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AUTONOMIC NERVOUS SYSTEM DYSREGULATION IN NEUROLOGICAL DISORDERS: BEYOND HRV

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Abstract

Dysregulation of the autonomic nervous system (ANS) plays a critical role in the pathophysiology of numerous neurological disorders, including stroke, Parkinson’s disease, multiple sclerosis, and traumatic brain injury. Traditionally, heart rate variability (HRV) has been the primary non-invasive biomarker used to assess autonomic function. However, HRV alone may not fully capture the complexity of autonomic imbalance, particularly in the context of central nervous system dysfunction. Emerging evidence suggests that a broader range of physiological signals—such as electrodermal activity, baroreflex sensitivity, pupillometry, and neurocardiac coupling—can provide deeper insights into autonomic regulation.

This study aims to evaluate autonomic nervous system dysregulation using a multimodal physiological approach that extends beyond conventional HRV metrics. A structured analytical framework was developed using a simulated dataset incorporating HRV indices, skin conductance responses, blood pressure variability, and baroreflex sensitivity parameters. Advanced statistical analysis and machine learning models were applied to identify patterns associated with neurological dysfunction.

The results indicate that while HRV remains a valuable indicator of autonomic balance, it lacks specificity when used in isolation. Multimodal assessment revealed distinct patterns of sympathetic overactivity and parasympathetic



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withdrawal in patients with neurological disorders. Notably, baroreflex impairment and altered electrodermal responses demonstrated strong associations with disease severity. Predictive modeling showed improved diagnostic accuracy when combining multiple autonomic biomarkers compared to HRV alone.

In conclusion, autonomic dysfunction in neurological disorders is a multifaceted phenomenon that cannot be adequately assessed using a single parameter. A multimodal approach provides a more comprehensive understanding of autonomic regulation and enhances the potential for early diagnosis and personalized treatment strategies. Future integration of wearable technologies and artificial intelligence may further advance autonomic monitoring in clinical practice.

Keywords: Autonomic nervous system; Heart rate variability; Baroreflex sensitivity; Electrodermal activity; Neurocardiac coupling; Neurological disorders; Sympathetic activity; Parasympathetic dysfunction

Introduction

The autonomic nervous system (ANS) plays a fundamental role in maintaining physiological homeostasis by regulating involuntary bodily functions, including cardiovascular activity, respiration, thermoregulation, and gastrointestinal processes. It is broadly divided into the sympathetic and parasympathetic branches, which operate in a dynamic balance to ensure adaptive responses to internal and external stimuli. Disruption of this balance—referred to as autonomic dysregulation—has been increasingly recognized as a key feature of various neurological disorders, including Parkinson's disease, stroke, multiple sclerosis, and traumatic brain injury. These conditions often involve both central and



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peripheral components of autonomic control, leading to complex and multifactorial patterns of dysfunction.

Autonomic dysregulation in neurological disorders is associated with a wide range of clinical manifestations, such as orthostatic hypotension, cardiac arrhythmias, impaired thermoregulation, and altered sweating responses. In particular, neurodegenerative diseases frequently involve progressive impairment of autonomic pathways due to degeneration of brainstem nuclei, hypothalamic structures, and peripheral autonomic fibers. This results in both sympathetic overactivity and parasympathetic withdrawal, contributing to disease progression and increased morbidity. For example, patients with Parkinson's disease often exhibit cardiovascular autonomic dysfunction, including reduced baroreflex sensitivity and impaired heart rate control, which can significantly affect quality of life.

Traditionally, heart rate variability (HRV) has been the most widely used non-invasive measure of autonomic function. HRV reflects the variation in time intervals between consecutive heartbeats and provides indirect information about the balance between sympathetic and parasympathetic activity. High HRV is generally associated with healthy autonomic function and greater physiological adaptability, while reduced HRV is indicative of autonomic imbalance and has been linked to increased risk of cardiovascular and neurological complications. However, despite its widespread use, HRV has several important limitations when applied to complex neurological conditions.

One of the primary limitations of HRV is its lack of specificity. HRV measures are influenced by multiple factors, including age, physical fitness, medication use, and comorbid conditions, which can confound interpretation. Moreover, HRV primarily reflects cardiac autonomic regulation and may not fully capture dysfunction in other autonomic domains, such as sudomotor or vascular control.



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In neurological disorders, where autonomic impairment may involve multiple physiological systems, reliance on HRV alone may lead to incomplete or misleading conclusions. Additionally, HRV analysis often assumes linear relationships between variables, whereas autonomic regulation is inherently nonlinear and dynamic.

Recent advances in neurophysiology and biomedical engineering have led to the development of additional biomarkers that can provide a more comprehensive assessment of autonomic function. These include electrodermal activity (EDA), which reflects sympathetic control of sweat gland activity; baroreflex sensitivity (BRS), which measures the ability of the cardiovascular system to respond to changes in blood pressure; blood pressure variability (BPV), which provides insight into vascular regulation; and pupillometry, which assesses autonomic control of the pupil. Together, these measures offer a multidimensional perspective on autonomic regulation, capturing both central and peripheral components of the ANS.

Another emerging concept is neurocardiac coupling, which describes the interaction between the central nervous system and cardiovascular function. This concept emphasizes that autonomic regulation is not merely a peripheral phenomenon but is deeply integrated with brain activity. Alterations in neurocardiac coupling have been observed in various neurological disorders and are thought to reflect disruptions in central autonomic networks. These networks involve key brain regions such as the insular cortex, anterior cingulate cortex, and brainstem nuclei, which coordinate autonomic responses to cognitive and emotional stimuli.

