



Short communication

Machine learning-based discrimination of panic disorder from other anxiety disorders

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ABSTRACT

Backgrounds: Panic disorder is a highly prevalent psychiatric disorder that substantially impairs quality of life and psychosocial function. Panic disorder arises from neurobiological substrates and developmental factors that distinguish it from other anxiety disorders. Differential diagnosis between panic disorder and other anxiety disorders has only been conducted in terms of a phenomenological spectrum.

Methods: Through a machine learning-based approach with heart rate variability (HRV) as input, we aimed to build algorithms that can differentiate panic disorder from other anxiety disorders. Five algorithms were used: random forest (RF), gradient boosting machine (GBM), support vector machine (SVM), artificial neural network (ANN), and regularized logistic regression (LR). 10-fold cross-validation with five repeats was used to build the final models.

Results: A total of 60 patients with panic disorder and 61 patients with other anxiety disorders (aged between 20 and 65 years) were recruited. The L1-regularized LR showed the best accuracy (0.784), followed by ANN (0.730), SVM (0.730), GBM (0.676), and finally RF (0.649). LR also had good performance in other measures, such as F₁-score (0.790), specificity (0.737), sensitivity (0.833), and Matthews correlation coefficient (0.572).

Limitations: Cross-sectional design and limited sample size is limitations.

Conclusion: This study demonstrated that HRV can be used to differentiate panic disorder from other anxiety disorders. Future studies with larger sample sizes and longitudinal design are required to replicate the diagnostic utility of HRV in a machine learning approach.

1. INTRODUCTION

Panic disorder is characterized by panic attacks of increased autonomic nervous symptoms, intense fear of losing control, and worry from anticipating attacks (Hamm et al., 2014; Locke et al., 2015). Panic attacks also occur in other anxiety disorders, such as obsessive-compulsive disorder, specific phobias, and generalized anxiety disorder (Locke et al., 2015). Given the high prevalence of panic attacks in other anxiety disorders, the specifier of panic attack has been newly added to the diagnosis of other anxiety disorders since the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders in 2015 (Bandelow, 2017).

Although the importance of sympathetic nervous dysregulation has been emphasized in panic disorder (Perna and Caldirola, 2018), panic disorder is commonly accompanied by other anxiety disorders

(Herr et al., 2014). Panic disorder and other anxiety disorders are distinguishable by several factors. First, panic disorder has the highest comorbidity with bipolar disorder (Nabavi et al., 2015). Secondly, panic disorder has fewer comorbid anxiety and depressive disorders compared to generalized anxiety disorder (GAD), which has comorbidity with psychiatric disorders such as depression, posttraumatic stress disorder (PTSD), and social phobia (Newman et al., 2016). Thirdly, there are differences in functional connectivity in the brain (Cui et al., 2016). GAD has increased connectivity in the hippocampus, parahippocampal formation, and fusiform gyrus and decreased connectivity from the precentral gyrus to visual areas. However, in panic disorder, the area of altered functional connectivity is much less than that in GAD. Interestingly, there have been several findings that patients with panic disorder have more cardiac diseases and deaths (Chalmers et al., 2014; Tully et al., 2015), but these findings are not

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limited to just cardiac symptoms. A recent study revealed that panic disorder had higher surface area in the left postcentral gyrus than in generalized anxiety disorder, major depressive disorder, and healthy controls (Maggioni et al., 2019).

Given the current evidence, panic disorder and other anxiety disorders are likely to be differentiable by observable measures despite their similar symptoms. One of the most widely used physiological measures is heart rate variability (HRV). HRV represents variations in the beat-to-beat interval of heartbeats (Shaffer and Ginsberg, 2017). The autonomic nervous system (i.e., sympathetic and parasympathetic nervous system) interacts with the sinoatrial node, which is the heart's primary natural pacemaker (Yaniv et al., 2014).

HRV is widely used in research related to stress and its related psychiatric disorders. The convenience, non-invasiveness, and cost-effectiveness of HRV are its advantages. Particularly, given the close association between autonomic nervous system and anxiety (Pohjavaara et al., 2003), there have been many studies measuring HRV among anxiety disorders. A meta-analysis showed that anxiety disorders had associations with various measures of HRV (Chalmers et al., 2014). Particularly, panic disorder was associated with lower high frequency (HF) in terms of healthy controls (Chalmers et al., 2014).

As anxiety disorders share similar etiological factors and psychopathology, using conventional methods to differentiate panic disorder from other anxiety disorders may not be easy. Using machine learning, we aimed to build a classification model to differentiate panic disorder from other anxiety disorders.

