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Dysregulated Signaling Pathways in Autism Spectrum Disorder: Molecular Mechanisms, Pharmacological Targets, and Therapeutic Perspectives

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ABSTRACT: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by persistent difficulties in social communication and interaction, restricted or repetitive patterns of behavior, and varying degrees of impairment in language, cognition, learning, and adaptive functioning. The etiology of ASD is multifactorial, involving complex interactions between genetic susceptibility and environmental factors. Increasing evidence suggests that genetic variants associated with synaptic development, neuronal connectivity, neurotransmission, and intracellular signaling pathways contribute substantially to ASD pathogenesis. Dysregulation of several molecular signaling networks involved in synaptic plasticity, neuronal differentiation, neurodevelopment, and brain connectivity has also been implicated in the development and progression of ASD. Despite considerable advances in understanding its biological basis, the precise molecular mechanisms underlying ASD remain incompletely elucidated because of its marked genetic and clinical heterogeneity. Consequently, therapeutic management primarily focuses on improving core symptoms, associated behavioral abnormalities, communication, adaptive functioning, and quality of life through individualized behavioral, educational, pharmacological, and supportive interventions. In this review, we critically examine the current evidence regarding molecular and neuronal signaling pathways implicated in ASD, with particular emphasis on their mechanistic roles in disease pathogenesis and their potential as therapeutic targets. We further discuss evidence-based pharmacological and emerging therapeutic strategies associated with these signaling pathways and highlight current knowledge gaps, challenges, and future opportunities for developing mechanism-based interventions for ASD.

1. INTRODUCTION

Autism can be defined as "happy in one's world", but as social interaction is the demand of time, this behavior is called an autism spectrum disorder (ASD). It is related to the misbalancing of neurological conditions, and its direct consequence is impaired development in social interaction and communication and thus deprived, restricted in terms of activity and level of interest in general (Devi et al. 2016). From the age perspective, it is not seen abruptly in an adult category (30% of cases), but its origin is in the age category 1–14 years (approximately 70% of cases) (Saqr et al. 2018). A major challenge for ASD patients is coping with the outside world, as they love to shell themselves. However, it is unlike normal expected behavior and needs to identify various methods for transitioning from the inside to the outside world (Mazurek et al. 2020). One study reported the non-competency of an adult with ASD to lead their everyday life independently (Kocabiyik and Fazlioglu 2018). Thus, parents

had to look after autistic subjects, and earnings got affected. Although ASD subjects like to be in the shell, they often experience and suffer from comorbid psychiatric illnesses, such as depressive and anxiety disorders, at potentially higher rates than the general population and individuals with other developmental disabilities (Dean et al. 2017).

Experimentation with various intervention training programs and treatments from an occupational and professional perspective is relatively new in the research domain. Some shreds of evidence proved that this direction could lead to success once a person is identified with ASD, as there is no complete cure reported to date (Upadhyay et al. 2021). Even though various treatments and costly intervention training are taking shape in the market, proven evidence still needs to be included, which creates confusion and distress among parents. Thus, to make life smooth for parents and ASD patients, evidence-based interventions, training, and therapy are in huge demand. As new developments in interventions are growing rapidly, new or established developers still need claims and support through systematic and controlled research. A very informative fact has been proposed: most ASD children may use words, but the intent is not to communicate (Sherratt 2005). Thus, interventions that mold the mere use of words to communicate intent are also in demand. Generally, emotions and language awareness are mostly delayed or completely deficient (Bal et al. 2020).

This paper investigates the various interventions developed and experimented with the ASD population, irrespective of age and gender. Systematically review the types of intervention in the form of social, behavioral, sensors-based, computer-assisted, siblings, and relation-based on ASD patients in the age category of children to adolescents from the perspective of the professional and social worker.

2. METHODS

Our study aimed to give clear insights into the pathophysiological mechanism, i.e., dysregulation of pathways involved in ASD and development in the area of interventions and its impact irrespective of age. The first and most crucial step is to identify the relevant research articles in the literature in this domain. An extensive literature search is key, with appropriate phrases and locations. In this article, locations were targeted using Google search, PsycINFO, MEDLINE, and the Web of Knowledge. The key phrases repeatedly and alternatively used were "autism" and "autism development" combined with "intervention", "treatment", "adult", and "adolescent". The preprint studies explored in the journals cover research on ASD and research in developmental disabilities. Papers selected based on abstracts and selection criteria include mentioning non-biological interventions for the betterment of ASD patients. The steps followed in designing the paper include identification, screening, eligibility, and inclusion (Fig. 1). The selected articles were categorized into 17 different types of intervention categories. The interventions and their impact on the autism society are shown in Table 1.

Table 1. Reviewed Intervention and its impact on betterment

Intervention	**Positive Impact**
Behavioural	Social Interaction; Linguistic; New Skills; Desirable Behaviour; Gesture; Verbal; High Fidelity; Spontaneity; medical Treatment attention; Comprehensive personality; family mental peace; working memory;
Early	Social Interaction; body functioning; cognitive development; pivotal development; emotional development; social development; motor activity; Language; behaviour; IQ; Adaptable development; spontaneity, Vocal, Social, Verbal, Adaptive; Sustainability
Social Based	Motor; Auditory; Linguistic; Language Development; Visual Interactive behaviour; Exploration; mainstream placement; Social network motivation; Initiation; Good Behavioural pattern; Cognitive Functioning; Execution Functioning; Quality of life; Adaptive behaviour
Social Cognition Based	Grasping of social cues; Social functioning; theory of mind skills; social communication skills
Motor and Physical Activities	Sleep efficiency; sleep onset; sleep latency; sleep duration; Level up physical activity; Socialization behaviour; Engagement time sleep quantity; metabolic health; Quality of life; motor skills; adaptive function

