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Research Article

Artificial Intelligence Applications for Diagnosis and Differentiation of Vestibular Disorders

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Abstract

Objective: The objective of this work lies in leveraging recent advances in Artificial Intelligence to enhance the diagnosis and treatment of vestibular disorders, crucially improving patients' conditions and their overall quality of life.

Methods: In this study, a Machine Learning algorithm was used to differentiate between four vestibular disorders considering an anamnestic questionnaire administered by the practitioner.

Results: The high diagnosis accuracy achieved by our algorithm shows its reliability in treating patients with vestibular disorders. For instance, our algorithm could help general practitioners optimize the diagnosis and management of patients with symptoms such as vertigo.

Conclusion: The results of this work highlight the potential of using machine learning algorithms to support the diagnosis of vestibular disorders, improving patients' management and, eventually, their quality of life.

Keywords: Artificial Intelligence (AI); General practitioners; Machine learning algorithms; Vertigo; Vestibular disorders

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Introduction

Vestibular disorders impact the inner ear's balance system, leading to symptoms like vertigo and imbalance [1]. Common examples include Meniere's Disease (MD) [2], Benign Positioning Paroxysmal Vertigo (BPPV) [3], Acute Vestibular Deficit (AVD) [4], and Vestibular Migraine (VM) [5]. These disorders can result in various symptoms, including vertigo, dizziness, imbalance, nausea, and difficulty with concentration or vision. Vestibular disorders stem from various causes, including infections, head injuries, autoimmune disorders, and medication side effects [6]. Accurate diagnosis and treatment are vital for symptom management and improved quality of life [7]. However, the complexity of symptoms makes it challenging for healthcare professionals, particularly those without expertise in this field. In this context, the application of Artificial Intelligence (AI) algorithms could provide significant aid for the differential diagnosis of these disorders. AI is a field of computer science that includes algorithms that can perform tasks that usually require human intelligence, such as recognizing speech, making decisions, and learning from experience [8]. Machine Learning (ML) is a subset of AI that involves training computer systems to automatically learn and improve from experience without being explicitly programmed [9]. ML aims to enable machines to learn from data, recognize patterns, and use those patterns to make predictions or decisions about new data. In the last few years, computers have learned to execute very challenging tasks using ML. Nowadays, ML has many practical applications in healthcare, finance, transportation, and entertainment, among others. For instance, using these algorithms has made it possible to improve diagnosis and support and optimize clinical decision-making [10,11]. In the context of the diagnosis of vestibular disorders, two recent works [12,13], have provided insights into the current state of the art. In vestibology, several AI-based expert systems for differential diagnosis have been designed to emulate the decision-making ability of a human expert. In these cases, the expert designs how the machines should process the data, for instance, to diagnose the different disorders that affect each one of the patients. The first example of this application, published in 1990 by Mira et al. [14], aimed to study the feasibility and potential utility of expert systems in assisting with the diagnosis of patients with neuro-otological disorders. For several years, most efforts have been devoted to the implementation of such algorithms, with several limitations. For instance, expert systems cannot learn new information from data, and thus their power is limited by the expert's knowledge that designed those algorithms. In the subsequent years, Kentala et al. [15], realized other neuro-otological expert systems.

The dataset used to evaluate the performances of the algorithms consisted of 170 variables related to the patient's symptoms, medical history, comorbidities, and vestibular, audiology, and imaging test findings. Then, several adaptive algorithms, i.e., algorithms that could learn directly from data overcoming the expert systems' characteristic drawbacks, were designed, and trained on this dataset, e.g. [16,17]. More recently, new datasets, such as the DizzyReg [18], have been collected. DizzyReg is a contemporary clinical registry encompassing data on patients with vertigo and dizziness; it includes information such as anamnestic and sociodemographic details, duration and type of vertigo, neurological examination findings, and audio vestibular and video head impulse test results, resulting in over 300 variables. In this paper, on the contrary, we study a very simple dataset, collected using a pactitioner-administrated anamnestic questionnaire comprising 27 questions for patients to answer. The simplicity of the data that we considered is crucial for our goal. Indeed, our aim was to create an algorithm that could help primary care physicians better manage patients with dizziness and vertigo. In fact, anamnestic variables are, at the same time, crucial information for the differential diagnosis of vestibular disorders and variables that are easy to obtain, as the patients themselves provide them and do not need special equipment to be collected. Starting from this information, we trained an algorithm to differentiate between the four most frequent vestibular disorders (MD, BPPV, AVD, and VM), diagnosing the pathology that affects each patient in the dataset. In addition, we applied dimensionality reduction techniques to visualize the dataset optimally, aiming to identify possible clusters. Furthermore, we identified a minimal set of three critical questions to be considered as they can provide important clues for the diagnosis. Finally, we evaluated the diagnostic accuracy obtained by considering only those three crucial questions.

