Use of an ANN to Value MTF and Melatonin Effect on ADHD Affected Children

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ABSTRACT Sleep disorders is one of the most frequent child medical consultation, indeed the rate of children that suffer it in a transitory way is considerably high. Among the most common sleep disorders is named ''children behavioral insomnia'', many different drugs has been used as treatment with poor results with relevant secondary effects. We focus on children with ADHD that present sleep disorders among most frequent comorbidities. The most relevant contribution of this work is the use of an artificial neural network (ANN) for unsupervised learning called the Growing Neural Forest (GNF), which is a variation of the Growing Neural Gas (GNG) model where a set of trees is learnt instead of a general graph so that input data can be better represented, to study actigraphic data to evaluate the use of MTF and melatonin in a group of children with sleep disorders. Thus, the GNF model is trained with actigraphic data from children ADHD affected as input data. The GNG and SOM (Self-Organizing Map) models are also trained with these data for comparative purposes. Experimental results demonstrate that sleep was not affected by administrating drugs (MFT and melatonin).

INDEX TERMS Artificial neural networks, application, children, melatonin, ADHD.

I. INTRODUCTION

Nowadays one of the most frequent child medical consultation is sleep disorders [24]. The rate of children that suffer it in a transitory way in considerably high, even it is foreseen that 30% children population suffer chronic alterations in sleep with a rate even higher than neurologic diseases affected patients.

These problems are usually stables along infancy in such a way that a child with sleep disorders in early 8 months it is highly probably that he still shows difficulties in his third year old. Similarly, those children with difficulties at two years old, they will go on with sleep disorders at 12 years old [58]. One on the most common sleep disorders are named ''children behavioral insomnia'', which consists in prolonged latency periods in initiating night sleeps and/or prolonged and frequent awakens during second half of the night 10, these problems are particularly frequent in ADHD children [6], [16], [51]. Different drugs has been used as treatment (antihistaminic, bariatrics, benzodiazepines, etc), but these have numerous and important secondary effects: tachycardia, mucosa dryness, heavy feeling, amnesias, sleep phases distortions, etc [29]. However, several works show how melatonin (aMT) is a good sleep instigator that does not present known secondary effects at the moment [20], [55], [59]. We highlight Jan and O'Donell [28] reviews about the use of aMT in children sleep disorders.

American Board of Sleep Medicine (ABSM) has claimed actigraphy as an useful methodology to evaluate children sleep disorders [35]. Its easy usage, dependability and cost rate have led to a generalize usage and it is being used in children with Asperger syndrome [61], disruption autistic spectrum [39], attention deficit/hyperactivity [11] and sleep disorders [7].

Children with ADHD presents sleep disorders among most frequent comorbidities, which can be increased when we use as treatment Metil-Fenidato (MTF) [13], [45]. Nevertheless, this drug has some secondary effects that could affect on these patients' quality of life [14]. The main target of this work is the use of an artificial neural network (ANN), which is fed with actigraphic data from children with ADHD, in order to evaluate whether combine administration of aMT and MFT allows keeping or improving sleep pattern in those patients before starting a treatment.

Some recent works on ANN applied to Actigraphy are found in the literature. Particularly, deep neural networks (NNs) have achieved, over last few years, state of the art performance on a wide variety of machine learning tasks in various domains such as speech recognition, computer vision and natural language processing. Nevertheless, there is a wave interested in adapting NNs to sleep/wake state detection [8]. They use a Recurrent Neural Network for multimodal ambulatory sleep detection.

Long *et al.* [36] present an actigraphy-based approach for sleep/wake detection for insomniacs. They use actigraphy to estimate overnight sleep-wake patterns in clinical practice using a Cohen's kappa from 0.49 to 0.55.

Hammerla *et al.* [22] present an approach for deep, convolutional, and recurrent models for human activity recognition using wearables as actigraphs. They focus on human activity recognition (HAR) in ubiquitous computing investigating the suitability of each model for HAR, across thousands of recognition experiments with randomly sampled model configurations.

In [21] authors present an study with two novel modeling schemes that utilize Deep Convolutional Neural Networks (CNN) to identify sleep/wake states. They propose two methods of deep CNN for detecting the four sleep/wake states in a raw activity data: sequential CNN, and Multi-Task Learning (MTL) based approach. Their model takes advantage of the reduced complexity of CNN architecture (relative to RNN), while leveraging the inherent strength of CNN to detect local motifs in a time augmented context.

All of these works focused on identifying different stages in the sleep using ANN for this classification, our approach focuses on valuing MTF and melatonin effect on ADHD affected children. For this purpose, we have taken real values from actigraphs of children with sleep disorders and we have designed and implemented a GNF model to analyze if MTF and melatonin affects the sleep of those children. Additionally, we have designed and modeled GNG and SOM models to perform a comparative of different alternatives with similar results.

The structure of this paper is as follows. First the methodology used in this research is explained in Section II. Then experimental results are presented in Section III. Some key findings are discussed in Section IV. Finally, Section V is devoted to conclusions.

II. METHODOLOGY

A. METHODS STUDY DESIGN

The study was an open label clinical trial involving a short term follow up for 1 month. Participants came from the Health Area of Granada (Spain). They received a suspected diagnosis of ADHD from their primary care pediatrician and were referred to the Neuropediatric, Neuropsychology and Early Intervention Unit of San Cecilio University Hospital (Granada) for subsequent monitoring and evaluation. At the hospital, the same study protocol was followed by all patients in order to reach the definitive diagnosis of the ADHD and possible comorbidities. A complete medical record and a careful physical examination were initially done. The medical record was based on the interviews done to the patient and parents, as well as the information provided by the teachers. A neuropsychological assessment was carried out in order to complement the diagnostic process, which included the following questionnaires: the NICHQ Vanderbilt Parent Assessment Scale [66] and the NICHQ Vanderbilt Teacher Assessment Scale [3]; the Kaufman Brief Intelligence Test [30] and the Wechsler Intelligence Scale for Children [26] to assess the intelligence and the cognitive capacity; the Magallanes Scale of Visual Attention [34] the Children's Depression Inventory [57] and the Spence Children's. Anxiety Scale41. The final diagnosis of ADHD and the specific subtype was made according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5).

