Future perspectives toward the early definition of a multivariate decision-support scheme employed in clinical decision making for senior citizens

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Recent neuroscientific studies focused on the identification of pathological neurophysiological patterns (emotions, geriatric depression, memory impairment and sleep disturbances) through computerised clinical decision-support systems. Almost all these research attempts employed either resting-state condition (e.g. eyes-closed) or event-related potentials extracted during a cognitive task known to be affected by the disease under consideration. This Letter reviews existing data mining techniques and aims to enhance their robustness by proposing a holistic decision framework dealing with comorbidities and early symptoms' identification, while it could be applied in realistic occasions. Multivariate features are elicited and fused in order to be compared with average activities characteristic of each neuropathology group. A proposed model of the specific cognitive function which may be based on previous findings (a priori information) and/or validated by current experimental data should be then formed. So, the proposed scheme facilitates the early identification and prevention of neurodegenerative phenomena. Neurophysiological semantic annotation is hypothesised to enhance the importance of the proposed framework in facilitating the personalised healthcare of the information society and medical informatics research community.

1. Introduction: The continually increasing population led to a subsequent increase of the number of senior citizens. However, this target group demonstrates prominent vulnerability to chronic disease such as diabetes, memory impairment, depression and sleep disorders [1]. Comorbidity due to chronic diseases is also frequent and greatly deteriorates quality of life and independent living. The lack of independence increases hospitalisation rates and socioeconomical burden especially for the carers. Therefore, recent neuroscientific studies focused on the identification of neurophysiological signatures related with mood disorders [2, 3], geriatric depression [4], memory impairment [5] and sleep disturbances [6].

A previous Letter investigated pathological patterns in decision making due to the co-existence of attention-deficit/hyperactivity disorder (ADHD) coexisted with bipolar disorder (BD) [7]. The study design employed 50 participants (BD: $n = 13$; ADHD: $n = 12$; controls: $n = 25$) who received a full clinical assessment in terms of neurocognitive and event-related potentials (ERPs) assessment. Neurological, neuropsychiatric and neuropsychological examinations were used for a standard diagnostic process of all participants. Two tasks were used: (i) the Iowa gambling task, a task of rational decision-making under risk and (ii) a rapid-decision gambling task which extracts behavioural measures as well as ERPs (ERPs: fERN and P3) in connection to the motivational impact of events.

The results indicate a clinical relation between neural substrates and the decision-making impairments in patients with BD and those with ADHD. Brain features provided better identification than traditional clinical praxis. Both patient groups present symptomatology of frontal structure, which may facilitate robust diagnosis and treatment. These results indicate the role of monitoring systems and their relevance in reward and decision processing.

Mood disorders may also be monitored through the neuroscientific-data mining approach proposed by Frantzidis *et al.* [2]. More specifically, discrimination of emotional biosignals is based on the bi-directional emotional model (valence and arousal

dimensions). Initially, valence discrimination is performed through a data mining approach called C4.5 tree algorithm. The valence and the gender information are then served as input to a Mahalanobis distance (MD) classifier which partitions the data according to their arousal degree (high against low). The success rate for the discrimination of four emotional states (high valence and high arousal, low valence and high arousal, high valence and low arousal and low valence and low arousal) was 77.68%. This result found to be promising for affective healthcare applications such as emotional monitoring of the elderly or chronically ill people.

Gait analysis is nowadays employed to monitor cognitive and physical deterioration to elderly people. A recent research examined a number of 69 instances (18 of which were discarded because they suffered from faulty skeleton detection) which were produced within 26 days [8]. Microsoft SDK recognised a human skeleton and its mobility patterns at nine locations which were selected as predominant regions of activity in the active and healthy ageing living lab. This research targets to open up innovative ways for context aware indoor trajectory and gait analysis and sequentially for decision-support systems on the field.

