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World Journal of Psychiatry and Mental Health Research

Research Article
Published: 30 May, 2019

Functional Neuroimages Analyzed by means of Artificial Neural Networks Can Help Psychiatrists to Diagnose Schizophrenia

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Abstract

Introduction: Schizophrenia-related spectrum disorders show functional images that permit to infer the existence of underlying neurobiological features: Inter-hemispheric asymmetries in metabolic activity, abnormal regional glucose absorption in prefrontal and temporo-occipital areas, basal ganglia, and claustrum, among others. We developed Artificial Neural Network (ANN) aids to help us detect cerebral absorption patterns of glucose in subjects diagnosed with Schizophrenia.

Methods: Positron Emission Tomography (PET) images of seven patients diagnosed with schizophrenia, with predominantly negative symptoms (Schz group) and seven matching control volunteers (Control group) were accessed and processed by means of the developed ANN software.

PET Scan: PET studies were acquired under resting conditions in Foundation School of Nuclear Medicine, Mendoza, Argentina.

Results: The diagnostic aid application was tested with ten randomized sets, formed by the two experimental groups, yielding highly compatible results with diagnostics obtained by trained psychiatrists. Test sensitivity=100%. Test specificity=95%.

Conclusions: At present, neuroimaging methods are used with reluctance for the purpose of psychiatric diagnostics, as since until now it had been difficult to detect specific metabolic absorption patterns for different nosological entities. According to our results, the ANN algorithms appear as promising tools for helping diagnose schizophrenia, and presumably, for diagnosing other neuropsychiatric disorders.

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Received Date: *03 May 2019*
Accepted Date: *27 May 2019*
Published Date: *30 May 2019*

Citation:
Molina ME, Carlos M, Luciana C, Silvina K, María Inés DM, Julieta M. Functional Neuroimages Analyzed by means of Artificial Neural Networks Can Help Psychiatrists to Diagnose Schizophrenia. World J Psychiatry Ment Health Res. 2019; 3(1): 1019.

Introduction

It has been observed that certain neuropsychiatric disorders, such as severe thought disturbances, show individual functional images in which it is possible to infer the existence of underlying neurobiological features, detectable through characteristic image patterns [1-6]. More precisely, schizophrenia-related spectrum conditions show inter-hemispheric asymmetries in metabolic activity, characteristic glucose uptake in prefrontal regions and temporo-occipital areas [7-22]. In addition, some other studies related to schizophrenia show abnormal patterns of glucose uptake in the Pale Globe and in the Claustrum [23-27].

Our group has been studying neural networks theories to help us understand the nature of mental functioning under normal and-certain- abnormal conditions. Among them, Post Traumatic Stress Disorder and Schizophrenia [6,27].

In this investigation we aimed to incorporate Artificial Neural Network theories as tools to help us detect the characteristic absorption patterns of glucose in the brains of subjects diagnosed with Schizophrenia. A brief reference to these theories proceeds.

In 1943 Warren McCulloch and Walter Pitts (psychiatrist and mathematician, respectively) published a paper entitled "A Logical Calculus of the Ideas Immanent in Nervous Activity", in which they communicated their research about the intrinsic logic of neural networks. In particular,

they sought to elucidate the way in which memory can be stored and accessed in a system of interconnected neural networks, both in their natural forms and in their artificial theoretical models. This work is considered as a fundamental milestone for the further development of cognitive sciences and artificial intelligence [28].

From a biophysical point of view it is known today that the transmission of signals (information) from one neuron to another through the synaptic scaffolding is a complex electrochemical process in which certain neurotransmitter substances are released from the pre-synaptic neuron to the sites of reception of the post-synaptic neuron. The effect of this process-that is described here in a very simplified manner-is to raise or to decrease the electrical potential of the cell body of the recipient cell, and along with it, the frequency of production of action potentials. The vicissitudes of this phenomenon are closely linked to the degree of *synaptic coupling* between the two neurons [29].