Caregiver Mediated	Social communication; gratitude; behavioural response
Parent Mediated	Reduce autism symptoms; Vocal response;360 Degree development; safe feel; retention; sustainability
Education Based	Employability; skillset
Centre and Home Based	Social Behaviour
Electrodes Based	Social Interaction
Hobby Based	Confidence in social behaviour; engagement, calmness; social behaviour
Communication Intervention	Mental Development; Initiate Communication; Collaborate; Use of Symbols; Gesture
Theatre Based	Subsidized Anxiety Level; Social Communication; Spontaneous Behaviour
Meditation Based	Functional Development
Technology-Based	Less urine accidents; Less fear of crowded places; easy escape adaptation; Social Behaviour; Social Skills; Correlation of face and voice recognition; conversation
Dance Intervention	Social; Motor; Focussed
Nutrition Based Intervention	Overall concentration development

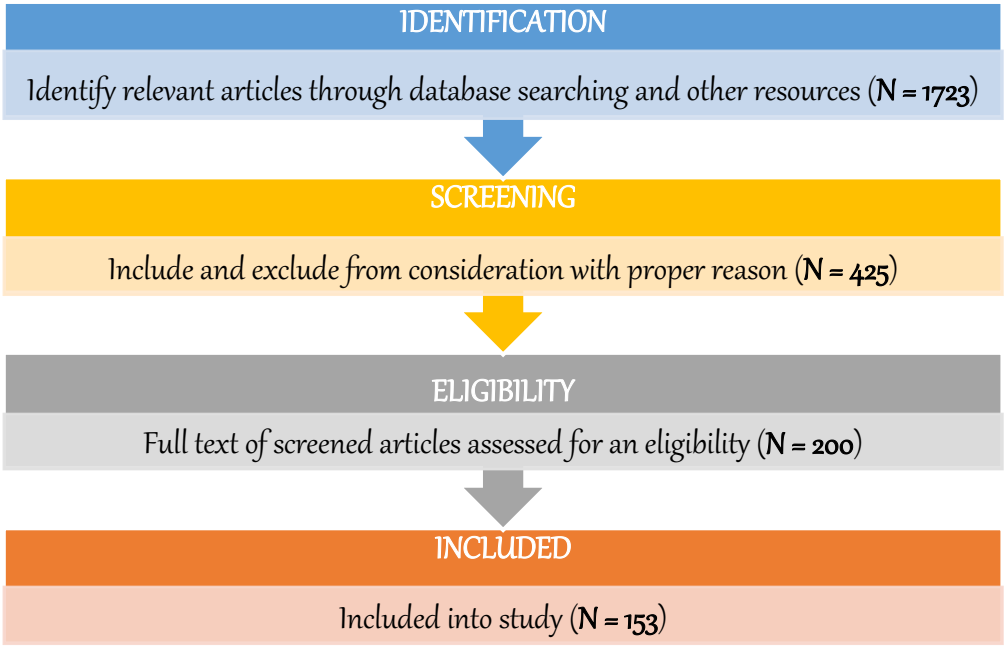


Figure 1: Complete Methodology Used for Systematic Review

3. NEURAL SIGNALING PATHWAYS OF ASD

Several reports documented that ASD patients showed dysregulation of many neuro-signaling pathways like Hedgehog (Hh), WT (Wingless), and retinoic acid (RA). Recent studies showed that FGF or TGF-β signaling contributes to ASD, but no direct evidence can be found. Further studies are needed to learn more about signaling pathways and their role in ASD. This review aims to discuss detailed insights into molecular signaling pathways individually and their therapeutic interventions.

3.1 Hedgehog Signaling Pathway

The hedgehog signaling pathway (Hh) performs an important function during embryonic development in vertebrates. It is also known as the Sonic Hedgehog signaling pathway and is responsible for intracellular signaling. It is important during organogenesis and responsible for regeneration and homeostasis. There are three important hedgehog proteins found in mammals: sonic hedgehog (Shh), Indian hedgehog (Ihh), and desert hedgehog (Dhh). Shh has a remarkable role in nervous tissues and limb patterning, whereas Ihh plays an important role in skeletal system development, especially endochondral ossification. Dhh is significantly restricted to reproductive organs in males and females, i.e., ovaries, granulosa cells, and Sertoli cells of the testes (Yao et al. 2002; Wijgerde et al. 2005). Shh functions as a morphogen, and it grades signals by stimulation and ventralization. During the formation of the spinal cord, Shh is produced ventrally in the floor plate cells and notochord, thus inducing several categories of ventral interneuron progenitors. It also aids in identifying motor neuron progenitors and forms five classes of neurons. Impairment of Shh signaling differentiation (Jessell 2000) Shh is synthesized from a precursor protein having a molecular weight of 45 kDa, which is cleaved into two proteins (26 KDa Shh-C and 19 KDa Shh-N) by auto-proteolysis. If any mutations block the process of autoproteolysis, it can impair the hedgehog's functions (Porter et al. 1995). Shh-C has been found to mediate autoproteolysis, and Shh-N is believed to mediate signaling (Hammerschmidt et al. 1997). Different levels of regulations are found to control the reception, release, and interpretation of the Hh signal. The sonic hedgehog does not interact with smoothened transmembrane protein (SMO). Instead, it interacts with its receptor PTCH-1 (Patched-1) and results in GLI activation, a transcription factor. It was observed that children with mild ASD have higher serum levels of oxygen-free radicals and serum SH proteins. Also, in the absence of Shh activity, SMO was repressed by PTCH, which causes phosphorylation of GLI, followed by further proteolytic breakdown into repressor forms inhibiting transcriptional activity (Hooper and Scott 2005; Halepoto et al. 2015). The transcription factor EN2 (engrailed 2) level has been found to be associated with ASD. Increased EN2 levels can cause elevated levels of Shh expression reported in post-mortem samples of ASD subjects (Choi et al. 2014). PTCHD1 (gene patched domain containing one) mutations were observed in ASD subjects. PTCHD1 knockout male mice show cognitive dysfunction (Tora et al. 2017). DHRC7 is the enzyme involved in cholesterol biosynthesis, and its impairment was also seen in ASD subjects. Reduced cholesterol biosynthesis affects the activation of SMO, which transduces Shh signaling and primary cilium localization (Blassberg et al. 2018). Hedgehog signaling affects neural patterns and neurogenesis during brain development. Dysregulation of this pathway can lead to ASD, a neurological disorder. Several causal genes are found to be associated with this pathway of dysregulation. Fig. 2 represents the possible association between ASD-causing genes and sonic hedgehog signaling. Genes responsible for encoding EN2, PTCHD1, and DHRC7 are found to be potential genes responsible for ASD.

