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RESEARCH ARTICLE

Characterization of hidden rules linking symptoms and selection of acupoint using an artificial neural network model

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Abstract **Comprehension of the medical diagnoses of doctors and treatment of diseases is important to understand the underlying principle in selecting appropriate acupoints. The pattern recognition process that pertains to symptoms and diseases and informs acupuncture treatment in a clinical setting was explored. A total of 232 clinical records were collected using a Charting Language program. The relationship between symptom information and selected acupoints was trained using an artificial neural network (ANN). A total of 11 hidden nodes with the highest average precision score were selected through a tenfold cross-validation. Our ANN model could predict the selected acupoints based on symptom and disease information with an average precision score of 0.865 (precision, 0.911; recall, 0.811). This model is a useful tool for diagnostic classification or pattern recognition and for the prediction and modeling of acupuncture treatment based on clinical data obtained in a real-world setting. The relationship between symptoms and selected acupoints could be systematically characterized through knowledge discovery processes, such as pattern identification.**

Keywords acupuncture; indication; neural network; pattern identification; prediction

Introduction

Medical decision-making is complex with nonlinear interactions occurring among various diagnostic factors [1]. All important information in patient assessment should be considered in diagnoses and clinical decision-making. Feature extraction processing from medical information is considered an essential diagnostic parameter [2]. In East Asian medicine, the term disease is used to refer to a biomedically defined disease, condition, or disorder, or even just a symptom or sign. Doctors typically engage in medical decision-making pertaining to diseases and symptoms based on clinical data collected through case history and clinical sign observation and analysis [3]. Pattern identification, a traditional method of diagnostic classification, is important to provide an appropriate framework for treatment selection [4–6]. In traditional Chinese medicine (TCM), pattern identification plays a pivotal role in identifying the relationship between symptoms and treatments [7].

Acupuncture practitioners engage in a series of medical decision-making processes, including assembling clinical data, identifying pattern, and selecting relevant acupoints [8,9]. Our previous study demonstrated that the underlying principle in acupoint selection is mainly associated with the spatial patterns of diseases derived from classical medical texts [10]. Each acupoint has various indications, and each disease or indication can in turn be treated by numerous acupoints [11,12]. The selection of acupoints for every symptom and the matching of symptoms for every acupoint show different distribution patterns [13]. With this direct one-to-one matching method, the complex relationship between symptoms and selected acupoints is difficult to explain. To characterize these highly complex

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relationships, it is important to understand the pattern identification process, the process of extracting and synthesizing clinical features from patient signs and symptoms.

Modern medicine is confronted with the challenge of acquiring, analyzing, and applying large amounts of knowledge vital in solving complex clinical problems [14]. Healthcare informatics research increasingly grew recently, and the prevalence of big data stimulated research on healthcare data mining and knowledge discovery [15]. The artificial neural network (ANN) is a learning algorithm inspired by the biological structure of a neural network [16]. The artificial neural networks, which gather knowledge by detecting patterns and relationships in data and by learning through experience, may provide a sophisticated mathematical model for processing nonlinear and complex problems [17,18]. This approach is commonly used for medical disease estimation in different areas of healthcare research [2,19,20]. The multilayer perceptron neural network is among the most typical structures consisting of an input layer, output layer, and at least one hidden layer between these two layers [21]. Appropriate hidden nodes should be identified to understand the solution to nonlinear problems because the hidden nodes extract important features in the input data.

In this report, the knowledge behind acupuncture prescription in a clinical setting was explored. The relationship among information on symptoms and diseases and the selected acupoints was investigated using an ANN in conjunction with the clinical data from Korea.

Methods

Data acquisition and preprocessing

All records were evaluated by an experienced Korean medical doctor using the "Charting Language" program, which aids the assessment of medical information through a semi-structured format [22]. The program uses specific syntax and medical terms unconstrained by the structure inherent to a defined language. Interoperable medical data can be collected for neural network analysis because this system uses medical terms drawn from a library of unique medical entities, including concepts, such as symptoms, anatomical locations, diagnoses, and treatments. For acupuncture treatment, medical doctors select particular acupoint combinations based on the symptoms of a patient (Fig. 1A).