2. METHODS

2.1. Participants

Data were obtained from a medical chart recorded between January 2011 and December 2017. The inclusion criteria were (1) aged between 20 and 65, (2) diagnosed with a panic disorder (according to the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code for F41.0) or other anxiety disorders (F41.1 to F41.9), and (3) had HRV measured for the first month of hospital visits. The exclusion criteria were (1) clinically significant comorbid cardiovascular diseases, such as arrhythmia and cardiomyopathy, and (2) comorbid psychiatric and substance disorder other than an anxiety disorder.

The diagnostic interview and HRV measurements were rigorously performed by board-certified psychiatrists. As this study retrospectively analyzed medical records, it was not possible to provide a full description of the study and obtain informed consent from the participants. The study protocol was approved by the Institutional Review Board in the Gachon University Gil Medical Center.

2.2. Procedures of hrv

The measurements of HRV were performed by a physician using a BFM-5000PLUS (Medicore; Seoul, Korea). Before the examination, the subjects were instructed to explain and comply with the following precautions. On the day before the measurement, no excessive drinking or strenuous exercise were allowed; for three hours before the test, no caffeinated drinks, cigarettes, or drugs were taken; and for two hours before the test, no food was consumed. The day before the examination, subjects were advised to get sufficient sleep and refrain from doing anything that would build up fatigue. Because HRV changes over the course of a day, measurements were conducted from 8 a.m. to 12 a.m. The examination room maintained bright and soft lights, blocked outside noise, and maintained an appropriate room temperature (20–25 °C).

The subjects were not allowed to wear accessories, such as precious metals, that could affect electrocardiogram waveforms, and three electrodes were attached to the left wrist, right wrist, and left ankle,

respectively, while the subjects were seated in a chair. HRV was measured for 5 min after having at least 5 min of preparation time to be sufficiently adapted to the test environment. During the examination, it was ensured that the subjects remained motionless and speechless, sat with a relaxed mind and posture with their eyes open, and breathing comfortably.

An electrocardiogram (ECG) signal was amplified at a sampling frequency of 400 Hz (width path 0.05–35 Hz) (Electrophysiology, 1996). When peak of the ECG or photoplethysmography (PPG) waveforms is detected, the interval between the peaks is measured. The measured heartbeat interval is constantly changed around 800 msec. The heart rate at a given time or the interval between normal pulses is measured. The inter-beat (RR) interval or instantaneous heart rate is determined through a continuous waveform (ECG/PPG). The heart rate variability in the time range mainly reflects the influence of the parasympathetic nervous system, and all units of the time range analysis are msec. In the time range analysis, a series of data is obtained in two ways. One is by direct measurement of the RR interval or instantaneous heart rate, and the other is based on the difference between the RR intervals.

2.3. Components of hrv

The main frequency band of the HRV signal is between 0 (or 0.2) and 0.4 Hz, clinically divided into two frequency areas: HF domain and low frequency (LF) domain. The specific criteria for dividing these areas differ between researchers, but generally the 0.15–0.4 Hz area is referred to as the high-frequency domain and the 0.04–0.15 Hz area as the low-frequency domain (Electrophysiology, 1996). Based on up-to-date knowledge of the association between components of HRV and panic disorder (Scott and Weems, 2014; Shaffer et al., 2014), the following signals were used as input to build the predictive model.

The very low frequency (VLF) band of 0.0033–0.04 Hz was additionally defined because it is known to provide additional information on sympathetic nerves. The major frequency bands of VLF, LF, and HF and their distribution of power are not static and vary according to the autonomic nervous system's control over respiration and the heart.

The variable size of the HF region is related to the activity of the parasympathetic nerve of the vagus nerve according to respiration, and the variable size of the LF region is influenced by both vagus nerve activity and sympathetic nerve activity. The ratio of LF/HF is an indicator that reflects the balance between activity of the sympathetic nerve and activity of the parasympathetic nerve.

The normal-to-normal (NN) intervals refer to all intervals between adjacent QRS complexes caused by sinus node depolarizations. The standard deviation of the NN interval (SDNN) is an index representing the degree of variability. It represents stress resistance, where the normal-to-normal interval is an indicator of how much the heart rate changes during the recording time.

The root mean square of the successive differences (RMSSD) is the square root of the mean square of the difference between adjacent RR intervals and is used to evaluate the HF domain, which indicates parasympathetic regulation of the heart. It is the most commonly used variable for assessing the activity of the parasympathetic nerve in autonomic nerves involved in the heart.

The physical stress index (PSI; sometimes referred to as pressure index) represents the stress index of the automatic analysis result paper and the degree of pressure applied to the regulation system using parameters such as HRV + SDNN + RMSSD in the time domain. Physical Stress Index (PSI) represents an accumulated physical load for a long time, and it refers to the pressure applied to the regulation system. Heart rate (HR) increases because of physical activities such as exercise, during which HRV (variability) decreases. This is due to an increase in the pressure on the regulation system. An increase in HRV implies that the heart rate is physiologically irregular and complex, whereas a decrease in HRV implies that the heart rate is regular and

constant. Therefore, the degree of pressure is expressed using time-domain parameters such as HR, HRV, and RR interval distribution.

