International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 24s, 2025
https://theaspd.com/index.php

Machine Learning Prediction of Autonomic Nervous System Dysfunction Using Multimodal Physiological Signals

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Abstract
Background: *This study was conducted to assess the Machine Learning Prediction of Autonomic Nervous System Dysfunction Using Multimodal Physiological Signals.*
Material and methods: *This research involved the recruitment and enrollment of 50 healthy, able-bodied individuals aged between 18 and 60 years, all with a BMI of less than 30. The average age (±SD) of the participants was 25.9 years, comprising sixteen males and five females. The average BMI recorded was 23.8. The exclusion criteria included: a history of cardiac arrhythmia, coronary artery disease, autoimmune disorders, chronic inflammatory diseases, anemia, malignancies, depression, neurological disorders, diabetes mellitus, renal diseases, dementia, psychiatric conditions including active psychosis, or any other chronic medical issues, treatment with anti-cholinergic medications, current use of tobacco, nicotine, or other recreational drugs, pre-existing neurological conditions, pregnancy, and the presence of implantable electronic devices. Participants were instructed to fast and avoid caffeine for a minimum of four hours before the testing commenced. Testing sessions occurred in a laboratory setting with shielded from external noise, light, or distractions, with an average humidity of 22% and average temperature of 22.1 °C. Lighting was set such that significant pupil changes were detected, averaging approximately 22 lm. Cardiovascular, pupil dilation, and EDA signals were synchronously recorded for each participant. The individual responses of calculated signals during each test were averaged to determine a response template.*
Results: *From all the physiological modalities we monitored, participants' cardiovascular measures (HR, MAP, and RMSSD) registered average responses with a peak above 1σ of their baseline, thus deemed significant responses, while the pupil dilation and EDA measures did not show a consistent, significant response and were discarded from further processing and feature extraction.*
Conclusion: *These findings illustrate the reliability and responsiveness of an algorithmic technique for extracting multimodal responses from conventional assessments. This innovative approach to quantifying autonomic nervous system (ANS) function can facilitate early diagnosis, track disease progression, or assess treatment efficacy.*
Keywords: *Machine learning prediction, ANS, Physiological signals.*

INTRODUCTION
The autonomic nervous system (ANS) plays a crucial role in regulating and integrating the physiological functions of various organs, including the heart, lungs, spleen, intestines, and additional organ systems. This physiological regulation encompasses the control of blood vessels, pupils, perspiration, and salivary glands. The balance between the sympathetic and parasympathetic systems is essential for this regulation, allowing for the real-time monitoring of ANS activity through the recording of neural activity from selected cranial and peripheral nerves.[1-3]
Nevertheless, undertaking this complex recording task necessitates the use of implanted electrodes, which presents significant challenges not only for animal studies but also for clinical diagnosis and treatment. In contrast, direct measurements of physiological signals that depend on the ANS provide clear alternative and verifiable methods that are less invasive than implant recordings.[4,5]
This study was conducted to assess the Machine Learning Prediction of Autonomic Nervous System Dysfunction Using Multimodal Physiological Signals.

MATERIAL AND METHODS

This research involved the recruitment and enrollment of 50 healthy, able-bodied individuals aged between 18 and 60 years, all with a BMI of less than 30. The average age (±SD) of the participants was 25.9 years, comprising sixteen males and five females. The average BMI recorded was 23.8. The exclusion criteria included: a history of cardiac arrhythmia, coronary artery disease, autoimmune disorders, chronic inflammatory diseases, anemia, malignancies, depression, neurological disorders, diabetes mellitus, renal diseases, dementia, psychiatric conditions including active psychosis, or any other chronic medical issues, treatment with anti-cholinergic medications, current use of tobacco, nicotine, or other recreational drugs, pre-existing neurological conditions, pregnancy, and the presence of implantable electronic devices. Participants were instructed to fast and avoid caffeine for a minimum of four hours before the testing commenced. Testing sessions occurred in a laboratory setting with shielded from external noise, light, or distractions, with an average humidity of 22% and average temperature of 22.1 °C. Lighting was set such that significant pupil changes were detected, averaging approximately 22 lm. Cardiovascular, pupil dilation, and EDA signals were synchronously recorded for each participant. The individual responses of calculated signals during each test were averaged to determine a response template.

RESULTS

From all the physiological modalities we monitored, participants' cardiovascular measures (HR, MAP, and RMSSD) registered average responses with a peak above 1σ of their baseline, thus deemed significant responses, while the pupil dilation and EDA measures did not show a consistent, significant response and were discarded from further processing and feature extraction.