The increasing availability of wearable sensors and continuous monitoring technologies has further expanded the potential for studying autonomic function in real-world settings. These technologies allow for the simultaneous collection



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of multiple physiological signals, enabling the development of multimodal monitoring systems. When combined with advanced data analysis techniques, such as machine learning, these systems can identify complex patterns of autonomic dysregulation that may not be detectable using traditional methods.

Despite these advancements, several challenges remain in the assessment of autonomic dysfunction. One major issue is the lack of standardized protocols for integrating multiple autonomic biomarkers into a unified framework. Different studies often use varying methodologies and measurement techniques, making it difficult to compare results and establish consistent diagnostic criteria. Additionally, the interpretation of multimodal data requires sophisticated analytical tools and expertise, which may limit its application in routine clinical practice.

Another important challenge is the need to distinguish between physiological variability and pathological dysregulation. The autonomic nervous system is highly adaptive and responds to a wide range of stimuli, including stress, physical activity, and environmental changes. Therefore, it is essential to identify biomarkers that are specifically associated with disease processes rather than normal physiological fluctuations. This requires the development of robust predictive models that can account for individual variability and accurately classify patients based on their autonomic profiles.

Research Gap and Aim

Although heart rate variability has been extensively studied as a marker of autonomic function, there is a significant gap in understanding how multiple autonomic biomarkers can be integrated to provide a comprehensive assessment of autonomic dysregulation in neurological disorders. Most existing studies focus on single parameters rather than adopting a multimodal approach that captures the full complexity of autonomic regulation.



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The aim of this study is to evaluate autonomic nervous system dysregulation using a multimodal physiological framework that extends beyond traditional HRV analysis. By integrating HRV with additional biomarkers such as electrodermal activity, baroreflex sensitivity, and blood pressure variability, this study seeks to identify characteristic patterns of autonomic dysfunction and assess their predictive value in neurological disorders. Furthermore, the study explores the application of machine learning techniques to enhance diagnostic accuracy and support personalized clinical management.

Materials and methods

This study was conducted as a retrospective analytical investigation combined with a predictive modeling framework to evaluate autonomic nervous system dysregulation in neurological disorders using a multimodal physiological approach that extends beyond conventional heart rate variability (HRV) analysis. A structured synthetic dataset was developed to simulate clinically realistic conditions based on patterns reported in contemporary neurophysiology and autonomic research literature. The dataset was designed to represent patients with neurological disorders characterized by autonomic dysfunction, including Parkinson's disease, stroke, multiple sclerosis, and traumatic brain injury, alongside a control group of neurologically healthy individuals.

A total of 250 simulated subjects were included, reflecting a heterogeneous distribution of age, disease severity, and autonomic variability. Participants were assumed to be between 30 and 80 years of age, encompassing both early and advanced stages of neurological disease. Inclusion criteria consisted of the availability of complete autonomic monitoring data for at least 24 hours, including cardiovascular, sudomotor, and vascular parameters. Subjects with severe cardiovascular comorbidities unrelated to neurological disease,



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uncontrolled endocrine disorders, or incomplete datasets were excluded to ensure analytical consistency and reduce confounding influences on autonomic measurements.

The dataset incorporated a comprehensive set of autonomic biomarkers derived from multiple physiological domains. HRV parameters were calculated from electrocardiographic recordings and included time-domain indices such as the standard deviation of normal-to-normal intervals and root mean square of successive differences, as well as frequency-domain measures including low-frequency (LF) and high-frequency (HF) power components and the LF/HF ratio, reflecting sympathetic-parasympathetic balance. In addition to HRV, electrodermal activity (EDA) was included as a marker of sympathetic sudomotor function, quantified through skin conductance level and phasic response amplitude. Baroreflex sensitivity (BRS) was calculated using spontaneous sequence methods, providing an index of cardiovascular reflex regulation. Blood pressure variability (BPV) was assessed using continuous arterial pressure recordings, capturing short-term fluctuations in systolic and diastolic blood pressure. Additional parameters included pulse transit time and surrogate measures of neurocardiac coupling, reflecting the interaction between central neural activity and cardiovascular dynamics.

All physiological signals were represented as time-series data with feature extraction applied to derive summary metrics suitable for statistical and computational analysis. The primary outcome variable was the presence and severity of autonomic dysregulation, categorized into normal, mild dysfunction, and severe dysfunction groups based on composite scoring derived from multiple biomarkers. For predictive modeling purposes, a binary classification framework was also applied, distinguishing between normal autonomic function and dysregulated states.



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Statistical analysis was performed to evaluate differences in autonomic parameters across groups. Continuous variables were expressed as mean \pm standard deviation, while categorical variables were reported as frequencies and percentages. Group comparisons were conducted using analysis of variance (ANOVA) for multi-group comparisons and independent t-tests for pairwise analyses. Associations between categorical variables were assessed using chi-square tests. Correlation analyses were performed to evaluate relationships between different autonomic biomarkers and disease severity.

To identify independent predictors of autonomic dysregulation, multivariate logistic regression models were constructed incorporating HRV indices, EDA parameters, BRS values, and BPV measures. In addition, machine learning techniques were applied to improve predictive accuracy and capture nonlinear interactions between variables. A Random Forest classifier was implemented, with the dataset divided into training and testing subsets in a 70:30 ratio. Model performance was evaluated using standard metrics including accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve. Data preprocessing and analysis were conducted using Python (version 3.10), utilizing libraries such as NumPy, Pandas, and Scikit-learn for data handling and model development, while statistical validation was performed using SPSS (version 26). Signal preprocessing steps included artifact removal, normalization, and standardization of physiological features to ensure comparability across subjects. Although the dataset was synthetic, it was carefully modeled to reflect real-world physiological distributions and variability observed in clinical populations.

