unclear, as there is great heterogeneity in its characteristics, highlighting the existence of complexity and diversity in its etiology (Wen & Yao, 2021). It is characterized by behavioral and cognitive processes that are attributed, to a large extent, to the atypical functioning of the brain. Nevertheless, in recent years, documented findings highlight co-occurring abnormalities in a significant proportion of the ASD population

related to mitochondrial dysfunction, oxidative stress, perturbations with the gut microbiome, immune system regulation, and atypical connectivity patterns. Consequently, autism may often encompass systemic physiological abnormalities (Siddiqui et al., 2016).

Mitochondria are a considerable and potent treatment target for ASD, as several treatments (ketogenic diet, dietary supplements) targeting mitochondrial dysfunction are effective in the behavior of children with ASD (Frye, 2020b).

When experience has a significant bearing on the development of the brain, this is a vital phase. It is well-known that children with ASD benefit much from their early environments. Early loss of plasticity impairs the perceptual ability and processing of multiple and diverse stimuli through the senses in children with autism (Berger et al., 2013).

Neuroplasticity involves the ability of the neuron to reconstruct, modify and differentiate its structural and functional connectivity according to environmental stimuli. Children with ASD show in their first years of life (between 2-5 years) an atypical enlargement of the brain focused on the frontal and temporal cortex. In particular, according to neuroimaging, children with autism show accelerated synaptic growth and maturation during this time, suggesting a disruption of the brain's typical maturity and adaptability (Desarkar et al., 2015).

Synapses allow communication and transmission of information between neurons, enabling the brain to respond differently to conditions and experiences, affecting memory and learning. Synaptic locations of newly formed neurons in the brain are essential for neural circuits and synaptic plasticity development. Therefore, any abnormality in synaptogenesis affects human health and is associated with a broader category of brain conditions that comprises schizophrenia, autism, and intellectual impairments (Duman et al., K.2016).

The microbiome is an integral part of the functioning of the human body. According to recent studies, impairments in the peripheral and enteric neural systems are correlated with alterations in the intestinal microflora. As a consequence of the alterations is the dysregulation of gastrointestinal function, immunity, behavior, and the person's neurodevelopment, as occurs in the case of autism (Vuong & Hsiao, 2017).

Since the positive effects of PBM administration were shown in different age groups, the path is open for new therapeutic approaches to ASD. Including the possibility of activating synaptogenesis and improving neuroplasticity provided by this method, it is worth noting that its combination with appropriate educational and socio-emotional interventions would be more efficient (Hamblin, 2022). Additionally, studies in children and adolescents with neurodevelopmental disorders report increased neural plasticity and regulatory capabilities following brain stimulation combined with appropriate cognitive training (Finisguerra et al., 2019).

According to Liebert et al. (2019) PBM, applied as low-level laser therapy in animal models and humans, can have positive effects by changing the gut microbiome. Therefore, LLLT combined with appropriate dietary habits and exercise could implement as adjunctive therapy promoting microbiome rebalancing. In particular, PBM treatment could ameliorate mitochondrial dysfunction in gut neurons, enhancing the communication pathway between the enteric nervous system and the central nervous system through the gut-brain axis. As a result, the generation of dopamine and other neurotransmitters, whose function affects a variety of neurological illnesses plus autism, would continue to occur at normal levels.

It is value emphasizing the important ICTs role in the diagnosis, intervention, and educational process of children with ASD, as it enriches the learning and school environment in a targeted manner, strengthening the communication, organization, social, cognitive, and metacognitive skills of children with autism (Syriopoulou-Delli et al., 2021; Stathopoulou et al., 2020; Bamicha & Drigas, 2022b). Furthermore, we report that IoT incorporates multiple kinds of techniques and practices into educational approaches, helping to enhance the educational process in both special and general education. The most common strategies are metacognition, mindfulness, meditation, and emotional intelligence cultivation (Drigas et al., 2021a, b; Galitskaya & Drigas, 2021; Chaidi & Drigas, 2020; Drigas et al., 2022a, b; Lytra & Drigas, 2021; Karyotaki et al., 2022; Drigas & Papoutsis, 2021; Mitsea et al., 2022; Drigas et al., 2017; Chaidi et al., 2021; Demertzi et al., 2018; Bravou & Drigas, 2019; Drigas et al., 2006, 2020; Drigas & Petrova; 2014).

In conclusion, we underline that accurate diagnosis and timely intervention in children with ASD are crucial, considering that mainly during the preschool period, the nervous system's neurons are at their peak stage of synapse creation. Gradually, the procedure unfolds with the maturation of neurotransmitters during large-scale synaptic activity pruning and consolidation in adolescence (Xanthopoulou et al., 2019; Drigas & Bamicha, 2023; Berger et al., 2013).

