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Can we use a biomarker detection algorithm to measure the effectiveness of 14-channel neurofeedback in dyslexia?

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Abstract

The most common neurological diversity that children experience is dyslexia and it manifests itself in reduced reading ability. There is a genetic predisposition for dyslexia, and more recent theories explain it as a delay in left hemispheric lateralization that reduces effective reading and writing. A software for smartphones called Auto Train Brain helps children with dyslexia to improve their reading comprehension and reading speed. Measuring the efficacy of the mobile app training was done manually with psychometric tests beforehand and we use a biomarker detection software to measure the efficacy of the neurofeedback. Machine learning (ML) techniques have recently been used to classify children with dyslexia and typically developing children (TDC). The data consists of 100 sessions of 2-minute resting-state eyes-open 14-channel Quantitative Electroencephalography (QEEG) data from 100 children with dyslexia and 100 TDC. We used the dyslexia biomarker detection software to assess the effectiveness of the 14-channel neurofeedback that was applied with Auto Train Brain. The results have shown that 30% of the sessions of children with dyslexia were classified as electrophysiologically normal, and 61% of the children with dyslexia were classified as electrophysiologically normal for at least 1 session after the 20th session of neurofeedback.

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1. Introduction

According to DSM V criteria, developmental dyslexia is defined as a subset of specific learning disorders (American Psychiatric Association, 2013). Dyslexia manifests itself in reduced reading ability that can not be attributed to low IQ. Many theories have been proposed about dyslexia. The most well-known of these hypotheses for dyslexia is its genetic basis (Francks et al., 2002). Dyslexic parents are more likely to have dyslexic children (Van Bergen et al., 2012). Cellular, regional, and network homeostasis in the brain are modulated by genetic programs that are balanced between epigenetic, stress-induced, and cognitive-growth programs (Kershner, 2021). According to D'Souza et al. (2016), additional prevalent ideas for dyslexia include maternal stress, an active maternal autoimmune response during pregnancy, and maternal infections throughout pregnancy. Dyslexia may be brought on by less neuroplasticity and an earlier peak of development of the posterior corpus callosum, the left hemisphere reading network, and the right hemisphere attentional network circuitry. This premature shortening of a generally lengthy maturation begins during pregnancy or in infancy (Kershner, 2019). The hypothalmic-pituitary-adrenal (HPA) stress axis can overactivate, disturbing the homeostatic balance and exposing the brain to dangerous quantities of stress hormones, even with mild chronic stress exposure. A defense against prolonged disequilibrium swiftly progresses maturation at the expense of neuroplasticity, which not only reduces stress axis reactivity but also impairs the prefrontal cortex and networks linked to dyslexia's learning potential (Kershner, 2021). In other research, dyslexia is characterized by the delay in the left lateralization of the brain (Yılmaz & Akyüz, 2021). It's crucial to establish left-brain dominance before children enter school (Kershner, 2020).

Even with the proper assistance, nutrition, and education, it takes a very long time for children with dyslexia to catch up to their classmates in terms of reading ability. The capacity to consciously modify speech sounds (phonological awareness), to momentarily store phonological information in the verbal short-term memory, and to quickly recover long-term phonological representations are among the components of phonological processing that are deficient (McDougall et al.,1994).

Different subtypes of dyslexia exist. Recent research has also found a strong correlation between dyslexia and a number of characteristics, including an underlying basic auditory processing deficiency (Schulte-Körne, 2010), impaired visual processing (Lassus-Sangosse et al., 2008), attentional deficits (Bednarek et al., 2004), defective eye movements (Bellocchi et al., 2013), and irregularities of processing (Eden et al (Horwitz, 1998). Dyslexics have trouble accurately translating written letters (graphemes) into matching sounds (phonemes) (Rubinsten et al., 2006). Some subcortical structures may also be impacted in addition to the cortex (Galaburda et al., 1985). Beginning in infancy, perceptions of audiovisual speech are integrated by mutual oscillatory phase-resetting between sensory cortices (Kershner, 2021). It is suggested that poor auditory/visual integration may be diagnostic for both forms of dyslexia, stemming from an encoding weakness in the early cross-sensory binding of audiovisual speech (Kershner, 2021). It presents a model of dyslexia as a dysfunction of the large-scale ventral and dorsal attention networks controlling such binding (Kershner, 2021). Excessive glutamatergic neuronal excitability of the attention networks by the Locus coeruleus-norepinephrine system may interfere with multisensory integration, with deleterious effects on the acquisition of reading by degrading grapheme/phoneme conversion (Kershner, 2021).

Numerous studies have shown that children with dyslexia exhibit slow brain waves at FC5 and F7 and do not

desynchronize beta-1 activity while completing a reading task in areas related to Broca's area (FC5; speech production, articulation) and the Angular gyrus (CP5, P3), understanding semantics and mathematics (Klimesch et al., 2001), as well as the left parieto-occipital area (P7, O1) (Rippon & Brunswick, 2000). In children with dyslexia, the right temporal and parietal (P8 and T8) regions of the brain have increased sluggish activity (Arns et al., 2007). The left temporal area, according to the researchers, is disrupted (Thornton & Carmody (2005). Additionally, people with dyslexia and ADHD may exhibit a high degree of frontal sluggish activity. The alpha and beta bands show a clear right-temporal central increase in coherence at T3 and T4, while the delta and theta bands show a symmetric rise in coherence (Arns et al., 2007). In the delta and theta bands, there is bi-hemispheric hyper-coherence (between T3 and T4); yet, between P7 and O1, there is hypo-coherence in the delta, theta, and alpha bands. Gamma band difficulties and less functioning connections are associated with dyslexia (Fraga González, 2018; Kraus, 2012). The left temporal low activity region reveals a significant relationship between reading difficulties and difficulties with auditory processing. Similar findings, among other posterior brain regions, provide neurobiological evidence of underlying nervous system dysfunction in the temporo-occipital and parietal-temporal regions namely ventral attentional networks. These uncommon anomalies in the left temporo-occipital area of the brain may have a major impact on dyslexia.

We focused on the study of the previous works in the publications that specialized in classifying dyslexia among children through supervised machine learning techniques using EEG datasets (Table 1).

Table 1. *Previous Works Summary for ML algorithms with EEG data.*

Reference	Used Dataset	Used ML Models	Highest Reached Accuracy
(Karim et al., 2013)	Dataset was collected using the Dyslexia Association of Malaysia, at Ampang Hilir and Titiwangsa branch for the dyslexic children, and the good-reader children were selected randomly from different schools. The age range was from 4 to 7 years old.	Multi-Layer Perceptron (MLP)	0.86 of accuracy with eyes closed
(Zainuddin et al., 2016)	Collected EEG data from 21 participants between 7 and 12 years old, 7 of them were classified as capable dyslexic, while 4 of them were classified as poor dyslexic, and the rest were good readers.	K-Nearest Neighbors (KNN) classifier.	1.00 for normal and capable dyslexic children using Euclidean with k-value at 5 for Random and Nearest rule. But no checking for overfitting was done.
(Zainuddin et al., 2018)	EEG data were recorded from 33 participants with the age ranging from 7 to 12 years old, 8 of them were normal, 17 were poor dyslexics and 8 were capable dyslexics. This data was acquired with the assistance of the Dyslexia Association of Malaysia and the Rakan Dyslexia Malaysia group.	Support Vector Machine (SVM) classifier with Radial Basis Function (RBF) kernel	0.91
(Alex & Larry, 2018)	The dataset was self-collected, and the total number of participants was 32 Hebrew native children 17 of them were dyslexic while the rest were good readers.	Several ML models were experimented such as Decision Trees (DT), Neural Networks (NN), and SVM, but they mentioned	The highest accuracy reached 0.78