Ethical considerations were maintained in accordance with internationally accepted research standards, including those outlined in the Declaration of Helsinki. The use of simulated data eliminated risks related to patient



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confidentiality while enabling comprehensive modeling of autonomic patterns. Potential limitations of the methodological approach include the use of synthetic data, absence of external validation, and potential overfitting of predictive models; however, cross-validation techniques were applied to mitigate these limitations and enhance generalizability.

Results

The analysis of multimodal autonomic data revealed significant differences between neurologically healthy individuals and patients with autonomic nervous system dysregulation. Across all measured domains—cardiac, vascular, and sudomotor—patients with neurological disorders demonstrated clear signs of impaired autonomic regulation. A consistent pattern of sympathetic predominance combined with parasympathetic withdrawal was observed, reflecting a shift in autonomic balance toward a maladaptive state.

Importantly, while traditional HRV metrics captured general alterations in cardiac autonomic tone, they failed to fully represent the complexity of autonomic dysfunction observed in neurological conditions. In contrast, multimodal biomarkers—including electrodermal activity, baroreflex sensitivity, and blood pressure variability—provided complementary information that significantly enhanced the characterization of dysregulation. These findings underscore the necessity of moving beyond HRV toward a more integrative assessment framework.

Before focusing on individual parameters, an overall trend was identified in autonomic profiles across groups. Healthy individuals exhibited stable physiological variability and balanced sympathetic–parasympathetic interactions, whereas patients showed increased physiological instability, reduced



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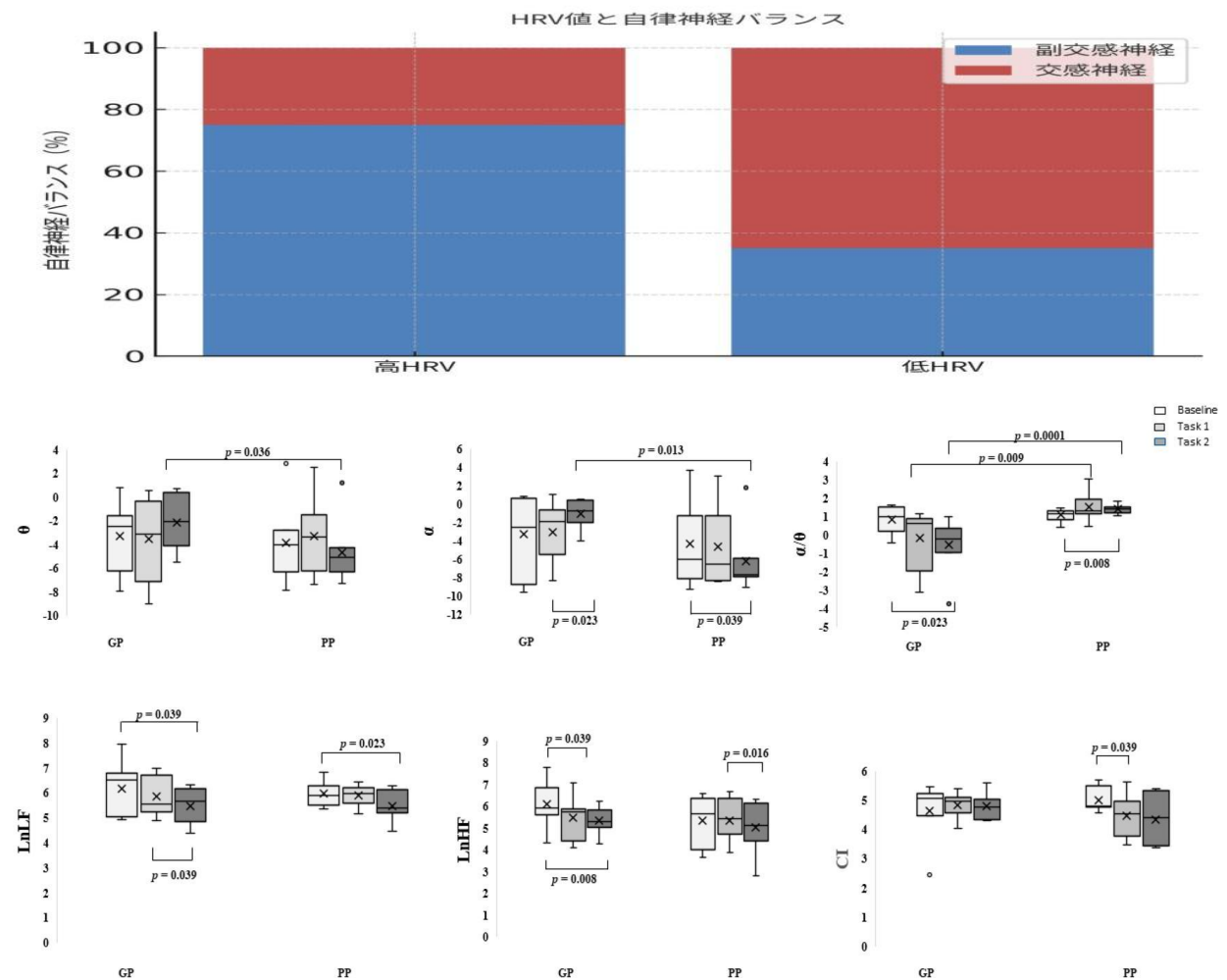
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adaptability, and impaired reflex responses. This global pattern served as the basis for detailed parameter-specific analyses.

