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Research Article

A Simple Preprocessing Method Enhances Machine Learning Application to EEG Data for Differential Diagnosis of Autism

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A new pre-processing approach to EEG data to detect topological EEG features has been applied to a continuous segment of artifact-free EEG data lasting 10 minutes in ASCII format, derived from 50 ASD children and 50 children with other Neuro-Psychiatric Disorders (NPD), matched for age and male/female ratios.

Each EEG is transformed into a triangular matrix of 171 values expressing all reciprocal Manhattan distances among the 19 electrodes of the international 10-20 system. From this matrix, the minimum spanning tree (MST) is calculated. Electrode identification serial codes sorted according to the decreasing number of links in the MST, and the number of links in the MST, are taken as input vectors for machine learning systems.

Machine learning systems have been applied to build a predictive model to distinguish between the two diagnostic classes (autism vs NPD) following a rigorous validation protocol.

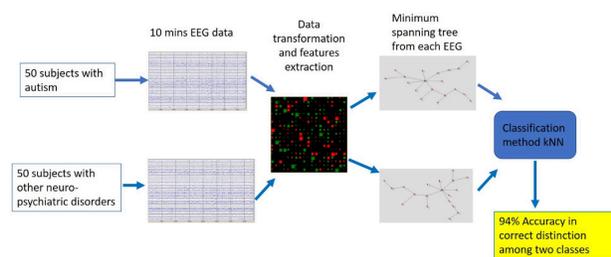
The best machine learning system (KNN algorithm) obtained a global accuracy of 93.2% (92.37% sensitivity and 94.03% specificity) in differentiating ASD subjects from NPD subjects.

The results obtained in this study suggest that, thanks to the new pre-processing method introduced, there is the possibility to discriminate subjects with autism from subjects affected by other psychiatric disorders with a modest computational time, reducing the information to 38 figures.

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Graphical abstract



Schematic representation of data processing and analysis

Introduction

Many different mathematical approaches have been tested in the last few years to disentangle the complexity of EEG data and determine if it is possible to distinguish children with ASD from typically developing children or children with other neuropsychiatric disorders. An electroencephalogram (EEG) records the electrical activity of the brain by recording the electrical impulses of different frequencies used by neurons for communication through electrodes attached to the scalp. The relevant involvement of the cerebral cortex in substantially altering cortical circuitry explains the unique pattern of deficits and strengths that characterize cognitive functioning. Therefore, EEG recordings can be potential biomarkers of these abnormalities. EEG signals are random, non-stationary, and non-linear. The most delicate phase in the overall EEG process is the preprocessing phase, which aims to extract relevant features that are offered to potent classifiers, generally based on machine learning techniques.

The native EEG signal contains noise due to various factors such as involuntary hand and eye movements or heartbeat interference [1]. These interferences increase the complexity of EEG signal processing and make the quality of mathematical calculations unstable in the later stages of processing and must, therefore, be eliminated before analysis. Good preprocessing will also reduce the cardinality of the input vectors for machine learning systems, reducing computation time and the risks of overtraining. As mentioned in a recent review [2], many different preprocessing methods have been described in the literature, such as Common Spatial Patterns (CSP), Principal Component Analysis (PCA) [1], Common Average Referencing (CAR) [1][3],

Surface Laplacian (SL), adaptive filtering [1][4], Independent Component Analysis (ICA), and digital filters [5], MS-ROM IFAST [6]. Each method has advantages and disadvantages. PCA, for example, is a potent dimensionality reduction technology but involves discarding non-principal components with small variance, which could potentially contain useful information [7]. Digital filters process EEG signals from the frequency domain and are broadly utilized in artifact processing of EEG signals; however, it is required that EEG signals and artifact signals have different frequency bands, which rarely exist in practical situations. Our group has originally proposed a new technique based on artificial neural networks called the MS-ROM / I-FAST system to extract desired features from EEG to achieve the differential diagnosis of children with autism [6]. The data assessment only requires a few minutes of EEG data collection and does not require any data preprocessing. The drawback of this approach is the large computational time required to achieve the final task.

