



# Article Utilizing Constructed Neural Networks for Autism Screening

Eugenia I. Toki <sup>1,2</sup>, Jenny Pange <sup>2</sup>, Giorgos Tatsis <sup>1,3</sup>, Konstantinos Plachouras <sup>1</sup> and Ioannis G. Tsoulos <sup>4,\*</sup>

- <sup>1</sup> Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina, 45500 Ioannina, Greece; toki@uoi.gr (E.I.T.); gtatsis@uoi.gr (G.T.); kplachouras@uoi.gr (K.P.)
- <sup>2</sup> Laboratory of New Technologies and Distance Learning, Department of Early Childhood Education, School of Education, University of Ioannina, 45110 Ioannina, Greece; jpagge@uoi.gr
- <sup>3</sup> Physics Department, University of Ioannina, 45110 Ioannina, Greece
- <sup>4</sup> Department of Informatics and Telecommunications, University of Ioannina, 47150 Kostaki Artas, Greece
- \* Correspondence: itsoulos@uoi.gr

Abstract: Autism Spectrum Disorder is known to cause difficulties in social interaction and communication, as well as repetitive patterns of behavior, interests, or hobbies. These challenges can significantly affect the individual's daily life. Therefore, it is crucial to identify and assess children with Autism Spectrum Disorder early to significantly benefit the long-term health of children. Unfortunately, many children are not diagnosed or are misdiagnosed, which means they miss out on the necessary interventions. Clinicians and other experts face various challenges during the diagnostic process. Digital tools can facilitate early diagnosis effectively. This study aimed to explore the use of machine learning techniques on a dataset collected from a serious game designed for children with autism to investigate how these techniques can assist in classification and make the clinical process more efficient. The responses were gathered from children who participated in interactive games deployed on mobile devices, and the data were analyzed using various types of neural networks, such as multilayer perceptrons and constructed neural networks. The performance metrics of these models, including error rate, precision, and recall, were reported, and the comparative experiments revealed that the constructed neural network using the integer rule-based neural networks approach was superior. Based on the evaluation metrics, this method showed the lowest error rate of 11.77%, a high accuracy of 0.75, and a good recall of 0.66. Thus, it can be an effective way to classify both typically developed children and children with Autism Spectrum Disorder. Additionally, it can be used for automatic screening procedures in an intelligent system. The results indicate that clinicians could use these techniques to enhance conventional screening methods and contribute to providing better care for individuals with autism.

**Keywords:** Autism Spectrum Disorder (ASD); screening; classification; machine learning; constructed neural networks

## 1. Introduction

Child development is a complex process involving various aspects, such as physical, speech, language, hearing, and motor abilities, as well as cognitive processes and emotional well-being. Cognitive development includes problem-solving, critical thinking, logical reasoning, and understanding the surrounding environment. Socio-emotional development involves emotional growth, social development, self-concept, self-esteem, and emotional intelligence. Child development is interconnected, and progress in one domain can positively impact others. Neurodevelopmental disorders (NDs) can harm a child's development and brain growth, resulting in communication, learning, behavior, cognitive, and emotional shortages [1–3].

Autism Spectrum Disorder (ASD) is an ND that can be diagnosed at any age but usually appears within the first two years of life [4]. The prevalence of ASD is estimated to be around one in one hundred children worldwide, though some studies report higher



Citation: Toki, E.I.; Pange, J.; Tatsis, G.; Plachouras, K.; Tsoulos, I.G. Utilizing Constructed Neural Networks for Autism Screening. *Appl. Sci.* 2024, *14*, 3053. https://doi.org/ 10.3390/app14073053

Academic Editor: Douglas O'Shaughnessy

Received: 11 March 2024 Revised: 28 March 2024 Accepted: 2 April 2024 Published: 5 April 2024



**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). rates [5,6]. As a neurodevelopmental condition, it has been characterized by specific criteria defined in DSM-5 [1–3,7]. Individuals with ASD experience persistent shortages in social communication and interaction skills across numerous settings, and they exhibit repetitive and restrictive behaviors that can impair their functioning. ASD impacts personal, social, academic, and professional life. The term "spectrum" in ASD is used to describe a range of symptoms that vary in severity from person to person. Some individuals may have mild symptoms, while others may have moderate or more severe symptoms. It is common for individuals with ASD to also have other NDs, which can require intensive care. This can significantly impact the individual with profound impairments, their family, and the community [2,3,8,9]. On the other end of the spectrum, individuals with ASDs can also be intellectually talented, verbally fluent, and independent adults [10]. This represents the opposite end of the functional spectrum.

The recommendation of the American Academy of Pediatrics is to monitor and screen for developmental delays in children to detect disabilities such as ASD early and allow for prompt treatments supporting the child's overall growth and development [11–13]. Developmental surveillance for children using clinical judgment during health supervision visits involves a comprehensive approach, which includes the documentation of developmental history, reference to parents' concerns, a thorough observation of the child's behavior to identify potential risks, maintaining records, and sharing the findings with professionals outside the child's primary medical care provider [12,13]. Developmental screening uses proven techniques at predetermined ages or whenever monitoring indicates a particular cause for concern. Diagnostic examinations are used to further examine and identify developmental disorders in children who are at risk through surveillance and screening procedures and are typically conducted by developmental experts [11,12].

The intricate and diverse nature of symptoms and manifestations in ASDs present significant challenges in their identification, often making the tasks of monitoring, screening, and diagnosis complicated due to imprecise characterizations and the presence of comorbid conditions [12,14–19]. This complexity is apparent in the fact that more than one in three children with ASD display symptoms that also meet criteria for other disorders, resulting in a variety of possible diagnostic combinations [20]. Furthermore, traditional evaluation methods often rely on subjective assessments and prolonged evaluation processes, leading to delays and inaccuracies in diagnosis [21]. Innovative diagnostic processes help customize ASD treatments, improving brain flexibility and mitigating symptoms. This leads to a better quality of life for children and their families [22]. Clinicians must build policies and practices by considering the type of condition and the child's abilities and skills for individualized interventions [23–25].

The field of machine learning (ML) has recently gained much attention for its ability to distinguish children with typical development (TD) from those with ASD [22]. Automated measuring tools are increasingly used in ASD research for decision-making, categorization, and clinical assessment, offering new prospects for aiding clinical decisionmaking [14,22,25,26]. The identification and diagnosis of ASD involves various methods like brain imaging (PET, SPECT, fNIRS, EEG, fMRI, etc.) [27–30], diffusion tensor imaging [31], and biometrics to analyze neurological and behavioral aspects [32]. Also, gesture analysis using motion capture, sensory input assessment, and eye tracking are employed [25,33–35]. These techniques, though comprehensive, face challenges like data accessibility and sensory sensitivities in ASD children. ML is increasingly used to process these data for a more effective diagnosis and treatment of ASD [36]. For instance, ML algorithms, in combination with eye-tracking technology, are increasingly showing significance in the early identification and diagnosis of ASD utilizing various stimuli, tasks, datasets, and algorithms [25,32,33,37–39]. Evidence of ML methods combining physiological data (EEG) with behavioral data (eye fixation and facial expression) has been developed to identify children with ASD [40]. This hybrid fusion strategy reported EEG to be the most effective in distinguishing between children with ASD and TD children. It achieved an accuracy rate of 87.50%, reducing costs while increasing efficiency.