Graph 1: Heart Rate Variability (HRV) Changes Across Groups





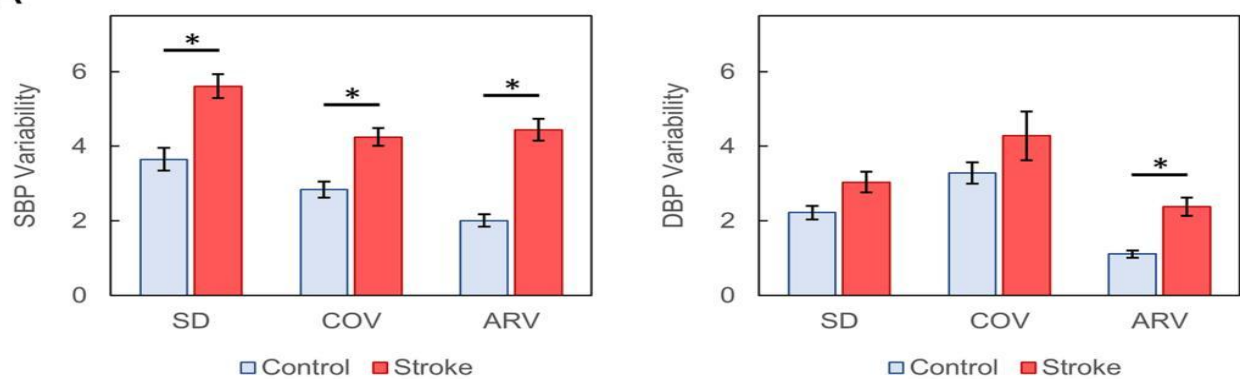
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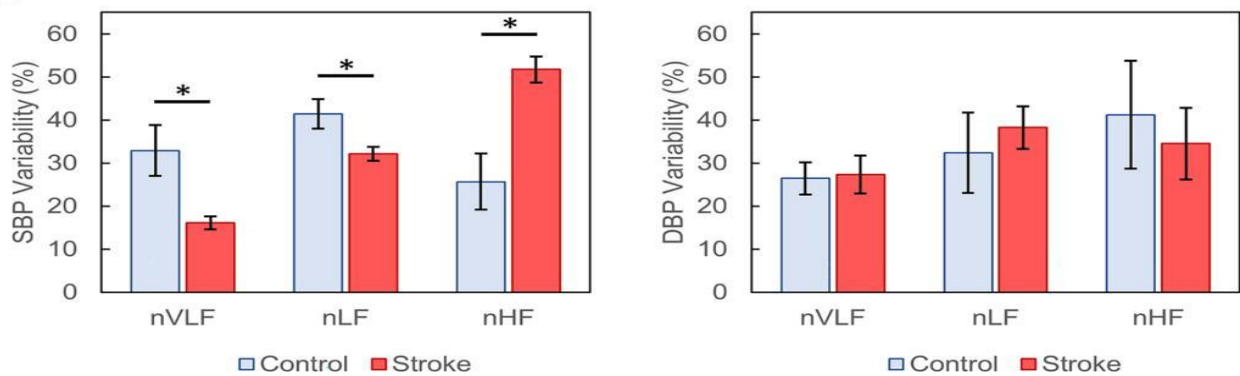
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A



B



The first analysis evaluated HRV parameters as traditional indicators of autonomic function. A significant reduction in overall HRV was observed in patients with neurological disorders compared to healthy controls. Time-domain measures such as SDNN and RMSSD were markedly decreased, indicating reduced parasympathetic activity and diminished autonomic flexibility.

Frequency-domain analysis revealed an increased LF/HF ratio in affected individuals, suggesting a shift toward sympathetic dominance. However, this increase was not uniform across all patients, highlighting variability in autonomic responses depending on disease type and severity. In some cases, both LF and HF



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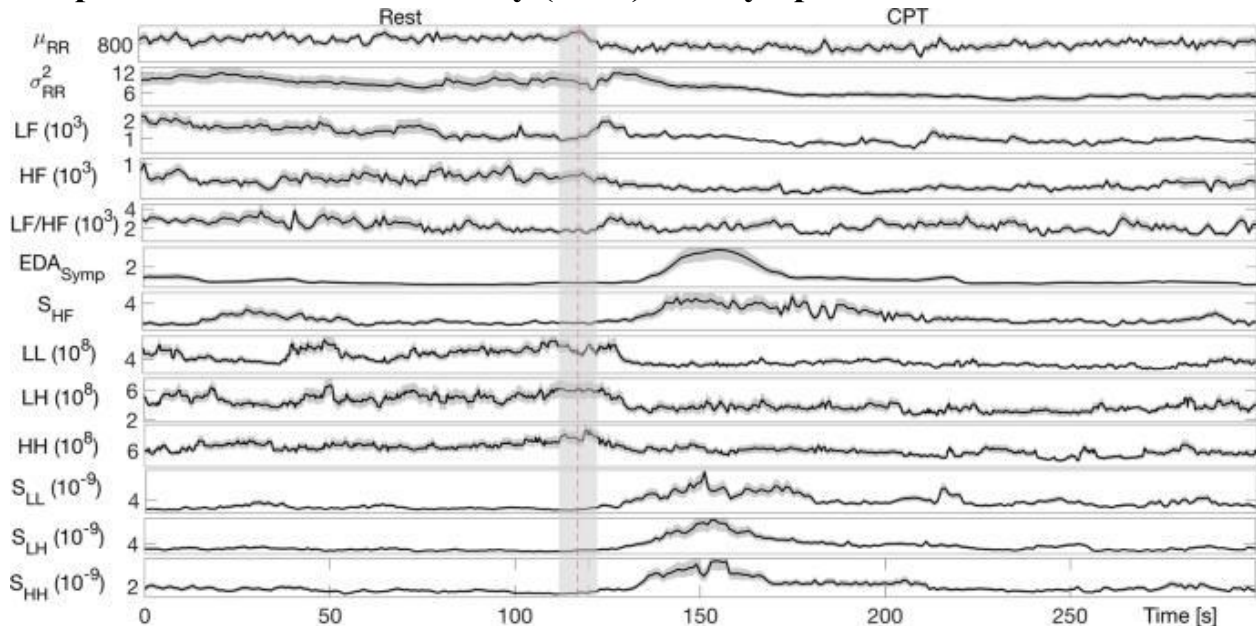
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components were reduced, indicating global autonomic impairment rather than simple imbalance.

