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REVIEW OPEN ACCESS

The Role of Machine Learning in Predicting the Onset and Progression of Neuropathic Pain After Spinal Cord Injury: A Literature Review

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Abstract

Introduction: Developing a diagnostic tool that can determine whether a patient will develop neuropathic pain following a spinal cord injury can aid clinicians in treatment procedures and improve patient outcomes. Developing new detection technology can take years, thus finding a way to use existing diagnostic tools would be optimal. Machine learning can be leveraged to incorporate existing data and classify patient outcomes when there are obvious patterns for classification.

Methods: A review of full reports published in English was conducted through PubMed. The relevant keywords used in this search included "neuropathic pain", "spinal cord injury", machine learning, and "predict" among others. Eight relevant citations were retrieved and reviewed.

Results: A decision tree regressor model using clinical measures for neuropathic pain and level of spinal cord injury found that BMI and anxiety scores were the most influential variables in predicting outcomes. A similar tree for functional magnetic resonance imaging (fMRI) data found ventral and dorsal tissue bridges to be predictors of neuropathic pain. Another fMRI study pointed to a strong correlation between changes in perioperative blood oxygen levels at the ipsilateral frontal lobe and neuropathic pain outcomes. Magnetic resonance spectroscopy (MRS) implicated a lower glutamate-glutamine/myoinositol ratio in high neuropathic pain. Various machine learning algorithms were evaluated in building an EEG classifier in two separate studies, and classification accuracies greater than 80% were reached in both. A classifier built using positron emission tomography data attained classification accuracies of 87.5%.

Discussion: The most common machine learning algorithm used in building classifiers was support vector machines, linear discriminant analysis and neural net. Regression trees were also used, but they were used to elucidate the variables influencing predictions. Each study has its limitations, either due to limitations of the study method, classification method or data type.

Conclusion: There exist many methods to study neuropathic pain and spinal cord injury and each method provides different information regarding the mechanism of pain, influential variables, and physiological changes that occur with pain. Classification can be done using any of these methods to achieve acceptable accuracies, but these accuracies are not enough for a clinical prognostic classifier.

Keywords: neuropathic pain; spinal cord injury; machine learning; artificial intelligence; biomarkers; EEG; fMRI; PET

Introduction

Pain following spinal cord injury (SCI) can consist of varied phenotypes encompassing multiple types of pain, thus making diagnoses and treatment difficult [1]. Neuropathic pain (NP) is defined as pain caused by lesion or disease of the somatosensory nervous system by the International Association for the Study of Pain (IASP) [2].

Many studies have identified and scored NP using questionnaires which combine clinical values and self-reported values [3,4]. Questionnaires like the visual analogue scale (VAS) for leg pain are used to quantify NP while the Oswestry Disability Index (ODI) measures severity of injury based on daily life complaints [5]. Despite the presence of clinical values, scales are variable due to the subjectivity of pain and their self-reported nature.

One method for attaining quantifiable data is electroencephalography (EEG) recorded at relaxed eyes open (EO) and eyes closed (EC) states. EEG can distinguish features that allow prediction based on the EEGs of individual participants and can then be used directly for predictive diagnostic purposes [6].

Resting state functional magnetic resonance imaging (fMRI), is used frequently to study chronic pain like NP, but has not been used to try to predict onset of NP

following SCI [7]. It has, however, been used to identify pain biomarkers in studies involving back pain, chronic pelvic pain, knee osteoarthritis and more [7]. Positron emission tomography (PET) is neuroimaging technique used to study brain function and relies on a radioactive tracer rather than magnetic resonance [8]. Hyperspectral imaging can be used to visualize metabolite and co-enzyme activity involved in various cellular pathways expressing autofluorescent signals due to reactive oxygen species [9]. This method can be used to study global fluorescent changes following nerve injury and identify autofluorescent fingerprints for associated NP [9].

NP is highly debilitating and severely impacts quality of life [3]. Currently, there are no treatments for NP and pain management options have limited effectiveness [10]. Determining prognostic outcomes in advance can greatly improve pain management options [5]. In addition, a better understanding of the mechanisms of NP and the course of the ailment can lend to the development of better treatments and management options [11]. To this extent, machine learning (ML) algorithms, for various data types, may hold the potential to improve the accuracy of prognosis of NP after SCI.