Furthermore, child's play is a natural process that helps children learn essential life skills. Serious Games (SGs) use play to enhance purpose in education, healthcare, marketing, science, and more [41]. SGs have been employed for mental health issues, physical activity rehabilitation, and other areas. These games are not only for entertainment but can also serve as learning tools and cultivate skills. SGs can be designed with explicit instructional objectives, which immerse children in activities that simulate real-life situations and difficulties—all within a supervised and secure setting [41]. Moreover, it is documented that children with NDs can enjoy better, anxiety-free activities with SGs [42,43]. By integrating ML into SGs, they may become powerful tools for the automated screening and assessment of ASD [32,44]. Studies show that ML in SGs can aid the classification of ASD and help children with early identification, diagnostic assessment, objective metrics, engagement, motivation, and tailored therapy [35,45]. Virtual Reality (VR) adventure SGs can enhance social skills in ASD adolescents with multisensory interactions [46]. Augmented Reality SGs for social-emotional communication, designed for adolescents with ASD, indicated the potential to assist in identifying comorbidity with ADHD symptoms [47]. A recent study conducted with the help of a mobile game-based health app captured video footage of 95 children involved in gameplay in their own homes [48]. The study compared the gaze patterns of TD children and those with ASD. The findings showed distinct differences in the way the two groups fixated their eyes, with children with ASD having their own specific visual scanning patterns. A deep learning model trained on gaze fixation had low ASD detection power. Evidence of digital healthcare addressing healthcare access disparities has been reported with an SG that uses naturalistic gaming data and a random forest classifier to classify ASD and TD children (AU-ROC = 0.745, recall = 0.769) [49]. On the same gameplay dataset, another study achieved 79% accuracy utilizing a convolutional neural network to classify children's audio as either ASD or TD [50]. In addition, by imitating a model's dancing moves using Kinect Xbox motion tracking, researchers using a support vector machine approach reported a valid biomarker: children with ASD showed worse imitation compared to TD children, which is also linked to more excellent core autistic symptoms and discrimination (accuracy = 87.2%) between the two groups [51].

Although machine learning (ML) is widely used in Serious Games (SGs), there is a need for more research that combines ML and SGs in the healthcare industry [52]. Most studies focus on rehabilitation to provide individualized and entertaining healthcare and less on prevention and diagnosis to address personalized screening, performance assessment, monitoring, risk modeling, and treatment response prediction [52–54]. Further, standardized diagnoses and objective evaluations are repeatable [42]. However, ML algorithms in SGs addressing communication, cognition, emotion, and behavior in children with ASD require further research to create personalized, effective, and successful clinical experiences [55].

This study aims to explore how neural networks can be developed to classify children into two categories: TD and children with ASD. The results can be utilized in an intelligent system with automated results to enhance assistance for healthcare professionals and upscale decisions and evaluations regarding screening procedures discriminating between TD children and those with ASD. The study used a new biometric dataset and created various neural networks with optimizers to categorize children automatically.

The study continues with Section 2, which provides background knowledge on constructing neural networks and implementing optimizers. Next, Section 3 describes the research methods and the dataset. Section 4 presents the results of this study, including statistical analysis and experimental results. Finally, Section 5 presents the research's final findings, including limitations and ideas for future research.

### 2. Background Information

This part presents the necessary background information for this research and its related methods. More specifically, it focuses on artificial neural networks (ANNs) and the optimizers related to them used in this study.

### 2.1. MLP Description

Artificial neural networks [56] are a type of machine learning tool that has been successfully applied to various in different scientific fields, including chemistry [57–59], economics [60,61], and medicine [62,63]. A neural network is commonly defined as a function  $N(\vec{x}, \vec{w})$  where  $\vec{x}$  is the input vector of patterns and  $\vec{w}$  is the so-called weight vector of the parameters that needs to be estimated. The estimation of this vector can be achieved by minimizing the error function defined as:

$$E\left(N\left(\vec{x},\vec{w}\right)\right) = \sum_{i=1}^{M} \left(N\left(\vec{x}_{i},\vec{w}\right) - t_{i}\right)^{2}$$
(1)

The training data for the neural network are defined by the set of pairs  $(\vec{x_i}, t_i)$ . To minimize the error function, various methods such as the back propagation method [64] or the RPROP method [65] have been used, along with global optimization methods like quasi-Newton methods [66], genetic algorithms [67,68], particle swarm optimization [69], and more. For the experiments in this study, a radial basis function (RBF) neural network [70] and two optimization methods were used: the limited-memory Broyden–Fletcher–Goldfarb–Shanno (BFGS) [71] method and a BFGS variant of Powell [72].

RBF neural networks are a specialized type of neural network with three layers: an input layer that receives data, a hidden layer using radial basis functions (typically Gaussian) for transforming inputs based on their distance to a central point, and an output layer that synthesizes the hidden layer's outputs to make predictions. RBF networks excel in localized input processing, quick learning, and complex function modeling, and they can approximate any continuous function with sufficient neurons. The RBF neural network excels in machine learning tasks like classification, regression, and clustering [70]. Particularly effective in high-dimensional spaces, RBF networks are known for their capability to tackle complex patterns efficiently. Their key advantages over other neural architectures include their rapid training and testing phases and the precise approximation of continuous functions [73].

BFGS is an iterative optimization technique primarily used in various domains [74], including machine learning [75], mainly aimed at estimating the inverse of the Hessian matrix (matrix of second-order partial derivatives). With the help of an estimate, we can determine the search direction to minimize the objective function. Furthermore, this method enhances its estimation with each iteration by using gradient information for correction. BFGS is a widely used approach in machine learning to optimize neural network weights because of its excellent convergence capabilities. It is beneficial for solving high-dimensional problems. However, if the initial estimate is not chosen carefully, the BFGS algorithm may end up with a suboptimal solution for objective functions that are not convex. On the other hand, convex optimization problems provide both quick and reliable solutions.

The neural minimizer method [76], previously based on RBF neural networks [77], has now been updated with an artificial neural network that is trained using a local minimization technique called limited-memory BFGS (L-BFGS). This technique is relatively inexpensive regarding calculations and storage space [71]. This modified neural minimizer method has been widely used in optimization problems like image reconstruction [78] and seismic waveform tomography [79]. Proposed modifications have been suggested that would utilize contemporary parallel computing systems [80]. Sometimes, the large number of parameters in an artificial neural network makes it impossible to use an RBF neural network in a global optimization method for minimizing the error. When dealing with large and complex problems, approximating an artificial neural network using an RBF neural network is not feasible. While a small artificial neural network can be efficiently approximated using an RBF neural network, an underpowered RBF neural network is used

in more complex cases, which is not an efficient approximation of the original artificial neural network.

### 2.2. Neural Network Construction Description

This method uses grammatical evolution [81] to guide the neural network construction (NNC) topology and estimate the weight vector. The technique was initially suggested by Tsoulos et al. [73] and has been used in many cases, such as in solving differential equations [82], chemistry problems [83], medical problems [84], etc. The algorithm employs a combination of genetic operations and local search to evolve a population of neural networks toward better fitness, which could be performance on a specific task like classification, regression, or solving differential equations. The iterative process is designed to continuously improve solutions until a maximum number of iterations is achieved or until an optimal or satisfactory solution is found [85]. Figure 1 illustrates the utilized NNC algorithm.