		SVM only	
(Zainuddin et al., 2019)	The EEG data was self-recorded. The number of participants was 20, equally separated between dyslexic and good reader children. The age range was from 7 to 12.	KNN and extreme learning machine (ELM) classifiers.	The highest accuracy was 0.89 and it was scored by ELM.
(Rezvani et al., 2019)	Data was collected using 44 participants, 29 of them were dyslexic and the rest were good readers. The studied age was the age of third grade.	SVM classifier.	0.95
(Kheyrkhah Shali & Setarehdan, 2020)	Data was taken from the Atiyeh clinic center. The sample group consisted of 30 primary school students equally separated between dyslexic and good reader children. They used 19 channels for EEG signals and sampled at 250 Hz.	SVM classifier.	This work focused on identifying the brain parts that are related to reading to improve them.
(Ortiz et al., 2020)	The EEG data used in this work was provided by the Leeduca Study Group at the University of Malaga.	Deep learning with SVM.	The highest scored accuracy was 0.96
(Formoso, Ortiz, Martinez-Murcia, et al., 2021)	Data was taken from the Leeduca group at the University of Málaga. Control and experimental groups are extracted by a careful screening process from a cohort (N = 700) followed from 4 years to the second evaluation of 7 years in 20 different primary schools (Junta de Andalucía).	Naïve Bayes (NB) Classifier.	0.82 with the 4.8 Hz stimulus.
(Formoso, Ortiz, Martínez-Murcia, et al., 2021)	The used data was provided by the Leeduca Research Group at the University of Málaga. EEG signals were recorded using the Brainvision acticHamp Plus with 32 active electrodes (actiCAP, Brain Products GmbH, Germany) at a sampling rate of 500 Hz during 15-minute sessions while presenting an auditory stimulus to the subject. The number of participants was 48, 17 of them were good readers while the rest were dyslexic.	They used SVM to detect the most discriminant nodes and then ensemble classifier using Random Forest (RF) and Gradient Boosting classifiers.	The Area Under Curve (AUC) metric was used and the highest value reached 0.73.
(Gallego-Molina et al., 2022)	EEG data were obtained by the Leeduca research group at the University of Málaga. The total number of participants was 48, 32 were good readers while the rest were dyslexic. The age range was from 88 to 100 months.	Phase–amplitude coupling (PAC) then SVM.	The highest accuracy was 0.729 for the 4.8 Hz stimulus.

From Table 1, we can see that the highest accuracy score was 1.00 (Zainuddin et al., 2016), however the overfitting issue that ML models have was not taken into consideration. Most of the previous works focused on SVM classifiers to solve the classification problem (Formoso, Ortiz, Martinez-Murcia, et al., 2021; Gallego-Molina et al., 2022; Kheyrkhah Shali & Setarehdan, 2020; Ortiz et al., 2020; Rezvani et al., 2019; Zainuddin et al., 2018), while other ML methods chose KNN classifier (Zainuddin et al., 2016; Zainuddin et al., 2019), NB classifier (Formoso, Ortiz, Martinez-Murcia, et al., 2021), and MLP (Karim et al., 2013). From the studied previous works, we can see that there was a limitation in choosing

supervised ML models, so there was no overall comparison of the performance of other ML models. The chosen supervised ML models were not also achieved good performances in the classification problem. Most of the previous works did not take into consideration the overfitting issues that ML models may face over the given datasets. Processing time for the studied previous works was also not mentioned.

The cutting-edge system Auto Train Brain incorporates multi-sensory learning, neurofeedback from 14 channels, and special education concepts (Eroğlu et al., 2021). Auto Train Brain includes machine learning algorithms. Clinical trials were used in earlier studies to examine the efficacy of 14-channel neurofeedback with Auto Train Brain (Eroğlu et al., 2021; Eroğlu et al., 2022). It was demonstrated that Auto Train Brain was an excellent method for enhancing the reading skills of dyslexic children when comparing pre- and post- Multiscale entropy and TILLS tests. In this study, we used a highly accurate dyslexia diagnostic system based on machine learning to assess 14-channel neurofeedback using Auto Train Brain.

2. Methods and materials

2.1. Participants

Our experiment group consisted of 100 children with dyslexia who regularly utilized Auto Train Brain at home for neurofeedback (Mage= 8.85, SD = 1.56, 75 males, 25 females; ethnic group is white). There were 100 healthy children present in the experiment (Mage = 8.75, SD = 1.50; 79 males, 21 females; ethnic group white). Psychiatrists identified the children in the experiment group as having dyslexia and advised their families to use Auto Train Brain at home. Psychiatrists used the TILLS tests to determine whether the test subjects satisfied the DSM-V criteria for dyslexia. The children were picked at random to take part in the experiment by using social media advertisements. In this retrospective study, the participant's main objective is to use Auto Train Brain software as a neurofeedback device at home. Individuals were advised to conduct a 2-minute resting state QEEG assessment for the purpose of data collection prior to each neurofeedback session. The participants utilized Auto Train Brain before leaving for school in the morning. The inclusion criteria for the study were that the participants hailed from middle-SES homes, did not use any medications, did not have any comorbid conditions aside from dyslexia, and aged between 7-10. They resided in numerous cities all around Turkey. A survey of the parents of the children was done to assess their socioeconomic position. The survey asks questions about employment, education (elementary, secondary, and graduate), and income (low income 6,000 TL, middle income 6,000 TL to 20,000 TL, high income >20,000 TL) (staff, blue-collar workers, white-collar workers).

Before each neurofeedback session, 2-minute resting-state eyes-open theta, alpha, beta1, beta2, and gamma-band powers were measured (60 sessions per subject on average). This study makes use of many measurements and a limited sample size (200 participants). Using Auto Train Brain, 2-minute resting-state QEEG data from typically developing children are collected 60 times per participant, and the data for the experiment and control groups are balanced to have an equal number of occurrences in each group.

2.2. The Test of Integrated Language & Literacy Skills (TILLS)

The TILLS is a test for the assessment of oral and written language abilities in students 6–18 years of age. Published in 2016 (Nelson, Plante, Helm-Estabrooks, & Hotz, 2016), it is unique in the way that it is aimed to thoroughly assess skills such as reading fluency, reading comprehension, phonological awareness, spelling, as well as writing in school-age children. The test is originally developed in English. Turkish Dyslexia Association has translated and adapted it to Turkish. This test has been used for diagnosing learning disabilities. For 6-7 years old children, a TILLS descriptive score of less than 24 indicates learning disability with 84% sensitivity and 84% specificity. For 8-11 years old children, a TILLS descriptive score of less than 34 indicates learning disability with 88% sensitivity and 85% specificity.

The TILLS test has 2 dimensions (language and modality). For listening modality, it has (1) Vocabulary awareness, (2) Phonemic awareness, (6) Listening comprehension, (8) Following directions; for speaking modality, it has (4) Nonword repetition, (3) Story retelling, (13) Social communication; for reading modality, it has (10) Nonword reading, (11) Reading fluency, (7) Reading comprehension; for writing modality, it has (5) Nonword spelling, (12a) Written expressions- Word score, (12b) Written expression -discourse score, (12c) Written Expression – sentence combining score; for Memory, (14) Digit span forward, (15) Digit span Backward, (9) Delayed story retelling subtests. The TILLS descriptive point is the sum of all subtests' scores.

2.3 Electroencephalography (EEG) recording

The EPOC-X headsets from EMOTIV were utilized throughout the tests. The headset's internal sampling rate for each channel was 2048 samples per second. Prior to down-sampling, the principal artifacts and alias frequencies were eliminated from the EEG data and each channel was sampled at 128 times per second. Two additional channels were employed as controls, and a total of 128 samples per second were applied to each of the 14 EEG channels. To ensure that each electrode could deliver high-quality EEG data, the EMOTIV EPOC-X headset was calibrated on the participants' scalps using the EMOTIV APP mobile applications prior to the training. The 14-channel EEG data were acquired in the theta (4–8 Hz), alpha (8–12 Hz), beta-1 (12–16 Hz), beta-2 (16–25 Hz), and gamma (25–45 Hz) bands for all analyses in this work. The EMOTIV headset interfaces lacked data from the delta (0–4 Hz) band. It has been shown that EMOTIV EPOC-X delivers high-quality QEEG data (Badcock et al, 2013). There are 70 features in the dataset. On the Auto Brain Train device, electrodes are used to collect the data (AF3, F3, F7, FC5, T7, P7, O1, O2, P8, T8, FC6, F8, F4, AF4).

2.4. Neurofeedback treatment protocol and multi-sensory learning method

Neurofeedback and multi-sensory learning techniques are employed in the Auto Train Brain smartphone app. The EMOTIV EPOC-X headsets are compatible with it. It is a non-invasive technique that helps people of all ages gradually improve their brain function. The only side effect that was occasionally seen was a headache. Traditional neurofeedback training may have surprising results when applied to the wrong brain regions or when the wrong neurofeedback protocols are used for the subject's condition. Before each neurofeedback session, Auto Train Brain's AI-assisted algorithms analyze the 2-minute resting state eyes-open QEEG data, and based on the results, the optimum neurofeedback protocol

is offered for the subsequent session. 1700 healthy people aged 4 to 80 gave norm data to Auto Train Brain.