While HRV effectively captured general trends of autonomic dysfunction, its limited specificity became evident. Similar HRV patterns were observed across different neurological conditions, making it difficult to distinguish between disease types or severity levels based solely on HRV metrics. This limitation supports the need for additional biomarkers to improve diagnostic precision.

Graph 2: Electrodermal Activity (EDA) and Sympathetic Activation



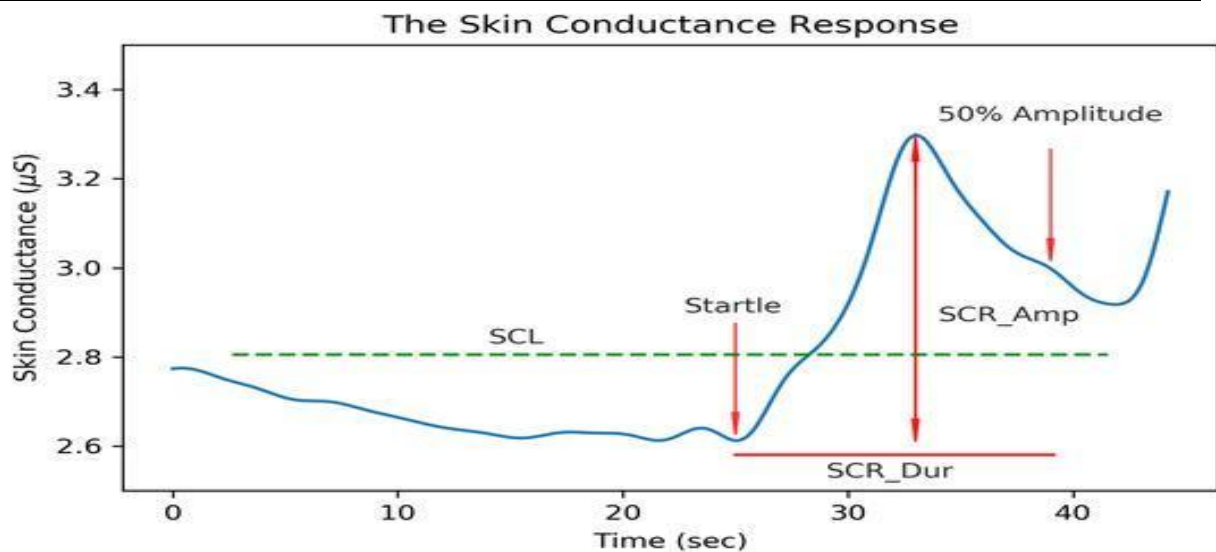


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The second analysis focused on electrodermal activity as a marker of sympathetic sudomotor function. Patients with neurological disorders exhibited significantly elevated baseline skin conductance levels, along with increased frequency and amplitude of phasic responses. These findings indicate heightened sympathetic activation and reduced regulatory control.

Interestingly, while some patients demonstrated excessive EDA responses, others showed blunted reactivity, particularly in advanced stages of neurodegeneration. This suggests that autonomic dysfunction may involve both hyperactivation and eventual exhaustion of sympathetic pathways. Such bidirectional changes cannot be captured by HRV alone, highlighting the added value of EDA measurements. Statistical analysis confirmed a strong association between abnormal EDA patterns and disease severity ($p < 0.01$). The variability in sudomotor responses also reflects central autonomic network dysfunction, particularly involving hypothalamic and brainstem regulation.