All patients were recruited at a traditional Korean medical clinic in the Republic of Korea. The anonymized electronic medical records of 81 patients were collected. A total of 232 clinical records were extracted in "json" file format, and a home-built Python script was used for further

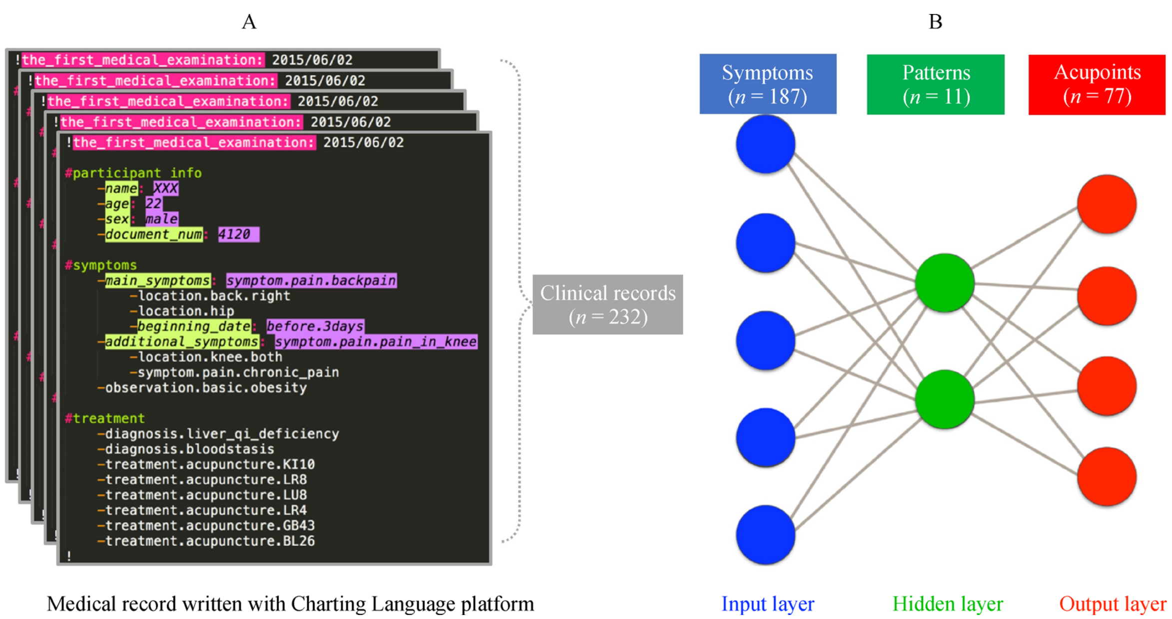

Fig. 1 (A) "Charting Language" program. This system uses specific syntax and medical terms unconstrained by the structure inherent to a defined language. A total of 232 clinical records were collected for neural network analysis. (B) ANN model. A feed-forward network that consists of input, hidden, and output layers was employed as an ANN model to learn the acupuncture treatment patterns in Korean medicine. A total of 87 nodes in the input layer corresponded to 87 symptoms present among the medical records (layer with blue circles). The number of hidden nodes was 11 based on the highly predictive performance achieved through a tenfold cross validation (layer with green circles). A total of 77 nodes in the output layer correspond to 77 acupoints identified from the medical records (layer with red circles).

preprocessing, including the correction of typographical errors and overlapping medical information. Finally, 87 entities that pertain to symptoms and 77 related to treated acupoints were identified for further analysis. The study was conducted in accordance with the *Declaration of Helsinki* and the Guidelines of the Human Subject Committee of Kyung Hee University, Seoul, Republic of Korea.

Training the ANN

A feed-forward network, with a single hidden layer between an input and an output layer, was implemented using the PyBrain library [23]. A rectified linear function was used as an activation function for input nodes to convert weighted input into activation output. A sigmoid function was used as the activation function for hidden and output nodes. From the extracted clinical data, 87 different symptoms were assigned to 87 input nodes and 77 acupoints were assigned to 77 output nodes (Fig. 1B).