This norm data is used to compare the subject's QEEG readings to those of TDC throughout the neurofeedback session. Neurofeedback training is carried out on the brain regions that are the most dysfunctional. In prior studies and clinical trials for kids, Auto Train Brain was found to be useful with the intention of minimizing adverse effects (Eroğlu et al., 2021). It provides online, real-time visual and aural neurofeedback while reading and interpreting QEEG signals from 14 channels. Within this software, a system and approach for increasing learning capacity are provided. We believed the following strategy might be helpful because dyslexia is described in the literature as a disconnection disorder in the left temporal area. On dyslexic children, this neurofeedback technique has already been tried in a clinical setting.

- Reduce absolute theta waves at FC5 if they are higher than the age-matched norm theta; and/or,
- Reduce absolute theta waves at T7- P7- O1 if they are higher than the age-matched norm theta; and/or, • Find the channels with the highest absolute power of theta waves in the left hemisphere and reduce absolute theta; and/or,
- Find the channels with the highest absolute power of theta waves in the right hemisphere and reduce absolute theta.

A green arrow on the screen denotes positive reinforcement, whereas a red arrow and a "beep" sound denote unfavorable comments. When a favorable reward is received, the score that is visible on the screen increases. If the participant's absolute theta levels are over the norm, a red arrow is shown on the screen, and they are encouraged to try to change it to a green one. Neurofeedback sessions typically last for 30 minutes. After the neurofeedback session, a phoneme-grapheme matching alphabet teaching approach is provided. The fact that the Auto Train Brain incorporates neurofeedback with multi-sensory learning ideas sets it apart from previous neurofeedback systems. A distinctive technique is the 14-channel neurofeedback system. According to Eroğlu et al. (2021), utilizing Auto Train Brain to lower theta reduces the dyslexia disconnection syndrome and improves the left lateralization of the brain. The results of the TILLS test show that reducing QEEG theta band power practically improves coherence across multiple brain regions.

2.5. Study Design

An app for mobile devices that may be used at home is the Auto Train Brain solution. The QEEG assessment electrodes were implanted while each participant sat in a chair. The participant was placed 0.5 meters away from the phone's display. Before each neurofeedback session, the resting-state QEEG readings were obtained for two minutes using the EMOTIV EPOC-X and the Auto Train Brain app. The individual was asked to relax and keep their eyes open while doing the QEEG assessment. This study is designed as a repeated measurement.

2.6. Statistical Analysis

The averaged 2-minute QEEG band power data (continuous data) are acquired from fourteen electrode channels each session. For the whole data set, the Z-scores are computed using the equation $z = (x-m)/s$ for each QEEG band power (including the experiment and the control group). Because EMOTIV does not offer Z-scores, m and s stand for the sample's mean and sample standard deviation, respectively. Outliers (>5 or -5) were removed from the analysis. The

missing values were replaced with the mean of the featured data. The data is labeled by a computer scientist following the psychiatrist's diagnosis of the participant. The diagnosis of the participant has not changed across the first neurofeedback sessions. The data were balanced with pre-processing operations and adjustments. The binary classification with a supervised ML model is applied. The model output is the dyslexia positivity probability score. The ML model architecture is Artificial Neural Network. The model features made in the study are epoch 60, batch size 32, and loss as binary cross-entropy. The best model is selected among many other varying hidden layers and activation functions. The k-fold cross-validation technique has been used to evaluate the model with ten-folded cross-validation. This method is generally used to test model performance to estimate how well the model performs on unseen data. The overfitting is prevented by applying the dropout between layers. The results have been tested with an external test set which contains a diverse set of input data.

Python/Google Collab, Sci-kit Learn, and TensorFlow ML libraries were used to conduct the statistical and data analysis. K-Folding, Cross-validation, and confusion matrix generator functions derived from ML libraries. Mat plot library stands for plotting learning, validation, and ROC curves.

2.7. Experimental Methodology

Figure 1 summarizes the methodology that we used to reach our results. After collecting the dataset and validating it, the QEEG records for the first 20 sessions are used in training the ML models after splitting it into training and testing according to the ratio 80:20. After the training process, testing the trained ML models was conducted. In order to check the effectiveness of the neurofeedback treatment protocol, a validation process was conducted using the QEEG records of children with dyslexia in the sessions from 21 to 100. Lastly, the results were analyzed.

To have better knowledge of the effectiveness of using specific parts of the brain in the classification process, the experiment is repeated for the following brain sections:

- Left Hemisphere (LH) represented by the electrodes: AF3, F3, FC5, T7, P7 and O1,
- Left Frontal (LF) represented by the electrodes: AF3, and F3,
- Left Temporal (LT) represented by the electrodes: T7, and FC5,
- Left Occipital (LO) represented by the electrodes: O1, and P7,
- Right Hemisphere (RH) represented by the electrodes: AF4, F4, FC6, T8, P8, and O2,
- Right Frontal (RF) represented by the electrodes: AF4, and F4,
- Right Temporal (RT) represented by the electrodes: T8, and FC6,
- Right Occipital (RO) represented by the electrodes: O2, and P8.

The used Supervised ML models in the conducted training are: Logistic Regression (LR), Random Forests (RFs), Support Vector Machines (SVMs), Gradient Boosting (GB), Light Gradient Boosting Machine (LGBM), and lastly hard and soft voting ensemble classifiers used a combination of the separately mentioned classifiers except for RF classifier since it had a negative effect on the learning process. Please refer to Appendix I for more details about the used parameters.