In this paper, we present an alternative preprocessing approach to EEG data based on a novel algorithm applied to raw data to detect topological EEG features. Our assumption is that brain connection abnormalities can be detected through a specific mathematical topological approach, which is able to compare the minimal structure of functional networks beneath scalp electrodes. Additionally, functional interconnections of different brain areas can be assessed by measuring the interdependence of time-series electrical signals recorded by scalp electrodes using distance functions (i.e., the Euclidean distance, the Manhattan distance, the Minkowski distance, the Cosine similarity, etc.). There are many clustering methods available, such as Principal Component Analysis, Hierarchical agglomerative clustering, Nearest-neighbor test, autocorrelation, and Cuzick-and-Edwards'. In our study, we have decided to rely on the minimum spanning tree (MST) algorithm as a base to perform electrodes clustering. A minimum spanning tree (MST) is a spanning tree of a connected, undirected graph. It connects all the vertices together with the minimal total weighting for its edges.

The MST algorithm, originally described by the Czech scientist Otakar Boruvka in 1926, aims to optimize the planning of electrical connections among cities and was later refined by Kruskal with a specific deterministic algorithm.

The MST is a spanning tree with a weight less than or equal to the weight of every other spanning tree. In

practical terms, MST shows the best way to connect the variables in a tree and the shortest possible combination, allowing the presentation of the data in a simplified graph.

In the biomedical field, the MST has been used particularly in microarray clustering. Although MST-based clustering is formally equivalent to the dendrograms produced by hierarchical clustering under certain conditions, visually they can be extremely different. Our assumption is that MST is a valuable approach to synthesize the interconnection scheme of time-series electrical signals recorded by scalp electrodes, which are expected to be different in subjects with autism in comparison with those affected by other diseases. The main advantage of the MST algorithm is that it gives a synthetic view of the variable ensemble and allows an easy understanding of clustering through links that directly connect variables that are very close to each other. The importance of the variables in the graph is related to the number of links. Hubs may be defined as the variables with the maximum number of connections in the graph.

To prove this hypothesis, the EEG data of fifty subjects with autism and 50 subjects with other neuropsychiatric disorders were pre-processed with MST. Machine learning systems were applied subsequently to build a predictive model to distinguish between the two diagnostic classes.

Patients and methods

Fifty subjects diagnosed with ASD and 50 control subjects diagnosed with other neuropsychiatric disorders, matched for age and gender, were obtained from a clinical archive in the United States. Both groups had the same age range (4-10 years) and the same gender distribution (m=39, f=11). None of the subjects were affected by genetic conditions, cerebral malformations, or epilepsy. In the control group, primary diagnoses were ADHD (n=7), mood disorders (n=4), anxiety disorders (n=16), sleep disorders (n=12), Oppositional Defiant Disorder (n=6), and Traumatic Brain Injury (n=5).

Methods

The EEG data were recorded at a psychiatric center in the US, at resting state, with eyes closed. EEG acquisition was performed using Mitsar-EEG-10/70-201 equipment, with impedance maintained below 10k ohm. The patients were seated in a slightly reclining chair in a silent and low-light environment. An Electrocap was used to collect the data according to the

international 10-20 system with a linked ears montage (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). A minimum of 20 minutes of total data were recorded in both eyes-open (10 minutes) and eyes-closed (10 minutes) resting conditions. The order of these could vary among patients. In this study, we used only the eyes-closed data to be consistent with our pilot study.

The EEG track was then saved in the database. Subsequently, ten minutes of recording were exported as ASCII files through the same acquisition program, SystemPlus Evolution, and saved to make it possible to read in numerical format.

Preprocessing phase

In the common practice of EEG registration, there are 19 electrodes registering brain activity related to different brain cortex regions. It is reasonable to assume that these regions are interconnected with each other through a complete matrix of mutual relationships. Measuring the similarity between time series registered in an EEG is a way to establish how close parts of the brain under given electrodes are coherent with each other. There are many types of similarity measures. One of the most popular is the Manhattan distance, also known as the city-block distance. The city-block distance is so named because it is the distance in blocks between any two points in a city (e.g., down 3 blocks and over 1 for a total of 4 blocks). This distance calculation has been applied to the 19 time series from EEG electrode derivations. After the calculation, we can visualize the matrix in this way (Figure 1).