The output from sigmoid function was constrained to derive values ranging from 0 to 1.0 for the output nodes. When an output node provided a value greater than 0.5, the selection of acupoints that corresponds to the output node was represented. Acupoints that correspond to the output nodes with values under 0.5 were predicted to not be selected for treatment. Thus, the selected combination of acupoints as treatments was estimated in ANN as output nodes of values greater than 0.5.

Performance of the ANN

ANN structures were trained repeatedly while varying the number of hidden nodes from 1 to 20 and testing the predictive performance through a tenfold cross validation. Average precision scores were used to indicate performance. In this study, precision is the ratio of matched acupoints to estimated acupoints, and recall is the ratio of the number of matched acupoints to the actual selected acupoints. Average precision scores are equivalent to the area under the precision–recall curve. When the estimation perfectly matches the answer, the average precision score is 1. The average precision score reflects precision and recall components, and it is often used in multi-labeling problems.

Identification of hidden nodes in the ANN

The multilayer perceptron neural network is a feed-forward ANN, in which learning is acquired through a back-propagation algorithm [21]. In the learning phase, the model propagates input values through different layers and optimizes link weights through the backward propagation rule to achieve the minimum difference between the predicted and actual values of the output. As the activation patterns of hidden nodes and the linkage weights connected to hidden nodes represent trained patterns, the hidden nodes of the ANN are typically described as learned-feature detectors or re-representation units [24].

Hidden nodes activate responses to a given input, thereby resulting in a specific output. To characterize the patterns trained inside hidden nodes, the five symptoms and acupoints with the strongest correlations to the activities of hidden nodes were extracted. To visualize the relationships among symptoms, acupoints, and hidden nodes, the selected nodes were aligned within a network using a directed acyclic graph layout algorithm.

Results

Baseline characteristics of symptoms and acupoints from clinical records

A total of 87 symptoms were observed, and a total of 77 acupoints were used from 232 clinical encounters. The most frequently observed symptoms included back pain (14.8%), shoulder pain (9.5%), strained muscle (4.5%), knee pain (4.1%), and lower limb pain (4.1%). The most frequently used acupoints included LI11 (7.9%), LU8 (5.3%), SP3 (4.8%), LR4 (4.5%), and BL23 (4.4%) (Table 1).

Table 1 Most frequently observed symptoms and acupoints of patients in 232 clinical records

No.	Most frequently observed symptoms	Most frequently used acupoints
1	Back pain (14.8%)	LI11 (7.9%)
2	Shoulder pain (9.5%)	LU8 (5.3%)
3	Strained muscle (4.5%)	SP3 (4.8%)
4	Knee pain (4.1%)	LR4 (4.5%)
5	Lower limb pain (4.1%)	BL23 (4.4%)
6	Upper limb pain (3.7%)	BL24 (4.4%)
7	Edema (3.6%)	BL26 (4.3%)
8	Neck pain (3.6%)	GB43 (4.3%)
9	Dyspepsia (2.9%)	ST36 (4.1%)
10	Ankle pain (2.8%)	KI10 (3.9%)
11	Finger joint pain (2.6%)	LU9 (3.9%)
12	Scapula pain (2.6%)	LR8 (3.8%)
13	Pressure pain on BL24 (2.1%)	TE6 (2.5%)
14	Arthralgia (1.8%)	TE15 (2.4%)
15	Foot pain (1.8%)	LI1 (2.1%)
16	Stiff neck (1.8%)	GB41 (2.0%)
17	Wrist pain (1.8%)	SI14 (2.0%)
18	Insomnia (1.7%)	SP9 (1.7%)
19	Headache (1.6%)	ST43 (1.7%)
20	Pressure pain on BL26 (1.6%)	LI5 (1.7%)

The most frequently used acupoint combinations were SI12–SI18, SI12–LI4, SI18–LI4, SP10–LI5, TE15–SP10, and TE15–LI5 (n = 38) (Table 2). Furthermore, the investigation of the visual pattern of the network facilitated intuitive and comprehensive analysis. The acupoint combination network contained 52 acupoints (Fig. 2).