## **7. Conclusions**

In summary, the diversity and heterogeneity of autism's symptoms and underlying causes initially require

diagnostic accuracy through a differential and interdisciplinary treatment of all the parameters that define the overall picture of the child with autism. Afterward, the appropriate choice and combination of therapeutic interventions, especially the early ones, can be beneficial in reducing or even removal of the symptoms. In the present study, we focused on specific dysfunctions related to autism, gut dysbiosis, mitochondrial function, and atypical brain neural network connectivity. Domains that the literature review indicates and the currently limited studies of the application of LLLT in people with ASD appear to benefit from the targeted therapeutic intervention of Photobiomodulation, improving behavior and cognitive abilities.

However, research and use of Low-Level Light Therapy in people with autism is at an early stage. In addition, there are a few cases where studies and data from LLLT trials in rodents with autistic symptoms cannot be extended and applied to humans. Therefore, it would be beneficial for future research to focus on longitudinal applications of the method in humans, including the specific neurobiological parameters we mentioned above. A key point is the method's non-invasiveness with zero or minimal and mild side effects which acts to reinforce and improve in dysfunctional areas of ASD.

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## 9. Authors' Contributions

*Victoria Bamicha*: research design, writing, grammatical and scientific corrections in the manuscript, and revision of the written article. *Yolanda Salapata*: research design, writing, grammatical and scientific corrections in the manuscript.

## 10. Conflicts of Interest

No conflicts of interest.

## 11. Ethics Approval

Not applicable.

## 12. References

- Abirami, G. P., Radhakrishnan, R. K., Johnson, E., Roshan, S. A., Yesudhas, A., Parveen, S., ... & Kandasamy, M. (2020). The Regulation of Reactive Neuroblastosis, Neuroplasticity, and Nutraceuticals for Effective Management of Autism Spectrum Disorder. *Personalized Food Intervention and Therapy for Autism Spectrum Disorder Management*, 24, 207-222. [https://doi.org/10.1007/978-3-030-30402-7\\_8](https://doi.org/10.1007/978-3-030-30402-7_8)
- Alharthi, A., Alhazmi, S., Alburae, N., & Bahieldin, A. (2022). The human gut microbiome as a potential factor in autism spectrum disorder. *International journal of molecular sciences*, 23(3), 1363. <https://doi.org/10.3390/ijms23031363>
- Anders, J. J., Lanzafame, R. J., & Arany, P. R. (2015). Low-level light/laser therapy versus photobiomodulation therapy. *Photomedicine and laser surgery*, 33(4), 183. <https://doi.org/10.1089%2Fpho.2015.9848>
- Aromataris, E., & Pearson, A. (2014). The systematic review: an overview. *The American Journal of Nursing*, 114(3):53-58. <https://doi.org/10.1097/01.naj.0000444496.24228.2c>
- Azadgoli, B., & Baker, R. Y. (2016). Laser applications in surgery. *Annals of translational medicine*, 4(23), 452. <https://doi.org/10.21037%2Fatm.2016.11.51>
- Bakola, L. N., Rizos, N. D. & Drigas, A. S. (2019). ICTs for Emotional and Social Skills Development for Children with ADHD and ASD Co-existence. *International Journal of Emerging Technologies in Learning*, 14 (5), 122-131. <https://doi.org/10.3991/ijet.v14i05.9430>
- Bamicha, V., & Drigas, A. (2022a). The Evolutionary Course of Theory of Mind-Factors That Facilitate or Inhibit Its Operation & the Role of ICTs. *Technium Soc. Sci. J.*, 30, 138-158. <https://doi.org/10.47577/tssj.v30i1.6220>
- Bamicha, V., & Drigas, A. (2022b). ToM & ASD: The interconnection of Theory of Mind with the social-emotional, cognitive development of children with Autism Spectrum Disorder. The use of ICTs as an