The study protocol was approved by the local Ethical Committee of Biomedical Research of Granada (Spain). All procedures were carried out in accordance with the Helsinki Declaration as revised in 2000 (World Medical Association 2000). Written informed consent signed by both parents or tutors was required to participate in the study and to publish the results, as well as the assent of school aged children to their involvement in the research. The written informed consent was also required from patients over 12 years and sufficiently mature in relation to their developmental age. Exclusion criteria to participate in our study included metabolic or endocrine disorders as well as other neurological diseases able to justify the present symptoms. However, comorbid disorders with ADHD were not considered as exclusion criteria. Patients taking medications that may disturb sleep or alter the metabolism of orally administered melatonin were not included either. Finally 27 children and adolescents with ADHD were recruited. The sample consisted of 17 boys (63%) and 10 girls (37%), aged 7-15 years ($10+/-2$ years) at start of the intervention period.

B. PROCEDURE

- Therapeutic intervention: once the diagnosis of ADHD was confirmed, a multimodal treatment regimen was designed based on the joint decision made by family, teachers, psychologists and pediatricians of our unit. The pharmacological treatment consisted of a combined therapy with extended-release methylphenidate hydrochloride (Concerta R, Janssen Pharmaceuticals, Inc., Titusville, NJ, US) (initial daily dose of 1 mg/kg/day) and immediate release-acting melatonin (dose of 1 mg administered 30 minutes before bedtime). It was also added a nutritional supplement with omega-3 fatty acids that contained eicosapentaenoic acid (EPA) 70 mg/day and docosahexaenoic acid (DHA) 250 mg/day. All medications started at the same time. Except melatonin, MPH and EPA/DHA were administered in the morning in one single dose. Sleep diary: in order to know the sleep habits of our patients,

the official sleep diary validated by the National Sleep Foundation (US) was completed by parents and adolescents before starting treatment. The diary collected information for a 7 day-period with identical questions for each day: 1) bedtime; 2) get-up time; 3) sleep onset; 4) night awakenings; 5) feeling at wake-up time (refreshed, somewhat refreshed or fatigued); 6) sleep duration; 7) sleep disturbances (any mental, emotional, physical or environmental factors that affected sleep, e.g., stress, snoring, physical discomfort, temperature); 8) caffeinated drink consumption; 9) physical exercise; 10) alcohol or a heavy meal intake 2-3 hours before going to bed; 11) medication intake; 12) activity carried out 1 hour before going to sleep (watch television, work, read).

- Sleep questionnaire: before treatment, the parents completed the Pediatric Sleep Questionnaire (PSQ) short version [62] translated into Spanish language. The PSQ is designed to screen for sleep problems in children. The shorter version specifically relates to sleep-disordered breathing (SDB) in children, apart from containing questions associated with symptoms of hyperactivity and inattention. It consists of 22 parent-reported items examining snoring and breathing problems, daytime sleepiness, inattention, hyperactivity, and other pediatric obstructive sleep apnea features. Responses are ''yes'' = 1, ''no'' = 0, and ''unknown'' = missing. The presence of 8 or more positive responses suggests a possible SDB [62].
- Actigraphy: actigraphs were used in sleep assessment to discriminate between sleep wake states through information provided by body movements. Actigraphs used in this study (MotionWatch, Cambridge Neurotechnology Ltd., Cambridge, UK) were worn on the non dominant wrist 24 hours a day, for 7 consecutive days. Recordings of the amount of movement were made at 0.5 minute (30 second)-epoch and at the higher threshold value of sensitivity (threshold value for each sensitivity setting: low sensitivity= 80, medium sensitivity = 40, high sensitivity = 20). The activity score for each epoch was then compared to the threshold to determine if the epoch was scored as wake or sleep (CamNtech Ltd 2016). This device model incorporated a light sensor to record luminous intensity of white light and compare this information with that one provided by sleep diary in relation to bedtime and get-up time. The data extraction and summary analysis were computed by using a software (MotionWare R version 1.1.20, Cambridge Neurotechnology Ltd., Cambridge, UK) that employed a validated sleep estimation algorithm [17]. Prior to data analysis, they were visually inspected in order to reject actigraphy artefacts (for example, any epochs where the device had been removed).

The Sleep Start calculation was based upon the assumption that the subject would have little or no movement in the period shortly after they have fallen asleep. The period used to determine sleep start was 10 minutes, hence at a 0.5 minute epoch, we tested 20 epochs. The process then began by checking the first 10 minute period following the bedtime. Each epoch was tested against the threshold as described above. The number of epochs exceeding the threshold was counted. It the number of epochs exceeding the threshold was greater than an allowed number dependent upon the epoch (for a 30 second-epoch the allowed counts above threshold were 2), the process was repeated with the start point 1 minute forward from the bedtime. This process continued until a 10 minute block was found that satisfied both the threshold and allowed counts criteria. The Sleep Start was then marked as the start of this 10 minute period (CamNtech Ltd 2016). The Sleep End calculation was similar to Sleep Start, except that the period of 5 minutes (10 epochs for a 30 second-epoch) before the get-up time that satisfied the test criteria was chosen in this case (CamNtech Ltd 2016). The actigraphic assessment of sleep was conducted before and after 1 month of treatment with MPH and melatonin. The sleep parameters estimated from actigraphic data are shown in Table 1.

Analyses were conducted using Statgraphics Centurion version XVII (Stat point Technologies, Inc., Warrengton, Virginia, US). Descriptive data were presented as standard deviation (SD) means.