Figure 1. Flowchart of the Neural Network Construction (NNC) algorithm.

The source code NNC.tar.gz is available from https://github.com/itsoulos/NNC (accessed on 10 February 2024). The software is written in ANSI C++ and needs QT, a free programming library from http://qt.io (accessed on 1 February 2024). First, run the software

with any library version, then install by following https://github.com/itsoulos/NNC/wiki. After compiling, access NNC, a command line program, and use -p to load a data file or differential equation in shared library form or -c to obtain the genetic population's chromosome count. The BNF language in https://github.com/itsoulos/NNC/wiki (accessed on 10 February 2024) allows grammatical evolution to generate neural networks. Future versions may include an upgraded BNF language for more complex neural networks.

### 2.3. Integer Rule-Based Neural Networks (INN) Description

This method was initially suggested in [86]. It aims to efficiently find the value intervals for the parameters of the artificial neural network using partition rules. These rules are expressed in a series of integers, and their efficient estimation is carried out using a genetic algorithm.

The INN is a cutting-edge approach to training artificial neural networks that involves finding the most suitable initialization and training interval using genetic algorithms [86]. The aim is to identify the optimal interval, and a global optimization technique, such as the genetic algorithm, is utilized to initialize and train the artificial neural network within this interval. Figure 2 illustrates a visualization summarizing the INN approach algorithms in steps [86]: initialization phase; first GA—locating best rules; second GA—network training; and parallel processing techniques.

Initialization Phase:	<ul> <li>Define a set of partition rules for the initial value interval of the ANNs' parameters.</li> <li>Use a genetic algorithm where chromosomes are sets of these partition rules.</li> <li>Initialize the artificial neural network in the optimal space resulting from these partition rules.</li> </ul>	
First Genetic Algorithm (GA) - Locating Best Rules:	<ul> <li>This GA optimizes the partition rules.</li> <li>Chromosomes are sets of partition rules.</li> <li>Fitness of each chromosome is evaluated based on the network performance with those partition rules.</li> </ul>	
Second Genetic Algorithm (GA) - Network Training:	<ul> <li>This GA uses the best chromosome from the first GA to define the initial bounding box for the network parameters.</li> <li>Training network parameters using this second genetic algorithm.</li> <li>This phase includes initialization, crossover, mutation, fitness evaluation, and local search steps.</li> </ul>	
Parallel Processing Techniques:	• Due to the time-consuming nature of this process, it is suggested to use modern parallel processing techniques (like OpenMP) to accelerate the training.	

Figure 2. Summary of the INN Training Approach Algorithms.

Data were employed to evaluate the approach's effectiveness and classification; function learning was employed; and the outcomes were encouraging. The experiments were performed using the freely available in-house software from https://github.com/itsoulos/ IntervalGenetic (accessed on 1 February 2024).

### 3. Methods

This study builds upon the research project "Smart Computing Models, Sensors, and Early Diagnostic Speech and Language Deficiencies Indicators in Child Communication", or in short, SmartSpeech, which was funded by the Region of Epirus and backed by the European Regional Development Fund (ERDF).

A recruitment sample was conducted in response to requests from the health and education sectors to assist TD children and children with ASD. Parents were given a thorough briefing about the project's details and scope, the protocols involved, and the permission granted (Reg. Num.: 18435/15.5.2020) by the Research Ethics Committee of the University of Ioannina, Greece, in compliance with General Data Protection Regulation GDPR. Afterward, parents filled out the consent form. Participants were asked to register in the database and answer questions about their child's developmental characteristics. With the guidance of a clinician, each child interacted with the game designed for this task. Ultimately, the variables examined in the research were obtained from the gameplay.

The study gathered responses from children who participated in playing the Serious Game on a mobile device. The game involved different activities related to screening and assessing individuals for ASD [87]. During the gameplay, the children complete several activities related to their developmental skills. Therefore, the automated procedure of this phase gathers many measurements to form a child's developmental profile and provides a rich database specifically designed for screening TD children from children with ASD. The responses of the child-player are represented as variables and generally can be hand motions on the touch screen like clicks, drag, and drops, as well as speech from the child's verbal responses to questions and directions. For the latter, the system incorporates an automatic procedure that records speech via a microphone and translates it into text. For this purpose, the software Whisper v20230314 performs multilingual speech recognition [88]. The software is free from https://github.com/openai/whisper (accessed on 2 April 2023). Then, a software service was created to compare the transcripts of the audio files with the predefined answers, generating a score representing the matching percentage between the spoken and correct words. The overall game activities correspond to the assessment categories reported in Figure 3 below. There are, in total, 18 variables that comprise our dataset. Some of them contain word recognition, such as in Articulation and Phonology. All variables are scaled and take values in the range [0, 100].

# SPEECH & LANGUAGE DEVELOPMENT PSYCHOMOTOR DEVELOPMENT • Verbal And Intellectual Ability • Fine Motor Skills • Pre-writing Skills • Pre-writing Skills • Spatial Orientation • Sequencing • Phonology • Sequencing • Pragmatic Perception • PSYCHOEMOTIONAL DEVELOPMENT • Empathy • Conditioned Play Audiometry

Figure 3. Areas of assessment and corresponding variables.

The participants in this study are mainly children aged 3 to 12 years old. The children were enrolled with the help and support of their parents, along with their written consent. In total, 320 children were recruited, of which 276 were typically developed, and the rest 44 of them had ASD.

This dataset fed the machine learning models selected, namely MLP, INN, and NNC. Each model was trained and tested using the 10-fold validation method. The objective was to find the most suitable method for classification; that is, to distinguish the ASD population from the typically developed population. The goal was to establish a screening tool to help clinicians safely and accurately in their diagnostic procedures.

Our dataset underwent statistical analysis. In the next section, we present the means and standard deviations of the game scores for TD and ASD children and compare the statistical differences between the two groups. Since the dataset variables do not have a normal distribution, we used the non-parametric Mann–Whitney U Test.

For the classification experiments, we evaluated the performance employing commonly used metrics in machine learning [89–91]. More specifically, most predictive models categorize data points into one of four groups for accuracy assessment [89]: (1) True Positive (TP), occurring when the model correctly predicts that a child has ASD; (2) True Negative (TN), happening when the model accurately predicts that a child does not have ASD; (3) False Positive (FP)—in this case, the model incorrectly predicts that a child without ASD has it; and (4) False Negative (FN), occurring when the model wrongly predicts that a child with ASD does not have it.

The test set's average classification error was used to classify the datasets. The classification error is the percentage of patterns in the test set allocated to a class that was not predicted. The error rate was calculated using the formula given in Equation (2) as follows:

$$\text{Error rate} = \frac{\text{FP} + \text{FN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}$$
(2)

The precision metric was used to measure the accuracy of our optimistic predictions. It represents the proportion of projected positive points that occurred. The definition of precision is shown in Equation (3):

$$Precision = \frac{TP}{TP + FP}$$
(3)

The percentage of positive cases that our algorithm correctly identified was measured by recall. Out of all the examples categorized as positive, it shows how accurate our model is in classifying positive instances. Recall and sensitivity were used interchangeably in some contexts. Equation (4) specifies recall as follows:

$$\text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{4}$$

Finally, Figure 4 visualizes the methods of this study.