Table 2 Most frequently used acupoint combinations in 232 clinical records

No.	Most frequently used acupoint combinations
1	SI12–SI18 (n = 38)
2	SI12–LI4 (n = 38)
3	SI18–LI4 (n = 38)
4	SP10–LI5 (n = 38)
5	TE15–SP10 (n = 38)
6	TE15–LI5 (n = 38)
7	EX-LE4–SP10 (n = 37)
8	SI12–SI2 (n = 32)
9	SI12–SP10 (n = 31)
10	SI18–SI2 (n = 31)
11	SI2–LI4 (n = 31)
12	SI18–SP10 (n = 30)
13	SP10–LI4 (n = 30)
14	SI2–SP10 (n = 29)
15	EX-LE4–TE15 (n = 23)
16	EX-LE4–LI5 (n = 23)
17	BL23–SP10 (n = 22)
18	EX-LE4–SI2 (n = 20)
19	LR2–SP10 (n = 20)
20	LR2–BL23 (n = 20)

Performance of the ANN

To further train the network, the number of hidden nodes in the further trained ANN was set as 11 based on the peaked estimation accuracy of the tenfold cross validation to extract heuristic knowledge from the collected data. When the ANN was trained with 11 hidden nodes for 2000 epochs, an average precision score of 0.865 was obtained (precision, 0.911; recall, 0.811) (Fig. 3).

Extracted activation patterns of hidden nodes

The relationships between symptom information and selected acupoints were visualized according to three layers, namely, input, hidden, and output layers. The five largest correlation coefficient values were extracted for each hidden layer. A total of 11 hidden nodes were associated with 22 symptoms and 26 acupoints (Fig. 4).

Symptoms have two distinct types, namely, (1) local pain, such as neck and knee or back pain, and (2) other systemic symptoms, such as insomnia, fatigue, and edema. Acupoints also have two distinct types, namely, (1) remote control acupoints, such as ST36, SP9, and HT8, and (2) regional control points, such as GB20 (for neck), EX-LE4 (for knee), and BL26 (for back).

Discussion

The current study describes the successful prediction of selected acupoints based on symptom and disease information. Knowledge-based systems are commonly used in the medical arena, where heuristic and logical reasoning are necessary to derive new types of knowledge [25]. Such systems are also used for acupuncture education. Commonly, in the course of learning acupuncture in clinical practice, the process of thinking for diagnosis and treatment should be defined first by an expert, the problems of symptoms, diagnosis, and selection of acupoints for treatment should be addressed by novice students by following this process of thinking. The recent application of artificial intelligence to the medical field provided a basis for clinicians to formulate diagnoses, make medical decisions, and ensure outcome precision after treatment [14]. Our study shows that when acupuncture practitioners select a treatment, ANNs that use previous medical data could guide appropriate medical decision-making. Machine learning and artificial intelligence advances in medicine call for the integration of domain-specific knowledge and data for the detection, diagnosis, interpretation, and treatment of diseases.

East Asian medicine uses a number of approaches to the human body, enabling a diagnosis that encompasses systemic and local perspectives [8,26]. Furthermore, acupuncture treatment is applied not only to local symptoms but also to symptoms distal from the selected acupoints. Our previous study demonstrated that the underlying principle in the selection of acupoints is mainly associated with pattern identification based on classical medical texts [27]. The commonality between the different diagnostic and treatment approaches of East Asian medicine and the principle that connects the sets of symptoms and acupoints to be treated and used for treatment, respectively, is pattern recognition and identification based on TCM theories.

Although most TCM theories originated hundreds of years ago based on the experiences of doctors with patients, a series of recent studies have focused on the statistical validation of these theories [28]. Natural clusters, in the form of a latent tree model derived from clinical data sets, corresponded well to the syndrome types defined in TCM [29]. Based on the co-occurrence of manifestation profiles in Chinese medicine, which in previous studies was defined as Chinese medicine syndrome classification,