C. ARTIFICIAL NEURAL NETWORKS

In addition, we applied an advanced methodology based on the use of artificial neural networks (ANNs) in order to technologically improve the interpretation of actigraphic data. ANNs have the ability to derive meaning from complicated or imprecise data and can be used to extract patterns and detect trends that are too complex to be detected by either humans or other computer techniques. They are inspired by the biological nervous systems and are composed of a large number of highly interconnected processing elements (neurons) working in unison to solve specific problems. It is worth mentioning that it has been recently found that the neurons of some cortical regions of the human brain are organized as densely connected components [25]. Other biological networks also exhibit the same kind of structure. Therefore, it could be affirmed that ANNs that learn connected components of neurons have a biological analogue.

ANNs can be used to model complex relationships between inputs and outputs or to find patterns in data. Among their advantages it is included abilities of adaptive learning, self-organization, real time operation and fault tolerance via redundant information coding [40]. They can be used for a specific application, such as data clustering or classification, through a learning process. Clustering is the unsupervised classification of patterns (observations, data items, or feature vectors) into groups (clusters) [27]. In our case, we are interested in applying clustering to sleep patterns based on actigraphic results. The Kohonen's Self-Organizing Map (SOM) [31] has been widely used as an ANN for

TABLE 1. Sleep parameters considered for the analysis from the actigraphic data set.

Parameter	Description
Time in bed	The total elapsed time between the 'Lights Out' and 'Get-Up' times (CamNtech Ltd, 2016)
Assumed sleep	The total elapsed time between the 'Fall Asleep' and 'Wake-Up' times (CamNtech Ltd, 2016)
Actual sleep time	The total time spent in sleep according to the epoch-by-epoch wake/sleep categorization (CamNtech Ltd, 2016).
Actual sleep time(%)	Actual sleep time expressed as a percentage of the assumed sleep time (CamNtech Ltd, 2016).
Actual wake time	The total time spent in wake according to the epoch-by-epoch wake/sleep categorisation (CamNtech Ltd, 2016).
Actual wake time(%)	Actual wake time expressed as a percentage of the assumed sleep time (CamNtech Ltd, 2016).
Sleep efficiency(%)	Actual sleep time expressed as a percentage of the time in bed (CamNtech Ltd, 2016).
Sleep onset latency	The time between 'Lights Out' and 'Fall Asleep' (CamNtech Ltd, 2016).
Sleep bouts	The number of contiguous sections categorised as sleep in the epochby-epoch wake/sleep categorisation. The number of sleep bouts was low if the sleep was of good quality (i.e. long uninterrupted periods) and higher if it was of poor quality (CamNtech Ltd, 2016).
Wake bouts	The number of contiguous sections categorised as wake in the epochby-epoch wake/sleep categorisation. Although wake bouts are the converse of sleep bouts, they were not considered to evaluate sleep quality. Actigraphy is better at detecting sleep that at detecting wake during the sleep period [35] because it tends to overestimate the number of wake bouts in comparison with PSG. A typical number of wake bouts for a normal sleeper is around 30 but can vary from 15 to 40 (CamNtech Ltd, 2016).
Mean sleep bouts	The average length of each of the sleep bouts (CamNtech Ltd, 2016).
Mean wake bouts	The average length of each of the wake bouts (CamNtech Ltd, 2016).
Inmobile minutes	The total time categorised as immobile in the epoch-by-epoch mobile/immobile categorisation (CamNtech Ltd,2016).
Inmobile time	The immobile time expressed as a percentage of the assumed sleep time (CamNtech Ltd, 2016).
Mobile minutes	The total time categorised as mobile in the epoch-by-epoch mobile/immobile categorisation. The higher this value the more disrupted the sleep (CamNtech Ltd, 2016).
Mobile time	The mobile time expressed as a percentage of the assumed sleep time (CamNtech Ltd, 2016).
Immobile bouts	The number of contiguous sections categorised as immobile in the epoch-by-epoch mobile/immobile categorisation. This value was low if there had been long periods of uninterrupted sleep. Therefore, it was considered as a measure of sleep quality (CamNtech Ltd, 2016).
Mean immobile bout	The average length of each of the immobile bouts (CamNtech Ltd, 2016).
Immobile bouts $\leqslant$ 1 minute	The number of immobile bouts which were $\leqslant$ 1 minute of length (CamNtech Ltd, 2016).
Immobile bouts $\leqslant$ 1 minute	The number of immobile bouts $\leqslant$ 1 minute expressed as a percentage of the total number of immobile bouts (CamNtech Ltd, 2016).
Total activity score	The total of all the activity counts during the assumed sleep period (CamNtech Ltd, 2016).
Mean activity per epoch	The total activity score divided by the number of epochs in the assumed sleep period. This result would be expected to scale depending on the length of the epoch (CamNtech Ltd, 2016).
Mean nonzero activity per epoch	The total activity score divided by the number of epochs with greater than zero activity in the assumed.
Sleep period	This result would be expected to scale depending on the length of the epoch (CamNtech Ltd, 2016).
Fragmentation index (%)	The sum of the mobile time % and the immobile bouts $\leqslant$ 1 minute (%). This is an indication of the degree of fragmentation of the sleep period and it was considered as an indication of sleep quality. A fragmentation index lesser than 20% suggested a high quality of sleep, whereas if this value was higher than 50% indicated a disrupted sleep (CamNtech Ltd 2016).

clustering tasks. Since the SOM's proposal, many ANNs based on self-organization have been proposed [32].