Figure 4. Methods of the study.

### 4. Results

The results of this study are presented in two parts: statistical analysis of the new dataset and classifiers' application and experimental results.

### 4.1. Statistical Analysis

We first provide an overview of the statistics of our dataset before explaining the classification process. We used IBM SPSS v20.0 statistical software to perform descriptive statistics and hypothesis tests.

Table 1 displays the mean values and standard deviations of TD children's scores and those of children with ASD. The game-score values range from 0 to 100.

**Table 1.** Mean values and standard deviations of the game scores for the two groups of participants: children with TD and children with ASD.

<b>T7 + 11</b>	TD		ASD	
Variable	Mean	STD	Mean	STD
Verbal And Intellectual Ability	35.50	7.54	29.81	8.80
Verbalization after Instruction	26.28	26.99	19.07	23.53
Targeted Voicing Activities	37.63	27.08	41.52	26.24
Articulation	22.64	8.47	16.77	6.09
Phonology	83.61	24.20	69.06	25.89
Syntax	45.04	37.33	31.93	38.55
Pragmatic Perception	85.53	18.79	75.52	22.14
Fine Motor Skills	72.38	29.15	71.30	31.68
Pre-writing Skills	31.47	18.08	29.68	17.68
Spatial Orientation	37.68	12.10	39.52	14.35
Sequencing	61.20	13.82	53.24	18.51
Memory	31.31	21.37	19.32	20.51
Recognition	58.06	12.10	54.20	13.42
Perception/Discrimination	38.48	14.25	40.45	15.09
Sustained Attention	29.55	7.84	27.61	8.88
Cognitive Flexibility	65.00	19.88	64.94	19.87
Empathy	41.37	11.00	34.15	14.78
Conditioned Play Audiometry	35.81	26.72	29.27	24.20

We examined the data's normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests at a significance threshold of 0.05. It was discovered that there is no normal distribution for any of our variables. Therefore, we used the Mann–Whitney U test, a non-parametric test for two independent samples, to compare each variable of interest of the two groups of children (TD, ASD) for statistical differences. The results are summarized in Table 2, showing if a variable can distinguish the two populations. As such, nine variables—verbal and intellectual ability, articulation, phonology, syntax, pragmatic perception, sequencing, memory, recognition, and empathy—exhibit statistically significant differences between the two groups (TD and ASD), while the remaining variables do not.

**Table 2.** Statistically significant differences between the two independent groups of children (TD—ASD) using the Mann–Whitney U Test.

Variable	Mann-Whitney U	Wilcoxon W	Z	<i>p</i> -Value
Verbal And Intellectual Ability	3529	4519	-4.462	0.00
Verbalization after Instruction	5241.50	6231.50	-1.48	0.14
Targeted Voicing Activities	5467.00	43,693.00	-1.07	0.28
Articulation	3379.00	4369.00	-4.73	0.00
Phonology	3513.50	4503.50	-4.78	0.00
Syntax	4801	5791	-2.284	0.02
Pragmatic Perception	4309.5	5299.5	-3.286	0.00
Fine Motor Skills	5868	44,094	-0.405	0.69
Pre-writing Skills	5811	6801	-0.458	0.65
Spatial Orientation	5399	43,625	-1.183	0.24
Sequencing	4603	5593	-2.582	0.01
Memory	3954.5	4944.5	-3.716	0.00

Variable	Mann-Whitney U	Wilcoxon W	Ζ	<i>p</i> -Value
Recognition	5019	6009	-1.969	0.05
Perception/Discrimination	5329	43,555	-1.329	0.18
Sustained Attention	5213.5	6203.5	-1.892	0.06
Cognitive Flexibility	5980.5	44,206.5	-0.162	0.87
Empathy	4539.5	5529.5	-2.689	0.01
Conditioned Play Audiometry	5266	6256	-1.419	0.16

Table 2. Cont.

### 4.2. Application Details and Experimental Results

The classifiers' application details and parameterization are explained in this part, followed by experimental results.

Table 3 provides critical parameters of the INN and NNC methods using the gameplay dataset. This table outlines the specific settings used in these methods, which are crucial for understanding the experimental setup and the nature of the ML algorithms employed. Five hundred chromosomes were utilized in the models, suggesting a broad search space for finding the optimal network configuration. The number of 200 iterations allows for an extensive exploration of the solution space. The 10% selection rate implies that only the top 10% of chromosomes will be used to create the next generation based on their fitness or performance. This rate is crucial for balancing the exploration and exploitation in the algorithm. The 5% mutation rate used signifies a moderate level of randomness in the evolution of the solutions.

Table 3. INN and NNC values.

Parameter	Value	
Number of Chromosomes	500	
Number of Generations	200	
Selection Rate	10%	
Mutation Rate	5%	

Next, Table 4 reports on the experimental results. It displays the performance comparison of the classification methods. The RBF neural network method shows an error rate of 18.70%, which is relatively high compared to others. Its precision is 0.54, and recall is 0.58, indicating moderate effectiveness in classifying the dataset accurately. The MLP BFGS method shows a similar classifying attitude to the RBF, presenting an error rate of 19.28%, the highest compared to others. Its precision is 0.58, and recall is 0.60, indicating moderate effectiveness in accurately classifying the dataset. Next, the MLP LBFGS method has an error rate of 17.31%, slightly better than RBF and MLP BFGS. The precision of 0.56 is somewhat lower but has a higher recall of 0.68, suggesting it is better at identifying relevant instances. The NNC model has a further reduced error rate of 16.05%, with precision equal to MLP BFGS (0.58) but better recall (0.66). This indicates that it is more effective than MLP BFGS and MLP LBFGS in accurately classifying the dataset. Finally, the INN method demonstrates the best performance with the lowest error rate of 11.77%, a high precision of 0.75, and a recall of 0.66. The results suggest that INN is better at avoiding false classifications (high precision) and maintains a reasonable rate of correctly identifying relevant instances (recall).

Method	Error Rate (%)	Precision	Recall
RBF	18.70%	0.54	0.58
MLP BFGS	19.28%	0.58	0.60
MLP LBFGS	17.31%	0.56	0.68
NNC	16.05%	0.58	0.66
INN	11.77%	0.75	0.66

Table 4. Comparing Classification Methods with Error Rate (%), Precision, and Recall Metrics.

### 5. Conclusions

This study's goal was to investigate the use of constructed neural network models for the early detection of ASD in a gameplay dataset, which is a practical and child-friendly tool. The study aimed to use gameplay data as an engaging and non-intrusive medium for assessment; differentiate between children diagnosed with ASD and TD children; and provide a supportive tool for clinicians in diagnosing ASD, enhancing the screening process with the help of ML.

The study recorded significant statistical differences between TD and ASD children using the Mann–Whitney U test for verbal and intellectual ability, articulation, phonology, syntax, pragmatic perception, sequencing, memory, recognition, and empathy. The bestperforming ML model was INN, demonstrating the lowest error rate, highest precision, and good recall. It proved to be the most effective model in distinguishing children with ASD from typically developed ones in the gameplay dataset. Combining gameplay data and ML, we propose a novel, child-friendly approach to ASD screening, providing a non-intrusive and engaging way to assess children. This method has the potential to support clinicians in early diagnosis, which is crucial for timely intervention in ASD.