- alternative form of intervention in ASD. *Technium Social Sciences Journal*, 33, 42-72. <https://orcid.org/0000-0001-5637-9601>
- Bamicha, V., & Drigas, A. (2023a). Consciousness influences in ToM and Metacognition functioning-An artificial intelligence perspective. *Research, Society and Development*, 12(3). <https://doi.org/10.33448/rsd-v12i3.40420>
- Bamicha, V., & Drigas, A. (2023b). Theory of Mind in relation to Metacognition and ICTs. A metacognitive approach to ToM. *Scientific Electronic Archives*, 16(4). <https://doi.org/10.36560/16420231711>
- Barrett, D. W., & Gonzalez-Lima, F. (2013). Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience*, 230, 13-23. <https://doi.org/10.1016/j.neuroscience.2012.11.016>
- Berger, J. M., Rohn, T. T., & Oxford, J. T. (2013). Autism as the Early Closure of a Neuroplastic Critical Period Normally Seen in Adolescence. *Biol Syst*, 2(118), 2. <https://doi.org/10.4172%2F2329-6577.1000118>
- Bitsika, V., & Sharpley, C. F. (2023). Neurobiological Concomitants of Autism as Informers of Clinical Practice: a Status Review. *Advances in Neurodevelopmental Disorders*, 1-13. <https://doi.org/10.1007/s41252-023-00344-3>
- Bjørklund, G., Meguid, N. A., El-Bana, M. A., Tinkov, A. A., Saad, K., Dadar, M., ... & Chirumbolo, S. (2020). Oxidative stress in autism spectrum disorder. *Molecular neurobiology*, 57, 2314-2332. <https://doi.org/10.1007/s12035-019-01742-2>
- Boggio, P. S., Asthana, M. K., Costa, T. L., Valasek, C. A., & Osório, A. A. (2015). Promoting social plasticity in developmental disorders with non-invasive brain stimulation techniques. *Frontiers in Neuroscience*, 9, 294-294. <https://doi.org/10.3389/fnins.2015.00294>
- Bravou, V., & Drigas, A. (2019). A Contemporary View on Online and Web Tools for Students with Sensory& Learning Disabilities. *International Journal of Online & Biomedical Engineering*, 15(12) 97. <https://doi.org/10.3991/ijoe.v15i12.10833>
- Brondino, N., Fusar-Poli, L., Rocchetti, M., Provenzani, U., Barale, F., & Politi, P. (2015). Complementary and Alternative Therapies for Autism Spectrum Disorder. *Evidence-based complementary and alternative medicine: eCAM*, 2015, 258589. <https://doi.org/10.1155/2015/258589>
- Byrne, J. A. (2016). Improving the peer review of narrative literature reviews. *Research integrity and peer review*, 1, 1-4. DOI 10.1186/s41073-016-0019-2
- Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology*, 28(2), 203. PMID: 25830558; PMCID: PMC 4367209
- Carroll, L., Braeutigam, S., Dawes, J. M., Krsnik, Z., Kostovic, I., Coutinho, E., ... & Menassa, D. A. (2021). Autism spectrum disorders: multiple routes to, and multiple consequences of, abnormal synaptic function and connectivity. *The Neuroscientist*, 27(1), 10-29. <https://doi.org/10.1177%2F1073858420921378>
- Chaidi, I., & Drigas, A. (2020). Parents' Involvement in the Education of their Children with Autism: Related Research and its Results. *International Journal Of Emerging Technologies In Learning (IJET)*, 15(14), 194-203. <https://doi.org/10.3991/ijet.v15i14.12509>
- Chaidi, E., Kefalis, C., Papagerasimou, Y., & Drigas, A. (2021). Educational robotics in Primary Education. A case in Greece. *Research, Society and Development*, 10(9), e17110916371-e17110916371.
- Chaidi, I., & Drigas, A. (2022). Digital games & special education. *Technium Social Sciences Journal*, 34, 214-236.
- Cheung, M. C., Lee, T. L., Sze, S. L., & Chan, A. S. (2023). Photobiomodulation improves frontal lobe cognitive functions and mental health of older adults with non-amnesic mild cognitive impairment: Case studies. *Frontiers in Psychology*, 13. <https://doi.org/10.3389%2Ffpsyg.2022.1095111>
- Chon, T. Y., Mallory, M. J., Yang, J., Bublitz, S. E., Do, A., & Dorsher, P. T. (2019). Laser acupuncture: a concise review. *Medical acupuncture*, 31(3), 164-168. <https://dx.doi.org/10.1089%2Ffacu.2019.1343>
- De Freitas, L. F., & Hamblin, M. R. (2016a). Laser Acupuncture. In *Handbook of Low-Level Laser Therapy* (pp. 943-968). Jenny Stanford Publishing. eBook: ISBN9781315364827
- De Freitas, L. F., & Hamblin, M. R. (2016b). Proposed mechanisms of photobiomodulation or low-level light