Materials and Methods

Dataset

The dataset analyzed for the study of vestibular disorders was collected in the Unit of Oncological Surgery (UOC) of Ear, Nose, and Throat (ENT) and Cervico-Facial Surgery of the "Ospedale del Mare" and in the ENT and Maxillofacial Surgery Department of the "Spaziani Hospital" in Frosinone where an anamnestic questionnaire of 27 questions was administered to 80 patients affected by one of the following disorders: MD, BPPV, AVD, or VM. The questions used are shown in table 1. These questions are related to the most frequent symptoms that allow an optimal characterization and distinction between the four vestibular disorders. In designing this dataset, we considered that in vestibology, the symptoms reported by the patients are the most important information for differential diagnosis. Moreover, given the simplicity of the questionnaire, our algorithm can be used by healthcare professionals, such as general practitioners, who cannot submit specific and advanced medical exams to patients.

Questions Considered in the Anamnestic Questionnaire
Do you feel dizzy: is the environment moving?
Do you feel dizzy: are you the one who is moving?
Do you have problems with equilibrium?
Does the vertigo last less than one minute?
Does vertigo arise when lying in bed?
Is vertigo generated by flexion and extension movements of the head/chest?
La vertigine è generata da movimenti di flessione ed estensione del capo/busto?
Is vertigo spontaneous?
Does the dizziness last at least 5 minutes to a maximum of 72 hours?
Does the dizziness last at least 20 minutes to a maximum of 24 hours?
Does spontaneous vertigo get worse with head movements?
Does spontaneous vertigo get worse with decubitus on the right side?
Does spontaneous vertigo get worse with decubitus on the left side?
Do you sweat, have nausea, or have to vomit during dizziness?
Did the disorder occur only once?
Do you have difficulty hearing on the right?
Do you have difficulty hearing on the left?
Do you hear a noise in your right ear?
Do you hear a noise in your left ear?
Do you feel pressure or a sensation of fullness in the right ear?
Do you feel pressure or a sensation of fullness in the right ear?
Did these symptoms appear long before vertigo appeared?
Do these symptoms worsen before vertigo and improve afterward?
In the past, did these symptoms worsen before vertigo and improve afterward?
Do you suffer from migraine diagnosed by a neurologist?
Are dizziness and imbalance often associated with migraine?
Does spontaneous vertigo last for many hours?

Table 1: Anamnestic questions whose answers were used as variables to describe patients in our dataset.

Dimensionality Reduction Techniques

The dataset was initially analysed using dimensionality reduction techniques, such as PCA (Principal Component Analysis) and t-SNE (t-distributed Stochastic Neighbor Embedding), in such a way to visualize data in a two-dimensional space, possibly finding some clusters, i.e., groups of similar elements. The idea behind dimensionality reduction techniques, such as PCA and t-SNE, basically consists of defining new variables that reduce the size with which elements within a dataset are described while minimizing information loss.

Specifically, PCA does this by finding the directions in which the data varies the most, called principal components, and projecting the data onto these components [19]. Those principal components will be defined as linear applications of the original variables and will allow to assess which variables separate the most the identified clusters of patients.

t-SNE (t-Distributed Stochastic Neighbour Embedding), instead, reduces the dimensionality of a dataset by identifying patterns and similarities in the data and grouping similar points in the lower-dimensional space [20]. In contrast to PCA, t-SNE applies nonlinear transformations to the original variables mapping multidimensional data into a reduced dimensionality space with the aim of preserving the local structure. This means that objects that are close in the original space turn out to be close in the reduced dimensionality space, and objects that are far away turn out to be far away. This results in an algorithm that, compared to PCA, can make it easier to understand complex data and identify relationships or clusters. However, in contrast to PCA, t-SNE does not identify a convenient set of variables that allows an optimal dispersion of the data.