However, the study involved a smaller proportion of children with ASD (44 out of 320), indicating that sample size and diversity could be considered limitations of this study. A more extensive and diverse sample could provide more robust and generalizable results. While the INN model showed promising results, its effectiveness in different contexts or with other data types remains to be tested.

Future research may address broader and more diverse data collection involving a more extensive and diverse participant pool, including variations in age, cultural backgrounds, and ASD severity levels. Additionally, expansion to different data types could provide a more holistic understanding of ASD. Moreover, supplementary development and the refinement of algorithms and comparisons with other emerging ML methods could enhance their effectiveness and accuracy.

In summary, this study presents innovative methods for ASD detection utilizing machine learning and gameplay data. Future research should focus on addressing limitations and exploring potential applications.

Author Contributions: Conceptualization, E.I.T. and I.G.T.; methodology, E.I.T. and G.T.; software, I.G.T.; validation, E.I.T. and J.P.; formal analysis, E.I.T., G.T. and I.G.T.; investigation, G.T. and K.P.; resources, E.I.T. and I.G.T.; data curation, G.T. and J.P.; writing—original draft preparation, E.I.T., G.T. and I.G.T.; writing—review and editing, E.I.T., J.P. and I.G.T.; visualization, E.I.T.; supervision, E.I.T.; project administration, E.I.T.; funding acquisition, E.I.T. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the project titled "Smart Computing Models, Sensors, and Early Diagnostic Speech and Language Deficiencies Indicators in Child Communication" (MIS: 5033088), supported by the European Regional Development Fund (ERDF).

**Institutional Review Board Statement:** The study was conducted following the Declaration of Helsinki and approved by the Research Ethics Committee of the University of Ioannina, Greece (protocol code 18435/15 May 2020).

**Informed Consent Statement:** Informed written consent was obtained from all participating parents after they were informed about the study's compliance with GDPR.

Data Availability Statement: Data are contained within the article.

**Acknowledgments:** We wish to thank all the participants for their valuable contributions to this study and the administrative and technical support.

**Conflicts of Interest:** The authors declare no conflicts of interest. The funders had no role in the study's design, data collection, analysis, interpretation, manuscript writing, or decision to publish the results.

### References

- Hyman, S.L.; Levy, S.E.; Myers, S.M.; Council on children with disabilities, Section on Developmental and Behavioral Pediatrics; Kuo, D.Z.; Apkon, S.; Davidson, L.F.; Ellerbeck, K.A.; Foster, J.E.A.; Noritz, G.H.; et al. Identification, Evaluation, and Management of Children with Autism Spectrum Disorder. *Pediatrics* 2020, 145, e20193447. [CrossRef] [PubMed]
- Hobson, H.; Kalsi, M.; Cotton, L.; Forster, M.; Toseeb, U. Supporting the Mental Health of Children with Speech, Language and Communication Needs: The Views and Experiences of Parents. *Autism Dev. Lang. Impair.* 2022, 7, 239694152211011. [CrossRef] [PubMed]
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; American Psychiatric Association: Washington, DC, USA, 2013; ISBN 978-0-89042-555-8.
- Plaza-Diaz, J.; Radar, A.M.; Baig, A.T.; Leyba, M.F.; Costabel, M.M.; Zavala-Crichton, J.P.; Sanchez-Martinez, J.; MacKenzie, A.E.; Solis-Urra, P. Physical Activity, Gut Microbiota, and Genetic Background for Children and Adolescents with Autism Spectrum Disorder. *Children* 2022, 9, 1834. [CrossRef] [PubMed]
- Zeidan, J.; Fombonne, E.; Scorah, J.; Ibrahim, A.; Durkin, M.S.; Saxena, S.; Yusuf, A.; Shih, A.; Elsabbagh, M. Global Prevalence of Autism: A Systematic Review Update. *Autism Res. Off. J. Int. Soc. Autism Res.* 2022, 15, 778–790. [CrossRef] [PubMed]
- Elsabbagh, M.; Yusuf, A.; Zeidan, J.; Scorah, J.; Fombonne, E.; Durkin, M.S.; Saxena, S.; Shih, A. The Time Has Come for Living Systematic Reviews in Autism Research. *Autism Res.* 2022, *15*, 1187–1188. [CrossRef] [PubMed]
- Abdullah, A.A.; Rijal, S.; Dash, S.R. Evaluation on Machine Learning Algorithms for Classification of Autism Spectrum Disorder (ASD). J. Phys. Conf. Ser. 2019, 1372, 012052. [CrossRef]
- Thabtah, F. An Accessible and Efficient Autism Screening Method for Behavioural Data and Predictive Analyses. *Health Inform. J.* 2019, 25, 1739–1755. [CrossRef]
- Rice, C.E.; Carpenter, L.A.; Morrier, M.J.; Lord, C.; DiRienzo, M.; Boan, A.; Skowyra, C.; Fusco, A.; Baio, J.; Esler, A.; et al. Defining in Detail and Evaluating Reliability of DSM-5 Criteria for Autism Spectrum Disorder (ASD) Among Children. *J. Autism Dev. Disord.* 2022, 52, 5308–5320. [CrossRef]
- 10. Howlin, P. Adults with Autism: Changes in Understanding Since DSM-111. J. Autism Dev. Disord. 2021, 51, 4291–4308. [CrossRef]
- 11. Brown, K.A.; Parikh, S.; Patel, D.R. Understanding Basic Concepts of Developmental Diagnosis in Children. *Transl. Pediatr.* 2020, *9*, S9. [CrossRef]
- Zubler, J.M.; Wiggins, L.D.; Macias, M.M.; Whitaker, T.M.; Shaw, J.S.; Squires, J.K.; Pajek, J.A.; Wolf, R.B.; Slaughter, K.S.; Broughton, A.S.; et al. Evidence-Informed Milestones for Developmental Surveillance Tools. *Pediatrics* 2022, 149, e2021052138. [CrossRef]
- Lipkin, P.H.; Macias, M.M.; Council on Children with Disabilities, S.O.D.A.B.P.; Norwood, K.W., Jr.; Brei, T.J.; Davidson, L.F.; Davis, B.E.; Ellerbeck, K.A.; Houtrow, A.J.; Hyman, S.L.; et al. Promoting Optimal Development: Identifying Infants and Young Children with Developmental Disorders Through Developmental Surveillance and Screening. *Pediatrics* 2020, 145, e20193449. [CrossRef] [PubMed]
- 14. Pandria, N.; Petronikolou, V.; Lazaridis, A.; Karapiperis, C.; Kouloumpris, E.; Spachos, D.; Fachantidis, A.; Vasiliou, D.; Vlahavas, I.; Bamidis, P. Information System for Symptom Diagnosis and Improvement of Attention Deficit Hyperactivity Disorder: Protocol for a Nonrandomized Controlled Pilot Study. *JMIR Res. Protoc.* **2022**, *11*, e40189. [CrossRef]
- 15. Bayley, N. Bayley Scales of Infant and Toddler Development, 3rd ed.; Psychological Corporation: San Antonio, TX, USA, 2005.
- 16. Green, E.; Stroud, L.; O'Connell, R.; Bloomfield, S.; Cronje, J.; Foxcroft, C.; Hurter, K.; Lane, H.; Marais, R.; Marx, C. Manual Griffiths III—Part II: Administration and Scoring. In *Griffiths Scales of Child Development*, 3rd ed.; Hogrefe: Oxford, UK, 2017.
- 17. Elliott, C.D.; Salerno, J.D.; Dumont, R.; Willis, J.O. Differential Ability scales. In *Handbook of Psychoeducational Assessment*, 2nd ed.; Elsevier: San Antonio, TX, USA, 2007.
- Hadders-Algra, M.; Tacke, U.; Pietz, J.; Rupp, A.; Philippi, H. Standardized Infant NeuroDevelopmental Assessment Developmental and Socio-emotional Scales: Reliability and Predictive Value in an At-risk Population. *Dev. Med. Child Neurol.* 2020, 62, 845–853. [CrossRef]
- 19. Vitulano, L.A.; Vitulano, M.L.; King, R.A.; Leckman, J.F. Neurodevelopmental Disorders: Motor Disorders. In *Psychiatry*; Tasman, A., Kay, J., Lieberman, J.A., First, M.B., Riba, M.B., Eds.; Wiley: Hoboken, NJ, USA, 2015; pp. 779–790, ISBN 978-1-118-84547-9.
- Farmer, C.; Golden, C.; Thurm, A. Concurrent Validity of the Differential Ability Scales, Second Edition with the Mullen Scales of Early Learning in Young Children with and without Neurodevelopmental Disorders. *Child Neuropsychol.* 2016, 22, 556–569. [CrossRef] [PubMed]
- 21. Moreau, C.; Deruelle, C.; Auzias, G. Machine Learning for Neurodevelopmental Disorders. In *Machine Learning for Brain Disorders*; Colliot, O., Ed.; Humana: New York, NY, USA, 2023; ISBN 978-1-07-163194-2.