In order to identify and cluster sleep patterns from actigraphs in patients, a novel self-organizing neural model called the Growing Neural Forest (GNF) [49] has been utilized, which has been implemented in MATLAB (The Math Works, Inc., Madrid, Spain).[1] This model is based on the Growing Neural Gas (GNG) [19], which is a self-organizing based model that learns a general graph with no special provisions for data sets with separated clusters. However, the GNF learns a set of trees of neurons so that each tree represents a connected cluster of data. High dimensional datasets often contain large empty regions among clusters, so this proposal is better suited to them than other self-organizing models because it represents these separated clusters as connected components made of neurons. In particular, the GNF is shown to correctly discover the connected component structure of some datasets. Moreover, the number of neurons are automatically determined by the GNF/GNG models during the unsupervised learning process according to input data, unlike other unsupervised clustering methods such as SOM or K-means. In our case, we make use of this model to identify and cluster sleep patterns from actigraphs in patients.

Formally, a GNF is defined as a graph with a variable number of nodes (neurons) and edges (connections). Nodes are inserted and removed from the graph during learning phase. Both nodes and edges are inserted and removed from the graph during the learning process. The current number of nodes is noted H. The training set for the graph is noted $\mathcal{S}$, with $\mathcal{S} \subset \mathbb{R}^D$, where D is the dimension of the input space. Each unit $i \in \{1, ..., H\}$ has an associated prototype $\mathbf{w}_i \in \mathbb{R}^D$ and an error variable $e_i \in \mathbb{R}$, $e_i \geq 0$. Each connection has an associated age, which is a non negative integer. The set of connections is noted $A \subseteq \{1, ..., H\} \times \{1, ..., H\}$, where no self-connections are allowed, $(i, i) \notin A$. It is also important to notice that A is an undirected graph, i.e. one cannot have $(i, j) \in A$ and $(j, i) \notin A$ at the same time. An example of the GNF architecture is given in Figure 1.

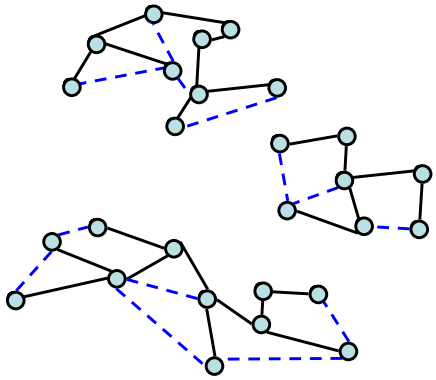

FIGURE 1. Structure of a GNF model with three subgraphs. The connections which do not belong the spanning trees are shown with dashed lines.

III. EXPERIMENTAL RESULTS

A. RESULTS WITH ACTIGRAPHY

Table 1 shows parameters description for every actigraphy exploration performed. First column lists every of 28 actigraphic variable names analyzed in every exploration. Second column shows results (median ED) from determined features, that is, before starting treatment, actigraphic values were taken in 27 children along seven days. Third column shows results from actigraphy one month after starting treatment with MTF (Metil-Fenidato), melatonin and additional nutrition supplementary with oily acids from 1-3 serial.

Before treatment: Around 33% from patients (9/27) showed values slightly higher in parameters mobility minutes

[1] Available online at http://www.lcc.uma.es/ejpalomo/software.html

TABLE 2. Parameter selection for the GNF and GNG models.

Parameter description	Values
Step size for the winning unit	$\epsilon_b = 0.2$
Step size for the neighbor unit	$\epsilon_n = 0.006$
Maximum edge for an edge	$a_{max} = 50$
New units insertion	$\lambda = 100$
Maximum number of units	$H_{max} = 50$
Reduction of the error variables	$\alpha = 0.5$
Error variable decay	$d = 0.995$

(between 57 and 168 minutes) and number of immobility episodes (between 61 and 82 episodes). From this percentage, more that 50% (5/9) also presented higher values to the group average in parameters from sleep episodes (between 48 and 61 episodes) and fragmentation index (between 38% and 73%), and values relatively lower than sleep efficiency (between 76% and 79%). Around 67% (6/9) of our patients recorded more than 40 night awakes, and latency times between 20 and 30 minutes in 45% (4/9). Generally around 67% (6/9) from patients with altered values in actigraphic parameters are straightly related with those that in daily sleeps recorded sleeps awakes, higher conciliation times and/or a lower resting sensation when awakes. A comparison between total sleep time with daily real time with actigraphy showed that total sleep time was overestimated in 15% of patients (4/27). A patient whose mother referred somniloquia showed higher scoring in mobility minutes and fragmentation indexes. Related to PSQ sleep questionnaire, 1 from 2 patients who answered positively more than 8 questions were among those 9 individuals with altered actigraphic parameters according to pre-treatment sample.

After treatment: One month after starting treatment with MTF and melatonin, we appreciated that around 15% (4/27) from total patients presented higher values in immobility episodes (between 60 and 83 episodes) and sleep episodes (between 48 and 61 episodes. These patients have presented altered actigraphic values in main register.

B. APPLICATION OF THE GNF MODEL TO ACTIGRAPHIC RESULTS

The GNF was trained with data resulting using actigraphs under particular conditions. The obtained dataset has $M = 32$ samples and a dimension of $D = 28$ (please note that we have high-dimensional data). An essential point when modeling with neural networks is choosing the appropriate number of neurons. For the GNF, the number of neurons is automatically determined during the unsupervised learning process according to input data. However, a maximum number of neurons on the overall size of the network (H_{max}) must be set. For our experiments, the GNF was trained with the actigraphic results by setting the H_{max} parameter to 5 and 10 neurons. Since the GNF is based on the GNG, the GNF has the same parameters than the GNG. Thus, the GNF parameter values have been set to the values recommended in the original GNG paper [19], which are given in Table 2.

Also, we have selected four subsets of features according to key values:

TABLE 3. Prototype values for a GNF with 5 neurons and using the first subset of features.

Assumed Sleep	Actual Sleep Time	Sleep Efficiency (%)
493.55	436.94	85.79
443.83	368.28	79.40
557.96	499.30	87.59
546.68	447.05	80.20
359.02	334.02	93.40

TABLE 4. Prototype values for a GNF with 5 neurons and using the second subset of features.