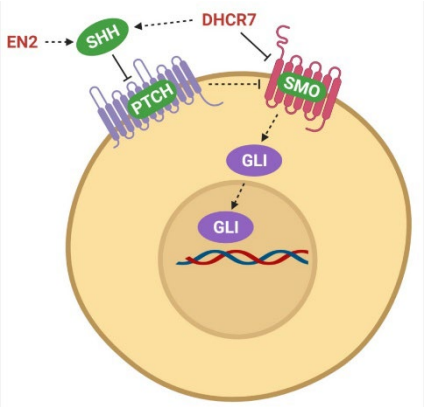


Figure 2: The possible association between ASD-causing genes and sonic hedgehog signaling

3.2 Wnt (Wingless) Signaling Pathways

Wnt signaling is the fundamental pathway of neurodevelopment and post-neurodevelopment processes like neural progenitor differentiation, neuronal regionalization, migration, axon supervision, the development of dendrites, neural plasticity, and neurogenesis. Any impairment in Wnt signaling triggers the advent of autism-related disorders related to brain functions and structure (Okerlund et al. 2011). The Wnt signaling pathway is divided into two major parts: (a) canonical signaling results in the maintenance of beta-catenin, a protein encoded by CTNNB1, which exerts its functions in the plasma membrane, nucleus,

and target gene expression modulation, and (b) non-canonical signaling is beta-catenin independent (Salinas and Zou 2008). The non-canonical signaling pathway includes planar cell polarity and calcium signaling pathways. By acting on these two pathways, many proteins play a role in the growth and maturation of synapses. Several animal studies have evidenced the clinical significance of Wnt signaling in developing cognitive disorders. Gene knockout models determine the role of brain regions and neural circuits responsible for ASD behavior, and other gene interrogation in the Wnt signaling pathway offers the opportunity to understand the pathophysiology of ASD. The aim of understanding this mechanistic pathway is to treat developmental cognitive disorders. Nineteen Wnt ligands were found, among which Wnt 1, 2, 3, and 9B were associated with ASD. An increased level of Wnt 3 expression in the prefrontal cortex of ASD subjects was observed. Wnt 1 is important for the cerebellum and mid-brain development, whereas Wnt 2 is essential for dendritic growth in the cortex region and dendritic spine development. Both functions are maintained by brain-derived growth factor (BDNF). Wnt 3 regulates the neurogenesis of the hippocampus and is important for gastrulation. Several modulators of the Wnt signaling pathway were found to be related to the etiology of ASD. Fig. 3 represents the Wnt signaling pathway and its modulators, upregulation and downregulation. Genes associated with ASD and act modulators of Wnt signaling pathways are ANK3 (ankyrin-G), CHD8 (chromodomain helicase DNA-binding protein 8), UBE3A (HECT domain E3 ubiquitin ligase), DIXDC1 (Dix domain containing 1), and PGE2 (prostaglandin E2). A recent study analyzed the gene Nlgn3 (Neuroligin 3), a downstream target gene in Wnt signaling involved during synaptogenesis (Kumar et al. 2019).

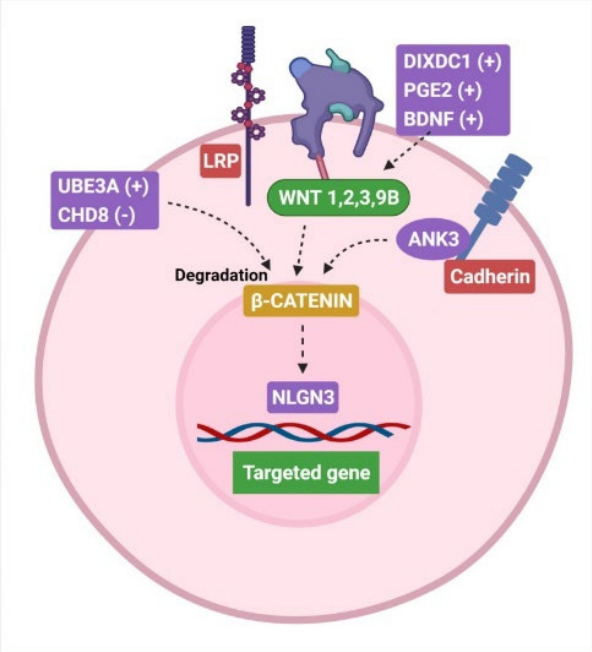


Figure 3: The Wnt signaling pathway and its modulators. Genes associated with ASD and act as modulators of Wnt signaling pathways are ANK3 (ankyrin-G), CHD8 (chromodomain helicase DNA-binding protein 8), UBE3A (HECT domain E3 ubiquitin ligase, DIXDC1 (Dix domain containing 1) and PGE2 (Prostaglandin E2). Nlgn3 (Neuroligin 3) is a downstream target gene involved during synaptogenesis.