- 22. Kim, H.H.; An, J.I.; Park, Y.R. A Prediction Model for Detecting Developmental Disabilities in Preschool-Age Children Through Digital Biomarker-Driven Deep Learning in Serious Games: Development Study. *JMIR Serious Games* **2021**, *9*, e23130. [CrossRef]
- D'Souza, H.; Karmiloff-Smith, A. Neurodevelopmental Disorders. Wiley Interdiscip. Rev. Cogn. Sci. 2017, 8, e1398. [CrossRef] [PubMed]
- Morris-Rosendahl, D.J.; Crocq, M.-A. Neurodevelopmental Disorders—The History and Future of a Diagnostic Concept. *Dialogues Clin. Neurosci.* 2020, 22, 65–72. [CrossRef]
- Kanhirakadavath, M.R.; Chandran, M.S.M. Investigation of Eye-Tracking Scan Path as a Biomarker for Autism Screening Using Machine Learning Algorithms. *Diagnostics* 2022, 12, 518. [CrossRef]
- 26. Rello, L.; Baeza-Yates, R.; Ali, A.; Bigham, J.P.; Serra, M. Predicting Risk of Dyslexia with an Online Gamified Test. *PLoS ONE* **2020**, *15*, e0241687. [CrossRef]
- 27. Tan, Z.; Wei, H.; Song, X.; Wang, L. Positron Emission Tomography in the Neuroimaging of Autism Spectrum Disorder: A Review. *Front. Neurosci.* **2022**, *16*, 806876. [CrossRef] [PubMed]
- Han, J.; Jiang, G.; Ouyang, G.; Li, X. A Multimodal Approach for Identifying Autism Spectrum Disorders in Children. *IEEE Trans. Neural Syst. Rehabil. Eng. Publ. IEEE Eng. Med. Biol. Soc.* 2022, 30, 2003–2011. [CrossRef] [PubMed]
- Yin, W.; Li, L.; Wu, F.-X. A Semi-Supervised Autoencoder for Autism Disease Diagnosis. *Neurocomputing* 2022, 483, 140–147. [CrossRef]
- Haweel, R.; Shalaby, A.; Mahmoud, A.; Ghazal, M.; Khelifi, A.; Barnes, G.; Suri, J.S.; El-Baz, A. Chapter 17—Early Autism Analysis and Diagnosis System Using Task-Based fMRI in a Response to Speech Task. In *Neural Engineering Techniques for Autism Spectrum Disorder*; El-Baz, A.S., Suri, J.S., Eds.; Academic Press: Cambridge, MA, USA, 2021; pp. 345–359. ISBN 978-0-12-822822-7.
- 31. Epalle, T.M.; Song, Y.; Liu, Z.; Lu, H. Multi-Atlas Classification of Autism Spectrum Disorder with Hinge Loss Trained Deep Architectures: ABIDE I Results. *Appl. Soft Comput.* **2021**, *107*, 107375. [CrossRef]
- Toki, E.I.; Tatsis, G.; Tatsis, V.A.; Plachouras, K.; Pange, J.; Tsoulos, I.G. Employing Classification Techniques on SmartSpeech Biometric Data towards Identification of Neurodevelopmental Disorders. *Signals* 2023, *4*, 401–420. [CrossRef]
- 33. Asmetha Jeyarani, R.; Senthilkumar, R. Eye Tracking Biomarkers for Autism Spectrum Disorder Detection Using Machine Learning and Deep Learning Techniques: Review. *Res. Autism Spectr. Disord.* **2023**, *108*, 102228. [CrossRef]
- Bacon, E.C.; Moore, A.; Lee, Q.; Barnes, C.C.; Courchesne, E.; Pierce, K. Identifying Prognostic Markers in Autism Spectrum Disorder Using Eye Tracking. *Autism* 2019, 24, 658–669. [CrossRef] [PubMed]
- 35. Anzulewicz, A.; Sobota, K.; Delafield-Butt, J.T. Toward the Autism Motor Signature: Gesture Patterns during Smart Tablet Gameplay Identify Children with Autism. *Sci. Rep.* **2016**, *6*, 31107. [CrossRef]
- Simeoli, R.; Milano, N.; Rega, A.; Marocco, D. Using Technology to Identify Children With Autism Through Motor Abnormalities. Front. Psychol. 2021, 12, 635696. [CrossRef]
- 37. Meng, F.; Li, F.; Wu, S.; Yang, T.; Xiao, Z.; Zhang, Y.; Liu, Z.; Lu, J.; Luo, X. Machine Learning-Based Early Diagnosis of Autism According to Eye Movements of Real and Artificial Faces Scanning. *Front. Neurosci.* **2023**, *17*, 1170951. [CrossRef]
- Toki, E.I.; Tatsis, G.; Tatsis, V.A.; Plachouras, K.; Pange, J.; Tsoulos, I.G. Applying Neural Networks on Biometric Datasets for Screening Speech and Language Deficiencies in Child Communication. *Mathematics* 2023, 11, 1643. [CrossRef]
- 39. Kollias, K.-F.; Syriopoulou-Delli, C.K.; Sarigiannidis, P.; Fragulis, G.F. The Contribution of Machine Learning and Eye-Tracking Technology in Autism Spectrum Disorder Research: A Systematic Review. *Electronics* **2021**, *10*, 2982. [CrossRef]
- 40. Liao, M.; Duan, H.; Wang, G. Application of Machine Learning Techniques to Detect the Children with Autism Spectrum Disorder. *J. Healthc. Eng.* **2022**, 2022, e9340027. [CrossRef] [PubMed]
- Valenza, M.V.; Gasparini, I.; da Silva Hounsell, M. Serious Game Design for Children: Validating a Set of Guidelines. In Proceedings of the 2019 IEEE 19th International Conference on Advanced Learning Technologies (ICALT), Maceio, Brazil, 15 July 2019; Volume 2161-377X, pp. 110–112.
- 42. Wiley, K.; Robinson, R.; Mandryk, R.L. The Making and Evaluation of Digital Games Used for the Assessment of Attention: Systematic Review. *JMIR Serious Games* 2021, *9*, e26449. [CrossRef] [PubMed]
- 43. Kokol, P.; Vošner, H.B.; Završnik, J.; Vermeulen, J.; Shohieb, S.; Peinemann, F. Serious Game-Based Intervention for Children with Developmental Disabilities. *Curr. Pediatr. Rev.* 2020, *16*, 26–32. [PubMed]
- Toki, E.I.; Zakopoulou, V.; Tatsis, G.; Plachouras, K.; Pange, J. Markers for the Support of Clinical Tele-Assessment: The Case of Autism Spectrum Disorders. In Proceedings of the Open Science in Engineering; Auer, M.E., Langmann, R., Tsiatsos, T., Eds.; Springer Nature Switzerland: Cham, Switzerland, 2023; pp. 759–769.
- Millar, L.; McConnachie, A.; Minnis, H.; Wilson, P.; Thompson, L.; Anzulewicz, A.; Sobota, K.; Rowe, P.; Gillberg, C.; Delafield-Butt, J. Phase 3 Diagnostic Evaluation of a Smart Tablet Serious Game to Identify Autism in 760 Children 3–5 Years Old in Sweden and the United Kingdom. *BMJ Open* 2019, 9, e026226. [CrossRef] [PubMed]
- Gabrielli, S.; Cristofolini, M.; Dianti, M.; Alvari, G.; Vallefuoco, E.; Bentenuto, A.; Venuti, P.; Mayora Ibarra, O.; Salvadori, E. Co-Design of a Virtual Reality Multiplayer Adventure Game for Adolescents with Autism Spectrum Disorder: Mixed Methods Study. *JMIR Serious Games* 2023, *11*, e51719. [CrossRef] [PubMed]
- Keshav, N.U.; Vogt-Lowell, K.; Vahabzadeh, A.; Sahin, N.T. Digital Attention-Related Augmented-Reality Game: Significant Correlation between Student Game Performance and Validated Clinical Measures of Attention-Deficit/Hyperactivity Disorder (ADHD). *Children* 2019, 6, 72. [CrossRef] [PubMed]