The approximate entropy (ApEn) represents the complexity of the signal, which is a statistic quantification of how complex the signal is in the time domain. The successful RR interval difference (SRD) refers to the reliability of the examination; it measures the degree of change by taking a baseline of a certain segment of the 5-minute interval, and a value of 1 indicates that the data is maintained constant.

The total power (TP) represents autonomic neural activity and the sum of all power sources, including VLF, LF, and HF. This reflects the overall activity of the autonomic nervous system, which indicates the ability to control the autonomic nervous system.

2.4. Overall process of machine learning

The training and hold-out test sets were taken as 70% and 30% of the data, respectively. The training set was again split into a sub-training set and a validation set as 70% (49% of total dataset) and 30% (21% of total dataset), respectively. Hyperparameters were tuned through 10-fold cross-validation with the sub-training and validation sets. These processes were repeated 5 times. The performances of the final predictive models obtained from the cross-validation were tested with the hold-out test set, which was unused up to this point. The whole machine learning process was conducted with the Scikit learn library ('sklearn') of Python version 3.5.

2.5. Predictive models and algorithms

For the practical objective of this study, a total of five algorithms were used: logistic regression (LR), artificial neural network (ANN), gradient boosting machine (GBM), random forest (RF), and support vector machine (SVM). The primary outcome measure for the performance of the predictive models was overall accuracy. Secondary measures were, sensitivity, specificity, F₁-score, and Matthews correlation coefficient (MCC). The meaning of each performance outcome is listed in **supplementary Table 1**.

Given the results of previous studies (Choi et al., 2008; Kim et al., 2018; Woo et al., 2005), all ECG parameters were included in the algorithm. We also included age, sex, and scores on the Beck Anxiety Inventory (Beck and Steer, 1993). There were no variable-transforming steps in the decision tree-based ensemble algorithms such as GBM and RF. However, for LR, ANN, and SVM, we scaled continuous variables to prevent overfitting.

3. RESULTS

3.1. Participants

Table 1 shows information on the demographic and HRV of patients with panic disorder and other anxiety disorders. There were no significant differences in age and sex between the subjects with panic disorder and those with other anxiety disorders. A total of 60 subjects were diagnosed to panic disorder, and 61 were diagnosed to other anxiety disorders. The mean (SD) age of panic disorder was 42.7 (11.8), which was significantly lower than that of other anxiety disorder, 49.3 (10.4).

The mean duration of illness among all the participants was 24.2 months. Among the 121 participants, 54 (44.6%) were recurrent and 29 (24.0%) had comorbid psychiatric disorders. Depressive disorders were the most common illness among the participants ($n = 13$, 44.8%). There were no differences in the duration of illness, comorbidity, and recurrence between panic disorder and other anxiety disorder groups (**Table 1**).

The most frequent diagnosis of the other anxiety disorders was other mixed anxiety disorder ($n = 24$), which followed by other specified anxiety disorder ($n = 18$), anxiety disorder, unspecified ($n = 11$), and

Table 1

Demographic and HRV measures between panic disorder and other anxiety disorders.

	Panic($n = 60$)	Other anxiety($n = 61$)	Statistics	P value
Age	42.7 (11.8)	49.3 (10.4)	3.265	0.001
Sex, female	29 (48.3)	27 (44.3)	0.202	0.653
Duration of illness, months	24.0 (38.3)	24.3 (38.7)	0.048	0.645
Recurrence, yes	24 (40.0)	27 (44.3)	0.231	0.631
Comorbidity, yes	11 (18.3)	12 (19.7)	0.156	0.693
Comorbid disorders			10.069	0.122
Depressive disorders	7 (63.3)	6 (50.0)		
Bipolar disorders	1 (9.1)	0 (0)		
Somatoform disorders	3 (27.3)	0 (0)		
Obsessive-compulsive disorder	0 (0)	2 (16.7)		
Tic disorder	0 (0)	3 (25.0)		
Conduct disorder	0 (0)	1 (8.3)		
Mean HR	78.2 (11.8)	74.5 (13.7)	−1.453	0.149
SDNN	35.0 (16.5)	37.9 (25.1)	0.739	0.462
RMSSD	25.5 (14.9)	27.5 (19.5)	0.627	0.532
PSI	74.1 (98.3)	80.0 (95.6)	0.336	0.738
ApEn	1.1 (0.1)	1.1 (0.2)	−2.652	0.009
SRD	0.9 (0.1)	0.9 (0.1)	−0.869	0.387
TSRD	107.8 (40.0)	112.1 (45.9)	0.543	0.588
TP	1121.0 (1257.8)	1199.0 (1812.5)	0.275	0.784
VLF	491.9 (645.2)	725.1 (1280.6)	1.262	0.210
LF	410.4 (522.8)	276.7 (421.0)	−1.551	0.124
HF	218.8 (258.5)	197.3 (259.0)	−0.458	0.648
LF/HF	2.40 (2.23)	2.31 (3.17)	−0.177	0.860
BAI	30.2 (13.7)	21.5 (11.3)	−3.815	0.000

