Medical imaging and artificial intelligence to investigate neuro-cardiac pathologies and discover hidden relationships – a state of the art review

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Abstract

Cardiovascular and neurological diseases including their interactions are getting the attention of researchers and physicians. Both diseases often share common biomarkers, risk factors, and biological pathways. By now, researchers have confirmed that problems related to cardiovascular lead to neurological bad outcomes and vice versa. In addition, researchers have started to use machine/deep learning algorithms for better diagnosis. By now, few examples are published on little datasets consisting of computed tomography images, electrocardiograms, electroencephalograms, and so on, but most of the work is not done by artificial intelligence (AI). In this work, we reviewed a number of studies that have either used AI or manual computation with conventional techniques on different imaging modalities. From all studies, it is found that imaging modalities can support physicians in better diagnosis of neurological outcomes following cardiac events and/or diseases and vice versa. Moreover, AI driven technologies, like machine learning and deep learning, could be useful to delineate accurate models of diseases related to neuro-cardiac pathologies for predictions of consequent bad outcomes related to the different stages.

Keywords

Cardiovascular and neurological diseases, Biomarkers, Computed tomography images, Electrocardiograms, Electroencephalograms, Machine learning and deep learning

1. Introduction

In 1956, John McCarthy coined the name Artificial Intelligence (AI) for the first time at the Dartmouth conference [1]. This idea was then elaborated by Kaplan and Haenlein as "the ability to process external data systematically and learn from it to achieve specific goals and tasks" [2]. With the advancement in AI, new computer science-related studies came into life namely intelligent machines, natural language processing, machine learning (ML), pattern recognition, expert systems, and image recognition [3]. These new domains have helped the researchers to

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solve complex problems by taking into account different steps such as planning, reasoning, and learning [4].

In addition, in 1959, Arthur Samuel is the researcher who conveyed the concept of "machine learning" (ML) for the first time in the life cycle of AI. He directed the category of algorithms and classifiers in ML's concept [5]. These constructions of the algorithms started to learn the input data's distribution automatically and predicted new data accurately [6]. Similarly, due to the machine learning concept, different other promising breakthroughs came such as the backpropagation algorithm [7] and then neural networks [8].

After the concept of AI, in the early 1970s, a new concept came that empowered the medical-related areas by intending to improve the efficiency of the diagnosis and also the treatment against the found pathology [9]. Peleg and Combi et. al. [10] have elaborated different cycles of artificial intelligence in the history of medical-related areas such as 1) Infancy stage: Decision tree algorithm came into life; 2) Adolescence stage: Expert systems theory was proposed; 3) Coming-of-age stage: Deep learning's concept was being surfaced with machine learning; 4) the most important stage named as Maturation period: technologies related to these fields are comparably advanced and different applications of deep learning has started to prevail.

On the other hand, the advancement in medical equipment has also enhanced people's health [11]. This advancement has not just improved the survival rate but also has brought improvements in the diagnosis of disease or injury [12]. With these advancements, researchers have started their work for medical healthcare services as they came to know that it is a crucial step toward the effectiveness of clinical engineers to investigate in a better way and to ensure the patients' safety [13, 14, 15].

On the combined advancements in AI and types of equipment of the medical world, International Business Machines (IBM) has estimated that an average of 1 million gigabytes are produced from a person in his lifetime [16]. To get intuitions about medical problems, clinicians are trying to collaborate with artificial intelligence experts to use the chunks from the big data and forecast about the healthcare solutions to improve the quality of the diagnosis and cure [17, 18]. In this way, deep learning is playing a very crucial role to enhance equipment's output to support the clinicians in their decision. With this, Convolutional neural networks (CNNs) started to become popular because they learn the importance of features by themselves from the whole raw data space which saves the data scientist's time to become a domain expert in this algorithm [19, 20]. On this topic, these studies [21, 22] have compared the diagnosing capabilities of AI systems against physicians' diagnostic abilities. Results clearly highlighted that AI may support and complement physicians' diagnostic capabilities by adding a knowledge base inferred by data. In the current era of medical AI, there are several medical problems which are not yet been solved successfully and are the main focus of clinicians and medical researchers such as cardiovascular diseases (CVDs) [23], neurology [24, 25], neuro-cardiac hidden interactions [26, 27, 28, 29, 30] , cancer [31], aids [32], and so forth.