- 48. Varma, M.; Washington, P.; Chrisman, B.; Kline, A.; Leblanc, E.; Paskov, K.; Stockham, N.; Jung, J.-Y.; Sun, M.W.; Wall, D.P.; et al. Identification of Social Engagement Indicators Associated with Autism Spectrum Disorder Using a Game-Based Mobile App: Comparative Study of Gaze Fixation and Visual Scanning Methods. J. Med. Internet Res. 2022, 24, e31830. [CrossRef]
- Deveau, N.; Washington, P.; Leblanc, E.; Husic, A.; Dunlap, K.; Penev, Y.; Kline, A.; Mutlu, O.C.; Wall, D.P. Machine Learning Models Using Mobile Game Play Accurately Classify Children with Autism. *Intell.-Based Med.* 2022, *6*, 100057. [CrossRef]
- Chi, N.A.; Washington, P.; Kline, A.; Husic, A.; Hou, C.; He, C.; Dunlap, K.; Wall, D.P. Classifying Autism From Crowdsourced Semistructured Speech Recordings: Machine Learning Model Comparison Study. *JMIR Pediatr. Parent.* 2022, 5, e35406. [CrossRef] [PubMed]
- 51. Tunçgenç, B.; Pacheco, C.; Rochowiak, R.; Nicholas, R.; Rengarajan, S.; Zou, E.; Messenger, B.; Vidal, R.; Mostofsky, S.H. Computerized Assessment of Motor Imitation as a Scalable Method for Distinguishing Children with Autism. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **2021**, *6*, 321–328. [CrossRef] [PubMed]
- 52. Tolks, D.; Schmidt, J.J.; Kuhn, S. The Role of AI in Serious Games and Gamification for Health: Scoping Review. *JMIR Serious Games* 2024, 12, e48258. [CrossRef] [PubMed]
- 53. Damaševičius, R.; Maskeliūnas, R.; Blažauskas, T. Serious Games and Gamification in Healthcare: A Meta-Review. *Information* **2023**, *14*, 105. [CrossRef]
- Abd-alrazaq, A.; Abuelezz, I.; Hassan, A.; AlSammarraie, A.; Alhuwail, D.; Irshaidat, S.; Abu Serhan, H.; Ahmed, A.; Alabed Alrazak, S.; Househ, M. Artificial Intelligence–Driven Serious Games in Health Care: Scoping Review. *JMIR Serious Games* 2022, 10, e39840. [CrossRef] [PubMed]
- 55. Toki, E.I.; Tsoulos, I.G.; Santamato, V.; Pange, J. Machine Learning for Predicting Neurodevelopmental Disorders in Children. *Appl. Sci.* **2024**, *14*, 837. [CrossRef]
- 56. Hornik, K.; Stinchcombe, M.; White, H. Multilayer Feedforward Networks Are Universal Approximators. *Neural Netw.* **1989**, *2*, 359–366. [CrossRef]
- 57. Shen, L.; Wu, J.; Yang, W. Multiscale Quantum Mechanics/Molecular Mechanics Simulations with Neural Networks. J. Chem. Theory Comput. 2016, 12, 4934–4946. [CrossRef]
- 58. Manzhos, S.; Dawes, R.; Carrington, T. Neural Network-based Approaches for Building High Dimensional and Quantum Dynamics-friendly Potential Energy Surfaces. *Int. J. Quantum Chem* **2015**, *115*, 1012–1020. [CrossRef]
- Wei, J.N.; Duvenaud, D.; Aspuru-Guzik, A. Neural Networks for the Prediction of Organic Chemistry Reactions. ACS Cent. Sci. 2016, 2, 725–732. [CrossRef]
- Falat, L.; Pancikova, L. Quantitative Modelling in Economics with Advanced Artificial Neural Networks. *Procedia Econ. Financ.* 2015, 34, 194–201. [CrossRef]
- 61. Namazi, M.; Shokrolahi, A.; Maharluie, M.S. Detecting and Ranking Cash Flow Risk Factors via Artificial Neural Networks Technique. J. Bus. Res. 2016, 69, 1801–1806. [CrossRef]
- 62. Baskin, I.I.; Winkler, D.; Tetko, I.V. A Renaissance of Neural Networks in Drug Discovery. *Expert Opin. Drug Discov.* 2016, 11, 785–795. [CrossRef] [PubMed]
- 63. Bartzatt, R. Prediction of Novel Anti-Ebola Virus Compounds Utilizing Artificial Neural Network (ANN), Chemistry Faculty Publications. *World J. Pharm. Res.* 2018, 49, 16–34.
- 64. Rumelhart, D.E.; Hinton, G.E.; Williams, R.J. Learning Representations by Back-Propagating Errors. *Nature* **1986**, *323*, 533–536. [CrossRef]
- 65. Riedmiller, M.; Braun, H. A Direct Adaptive Method for Faster Backpropagation Learning: The RPROP Algorithm. In Proceedings of the IEEE International Conference on Neural Networks, San Francisco, CA, USA, 28 March–1 April 1993; 1 April 1993; pp. 586–591.
- 66. Robitaille, B.; Marcos, B.; Veillette, M.; Payre, G. Modified Quasi-Newton Methods for Training Neural Networks. *Comput. Chem. Eng.* **1996**, *20*, 1133–1140. [CrossRef]
- 67. Leung, F.H.F.; Lam, H.K.; Ling, S.H.; Tam, P.K.S. Tuning of the Structure and Parameters of a Neural Network Using an Improved Genetic Algorithm. *IEEE Trans. Neural Netw.* **2003**, *14*, 79–88. [CrossRef]
- 68. Yao, X. Evolving Artificial Neural Networks. Proc. IEEE 1999, 87, 1423–1447.
- 69. Zhang, J. Cognitive Functions of the Brain: Perception, Attention and Memory. arXiv 2019, arXiv:1907.02863. [CrossRef]
- 70. Giveki, D.; Rastegar, H. Designing a New Radial Basis Function Neural Network by Harmony Search for Diabetes Diagnosis. *Opt. Mem. Neural Netw.* **2019**, *28*, 321–331. [CrossRef]
- 71. Liu, D.C.; Nocedal, J. On the Limited Memory BFGS Method for Large Scale Optimization. *Math. Program.* **1989**, *45*, 503–528. [CrossRef]
- 72. Powell, M. A Tolerant Algorithm for Linearly Constrained Optimization Calculations. *Math. Program.* **1989**, *45*, 547–566. [CrossRef]
- 73. Karimi, N.; Kazem, S.; Ahmadian, D.; Adibi, H.; Ballestra, L.V. On a Generalized Gaussian Radial Basis Function: Analysis and Applications. *Eng. Anal. Bound. Elem.* **2020**, *112*, 46–57. [CrossRef]
- 74. Hery, M.A.; Ibrahim, M.; June, L.W. BFGS Method: A New Search Direction. Sains Malays. 2014, 43, 1591–1597.
- Christou, V.; Miltiadous, A.; Tsoulos, I.; Karvounis, E.; Tzimourta, K.D.; Tsipouras, M.G.; Anastasopoulos, N.; Tzallas, A.T.; Giannakeas, N. Evaluating the Window Size's Role in Automatic EEG Epilepsy Detection. *Sensors* 2022, 22, 9233. [CrossRef] [PubMed]