3.3 Retinoic Acid (RA) Signaling Pathway

Retinoic acid is the metabolite of vitamin A and acts as a morphogen during embryogenesis. RA acts on nuclear receptors called retinoic acid receptors (RAR) and mediates genomic transcription (Duester 2008). Retinoid X receptors (RXRs) are non-genomic receptors that cause retinoic acid acylation (retinoylation) and post-translational modifications. Several co-repressors and co-activators are reported to modulate retinoic acid signaling. Retinoic acid in the developing brain is responsible for the differentiation, patterning, propagation, and establishment of neuronal networks and neurotransmitter systems. Investigating the role of these pathways in ASD and their regulation may increase knowledge and understanding of the possible mechanisms responsible as well as develop novel therapeutic interventions for this disorder (Zieger and Schubert 2017). Decreased expression of the protein RA associated with orphan receptor alpha (RORA) and abnormal methylation were found in the

brains of ASD subjects. RORA variants were also reported in autistic subjects. A study in the South American cohort related to whole exome sequencing relates genes associated with RA signaling like ALDH1A3 (RA synthesizing aldehyde dehydrogenase 1 family A3) and FOXN1 regulated by orphan receptor alpha (Moreno-Ramos et al. 2015). A decreased level of ALDH1A1 was found in ASD subjects, and Lenovo mutations in RERE (arginine-glutamic acid dipeptide repeats), which acts on nuclear receptors and encodes this coregulator, cause other defects and ASD related to 1p36 deletions. Various ASD-relevant genes involving NLGN1 are regulated by RORA and were analyzed by immunoprecipitation analysis (Moreno-Ramos et al. 2015). Fig. 4 represents the interaction between ASD genes acting as effectors in RA signaling.

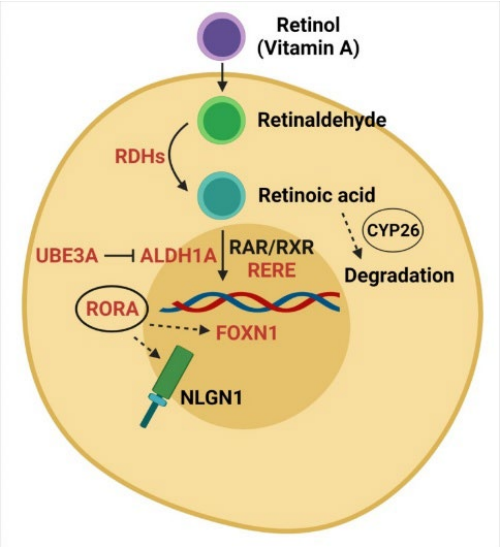


Figure 4: The interaction between ASD genes. Retinoic acid acts on nuclear receptors called retinoic acid receptors (RAR) and mediates genomic transcription. Retinoid X receptors (RXRs) are non-genomic receptors that cause retinoic acid acylation (retinoylation) and post-translational modifications. Decreased expression of protein RA associated with orphan receptor alpha (RORA) and abnormal methylation were found in the brains of ASD subjects. Genes associated with RA signaling, like ALDH1A3 (RA synthesizing aldehyde dehydrogenase 1 family A3) and FOXN1 regulated by orphan receptor alpha. A decreased level of ALDH1A1 was found in ASD subjects and denovo mutations in RERE (arginine-glutamic acid dipeptide repeats). RORA regulates various ASD-relevant genes involving NLGN1.

3.4 FGF and TGF-β1 (Transforming growth factor-β1)/activin signaling

FGF signaling plays a significant role in brain functioning, psychological disorders, and autism spectrum disorders (ASD). Dysfunction of FGF neural signaling leads to cortical abnormalities and disruption of the number of excitatory and inhibitory neurotransmitters in the pathogenesis of ASD (Turner et al. 2016). This data has been supported by recent studies that suggest a disturbance in FGF signaling in mutant mice leads to impaired synapse formation in the pyramidal neurons' CA3 regions (Moreno-Ramos et al. 2015).

There are two prevalent subgroups of the TGF-β superfamily, like bone morphogenetic protein (BMP) and growth and differentiation factors (GDF), which play a crucial role in developing the central nervous system (Zi et al. 2012). Both factors are responsible for dysregulation in ASD by regulating the expression of various genes through two pathways (the Smad and MAPK cascades) (Wang et al. 2014). One research study revealed a decrease in the level of plasma TGFβ1 in autistic patients, but a lot of research is needed to prove this hypothesis and its exact mechanism. For a better understanding of the signaling pathways of FGF and TGF-β1, future clinical trials are needed to understand the molecular mechanism and its potential therapeutic interventions.

4. SCIENTIFIC EVIDENCE-BASED INTERVENTIONS

Many interventions have been developed and experimented with in small to large-scale groups and age categories. Interventional studies were chosen based on randomized control trials, case studies, single subjects, age, gender, and intervention impact and were presented and categorized where applicable.

4.1 Social and Behavioral Intervention

Cognitive and emotional developments are directly associated with floor playtime, as it gives a sense of gratitude. In the 1980s, Dr. Stanley considered this association to motivate ASD subjects. The main intention behind this approach is to inculcate and enhance relationships. This intervention experimented with ASD subjects where the deficit was identified beforehand in motor skills, auditory, linguistic, language development, visual, and sense, and after using the proposed approach as an intervention, improvement was reported in these areas (Myers and Johnson 2007). Interaction is the primary source for gaining confidence, and an intervention focusing on interactive behavior plays an important role. As involvement in the social relationship is mandatory, retention of the established relationship is equally important, and it also gives the child a chance to craft a pathway and discover the values of positive interpersonal activity. It was observed that the tendency to explore more was increased once positive and beneficial values were discovered. An autistic child feels motivated to learn the skills and thirst for the sustainability of an established relationship (Wang et al. 2014; Myers and Johnson 2007). An RCT study conducted by Locke et al. (2019) with adolescents shows a significant impact on higher social networks and more friendship nominations. In contrast, Sutton et al. (2019) observed that initiation and response to peers significantly rise, provided the teacher must be a facilitator.