Methods

A title and abstract search was conducted through PubMed using the keywords "spinal cord injury", AND "neuropathic pain", AND "machine learning" and retrieved three records. A complication was the term "spinal cord injury" is quite broad and encompasses many injuries with more specific terms and studies may choose not to use the term "spinal cord injury". An ensuing search using the keywords "neuropathic pain" AND "machine learning" retrieved 54 records. These results were manually reviewed for mentions of specific spinal cord injuries subsequently excluding 49 records. As fMRIs were mentioned as one of the most common methods used to study NP, another search using the keywords "neuropathic pain", AND "spinal cord injury", AND "fMRI", AND "predict" was performed, retrieving seven records. Four records were excluded upon reviewing their relevance. The resulting records were screened to make sure they were full reports published in English, and not duplicates from previous searches. Eight papers were finally included in the literature review. The topics of interest during review were the medium of data collection, variables being studied, application of machine learning within the study, evaluation of machine learning tools used and the results of the studies. A limitation of this review is that all of the records were retrieved from PubMed only.

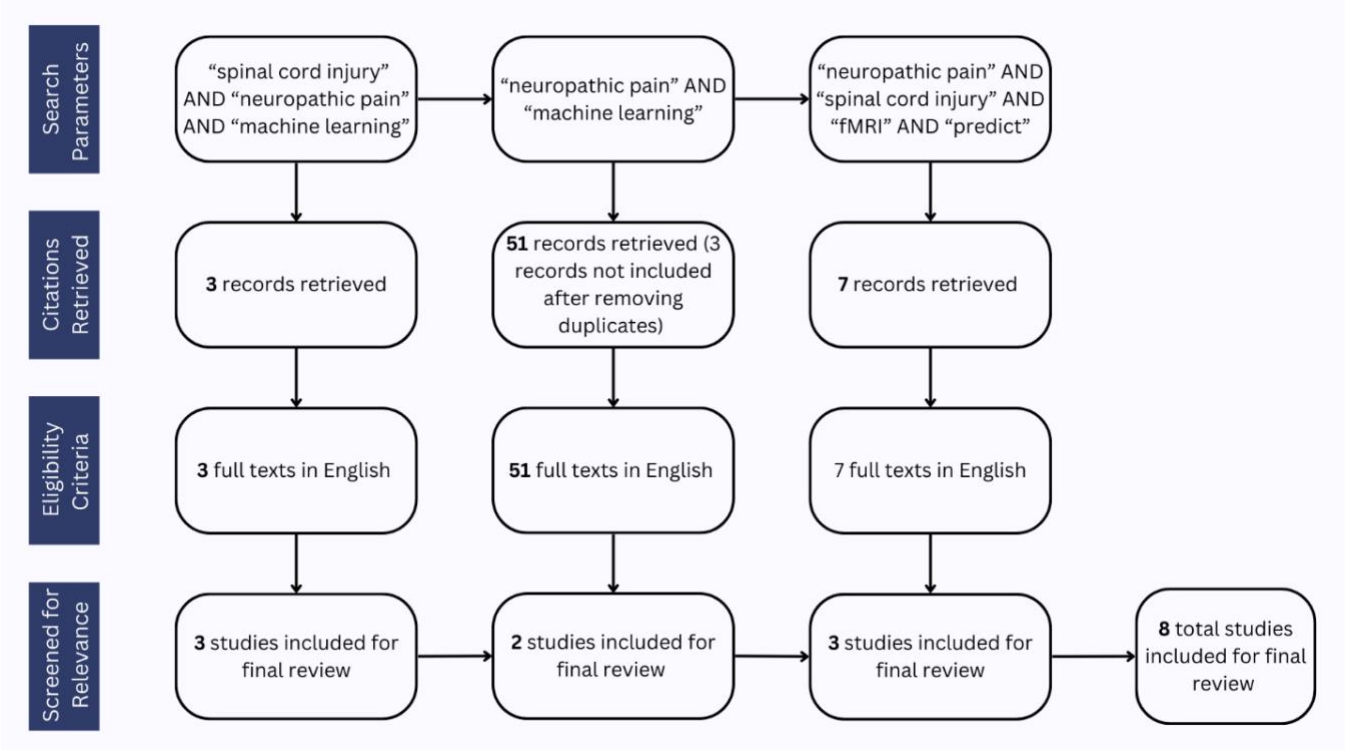

Figure 1. Flowchart for studies selected for review created using Canva.