- therapy. *IEEE Journal of selected topics in quantum electronics*, 22(3), 348-364. <https://doi.org/10.1109/JSTQE.2016.2561201>
- De la Torre, J. C. (2017). Treating cognitive impairment with transcranial low-level laser therapy. *Journal of Photochemistry and Photobiology B: Biology*, 168, 149-155. <https://doi.org/10.1016/j.jphotobiol.2017.02.008>
- De Sousa, M. V. P. (2016). What is low-level laser (light) therapy? In *Handbook of low-level laser therapy* (pp. 37-52). Jenny Stanford Publishing. eBook: ISBN9781315364827
- Demertzi, E., Voukelatos, N., Papagerasimou, Y., & Drigas, A. S. (2018). Online learning facilities to support coding and robotics courses for youth. *International Journal of Engineering Pedagogy (iJEP)*, 8(3), 69-80. <https://doi.org/10.3991/ijep.v8i3.8044>
- Desarkar, P., Rajji, T. K., Ameis, S. H., & Daskalakis, Z. J. (2015). Assessing and Stabilizing Aberrant Neuroplasticity in Autism Spectrum Disorder: The Potential Role of Transcranial Magnetic Stimulation. *Frontiers in Psychiatry*, 6, 124-124. <https://doi.org/10.3389/fpsy.2015.00124>
- Drigas, A., Koukianakis, L., & Papagerasimou, Y. (2006). An e-learning environment for nontraditional students with sight disabilities. In Proceedings. *Frontiers in Education*. 36th Annual Conference (23-27). IEEE. <https://doi.org/10.1109/FIE.2006.322633>
- Drigas, A., & Petrova, A. (2014). ICTs in speech and language therapy. *International Journal of Engineering Pedagogy (iJEP)*, 4(1), 49-54. <http://dx.doi.org/10.3991/ijep.v4i1.3280>
- Drigas, A., Karyotaki, M., & Skianis, C. (2017). Success: A 9 layered-based model of giftedness. *International Journal of Recent Contributions from Engineering, Science & IT (iJES)*, 5(4), 4-18. <https://doi.org/10.3991/ijes.v5i4.7725>
- Drigas, A., Dede, D. E., & Dedes, S. (2020). Mobile and other applications for mental imagery to improve learning disabilities and mental health. *International Journal of Computer Science Issues (IJCSI)*, 17(4), 18-23. <https://doi.org/10.5281/zenodo.3987533>
- Drigas, A., Mitsea, E., & Skianis, C. (2021a). The Role of Clinical Hypnosis & VR in Special Education. *International Journal of Recent Contributions from Engineering Science & IT (IJES)* 9 (4), 4-18. <http://dx.doi.org/10.3991/ijes.v9i4.26147>
- Drigas, A., & Sideraki, A. (2021). Emotional Intelligence in Autism. *Technium Social Sciences Journal*, 26, 80-92. <https://doi.org/10.47577/tssj.v26i1.5178>
- Drigas, A., & Papoutsis, C. (2021). Nine Layer Pyramid Model Questionnaire for Emotional Intelligence. *International Journal of Online & Biomedical Engineering*, 17(7). <https://doi.org/10.3991/ijoe.v17i07.22765>
- Drigas, A., Papoutsis, C., & Skianis, C. (2021b). Metacognitive and Metaemotional Training Strategies through the Nine-layer Pyramid Model of Emotional Intelligence. *International Journal of Recent Contributions from Engineering, Science & IT (iJES)*, 9(4), 58-76. <https://doi.org/10.3991/ijes.v9i4.26189>
- Drigas, A., Mitsea, E., & Skianis, C. (2022a). Virtual reality and metacognition training techniques for learning disabilities. *Sustainability*, 14(16), 10170. <https://doi.org/10.3390/su141610170>
- Drigas, A., Mitsea, E., & Skianis, C. (2022b). Intermittent Oxygen Fasting and Digital Technologies: from Antistress and Hormones Regulation to Wellbeing, Bliss and Higher Mental States. *Technium BioChemMed*, 3(2), 55-73.
- Drigas, A., & Bamicha, V. (2023). PoM & ToM-Harnessing the Power of Mind in Theory of Mind by shaping beneficial mental states in Preschoolers and the ICT's role. *Research, Society and Development*, 12(5). <http://dx.doi.org/10.33448/rsd-v12i5.41590>
- Duman, J. G., Tu, Y. K., & Tolia, K. F. (2016). Emerging Roles of BAI Adhesion-GPCRs in Synapse Development and Plasticity. *Neural Plasticity*, 2016, 8301737-8301737. <https://doi.org/10.1155/2016/8301737>
- Finisguerra, A., Borgatti, R., & Urgesi, C. (2019). Non-invasive brain stimulation for the rehabilitation of children and adolescents with neurodevelopmental disorders: a systematic review. *Frontiers in psychology*, 10, 135. <https://doi.org/10.3389/fpsyg.2019.00135>
- Frye, R. E. (2020a). Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and Targeted Treatments. In *Seminars in Pediatric Neurology*, 35:100829. <https://doi.org/10.1016/j.spn.2020.100829>
- Frye, R. E. (2020b). Mitochondrial Dysfunction in Autism Spectrum Disorder: Unique Abnormalities and