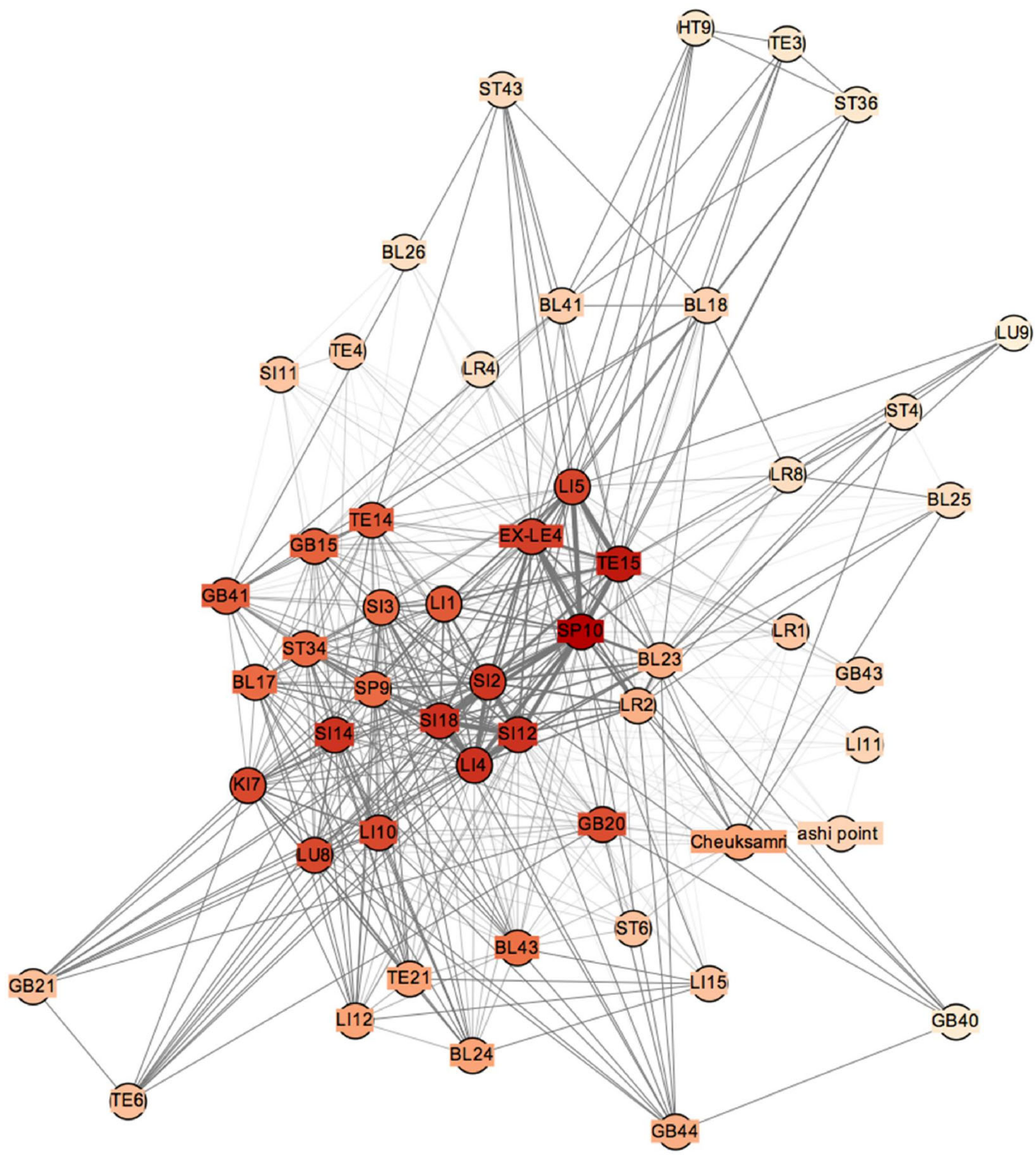

Fig. 2 Network analysis of acupoint combinations. The collected data contained 232 acupoint prescriptions. Acupoint combination network is generated with nodes (acupoints) and edges (co-occurrences between two acupoints). Networkx 1.11.0 (Python library) is used to construct the network, and Gephi 0.8.2 is utilized to visualize the network. The investigation of the visual pattern of the network is facilitated by intuitive and comprehensive analyses. The acupoint combination network contained 52 acupoints. The color of the node represents eigenvector centrality (colors closer to red represent higher values). Edge thickness is proportional to the frequency of the co-occurrences among linked nodes.

the latent tree model was used to identify the clinical features of depressed patients with insomnia [30]. Furthermore, the combinations of acupoints were selected to treat a particular set of symptoms that exhibited differences with high complexities in acupuncture clinics [13]. Thus, the hidden rules that link symptoms and selected acupoints are difficult to identify. A learning model that links a combination of acupoints to a certain pattern of symptoms corresponds to the multi-label classification problem, which does not have a fixed number of answers. Neural networks are considered to be among the best solutions to this problem.