What has been said is schematized in Figure 1, where I_1, I_2... I_n: represent the inputs generated by signals coming from pre-synaptic neurons, W_1, W_2... W_n: represent the synaptic weights (or strength of synaptic coupling between pre and post-synaptic neurons). The sum of all the products "signal times synaptic weight" is transferred to a comparative function of a “step” or “sigmoid” type, after which only those signals that have reached a certain threshold level are finally transferred to the output of the system.

McCulloch and Pitts showed how the artificial neurons that respond to this model have the ability to learn and to perform mathematical and logical operations, provided that in the neuronal model the synaptic weights-or the degree of synaptic coupling-are gradually modified according to a series of comparisons between the results obtained and the results expected to be obtained at the final output of the post-synaptic neuron. This is known as the *learning algorithm* [30,31]. In other words, after an iterative training process, the information incorporated by the neuron is recorded in its synapses, or to be even more precise, in the relationships between the weights of the concurrent synapses of the post-synaptic neuron. The ability of neural networks and systems to re-configure their internal connectivity is known as *neural plasticity* [32]. Figure 2 shows how a single artificial neuron can be programmed to operate as an AND, OR, or NOT computational gate, according to the value of its synaptic weights. Figure 3 illustrates the learning process of an artificial neuron, programmed to behave as an "AND" logic gate. In this graph it can be seen that, to the provided that the synaptic weights adopt the appropriate values, the processing errors (difference between the obtained and the expected record for the model) are gradually reduced to zero. When this happens the artificial neuron responds to the stimuli or input signals according to what is needed and it is said that the neuron has learned to perform the process for which it has been designed and trained.

Now, if several artificial neurons are interconnected, forming multi-layered networks, it is possible to configure computational models that are suitable for the recognition of complex patterns [33]. Figure 4 shows a neural network of feed-forward architecture that is known to be fully connected (each neuron transfers its output to all the neurons in the next layer), with an input layer of three, a hidden layer of four, and an output layer of two neurons. In this type of networks it has been also verified that the learned information is stored, in a distributed manner, in the relationships of the synaptic weights-or the coupling strength-that link different neurons.

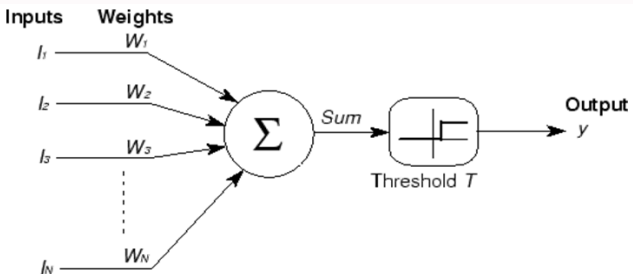

Figure 1: A simplified model of an artificial neuron as it was proposed by Mc Culloch and Pitts in 1943. The information is not stored in a *single location*, but in the *distributed values* of the concurrent synaptic weights (w_1, w_2,...w_N).

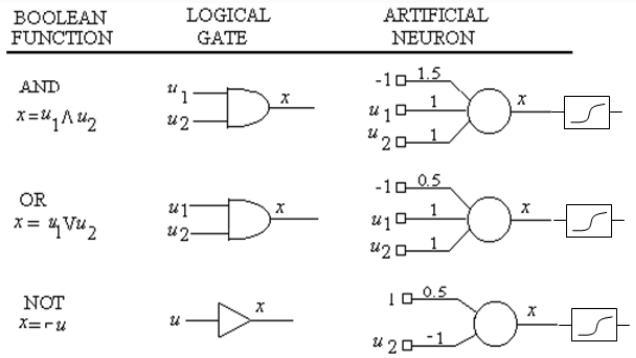

Figure 2: Artificial neurons are models that demonstrate the way in which a neuron is able to "learn" to perform basic logical and mathematical operations by modifying the degree of synaptic coupling. For instance, as can be seen in this figure, a single artificial neuron can function as a logical computational gateway "AND", "OR" or "NOT" according to the values adopted by its synaptic weights.

To apply these theoretical models to the field of biology, still we need to show that the synaptic networks of real biological neurons are also reconfigured in accordance with learning experiences. A clear and elegant demonstration of this hypothesis can be found in Rose, who studied the neurobiological processes involved in learning in animal models, and described the way in which biochemical signaling-based on subjective experience-establishes changes in the synaptic coupling [34].