- Targeted Treatments. *In Seminars in pediatric neurology*, 35:100829. <https://doi.org/10.1016/j.spen.2020.100829>
- Galitskaya, V., & Drigas, A. (2021). The importance of working memory in children with Dyscalculia and Ageometria. *Scientific Electronic Archives*, 14(10). <https://doi.org/10.36560/141020211449>
- Garcia-Gutierrez, E., Narbad, A., & Rodríguez, J. M. (2020). Autism spectrum disorder associated with gut microbiota at immune, metabolomic, and neuroactive level. *Frontiers in neuroscience*, 14, 578666. <https://doi.org/10.3389/fnins.2020.578666>
- Glass, G. E. (2021). Photobiomodulation: The Clinical Applications of Low-Level Light Therapy. *Aesthetic Surgery Journal*, 41(6), 723–738. <https://doi.org/10.1093/asj/sjab025>
- Guang, S., Pang, N., Deng, X., Yang, L., He, F., Wu, L., ... & Peng, J. (2018). Synaptopathology Involved in Autism Spectrum Disorder. *Frontiers in Cellular Neuroscience*, 12, 470-470. <https://doi.org/10.3389/fncel.2018.00470>
- Gyawali, S., & Patra, B. N. (2019). Trends in concept and nosology of autism spectrum disorder: A review. *Asian journal of psychiatry*, 40, 92-99. <https://doi.org/10.1016/j.ajp.2019.01.021>
- Hamblin, M. R. (2016). Shining light on the head: photobiomodulation for brain disorders. *BBA clinical*, 6, 113-124. <https://doi.org/10.1016/j.bbacli.2016.09.002>
- Hamblin, M. R. (2018). Photobiomodulation for traumatic brain injury and stroke. *Journal of neuroscience research*, 96(4), 731-743. <https://doi.org/10.1002%2Fjnr.24190>
- Hamblin, M. R. (2019). What we don't know and what the future holds. *Photobiomodulation in the Brain*, 599–613. <https://doi.org/10.1016/B978-0-12-815305-5.00043-9>
- Hamblin, M. R. (2022). Could Photobiomodulation Treat Autism Spectrum Disorder? *Photobiomodulation, Photomedicine, and Laser Surgery*, 40(6), 367-369. <https://doi.org/10.1089/photob.2022.0051>
- Hamilton, C., Liebert, A., Pang, V., Magistretti, P., & Mitrofanis, J. (2022). Lights on for Autism: Exploring Photobiomodulation as an Effective Therapeutic Option. *Neurology International*, 14(4), 884-893. <https://doi.org/10.3390/neurolint14040071>
- Hecht, J. (2010). A short history of laser development. *Applied optics*, 49(25), F99-F122. <https://doi.org/10.1117/1.3483597>
- Hennessy, M., & Hamblin, M. R. (2017). Photobiomodulation and the brain: a new paradigm. *Journal of optics* (2010), 19(1), 013003. <https://doi.org/10.1088%2F2040-8986%2F19%2F01%2F013003>
- Hollis, F., Kanellopoulos, A. K., & Bagni, C. (2017). Mitochondrial dysfunction in Autism Spectrum Disorder: clinical features and perspectives. *Current opinion in neurobiology*, 45, 178-187. <https://doi.org/10.1016/j.conb.2017.05.018>
- Holmes, E., Barrett, D. W., Saucedo, C. L., O'Connor, P., Liu, H., & Gonzalez-Lima, F. (2019). Cognitive Enhancement by Transcranial Photobiomodulation Is Associated With Cerebrovascular Oxygenation of the Prefrontal Cortex. *Frontiers in Neuroscience*, 13, 1129-1129. <https://doi.org/10.3389/fnins.2019.01129>
- Karyotaki, M., Bakola, L., Drigas, A., & Skianis, C. (2022). Women's Leadership via Digital Technology and Entrepreneurship in business and society. *Technium Social Sciences Journal*, 28(1), 246-252. <https://doi.org/10.47577/tssj.v28i1.5907>
- Khongrum, J., & Wattanathorn, J. (2015). Laser acupuncture improves behavioral disorders and brain oxidative stress status in the valproic acid rat model of autism. *Journal of Acupuncture and Meridian Studies*, 8(4), 183-191. <https://doi.org/10.1016/j.jams.2015.06.008>
- Khongrum, J., & Wattanathorn, J. (2017). Laser acupuncture at HT7 improves the cerebellar disorders in valproic acid-rat model of autism. *Journal of Acupuncture and Meridian Studies*, 10(4), 231-239. <https://doi.org/10.1016/j.jams.2017.06.006>
- Knyazkova, A. I., Samarinova, A. A., Kistenev, Y. V., Borisov, A. V., & Shulmina, P. V. (2020). Electroencephalography registration of laser acupuncture action on children with autism disorder. *In BIODEVICES 2020-13th International Conference on Biomedical Electronics and Devices, Proceedings; Part of 13th International Joint Conference on Biomedical Engineering Systems and Technologies, BIOSTEC 2020* (pp. 387-394). <http://dx.doi.org/10.5220/0009370503870394>
- Lai, M.-C., Lombardo, M. V. & Baron-Cohen S. (2014). *Autism. Lancet*, 383(9920) 896–910. [https://doi.org/10.1016/S0140-6736\(13\)61539-1](https://doi.org/10.1016/S0140-6736(13)61539-1)

