Progress in Neuro-Psychopharmacology & Biological Psychiatry 76 (2017) 65–71

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Diagnosis of major depressive disorder by combining multimodal information from heart rate dynamics and serum proteomics using machine-learning algorithm

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ARTICLE INFO

Article history:
Received 8 September 2016
Received in revised form 2 February 2017
Accepted 16 February 2017
Available online 20 February 2017

Keywords:
Major depressive disorder
Biomarker
Proteomics
Heart rate variability
Machine-learning

ABSTRACT

Objective: Major depressive disorder (MDD) is a systemic and multifactorial disorder that involves abnormalities in multiple biochemical pathways and the autonomic nervous system. This study applied a machine-learning method to classify MDD and control groups by incorporating data from serum proteomic analysis and heart rate variability (HRV) analysis for the identification of novel peripheral biomarkers.
Methods: The study subjects consisted of 25 drug-free female MDD patients and 25 age- and sex-matched healthy controls. First, quantitative serum proteome profiles were analyzed by liquid chromatography-tandem mass spectrometry using pooled serum samples from 10 patients and 10 controls. Next, candidate proteins were quantified with multiple reaction monitoring (MRM) in 50 subjects. We also analyzed 22 linear and nonlinear HRV parameters in 50 subjects. Finally, we identified a combined biomarker panel consisting of proteins and HRV indexes using a support vector machine with recursive feature elimination.
Results: A separation between MDD and control groups was achieved using five parameters (apolipoprotein B, group-specific component, ceruloplasmin, RMSSD, and SampEn) at 80.1% classification accuracy. A combination of HRV and proteomic data achieved better classification accuracy.
Conclusions: A high classification accuracy can be achieved by combining multimodal information from heart rate dynamics and serum proteomics in MDD. Our approach can be helpful for accurate clinical diagnosis of MDD. Further studies using larger, independent cohorts are needed to verify the role of these candidate biomarkers for MDD diagnosis.

1. Introduction

Major depressive disorder (MDD) affects entire organ systems, including the neurotransmitter, endocrinological, immunological, and autonomic nervous systems, through interactions between the brain and the body (Thase, 2000). Although several biomarkers based on the hypothetical pathophysiology of depression have been studied, a clinically applicable test has not been developed since each biomarker individually contributes a very modest proportion of depression risk. In a multifactorial complex disorder such as depression, candidate approaches cannot provide comprehensive coverage of multiple biological abnormalities that contribute to the pathophysiology. Global and systemic approaches to multifactorial etiology with multiparametric analysis are needed.

Proteomics have been considered to be a robust method for the hypothesis-free and unbiased detection of novel biomarkers related to functional abnormalities involved in MDD pathophysiology (Bot et al., 2015; Martins-de-Souza et al., 2010). Recent proteomic technologies enable simultaneous quantitative measurement of numerous proteins in individual samples. Prior proteomic studies using samples from MDD patients have found altered protein levels during lipid metabolism, immunoregulation, oxidative stress, and growth factor regulation in MDD (Stelzhammer et al., 2014; Xu et al., 2012). However, the numbers of differentially expressed proteins (DEPs) between patients and controls were limited, their abundances showed large variations, and the mean differences were marginal (Stelzhammer et al., 2014; Xu

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http://dx.doi.org/10.1016/j.pnpbp.2017.02.014
0278-5846/

et al., 2012). The protein biomarker panel discovered from proteomics experiments in a recent study showed 68% diagnostic accuracy (Lee et al., 2016). These results indicated that proteomics provided important insights into pathophysiology but failed to achieve sufficient classification accuracy to diagnose MDD.

In the context of complex diseases, a valid biomarker may be identified from a combination of multimodal information that reveals different aspects of disease pathophysiology, rather than a single one; thus, combining proteomic data with heart rate variability (HRV) as physiological correlates of depression is a potentially useful approach to classify MDD. As a reliable and sensitive method to quantify cardiac autonomic control, HRV has been successfully applied as both research and monitoring tool to assess various medical and psychiatric conditions. Reduced HRV is associated with diverse cardiovascular and endocrine abnormalities, and increased risk of the development of diabetes and metabolic syndrome in adults (Dekker et al., 2000; Kemp and Quintana, 2013; Koskinen et al., 2009; Licht et al., 2013; Soares-Miranda et al., 2012; Windham et al., 2012). Abnormal values of several linear and non-linear HRV indexes are important predictors of mortality in elderly people (Tsuji et al., 1994) and in diverse clinical populations (Thayer et al., 2010; Kleiger et al., 1987). Recent meta-analyses suggested that depression and anxiety disorders are associated with reduced HRV and the reduction in HRV is related to the severity of depression (Chalmers et al., 2014; Kemp et al., 2010). The central autonomic network (CAN), a network including the prefrontal cortex (PFC), cingulate, insula, amygdala, and brainstem structures, has been suggested to be a key player in psychiatric symptoms and reduced HRV. Depression symptoms can be indicated by a failure of inhibition in affective, cognitive, physiological, and behavioral responses implicated in the CAN, which results in decreased vagal outflow and altered HRV (Chalmers et al., 2014). So far, although the linear parameters of the time and frequency domains are used as standard HRV measures, HRV is an intrinsically non-linear, high-dimensional dynamic system that is generated from multi-feedback interactions between hemodynamic, electrophysiological, and humeral variables (Costa et al., 2008). Therefore, nonlinear indexes that reveal the complexity and correlational properties of HRV, as well as the linear parameters, should be evaluated (Nardelli et al., 2015).