The relationship between symptoms and selected acupoints can be systematically explored using a knowledge discovery process, such as pattern identification. The neural network is suited to solve problems that involve pattern recognition, such as diagnosis and clinical decision-making. In the present study, hidden node No. 3

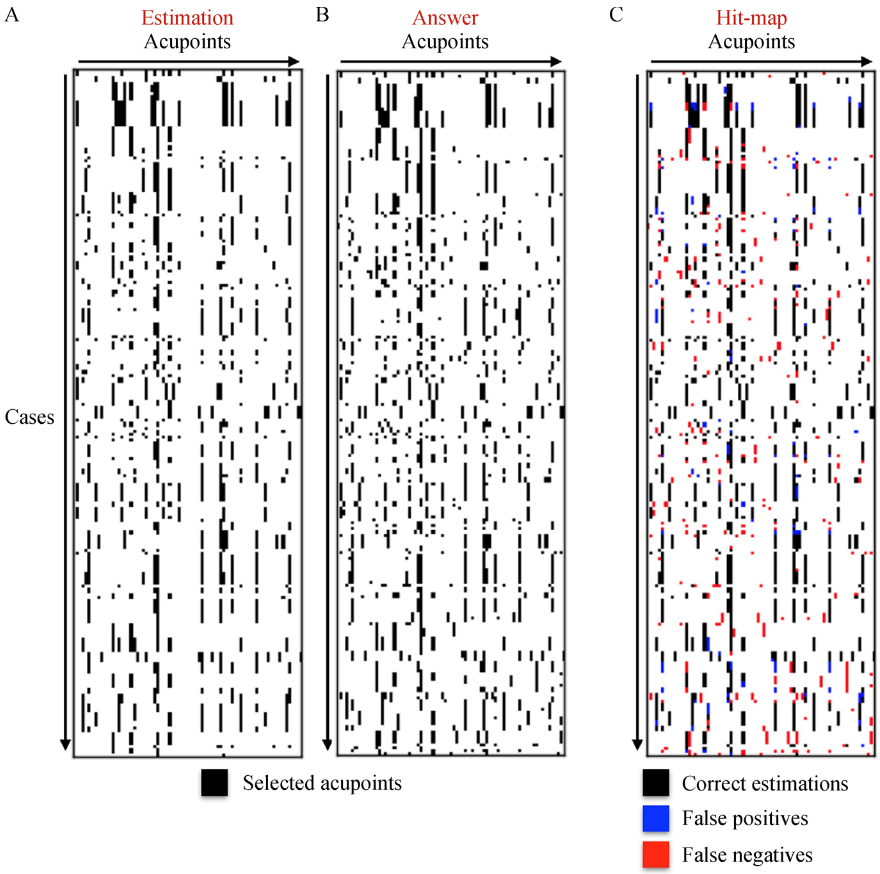

Fig. 3 Selected acupoints for 232 cases were represented in a color-coded matrix. (A) Estimated acupoints from the fully fitted ANN model (average precision score, 0.865; precision, 0.911; recall, 0.811). (B) Actual acupoint selections in 232 cases. Selected acupoints were coded in black in the two matrices. (C) Correct estimations (black), false positive errors (blue), and false negative errors (red).

mainly used acupoint GB20 (correlation coefficient, 0.62), SI12 (0.59), TE15 (0.58), SI14 (0.54), and LU9 (0.54) to address symptoms, such as neck (correlation coefficient, 0.65), upper limb (0.53), scapula (0.50), ankle pain (0.45), and edema (0.43). This hidden node is mainly involved in the regional control of acupoints included in the treatment of musculoskeletal pain. By contrast, hidden node No. 8 used acupoints SP9 (0.48), LI1 (0.42), LR2 (0.40), ST45 (0.40), and ST43 (0.39) to address symptoms, such as edema (0.56), ankle (0.47) and lower limb pain (0.44), insomnia (0.44), and fatigue (0.43). This hidden node is mainly involved in the remote control effect on the body of acupoints for more systemic symptoms. These hidden nodes, which strongly resemble the pattern identifications of traditional medicine, may play a pivotal role in explaining the complex relationships between symptoms and treatment. The activity pattern in the hidden layer of a network encodes what that network considers significant features of the input [24]. Neural networks are useful tools for diagnostic classification or pattern recognition and for the prediction and modeling of acupuncture treatment data in a real-world setting.