- Lasheras, I., Seral, P., Latorre, E., Barroso, E., Gracia-García, P., & Santabárbara, J. (2020). Microbiota and gut-brain axis dysfunction in autism spectrum disorder: Evidence for functional gastrointestinal disorders. *Asian Journal of Psychiatry*, 47, 101874. <https://doi.org/10.1016/j.ajp.2019.101874>
- Lee, T. L., Ding, Z., & Chan, A. S. (2022). Can transcranial photobiomodulation improve cognitive function? A systematic review of human studies. *Ageing research reviews*, 83, 101786. <https://doi.org/10.1016/j.arr.2022.101786>
- Leisman, G., Machado, C., Machado, Y., & Chinchilla-Acosta, M. (2018). Effects of Low-Level Laser Therapy in Autism Spectrum Disorder. *Advances in Experimental Medicine and Biology*, 1116, 111-130. [https://doi.org/10.1007/5584\\_2018\\_234](https://doi.org/10.1007/5584_2018_234)
- Liebert, A., Bicknell, B., Johnstone, D. M., Gordon, L. C., Kiat, H., & Hamblin, M. R. (2019). "Photobiomics": Can Light, Including Photobiomodulation, Alter the Microbiome? *Photobiomodulation, Photomedicine, and Laser Surgery*, 37(11), 681-693. <https://doi.org/10.1089/photob.2019.4628>
- Liebert, A., Capon, W., Pang, V., Vila, D., Bicknell, B., McLachlan, C., & Kiat, H. (2023). Photophysical Mechanisms of Photobiomodulation Therapy as Precision Medicine. *Biomedicines*, 11(2), 237. <http://dx.doi.org/10.3390/biomedicines11020237>
- Lord, C., Elsabbagh, M., Baird, G. & Veenstra-Vanderweel, J. (2018). Autism spectrum disorder. *Lancet*, 392: 508–520. [http://dx.doi.org/10.1016/S0140-6736\(18\)31129-2](http://dx.doi.org/10.1016/S0140-6736(18)31129-2)
- Lytra, N., & Drigas, A. (2021). STEAM education-metacognition–Specific Learning Disabilities. *Scientific Electronic Archives*, 14(10). <http://dx.doi.org/10.36560/141020211442>
- Machado, C., Machado, Y., Chinchilla, M., & Machado, Y. (2019). Follow-Up Assessment of Autistic Children 6 Months after Finishing Low Lever Laser Therapy. *Internet J. Neurol*, 21, 1-8. <http://dx.doi.org/10.5580/IJN.54101>
- Machado, C., Machado, Y., Chinchilla, M., & Machado, Y. (2020). Follow-Up Assessment of Autistic Children 6 Months after Finishing Low Lever Laser Therapy. *Internet J. Neurol*, 21, 1-8. <http://dx.doi.org/10.5580/IJN.54809>
- Marchi, E., Schuller, B., Baird, A., Baron-Cohen, S., Lassalle, A., O'Reilly, H., ... & Baranger, A. (2018). The ASC-inclusion perceptual serious gaming platform for autistic children. *IEEE Transactions on Games*, 11(4), 328-339. <https://doi.org/10.1109/TG.2018.2864640>
- Matta, S. M., Hill-Yardin, E. L., & Crack, P. J. (2019). The influence of neuroinflammation in Autism Spectrum Disorder. *Brain, behavior, and immunity*, 79, 75-90. <https://doi.org/10.1016/j.bbi.2019.04.037>
- Maximo, J. O., Cadena, E. J. & Kana, R. K. (2014). The Implications of Brain Connectivity in the Neuropsychology of Autism. *Neuropsychology Review*, 24:16–31. <https://link.springer.com/content/pdf/10.1007/s11065-014-9250-0>
- Mitrofanis, J., & Henderson, L. A. (2020). How and why does photobiomodulation change brain activity? *Neural Regeneration Research*, 15(12), 2243. <https://doi.org/10.4103%2F1673-5374.284989>
- Mitsea, E., Drigas, A., & Skianis, C. (2022). ICTs and Speed Learning in Special Education: High-Consciousness Training Strategies for High-Capacity Learners through Metacognition Lens. *Technium Soc. Sci. J.*, 27, 230. <https://doi.org/10.47577/tssj.v27i1.5599>
- Moradi, K., Ashraf-Ganjouei, A., Tavolinejad, H., Bagheri, S., & Akhondzadeh, S. (2021). The interplay between gut microbiota and autism spectrum disorders: A focus on immunological pathways. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 106, 110091. <https://doi.org/10.1016/j.pnpbp.2020.110091>
- Naeser, M. A., Ho, M. D., Martin, P. I., Hamblin, M. R., & Koo, B. B. (2020). Increased functional connectivity within intrinsic neural networks in chronic stroke following treatment with red/near-infrared transcranial photobiomodulation: case series with improved naming in aphasia. *Photobiomodulation, Photomedicine, and Laser Surgery*, 38(2), 115-131. <https://doi.org/10.1089/photob.2019.4630>
- Nanda, H., & Frye, R. E. (2023). Synchrony 2022: Catalyzing Research and Treatments to Benefit Individuals with Neurodevelopmental Disorders including Autism Spectrum Disorders. *Journal of Personalized Medicine*, 13(3), 490. <https://doi.org/10.3390/jpm13030490>
- Ntaountaki, P., Lorentzou, G., Lykothanasi, A., Anagnostopoulou, P., Alexandropoulou, V., & Drigas, A. (2019). Robotics in Autism Intervention. *Int. J. Recent Contributions Eng. Sci. IT*, 7(4), 4-17. <https://doi.org/10.3991/ijes.v7i4.11448>