Artificial Neural Networks (ANN) have been used in several biomedical areas, specifically in Psychiatry, and related to certain diagnostic aspects of the Schizophrenia disorders [35-39].

To conduct this investigation we designed and trained an ANN to detect patterns of neural metabolic activity which could be considered as associated to patients diagnosed with schizophrenia, with a predominance of negative symptoms in the *Positive and Negative Syndrome Scale* (*PANSS*) [40]. The parameter which helps us for these diagnostics, is the output of the developed algorithm, this is the numerical level at the last neuron of the ANN. Thus, after the required number of iterations needed to complete the training stage, the software classifies the subject as a possible non schizophrenic subject when this parameter value is within the range from 0 to 0.3, and as a possible schizophrenic patient when this value is within the range from 0.7 to 1. After applying statistical grouping methods and performing various experimental tests upon the subjects’ images we compared the diagnostic results we obtained by means of the ANN with those of two trained psychiatrists and found significant concordances.

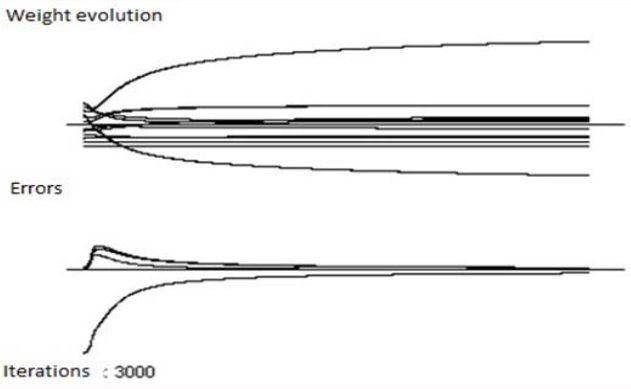

Figure 3: Training session of an artificial neural network. Initially, a small random value is assigned to each synaptic weight, which is then "adjusted" by an iterative algorithm. As the weights reach the required values, the system errors tend to 0.

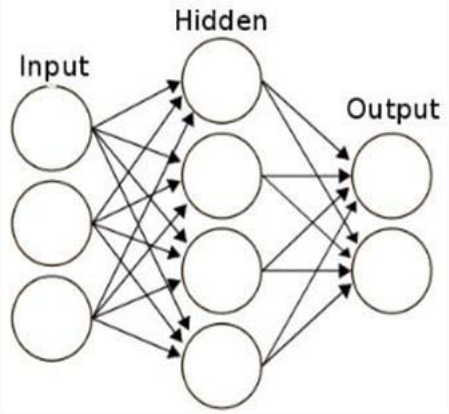

Figure 4: Multilayer neural networks are able to solve problems of greater complexity, such as recognition, classification, prediction and diagnosis.

Methods

Subjects: A group of psychiatric patients was evaluated by two trained clinical psychiatrists through open and semi-structured personal and family interviews. Among them, 47 met the DSM-IV criteria for the diagnostic of schizophrenia, and were submitted to Positron Emission Tomography (PET) scanning, which was performed at resting conditions [41]. Subsequently, and after a 5 day wash-out period, these 47 patients were evaluated through the PANSS [40]. PET images from those who had reached scores equal to or higher than 42 on the negative sub-scale of PANSS and lower than 20 in the positive sub-scale were select to establish the image database for this investigation. PET images of seven patients were retrieved: 5 from male subjects and 2 from female subjects, aged between 18 and 67 years (m=39). Thereafter, seven control volunteers, with a similar gender distribution and age range between 23 and 49 years old (m=35) were recruited and submitted to PET scanning. These subjects did not meet the criteria for any psychiatric disorder diagnostic. Their PET images were needed to train and perform the experimental diagnostics through the ANN, complementing the images of the first group. After receiving a detailed explanation about the study, patients and control subjects signed the corresponding informed consent, approved by the Ethics Committee of the Nuclear Medicine School Foundation, and prepared in accordance with the Helsinski Declaration of 1964 [42].