Actual Wake Time	Actual Wake (%)	Wake Bouts	Mean Wake Bout
68.86	13.68	19.61	3.87
77.69	14.78	44.87	1.06
80.09	14.77	34.13	2.00
24.44	5.16	17.06	1.00
55.07	10.24	39.28	1.00

TABLE 5. Prototype values for a GNF with 5 neurons and using the third subset of features.

Immobile Mins	Immobile Time (%)	Sleep Bouts
499.93	89.26	45.89
371.45	85.09	24.04
403.82	94.20	27.63
498.89	98.11	8.12
495.91	92.42	30.91

TABLE 6. Prototype values for a GNF with 5 neurons and using the fourth subset of features.

Mean Sleep Bout	Sleep Latency (%)
14.35	4.98
32.19	18.37
9.72	64.38
99.85	6.24
504.95	1.01

TABLE 7. Prototype values for a GNF with 10 neurons and using the first subset of features.

Assumed Sleep	Actual Sleep Time	Sleep Efficiency (%)
447,93	386,12	72,32
537,03	483,31	87,88
552,99	465,46	81,75
497,86	447,98	87,14
365,83	337,47	92,23
429,58	372,05	81,04
505,94	504,97	99,50
543,73	436,38	79,06
572,29	507,59	86,23
489,87	423,09	81,37

1) First subset includes assumed sleep time, real sleep time and sleep efficiency.
2) Second subset contains real awake time, percentage of real time awake, number of awakes and number of falling sleep.
3) Third subset includes immobility minutes, percentage of immobility time and number of falling sleeps.
4) Finally, fourth subset contains longer sleep and sleep latency.

TABLE 8. Prototype values for a GNF with 10 neurons and using the second subset of features.

Actual Wake Time	Actual Wake (%)	Wake Bouts	Mean Wake Bout
1,51	0,42	1,61	1,00
39,47	8,56	15,36	3,95
98,73	17,98	50,95	1,13
58,71	10,18	44,57	1,00
61,48	11,42	30,82	2,00
46,56	9,67	29,80	1,00
106,44	20,27	24,46	3,82
77,84	13,63	48,46	1,00
80,02	15,13	33,78	2,00
27,01	5,87	20,57	1,00

TABLE 9. Prototype values for a GNF with 10 neurons and using the third subset of features.

Immobile Mins	Immobile Time (%)	Sleep Bouts
366,44	83,65	23,11
508,04	87,37	55,41
500,64	99,33	3,40
441,15	90,60	37,31
462,55	93,48	25,15
347,13	96,80	19,93
509,93	92,75	31,49
393,89	93,37	27,08
503,18	90,53	45,37
496,29	89,38	34,02

TABLE 10. Prototype values for a GNF with 10 neurons and using the fourth subset of features.

Mean Sleep Bout	Sleep Latency (%)
504,95	1,01
8,12	79,32
13,68	4,77
12,46	13,55
99,09	14,92
121,94	2,74
12,56	25,46
311,87	2,99
57,91	2,38
11,05	52,00

The values of the prototypes for the GNF trained with 5 neurons and the first, second, third and fourth subset of actigraphic features, are shown in Tables 3-6, respectively, for both groups of patients. Also, the same values are given in Tables 7-10 for the GNF trained with 10 neurons and the first, second, third and fourth subset of actigraphic features, respectively. In these tables, every column represents one feature from the corresponding subset of features from actigraphy and rows represent synaptic weights of every neuron (prototypes), also known as cluster centroids.

The GNF results have been compared with those achieved by two well-known ANNs used in unsupervised learning, namely, the Growing Neural Gas (GNG) in which the GNF is based on [19] and the Self-Organizing Map (SOM) [31]. These two ANNs represent the most outstanding models for unsupervised learning. The GNG paremeter setup is the same than the used for the GNF. The SOM has been trained using the SOM Toolbox [2] for Matlab from the Helsinki University

[2]http://www.cis.hut.fi/somtoolbox/

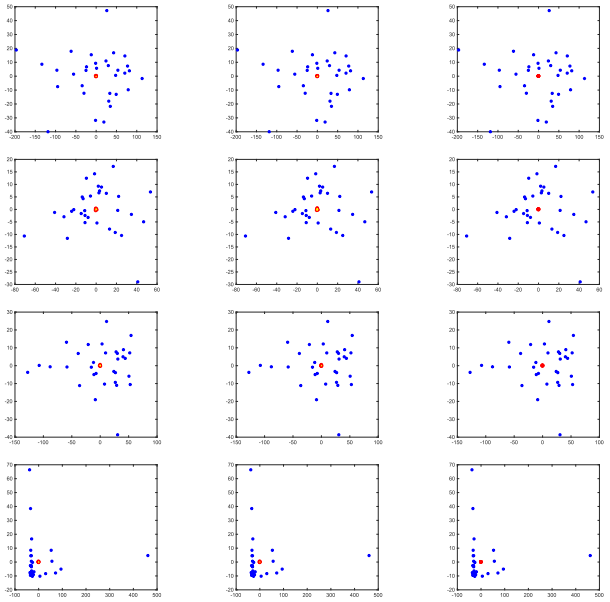

FIGURE 2. Clustering results for each subset of features (rows) performed by the following ANNs: (a) 5-neuron GNF, (b) 5-neuron GNG, and (c) 2 × 3 SOM. The prototype values are drawn as red circles, whereas input data is plotted in blue. The two first principal components are plotted after performing a PCA.

of Technology and setting its parameters to the default values. The map sizes chosen for the SOM are 2 × 3 and 3 × 3 neurons to be as similar as possible to the number of neurons of the GNF and GNG. The resulting prototypes for the GNF, GNG and SOM models trained with two different number of neurons and four subsets of features are shown in Figures 2 and 3. In these plots, prototype values are drawn as red circles, whereas input data is plotted in blue. The two first principal components are plotted after performing a PCA to the input data and to the synaptic weight vectors given by the trained GNF models. By observing these plots, we can see that there is no difference among GNFs trained with 5 and 10 neurons, since prototypes are always placed in the same place. Therefore, only one cluster was detected, so that input data are similar among them and cannot be grouped in other clusters.