Some studies have reported the involvement of the Wnt pathway in the pathophysiology of mood disorders. Behavioral and neurodevelopmental data provide evidence of this pathway mechanism in stress and mood-related disorders (Sani et al. 2012). In some models, i.e., human-induced pluripotent stem cells and animal studies, modulation of the Wnt pathway has the potential to treat ASD. Mutations in the Dvl gene in mouse models show behavioral abnormalities and symptoms like decreased social behavior and increased repetitive behavior (Mulligan and Cheyette 2016).

Various studies have also reported that increased social interaction and promising behavioral pattern interventions must be provided to ASD subjects in a social environment (Bellini et al. 2007; Stichter et al. 2012). In this regard, two studies have been identified that solely rely on the support of the community in order to bring development to the autistic patient. One of the studies included a supported employment program, and the other study included a leisure-based program (Baker-Ericzén et al. 2018; Nepo et al. 2021). The primary purpose of an intervention is to measure the rise in cognitive functioning with the help of classic and community-based supported employment programs. As we know, even slight deviations from normal impact the patient's life. As in another study, the different approaches were considered through leisure-based activities, which include games, crafts, group activities, community events, and socialization, to relieve them from life. Parameters measured for the effectiveness of the study were stress and quality of life, and a decrease in stress and an increase in quality of life were reported. The effect sizes reported in these two studies are 0.45 and 0.83 for cognitive functioning and adaptive behavior improvement, respectively (Rollins et al. 2016).

4.1.1 Early Intervention

Early intervention (EI) has a good impact and shows improvement in various spheres of life compared to late intervention. This type of intervention is most suitable for children showing autism symptoms at an early age of less than 5. Myers and Johnson (2007) emphasized the timing of the initiation of interventions and suggested that EI timing plays a vital role in the neurodevelopment of the autistic population. Estes et al. (2015) found that if the autistic population receives an intervention at an early age, its impact is sustained in the long run. It works on the concept of starting early and failing early; thus, it can give enough time to restart with another appropriate intervention if the existing approach fails to show the outcome. It is categorized as an EI category as its thirst area is to cater to the need for language, cognitive, and social-emotional needs of young children. The study experimented with the impact of recreational therapy interventions and reported a significant rise in social interaction, body functioning, and cognitive development. Dunst et al. (2012), performed a meta-analysis of studies showing the impact of EI practices in ASD subjects and suggested that proper training given to the parents to use EI and the implementation of strategies can effectively encourage young autistic children to get familiar with and make use of pivotal development and behavior.

Prostaglandins (PGE2), an endogenous lipid-derived molecule, are the major component of membrane lipids. Drug exposure like valproic acid and misoprostol during pregnancy triggers the biosynthetic pathway of PGE2 production, causing alterations in the transmission of cell signaling pathways, and it affects several biological functions, causing fever, inflammation, and pain. During early pregnancy, an elevation of PGE2 and COX2 synthase was observed, which indicates the involvement of PGE2 in prenatal development. Interaction between the canonical Wnt signaling pathway and PGE2 activation was observed (Wong

et al. 2014). Their study reported that the interaction between these two pathways may impair the neurodevelopment of neonates. A study was conducted on ASD subjects and reported that ASD children have higher levels of Sonic hedgehog proteins, Indian hedgehog proteins, and lower levels of Desert hedgehog proteins in their blood serum than normal individuals (Bashir et al. 2014). Early detection of these protein levels can be used to prevent ASD, as they may play a significant role in its pathophysiology.

In some studies, the analytics of EI by parents and general interventions like community were analyzed, and results were presented with significant improvement in areas like behavior, language, and IQ scores for parent-mediated EI (Debodinance et al. 2017). To report the long-term benefits, follow-up studies play a vital role; thus, this model must conduct a primary study and follow-up to claim sustainability. Vivanti et al. (2019) developed an Early Start Denver Model and studied its impact on 44 preschool children in a classroom setting. It also evidenced high achievement in spontaneous vocalization, social interaction, verbal cognition, and adaptive behavior. Thus, it is also proposed as an innovative practice for treating autism (Vismara and Rogers 2008).

4.1.2 Social Cognition Training

Though applied behavioral analysis (ABA) has proven to be an effective solution, new forms of training continue to emerge, and research on the ASD population has been conducted. These types of interventions applied to child-age groups were systematically reviewed (Schoen et al. 2019). However, it was observed that sometimes more than merely ABA is needed for a certain category, and research is still required in this domain to prove its effectiveness. Thus, other than ABA, more training interventions in the area of social cognition training were proposed by various studies (Kupferstein 2020). Recent studies claimed improvement in the dimension of grasping social cues, ultimately improving social functioning (Yang et al. 2018). Pasco (2018) reported an intervention that claimed improvement in parent-child dyads. Turner-Brown et al. (2008) intervened in a group-based cognitive-behavioral intervention. The intervention was planned and executed systematically, comprising three integrated phases: training, identification of the situation, and integration in a group setting. The objective of the study was to measure the impact on social cognitive functioning. The outcome of this study was that participants who have gone through training showed marked improvement in the theory of mind skills, and as per trend, improvement in social communication skills was observed. Other studies verified the efficiency of social cognition training-type interventions (Park et al. 2019). All social cognition training methods demonstrated substantial improvements in participant scores on included measures, indicating a tendency toward development in social cognition (Trepagneir et al. 2018).