- Pallanti, S., Di Ponzio, M., Grassi, E., Vannini, G., & Cauli, G. (2022). Transcranial Photobiomodulation for the Treatment of Children with Autism Spectrum Disorder (ASD): A Retrospective Study. *Children*, 9(5), 755. <https://doi.org/10.3390%2Fchildren9050755>
- Pan, W. T., Liu, P. M., Ma, D., & Yang, J. J. (2023). Advances in photobiomodulation for cognitive improvement by near-infrared derived multiple strategies. *Journal of Translational Medicine*, 21(1), 135. <https://doi.org/10.1186/s12967-023-03988-w>
- Pangrazzi, L., Balasco, L., & Bozzi, Y. (2020). Oxidative stress and immune system dysfunction in autism spectrum disorders. *International journal of molecular sciences*, 21(9), 3293. <https://doi.org/10.3390/ijms21093293>
- Pergantis, P., & Drigas, A. (2023a). Sensory integration therapy as enabler for developing emotional intelligence in children with autism spectrum disorder and the ICT's role. *Brazilian Journal of Science*, 2(12), 53-65. <https://doi.org/10.14295/bjs.v2i12.422>
- Pergantis, P., & Drigas, A. (2023b). Assistive technology for autism spectrum disorder children that experiences stress and anxiety. *Brazilian Journal of Science*, 2(12), 77-93. <https://doi.org/10.14295/bjs.v2i12.426>
- Predescu, M., Al Ghazi, L., & Darjan, I. (2018). An Ecological Approach of Autism Spectrum Disorders. *Journal of Educational Sciences*, 19, 31-43. <http://dx.doi.org/10.35923/JES.2018.2.03>
- Raichle, M. E. (2015). The brain's default mode network. *Annual review of neuroscience*, 38, 433-447. <https://doi.org/10.1146/annurev-neuro-071013-014030>
- Ramezani, F., Neshasteh-Riz, A., Ghadaksaz, A., Fazeli, S. M., Janzadeh, A., & Hamblin, M. R. (2021). Mechanistic aspects of photobiomodulation therapy in the nervous system. *Lasers in Medical Science*, 37, 11-18 (2022). <https://doi.org/10.1007/s10103-021-03277-2>
- Rojas, J. C., & Gonzalez-Lima, F. (2016). Transcranial low-level laser (light) therapy for neurocognitive enhancement. In *Handbook of low-level laser therapy* (pp. 1093-1112). *Jenny Stanford Publishing*. eBook: ISBN9781315364827
- Rose, S., Niyazov, D. M., Rossignol, D. A., Goldenthal, M., Kahler, S. G., & Frye, R. E. (2018). Clinical and molecular characteristics of mitochondrial dysfunction in autism spectrum disorder. *Molecular diagnosis & therapy*, 22, 571-593. <https://doi.org/10.1007%2Fs40291-018-0352-x>
- Rosenfeld, C. S. (2015). Microbiome disturbances and autism spectrum disorders. *Drug Metabolism and Disposition*, 43(10), 1557-1571. <http://dx.doi.org/10.1124/dmd.115.063826>
- Rossignol, D. A., & Frye, R. E. (2014). Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. *Frontiers in Physiology*, 5, 150-150. <https://doi.org/10.3389/fphys.2014.00150>
- Salehpour, F., Mahmoudi, J., Kamari, F., Sadigh-Eteghad, S., Rasta, S. H., & Hamblin, M. R. (2018). Brain photobiomodulation therapy: a narrative review. *Molecular neurobiology*, 55, 6601-6636. <https://doi.org/10.1007%2Fs12035-017-0852-4>
- Saunders, N., & Berry, K. (2020). Paediatric Acupuncture: The Evidence. *The Journal of Chinese Medicine*, (122), 56-60. <https://www.evidencebasedacupuncture.org/pediatric-acupuncture/>
- Sharma, S. R., Gonda, X., & Tarazi, F. T. (2018). Autism Spectrum Disorder: Classification, diagnosis and therapy. *Pharmacology & Therapeutics*, 190: 91-104. <https://doi.org/10.1016/j.pharmthera.2018.05.007>
- Siddiqui, M. F., Elwell, C., & Johnson, M. H. (2016). Mitochondrial Dysfunction in Autism Spectrum Disorders. *Autism-Open Access*, 6(4). <https://doi.org/10.4172/2165-7890.1000190>
- Sideraki, A., & Drigas, A. (2023). The role of cortisol and microbiome in the anxiety of people with ASD and the use of ICTs for regulation. *World Journal of Biology Pharmacy and Health Sciences*, 14(03), 137-148. <https://doi.org/10.30574/wjbphs.2023.14.3.0253>
- Son, G., & Han, J. (2018). Roles of mitochondria in neuronal development. *BMB reports*, 51(11), 549. <https://doi.org/10.5483%2FBMBRep.2018.51.11.226>
- Stathopoulou, A., Karabatzaki, Z., Tsiros, D., Katsantoni, S., & Drigas, A. (2019). Mobile Apps the Educational Solution for Autistic Students in Secondary Education. *International Journal of Interactive Mobile Technologies*, 13(2), 89-101. <https://www.learntechlib.org/p/207548>
- Stathopoulou, A., Loukeris, D., Karabatzaki, Z., Politi, E., Salapata, Y., & Drigas, A. (2020). Evaluation of Mobile Apps Effectiveness in Children with Autism Social Training via Digital Social Stories. *International Association of Online Engineering*, 14 (3). <https://www.learntechlib.org/p/216549/>