Cognitive importance is also monitored through an ontology driven decision-support method aimed at the identification of mild cognitive impairment (MCI) anatomical patterns [9]. Specialised magnetic resonance imaging knowledge encoded into ontology and a rule set constructed using machine learning algorithms. These two parts applied in conjunction with a reasoning engine to automatically distinguish MCI patients from normal controls (NCs). The classification scheme was validated through 187 MCI patients and 177 NCs chosen from the Alzheimer's disease neuroimaging initiative. The classification method was the C4.5 algorithm applied through a ten-fold cross-validation. The methodology reached 80.2% sensitivity, which was better than other algorithms such as Bayesian network, back propagation neural networks and support vector machine (SVM). The C4.5 algorithm was also a suitable approach for the construction of reasoning rules. The

research indicated that this methodology would be helpful toward the early identification of MCI methodology.

Neuromuscular disorders may be a crucial factor in case of comorbidities. A recent research attempt aimed at the optimisation of the parameters involved in the diagnosis of neuromuscular disorders [10]. It proposed an SVM-based classifier (ESVM) and optimisation of automatic parameter tuning through a genetic algorithm. The efficiency of ESVM illustrated by a typical application to electromyogrammic (EMG) signals classification using normal, neurogenic and myopathic datasets. In this approach, EMG signals were analysed by means of a discrete wavelet transform and a set of statistical features was extracted. The system's validation demonstrated that ESVM is an efficient tool for diagnosis of neuromuscular disorders.

Blood pressure patterns were also analysed in a study which developed a decision-support algorithm to predict pathological nocturnal BP profiles during a standard examination in multiple system atrophy (MSA) and Parkinson's disease (PD) [11]. The study enrolled 16 patients with PD and 16 patients with MSA at a 24 h ambulatory BP pressure. Clinical and tilt test differences appeared between patients with normal and pathological nocturnal BP profile. Pathological nocturnal BP profiles are related with cardiovascular noradrenergic failure in MSA and PD. In this piece of work, it is proposed the naked-eye evaluation of BP behaviour during phase II-L and phase IV of the Valsalva manoeuvre as screening test.

Most of these studies proposed computerised systems able to discriminate pathological symptoms with accuracy better than pure chance. Despite the promising results, their main drawback is that they mainly include a patient (target) group which is affected by a single disorder usually characterised by distinct neuropathological pattern. However, this situation is not frequent in daily clinical practice and it neglects the common case of comorbidities. Furthermore, most of the previous research employs mainly a single either, e.g. resting-state condition (e.g. eyes-closed) or ERPs elicited during a cognitive task known to be affected by the disease under consideration. The novelty of our framework is the integration of several recording modalities through multi-parametric data mining. Therefore, holistic and dynamically updated information would be given as input to the classification component, facilitating the early identification of patients with increased risk of suffering from chronic conditions and comorbidities. Semantic annotation would promote data unification and avoid study isolation.

A great challenge of future clinical decision making would be the demonstration of more realistic systems. These would be applicable to clinical daily routine by detecting multivariate neuropathological patterns induced by comorbidities. Such systems may receive as an input raw data derived from heterogeneous conditions either experimental or real-world and extract a multifactorial set of features. These set of features would be then compared either to distinct or multiple pathological patterns and a probability of symptoms' existence would be extracted for each case.

This Letter aims to outline a generic conceptual framework that faces the aforementioned challenges and could be applied in realistic use cases. It demonstrates the utilisation of heterogeneous features derived from different experimental conditions such as resting-state, emotional processing and sleep electroencephalographic (EEG). Multivariate features are then extracted and fused in order to be compared with average activities characteristic of each neuropathology group.

The proposed clinical decision framework is designed to be employed in problems requiring multifactorial analysis of different experimental conditions. Aiming to enhance the system's sustainability and applicability, this framework must be flexible enough to be adapted to specific use cases. Therefore, a semantic annotation through ontologies and semantic rules is employed to describe study aspects (e.g. participant groups, recording modalities), aims (type of outcomes, warnings, alerts, decisions), experimental

procedures (cognitive tasks, interventions, recording states) and neurophysiological patterns.

2. Methodology

2.1. Experimental conditions

2.1.1. Resting state: Previous neuroscientific studies investigated whether the intrinsic brain activity during rest may be employed in order to identify pathological brain signs [12]. Resting-state activity has been demonstrated not to be an inertia brain phase rather than a dynamic one during which the brain activates several brain networks such as the default-mode network, attention network etc. and investigates optimal network configurations [13]. This time-evolving brain state is suitable for quantifying functional operations among distant brain regions. Co-operative activity is then quantified through synchronisation metrics such as relative-wavelet entropy [14]. Estimation of synchronisation patterns may then provide valuable brain-related markers for several disease symptoms [5]. Therefore, resting-state recordings offer a cheap, non-invasive and easy to implement direct window of brain functioning which can robustly identify pathological deviations [14].