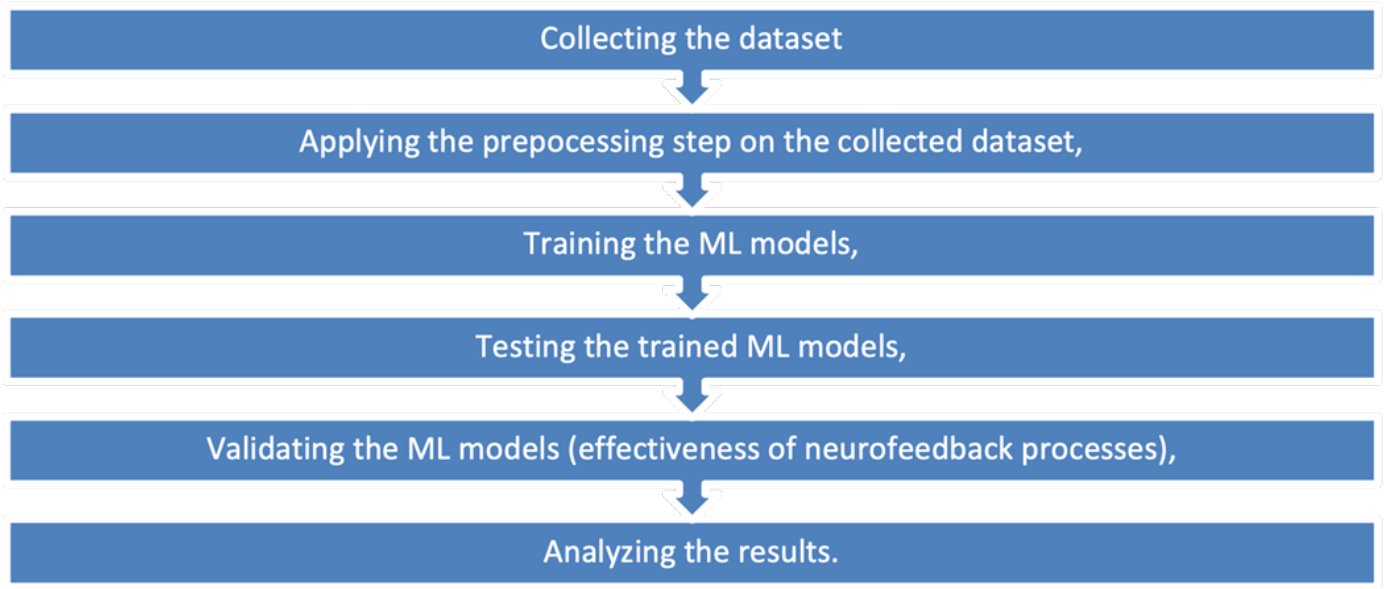


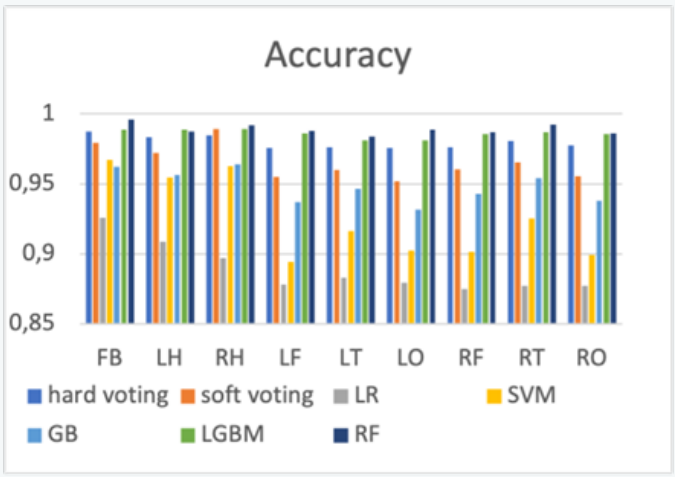
Figure 1. described below shows the methodology that we use

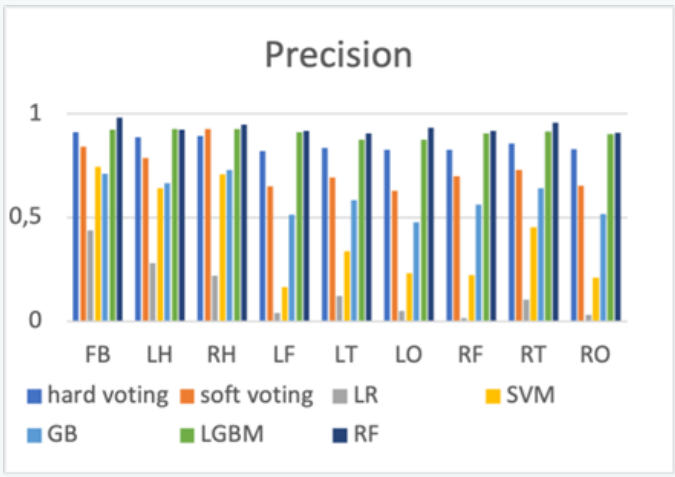
3. Results

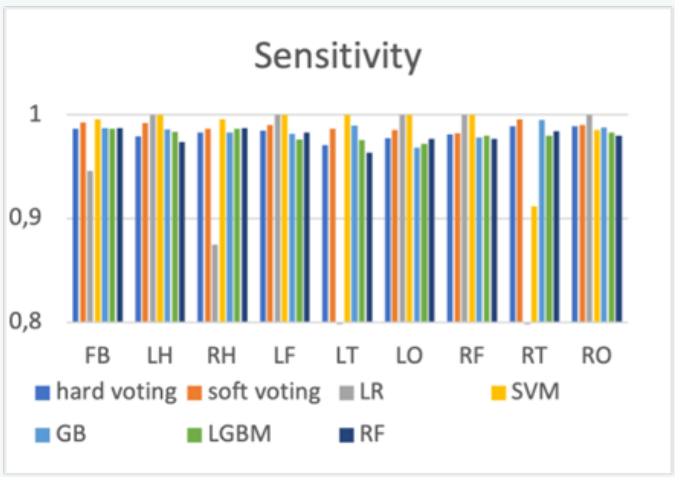
The results have shown that 30% of the sessions of children with dyslexia were classified with the dyslexia biomarker detection algorithm as electrophysiologically normal, and 61% of the children with dyslexia were classified as electrophysiologically normal for at least 1 session after 20th sessions of neurofeedback.

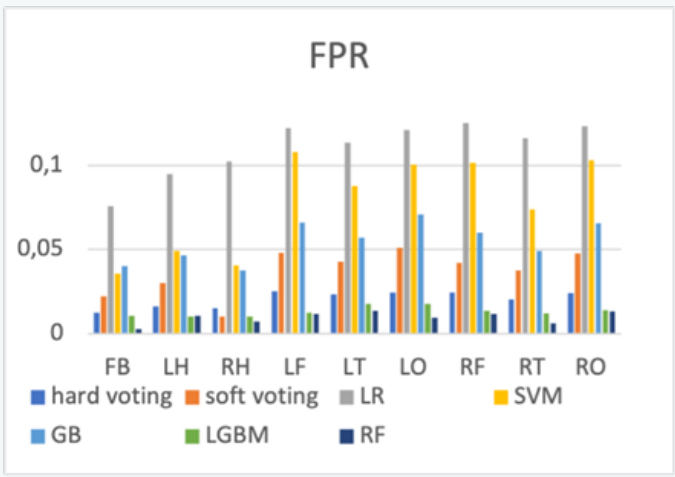
In this research, we have tested the effectiveness of using supervised ML techniques in dyslexia biomarker detection. All the results in this section are rounded to 4 digits after the floating point. Table 1 shows the results of the classifying process. The mentioned results in Table 1 are based on the ML evaluation measurements: accuracy, sensitivity, specificity, precision, False Positive Rate (FPR) and Mean Squared Error (MSE). Table 2 shows the implementation time details in seconds.

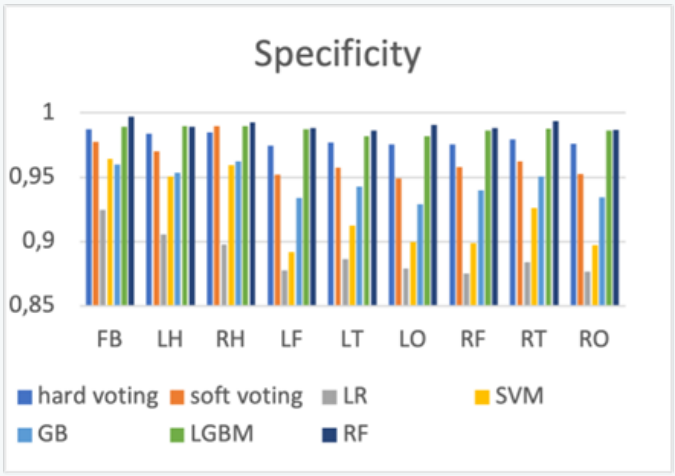
Table 1. Classification Results.











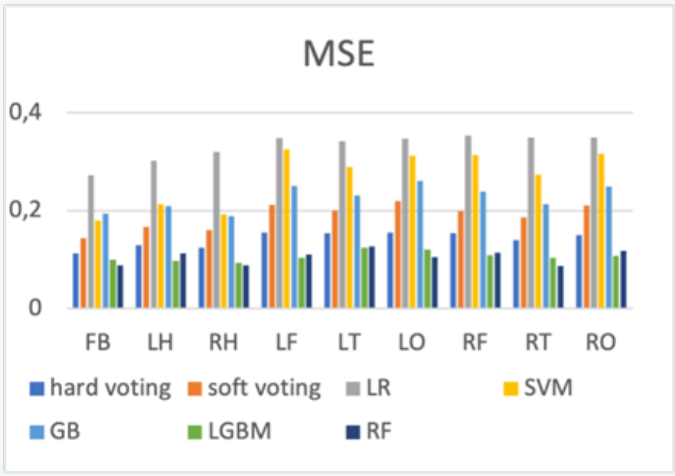
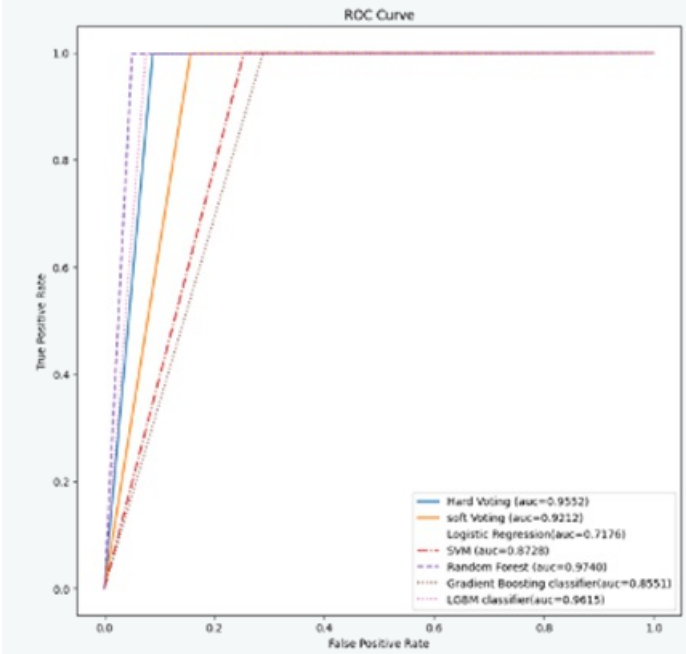


Table 2 Implementation time.