Classification Algorithms

Moreover, we used SVM (Support Vector Machine) classifier as a supervised learning algorithm to realize an automatic diagnostic

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system of patients' disorders starting from the anamnestic questionnaire defined above. SVM is an ML algorithm whose target is to find a boundary that separates two or more groups of data points as clearly as possible [21]. In cases of complex datasets with multiple classes and nonlinear relationships, a mapping of the dataset into a higher dimensional feature space, where patients are described by a higher number of convenient and automatically found variables, is performed. This higher feature space makes the events linearly separable so that the classes can be separated using a hyperplane, i.e. a multi-dimensional linear boundary. Once this boundary has been identified, new patients can be classified into one class, associating each patient with a specific disorder.

To find the boundary, i.e. to train the SVM classifier, we split the dataset into a training set, accounting for 80% of the patients, and test counting for the remaining 20%. The training set was initially used to tune the classifiers' parameters using k-fold cross-validation [22]. In k-fold cross-validation, the dataset is divided into k subsets, or "folds", of equal size. A high number of these folds, k-1, are used for training, while the remaining fold is used for testing. This process is repeated k times, with each fold used for testing exactly once. The results of each iteration are then averaged to provide an overall estimate of the model's performance. In this way, we evaluated the performance of different SVM models characterized by different parameters, choosing the best-performing one. Then, we used all the training set to train the model and the test set to evaluate its performance. Following this procedure, we trained two different models. The first exploits all the 27 anamnestic questions to associate each patient with a specific disorder. The second, instead, uses only the three most relevant questions to provide the diagnosis.

To identify this set of three critical questions, we first checked for eventual highly correlated questions excluding them to avoid multicollinearity issues [23]. Then, we used another classification model, the ExtraTreesClassifier [24], to assign a value of importance to each of the questions left. The ExtraTreesClassifier is a machine-learning algorithm that uses an ensemble of decision trees [25] to make predictions about new data. To create each decision tree, the algorithm randomly selects a subset of the available data and a subset of the features. At each node of the tree, the algorithm selects the feature that separates in the clearest manner the data into different classes. After building all the decision trees, the algorithm looks at which features were used the most frequently for splitting the data. These frequently used features are considered the most important for predicting the outcome. This approach is particularly useful in decreasing the influence that the choice of the model has on the results. Therefore, the resulting feature importance scores are more reflective of the true intrinsic importance of the features.

All the analyses were conducted by means of Python 3.11 scripts.

Results

The results obtained through the two-dimensionality reduction techniques, PCA and t-SNE, show that the MD and BPPV patients form two distinct and recognizable clusters. In contrast, the AVD and VM classes appear similar, blending into each other as if they belonged to a single cluster (Figure 1).

As shown in the PCA graph, the first principal component defined by PCA, i.e. "pca-one", allows separating patients affected by BPPV with respect to all the others. In these terms, the most important

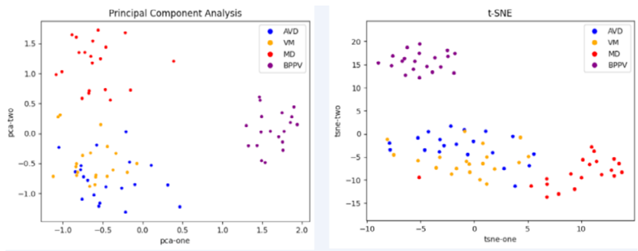

Figure 1: In the two figures, we can observe the results of the application of PCA (Principal Component Analysis) and t-SNE (t-distributed Stochastic Neighbor Embedding). Each point corresponds to a different patient, and each color to a different disorder. We can observe how the BPPV (Benign Positioning Paroxysmal Vertigo) and MD (Meniere's Disease) classes, in yellow and orange, respectively, give rise to two distinct clusters, while the AVD (Acute Vestibular Deficit) and VM (Vestibular Migraine) classes, in blue and purple, respectively, blur together more.

variables to distinguish between BPPV patients and all the others are the duration of vertigo, that do not last for many hours in BPPV patients, the occurrence of vertigo when the patient lies down, turns, or moves the head, and the absence of spontaneous vertigo in patients affected by BPPV.

The same can be said regarding the second principal component, PCA-two, that allows separating MD patients from AVD and VM patients. In this case, MD patients are characterized by the lower occurrence of subjective vertigo, by the duration of vertigo, that typically ranges between 20 minutes and 24 hours, and by the typical worsening of patients' conditions before vertigo and improving afterward.