In this work, we are focusing on a detailed study of neuro-cardiac pathologies and their interrelations with the help of different imaging modalities using AI. In this essence, several researchers have proven that neuro-cardiac has a very strong relation among them. A disease, dysfunctioning, irregularity, or even surgery of cardiac can cause to other diseases or abnormalities to neuro [24, 33, 34, 35, 36], and same in vice versa like hypertension [37, 38], brain injury [39, 40], hypoxic-ischemic [41], brain tumor [42], neurogenic stress [43], and so on.

In the investigation of interrelation between Neuro-Cardiac Pathologies (NCPs), biologists have found several useful biomarkers to diagnose the influence of NCPs issues such as hs-TroponinT, hs-cTn, CK-MB and NTproBNP, galectin-3, lysophosphatidylcholine, copeptin, sST2, S100B, myeloperoxidase and GDF-15, and others [43, 44, 45]. Gopinath et. al. [43] have described that understanding the interaction between brain and heart is a very complex task and vital to keep maintaining the normal functioning of the cardiovascular system. Even sometimes, there is no cardiac disease but due to neuronal disease or injury, many cardiac diseases can be induced. The important thing is, there are different brain areas namely anterior cingulate gyrus, insular cortex, and amygdala controlling the automatic nervous system. If one of these gets damaged then many cardiac issues, interlinked with the damaged brain region, may elevate.

In the better diagnosis of the disease, nowadays radiologists and physicians are taking the support of new imaging modalities [46]. These new techniques have introduced so much improvement in revealing information with very high accuracy [47]. There are several different imaging modalities which are being used to identify the region of interest such as Perfusion Magnetic Resonance Imaging (MRI) [48], Diffusion weighted Imaging [49], Diffusion Tensor Imaging [49, 50], Proton MR Spectroscopy [51], Susceptibility-weighted Imaging [52], Cerebrospinal Fluid Flow MRI [53], etc. for neuro pathologies and Cardiac MRI with T1 and T2 Mapping [54, 55], and Dual Energy Cardiac Imaging [56] for cardiac pathologies.

In the next section, a number of states of art methodologies related to different findings about neuro-cardiac hidden interactions are being discussed in detail while the conclusion section is ending this work with final remarks.

2. State of the art methodologies related to neuro-cardiac interactions and complications

In this section, a selection of literature studies concerning methodologies employed in the field of neuro-cardiac interactions and complications will be considered. The selected studies have shown potential applications of imaging and signal analysis to unravel and investigate hidden relationships and complications between neuro-cardiac interactions. In literature, some of previous studies reported examples of imaging techniques mainly based on operator's work (clinicians' expert opinion) whereas others have taken advantage of statistical algorithms or artificial intelligence. In this review, the literature selection criteria took into account for two main factors 1) how different imaging approaches may be helpful in investigating distinctive neuro-cardiac interactions and 2) how expert opinion, statistical algorithms, and machine learning are beneficial in finding the interlinked markers. It is worth noting that, to date, only very few studies employed ML or DL to investigate neuro-cardiac relationships being medical-imaging aided investigations in the field mostly focused either on neurological or on cardiac diseases. Thus, the lack of attention indicates that this specific field of research has not yet been overburdened by studies concerning AI applications. Our comparative review may then stimulate the use of AI in this field to overcome main issues of more classical approaches in the field of neuro-cardiac pathologies.

The section is divided into four main sub-sections as also mentioned in Table 1, each referred to specific applied methodologies in the field concerning heart and brain interactions in pathology.

A first subsection concerns image analysis for heart and brain interactions, a second subsection deals with physicians' expert limitation to understand the complex neuro-cardiac interactions, a third considers signal analysis toward early diagnosis of heart and brain pathological events, and, a final subsection considers ML driven early-stage detection of heart and brain disease to support decision making. For each subsection, selected studies will be comparatively described in terms of purpose of the work, datasets, results, and then conclusive remarks at the end.