	Fp1	Fp2	F7	F3	Fz	F4	F8	T3	C3	Cz	C4	T4	T5	P3	Pz	P4	T6	O1	O2
Fp1	0	63832	6302	3786	4671	14903	12130	4902	93495	145749	80668	29305	5812	95070	139540	174434	14875	193659	25544
Fp2	63832	0	69391	66212	60557	78304	75339	62097	31790	82679	15218	35079	61641	33417	76732	111692	76788	130830	41917
F7	6302	69391	0	3930	9178	9182	6636	7650	90553	151344	80235	34765	6657	100294	145134	100019	9705	199217	30718
F3	3786	66212	3930	0	5839	12235	9521	4955	95873	148164	83049	31586	5891	97429	141943	176845	12330	196047	27619
Fz	4671	60557	9178	5839	0	17801	15027	3744	90381	142521	77443	25953	4205	91859	136327	171245	17426	190432	22236
F4	14903	78304	9183	12235	17801	0	3685	16325	107931	160276	95104	43639	17010	109434	154056	188904	6399	208091	39373
F8	12130	75339	6636	9521	15027	3685	0	13426	104979	157307	92154	40660	14205	106479	151100	185968	5903	205147	36530
T3	4902	62097	7650	4955	3744	16325	13426	0	91797	144015	70967	27465	3248	93127	137834	172750	3597	191912	23781
C3	93495	31790	99037	95873	90281	107931	104979	91797	0	54944	14327	64717	91295	10270	49047	83485	106326	103000	70915
Cz	145749	82679	151344	148164	142521	160276	157307	144015	54944	0	66647	116780	143534	53992	8236	30348	158418	50000	122945
C4	80668	19218	86235	83049	77443	95104	92154	78967	14327	66647	0	51788	78468	18863	60823	95431	93578	114803	58291
T4	29305	35079	34765	31586	25953	43639	40660	27465	64717	116780	51788	0	26984	66429	110716	145409	42495	184878	9737
T5	5812	61641	6657	5891	4205	17010	14205	3248	91295	143534	78468	26984	0	92687	137378	172205	16621	194420	23249
P3	95070	33417	100294	97429	91859	109434	106479	93327	10270	53992	18863	66429	92687	0	47501	82040	107931	101178	72475
Pz	139540	76732	145134	141943	136327	154056	151100	137824	49047	8236	60823	110716	137378	47501	0	36063	152368	55858	116685
P4	174434	111692	100019	176845	171245	188904	165968	172750	83485	30348	95433	145609	172265	82040	36063	0	187207	24465	151519
T6	14875	76788	9705	12330	17426	6399	5903	15997	105268	158418	93578	42495	16621	107931	152368	187207	0	206353	37982
O1	193659	130830	199217	196047	190432	208091	205147	191812	103000	50000	114803	146878	191423	101178	55858	24465	206353	0	170749
O2	25544	41917	30718	27619	22236	39373	36530	23781	70915	122945	58291	9737	23249	72475	116685	151519	37982	170749	0

Figure 1.

Distance matrix of 19 EEG electrodes according to their Manhattan distance in an EEG of a study participant taken as an example.

The cells contain values expressing time series distances relative to each channel's couple according to the

the specific metric chosen (Manhattan distance). The value in each cell is proportional to the distance between the respective electrodes. Higher values indicate that two electrode time series are more distant, indicating that the two brain areas are more disconnected.

From each EEG Manhattan distance matrix, the MST has been derived.

The following two figures summarize the MST of nine EEG subjects with ASD and nine other subjects without ASD. To make the information contained in the MST computable, the electrode names are numbered (Fp1=1, Fp2=2, F7=3, F3=4, Fz=5, F4=6, F8=7, T3=8, C3=9, Cz=10, C4=11, T4=12, T5=13, P3=14, Pz=15, P4=16, T6=17, O1=18, O2=19).



Figure 2. MST of EEG from nine exemplified subjects with ASD

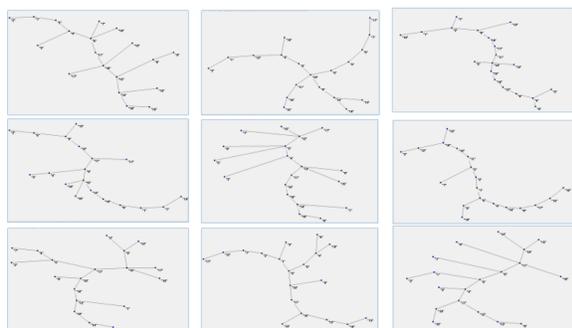


Figure 3. MST of EEG from nine exemplified subjects with NPD

The different electrodes are then listed according to their decreasing number of links in the Minimum Spanning Tree, as in this example (Figure 4).