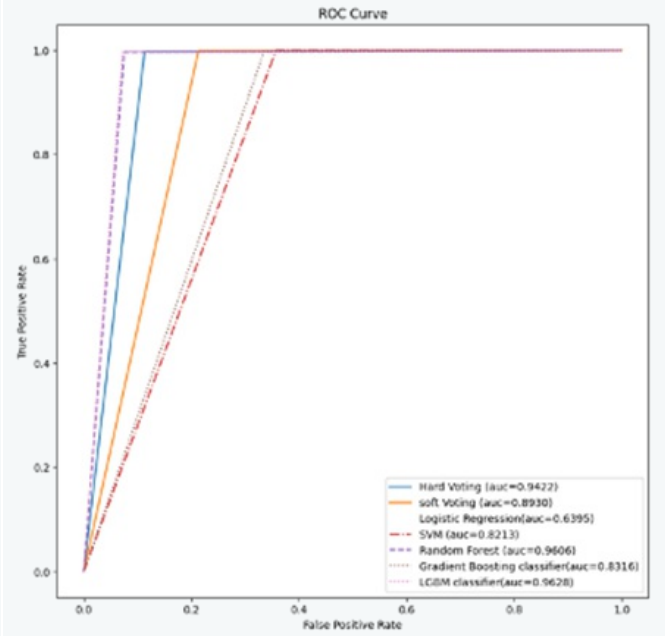
	FB	LH	RH	LF	LT	LO	RF	RT	RO
hard voting	5.5871	2.767	2.6854	1.4475	1.6323	1.492	1.4643	1.4356	2.3205
soft voting	5.6782	2.5382	2.5947	1.3643	1.4542	1.3681	1.3608	1.4852	2.9106
LR	0.4875	0.4243	0.3703	0.1563	0.1528	0.1872	0.1556	0.192	0.1374
SVM	2.2846	2.2941	2.1608	2.473	2.1793	2.6697	2.4271	1.9177	3.3719
GB	0.362	0.2812	0.279	0.275	0.3259	0.269	0.2738	0.2597	0.4214
LGBM	2.5294	1.0677	1.1097	0.4787	0.4889	0.4574	0.4854	0.4888	1.4723
RF	0.6788	0.538	0.5108	0.4314	0.4063	0.4831	0.4028	0.3844	0.45

Table 3 contains the ROC curves and AUC values for the used ML models.

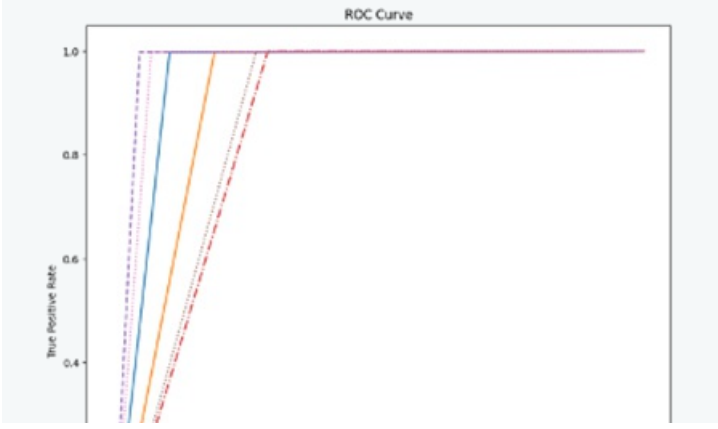
Table3. ROC Curves and AUC for the Used Supervised ML.