Subject grouping: Using bootstrapping permutation techniques, and Monte Carlo randomizing techniques, ten experimental sets were generated for testing the diagnostic aid algorithm, each of them counting [43-45]:

a) Five subjects from the Schz group for training the system.

b) Five subjects from de Control group for training the system.

c) Two subjects from the Schz group for obtaining their diagnostics through the ANN.

d) Two subjects from the Control group for obtaining their diagnostics through the ANN.

PET Scan: PET studies were performed under baseline conditions, in a QUEST PET scanner (UGM Inc. PA, USA) of the Foundation School of Nuclear Medicine of Mendoza (FUESMEN) [46]. This PET Scanner is equipped with six detectors of Sodium Iodide (INa), arranged in hexagonal form, with extended axial field of 25.6 cm, and spatial resolution of 5.5 mm. The sensitivity of this instrument has been set at 400,000 kcps/microCi/ml. The scanner can handle up to 5 mCi in the field of vision, at which point it reaches the maximum count. For biological studies, t reaches its maximum sensitivity for activities as low as 1.5 mCi in its field of vision [47].

The patients were accommodated in supine position on the scanner table which has a head support device. The skull was aligned to the center of the FOV by the cantomeatal line using a laser alignment system. Once in position, the patients were injected intravenously with 5 mCi of Fluoro-Deoxy-Glucose [F-18] FDG, with open eyes and ears without plugs, in a dim and silent environment. At the time of injection and during the 60-minute dynamic scan, arterialized blood samples (1 ml) were taken from the forearm to monitor the plasma concentration of [18]FDG.

Software: We developed a Backpropagation Neural Network Algorithm, with parameterizable number of inputs, hidden layer neurons, learning rate and iterations number [30,31,48]. The algorithm was trained with the images taken at the level Zmm=0 referred to Talairach J and Tournoux P, from the two experimental groups [49]. The diagnostic signals of the ANN were contrasted with the diagnostics produced by the clinical psychiatrists. The results obtained by applying the developed algorithm are shown in Figure 5.

Algorithm parameters: The following parameters were used for image analysis:

a) Number of pixels of the training images (7680).

b) Number of training images to be used (10).

c) Number of hidden layer neurons to be used (150).

d) Learning rate (0.9753).

e) Number of iterations (420).

f) Show numeric values of initial weights (n(no)).

g) Method of generation of initial weights (4-Monte Carlo method).

h) Horizontal scale factor X (1).

i) Vertical expansion factor% (100).

j) Filename of initial weights (as input).

k) Filename of initial weights (as output).