Electrode number	Number of links
------------------	-----------------

4	3
10	3
2	2
5	2
6	2
7	2
8	2
9	2
3	2
13	2
14	2
15	2
16	2
17	2
18	2
1	1
11	1
12	1
19	1

Figure 4. Example of electrode number listing according to the number of links in MST

The two columns shown in Figure 4 are joined in a single row to form an input vector, which is used to train the final classifiers.

In this way, all of the content of an EEG file is transformed into just 38 numbers. This input vector is then used to train machine learning systems in an attempt to develop a classification model to distinguish between the two diagnostic classes.

Predictive modelling

The robust sets of 38 features related to MST were used as input for Machine Learning classifiers. The KNN algorithm was used to develop a predictive model to distinguish subjects belonging to the two diagnostic classes (autism vs. other disorders). The models' performances were tested with training/testing cross-validation procedures.

Training-testing protocol

These classification tools were applied to predict the diagnostic class using the Training and Testing validation protocol, with the following steps:

1. Random subdivision of the dataset into two sub-samples: A and B, each containing 50% of the records and having an equal proportion of cases belonging to the two classes. We performed a homogeneity check, which confirmed the substantial equivalence of the two subsets with respect to the distribution of variable values. In the first run, A is used as the Training Set and B as the Testing Set.
2. Application of ANN on the Training Set. In this phase, the ANN learns to associate the input variables with those indicated as targets.
3. After the training phase, the weights matrix produced by the algorithm is saved and frozen together with all the other parameters used for the training.
4. The Testing Set is then shown to a virgin twin (same architecture and base parameters) ANN with the same weights matrix as the trained ANN, acting as the final classifier. This operation takes place for all records, and the results (right or wrong classification) are not communicated to the classifier. This allows us to assess the generalization ability of the trained ANN.
5. In a second run, another virgin ANN is applied to subset B, which is used as a training subset, and then to subset A, which is used as a testing subset.
6. Therefore, the results are relevant to two sequences of the training-testing protocol: A-B and B-A.

Results are expressed in terms of sensitivity (correct classification of positive patients), specificity (correct classification of negative patients), and global accuracy (arithmetic mean between sensitivity and specificity). Overall results are expressed as the average of the two experiments.

This crossover procedure allows us to blindly classify all records with the trained algorithm, ensuring the generalization capability of the model on records that have never been seen before.

Natural clustering of records

The Pick and Squash Tracking (PST), an unsupervised machine learning system developed at the Semeion Research Centre based on an evolutionary algorithm called GenD [8] has been used to cluster records according to the features selected by the TWIST system. Such a system can find the best spatial distribution of a given number of points with respect to the maximum degree of their reciprocal Euclidean distances without exploring all the possible combinations, but adaptively evolving through the optimal solution.

The PST system locates the points of the dataset onto a 2D space, minimizing the projection error; thus, the original distances between the points suffer only minimal distortions. The algorithm is particularly useful when the matrix distance of the point of interest is imprecise for different reasons, and consequently, the map doesn't correspond precisely to reality.

The PST algorithm carries out a multidimensional scaling from an N-dimensional to an L-dimensional space (where $N \gg L$), and typically where $L=2$ or $L=3$. PST acts in this dimensional reduction to ensure that the original distance between points has a minimal amount of distortion in the L-dimensional space.

Results

Acting on the features related to MST, the KNN algorithm reached the best predictive capability in distinguishing autistic cases from NPD subjects with an overall accuracy of 93.2% (Table 1).

machine learning	Recs	ASD	Other	sensitivity	specificity	overall accuracy
KNN	55	22	33	95.45%	93.94%	94.70%
KNN	45	28	17	89.29%	94.12%	91.70%
Mean/sum	100	50	50	92.37%	94.03%	93.20%

Table 1. Predictive performance of machine learning systems

The natural clustering of subjects with the PST system allowed an almost perfect separation of records according to their diagnostic classes (Figure 5).