Results

ML Models Based on Clinical Scales for Pain

Wirries et al. measured demographic data, the MOS 36-Item Short Form Survey (a self-reported patient outcomes survey), ODI, leg and back pain measured on a 100 mm VAS and the Hospital Anxiety and Depression Scale (HADS) [5]. The ODI score and the VAS values 6, 12, and 24 months after start of treatment were the target values for prediction, yielding a linear regression problem [5]. Recursive feature elimination was used to drop some parameters and determine the features to be used in the model [5]. A 10-fold cross validation for a simple decision tree regressor algorithm yielded mean absolute errors between 1.79 and 1.97 for the VAS predictions and 8.68 and 10.02 for the ODI predictions [5]. The standard deviations for both predictions were very low [5]. The algorithm allowed for weighted identification of the features that contributed to making predictions [5]. The top four features that influenced prediction values, in order of importance, were 1) BMI at the beginning of therapy, 2) HADS anxiety score, 3) age, 4) ODI [5].

ML Models Based on Oscillatory EEG Features

Vuckovic et al. investigated multichannel EEG which was processed by removing artifacts [6]. Power spectrum densities were calculated based on Welsh periodograms [6]. The features extracted for each channel were relative theta band power (EO and EC), relative alpha band power (EO and EC), relative beta power band (EC and EO), and EO/EC ratio of theta, alpha and beta band powers [6].

Classification was carried out via Linear Discriminant Analysis (LDA), Support Vector Machine (SVM), Naive Bayesian (NB), and Artificial Neuronal Network (ANN) [6]. The average classification accuracy, when using all 9 features and a number of channels between 1 and 18, ranged from 65% to 79% [6]. The ANN average classification accuracy, at 79 ± 7%, was significantly higher than that of SVM and NB [6]. NB, with an average classification accuracy of 65 ± 4%, had a significantly lower classification accuracy than the other three methods [6]. The LDA average classification accuracy was quite high at 77 ± 5%, but accuracy and sensitivity dropped as the number of channels increased [6]. ANN and SVM accuracy and sensitivity were relatively unaffected by increased number of channels and redundant features [6].

Patients were grouped into three groups: patients with NP (PWP), patients who developed NP within six months of initial EEG (PDP), and patients who did not develop pain within six months of initial EEG (PNP) [6]. A fourth group of participants, able bodied participants (AB), was also included [6]. The classification accuracy, with optimal number of channels for each condition, between all 6 pairs of patient conditions ranged from 87% to 90% [6]. Classification with the optimal features and the 10 best EEG channels yielded comparable, high accuracies for all the pairings except for PDP vs PWP [6].

Feature analysis showed that the EO alpha feature resulted in the highest classification accuracy using LDA and EO beta using ANN [6]. The EO/EC beta ratio and the EO theta features resulted in the worst accuracy across all 4 classifiers. PWP vs PNP and PWP vs PDP were the most complex tasks as they required the greatest number of EEG channels [6].

ML Models Based on Non-Linear Non-Oscillatory EEG Features

Anderson et al. sought to find non-linear, non-oscillatory features in the form of Higuchi's Fractal Dimension (HFD) [10]. Data preprocessing was done according to the Vuckovic et al. protocol, except for feature extraction which followed Higuchi's protocol [6,10]. Linear SVM was used to classify based on the HFD features [10]. This yielded that classification markers are transferable from diagnostic classification to prognostic classification; markers for chronic pain can be used to predict future pain [10]. The classification based on this assumption yielded a mean accuracy ≥ 85% in distinguishing between PDP and PNP [10].

Other findings from this analysis showed that PDP participants, overall, had a higher mean HFD than PNP participants [10]. The largest difference in HFD values between PDP and PNP groups was observed in occipital electrodes and the frontal-parietal electrodes [10]. This finding does not hold for the movement imagination of legs condition, where electrodes over the right central cortex observed greater HFD values of statistical significance in PNP participants than PDP participants [10].

ML Models Based on Magnetic Resonance Imaging

Pfyffer et al. used multivariable linear regression analysis to look at the association between fMRI data and pain. An unbiased recursive partitioning technique called conditional inference tree (URP-CTREE) was used to separate patients into subgroups [12]. The most significant predictor variable is used to separate patients until the association between the predictor variable and a predefined clinical end point has a significant p-value (>0.05) [12]. The classification accuracy of this method was not determined [12]. The inference tree model revealed that the most significant predictor of NP at 12 months after injury was ventral tissue bridge width at 1 month after injury [12]. The second most influential variable was width of the dorsal tissue bridge [12].

Stimulation of the big toe during fMRI, as done by Lee et al., found a correlation between incidences of NP and blood oxygen level dependent (BOLD) responses [13]. Change in BOLD response at the ipsilateral frontal lobe between preoperative fMRI and postoperative fMRI has a statistically significant correlation with development of NP [13].