DISCUSSION

Prognosis after stroke is often poor, with more than 40% of patients becoming disabled, institutionalized, or dying within 3 months of the index event.[6] Early medical intervention to treat major modifiable factors may limit mortality and morbidity in stroke.[7,8] In particular stroke-associated pneumonia (SAP) is consistently associated with a high risk of early mortality in acute stroke.[9]

The pathogenesis of SAP includes a stroke-induced immunodepression characterized by lymphopenia as well as lymphocytic and monocytic dysfunction impairing antibacterial defenses.[10-12] The stroke-induced immunodepression may protect against excessive neuroinflammation but increases the risk of post-stroke infections, especially pneumonia. Several clinical parameters are associated with SAP including old age, stroke severity, autonomic dysfunction, impaired consciousness and, most importantly, dysphagia and immune dysfunction.[13]

However, identifying patients at high risk for SAP remains challenging and is currently not broadly implemented in clinical routine despite the availability of widely validated risk scores like the A2DS2 score. The increasing availability of clinical data warehouses for large-scale data acquisition and analysis in many clinical centers may provide novel opportunities for automated, machine learning (ML)-based predictions of SAP and targeted timely interventions.[14]

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Nelde A et al.[15] The aim of this study was to develop a prediction model for identifying clinically apparent SAP using automated ML. The ML model used clinical and laboratory parameters along with heart rate (HR), heart rate variability (HRV), and blood pressure (BP) values obtained during the first 48 h after stroke unit admission. A logistic regression classifier was developed and internally validated with a nested-cross-validation (nCV) approach. For every shuffle, the model was first trained and validated with a fixed threshold for 0.9 sensitivity, then finally tested on the out-of-sample data and benchmarked against a widely validated clinical score (A2DS2). They identified 2390 eligible patients admitted to two-stroke units at Charité between October 2020 and June 2023, of whom 1755 had all parameters available. SAP was diagnosed in 96/1755 (5.5%). Circadian profiles in HR, HRV, and BP metrics during the first 48 h after admission exhibited distinct differences between patients with SAP diagnosis vs. those without. CRP, mRS at admission, leukocyte count, high-frequency power in HRV, stroke severity at admission, sex, and diastolic BP were identified as the most informative ML features. They obtained an AUC of 0.91

(CI 0.88–0.95) for the ML model on the out-of-sample data in comparison to an AUC of 0.84 (CI 0.76–0.91) for the previously established A2DS2 score ($p < 0.001$). The ML model provided a sensitivity of 0.87 (CI 0.75–0.97) with a corresponding specificity of 0.82 (CI 0.78–0.85) which outperformed the A2DS2 score for multiple cutoffs. Automated, data warehouse-based prediction of clinically apparent SAP in the stroke unit setting is feasible, benefits from the inclusion of vital signs, and could be useful for identifying high-risk patients or prophylactic pneumonia management in clinical routine.

Debnath S et al.[16] Twenty-one individuals were assessed in two morning and two afternoon sessions over two weeks. Each session included five standard clinical tests probing autonomic function: squat test, cold pressor test, diving reflex test, deep breathing, and Valsalva maneuver. Noninvasive sensors captured continuous electrocardiography, blood pressure, breathing, electrodermal activity, and pupil diameter. Heart rate, heart rate variability, mean arterial pressure, electrodermal activity, and pupil diameter responses to the perturbations were extracted, and averages across participants were computed. A template matching algorithm calculated scaling and stretching features that optimally fit the average to an individual response. These features were grouped based on test and modality to derive sympathetic and parasympathetic indices for this healthy population. A significant positive correlation ($p = 0.000377$) was found between sympathetic amplitude response and body mass index. Additionally, longer duration and larger amplitude sympathetic and longer duration parasympathetic responses occurred in afternoon testing sessions; larger amplitude parasympathetic responses occurred in morning sessions. These results demonstrate the robustness and sensitivity of an algorithmic approach to extract multimodal responses from standard tests. This novel method of quantifying ANS function can be used for early diagnosis, measurement of disease progression, or treatment evaluation.

CONCLUSION

These findings illustrate the reliability and responsiveness of an algorithmic technique for extracting multimodal responses from conventional assessments. This innovative approach to quantifying autonomic nervous system (ANS) function can facilitate early diagnosis, track disease progression, or assess treatment efficacy.

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