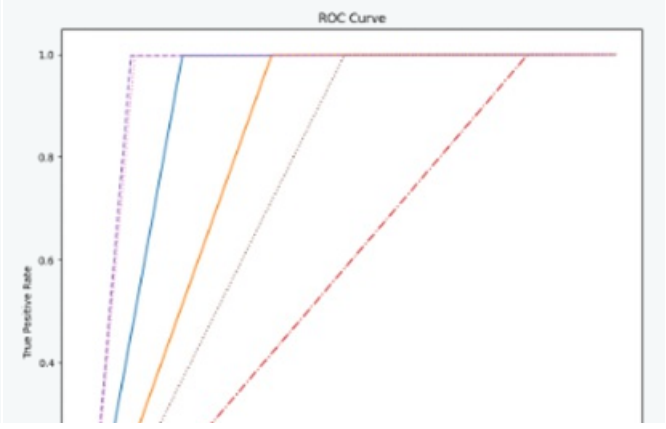


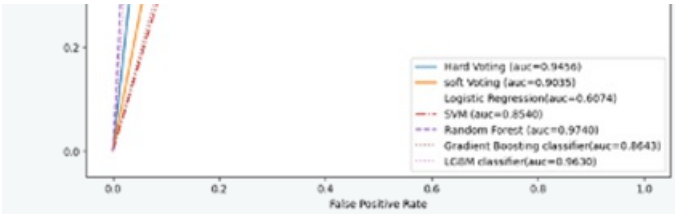
a. FB



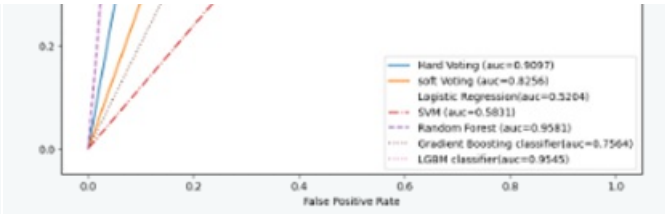
b. LH



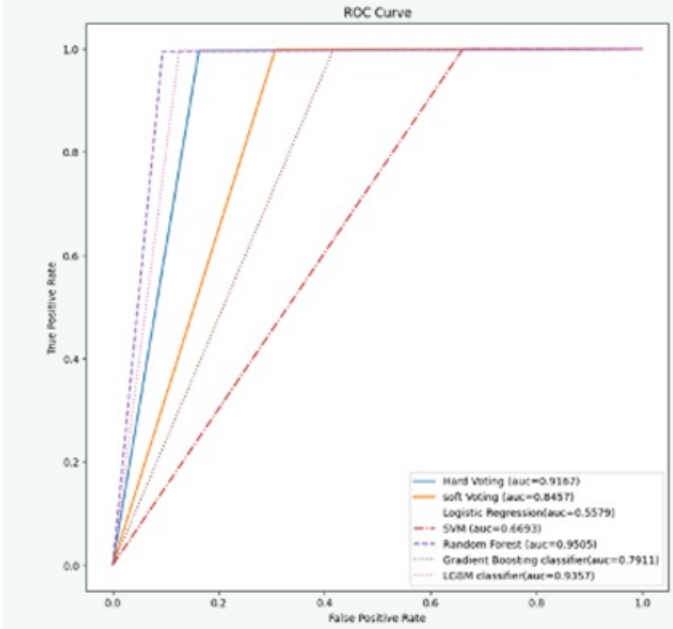




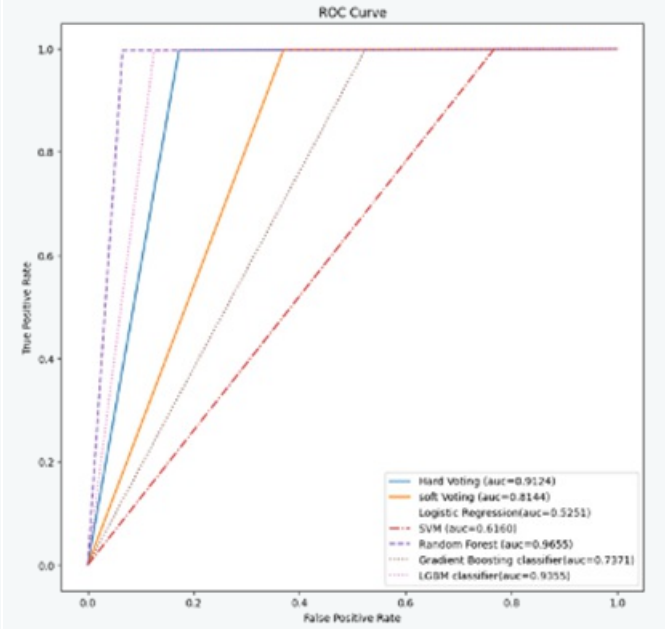
c. RH



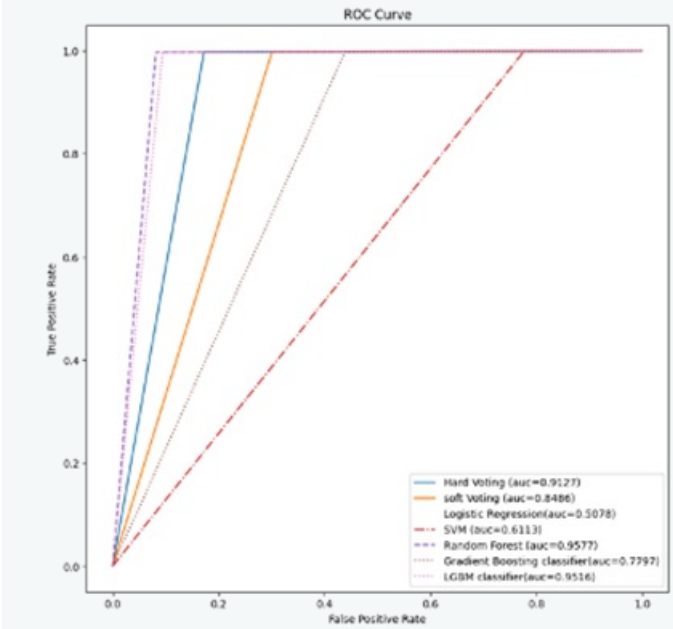
d. LF



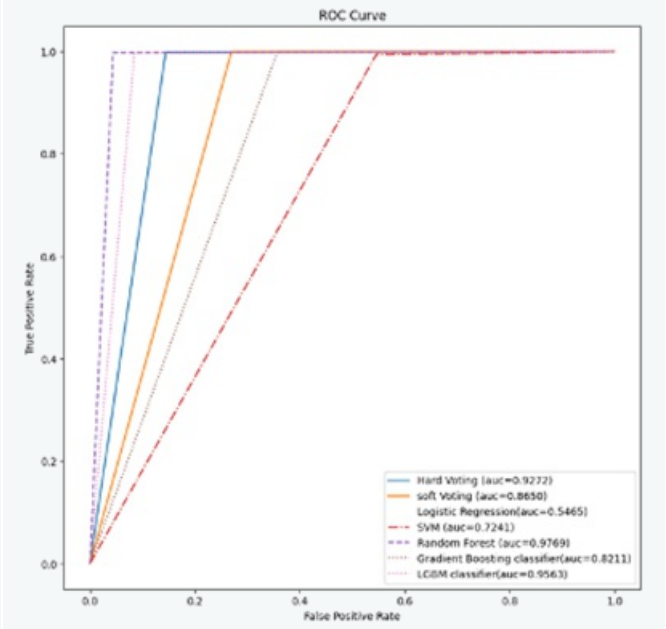
e. LT



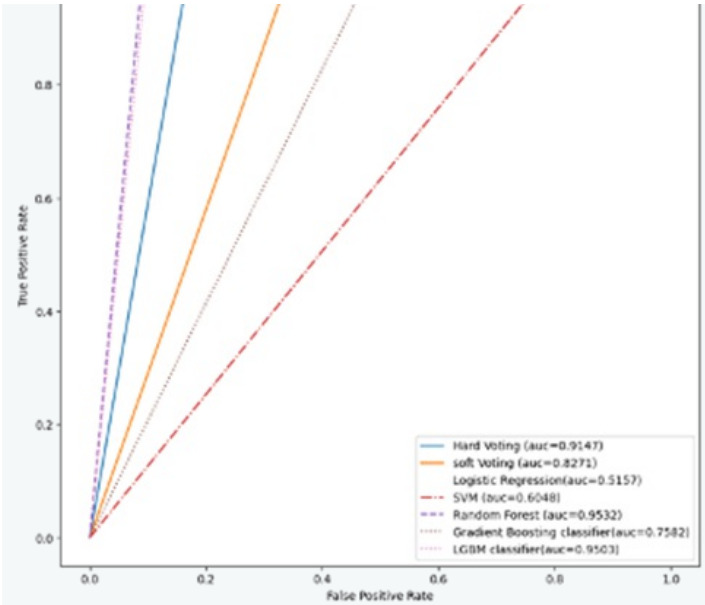
f. LO



g. RF



h. RT



i. RO

For the validation results, the bar chart in Figure 2 shows the percentage of the dyslexic cases that were classified as TDC after the neurofeedback procedure from the sessions of 21 to 100.

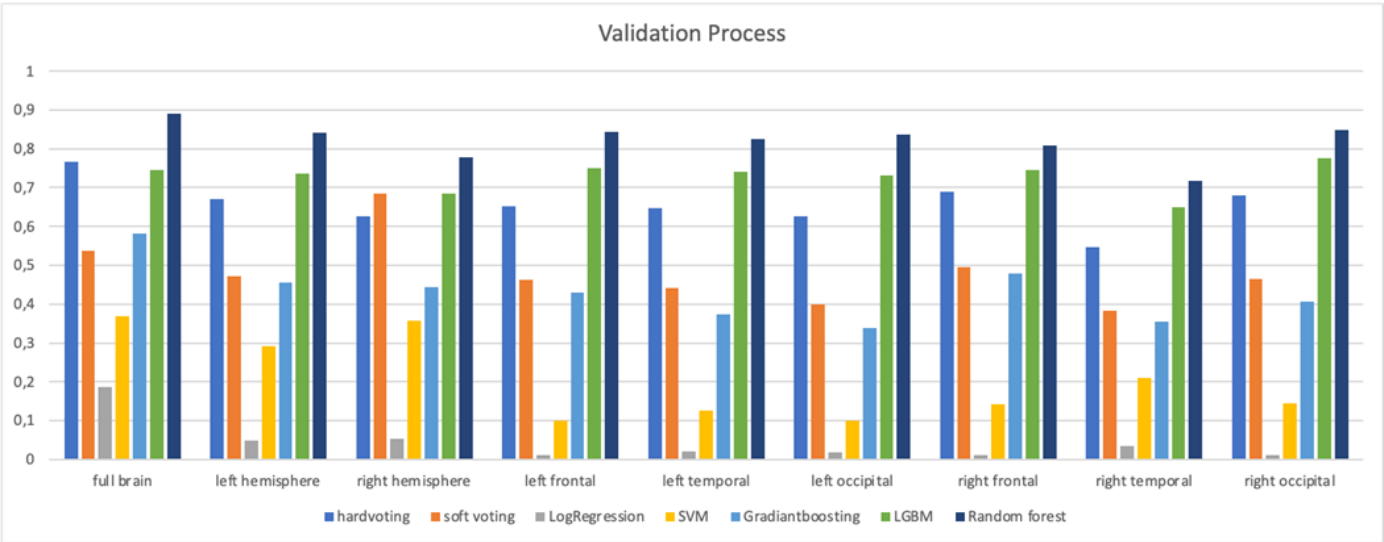


Figure 2. The Validation Process of the Supervised ML Models.

4. Discussion

The novelty of this research is that the dyslexia biomarker detection software was used to assess the efficacy of 14-

channel neurofeedback with Auto Train Brain.

In prior research, the efficacy of the 14-channel neurofeedback with Auto Train Brain was measured using the pre- and post- TILLS tests and multi-scale entropy (Eroglu, 2021). The reading speed of the experimental group was increased from 38 to 65 and TILLS descriptive point was increased from 20.25 to 24.12 in the clinical trial (Eroglu, 2020). The experiment group's reading comprehension was increased after 60 sessions. For the experimental group, the simple effect of time in the subtests of reading comprehension [$F_{(1, 14)} = 4.98$, p=.042] was statistically significant. Post-hoc tests indicated that Auto Train Brain training improved reading comprehension statistically significantly more than that of special education. The experimental group progressed from $m = 3.06$ ($SD = 4.22$) to 5.20 ($SD = 4.41$), a 70% improvement, whereas the control group regressed from $m = 7.12$ ($SD = 3.18$) to $m = 6.36$ ($SD = 4.22$), a -10% improvement (Eroglu, 2020).