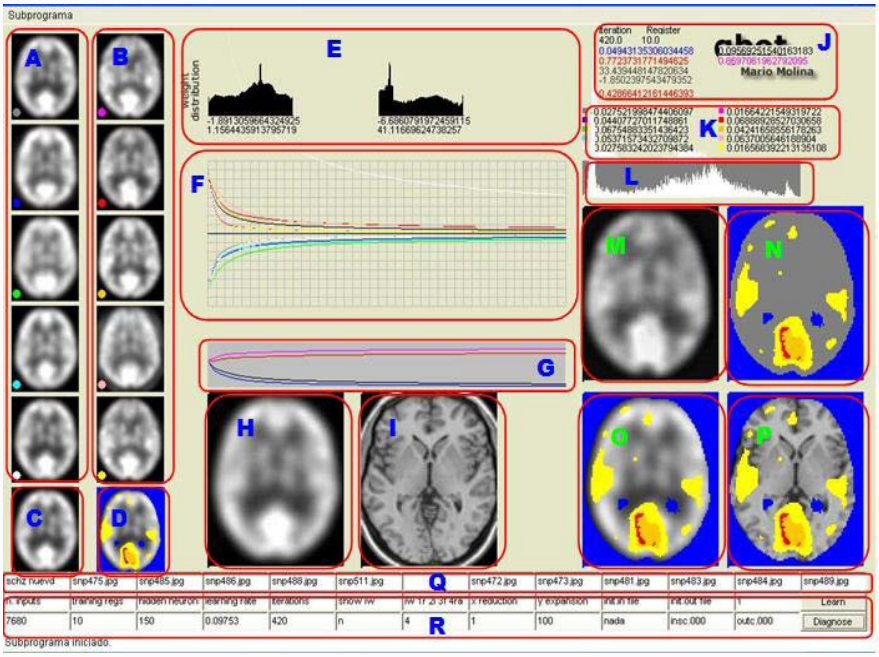

Figure 5: The developed algorithm: Qbot. Compare area F of this figure with Figure 3. The system detects the characteristic metabolic patterns of the disorder and the error curves converge to 0, which indicates that the algorithm can find specific activation patterns in the analyzed images. **A and B:** Training PET images, level 0 (Talairach, 1988). **C and D:** First patient to diagnose. E: Final histogram of the weighted topographic image. **F:** Relative Errors of the algorithm. **G:** Diagnostics area. **H:** First patient to diagnose amplified. **I:** MRI reference. **J, K and L:** Learning process, numeric evolution, real time. **L:** histogram of the weighted topographic image, real time. **M:** weighted topographic image. **N, O, and P:** Auxiliar images, superimposed.

l) Filename of final weights (as output).

m) Learn: Training stage (command).

n) Diagnose: Application or diagnostic stage (command).

Interface:

1. The names of the images to be processed were entered in the Q area of the interface.

2. The parameters indicated in the previous section were entered in the R area of the interface.

The parameters a-e are described in Arbib, and are standard for feed-forward ANN architectures with supervised training using the Backpropagation Algorithm [30,31].

3. When selecting Diagnose, the training and diagnostic stages were sequentially executed.

4. The iterative reduction of the training errors E is plotted in the area "F" of the interface. In a characteristic training stage, a gradual approximation of all error dots to the "0" (zero) axis should be observed. For diagnostics to be valid, an Error level indicator E greater than 150 was required.

5. The M, N, O and P areas of the interface show the *weighted topographic images*. These are indicative of the neuroanatomical regions that the system considers, throughout its training, as relevant for the diagnostic process.

6. The diagnostic area (Zone "G" of the interface) shows the temporal evolution of the diagnostics of the subjects. The system allows the diagnostic of up to four subjects, simultaneously. The software classifies the subject as a possible non schizophrenic subject when this parameter value is within the range from 0 to 0.40, and as a possible schizophrenic patient when it is within the range from 0.60 to 1.

7. If the convergence of errors to zero is slow, parameter d) "Learning Rate" can be increased. If the system shows oscillating error or diagnostic values, this parameter must be reduced.

Results

The software was tested with the ten experimental sets, which were established in random combinations as previously described, specifying 50 iterations, and obtaining the diagnostic results presented in Figure 6. Numerical values are shown in Figure 7, and a graphical distribution of them can be seen in Figure 8. In all cases it was possible to observe that the ANN produced appropriate error reduction plots and concordant diagnostics in relation to those of the evaluator psychiatrists, with only one exception: the experimental test #9, in which a normal subject reached a percentage of 55.92% in the diagnostic indicator parameter value, so the system was not able to classify it as part of the control group. However, the error parameter E warned this test did not reach the adequate error level to be considered reliable (242>150).

Sensivity and Specificity

According with Loong [50]:

Sensitivity=true positive × 100/(true positive+false negative)=20 × 100/20+0=100%

Specificity=true negative × 100/(true negative+false positive)=19 × 100/19+1=95%

Conclusions

At present, neuroimaging methods are used with reluctance for the purpose of psychiatric diagnostics, since it has been difficult to detect specific patterns to link images with unequivocally determined