Researchers have designed software capable of training participants to express seven emotions that a human generally expresses. The training phase used intervention in the form of a complete picture of the face or eyes only. Testing was done after training the participant using face and eye stimuli for a reasonable time. Under this theory, an author would like to propose the same intervention and analysis of brain signals in response to various facial expressions. Though different interventions were helpful in reading minds, Baron-Cohen's Reading the Mind in Eyes (Rojas et al. 2011) and Reading the Mind in Face tests (Tajmirriyahi et al. 2013) were the most effective approaches.

4.1.3 Parent-Mediated Intervention

In a family where a child is autistic, parents are primarily responsible for the child's development; thus, in this intervention, the primary focus is to train parents with the focus area and make them comfortable and helpful in the child's autistic journey. An RCT study was conducted with 152 children; 77 were treated with parent-mediated intervention, and 75 were treated with the usual treatment method (Green et al. 2010). A reduction in autism symptoms was reported immediately, but there was a very marginal difference between these two approaches. However, after 5–6 years, they reconducted the study, and this time, they reported a drastic change in the reduction of autism symptoms in children with parental intervention. Thus, it proves to be a long-term, effective intervention. As this intervention only needs the help of external support for a short time, except for the initial training of parents, it was comparatively less inexpensive from a financial perspective (Nevill et al. 2018).

In 2015, two RCT studies related to parent-mediated intervention were conducted (Kasari et al. 2014). The first study was related to JASPER, which holistically focuses on naturalistic and behavioral development. The second study was about parent-only psychoeducational intervention. Participants in the randomized trial were 86 toddlers (age range: 22–36 months). The parent-mediated intervention has proven its track record of improvement in comparison studies where this intervention was executed in two different versions. JASPER proved its efficiency over the parent-mediated intervention.

Another RCT study using parent-mediated interventions was conducted among 63 autistic children, and it showed an impact on the vocal response of children's initiation to the caregiver activity and showed signs of improvement in social communication (Siller et al. 2013).

4.1.4 Caregiver-Mediated Intervention

In some interventions, parents and guardians play a significant role, but sometimes, it is impossible for many reasons, and caregivers must be appointed to care for them. Thus, the caregiver coaches interventions that are helpful for daily life. The caregiver-mediated intervention followed the protocol of JASPER (joint attention symbolic play engagement and regulation) treatment (Kasari et al. 2014). Pre- and post-assessments were performed for social communication, with a follow-up study lasting three months. This study reported an improvement in the social communication growth of ASD subjects. In order to address the mindset of caregivers, a study was conducted where 28 caregivers of young children with autism were interviewed, and responses received were like affordable, in-home, individualized, early autism intervention where they have raised an active voice in shaping treatment goals (Gantman et al. 2012). The limitation of this type of intervention is the need for more constant support from the caregiver, and it is not easy to continue for the long term due to the need for proper resources. It could be monetary support. The caregiver-assisted intervention also reported a significant gain in empathy and frequency of getting together.

4.1.5 Education-based Intervention

In the early 1970s, Schopler and colleagues proposed a method consisting of structured teaching. The main focus of this teaching is the organization of five essential elements with broad to limited visibility (Myers and Johnson 2007). This method was restricted to enlisting five components and indulged in services related to clinical trials, social interaction, and support for parents in the form of training. It was also associated with the evaluation of the diagnosis for its appropriateness. Under this intervention, a collaboration of all parameters, as mentioned in Fig. 5, provided the student with a well-defined and structured environment. A primary concern was about the commute of ASD, and this intervention can be adopted in any preferred environment, either in an individualized or group setting. Various studies were conducted to evaluate the effectiveness of this intervention. One is associated with public education and found a significant rise in the scores of psychoeducational profiles revised in a structured environment (Novek and Berry 2014).

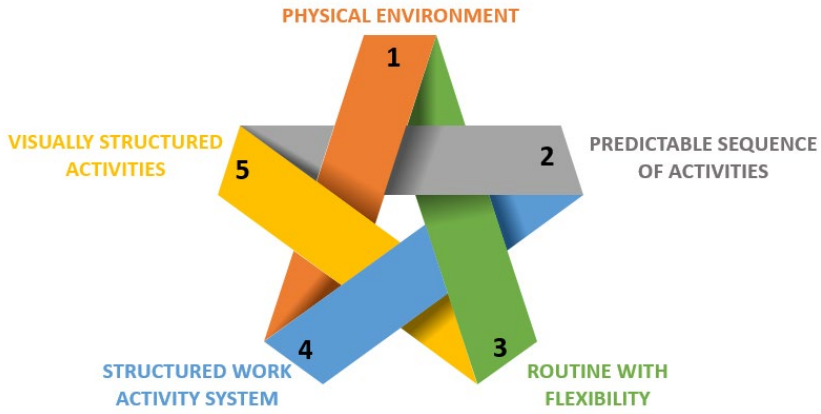


Figure 5: Impact of Education-Based Intervention

4.2 Motor and Physical Activity Intervention

Various motor and physical activity interventions were studied and verified for their impact on autism at three levels (Ruggeri et al. 2020). Involvement in participation plays a crucial role in the ASD population. It encourages participation in awareness about physical education and plays a crucial role in involving intervention in play sessions and verbal awareness sessions. The second includes encouragement for activity participation and analysis that simulated activities in aquatic, horse riding, and motor activity correlate with significant changes in the body structure and functioning.