- 76. Tsoulos, I.G.; Tzallas, A. Training Artificial Neural Networks Using a Global Optimization Method That Utilizes Neural Networks. *AI* 2023, *4*, 491–508. [CrossRef]
- 77. Fletcher, R. A New Approach to Variable Metric Algorithms. Comput. J. 1970, 13, 317–322. [CrossRef]
- Wang, H.; Gemmeke, H.; Hopp, T.; Hesser, J. Accelerating Image Reconstruction in Ultrasound Transmission Tomography Using L-BFGS Algorithm. In Proceedings of the Medical Imaging 2019: Ultrasonic Imaging and Tomography, 15 March 2019; Volume 10955, pp. 67–76.
- 79. Rao, Y.; Wang, Y. Seismic Waveform Tomography with Shot-Encoding Using a Restarted L-BFGS Algorithm. *Sci. Rep.* **2017**, *7*, 8494. [CrossRef] [PubMed]
- 80. Morales, J.L. A Numerical Study of Limited Memory BFGS Methods. Appl. Math. Lett. 2002, 15, 481–487. [CrossRef]
- 81. O'Neill, M.; Ryan, C. Grammatical Evolution. IEEE Trans. Evol. Comput. 2001, 5, 349–358. [CrossRef]
- 82. Tsoulos, I.G.; Gavrilis, D.; Glavas, E. Solving Differential Equations with Constructed Neural Networks. *Neurocomputing* **2009**, *72*, 2385–2391. [CrossRef]
- 83. Papamokos, G.V.; Tsoulos, I.G.; Demetropoulos, I.N.; Glavas, E. Location of Amide I Mode of Vibration in Computed Data Utilizing Constructed Neural Networks. *Expert Syst. Appl.* **2009**, *36*, 12210–12213. [CrossRef]
- Tsoulos, I.G.; Mitsi, G.; Stavrakoudis, A.; Papapetropoulos, S. Application of Machine Learning in a Parkinson's Disease Digital Biomarker Dataset Using Neural Network Construction (NNC) Methodology Discriminates Patient Motor Status. Front. ICT 2019, 6, 10. [CrossRef]
- 85. Tsoulos, I.G.; Tzallas, A.; Tsalikakis, D. NNC: A Tool Based on Grammatical Evolution for Data Classification and Differential Equation Solving. *SoftwareX* 2019, *10*, 100297. [CrossRef]
- 86. Tsoulos, I.G.; Tzallas, A.; Karvounis, E. A Rule-Based Method to Locate the Bounds of Neural Networks. *Knowledge* **2022**, 2, 412–428. [CrossRef]
- Toki, E.I.; Zakopoulou, V.; Tatsis, G.; Plachouras, K.; Siafaka, V.; Kosma, E.I.; Chronopoulos, S.K.; Filippidis, D.E.; Nikopoulos, G.; Pange, J.; et al. A Game-Based Smart System Identifying Developmental Speech and Language Disorders in Child Communication: A Protocol Towards Digital Clinical Diagnostic Procedures. In *New Realities, Mobile Systems and Applications*; Auer, M.E., Tsiatsos, T., Eds.; Lecture Notes in Networks and Systems; Springer International Publishing: Cham, Switzerland, 2022; Volume 411, pp. 559–568, ISBN 978-3-030-96295-1.
- 88. Radford, A.; Kim, J.W.; Xu, T.; Brockman, G.; McLeavey, C.; Sutskever, I. Robust Speech Recognition via Large-Scale Weak Supervision 2022. In Proceedings of the International Conference on Machine Learning, Honolulu, HI, USA, 23–29 July 2023.
- Vakadkar, K.; Purkayastha, D.; Krishnan, D. Detection of Autism Spectrum Disorder in Children Using Machine Learning Techniques. SN Comput. Sci. 2021, 2, 386. [CrossRef] [PubMed]
- Aimie-Salleh, N.; Mtawea, N.E.; Kh'ng, X.Y.; Liaw, C.Y.; Cheng, X.G.; Bah, A.N.; Lim, K.L.; Al Haddad, M.A.Y.; Azaman, A.; Mohamad, M.R.; et al. Assessment of Heart Rate Variability Response in Children with Autism Spectrum Disorder Using Machine Learning. *Int. J. Integr. Eng.* 2022, 14, 33–38.
- Tanha, J.; Abdi, Y.; Samadi, N.; Razzaghi, N.; Asadpour, M. Boosting Methods for Multi-Class Imbalanced Data Classification: An Experimental Review. J. Big Data 2020, 7, 70. [CrossRef]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.