We represented the data according to the third, fourth, and fifth principal components, but none of them was able to distinguish between AVD and VM patients. So, we applied PCA only to the patients of our dataset affected by these two disorders, obtaining the graph represented in figure 2.

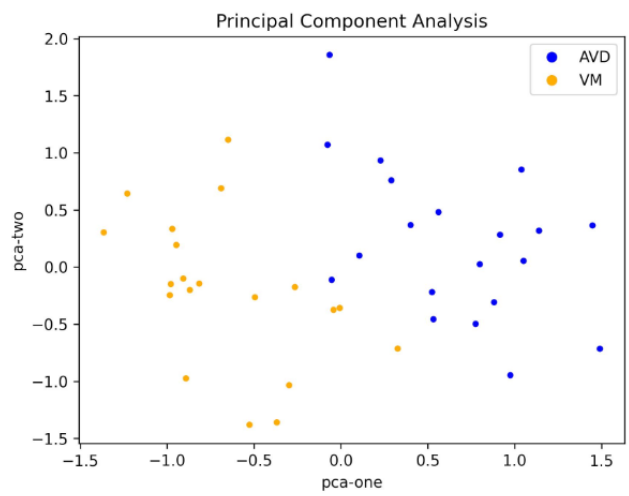

Figure 2: In the figure, the result of the application of PCA on the portion of our dataset, including only MD (Meniere's Disease) and AVD (Acute Vestibular Deficit) patients. We can see that, in this case, the algorithm allows a linear separation of the two classes.

In this case, we succeeded in disentangling the two classes. For this purpose, the most important variables are the co-occurrence of vertigo, disequilibrium, and migraine, together with the presence of migraine diagnosed by a neurologist, both symptoms that occur way more often in VM patients than in AVD ones. Also, other important variables are the number of times the symptoms have occurred, once for AVD patients, several for VM patients, and sweating, nausea, and vomiting that occur way more often in AVD patients than in VM ones. Then, we trained the SVM classifier to recognize the vestibular disorder that affects each of the patients in our dataset, taking into consideration the 26 anamnestic variables considered. The performance obtained is shown in table 2 by means of a confusion matrix where the predicted classes, represented on the different columns, are compared with the true classes, represented by the different rows.

True \ Predicted	AVD	VM	MD	BPPV
AVD	0.95	0.05	0	0
VM	0.09	0.91	0	0
MD	0	0	1	0
BPPV	0	0	0	1

Table 2: The table summarizes the performance of the SVM (Support Vector Machine) classifier in identifying the vestibular disorder that affects each patient. Each column indicates a different vestibular disorder predicted by the algorithm, each row the true disorder that affects each group of patients. For instance, 95% of the patients affected by AVD (Acute Vestibular Deficit) were diagnosed correctly, while the other 5% were diagnosed as if they were affected by VM (vestibular Migraine).

The model always successfully diagnoses the patients affected by MD and BPPV correctly, while it diagnoses AVD and VM successfully in more than 90% of the cases.

Then, we found a maximally predictive set of three questions using an Extra Tree Classifier, as explained in the section on the methods. The information identified as the most relevant are those provided by the patients answering the following questions: "Do the auditory symptoms worsen before vertigo and improve afterward?", "Are dizziness and imbalance often associated with migraine?", and "Does spontaneous vertigo last for many hours?". The classification performance obtained in this case is represented in table 3. On average, this model got a diagnostic accuracy of 88%.

True \ Predicted	AVD	VM	MD	BPPV
AVD	0.81	0.19	0	0
VM	0.04	0.96	0	0
MD	0	0.20	0.80	0
BPPV	0	0	0	1

Table 3: The table summarizes the performance of the SVM (Support Vector Machine) classifier in identifying the vestibular disorder that affects each patient. In this case, we considered just the most predictive set of 3 anamnestic questions. Again, each column represents a different predicted disorder while each row represents the actual disorder. In this case, 81% of the patients affected by AVD (Acute Vestibular Deficit) were diagnosed correctly, while the remaining 19% were diagnosed as if they were affected by VM (Vestibular Migraine).