Play sessions were intervened in the form of intervention, and significant improvements were observed in sleep efficiency, sleep onset latency, and sleep duration. However, no significant evidence was supported for improvement in working memory (Tse

et al. 2019). Regular motor activity is essential for survival, and focusing on improving motor activity through an intervention will be very helpful. In RCT, motor skills were utilized as an intervention, and changes in physical activity and socializing behavior were observed (Ketcheson et al. 2017). It was observed that group activity helps in the improvement and causes a drastic change in engagement time (Locke et al. 2016). Autism children have always been a deficit of sound sleep, as consumption of their body-level energy is poor. Thus, physical activity involved in an intervention result in better sleep quantity compared to those who have not been made available for motor skills as an intervention (Tse et al. 2019). Physical activity has an overall impact on ASD children. It causes a significant rise in metabolic health, affects the quality of life, and uses motor skills as an impact of exercise, which can be used as an intervention (Toscano et al. 2018). Generally, the design of an intervention is done from the perspective of either the researcher or health workers, but the least priority is given to the intervention preferences of parents (Leadbitter et al. 2018). In this type of intervention design, the questionnaire based on parent's experience has been designed through a mode of focus group as well as consultation with parents.

Physical activity has been shown to repair age-related cognitive decline and prevent diseases such as regenerative neurogenesis, osteoporosis, neuromuscular junction formation, and hippocampus functioning, and age-related decline is substantially connected with Wnt signaling pathways (Hu et al. 2019). The physical exercise and biological processes affect the Wnt signaling in the locomotor system. Bone and skeletal muscles originate from the mesoderm layer and somatic cells during the embryonic phase. Somatic cells then get differentiated to form ventral sclera and dorsal cells, forming bones and skeletal muscles. Any imbalance in bone homeostasis can lead to bone-related diseases that can be observed in ASD (Case et al. 2008).

A study suggested that the expression of β-catenin increased after five weeks of physical exercise (medium intensity level). However, it did not express the Wnt1 gene, suggesting that Akt/GSK3β may combine with Wnt signaling pathways during the early stage of bone formation mediated by exercise (Chen et al. 2016). This study investigates that Wnt signaling activation is essential for preventing osteoporosis, as observed in the rodent exercise model (Chen et al. 2016). Physical exercise causes changes through epigenetic alterations in the DNA in the nucleus, such as DNA methylation, histone modifications, micro-RNA expressions, and chromatin structure changes. These alterations may have clinical significance, as they are essential in confronting and preventing various neurophysiological diseases (Case et al. 2008). Some studies suggested an association between physical exercise and inflammatory response. ASC (apoptosis-linked spec-like proteins) contains a domain mediating inflammatory signaling pathways in the cytosol. It causes the induction of procaspase-166 and activates interleukins that lead to the induction of innate immune response. The transcription process of the ASC gene is controlled by epigenetic processes, particularly methylation of CpG that surrounds exon 1, which has an inverse relation with an expression of ASC protein. It was reported that moderate exercise for a longer duration could upregulate the ASC methylation, causing lesser activity of genes in monocyte cells, thus preventing the induction of inflammatory cytokines like TNF (tumor necrosis factor) and interleukins (Ntanasis-Stathopoulos et al. 2013).

4.2.1 Electrodes-based brain-computer interface intervention

According to research, reading and interpreting brain waves based on intervention can convey relevant information to autistic patients of all ages (Fig. 6). An interface was created to understand and correlate communication through brain waves (Fan et al. 2015). An intervention study was performed for the improvement of sensory difficulties (Schaaf et al. 2014). We know that altering brain waves was not easy and could convey appropriate information, unlike speech and emotions. Thus, receiving neurofeedback plays an important function, as the Friedrich et al. (2015) study demonstrated its importance in improved social interaction. Though sensors were proven to have good information communication, their integration also played a crucial role and is represented in study integration in the form of Ayres (Schoen et al. 2019). Shabani and Fisher (2006) explained the importance of stimulus fading and differential reinforcement techniques used in autistic adults with diabetes. Their study reported successful treatment with these interventions of ASD adults who have needle phobia.

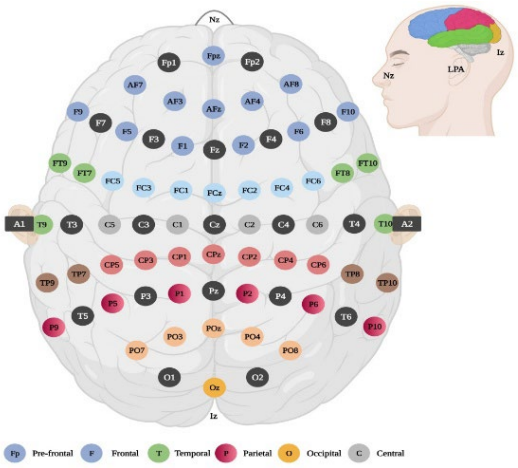


Figure 6: Electrode based intervention

4.2.2 Hobby Intervention

The impact of the hobby-based intervention was studied and observed that students who received this therapeutic intervention exhibited much confidence in their social behavior (Casey et al. 2015). Modes of intervention are considered very important, like animations that mostly fascinate every age, and their benefit was observed in a study conducted by Golan et al. (2010), another form of intervention brings intelligence and social involvement. It helps in engagement for a long time, and thus, its impact was found in the long run in the autistic population if they are being engaged in logo activity as an early intervention model (Peckett et al. 2016). A significant rise in calmness and engagement was observed in a study of 12 children exposed to art therapy interventions compared to those who had not received this intervention at an early age (Emery 2004). Music is known as getting soul, and its impact in a group as well as in an individual setting has proven overall improvement in social behavior (Sharda et al. 2018).