2.1.2. Event-related potentials: The ERPs are regarded to be brain responses time-locked to the stimulus onset [15]. Stimuli may be either visual or auditory and in some cases even multimodal according to the cognitive function under investigation. These electrical waveforms appear to distinct time latencies and reflect the brain performance on sensory stimulation. More specifically they are related with identification of stimulus salient features, attention and memory [16]. The temporal characteristics, both amplitude and latency of the ERPs are then investigated. Previous research efforts have demonstrated that the biological importance of the stimulus is quantified by the arousal dimension, while life-threatening situations are faster processed by the human brain [17]. These ERP characteristics have also been employed by decision-support systems for emotion identification [2, 3] or disease identification [18].

2.1.3. Dipole fitting: Current dipole modelling is a mathematical notion employed to localise brain sources, which are combined in order to produce the electrical activity measured at scalp electrode locations. The dipole identification requires the solution of the inverse problem which is a relative computationally intensive and ill-posed neuroscientific problem [19]. However, research has been recently benefited by the development of the DIPFIT plug in: Equivalent dipole source localization of independent components, through the Electroencephalographic Laboratory (EEGLAB) graphical interface [20]. This specific tool performs dipole fitting by means of independent component analysis (ICA) decomposition. ICA is a reliable method for the detection of dipoles created from elementary current sources. Each component corresponds to a dipole which describes the brain region activated during the experimental procedure. The localisation of these regions may contribute to the early diagnosis of symptoms due to epilepsy, sleep disorders, strokes and Alzheimer's disease. The ICA is a method of finding components which are derived from multiple variables. The difference of ICA from other methodologies is that its components are statistically independent and do not follow Gaussian distribution. The experimental procedure may involve visual stimuli. EEG data acquisition could be performed to extract ERPs which are time-locked to the stimulus onset. A proposed model of the specific cognitive function which may be based on previous findings (a priori information) and/or validated by current experimental data should be then formed. The brain regions proposed by this model are then identified in each participant and their synchronisation degree is estimated. So, the proposed scheme facilitates the early identification and prevention of neurodegenerative phenomena. Furthermore, the combination of the ICA methodology with a metric of synchronisation degree may offer an innovative

mathematical approach since localisation information is fused with the quantification of functional activity.

2.1.4. Sleep physiology: Sleep is regarded to be important for a wide range of cognitive and emotional processes [21]. The prevalence of sleep disturbances is quite high [22]. The sleep process is divided into the rapid eye movement (REM) and the non-REM stage, while the latter is further subdivided into four distinct stages ranging from the lightest to the deepest phase [23]. The sleep research is performed based on the polysomnographic (PSG) recordings, which involve EEG, electro-oculogrammic and EMG activity. The stages are scored according to a standardised set of well-defined criteria [24]. The stage scoring is performed in epochs of 30 s.

2.2. Feature set: The proposed computational framework is a multi-layer one since it integrates the aforementioned experimental conditions. For each one of these conditions the following features could be computed:

- Oscillatory activity (relative energy contribution, individual alpha frequency, theta/alpha transition frequency and ratios among energy bands) [5].
- Synchronisation/connectivity features in terms of $N \times N$ synchronisation matrices, where N stands for the number of recording sites [5, 14].
- Brain network characteristics such as the small-world property, characteristic path length, cluster coefficient, centrality metrics [5] etc.
- Temporal ERP characteristics (amplitude and latency) [17].

2.3. Feature selection: The proposed decision-making scheme employs a rather holistic procedure which involves multiple experimental conditions, while each condition consists of various features as described in the previous section. Subsequently, the analysis results in a large number of features which greatly increase the problem's complexity and may be partially overlapping or even correlated. Therefore, feature selection is an important step facilitating the practical implementation of the proposed system. Previous attempts mainly employ commonly used feature selection algorithms [25]. Despite the promising results of these attempts, their main drawback is that they do not allow the medical/clinical expert to intervene in the selection phase which is performed automatically based on algorithmic approaches. Therefore, the system's parameterisation and acceptability from the end-users is low.