Discussion

By means of the analyses performed, we succeeded in characterizing each of the four disorders taken into consideration, highlighting the differences between them through PCA. Also, we mapped patients in a bi-dimensional space through t-SNE to check whether they give rise to clusters of similar elements. In this way, we saw that BPPV patients gave rise to a very different cluster with respect to all the other patients. The same is true, even though less marked, for MD patients. Overall, these results confirm what has been experienced by the experts in daily practice. In fact, except for migraine and frequency of occurrence, the symptoms that patients with vestibular migraine and acute vestibular disorder show are way more similar than those shown by the other classes. The good description and distinction we obtain through PCA and t-SNE highlight the efficacy of our dataset's set of anamnestic questions to distinguish between the four disorders. Such a good dataset, despite its simplicity, allowed us to define a reliable predictor for identifying each patient's disorder. As a matter of fact, the very high performance of the first model, the one that takes into consideration all the 27 features, showed that the questions used to collect clinical data provided sufficient information to achieve good discrimination among the four diseases under consideration. Then, we identified the maximally predictive set of three variables that allow the distinction of patients in the four classes. The identified questions, i.e. "Do the auditory symptoms worsen before vertigo and improve afterward?", "Are dizziness and imbalance often associated with migraine?" and "Does spontaneous vertigo last for many hours?" are the most significant because they describe three distinctive features that allow us to discriminate the major groups of patients. The first question identifies the patients with Meniere disease, the second enables recognizing the ones with vestibular migraine, and the third discriminates between BPPV and AVD patients according to the duration of the symptoms. The performance of this second classification algorithm was lower than that of the first algorithm. This was expected since we removed 24 variables that the algorithm could use to classify patients. However, the performance obtained by this second algorithm (Table 3) was still unexpectedly high. This result suggests that by asking patients the set of 3 questions identified, we can correctly diagnose around 9 out of 10 patients with the above disorders. This justifies using just these variables in cases where collecting all 27 variables is unfeasible. We believe the results obtained in this work could be an important aid to general practitioners in dealing with patients with vertigo. Once confirmed on a larger dataset and in clinical practice, these results could draw important guidelines for the differential diagnosis and optimal management of patients affected by vestibular disorders.

Conclusion

In this work, we have analysed the potential of the application of AI in the context of the differential diagnosis of vestibular disorders (Figure 3). The results obtained show that ML algorithms could provide important aid to healthcare professionals and general practitioners in optimizing the patient's diagnosis and management. This is particularly crucial in vestibular disorders, where such a result could turn into an improvement in the patients' quality of life. The next step would include training and testing the algorithm on a larger dataset, possibly including also other vestibular disorders and healthy patients, as well as testing it in clinical practice. Also, as other works did, our goal was to highlight the power of AI applications in vestibology, presenting a general pipeline that could be applied to design new differential diagnostic AI-based tools as well as finding the most important variables to recognize a pathology with respect to the others. We believe that a similar analysis has the potential to be applied also to other clinical open problems, such as the identification of different forms of VPPB or the prediction of therapeutic outcomes.

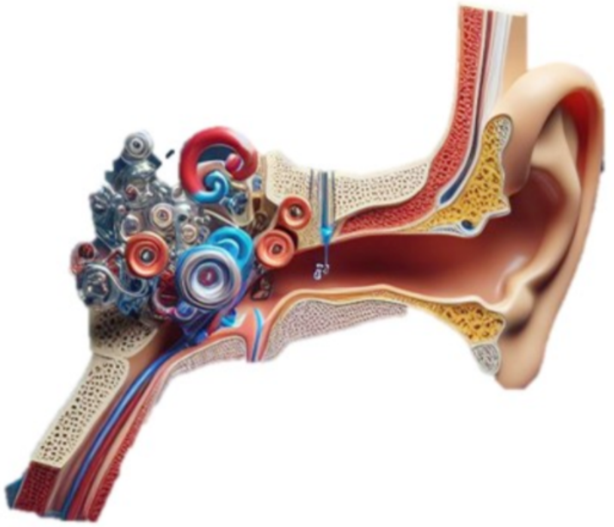

Figure 3: Representation of vestibular disorders using an AI imaging tool.

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None.

Conflicts of Interest

The authors declare no conflict of interest.

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Author's Contribution

Emanuele Agrimi: Study design, analysis, Algorithm creation and validation.

Caterina Tripodi: Study design, data collecting and data interpretation.

Ingrid Raponi: manuscript formal revision and submission.

Eugenio Martino: Data collecting and data analysis.

Edoardo Marcelli: Literature revision and data collecting.