It is commonly known that neurofeedback can minimize the symptoms of dyslexia. EEG data is read in real-time and displayed to the subject. Through operant conditioning, the patient gains better mental control (Ninaus et al., 2015). It has been shown that as a user learns to control a certain area of the brain, this phenomenon may change and establish weak connections that help the person pay attention and learn better (Niv, 2013). Neurofeedback is a "possibly efficacious" method, per APA recommendations (Melnikov, 2021). It is challenging to demonstrate the usefulness of neurofeedback. Clinical trials have often been carried out to show improvements between the pre- and post-experiment psychometric testing. Numerous studies have shown that neurofeedback enhances brain structure (Wing, 2001). After an hour of NFB training, participants displayed enhanced fractional anisotropy (FA) in the corpus callosum and better functional connectivity of the sensorimotor resting state network. Additionally, the default network configuration showed a more functioning connection (Marins et al., 2018). In this study, fMRI is commonly used to show the tightly associated brain areas after neurofeedback. It is difficult to use QEEG to show changes in the brain after neurofeedback. There is evidence linking neurofeedback to an improvement in cognitive function (Canolty et al., 2006; Lubar et al., 1976; Mayoral Rodrigez et al., 2022; Terrasa et al., 2020).

In this research, we developed a dyslexia biomarker detection software that classifies children with dyslexia and TDC with high accuracy. Then, we applied the software to the QEEG data read during the resting state in the latter neurofeedback sessions. We have checked whether they are classified as children with dyslexia or TDC. The results have shown that 30% of the sessions of children with dyslexia were classified as electrophysiologically normal, and 61% of the children with dyslexia were classified as electrophysiologically normal for at least 1 session after the 20th session of neurofeedback.

In 100 sessions of neurofeedback, these results are very promising and have correlations with what we have found in the clinical trial.

In the future, we will further develop ML models to make different types of classifications that determine the level of dyslexia, instead of the binary classification of dyslexia and TDC. In this way, we will have a chance to show that people who are still classified as dyslexic after neurofeedback have a positive improvement in their dyslexia symptoms.

4.1. Limitations of the Study

The first limitation of the study, we used repeated measures from the same subjects to collect QEEG data from each session. The second limitation of the study is the possibility of placebo effects. According to Gaab et al.(2019), children who receive individualized attention and specialized therapies may improve their functioning primarily as a result of the social and environmental effects of those interventions. The maturation effects are the third limitation of the study. All children's brains change significantly as they grow. Therefore, it is anticipated that maturation will have an impact on QEEG changes over the next six months.

5. Conclusions

Machine learning techniques might offer fresh perspectives on the dyslexia training process. In this study, we developed a classification system for diagnosing dyslexia based on Z-scores produced from QEEG data and ANN and we have applied it to measure the efficacy of the neurofeedback.

Declarations

Ethics approval and consent to participate

All of the participants provided their informed consent after the research ethics committee explained the experimental procedure to them, the Yeditepe University ethics committee approved the study protocol, and the clinical trial was registered with the Turkey Pharmaceuticals and Medical Devices Agency (Nbr: 71146310-511.06,2.11.2018).

Availability of data and material

The corresponding author will provide the datasets produced and/or analyzed during the current work upon reasonable request.

Code availability

None.

Competing interests

None

Funding

None

Authors' contributions

The title, abstract, introduction, materials and techniques, findings, and discussion of the main manuscript text were all written by G.E. who also created the charts and tables.

M.R.A.H. enhanced the introduction in relation to the ML techniques, tools, and approaches and written results section. M.R.A.H. created the tables and graphics.

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References

- Alex, F., & Larry, M. M. (2018). Features and Machine Learning for Correlating and Classifying between Brain Areas and Dyslexia. *ArXiv Preprint ArXiv:1812.10622*.
- American Psychiatric Association. (2013). Anxiety disorders. In Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780896425596.dsm05
- Arns, M., Peters, S., Breteler, R., & Verhoeven, L. (2007). Different brain activation patterns in dyslexic children: evidence from EEG power and coherence patterns for the double-deficit theory of dyslexia. *Journal of integrative neuroscience*, *6*(01), 175-190.
- Badcock, N. A., Mousikou, P., Mahajan, Y., De Lissa, P., Thie, J., & McArthur, G. (2013). Validation of the Emotiv EPOC® EEG gaming system for measuring research quality auditory ERPs. *PeerJ*, *1*, e38.
- Bednarek, D. B., Saldaña, D., Quintero-Gallego, E., García, I., Grabowska, A., & Gómez, C. M. (2004). Attentional deficit in dyslexia: a general or specific impairment?. *Neuroreport*, *15*(11), 1787-1790.
- Bellocchi, S., Muneaux, M., Bastien-Toniazzo, M., & Ducrot, S. (2013). I can read it in your eyes: What eye movements tell us about visuo-attentional processes in developmental dyslexia. *Research in developmental disabilities*, *34*(1), 452-460.
- Benfatto, M., Öqvist Seimyr, G., Ygge, J., Pansell, T., Rydberg, A., & Jacobson, C. (2016). Screening for dyslexia using eye tracking during reading. *PloS one*, *11*(12), e0165508.
- Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT (2006). High gamma power is phase-locked to theta oscillations in human neocortex. Science. 2006 Sep 15;313(5793):1626-8. doi: 10.1126/science.1128115.

- Dunn, L. M., & Dunn, L. M. (1965). Peabody picture vocabulary test--.
- D'Souza, S., Backhouse-Smith, A., Thompson, J. M., Slykerman, R., Marlow, G., Wall, C., ... & Waldie,
- K. E. (2016). Associations between the KIAA0319 dyslexia susceptibility gene variants, antenatal maternal stress, and reading ability in a longitudinal birth cohort. *Dyslexia*, *22*(4), 379-393.
- Eden, G. F., VanMeter, J. W., Rumsey, J. M., Maisog, J. M., Woods, R. P., & Zeffiro, T. A. (1996).
- Abnormal processing of visual motion in dyslexia revealed by functional brain imaging.*Nature*, *382*(6586), 66-69.
- Eroğlu, G., Gürkan, M., Teber, S., Ertürk, K., Kırmızı, M., Ekici, B., ... &Çetin, M. (2020). Changes in EEG complexity with neurofeedback and multi-sensory learning in children with dyslexia: A multiscale entropy analysis. *Applied Neuropsychology: Child*, 1-12.
- Eroğlu, G., Teber, S., Ertürk, K., Kırmızı, M., Ekici, B., Arman, F., ... &Çetin, M. (2021). A mobile app that uses neurofeedback and multi-sensory learning methods improves reading abilities in dyslexia: A pilot study. *Applied Neuropsychology: Child*, 1-11.
- Eroğlu Günet (2022). Auto Train Brain increases the variance of the gamma band sample entropy in the left hemisphere in dyslexia: A pilot study. WORLD S4 2022 (Tam Metin Bildiri/Sözlü Sunum)(Yayın No:7773551)
-
- Francks, C., MacPhie, I. L., & Monaco, A. P. (2002). The genetic basis of dyslexia.*The Lancet Neurology*, *1*(8), 483-490.
- Fraga González, G., Smit, D. J., Van der Molen, M. J., Tijms, J., Stam, C. J., De Geus, E. J., & Van der Molen, M. W. (2018). EEG resting state functional connectivity in adult dyslexics using phase lag index and graph analysis. *Frontiers in human neuroscience*, *12*, 341.
- Formoso, M. A., Ortiz, A., Martinez-Murcia, F. J., Gallego, N., & Luque, J. L. (2021). Detecting Phase-Synchrony Connectivity Anomalies in EEG Signals. Application to Dyslexia Diagnosis. *Sensors*, *21*(21), 7061. https://doi.org/10.3390/s21217061
- Formoso, M. A., Ortiz, A., Martínez-Murcia, F. J., Gallego-Molina, N., & Luque, J. L. (2021).*Modelling Brain Connectivity Networks by Graph Embedding for Dyslexia Diagnosis*.
- Gaab, J., Kossowsky, J., Ehlert, U., &Locher, C." Effects and components of placebos with a psychological treatment rationale–three randomized-controlled studies". Scientific reports, 9(1) ((2019): 1-8.
- Gallego-Molina, N. J., Ortiz, A., Martínez-Murcia, F. J., Formoso, M. A., & Giménez, A. (2022). Complex network modeling of EEG band coupling in dyslexia: An exploratory analysis of auditory processing and diagnosis. *Knowledge-Based Systems*, *240*, 108098. https://doi.org/10.1016/j.knosys.2021.108098
- García Chimeno, Y., Garcia Zapirain, B., Saralegui Prieto, I., & Fernandez-Ruanova, B. (2014). Automatic classification of dyslexic children by applying machine learning to fMRI images. *Bio-medical materials and engineering*, *24*(6), 2995-3002.
- Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences*, *95*(15), 8939-8944.
- Karim, I., Abdul, W., & Kamaruddin, N. (2013, March). Classification of dyslexic and normal children during resting condition using KDE and MLP. In *2013 5th International Conference on Information and Communication Technology for*

the Muslim World (ICT4M) (pp. 1-5). IEEE.