Widerstrom-Noga et al. studied the metabolite concentrations in the anterior cingulate cortex after SCI using magnetic resonance spectroscopy (MRS) and found that lower glutamate-glutamine (Glx)/myoinositol (Ins) ratio significantly discriminated the group of participants

with high NP after SCI from the able-bodied and no–pain–following–SCI groups [14].

ML Models Based on PET/CT Imaging

Hou et al. used multivariate pattern analysis (MVPA) on PET scans to assess the role of metabolite activity in the whole brain [8]. Linear SVM analysis in the PRoNTo (Pattern Recognition for Neuroimaging Toolbox) was performed for regions of interest analysis: the sensorimotor cortex and the pain matrix [8]. The balanced accuracy for classifying rats with brachial plexus avulsion injuries (BPAI) and normal rats using a whole brain binary mask was 87.5% [8]. Linear SVM analysis with the SearchlightSearchlight and Principal Component Analysis (PCA) method was used to analyze all the voxels within a region so as not to miss any anatomical regions during analysis [8]. Spherical clusters were defined on smoothed PET images, the Searchlight portion, and then PCA was performed. Searchlight analysis of a whole brain image yielded a classification accuracy of 87.5% [8].

Correlation analysis to determine the discriminating brain regions in the PRoNTo analysis found a positive correlation between mechanical withdrawal test (MWT) and standardized uptake values (SUVs) in regions of interest (ROIs) of the left olfactory nucleus and right entorhinal cortex [8]. Correlation analysis for the discriminating brain regions in the Searchlight and PCA analysis showed a positive correlation between MWT and SUVs of the bilateral amygdala, right piriform cortex and right ventral hippocampus [8].

ML Models Based on Autofluorescent Signals

Gosnell et al. aimed to leverage tissue autofluorescence that is normally dismissed as background to capture endogenous signals [9]. LDA on lumbar tissue images confirmed that healthy mice could be distinguished from injured mice based on the autofluorescent signal [9]. The images were studied using a deep learning method that identified changes in fluorescent signals following chronic constriction injury (CCI) [15]. A search algorithm to identify selective pixels associated with CCI and create masks was used to conduct an in-depth discriminatory analysis on the images [9]. This confirmed that there are specific regions in the spinal cord tissue that are different between the injured control groups [9]. An additional finding was that the color of the autofluorescence was different in male and female mice in the injured condition [9].

Table 1. Summary of studies included for review

Study	Data collection tool	Study population of interest	Features (variables) studied	ML tools evaluated	Method for evaluating ML tools	Classification accuracy	Biomarkers identified
Wirries et al.	Clinical scales	Study population with lumbar disc herniation	Demographic data, the MOS 36-Item Short Form Survey (a self-reported patient outcomes survey), ODI, leg and back pain measured on a 100 mm VAS and the Hospital Anxiety and Depression Scale (HADS)	Decision tree regressor	10-fold cross validation	No accuracy measured; low standard deviation values for VAS and ODI predictions	1) BMI at the beginning of therapy, 2) HADS anxiety score, 3) age, 4) ODI
Vuckovic et al.	EEG	Human patient population with spinal cord injuries	Clinical values: demographic data, pain, location of injury, extent of injury. EEG features: theta band power (EO and EC), relative alpha band power (EO and EC), relative beta power band (EC and EO), and EO/EC ratio of theta, alpha and beta band powers	LDA, NB, SVM, ANN	Calculating classification accuracy, specificity, and sensitivity for each classifier and analysis of variance (ANOVA) for comparative analysis	87-90% for all the conditions (PNP vs PDP, PNP vs PWP, PNP vs AB, PDP vs PWP, PDP vs AB, PWP vs AB) at their optimal number of channels.	EO alpha and EO beta yielded the highest classification accuracies, while EO/EC beta ration and EO theta yielded the lowest.
Anderson et al.	EEG	Human patient populations with chronic or subacute spinal cord injuries	Demographic data, pain, HFD from EEG data recorded during imagined movement	Linear SVM	Calculating classification accuracy	≥ 85% in the PDP vs PNP condition	EEG diagnostic markers for chronic pain are transferable to prognostic classification. Higher mean HFD in PDP than PNP in occipital and frontal-parietal regions.
Pfyffer et al.	fMRI	Human patient population with subacute spinal cord injuries	Extent of injury, pain (pink prick scores), 1 month and 12 month post-injury neuroimaging data	URP-CTREE	Mann-Whitney U tests and multivariable linear regression to investigate associations between pain and tissue bridges	No accuracy measured	1) Ventral tissue bridge width at 1 month after injury, 2) dorsal tissue bridge width at 1 month after injury