In this study, we used a supervised machine-learning method to classify MDD and control groups for finding an optimal subset of features that would simultaneously maximize classification accuracy. Both, protein data from a multiple reaction monitoring (MRM) experiment and HRV linear and non-linear parameters, were analyzed in the proposed framework for the identification of novel peripheral markers for MDD. A supervised classification algorithm builds an inferring function that can predict the presence or absence of a disease for a new subject. Feature selection improves classification accuracy for future subjects by removing irrelevant features and avoiding overfitting. The reduction of the number of features is also cost-efficient for future application and makes it easier to verify the relevance of selected features. We applied a support vector machine with recursive feature elimination (SVM-RFE) algorithm that outperformed other methods in cancer classification using microarray data (Guyon et al., 2002). SVMs are known to deliver robust solutions by controlling overfitting to noisy data with a regularization parameter and classifying them with a maximum margin hyperplane. Moreover, SVMs yield a unique solution since the optimization problem is convex. RFE is a practical approach to select an optimal subset of features by ranking features based on their contribution to the classification decision. By utilizing repeated cross-validations along with SVM-RFE, the best performing classification system can be built with a small number of features that are selected from a large number of candidate proteins and HRV parameters. The reliability and generalization performance of the results were evaluated.

The aim of this study was to identify a multiparametric biomarker panel for MDD through combinatorial analysis of HRV data and serum proteomics using the supervised machine-learning method, SVM-RFE. This approach might be able to contribute to the discovery of objective peripheral biomarkers for MDD with high accuracy. In addition, it may ultimately lead to a better understanding of the pathophysiology of MDD.

2. Material and methods

2.1. Participants

The study subjects comprised 25 drug-free female MDD patients according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000), and 25 age- and sex-matched healthy controls, aged between 18 and 65, from Seoul National University Hospital, Seoul, South Korea, between November 2012 and October 2013. Subjects were diagnosed using the Mini International Neuropsychiatric Interview. MDD patients diagnosed with other comorbid psychiatric diseases (such as psychotic disorder, anxiety disorder, or substance use disorders), or who had taken psychotropic medications (including anxiolytics, antidepressants, antipsychotic medications, and anticonvulsants) during the past 8 weeks were excluded from the study. Healthy controls had no current or past diagnosis of MDD and other psychiatric disorders, and no family history of any psychiatric disorder. None of the subjects were taking medication that could affect variation in cardiac rhythm or alter the blood levels of relevant factors (such as nonsteroidal anti-inflammatory agents, anti-hypertensive agents, and steroids), and none had suffered from chronic or acute diseases such as cardiovascular disease, pulmonary disease, endocrine or immune abnormalities, rheumatic diseases, or cerebrovascular disease. Subjects who were pregnant, nursing, or menstruating were also excluded.

The objective severity of depressive symptoms was measured using the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960; Yi et al., 2004). The item response options are on a 3-point scale ranging from 0 to 2 for insomnia, gastrointestinal somatic, general somatic, genital symptoms, loss of weight and insight, and on a 5-point scale ranging from 0 to 4 for the other symptoms. The total score ranges from 0 to 52, and higher scores reflect severe depressive symptoms. A score of 0–8 is accepted to be within normal or euthymic limits, while a score of ≥17 indicates major depression (Martinez-Aran et al., 2004). The 30-item Inventory of Depressive Symptomatology-Self-Report (IDS-SR) was used as a self-administered assessment of depressive symptoms during the week prior to the interview (Rush et al., 1996). Each question is scored from 0 to 3 and the total score calculated by summing responses to 28 of the 30 items to obtain a total score ranging between 0 and 84, with higher scores indicating a greater depressive symptom severity. Scores of 0–13, 14–25, 26–38, 39–48 or over 49 indicate the severity of symptoms as none, mild, moderate, severe, or very severe depression, respectively (Rush et al., 1996). The 21-item Beck Anxiety Inventory (BAI) was used to measure the severity of anxiety (Beck et al., 1988). BAI includes self-report item response options on a 4-point scale ranging from the absence of a symptom (0) to the severe or persistent expression of the symptom (3) during the past 1 week; the total score ranges from 0 to 63, and higher scores reflect more severe anxiety symptoms (Beck et al., 1988). A score of ≥22 indicates having anxiety symptoms (Yuk and Kim, 1997). The protocol was approved by the Ethics Committee of Seoul National University Hospital, and this study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient before enrollment.

2.2. Proteomics

The serum proteomes were analyzed as described previously (Lee et al., 2016). In brief, equal volume of individual serum samples from 10 patients with MDD and 10 healthy controls were pooled separately. Immuno-depletion of six high-abundant serum proteins was