2.1. Image based analysis for heart and brain interactions in pathology

In this section, we are presenting two imaging-based clinical investigations [26, 27] employing physicians' expert opinions on CT and MRI images used to investigate neuro-cardiac pathologies through time-based checkups. More in detail, researchers have applied a conventional medical checkup approach. They gathered data from patients at first diagnosis and then at the follow-up. From this set of medical data, they tried to infer possible neuro-cardiac interactions by highlighting clinical parameter variations.

In the first study [26], authors have shown a detailed elaboration of heart and brain interactions with the pathophysiology of neuro-cardiac disorders. Mental and neurological disorders (MND) and cardiovascular diseases (CVD) are the two most prevalent disorders that lead to a large number of deaths in the world. They started their study with stress cardiomyopathy syndrome (SCS), a benign disease, in which roughly 290 patients went under observation. Different parameters like predisposing conditions/risk, physical, emotional, biological, and clinical factors were taken into account to analyze the predictions. They predicted the diagnostic score higher in females as compared to males. In addition, emotional and physical triggers, absence of ST segment depression, psychiatric and neuro disorders, and QTc prolongation were found in patients with a mortality rate of 25%.

Further, the first study has discussed another disease namely peripartum cardiomy- opathy (PPCM) which is a left ventricle (LV) systolic dysfunction. It generally affects 1 out of 1000 pregnancies but it also depends on ethnic background and most of these patients are generally diagnosed after their delivery. In the PPCM study, 740 patients were observed with different details like ethnicity, maternal age, lifestyle, history of cardiac disorders, and others. They resulted in a number of complications that appear after 6 months with mortality rate of 7% in women and mortality the rate of 6% in neonates. In the end, the first work conducted another experiment on patients with atrial fibrillation (AF) and cognitive decline diseases. AF is a very prevalent disease in aging people. For this study, 2400 patients were taken into account and all patients underwent magnetic resonance imaging (MRI) at the time of first checking, and after 2 years with cognitive tests. It was found that silent brain lesions have prevailed in the brain. Due to these detected lesions in MRI, patients started to face a reduction in cognition.

In the second study [27], they evaluated the prognostic performance of ventricular characteristics on brain computed tomography (CT) in cardiac arrest survivors based on the cerebral performance categories (CPC) score scheme. They enrolled a total of 320 survivors who faced cardiac arrest event/s (age > 18 years) and accordingly tried to calculate the score where CPC-1 is a good performance and CPC-5 is brain death or death. For each patient, they considered several features such as: age, sex, comorbidities, blood and circulation parameters, and brain CT findings to predict the neurological outcome. In addition to these features, few clinical features such as ventricular areas (lateral, third, and fourth ventricle), distance between both anterior horns and both posterior horns of the lateral ventricle (LV), the Hounsfield units (HUs) of the putamen and corpus callosum and Grey-to-white matter ratio (GWR) were calculated.

Unfavorable outcomes were found after 6 months of cardiac arrest activity in 180 patients with the rate of 68%. Patients with favorable neurologic outcomes were younger, had a lower incidence of comorbidities (hypertension and diabetes), and had a shorter time to ROSC. They also showed significantly higher GWR, smaller LV and third ventricle areas, a significantly shorter distance between both the anterior horn of the LVs and the posterior horn of the LV, and a lower relative LV area.

At the end, ventricular characteristics were significantly different between favorable and unfavorable neurological outcomes at 6 months after cardiac arrest activity. In this regard, CT findings could be directly used to delineate accurate neurological predictions about the patients after their cardiac event.

From above-described literature studies, it emerges how neuro-cardiac interactions in pathology are investigated through physicians' opinions and score-based techniques on time-based diagnostics. Although some evidence was found, a lack of confidence characterizes results in terms of features importance related to neuro-cardiac interaction analysis. Other drawbacks are related to the choice of follow-up end point for evaluation and limitations in early diagnosis of neurological diseases and correlated to cardiac events.