Study	Data collection tool	Study population of interest	Features (variables) studied	ML tools evaluated	Method for evaluating ML tools	Classification accuracy	Biomarkers identified
Lee et al.	fMRI	Human patient population with spinal cord injuries that underwent surgical decompression with fixation and conservative therapy	Presence of NP, pre- and post-operative neuroimaging data, American Spinal Cord Injury (ASIA) score	N/A	N/A	N/A	Perioperative blood oxygen at the ipsilateral frontal lobe
Widerstrom-Noga et al.	MRS	Human patient population 1 year post-traumatic spinal cord injury	Presence of chronic NP, pain evaluation, pain history, psychosocial measures	N/A	N/A	N/A	Lower glutamate-glutamine (Glx)/myoinositol (Ins) ratio in high NP patients
Hou et al.	PET/CT	Rats with surgically induced brachial plexus avulsion injury (BPAI) and confirmed post-surgical NP	Mechanical withdrawal tests to confirm NP, PET data	linear SVM with PRoNTo Toolbox or Searchlight and PCA method	Leave-one-out cross-validation (LOOCV)	87.5% for both methods	ROIs of the left olfactory nucleus and right entorhinal cortex and SUVs of the bilateral amygdala, right piriform cortex and right ventral hippocampus
Gosnell et al.	Autofluorescence imaging	Mice with surgically induced CCI of the sciatic nerve and confirmed NP	Hyperspectral imaging for autofluorescence, von Frey test for pain	LDA, deep learning, discriminatory analysis	Kolmogorov-Smirnov, ANOVA tests	N/A	Algorithms are able to identify fluorescence patterns in that distinguish nerve-injured tissue

Discussion

Models Based on Clinical Scales

Even upon confirmation of "definitive" NP, using tests like neurophysiological tests, pain is subjective. Despite these limitations, Wirries et al. predicted NP and injury with minimal standard deviation, indicating that the prediction values are stable [5]. The precision of the predictions may be owed to BMI, age and ODI being predictors in addition to the HADS [5]. HADS asks patients to score themselves and their experiences on a scale, which makes it subject to the aforementioned issues [16]. The ODI only asks patients to select correct versus incorrect statements, which reduces variability due to differences in perception [17]. BMI and age are also quantitative variables that are not are not subjective measures. While this study is significant in understanding variables that affect NP onset after SCI, it is unlikely to be used as a classifier on its own.

Models Based on EEG Features

EEG data is a promising tool for building a prognostic classifier as markers are transferable from the "patients with NP" to the "patients who developed pain" phenotype [10]. The classifiers by Vuckovic et al. showed the ability to achieve high classification accuracies [6]. The exception to this was the PWP vs DP condition as NP signatures are present in both data sets [6]. However, this is not problematic as a prognostic classifier does not need to be able to distinguish between patients with pain and patients who will develop pain [6]. The classifiers that yielded the best results were LDA and ANN, and with comparable accuracies, LDA is preferential as it is a lot easier to set parameters for LDA than ANN [6]. The similar accuracies indicate that the EEG features of interest are linearly separable [6]. Unfortunately, LDA is limited in its ability to handle a larger number of channels in a way that ANN and SVM do not appear to be [6]. It is safe to assume that linear SVM was not an evaluated classifier in this study as linear SVM is not mentioned. As linear SVM is the primary classification method in the non-oscillatory EEG analysis and the PET analysis, evaluation of linear SVM as a classifier for oscillatory EEG may be worthwhile [10,8].

Anderson et al. makes headway in using non-linear non-oscillatory features for classification, with the intent of identifying more biomarkers that can facilitate better prognosis [10]. If classification based on oscillatory features can be combined with non-oscillatory feature-based classification, that accuracy of classification can potentially increase [10]. This preliminary, linear SVM classifier yields accuracies over 80% [10]. Considering the valuations of the Vuckovic et al. study and the intent to combine oscillatory and non-oscillatory data in classification, testing other classifiers such as LDA and ANN is merited [6]. A limitation of both EEG studies was a lack of follow up data on patients as to whether patients developed pain after the 6-month scope of the study [6,10].