In order to provide quantitative results, the mean squared error (MSE), the Davis-Bouldin index (DBI), and the Dunn index have been used to evaluate the clustering performance of the three competitive models. The MSE, which is a measure of the intra-cluster variance that must be minimized in a clustering task is defined as follows:

$$MSE = \frac{1}{M}\sum_{i=1}^{M} \|\mathbf{w}_i - \mathbf{x}_i\|^2 \qquad (1)$$

where M is the number of samples in the dataset, $\mathbf{x}_i$ is the i-th input sample and $\mathbf{w}_i$ is the prototype of the winning neuron corresponding to x_i.

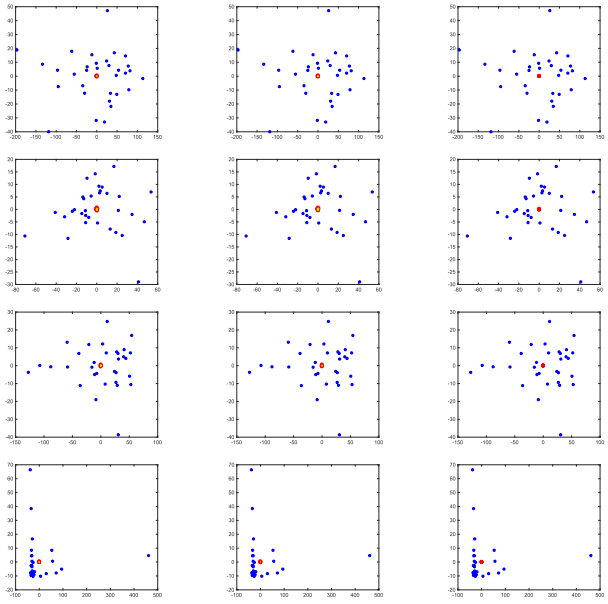

FIGURE 3. Clustering results for each subset of features (rows) performed by the following ANNs: (a) 10-neuron GNF, (b) 10-neuron GNG, and (c) 3 × 3 SOM. The prototype values are drawn as red circles, whereas input data is plotted in blue. The two first principal components are plotted after performing a PCA.

The Davis-Bouldin index (DB) is a metric for evaluating clustering algorithms based on a ratio of within-cluster and between-cluster distances. The Davis-Bouldin index is defined as follows (lower is better):

$$DB = \frac{1}{K}\sum_{i=1}^{K} max_{j\neq i}\{D_{ij}\} \tag{2}$$

where D_{ij} is the within-to-between cluster distance ratio for the ith and jth clusters:

$$D_{ij} = \frac{(\bar{d}_i + \bar{d}_j)}{d_{ij}} \tag{3}$$

where $\bar{d}_i$ is the average distance between each point in the ith cluster and the centroid of the ith cluster; $\bar{d}_j$ is the average distance between each point in the ith cluster and the centroid of the jth cluster; and the d_{ij} is the Euclidean distance between the centroids of the ith and jth clusters.

The last considered performance measure is the Dunn index, which is expressed as follows (higher is better):

$$Dunn = \min_{i\in\{1,\ldots,N\}}\left\{\min_{j:i\neq j}\frac{\|\boldsymbol{\mu}_i - \boldsymbol{\mu}_j\|}{\Delta}\right\} \tag{4}$$

$$\Delta = \max_{i\in\{1,\ldots,N\}}\frac{1}{|C_i|\,(|C_i|-1)}\sum_{\mathbf{x}_k\in C_i}\sum_{\mathbf{x}_l\in C_i-\{\mathbf{x}_k\}}\|\mathbf{x}_l - \mathbf{x}_k\| \tag{5}$$

A statistical significance study has been carried out for the three considered quantitative performance measures, namely *MSE*, *DBI*, and *Dunn*. The reported quantitative values are the mean and standard deviation computed over the 10 runs corresponding to each competing method. Besides that, the nonparametric Friedman test with the corresponding post-hoc Dunn test are used to determine whether the difference of the best competing method with respect to all the others is statistically significant. A 95% confidence level has been chosen in all cases. Furthermore, the Holm-Bonferroni method [56] has been applied and the corresponding adjusted p-values have been obtained.

The GNF, GNG and SOM clustering results for each subset of features (S1, S2, S3, and S4) are given in Tables 11 and 12 for the two different network sizes (5-neuron GNF/GNG, 2 × 3 SOM and 10-neuron GNF/GNG, 3 × 3 SOM), respectively. Best results are in bold for each performance measure and subset of features. Standard deviations are in parenthesis. Note that results are very similar, although the GNF obtains better results in general terms. As seen from the Bonferroni-Holm adjusted p-values, none of the methods

TABLE 11. MSE, DBI and Dunn results for the 5-neuron GNF, 5-neuron GNG and 2 × 3 SOM for each subset of features (S1, S2, S3, and S4). Best results are in bold. Standard deviations are in parenthesis. Adjusted p-values have been obtained after applying the Holm-Bonferroni method with a 95% confidence level.