- Kaufman, A. S. (1994). *Intelligent testing with the WISC-III* John Wiley & Sons.
- Kershner, J. R. (2019). Neurobiological systems in dyslexia. Trends in neuroscience and education, 14, 11-24.
- Kershner, J. R. (2020). Neuroscience and education: cerebral lateralization of networks and oscillations in dyslexia. *Laterality*, *25*(1), 109-125.
- Kershner, J. R. (2020). Dyslexia as an adaptation to cortico-limbic stress system reactivity. Neurobiology of Stress, 12, 100223.
- Kershner, J. R. (2021). Multisensory deficits in dyslexia may result from a locus coeruleus attentional network dysfunction. Neuropsychologia, 161, 108023.
- Kheyrkhah Shali, R., & Setarehdan, S. K. (2020). The Effective Brain Areas in Recognition of Dyslexia*International Clinical Neuroscience Journal*, *7*(3), 147–152. https://doi.org/10.34172/icnj.2020.16
- Klimesch, W., Doppelmayr, M., Wimmer, H., Gruber, W., Röhm, D., Schwaiger, J., &Hutzler, F. (2001). Alpha and beta band power changes in normal and dyslexic children. *Clinical Neurophysiology*, *112*(7), 1186-1195.
- Klimesch, W., Doppelmayr, M., Yonelinas, A., Kroll, N. E., Lazzara, M., Röhm, D., & Gruber, W. (2001). Theta synchronization during episodic retrieval: neural correlates of conscious awareness. *Cognitive Brain Research*, *12*(1), 33-38.
- Kraus, N. (2012). Atypical brain oscillations: a biological basis for dyslexia. *Trends in cognitive sciences*, *16*(1), 12-13.
- Lassus-Sangosse, D., N'guyen-Morel, M. A., & Valdois, S. (2008). Sequential or simultaneous visual processing deficit in developmental dyslexia?. *Vision Research*, *48*(8), 979-988.
- Lubar, J.F., Shouse, M.N. EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR). Biofeedback and Self-Regulation 1, 293–306 (1976). https://doi.org/10.1007/BF01001170
- Marins, T., Rodrigues, E. C., Bortolini, T., Melo, B., Moll, J., & Tovar-Moll, F. (2019). Structural and functional connectivity changes in response to short-term neurofeedback training with motor
- McDougall, S., Hulme, C., Ellis, A., & Monk, A. (1994). Learning to read: The role of short-term memory and phonological skills. *Journal of experimental child psychology*, *58*(1), 112-133.
- Melnikov, M. Y. (2021). The current evidence levels for biofeedback and neurofeedback interventions in treating depression: A narrative review. *Neural Plasticity*.
- Nelson, N. W., Plante, E., Helm-Estabrooks, N., & Hotz, G. (2016). Test of integrated language and literacy skills (TILLS). *Baltimore, MD: Brookes*.
- Ninaus, M., Witte, M., Kober, S.E., Friedrich, E.V., Kurzmann, J., Hartsuiker, E., Neuper, C., & Wood, G. (2015). Neurofeedback and Serious Games. In me. Management Association (Ed.), *Gamification: Concepts, Methodologies, Tools, and Applications* (pp. 83-112). Hershey, PA: IGI Global. doi:10.4018/978-1-4666-8200-9.ch005
- Niv, S. (2013). Clinical efficacy and potential mechanisms of neurofeedback. *Personality and Individual Differences, 54*(6), 676-686. doi:10.1016/j.paid.2012.11.037
- Ortiz, A., Martinez-Murcia, F. J., Luque, J. L., Giménez, A., Morales-Ortega, R., & Ortega, J. (2020). Dyslexia Diagnosis by EEG Temporal and Spectral Descriptors: An Anomaly Detection Approach. *International Journal of Neural Systems*, *30*(07), 2050029. https://doi.org/10.1142/S012906572050029X

- Rezvani, Z., Zare, M., Žarić, G., Bonte, M., Tijms, J., van der Molen, M. W., & raga González, G. (2019). Machine learning Classification of Dyslexic Children based on EEG Local Network Features. *BioRxiv, 569996*.
- Richardson, A. J. (2004). Long-chain polyunsaturated fatty acids in childhood developmental and psychiatric disorders. *Lipids*, *39*(12), 1215-1222.
- Rippon, G., & Brunswick, N. (2000). Trait and state EEG indices of information processing in developmental dyslexia. *International Journal of Psychophysiology*, *36*(3), 251-265.
- Rubinsten, O., & Henik, A. (2006). Double dissociation of functions in developmental dyslexia and dyscalculia.*Journal of Educational Psychology*, *98*(4), 854.
- Schulte-Körne, G., & Bruder, J. (2010). Clinical neurophysiology of visual and auditory processing in dyslexia: a review. *Clinical neurophysiology*, *121*(11), 1794-1809.
- Siegel, L. S. (1988). Evidence that IQ scores are irrelevant to the definition and analysis of reading disability.*Canadian Journal of Psychology/Revue canadienne de psychologie*, *42*(2), 201.
- Terrasa, J.L.; Barros-Loscertales, A.; Montoya, P. & Muñoz, M. A. (2020). «Self-Regulation of SMR Power Led to an Enhancement of Functional Connectivity of Somatomotor Cortices in Fibromyalgia Patients». Frontiers in Neuroscience. 14:236. doi: 10.3389/fnins.2020.00236
- Thornton, K. E., & Carmody, D. P. (2005). Electroencephalogram biofeedback for reading disability and traumatic brain injury. *Child and Adolescent Psychiatric Clinics*, *14*(1), 137-162.
- Van Bergen, E., De Jong, P. F., Plakas, A., Maassen, B., & van der Leij, A. (2012). Child and parental literacy levels within families with a history of dyslexia. *Journal of Child Psychology and Psychiatry*, *53*(1), 28-36.
- Wechsler, D. (1999). Wechsler abbreviated scale of intelligence--.
- Yılmaz, S., & Akyüz, F. (2021).The relationship between speech difficulties and brain laterality in Attention Deficit Hyperactivity Disorder and Specific Learning Disorder. *Acta Medica Alanya*, *5*(3), 250-256.
- Zainuddin, A. and L., Khuan Y and Mansor, W., & Mahmoodin, Z. (2016). Optimized KNN classify rule for EEG based differentiation between capable dyslexic and normal children. *2016 IEEE EMBS Conference on Biomedical Engineering and Sciences (IECBES)*, 685–688.
- Zainuddin, A., Mansor, W., Y. Lee, K., & Mahmoodin, Z. (2018). Performance of Support Vector Machine in Classifying EEG Signal of Dyslexic Children using RBF Kernel. *Indonesian Journal of Electrical Engineering and Computer Science*, *9*(2), 403. https://doi.org/10.11591/ijeecs.v9.i2.pp403-409
- Zainuddin, A. Z. A., Mansor, W., Lee, K. Y., & Mahmoodin, Z. (2019). Comparison of Extreme Learning Machine and K-Nearest Neighbour Performance in Classifying EEG Signal of Normal, Poor and Capable Dyslexic Children. *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 4513–4516. https://doi.org/10.1109/EMBC.2019.8857569