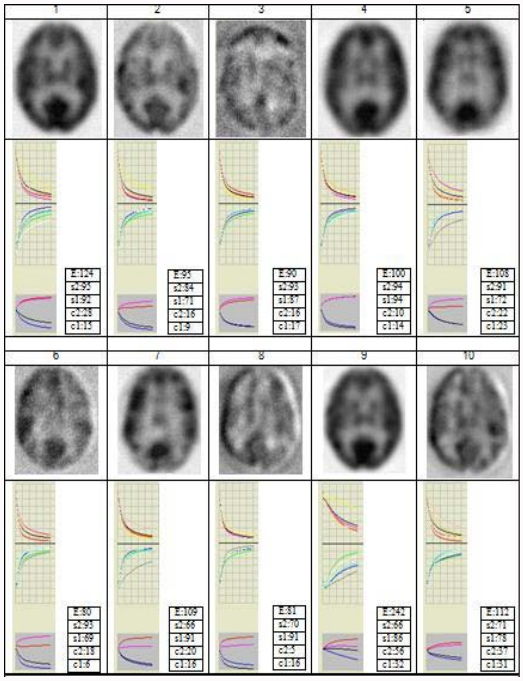

Figure 6: Ten diagnostic results of the ANN, showing the weighted topographic images and the numerical diagnostics obtained results after 50 iterations. E: parametric error level. Diagnostic indicator value for each tested subject: s2: Schz subject 2; s1: Schz subject 1; c2: Control subject 2; c1: Control subject 1. Values between 0 to 40% indicate control subject, between 60% and 100%: schz patient. E must be<150 for this test to be valid.

Diagnostic Experiment	Control subject a	Control subject b	Schz patient a	Schz patient b
1	14,89%	28,29%	94,82%	92,23%
2	9,07%	15,74%	70,85%	84,20%
3	17,49%	16,08%	87,26%	92,97%
4	13,73%	9,80%	94,19%	93,89%
5	22,70%	22,50%	71,77%	90,80%
6	6,43%	17,77%	68,96%	92,90%
7	15,89%	19,66%	90,71%	66,16%
8	15,61%	5,30%	90,84%	70,21%
9	31,89%	55,92%	86,49%	66,19%
10	30,86%	37,00%	77,77%	71,00%

Figure 7: Diagnostics result tests presented in table form, where it can be seen that the diagnostics generated by the software are clearly concordant to the diagnostics produced by the intervening psychiatrists. Values between 0 to 40% indicate control group subject, between 60% and 100%: schz group patient. Test number 9 is the only exception.

nosological entities. However, by using the proposed algorithm, the diagnostics results obtained by this software are significantly concordant with the diagnostics produced by the intervening psychiatrists, also providing information about the areas that may be neurobiologically affected, through the topographic weighted

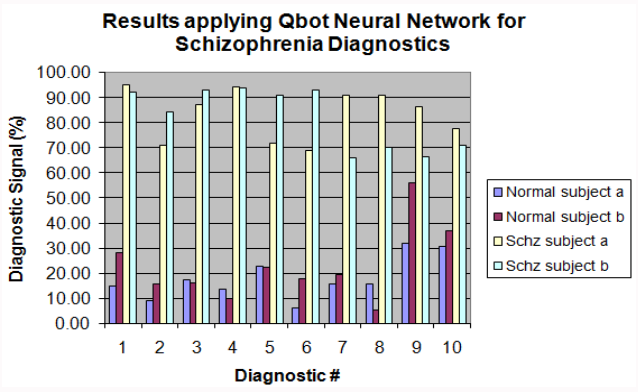

Figure 8: Diagnostics result tests presented in graphics form. Diagnostics generated by the software are clearly concordant to the diagnostics produced by the intervening psychiatrists. Values between 0 to 40% indicate control group subject, between 60% and 100%: schz group patient. Test number 9 is the only exception. For a test to be valid: E<150.

images. These considerations may be relevant when it comes to selecting therapeutic strategies linked to specific neurotransmitter systems characteristic of different brain regions. According to the results obtained, the algorithm appears as a promising tool for the diagnosis of schizophrenia. Further developments and trials are needed to determine the capabilities of this algorithm and to extend its application to other neuropsychiatric disorders.

This paper constitutes a Preliminary Report of the Research Project "Quantitative Electroencephalography in the Evaluation of Anxiety Disorders. Psychotherapeutic and Pharmacological Interventions". Research Department of the University of Mendoza, Hospital Escuela Carlos Pereyra, Mendoza, Argentina.

Acknowledgments

Roberto Isoardi, from Foundation School of Nuclear Medicine, processed the neuroimages to develop this investigation.

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