In China, a TCM clinical data "warehouse" was developed to manage various types of information and provide clinical knowledge that pertains to pattern identification [31,32]. These authors conducted a preliminary study on acupuncture prescription knowledge discovery [33]. However, the collection of structured electronic medical records confers the risk of limiting stored information in a strict and rigid format in clinical situations where practitioners are largely varied. The current study used the "Charting Language" program, which has a specifically defined syntax and uses medical terms unconstrained by the structure inherent to a defined language [22]. Our system uses medical terms with semantic interoperability. Therefore, the text-based data generated through this system in a dynamic situation in clinical settings can be easily used to extract information. This method could be used to efficiently identify hidden knowledge from heterogeneous information sources. Our results might be difficult to extend to all other clinical settings because it included only 232 clinical records from one Korean medical clinic. To generalize our results, a larger data from many clinical encounters in the near future

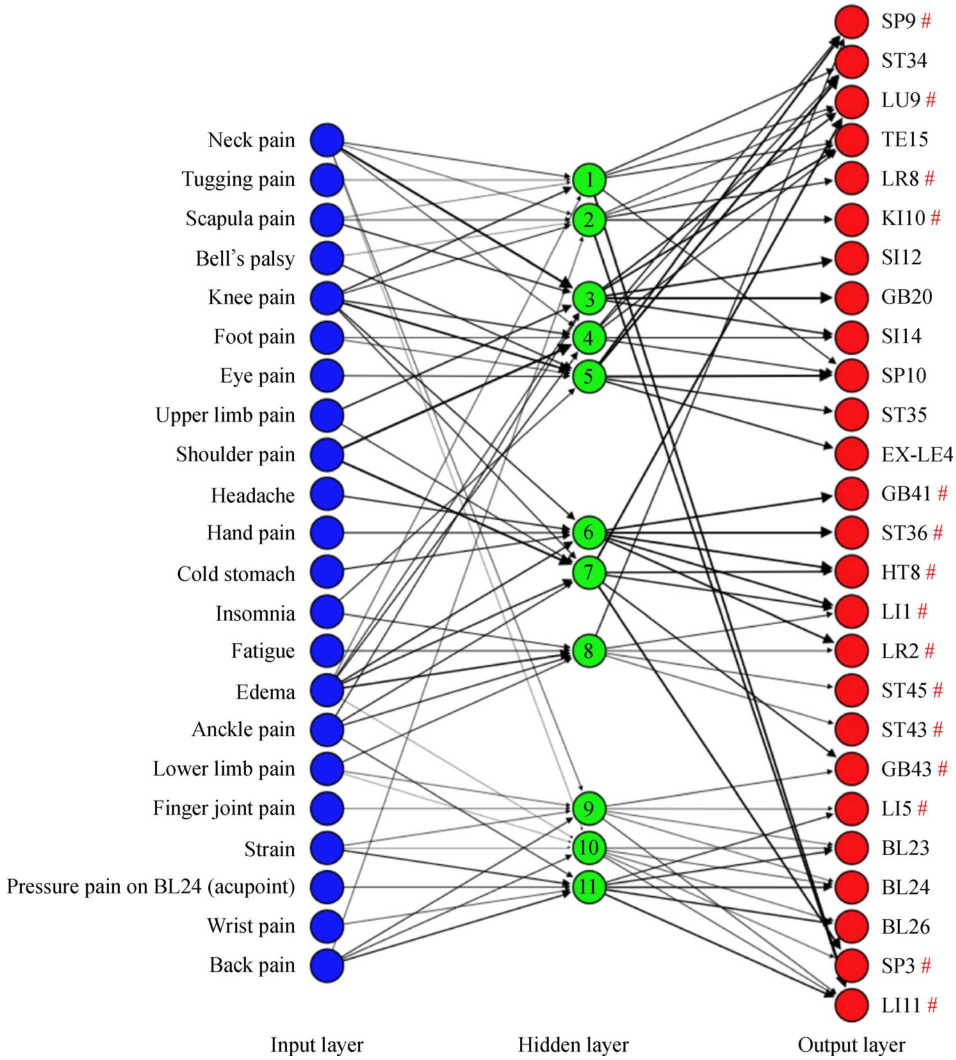

Fig. 4 Network visualization of relationships among symptoms, acupoints, and hidden nodes based on the correlation of activity patterns. The five symptoms and acupoints that show the strongest correlations with the activity patterns of the 11 hidden nodes were extracted. In total, 11 hidden nodes were associated with 22 symptoms and 26 acupoints (5 element acupoints are marked with a red "#."). Line widths are proportional to the size of the correlation coefficients that describe the relationships among connected nodes.

should be gathered. Moreover, not only symptom information but also pulse and tongue diagnoses would be important factors to extract and synthesize the information of patients for pattern identification. Such information should be included in future studies with different real-world clinical data, such as the four examinations, including looking, listening/smelling, inquiring, and pulse taking, because information on different types of diagnostic methods is limited in the current study.

In this study, our ANN model could predict the selected acupoints based on symptom information. However, the diagnostic information obtained from patients during acupuncture treatment can have a multi-level, complex structure. The selected acupoints for treatment also form a complex structure of information that can be grouped into various layers, such as meridian pattern identification or five viscera pattern identification [10,34]. The important issue of integrating heterogeneous multi-source data in biomedicine was recently raised [35]. Liang *et al*. developed a multi-modal deep belief network to handle input data from heterogeneous sources and showed that they can successfully cluster cancer patients [36]. In TCM, a complex system entropy cluster was used to analyze the prescribing data of old famous TCM physicians, which are structured with complexity [37]. Deep learning or Bayesian hierarchical modeling can be considered to learn high-level interaction without an explicit knowledge of structure or multi-level modeling in future studies.