2.2. Physians' opinion limitation for diagnosing neuro-cardiac pathological events using imaging modalities

This section elaborates on a study [29], based on ECGs, which has shown the physicians' opinion limitation towards understanding and predicting the complex neuro-cardiac pathological event. In the ECG work, they evaluated the cardiac alterations caused by central nervous system disorders by the observation of abnormalities on electrocardiogram (ECG) patterns. They mainly focused on different patterns namely ST segment, QT segment, QT interval prolongation, T wave, and QRS complex. The data collection was made on 161 patients as 12-lead ECGs including age of ranging from 10 to 60 years. These ECGs were having different diseases such as brain tumor (66 cases), stroke (44 cases), subarachnoid hemorrhage (11 cases), subdural hemorrhage (8 cases), brain aneurysm (25 cases), and head injury (7 cases).

The selected ECGs were then analyzed and corrected with the help of Bazett's formula. After correction, all ECGs were shown to experts, who were blinded to all data and predicted the outcomes based on different ECG components. The expert predictions showed that they put their whole attention on ST-segment's elevation or depression, inverse T-wave, non-specific ST-T abnormalities, and QT prolongation. According to them, these are the main features that are causing tumor, subarachnoid hemorrhage, or subdural hemorrhage.

This study's results are very interesting in this way that the total dataset contains different neurological diseases. In adverse, doctors' expert opinions' predictions have shown just 35.4%. It means the markers related to neuro-cardiac interactions are not observable by the naked eye. To predict the complex interactions between neuro-cardiac, it is necessary to introduce promising tools in this domain to achieve some delineate models.

2.3. Statistical analysis: signal analysis toward early diagnosis of heart and brain pathological event

This section has focused on signaling based statistical techniques that have used ECGs abnormalities to diagnose heart and brain related pathologies. In the related study [28], they have evaluated the relationship between ECGs and the outcome with mortality of 3 months after an acute stroke. On start, a total of 1070 ECGs (12-leads) were taken into account which were having three abnormalities namely acute cerebral infarction (ACI) (692 patients), intracerebral haemorrhage (ICH) (155 patients), and transient ischaemic attack (TIA) (223 patients). On these ECGs, different features were computed based on clinical parameters and CT-scans. To evaluate these features, a logistic regression classifier based on Scandinavian Stroke Scale (SSS) score, using SPSS software, has been used. After the computation of score, outcome was then rescaled on the modified Ranking Scale (mRS) algorithm for better understanding.

In results, ECG-abnormalities were predicted as 416 ECGs were containing ACI, 77 ECGs were having ICH, and 98 patients were facing TIA complications. In this multivariate analysis, they predicted that ACI strokes were detected through atrial fibrillation, atrio-ventricular block, ST-elevation, ST-depression, and inverted T-waves on ECGs. The important thing about ACI is, it is totally independent of stroke severity and age. Then, ICH was predicted by analyzing sinus tachycardia, ST-depression, and inverted T-waves. At the end, none of the ECG changes had prognostic significance in patients with TIA. In the whole experiment, they noticed that the patients with severe cerebral infarction faced high rate of heart beat for the first 12 hours. With this, at every increase in heart rate of 10/min gave another indication to the physicians that this kind of trend is directly associated to mortality at 3 months.

From the whole experiment, physicians have predicted that stroke severity SSS score decides the amount of augmentation in the frequency of ECG components. Some ECG abnormalities and increasing heart rate predict poor outcome and 3 months of mortality after an acute stroke. However, this study showed a low accuracy (only 55% of the entire dataset was correctly predicted). The reason probably lies in the ECGs feature space, which does not contain enough information to diagnose and understand this type of interaction.

2.4. ML driven early-stage detection of heart and brain disease and support to clinical decision

In this section, we have included machine learning based methodology [30] in which they have used several machine learning algorithms on cardiac arrest patients' data. At the end, they used artificial intelligence (AI) explainability and predicted the important features. In the selected ML study, researchers designed a multi-modal machine learning system to predict the survival rate of cardiac arrest patients who received cardiopulmonary resuscitation (CPR) without going to the hospital. In a greater detail, a ML model was developed to predict neurological outcome based on the scale of cerebral performance category (CPC) scores in which CPC-1 and CPC-2 were declared good neurological outcomes and CPC-3 to CPC-5 as bad outcomes.