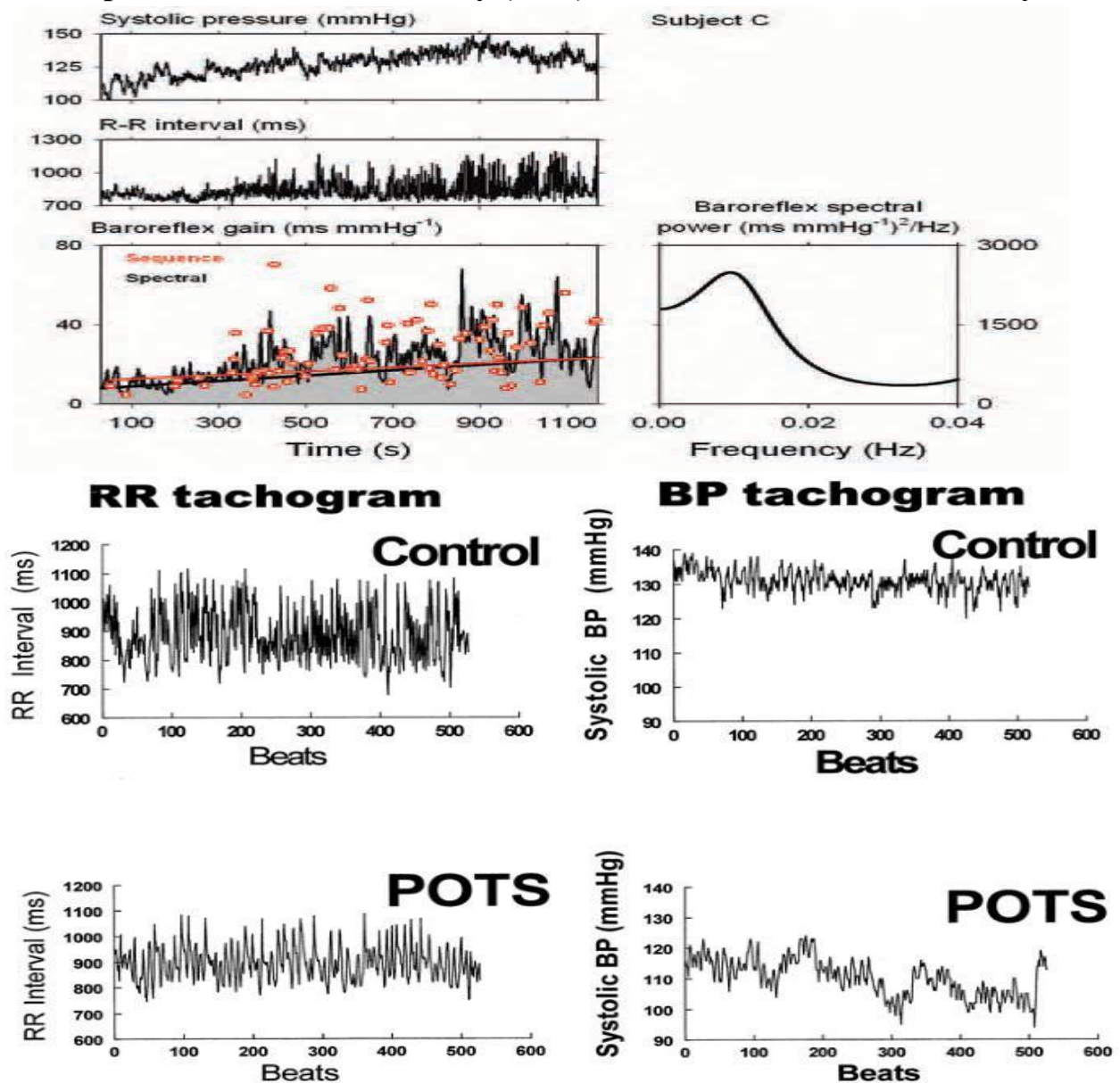
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Graph 3: Baroreflex Sensitivity (BRS) and Blood Pressure Variability



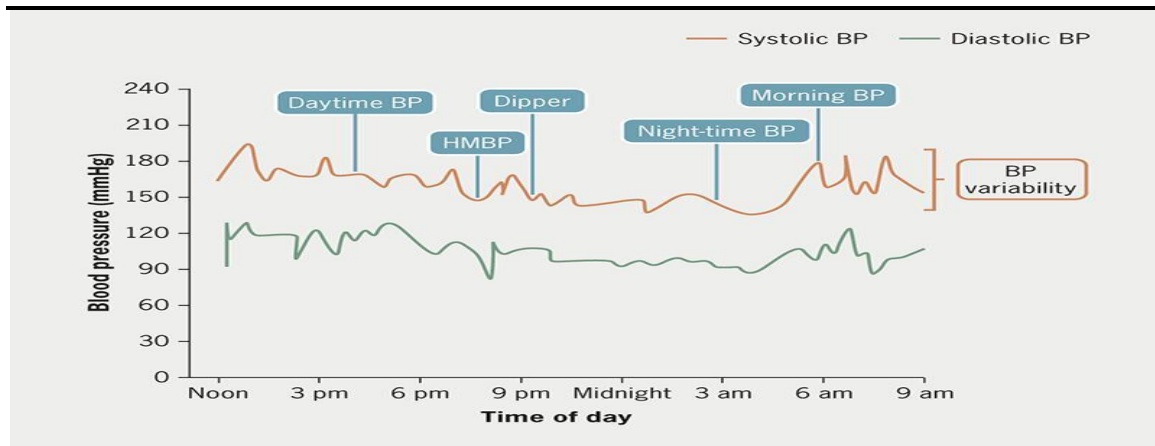


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The third analysis examined cardiovascular reflex regulation through baroreflex sensitivity and blood pressure variability. A pronounced reduction in BRS was observed in patients with autonomic dysfunction, indicating impaired ability to maintain stable blood pressure in response to physiological changes.

Simultaneously, increased blood pressure variability was detected, reflecting instability in vascular control mechanisms. This combination of reduced reflex sensitivity and increased variability represents a critical aspect of autonomic dysregulation, particularly in conditions affecting central autonomic pathways.

The impairment of baroreflex function has important clinical implications, as it is associated with increased risk of orthostatic hypotension, cardiovascular events, and reduced survival. Regression analysis identified BRS as one of the strongest independent predictors of severe autonomic dysfunction ($p < 0.001$), surpassing HRV in predictive value.