The sex, recurrence, and comorbidity were shown as N (%), which were analyzed by χ^2 test. All other variables were presented as mean (standard deviation), which were analyzed by an independent t -test. The Statistics represents t (for independent t -test) or χ^2 (for χ^2 test).

SDNN: standard deviation of the normal-to-normal interval; RMSSD: root mean square of the successive differences; PSI: physical stress index; ApEn: approximate entropy; SRD: successful RR interval difference; TSRD: TP: total power; VLF: very low frequency; LF: low frequency; HF: high frequency; LF/HF: ratio of LF/HF; BAI: Beck Anxiety Inventory.

general anxiety disorder ($n = 8$).

3.2. Machine learning

The hyperparameters of the regularized LR are as follows; penalty = 'l1', solver = 'liblinear', tolerability = 0.0001, $C = 0.3$, and maximum iterations = 100. The hyperparameters of the SVM are as follows: $C = 0.21$, gamma = 0.0645, kernel = "poly," and degree = 2). As shown in **Table 2**, L1-regularized LR and SVM had the greatest classifying performance. The regularized LR and SVM analysis showed not only good overall accuracy but also good MCC and F₁-score. The hyperparameters of other algorithms are described in **Supplementary Table 2**.

4. DISCUSSION

To the best of our knowledge, this is the first study to discriminate panic disorder from other anxiety disorders by machine learning algorithms. Through this study, we have found that LR has the greatest performance in terms of accuracy (0.785) and F₁-score (0.790).

Although we already know that patients with anxiety disorders, including panic disorder, have a reduced HF in their HRV compared to individuals without an anxiety disorder (Chalmers et al., 2014), we are unable to use this knowledge and directly obtained HRV data from

Table 2

Performances of the machine learning-based classification model for panic disorder and other anxiety disorders.

	RF	GBM	SVM	ANN	LR
Accuracy	0.649	0.676	0.784	0.730	0.784
Sensitivity	0.667	0.722	0.611	0.833	0.833
Specificity	0.632	0.632	0.947	0.632	0.737
Precision	0.632	0.650	0.917	0.682	0.750
NPV	0.667	0.706	0.720	0.800	0.824
FPR	0.368	0.368	0.053	0.368	0.263
FDR	0.368	0.350	0.083	0.318	0.250
FNR	0.333	0.278	0.389	0.167	0.167
F1-score	0.649	0.684	0.733	0.750	0.790
MCC	0.298	0.355	0.596	0.473	0.572

NPV: negative predictive value; FPR: false positive rate; FDR: false discovery rate; FNR: false negative rate; MCC: Matthews correlation coefficient.

participants. This is the case with many studies that have reported HRV being associated with neurobiological and clinical aspects of anxiety disorders, but such results could not be translated to clinical practice (Chang et al., 2019; Koszycki et al., 2019). The non-applicability of the results has raised criticism of the role of the research findings. Indeed, the need for personalized diagnoses and intervention has become an inevitable trend in the field of psychiatry (Fernandes et al., 2017).

For example, with only HRV data, can we determine whether a person has panic disorder or other anxiety disorders? Our results provide an answer to this question and can be applied in various institutions, such as community mental health centers, primary health care institutions, and even in the workplace or for school-based mental health management (Huang and Wan, 2013; Thayer et al., 2010).

This study has several limitations that should be noted. First, due to the cross-sectional design, we could not confirm any possible diagnostic changes from the initial diagnosis when entering the study. Secondly, due to the limited sample size, we could not separate individual anxiety disorders. Because GAD (Maron and Nutt, 2017), specific phobias (Linares et al., 2014), and social phobia (Rapee and Spence, 2004) have their own disease-specific neurobiological substrates and clinical dimension, the unified grouping of these anxiety disorders will have confounding factors. Thirdly, the lack of normal control limits the possibility of generalizing the classifying algorithm for widespread use.

In summary, classifying algorithms for panic disorder and other anxiety disorders are expected to be helpful for health workers in the various institutions. In terms of personalized evaluation and intervention, we believe that our results have strengths in the field of clinical psychiatry and public mental health systems. Future studies to validate the classification accuracy of this model with longitudinal design and based on more participants are required.

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Declaration of competing interest

The authors declare no conflict of interest.

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Supplementary materials

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