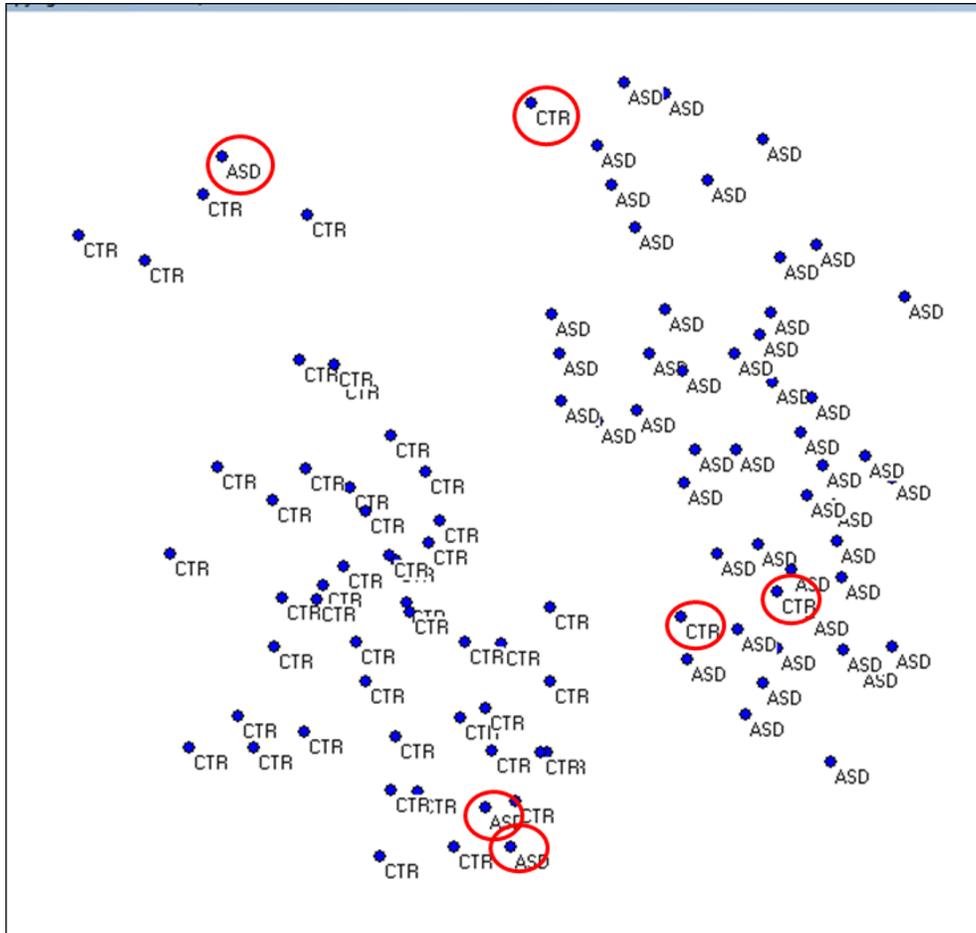


Figure 5. Natural clustering of subjects with an unsupervised machine learning system. ASD = subjects with autism spectrum disorder; CTR = subjects with other neuropsychiatric disorders. There is a notable separation of the two diagnostic classes. Clustering errors are marked in red.

Discussion

Several papers have been published recently using EEG data processed by advanced mathematical techniques (often based on machine learning) to distinguish children with autism from typically developing children.

Table 2 summarizes the studies published in articles of international journals or congress proceedings.

Almost all studies have employed machine learning systems acting as classifiers after suitable data preprocessing. Among the preprocessing methods, the most prevalent appears to be the discrete wavelet transform followed by the Fast Fourier Transform.