In general, TCM pattern identification in clinical diagnosis and treatment is composed of four steps, namely, pattern identification, legislation, selection prescription, and drug delivery. The pattern identification process is a key step to clinical diagnosis and treatment of TCM and reflects the synthesis of pathophysiological information in the disease development course [38]. In this course, the syndrome of a patient is manifested through a temporal course of dynamic symptom changes. Different acupuncture practitioners can prescribe various acupuncture prescriptions for the same pattern identification [39]. Substantial variability in acupuncture prescriptions exists among medical practitioners [9]. The hidden rules between symptoms and selected acupoints can also vary by different providers. Given that acupuncture prescriptions and syndromes are complex systems, many factors or indicators should be continuously scientifically integrated, and an objective description and evaluation of the system should be formed. In the current study, our ANN model could predict the selected acupoints with an average precision score of 0.865 by learning through experience. These findings suggest that the ANN model could gather knowledge by detecting the pattern and relationships in clinical data obtained in a real-world setting. This approach is an important tool for the statistical modeling of acupuncture prescriptions. Although different acupuncture prescriptions among different practitioners were not compared further, our ANN model is believed to be applicable to other large-scale clinical investigation sites in the future. To find the best method among the different styles of pattern identification, the information on the outcome of the patients should be included in future studies.

In summary, neural networks can extract novel medical information from clinical data and generate computer models useful for the discovery of medical knowledge and clinical decision-making as they pertain to acupuncture treatment. Neural networks could play a crucial supporting role with respect to future medical decision-making and patient management systems that could be used in routine medical practice. Patterns identified from neural networks may be useful to extract information from complex clinical data.

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Compliance with ethics guidelines

Won-Mo Jung, In-Soo Park, Ye-Seul Lee, Chang-Eop Kim, Hyangsook Lee, Dae-Hyun Hahm, Hi-Joon Park, Bo-Hyoung Jang, and Younbyoung Chae declare that no competing interests exist. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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