Aiming to deal with this problem, we propose that future attempts may follow a hybrid procedure by integrating these feature selection methodologies with a priori information defined by the experts or guidelines semantically described. So, previous scientific results may be re-used and validated by forthcoming studies which would extend the already acquired knowledge, preventing thus studies' isolation.

2.4. Classification of neurophysiological data: The classification of multi-parametric data may re-use traditional multifactorial analysis as follows.

2.4.1. Support vector machine: The SVM classifier seeks for the optimal solution of the following problem which is described by the following equations:

$$\min_{(w, b, \xi)} = \frac{1}{2} w^T w + C \sum_{i=1}^l \xi_i, \quad (1)$$

which is subject to

$$y_i(w^T \varphi(x_i) + b) \geq 1 - \xi_i, \quad (2)$$

$$\xi_i \geq 0 \quad (3)$$

The data are denoted as x and their labels as y . The input arguments of function $\varphi(\cdot)$ are the training vectors which correspond to a higher dimensional space. So, the SVM classifier seeks for a linear separating hyperplane with the maximal margin. The ξ and b parameters related in the minimisation function. The C , γ , d and r are kernel parameters. The penalty parameter C is non-negative while $K(x_i, x_j)$ is the kernel function. The use of the kernel functions in this Letter is as below:

(1) Linear

$$K(x_i, x_j) = x_i^T x_j; \quad (4)$$

(2) Polynomial

$$K(x_i, x_j) = (\gamma x_i^T x_j + r)^d, \quad \gamma > 0; \quad (5)$$

(3) Radial basis function

$$K(x_i, x_j) = e^{-\gamma \|x_i - x_j\|^2}, \quad \gamma > 0; \quad (6)$$

2.4.2. Mahalanobis distance: The MD classifier may also be combined with the SVMs toward the neurophysiological classification of biosignals. Its technique is known as a minimum distance and is defined by the following equation:

$$dM = \sqrt{(x - \mu) \sum_{i=1}^M i^{-1} (x - \mu)^T}, \quad i = 1, 2, \dots, M \quad (7)$$

Here, x is every distance for classification and μ is the vector containing the centroids for each feature in the form of a multivariate feature vector as defined by

$$x = (x_1, x_2, \dots, x_N)^T, \quad \mu = (\mu_1, \mu_2, \dots, \mu_N)^T, \quad (8)$$

where N is the total number of features. Σ is the covariance matrix of the normally distributed training set for every class i that should be classified and the number of the different classes is denoted as M .

2.5. Semantic framework description: A semantic annotation through ontologies and rules is proposed to be involved toward the description of the various study parameters. The semantic framework of the proposed decision scheme targets to enhance the integration of the involved parameters and results enhancing thus the framework's integration and sustainability. The semantic model is related with an emotion recognition protocol, described in a previous research attempt [26]. Neurophysiological semantic annotation is hypothesised to enhance the importance of the proposed framework in facilitating the personalised healthcare of the information society and medical informatics research community. Examples of some categories of ontologies are as follows:

- Experiment ontology, which describes the research targets of a study, the conditions of the specific experiment. It also provides information of the study duration and deals with recording modalities and experimental conditions (EEG).
- Research ontology, which is linked with experiment ontology in order to describe semantically the research team including the specific study or experiment.
- Neuroscience domain ontology, which is used to describe specific categories of neuroscience research (brain ontology, attention ontology etc.).

Fig. 1 Description of the proposed clinical decision scheme. Raw data from resting-state EEG activity, ERPs and sleep PSG data are pre-processed. Various features are extracted and semantically described. Then, a hybrid feature selection procedure is performed by combining well-established algorithms with a priori expert knowledge. Finally, a multivariate DSS is applied to provide the expert with suggestions about the participant's state regarding common chronic diseases affecting the elderly (e.g. memory impairment, dementia, geriatric depression and emotional moods)

- Bibtex ontology, which is linked with experiment ontology in order to offer information about the reference of the study.