Data to train and test the ML algorithm were taken from the Korean Cardiac Arrest Research Consortium (KoCARC) dataset [57] which is publicly available with committee approval. This dataset contains data from roughly 6000 patients who faced the return of spontaneous circulation

(ROSC). It is worth noticing that this database is highly unbalanced given that only a hundred patients had bad neurological outcomes among all the available patient data. For each patient, around 20 independent features per patient were available such as: age, sex, ECG rhythms, CPR values, defibrillation and pre-hospital intervals, etc.

Before going to ML techniques, missing value issue was faced by multiple imputation by chained equation (MICE) algorithm. MICE is basically an iterative model which imputes values step by step in all variables. Then four renowned classifiers were trained namely voting classifier (VC), XGBoost (XGB), random forest (RF), and regularized logistic regression (RLR) classifier. A five-fold cross-validation technique was applied for the training of the multimodal system. Grid search technique which helped in predicting the optimized parameters. To compute the robustness of this model, different renowned measures were used namely Brier score, log loss, area under the curve (AUC), F1-score, negative predictive value, and positive predictive value. With the help of these measures, it was found that XGB, VC, and RLR performed very well with greater than 90% AUC while RF had less than 90% AUC.

Table 1
Comparsion of different analysis techniques related to neuro-cardiac pathologies

Analysis type	*Study*	*Data Size*	*Features*	*Results*	*Drawbacks*
Imaging Modalities	[26]	3430	ECG, MRI, and so on	Mortality rate of 28% and Cognitive decline	Time taking and disease detection at appearance
	[27]	320	Age, sex, brain CT findings, and so forth	68% bad neurological outcome	
Physicians' opinion	[29]	160	Age, Gender, and ECG components	Predicted: 35%	Physicians' opinion is limited by using imaging modalities
Statistical analysis	[28]	1100	Age, 12 lead ECG, hypertension history and so on	Predicted: 55%	Features are not having promising information
Machine learning	[30]	110	Age, pre-hospital ECG rhythm, hospital ECG rhythm, and so forth	90% AUC	More samples to improve more

In contrast to best performances, it was found that XGB algorithm focused on predicting the true-positive and false negative samples while RLR focused on the true positive and false negative samples. In regard to predicting the poor neurological outcomes, these model were not able to predict bad neurological outcomes in a good way even though 68 patients were existed in the test set. Due to this drawback, the authors selected voting classifiers (VC) which has shown good performance in the prediction of neurological outcomes. On VC, authors applied further explainable AI technique to take out, from the whole feature space, the six most important variables for the prediction of the neurological outcome. In other words, those clinical feature, e.g., age, ECG rhythm, cardiac arrest event, and others, are mainly responsible for high scores in VC driven classification and prediction of neurological outcomes.

3. Conclusions

Advancements in imaging and signal analysis have made physicians and researchers more able to infer the structural and functional properties of the brain and heart. Continuous improvement in computational power, algorithms and finally the raise of ML and DL-driven technologies have allowed scientists to start to deepen their knowledge on hidden neuro-cardiac interactions. However, this intriguing research field is only at the beginning. In this review paper, we have collected and compared some relevant examples of research applications in the field with particular attention to neuro-cardiac imaging and signal analysis techniques aided by expert opinions (physicians), statistical algorithms, and machine learning. It is found that there are not a high number of studies reporting examples of AI techniques applied to the field. As most researchers are employing heart imaging-based models to diagnose heart diseases and brain imaging-based models for brain diseases but not in inter-related interactions. In this domain, most reported studies are based on more classical approaches, which are usually limited in quantifying feature importance and clinical variable connections given by the complexity of the investigated system. On the other side, artificial intelligence (AI) techniques has the well-known ability to surface up more hidden interactions and interlinked complications to support clinicians' decisions. In the near future, it is likely that ML/DL-driven technologies already effectively developed in other medicine areas (e.g., cancer, Cardiovascular risk, etc..) will be tailored to empower our knowledge on hidden relationships characterizing heart-brain connections.

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Conflicts of Interest

The authors declare no conflict of interest.

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