Subset of features	ANN	MSE	DBI	Dunn
S1	GNF	**0.03 (0.00)**	**0.44 (0.04)**	**1.09 (0.05)**
	GNG	**0.03 (0.00)**	0.55 (0.07)	0.93 (0.15)
	SOM	0.07 (0.00)	2.92 (0.10)	0.45 (0.07)
	p-values	1.00	0.96	0.75
S2	GNF	0.06 (0.00)	**0.50 (0.07)**	**0.71 (0.39)**
	GNG	**0.05 (0.00)**	0.53 (0.06)	0.51 (0.16)
	SOM	0.11 (0.00)	2.88 (0.31)	0.35 (0.06)
	p-values	0.96	0.75	0.59
S3	GNF	**0.04 (0.00)**	**0.58 (0.08)**	**0.90 (0.12)**
	GNG	**0.04 (0.00)**	0.63 (0.09)	0.90 (0.20)
	SOM	0.07 (0.00)	3.33 (0.03)	0.39 (0.00)
	p-values	1.00	0.96	0.30
S4	GNF	**0.01 (0.00)**	**0.46 (0.04)**	**0.48 (0.03)**
	GNG	**0.01 (0.00)**	0.48 (0.07)	0.47 (0.04)
	SOM	0.05 (0.00)	4.60 (0.20)	0.21 (0.00)
	p-values	0.96	0.96	0.45

TABLE 12. MSE, DBI and Dunn results for the 5-neuron GNF, 5-neuron GNG and 2 × 3 SOM for each subset of features (S1, S2, S3, and S4). Best results are in bold. Standard deviations are in parenthesis. Adjusted p-values have been obtained after applying the Holm-Bonferroni method with a 95% confidence level.

Subset of features	ANN	MSE	DBI	Dunn
S1	GNF	**0.01 (0.00)**	**0.41 (0.04)**	**0.82 (0.18)**
	GNG	**0.01 (0.00)**	0.43 (0.04)	0.73 (0.15)
	SOM	0.05 (0.00)	1.53 (0.10)	0.24 (0.08)
	p-values	1.00	0.96	0.75
S2	GNF	**0.01 (0.00)**	**0.30 (0.03)**	**0.77 (0.27)**
	GNG	**0.01 (0.00)**	0.33 (0.03)	0.63 (0.14)
	SOM	0.08 (0.00)	1.45 (0.02)	0.19 (0.00)
	p-values	0.96	0.75	0.59
S3	GNF	**0.01 (0.00)**	**0.43 (0.04)**	**0.78 (0.09)**
	GNG	**0.01 (0.00)**	0.46 (0.03)	0.71 (0.08)
	SOM	0.06 (0.00)	1.88 (0.16)	0.36 (0.10)
	p-values	1.00	0.96	0.30
S4	GNF	**0.00 (0.00)**	**0.31 (0.03)**	**0.95 (0.12)**
	GNG	**0.00 (0.00)**	0.33 (0.03)	0.88 (0.05)
	SOM	0.03 (0.00)	1.96 (0.04)	0.10 (0.01)
	p-values	0.96	0.96	0.45

attains an average performance which is significantly better than all the others, i.e. none of the adjusted p-values is lower than 0.05.

IV. DISCUSSION

A. SLEEP IN CHILDREN WITH ADHD

An evaluation of sleep disorders in children can be afforded from two different perspectives: using objective methods (polysomnography, cardiorespiratory poligraphy, actigraphy, etc) or by means of subjective methods. In these usually a sleep survey is the element to evaluate. Both methods have their own advantages and disadvantages. In this work me made use of different subjective procedures (daily report, sleep survey) and other objective one (actigraphy), and additionally we have introduced the ANN of GNF type. Only few reviews exist to evaluate the sleep in children that are receiving treatment which only evaluate somnolence as the unique sleep disorder derived from using particular drugs on [46]. In this work, we used a reduced version and adapted from the Pediatric Sleep Questionnaire (PSQ) [9] that allows evaluate through 22 questions insomnia, day somnolence, parasomnias, breathing disorders related with sleep and resistance to go to bed. This leads us to use a quick questionnaire in pediatric consult to evaluate the sleep in patients under treatment during a longer period. Particularly, in our case we established one moth since it is the most frequent period when sleep disorders are expressed. ADHD association studies sleep disorders (TS) and frequently some factors are related with sleep disorders as executive structure alterations within ADHD [33], [50], breathing disorders during sleeping, interactive environmental conditions between sleep and ADHD, treatment with drugs for this disorder, children sleep features, among others.

Cortese [10] work on a metanalysis with ADHD and sleep disorders in children that collected studies both from objective parameters (polysomnography and/or actigraphy) and subjective ones (questionnaires) published between 1987 and 2008. The conclusion established is that according to subjective indicators, ADHD affected children present more sleep disorders (sleep and awakes) than others. Objective indicators revealed sleep fragmentation, poor sleep efficiency, breathing disorders while sleeping and excusive day somnolence. Some works [4], [11] refers to sleep disorder affecting more than 50% of families with ADHD affected children, mainly difficulties to start sleeping and to keep sleeping with frequent awakes. An epidemiologic study with ADHD and TS [63] was performed in Spain, this showed an associated snoring (more than half of the night), enuresis, difficulty to keep sleep (more than two awakes per night), resistance to go to bed and rhythm movement disorders. It is important to mention that sleep disorders are added factors that limit life quality in these children and their families [60]. Main cause of sleep disorders in children with ADHD is complex and broadly unknown. We defend that this field requests more research to understand the complex relation existing between sleep and ADHD. In this line, we have to consider several specific causes that take part in this relation: 1) Resistence to go to sleep. 2) Stimulant ingestion substances as coffee, tea, chocolate, carbonated drinks y psychostimulant drugs used in ADHD. 3) Suffering other affections. Anxiety and depression disorders can bring difficulties to sleep, and these are illnesses frequently related to ADHD. Both diversity of causes, multiplicity of sleep disorders included in International Classification of Sleep Disorders ICSD [15] related with children and difficulties to define and interpret each of them in ADHD affected children lead to go on searching procedures and techniques, as ANN, to simplify how to interpret different cases in a more efficient, accurate and reliable way.