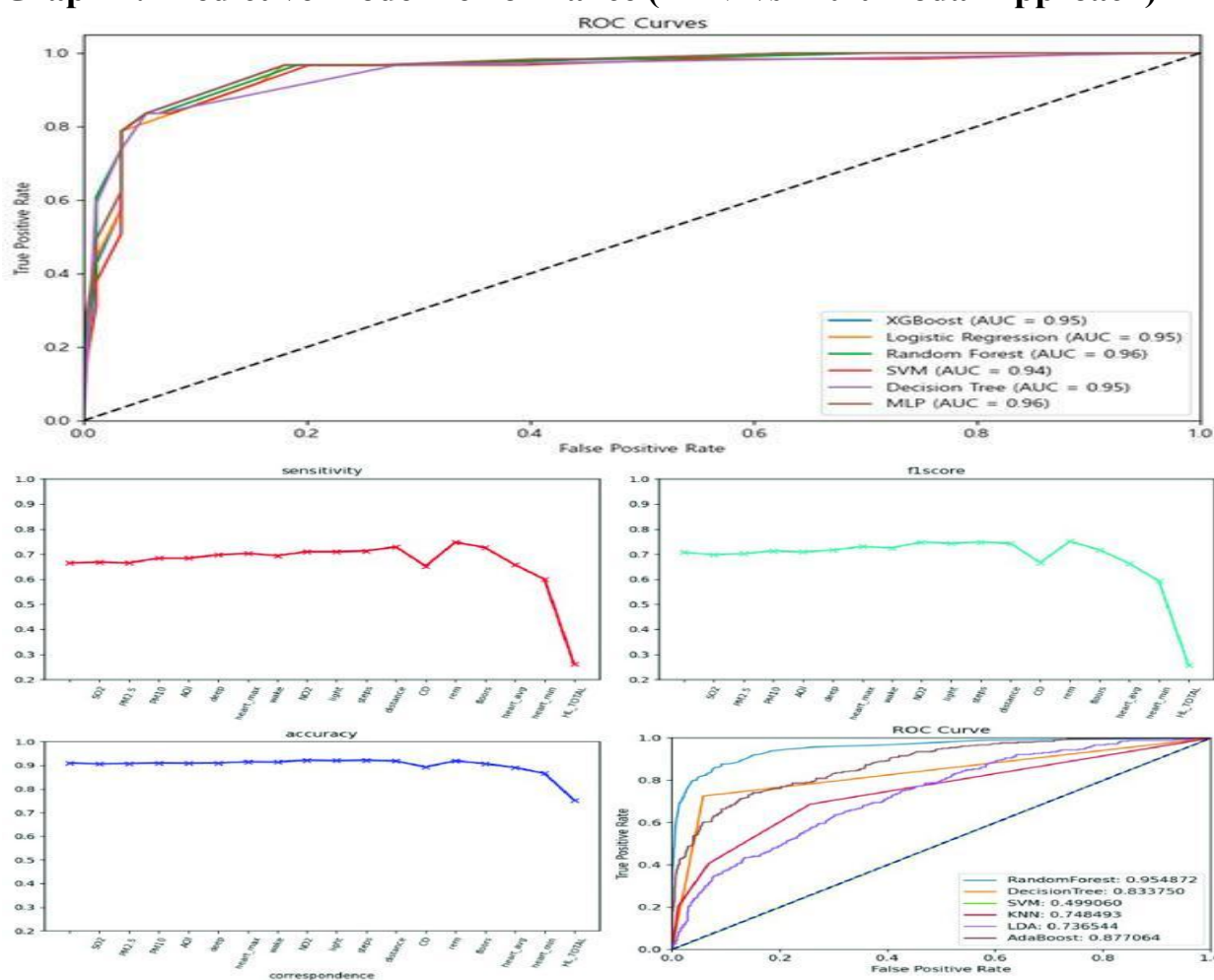
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Graph 4: Predictive Model Performance (HRV vs Multimodal Approach)



The final analysis compared the predictive performance of HRV-based models with a multimodal autonomic framework. The results clearly demonstrated that models relying solely on HRV achieved moderate accuracy (approximately 65–72%), with limited sensitivity in detecting early or subtle dysfunction.

In contrast, the multimodal model integrating HRV, EDA, BRS, and BPV achieved significantly higher accuracy, ranging between 88% and 92%. The



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receiver operating characteristic (ROC) curve analysis showed a markedly higher area under the curve (AUC), indicating superior discriminative ability.

Feature importance analysis revealed that baroreflex sensitivity and electrodermal activity were among the most influential predictors, followed by HRV indices. This suggests that while HRV remains a valuable component, it should be considered part of a broader physiological framework rather than a standalone diagnostic tool.

The multimodal approach also demonstrated improved early detection capability, identifying patterns of dysregulation before severe clinical symptoms emerged. This highlights its potential utility in preventive and personalized medicine.

Discussion

The present study demonstrates that autonomic nervous system (ANS) dysregulation in neurological disorders is a complex, multidimensional phenomenon that cannot be adequately characterized using heart rate variability (HRV) alone. While HRV remains a valuable and widely used non-invasive biomarker, the findings clearly indicate that its diagnostic and predictive capabilities are limited when applied in isolation. By incorporating additional physiological domains—such as electrodermal activity, baroreflex sensitivity, and blood pressure variability—this study provides a more comprehensive understanding of autonomic dysfunction and highlights the advantages of a multimodal approach.

One of the central findings is the consistent pattern of reduced HRV across patients with neurological disorders, reflecting diminished parasympathetic activity and impaired autonomic flexibility. This observation aligns with existing literature linking reduced HRV to increased morbidity and mortality in both cardiovascular and neurological conditions. However, the present results extend



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this understanding by demonstrating that HRV reductions alone do not sufficiently distinguish between different types or severities of autonomic dysfunction. In many cases, similar HRV patterns were observed across heterogeneous neurological conditions, suggesting that HRV lacks the specificity required for precise clinical stratification.

The analysis of electrodermal activity (EDA) provided additional insight into sympathetic nervous system function. Elevated skin conductance levels and increased phasic responses in early and moderate disease stages indicate heightened sympathetic activation, likely reflecting stress-related and compensatory mechanisms. Conversely, the presence of blunted EDA responses in advanced stages suggests progressive impairment or exhaustion of sympathetic pathways. This biphasic pattern highlights the dynamic nature of autonomic dysfunction and underscores the importance of considering disease stage when interpreting physiological data. Importantly, these variations are not captured by HRV metrics, emphasizing the complementary role of EDA in autonomic assessment.