4.2.3 Theatre-based Intervention

It is a common phrase, and most people use this term. If he had gotten the chance to exhibit, he would have become a different person, and the same applies to autism as well. Rather than only having a stereotype tendency that he or she cannot do anything, being provided exposure can change a thing completely to 180 degrees, and it is being proven by studies conducted in RCT for youth that children who have exhibited a deficit in social behavior before providing them an intervention. Significant changes have been observed in subsidized anxiety levels, social communication, and spontaneity (Corbett et al. 2017).

4.2.4 Meditation training

Yoga became a superpower for all-around development, and its implication is also visible in the autistic population. An RCT study conducted for the identification of the implications of yoga and meditation in autistic people and functional development was reported (Spek et al. 2013).

4.2.5 Technology-based Intervention

As computers were trained to identify the objects, the same approach was used for the autistic population (Faza et al. 2012). The training program was designed with the help of a computer to identify images of faces and houses. The randomized training with the goal is in two phases. The first phase involves segregating apparent differences between the house and face image. The second phase involves identifying gender in face and shape in the house. Performance was measured based on recognition of house, face, gender, and shape, and authors have reported improvement in these performance parameters. However, weak growth was reported in the identification of shape. It might be because various shapes were available in houses and needed to split the training of shapes into phases. An IOS-based app was developed as an intervention to provide training to autistic people. In this pilot study, 70% of the population benefited from the intervention, and the remaining 30% did not benefit, and this could be because of the age factor. In a study, few urine accidents were recorded in a three-year follow-up research, and the population under instruction is between the ages of 3-6 years (Mruzek et al. 2019). Most interventions were in play, sense,

and verbal, but in some studies, computer-assisted interventions were also used and proved to impact the development of autism significantly. To intervene in the form of social training rather than only using person-to-person interaction, support has been taken from the software specially designed and focused on social cognition training (Bolte et al. 2002).

A virtual social environment in the form of intervention for autism treatment helped ASD subjects, to a great extent, escape the crowd and fear of getting exposed to the crowd in the age group of 3-6 years (Parsons 2016).

Computer games are also a prominent tool for improving hand movement, and social behavior and skills in the autistic population (Hopkins et al. 2011). The issue, which can be monitored by mere visual impact in the autistic population, is a lack of emotional familiarity. Thus, many times, even though a person is crying, an autistic person does not pay attention or does not correlate the associated emotions. In this direction, an attempt was made to design a training program with the help of a computer to teach people with ASD an appropriate identification of facial emotions (Golan and Baron-Cohen 2006). After training, they performed the testing phase and came up with a significant improvement in the measure of face and voice recognition. Another study used intervention to teach conversation skills to age groups ranging from adolescents to adults with ASD (Trepagneir et al. 2018).

4.2.6 Dance Intervention

The most common form of developmental disabilities in ASD is rooted deep into language and social development along with some specific pattern behavior. Less participation in physical activity also leads to less muscular movement; thus, to increase participation in physical activity, dance intervention is used for the well-being of the autistic population. Dance interventions provide both physical and physiological benefits to the autistic population (Scharoun et al. 2014).

4.2.7 Nutrition Based Intervention

Research-based studies support the evidence that docosahexaenoic acid supplements, when given to ASD subjects, show marked improvement in communication behavior compared to the placebo-treated group (Voigt et al. 2014). Two randomized controlled trials addressed the beneficial effect of a digestive enzyme supplement (Neo-digestin) compared with placebo and showed significant improvement in symptom severity score (Saad et al. 2015). An RCT study showed significant improvement in Clinical Global Impression (CGI) scores of ASD subjects when supplemented with methyl B12 (Hendren et al. 2016). Another RCT study addressed the significant effect of moderate and high doses of levocarnitine on severe ASD symptoms (Geier et al. 2011). One RCT study assessed the impact of a gluten-free/casein-free diet compared with a regular diet in ASD subjects and observed a significant improvement in communication behavior, social isolation, resistance to communication, and repetitive behavior (Knivsberg et al. 2003). In addition, another study with a gluten-free diet in children reported improved stereotyped behavior, communication, and gastrointestinal symptoms compared with control children (Ghalichi et al. 2016).

4.2.8 Psychometric Tools

A proper measure of a child's intelligence quotient is required to start an intervention, and it can be done by using psychometric tools. Although multiple researchers have reported and tried with ASD populations, additional experimentation with diverse age groups is expected, as most studies have been conducted on one age category, and it is probable that interventions and their consequences are either not appropriate for another age category or gender. Mostly, the autistic population suffers from a deficit of social interaction and communication impairment. An intervention was designed with a plan that depends upon the diagnosis. However, psychometric tools play a significant role in providing a full assessment with proper identification of areas of strength and weakness in affected children and assisting in measuring the child's intelligence quotient, which is crucial in determining the best intervention strategy (Naglieri and Chambers 2009).

5. CONCLUSION

The main aim of this article is to collaborate on the mechanistic pathways and their pathophysiological role, all the proposed ideas, interventions, and their identified implications on the ASD population so that it could be easy to extend and analyze the current situation of the development of an intervention. Recently, the design and development of interventions for the well-being of an autistic population have gained more attention. This paper discusses various types of interventions ranging from movement-social-cognition-nutrition with their feasibility and implications on particular age categories and genders. Different domains like technology, healthcare, and social workers are putting their efforts into feasible interventions. It is concluded from the review of different interventions that each type of intervention is beneficial for the autism population, and mere exposure

to any feasible intervention for the sufferer can lead to maximum benefit and gain at some of the personality levels. In the future, fusion and hybrid approaches will be developed to design an intervention.

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AUTHOR CONTRIBUTIONS

Nilima Salankar: Conceptualization, Literature search, Writing—Original Draft.

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Mohd Nazam Ansari: Supervision, Writing—Review & Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

This review article does not involve any studies with human participants or animals performed by any of the authors; therefore, ethical approval and consent to participate are not applicable.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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