Author (ref)	year	N. Cases autism	N. Cases typicals	N. Cases with other NPD	Age range	Feature extraction	Classification method	Accuracy	Channels number
Ahmadlou(9)	2010	9	8		7-13	DWT	RBNN	90	19
Bosli(10)	2011	46	33			ADJ & MRMR	SVM	90	64
Ahmadlou(11)	2012	9	9			DWT	EPNN	95.5	19
Sheikhani(12)	2012	17	11		6-11	STFT	KNN	96.4	19
Jamal(13)	2014	12	12		nd	nd		94.7	128
Alsagoff(14)	2014	8	10		nd	nd	FLDA	80.27	
Cheong(15)	2015	26			nd	DWT	ANN	92.3	3
Grossi(16)	2017	15	10		5-10	MS-ROM/FAST	ANN	100	19
Djema(17)	2017	9	10		10-16	DWT shannon entropy	ANN	99.7	16
Bosli(18)	2018	99	89		0.4-3	Modified multiscale entropy	SVM	100	128
Thapaliya(19)	2018	24	28		nd	nd	SVM	100	128
Grossi(20)	2018	30		20	2-10	MS-ROM/FAST	ANN	95	19
Haputhanthri(21)	2019	10	5			DWT	SVM	93.3	32
Hadoush(22)	2019	36			nd	EWD	ANN	94.4	128
Kang(23)	2020	50	47		3-6	ADJ & MRMR	SVM	85.44	19
Grossi(24)	2020	35	10	20	4-10	Phyton features extraction	ANN	94.95	2
Abdolzadegan(25)	2020					Wavelet+FFT	SVM,KNN	90.57	
Our work	2021	50		50	4-10	MST	KNN	94.8	19

Table 2. Summary of published studies on autism diagnosis through digital EEG

Table legend. DWT = discrete wavelet transform; AOI & MRMR = area of interest & minimum redundancy/maximum relevance; STFT = Short time Fourier transform; EMD = empirical mode decomposition; FFT = Fast Fourier Transform; MS-ROM/IFAST = Multi-Scale Ranked Organizing Map/Implicit Function As Squashing Time; MST = Minimum spanning tree

In our study, the minimum spanning tree has been employed on the electrodes distance matrix as a robust pre-processing method, representing a novel application of this technique in the biomedical field.

As happens in variables clustering efforts, MST captures the implicit complexity of a data set and returns a synthetic representation of it, while still retaining its complexity. When processing EEG data, it is very important to avoid overwhelming the machine learning system with extraneous unimportant data. Data that does not contain pertinent information, when inserted into the model, can cause an increase in noise and therefore a greater difficulty for the machine learning systems to correctly generalize new cases not seen during the training phase. The results obtained are promising and introduce a new philosophy in handling this kind of data.

Looking at Table 2, few studies have focused on the distinction between autism and other neuropsychiatric disorders with a consistent sample size. From this point of view, this is the largest study published so far that aims at differential diagnosis, rather than simply distinguishing children with autism from typically

developing children. This is important because, in the real world, the application of these diagnostic techniques will take place only for subjects seeking medical care for some symptoms, rather than for simple screening.

Looking at Table 2, it is quite clear that we are still in a research phase with proof-of-concept efforts. The next step is to validate these results in large cohorts with multicentric studies where clinicians employ different technical apparatus and different protocols to ensure that EEG data processing methods are robust enough to resist a certain degree of heterogeneity.

Further studies with more robust data and less potential bias are probably required.

Research in this area is vital to the well-being of those diagnosed with ASD. There are many disorders, such as epilepsy, that are commonly misdiagnosed as ASD. Because of this, those with misdiagnoses, especially children, tend to be prescribed medications that worsen their symptoms [9]. By adding a biological basis to the diagnosis of ASD through recognition of specified EEG patterns, we can minimize the misdiagnosis of certain neuropsychiatric disorders.

There is also a need to increase adaptability in the systems, enabling the incorporation of new medical knowledge as new technology appears. A further step will be to engineer machine learning systems to make them work automatically on commercial EEG machines, with the intervention of EEG companies able to embed these trained systems in their technical devices.



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Statements and Declarations

Compliance with Ethical Standards

- Disclosure of potential conflicts of interest: the authors declare that they have no conflict of interest to disclose.
- Research involving Human Participants and/or Animals: The data were collected over a 5-year period for those referred for an EEG assessment. The data were submitted to an institutional review board and granted a “waiver of approval,” meeting the exemption categories set forth by federal regulation 45 CFR 46.101(b).
- Informed consent: informed consent was collected from all human subjects participating in the study.

Declarations of interest

None

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