These ontologies can be reused or adapted in our ontological framework, in order to semantically describe our data. This can be achieved by research description framework (RDF)ising our data using tools such as OpenRefine [27], UnifiedViews [28] and then triples of semantic data can be stored in a Linked Data Server (i.e. Virtuoso) [29]. Finally, employing the SILK [30] we can enrich the semantic description of our data by linking them with other datasets in Linked Open Data Cloud [31]. In this way, semantic interoperability can be achieved via Semantic Protocol and Resource Query Language (SPARQL) queries [32].

3. Use case: Mrs. Papadopoulou is a widow for the past 2 years and lives alone in a small village in Thessaloniki municipality. Her daughter lives with her family in the city centre which is 50 km away from her mother's house. However, she visits Mrs. Papadopoulou almost every weekend. Lately, she observed that her mother neglects to clean her house carefully. This was a bit strange since Mrs. Papadopoulou was always very fastidious with housekeeping activities. Moreover, her grandchildren complained to their mother this Sunday noon that the lunch was too salty and spicy, while her grandmother could not finish

the story she began to tell them. Next day the daughter of Mrs. Papadopoulou visited with her mother a specialist neurologist and described the symptoms observed. The experts performed a brief neuropsychological examination to Mrs. Papadopoulou. The mini mental state examination was almost fine and gave no sign of deterioration. There was also a minimal deterioration in the Montreal cognitive assessment test, which was not indicative of dementia. The neurologist asked for a further neurophysiological examination, which included an experimental protocol combining resting-state activity, an emotion evocative condition through visual word stimuli and one-night sleep recording. The results from the oscillatory analysis demonstrated an increase of the ratio of the high/low alpha frequency band accompanied by an increase of the delta/theta energy ratio in prefrontal brain regions. The subsequent brain network analysis through graph theory revealed a gradual loss of the optimal brain network organisation due to reduced cluster coefficient and a small increase in the characteristic path length. Moreover, hub regions were observed on parietal regions. The ERP analysis demonstrated increased amplitude in unpleasant stimuli, while sleep PSG activity demonstrated an abnormal increased number of awake events, minimal stages of REM, while the number of light sleep stages (1 and 2) were increased in comparison with stages (3 and 4). The neurologist was equipped with an experimental clinical decision-making scheme which received as an input all the available features. The decision-support

scheme (DSS) system integrated all the available recording modalities and data so as to facilitate the prognosis of the patient. Otherwise, the neurologist would not be able to provide a definitive diagnosis. MCI during its early stage is easily confused with cognitive deterioration due to physiological ageing. So, fusion of different recording modalities aims to provide a combination of cognitive-related neurophysiological markers and to enhance the diagnostic accuracy during the asymptomatic phase. Therefore, the proposed data mining approach may provide a holistic investigation of neurologic abnormalities so as to predict cognitive and affective alterations of senior citizens and to suggest the proper treatment. The DSS also offers the opportunity for semantically annotating the data regarded by the expert as most important for Mrs. Papadopoulou. So, the system execution demonstrated that Mrs. Papadopoulou is likely to suffer from MCI of amnesic type coexisting with geriatric depression. On the basis of the system's notifications, the neurologist prescribed neuroimaging test and further neuropsychological examination which verified the system's decision. The above use case is also visualised in Fig. 1.

4. Conclusion: To sum up, this Letter does not intend to propose either a new data mining algorithm or a new approach of neurophysiological analysis. Its aim is to identify current limitations of the already proposed classification schemes and to highlight the reasons of their limited applicability to clinical practices. The most important cause is that most of the already proposed systems have been designed and tested under experimental conditions which are regarded as ideal concerning the symptomatology of the patient group, the group formation etc. However, in real cases senior citizens suffer from multiple chronic diseases. So, their neuropathological pattern is a superposition of several disease signatures.

The semantic description of each study parameters, experimental conditions and results is employed toward the facilitation of the cross-modal integration of the various clinical paradigms and to facilitate data re-usability. Semantic description is expected to increase the sustainability of the proposed system and to allow its future adaption to specific scenarios, improving thus the personalised healthcare quality. Though the importance of the proposed framework cannot be underestimated, the added value that is hypothesised by the present framework has to be evaluated before claiming success.

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