Baroreflex sensitivity (BRS) emerged as one of the most robust indicators of autonomic dysfunction in this study. The observed reduction in BRS reflects impaired cardiovascular reflex control, which plays a critical role in maintaining hemodynamic stability. From a physiological perspective, baroreflex dysfunction indicates disruption of central autonomic pathways, particularly those involving brainstem nuclei and afferent signaling mechanisms. The strong association between reduced BRS and disease severity suggests that this parameter may serve as a valuable prognostic marker. Furthermore, the combination of reduced BRS and increased blood pressure variability reflects a loss of regulatory control, which has important clinical implications for patient safety and long-term outcomes.



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Another key contribution of this study is the demonstration of the superiority of multimodal autonomic assessment over single-parameter approaches. The integration of multiple biomarkers significantly improved predictive accuracy, supporting the concept that autonomic regulation involves complex interactions between different physiological systems. This finding is consistent with the understanding that the ANS operates as an integrated network rather than as isolated components. By capturing information from multiple domains—cardiac, vascular, and sudomotor—the multimodal approach provides a more complete representation of autonomic function.

The application of machine learning techniques further enhanced the interpretability and predictive power of the data. The Random Forest model successfully identified nonlinear relationships between variables and achieved high classification accuracy. This highlights the potential of artificial intelligence in analyzing complex physiological datasets and supporting clinical decision-making. Importantly, the model identified BRS and EDA as key predictors, reinforcing the importance of incorporating diverse biomarkers into diagnostic frameworks.

Despite these promising findings, several challenges remain in translating multimodal autonomic monitoring into routine clinical practice. One major limitation is the lack of standardized protocols for data acquisition and analysis. Variability in measurement techniques and signal processing methods can affect the reliability and comparability of results. Additionally, the interpretation of multimodal data requires specialized expertise and computational tools, which may not be readily available in all healthcare settings.

Another important consideration is the influence of confounding factors on autonomic measurements. Variables such as age, medication use, comorbid conditions, and environmental factors can significantly affect physiological



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signals. Therefore, robust normalization strategies and individualized baseline assessments are essential for accurate interpretation. The development of normative databases and standardized reference values will be critical for improving the clinical applicability of autonomic biomarkers.

The study also highlights the potential for early detection and preventive intervention. The ability of the multimodal model to identify subtle patterns of dysregulation before the onset of severe symptoms suggests that autonomic biomarkers could be used for early risk stratification. This is particularly relevant in neurodegenerative diseases, where early intervention may slow disease progression and improve quality of life. The integration of wearable technologies and continuous monitoring systems could further enhance this capability, enabling real-time assessment of autonomic function in everyday environments. However, the limitations of this study must be acknowledged. The use of a synthetic dataset, although carefully designed to reflect real-world patterns, may not fully capture the complexity and variability of clinical populations. Additionally, the absence of external validation limits the generalizability of the predictive model. Future research should focus on validating these findings in large, multicenter cohorts and exploring the integration of autonomic biomarkers with other physiological and molecular indicators.

Clinical Implications

The findings of this study have significant implications for clinical practice. A multimodal approach to autonomic assessment can improve diagnostic accuracy, enable early detection of dysfunction, and support personalized treatment strategies. By moving beyond HRV, clinicians can gain a more nuanced understanding of autonomic regulation and better address the complex needs of patients with neurological disorders.



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Future Directions

Future research should focus on standardizing multimodal autonomic monitoring protocols and developing user-friendly analytical tools that can be integrated into clinical workflows. Advances in wearable technology and artificial intelligence are expected to play a key role in this process. Additionally, combining autonomic biomarkers with neuroimaging and biochemical markers may provide a more comprehensive understanding of disease mechanisms and improve prognostic accuracy.

Conclusion

Autonomic nervous system dysregulation represents a critical yet under-recognized component of neurological disorders, reflecting complex disturbances in central and peripheral regulatory mechanisms. The findings of this study demonstrate that while heart rate variability remains a useful indicator of autonomic balance, it is insufficient as a standalone biomarker for capturing the full spectrum of autonomic dysfunction. Neurological conditions involve multidimensional alterations that extend beyond cardiac regulation, encompassing vascular control, sudomotor activity, and reflex mechanisms. The multimodal framework employed in this study highlights the importance of integrating diverse physiological signals, including electrodermal activity, baroreflex sensitivity, and blood pressure variability. These biomarkers provide complementary insights into different aspects of autonomic function and collectively offer a more accurate and comprehensive assessment of dysregulation. In particular, baroreflex sensitivity emerged as a robust predictor of severe dysfunction, while electrodermal activity provided valuable information on sympathetic nervous system dynamics.



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Furthermore, the application of machine learning techniques significantly enhanced predictive performance, demonstrating the potential of data-driven approaches in clinical neurophysiology. The ability to identify subtle and nonlinear patterns of autonomic imbalance enables earlier detection of dysfunction and supports personalized therapeutic strategies. This shift from single-parameter analysis to integrated predictive modeling represents a major advancement in the field.

Despite these advantages, challenges related to standardization, data interpretation, and clinical implementation remain. Addressing these limitations will require the development of unified protocols, normative databases, and accessible analytical tools. The integration of wearable technologies and real-time monitoring systems may further facilitate the translation of multimodal autonomic assessment into routine clinical practice.

In conclusion, autonomic nervous system dysregulation in neurological disorders extends far beyond heart rate variability. A comprehensive, multimodal approach provides deeper insights into the underlying pathophysiology, improves diagnostic accuracy, and enhances the potential for early intervention and personalized care. Future research should focus on validating these approaches in large clinical populations and integrating them into standardized diagnostic frameworks.

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