Models Based on Neuroimaging Features

FMRI has become the predominant imaging mechanism in pain studies for numerous reasons including better spatial and temporal resolution, lack of radiation and better cost [18]. A regression tree method was used by Pfyffer et al. to sort the patients into subgroups using a predefined clinical end point [12]. A major limitation in this study was not assessing the effectiveness of URP-CTREE for predicting outcomes [12]. Attempting SVM, or other ML strategies, on this data set and evaluating accuracies would be a step to building a more reliable classifier using fMRI data [7]. This would be especially useful as MRIs are among the more commonly used diagnostic tools for spinal cord injuries, meaning this data is likely to already exist for patients and it would be easier to run an algorithm on this data rather than collecting new data [8].

Compared to fMRI, PET is advantaged when obtaining quantitative results and its signal-to-noise ratio for a single

scan, and classified mice with an accuracy of 87.5% [18,8]. The limitation of this study is that it is not clear whether the PET markers identified by the MVPA are prognostic markers as well as diagnostic as this study assumes that all mice in the BPAI condition have NP [8]. This assumption makes some sense as seventy to ninety percent of BPAI patients are observed to develop NP [8]. The second assumption is verified with an MWT, but it's not clear if this can be used to predict the onset of NP [8]. This study is conducted in rodents, and while rodents are effective models, conducting this study in a human population would yield more reliable measures as to whether this classifier can be extended to a patient population [8].

The MRS result supports the pre-existing hypothesis that lower glutamatergic metabolism and proliferation of glia and glial activation play a significant role in the development and maintenance of NP [14]. However, the observed changes in metabolite level are not enough to be used to classify patients on their own.

While fluorescence imaging is not a method that can be used in patients, it can still be useful in extracting information about how NP occurs and changes that occur before the onset of NP. This study identified autofluorescent fingerprints that can be used to identify healthy and affected tissue and point to affected mechanisms [9]. This aids a long-term goal of understanding the metabolic changes that occur due to chronic pain, a finding that can contribute to the development of treatments for chronic pains like NP [9]. The study is limited in that it is conducted in mouse models and the technique cannot be extended to human patients [9].

Conclusions

Data produced by EEG, fMRI, PET, clinical scales for measurement or other sources provides insight into the mechanisms associated with NP and can be analyzed to identify diagnostic and prognostic markers for NP. In the included studies, SVM was the most used ML algorithm, but regression trees, neural networks and LDA are almost as common. The idea of identifying multiple EEG biomarkers that can be used in tandem to improve accuracy, can be extended to a larger scope; the classification process can rely on multiple, independent, markers of high accuracy to increase the overall classification accuracy [10]. Multiple markers within one data set, such as multiple EEG markers, increases accuracy but leaves the classification subject to all the biases of the single data set [7]. Increasing the input data set to include additional data such as fMRI or PET could serve to eliminate this bias, thereby increasing the reliability of the classification [7]. SVM is known to perform well with multiple data types and is a good starting point for building a multimodal classifier, the logical next step [7]. Patients at high risk of developing chronic NP can greatly benefit from early surgical therapy because late surgical therapy is less likely to prevent chronic pain; however conservative therapies are optimal to avoid unnecessary surgeries [5]. It is important to make the distinction prior to the onset of chronic NP and building an accurate prognostic classifier can do that.

List of Abbreviations Used

SCI: spinal cord injury
NP: neuropathic pain
IASP: International Association for the Study of Pain
VAS: visual analogue scale
ODI: The Oswestry Disability Index
EEG: electroencephalography
EO: eyes open
EC: eyes closed
fMRI: functional magnetic resonance imaging
PET: positron emission tomography
ML: machine learning
HADS: hospital anxiety and depression scale
LDA: linear discriminant analysis
SVM: support vector machine
NB: naïve bayesian
ANN: artificial neuronal network
PWP: patients with neuropathic pain
PDP: patients who developed neuropathic pain
PNP: patients who did not develop neuropathic pain
AB: able-bodied participants
HFD: higuchi fractal dimension
URP-CTREE: unbiased recursive partitioning-conditional inference tree
BOLD: blood oxygen level dependent
MRS: magnetic resonance spectroscopy
MVPA: multivariate pattern analysis
PRoNTo: Pattern Recognition for Neuroimaging Toolbox
BPAI: brachial plexus avulsion injury
PCA: principal component analysis
MWT: mechanical withdrawal test
SUV: standardized uptake value
ROI: region of interest
CCI: chronic constriction injury

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

The article was a review of other existing studies and therefore did not need ethics approval or participant consent.

Authors' Contributions

AK: designed the review method, reviewed the literature, wrote the manuscript and gave final approval of the version to be published.

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