B. ACTIGRAPHY

Currently polysomnography is considered as ''gold standard'' method to study sleep disorders. However, implementing this method on children presents some issues as, it leads to cost in budget, its adaptation in younger children presents problems, relevant difficulties in children affected with particular pathologies (ADHD, autism, cerebral palsy, etc), children with frequent and important TS [12], [39], [54]. Recently, to supply these deficiencies and its demonstrated reliability and efficiency this methodology is being applied on child population [64]. This procedure has been proven as easy, cost afforded, and highly reliable [23], [41]. Actigraphy determines sleep and awake evaluation along multiple days, this is the reason why are used in sleep disorders, circadian rhythms and insomnia [2], [38]. Nevertheless, other disorders exist that can be useful to monitor the evolution of Restless Legs Syndrome (RLS) or periodical movements in limbs61. American Academia of Sleep Medicine (AASM) recommends to apply actigraphy [15]. 1) Sleep disorders evaluation. 2) Assessment of response to sleep disorder treatment. 3) In special situations as children, where to perform a polysomnography and or interpret it is highly difficult and tedious and exponentially increasing, in these cases actigraphy becomes an important alternative. Children sleep unit from Paediatric department at University of Granada had taken efficient results in applying actigraphy on children, but in particular cases it presents deficiencies to interpret concrete responses to new treatments and classification systems. This approach is focused on a combined usage of MTF able to transitory cause sleep disorders when is administered to ADHD and aMT affected children. Actigraphy per se is potentially useful to numerically quantifies and compares params in ADHD affected children. However, this is not sufficiently powerful since it is difficult to accurately define whether sleep patterns are modified after the treatment. Fortunately, ANN provides the appropriate tool to establish groups to define particular groups of variables that define a concrete pathology and different ways to make sick in the context of sleep disorders.

Indeed, we have implemented different ANN models using important referent parameters. Results from ANN application in this context are inspiring since these conclude that the

impossibility to differentiate patients before and after being medicated. This plays and important role in clinic because it opens new fields on children in which specific medication for ADHD and sleep disorders are problems that alter daily activities and academicals in those patients.

C. METIL-FENIDATO

Recently an important increasing in the use of MTF in children population is happening [37], [42], for this reason is relevant deeply know their secondary effects. Different mechanisms have been described to explain this relation; by straight pharmacological effect, by sleep disorders patterns (i.e. knigthmares), by exacerbation of a previous disorder or finally triggering somnolence [43]. We highlight the fact that this is a field to be defined this arouses important interest to find new drugs as substitutes and less secondary effects [44]. Franco *et al.* presents a broad review of 393 ADHD affected children are treated with MTF compared with placebo, they conclude that treated children are negatively affected in their sleeps [13]. These results coincide with presented by Soutullo and Buñuel who aim that applying MTF in children decreases appetite and negatively affects sleep. Ross and Ross [53]. defends that collateral effects of administrating psychostimulants, at short term, tends to be insomnia and anorexia and generally are short term long. These effects use to be frequent during the first month, this is the reason why our project was performed in this transition phase. In this sense, we highlight the fact that in our patients the percentage of children with appetite disorders and loss of weight was 33% (9/27).

D. MELATONIN

A combined administration of MTF and melatonin is one of the most novelty aspects of this work. Melatonin presents an important action as antioxidant [18], [48], [52], as well as it plays an important role in sleep disorders in children with different clinic problems [47]. This experiment has proved how possible secondary effects of applying MTF during the first month are observed. Moreover, children were treated with a relevant improvement in their sleep quality. In this case, melatonin dose was 1 mg. Currently we have a cohort of patients with a longer period of treatment with 3 mg of melatonin administered. These results together with a combined administration of fatty acids, MTF and melatonin lead to think of important benefits on life quality in ADHD affected children.

E. ARTIFICIAL NEURAL NETWORKS

As it was previously described, we present an ANN called Growing Neural Forest (GNF) to perform a clustering task for data extracted from children under treatment and not treated children. ANNs are powered tool as classifier and provide advantages to perform quantitative tests in medical practice. Medical records contain valuable information to be use for designing and training ANN to enrich diagnosis in general medicine and offers new perspectives to specialist doctors. Most interesting approach of applying ANN, from a clinical point of view, brings with the possibility to study set of data and variables simultaneously to classify particular situations not considered a priori. This is potentially powerful not just for general sleep disorders but for particular sleep disorders. Indeed, ANNs have been broadly applied in different fields [1], [5], [25], [65].

GNF results showed the impossibility to classify patients as treated and not treated according to input data, then as a result we had that sleep was not affected by administrating drugs (MFT and melatonin). These results demonstrate that melatonin attenuated possible sleep disorders induced by psychostimulant drugs in patients with ADHD. Moreover, the Growing Neural Forest (GNG) and the Self-Organizing Map (SOM) have been used to provide comparative results. The GNG and SOM results are similar to those achieved by the GNF according to the obtained adjusted p-values with the Holm-Bonferroni method. Thus, these results corroborates that a combined use of melatonin and MTF can keep and even improve in some cases sleep pattern in ADHD affected children. Therefore, ANNs open new expectations for ongoing TS and ADHD in children as it was proven.

V. CONCLUSION

In this paper, we have used a novel ANN model called the Growing Neural Forest (GNF) that concludes the impossibility to differentiate patients before and after being medicated for ADHD. GNF results have been compared with those achieved by another two ANNs also used in unsupervised learning, namely the Growing Neural Gas (GNG) and the Self-Organizing Map (SOM). These ANNs showed the impossibility to classify patients as treated and not treated according to input data, then as a result we had that sleep was not affected by administrating drugs (MFT and melatonin). Data clustering performed by the ANNs demonstrated that melatonin attenuated possible sleep disorders induced by psychostimulant drugs in patients with ADHD. Melatonin presents an important action as antioxidant playing an important role in sleep disorders in children with different clinic problems. We concluded that possible secondary effects of applying MTF during the first month are observed. Ongoing work includes an extension of data for training the ANNs from a higher number of patients to extract more information and to study the possible emerging of different profiles of patients. This fact becomes the ANN methodology as an important tool really useful for future works in this field.

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