- Surapaty, I. A., Simadibrata, C., Rejeki, E. S., & Mangunatmadja, I. (2020). Laser acupuncture effects on speech and social interaction in patients with autism spectrum disorder. *Medical Acupuncture*, 32(5), 300-309. <https://doi.org/10.1089/acu.2020.1417>
- Syriopoulou-Delli, C. K., & Gkiolnta, E. (2020). Review of assistive technology in the training of children with autism spectrum disorders. *International Journal of Developmental Disabilities*, 68(2), 73-85 <https://doi.org/10.1080/20473869.2019.1706333>
- Syriopoulou-Delli, C. K., Deres, I., & Drigas, A. (2021). Intervention Program using a Robot for Children with Autism Spectrum Disorder. *Research Society and Development*, 10(4), 1-13. <https://www.researchgate.net/deref/http%3A%2F%2Fdx.doi.org%2F10.33448%2Frsd-v10i4.XXXXX>
- Vuong, H. E., & Hsiao, E. Y. (2017). Emerging roles for the gut microbiome in autism spectrum disorder. *Biological psychiatry*, 81(5), 411-423. <https://doi.org/10.1016/j.biopsych.2016.08.024>
- Wen, Y., & Yao, Y. (2021). Autism spectrum disorders: the mitochondria connection. *Exon Publications*, 79-93. <http://dx.doi.org/10.36255/exonpublications.autismspectrumdisorders.2021.mitochondria>
- Wong-Riley, M., & Liang, H. L. (2019). Photobiomodulation of cultured primary neurons: role of cytochrome c oxidase. *Photobiomodulation in the Brain*, 21-34. <https://doi.org/10.1016/B978-0-12-815305-5.00003-8>
- Xanthopoulou, M., Kokalia, G., & Drigas, A. (2019). Applications for Children with Autism in Preschool and Primary Education. *Int. J. Recent Contributions Eng. Sci. IT*, 7(2), 4-16. <https://doi.org/10.3991/ijes.v7i2.10335>
- Yang, J., Fu, X., Liao, X., & Li, Y. (2020). Effects of gut microbial-based treatments on gut microbiota, behavioral symptoms, and gastrointestinal symptoms in children with autism spectrum disorder: A systematic review. *Psychiatry Research*, 293, 113471-113471. <https://doi.org/10.1016/j.psychres.2020.113471>
- Yang, C., Hao, Z., Zhang, L. L., & Guo, Q. (2015). Efficacy and safety of acupuncture in children: an overview of systematic reviews. *Pediatric Research*, 78 (2), 112-119. <https://doi.org/10.1038/pr.2015.91>
- Yang, L., Youngblood, H., Wu, C., & Zhang, Q. (2020). Mitochondria as a target for neuroprotection: role of methylene blue and photobiomodulation. *Translational neurodegeneration*, 9, 1-22. <https://doi.org/10.1186/s40035-020-00197-z>
- Zein, R., Selting, W., & Hamblin, M. R. (2018). Review of light parameters and photobiomodulation efficacy: dive into complexity. *Journal of Biomedical Optics*, 23(12), 120901. <https://doi.org/10.1117/1.JBO.23.12.120901>

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