Arcangelo Menna: Data collecting and interpretation of data.

Giuseppe Tortoriello: Data collecting and analysis.

Andrea Marzetti: Final revision.

Vincenzo Marcelli: Algorithm validation, final revision.

Ethical Consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. The questionnaire was submitted to all patients after obtaining informed consent. No patient identifiable data or patient specific information is used in this manuscript.

References

1. Brandt T (2013) Vertigo: Its Multisensory Syndromes. Springer Science and Business Media, New York, USA.
2. Teixeira LS, Cavalcante AMG (2017) Ménière's Disease: Epidemiology. In: Up to Date on Meniere's Disease. InTech, London, UK.
3. Brevern MV, Radtke A, Lezius F, Feldmann M, Ziese T, et al. (2007) Epidemiology of benign paroxysmal positional vertigo: A population based study. J Neurol Neurosurg Psychiatry 78: 710-715.
4. Ljunggren M, Persson J, Salzer J (2018) Dizziness and the acute vestibular syndrome at the emergency department: A population-based descriptive study. Eur Neurol 79: 5-12.
5. Formeister EJ, Rizk HG, Kohn MA, Sharon JD (2018) The epidemiology of vestibular migraine: A population-based survey study. Otol Neurotol 39: 1037-1044.
6. Leigh RJ, Zee DS (2015) The Neurology of Eye Movements (5th edn). Contemporary Neurology Series, New York, USA.
7. Furman JM, Cass SP, Whitney SL (2010) Vestibular disorders: A case study approach to diagnosis and treatment. Oxford University Press, Oxford, UK.
8. Poole D, Mackworth A, Goebel R (1998) Computational intelligence: A logical approach. Oxford University Press, New York, USA.
9. Mitchell TM (1997) Machine Learning. McGraw Hill, New York, USA.
10. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, et al. (2017) Dermatologist-level classification of skin cancer with deep neural networks. Nature 542: 115-118.
11. Agrimi E, Diko A, Carlotti D, Ciardiello A, Borthakur M, et al. (2023) COVID-19 therapy optimization by AI-driven biomechanical simulations. Eur Phys J Plus 138: 182.
12. You E, Lin V, Mijovic T, Eskander A, Crowson MG (2020) Artificial intelligence applications in otology: A state of the art review. Otolaryngol Head Neck Surg 163: 1123-1133.
13. Kabade V, Hooda R, Raj C, Awan Z, Young AS, et al. (2021) Machine learning techniques for differential diagnosis of vertigo and dizziness: A review. Sensors (Basel) 21: 7565.
14. Mira E, Buizza A, Magenes G, Manfrin M, Schmid R (1990) Expert systems as a diagnostic aid in otoneurology. ORL J Otorhinolaryngol Relat Spec 52: 96-103.
15. Kentala E, Pyykkö I, Auramo Y, Juhola M (1996) Otoneurological expert system. Ann Otol Rhinol Laryngol 105: 654-658.
16. Laurikkala JP, Kentala EL, Juhola M, Pyvkkö IV (2001) A novel machine learning program applied to discover otological diagnoses. Scand Audiol Suppl 2001: 100-102.
17. Siermala M, Juhola M, Kentala E (2008) Neural network classification of otoneurological data and its visualization. Comput Biol Med 38: 858-866.
18. Grill E, Müller T, Becker-Bense S, Gürkov R, Heinen F, et al. (2017) DizzyReg: The prospective patient registry of the German Center for Vertigo and Balance Disorders. J Neurol 264: 34-36.
19. Jolliffe IT (2022) Principal Component Analysis. Springer, New York, USA.
20. Van der Maaten L, Hinton G (2008) Visualizing data using t-SNE. Journal of Machine Learning Research 9: 2579-2605.
21. Cortes C, Vapnik V (1995) Support-vector networks. Machine Learning 20: 273-297.

22. Goldberger A (1991) A Course in Econometrics. Harvard University Press, Cambridge, USA.

23. Geurts P, Ernst D, Wehenkel L (2006) Extremely randomized trees. Machine Learning 63: 3-42.

24. Von Winterfeldt D, Edwards W (1986) Decision Analysis and Behavioral Research. Cambridge University Press, Cambridge, UK.

25. Molinaro AM, Simon R, Pfeiffer RM (2005) Prediction error estimation: A comparison of resampling methods. Bioinformatics 21: 3301-3307.